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 (1:1:2H_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 (1:1:2H_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_3*C*O), 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 CH_3CO); 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_3*C*O), 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 CH_3CO); 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, $CHCl_3$); ^1H 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, CH_2OH), 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, $NHCH_2$), 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); ^1H 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, CH_2OH), 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, $NHCH_2$), 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, $CHCl_3$); ^1H 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, CH_2OH), 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); ^1H 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, CH_2OH), 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, $CHCl_3$); ^1H 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, CH_2OH), 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, $NHCH_2$), 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); ^1H 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, CH_2OH), 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, $NHCH_2$), 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, $CHCl_3$); ^1H 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, CH_2OH), 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, $NHCH_2$), 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.

Acknowledgements

The authors would like to thank Drs. Atsushi Takahashi and Akihiro Tomoda (Hokko Chemical Industry Co. Ltd., Atsugi) for biological assays, Profs. Naoki Asano (Hokuriku University, Kanazawa) and Yoshiyuki Suzuki (International University of Health and Welfare, Otawara) for helpful discussion, Misses. Yoriko Ooki and Midori Mori (Tokyo Metropolitan University, Hachioji) for measurement of mass spectra, and Ms. Miki Kanto for assistance in preparing this manuscript.

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12. The protected N-alkylamines were here demonstrated to be easily isolated and purified, allowing us to subject them to further chemical modification. Practically, one-pot processing of treatment of **13α,β** with alkyl amines, followed by hydrolysis, can improve isolated yields of the corresponding free amines. The reaction conditions have not yet been optimized.
13. All biological assays were carried out in a standard manner by Dr. Akihiro Tomoda (Hokko Chemical Industry, Co. Ltd.).
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Bioorganic & Medicinal Chemistry 12 (2004) 6569–6579

Synthesis and glycosidase inhibitory activity of some N-substituted 5a-carba-β-fuco- and β-galactopyranosylamines, and selected derivatives☆

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Received 26 July 2004; revised 8 September 2004; accepted 8 September 2004

Abstract—In the course of chemical modification of α-fucosidase inhibitors of 5a-carba-fucopyranosylamine type, an *N*-dodecyl derivative of the enantiomer 6-deoxy-5a-carba-β-D-galactopyranosylamine demonstrated very strong inhibition of β-galactosidase and β-glucosidase. This finding led us to synthesize corresponding 6-hydroxy compounds, in order to elucidate structure–activity relationships for inhibitors of this type. Among four *N*-alkyl-5a-carba-β-D-galactopyranosylamines prepared, the *N*-octyl derivative could be demonstrated to possess moderate activity toward α- and β-galactosidases, and β-glucosidase.

1. Introduction

Recently, the *N*-octyl derivative[1] **2** of 5a-carba-α-fucopyranosylamine[2] (**1**), α-5a-CFucamine, was demonstrated to be a very strong α-L-fucosidase inhibitor (bovine kidney) with *p*-nitrophenyl-α-L-fucopyranoside, essentially comparable with deoxyfuconojirimycin (DFJ) in this regard. Although oxocarbenium ion transition-state analogs, the (5,5a)-unsaturated derivatives of **1**, were shown to possess weak activity, contrary to expectation, it is of interest to note that the β-anomer[3] **3** also possessed high activity against α-L-fucosidase. These results are in contrast with the α-glucosidase inhibitory activity relationship[4] observed between the ground-state mimic validamine, and a transition-state mimic, its unsaturated derivative, valienamine.

The present paper documents details for synthesis of some N-substituted derivatives[5] of **3** with both racemic and L-enantiomeric modifications, and a comparison of their inhibitory activity regarding four glycosidases. In addition, the corresponding 6-hydroxy derivatives of **3** were prepared in order to elucidate roles of C-5 substituents in displaying inhibition potential (Fig. 1).

Chemical modification of the β-anomer **3** was carried out by incorporation of hydrophobic alkyl and phenylalkyl portions into the amino group by direct treatment of the carba-sugar epoxide **13**, a newly prepared versatile precursor, with alkyl and phenylalkylamines. For convenience, rough screening of the activity of several racemic compounds **5a–f** readily available was performed, to allow estimation of the approximate enantiomeric contribution to the activity, based on comparison of data observed for D- and/or L-enantiomers (Fig. 2). The antipode of 5a-carba-β-L-fucopyranosylamine should be 6-deoxy-5a-carba-β-D-galactopyranosylamine. Therefore, inhibitory activity of the racemic modification of 5a-carba-hexopyranosylamine should be a sum of those of its components. This consideration is based on the assumption that each enantiomer does not interfere with the competitive inhibitory action of the others. For example, with racemic DL-**5d**, activity (IC_{50} 3.8 μM) against L-fucosidase should be largely due to the

Keywords: Glycosidase inhibitor; Galactopyranosylamine.
☆ In this paper, the nomenclature of carba-sugar derivatives follows the IUPAC-IUB Recommendations 1996 (*Carbohydr. Res.* **1997**, *297*, 1).
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doi:10.1016/j.bmc.2004.09.023

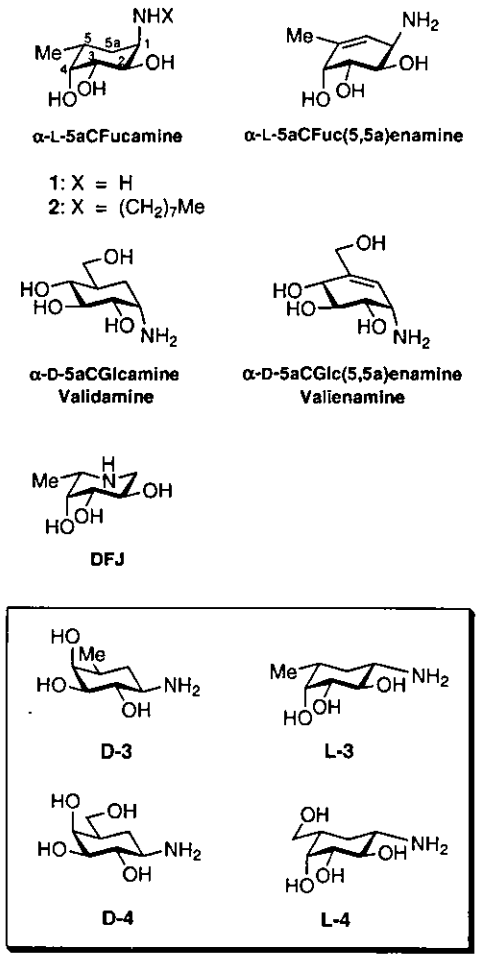
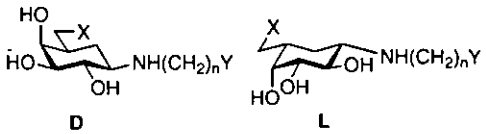


Figure 1. 5a-Carba-β-fucopyranosylamine (**3**) and β-galactopyranosylamine (**4**).



Compd	X	Y	n
5a	H	Me	5
b	H	Me	7
c	H	Me	9
d	H	Me	11
e	H	Ph	2
f	H	Ph	4
6a	OH	Me	3
b	OH	Me	7
c	OH	Me	9
d	OH	Me	11

Figure 2. N-Substituted 5a-carba-β-fucopyranosylamines and β-galactopyranosylamines, assayed for inhibitory activity against seven glycosidases.

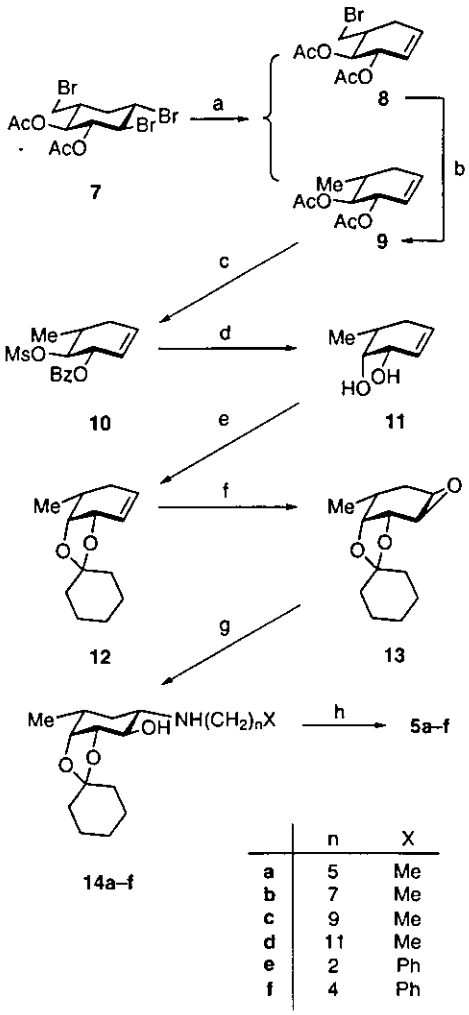
L-enantiomer, and high inhibition toward β-galactosidase (IC_{50} 0.02 μM) and β-glucosidase (IC_{50} 0.50 μM) would be probably attributable to the D-enantiomer (Table 1). This conclusion is partially supported by data obtained for the newly synthesized optically active L-**5d** (IC_{50} 0.91 μM, α-fucosidase) (Table 2). Therefore, these results stimulated us to synthesize the corresponding parent 6-hydroxy compounds **6a–d** in order to elucidate structure–inhibitory activity relationships for inhibitors of this type, especially regarding the hydrophobic region due to C-5 substituents. As indicated by N-substitution[1] of the α-anomer **1**, chemical modification[5] of the β-anomer **3** and its parent might be expected to increase its potential.

2. Results and discussion

Treatment of 3,4-di-*O*-acetyl-2,6-dibromo-2,6-dideoxy-5a-carba-β-L-glucopyranosyl bromide[6] (L-**7**) with slight excess of zinc dust in DMF for 2 h at 80 °C gave 1,2-diacetoxy-6-bromomethyl-3-cyclohexene (D-**8**, 59%), together with the 6-debromo compound D-**9** (32%). When the reaction time was prolonged at a similar temperature, compound D-**9** was mainly obtained but in poor yield due to its simultaneous decomposition. Compound D-**8** isolated by fractionation was conventionally debrominated with tributyltinhydride in toluene in the presence of AIBN to give D-**9** (86%). Zemplén O-deacetylation of D-**9** with methanolic sodium methoxide, selective benzoylation of the allylic hydroxyl group, and subsequent mesylation afforded the 1-mesylate D-**10** (64%). Direct nucleophilic substitution of D-**10** with an benzoate anion in DMF at 110 °C and successive deprotection with methanolic sodium methoxide gave (1*R*,2*S*,6*R*)-1,2-dihydroxy-6-methyl-3-cyclohexene L-**11** (93%). Conventional protection of L-**11** with cyclohexylidene group (→L-**12**, 85%) and epoxidation with *m*-chloroperbenzoic acid in a phosphate buffer solution (pH ~ 6) gave the single β-epoxide L-**13** selectively in 90% yield. Rear attack of the peracid seems to be adequately restricted by the presence of a bulky cyclohexylidene group.[7] The corresponding isopropylidene derivatives also gave similar results, but isolation of the products was somewhat difficult, compared to those for L-**12** and L-**13**.

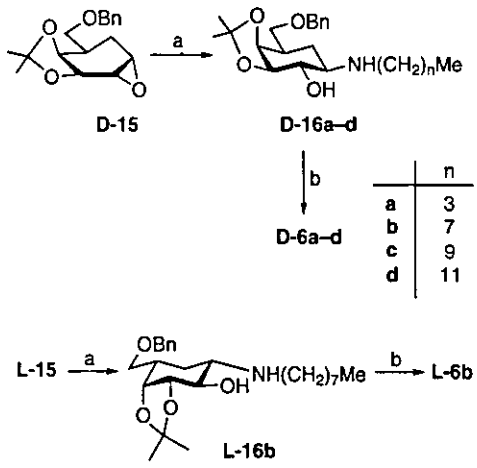
Reaction of the racemate[8] DL-**13** with alkylamines or phenylalkylamines in 2-propanol in sealed tubes at 120 °C proceeded slowly but almost regio-selectively to afford the respective N-substituted 5a-carba-β-galactopyranosylamines DL-**14a–f**, in 70–90% yields, which, without isolation, were treated with 80% aqueous acetic acid at 80 °C, and the resulting amine acetates were purified over a column of Dowex-50W × 2 (H^+) resin with 1% methanolic ammonia to give the free bases DL-**5a–f** almost quantitatively. The optically active L-**5b–d,f** were similarly prepared from L-**13** (Scheme 1).

Since N-substituted 6-deoxy-5a-carba-β-galactopyranosylamines have been shown to possess strong inhibitory activity[5] (see Section 4.28) against β-galactosidase and β-glucosidase, the findings stimulated our evaluation of inhibitory potential of the corresponding 5a-carba-β-galactopyranosylamines **4**, the structures of which more resemble those of the substrates.



	n	X
a	5	Me
b	7	Me
c	9	Me
d	11	Me
e	2	Ph
f	4	Ph

Scheme 1. Synthesis of N-substituted 5a-carba-β-DL- and L-fucopyranosylamines **5a–f**. For convenience, the formulae only depict those of the L-enantiomers. Reagents and conditions: (a) Zn powder, AcOH, 80 °C; (b) Bu_3SnH, AIBN, toluene; (c) methanolic NaOMe; BzCl (1.2 molar equiv), pyridine; MsCl, DMAP, pyridine; (d) NaOBz, 90% aqueous DMF, 110 °C; methanolic NaOMe; (e) $(MeO)_2C_6H_{10}$, TsOH, DMF; (f) *m*CPBA, CH_2Cl_2, phosphate buffer; (g) alkyl or phenylalkylamines (molar equiv), 2-propanol, 120 °C, 4–10 days; (h) 80% aq AcOH, Dowex-50W × 2 (H^+) resin, 1% aq NH_3.



	n
a	3
b	7
c	9
d	11

Scheme 2. Synthesis of N-substituted 5a-carba-β-galactopyranosylamines **6a–d**. Reagents and conditions: (a) alkylamines (molar equiv), 2-propanol, 120 °C, 2–6 days; (b) 80% aq AcOH; H_2, EtOH, 10% Pd/C, purified by a column of Dowex-50W × 2 (H^+) resin, with 1% methanolic ammonia, or that of silica gel.

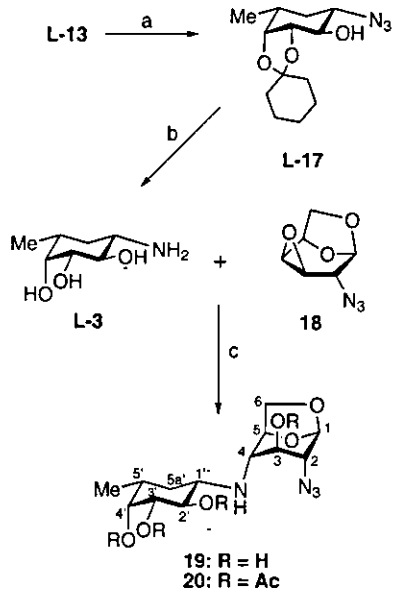
1,2-Anhydro-6-*O*-benzyl-3,4-*O*-isopropylidene-5a-carba-α-D-galactopyranose[9] (D-**15**) was chosen as the synthetic precursor of *N*-alkyl-5a-carba-β-galactopyranosylamines. Diequatorial cleavage at C-1 with alkylamines was expected to occur preferentially in consideration of the previous synthesis of *N*-acetyl-5a′-carba-lactosaminide.[10] Thus, a mixture of a molar equivalent of D-**15** and alkylamines was heated in a sealed tube at 120 °C for 2–3 weeks, producing the corresponding secondary amines D-**16a–d** in 50–60% yields. The protected amine **16a** was O-deisopropylidenated with aqueous acetic acid, followed by hydrogenolysis with Pd/C, to give, after purification by an acid resin column, the amine D-**6a** (93%) as a white solid. Similarly, compounds D-**16b–d** were converted into the corresponding amines D-**6b–d**. Attempted isolation of the di-*N*,*O*-acetyl derivative of D-**16b** was successful, but its NMR spectrum was complex due to the restricted rotation around the secondary amido group, so that confirmation of the structure was rather difficult. The *N*-acetyl derivative was hydrolyzed with 1 M hydrochloric acid and the resulting hydrochloride was purified similarly to afford the amine D-**6b** (Scheme 2).

The enantiomeric epoxide L-**15** was prepared from 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-5a-carba-D-*xylo*-hex-1-enitol according to the standard procedure,[9] in a 15% over-all yield. Reaction of L-**15** with a molar equivalent of octylamine gave the *N*-octyl derivative, which was deprotected usually to give L-**6b**.

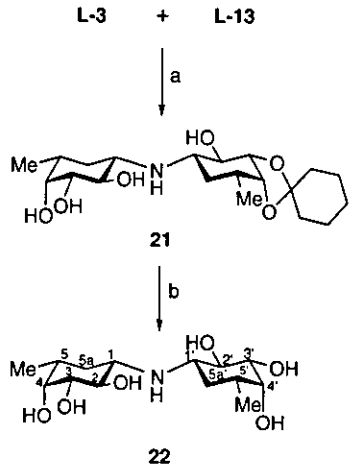
Taking advantage of the readily available free base L-**3**, the N-linked carba-disaccharides[11] with carba-β-fucopyranosylamine residues were prepared in order to ascertain enzyme-inhibitory functions of the derivatives, the alkyl chains of which were replaced with sugar residues.

The epoxide L-**13** was treated with sodium azide in DMF to give a sole azide **17**, having a 5a-carba-β-fucopyranose structure. This compound was catalytically reduced with Pd/C to give, after elution through an acid column with methanolic ammonia, the free base L-**3** (72%). Coupling of L-**3** and 1,6:3,4-dianhydro-2-azido-2-deoxy-β-D-galactopyranose[12] **18** (1.6 molar equiv), in 2-propanol for two weeks 120 °C gave a single condensate **19** (93%), the structure of which was confirmed with reference to the ^1H NMR spectrum of its tetra-*O*-acetyl derivative **20** conventionally prepared (Scheme 3).

Synthesis of symmetric N-linked bis(5a-carba-β-fucopyranosyl) disaccharide was attempted by conventional coupling of L-**3** and L-**13**, affording the protected dicarbadisaccharide **21** (40%), which was O-decyclohexylidenated to give a symmetric compound **22** (~100%). The structure was fully supported by ^1H NMR spectral data (Scheme 4).



Scheme 3. Synthesis of N-linked carba-disaccharide **19** containing 5a-carba-β-L-fucopyranose residue. Reagents and conditions: (a) excess NaN_3, DMF, 110 °C; (b) H_2, EtOH, 10% Pd/C; (c) **18** (1.6 molar equiv), 2-propanol, 120 °C, two weeks.



Scheme 4. Synthesis of N-linked 5a,5a'-dicarbadisaccharide: bis(5a-carba-β-L-fucopyranosyl)amine **22**. Reagents and conditions: (a) L-**13** (1.5 molar equiv), 2-propanol, 120 °C, three weeks; (b) 80% aq AcOH, 80 °C.

3. Enzyme inhibitory activity

Four *N*-alkyl and two *N*-phenylalkyl derivatives **5a–f** of 5a-carba-β-fucopyranosylamine (**3**) and four *N*-alkyl derivatives **6a–d** of 5a-carba-β-galactopyranosylamine (**4**) were assayed for activity in a standard manner,[13] against seven glycosidases: α-galactosidase (green coffee beans), β-galactosidase (bovine liver), α-glucosidase (Baker's yeast), β-glucosidase (almond), β-glucosaminidase (bovine kidney), α-mannosidase (Jack beans), and α-fucosidase (bovine kidney), as listed in Tables 1 and 2. None of the compounds were found to be inhibitors of α-glucosidase, β-glucosaminidase, or α-mannosidase.

Table 1. Inhibitory activity [IC_{50} (K_i) μM] of N-substituted 5a-carba-β-DL-fucopyranosylamines against three glycosidases

Compound[a]				Inhibitory activity, IC_{50} (K_i), (μM)		
	n	X	Y	α-Fucosidase (bovine kidney)	β-Galactosidase (bovine liver)	β-Glucosidase (almond)
DL-**5a**	5	H	Me	8.2	3.7	0.73
DL-**5b**	7	H	Me	5.5	0.7 (0.11)	1.5 (3.2)
DL-**5c**	9	H	Me	2.7	0.2 (0.009)	2.0 (0.4)
DL-**5d**	11	H	Me	3.8	0.02 (0.0045)	0.50 (0.53)
DL-**5e**	2	H	Ph	7.5	5.7	0.38 (0.057)
DL-**5f**	4	H	Ph	5.1	0.9 (0.046)	1.4 (1.2)

[a] All compounds did not show any notable inhibitory activity against α-galactosidase, α-glucosidase, β-glucosaminidase, and α-mannosidase.

Table 2. Inhibitory activity (IC_{50}, μM) of 5a-carba-β-fuco- and β-galactopyranosylamines and its N-substituted derivatives against four glycosidases

Compound[a]				Inhibitory activity, IC_{50} (μM)			
	X	Y	*n*	α-Fucosidase (bovine kidney)	α-Galactosidase (green coffee beans)	β-Oalactosidase (bovine liver)	β-Glucosidase (almond)
L-**3**	H	H	0	4.3	NI	NI	NI
D-**4**	OH	H	0	NI	2.8	NI	NI
L-**5b**	H	Me	7	1.8	NI	3.7	15
L-**5c**	H	Me	9	0.7	NI	1.0	17
L-**5d**	H	Me	11	0.91	NI	0.46	6.1
L-**5f**	H	Ph	4	1.2	NI	2.4	10
D-**6a**	OH	Me	3	NI	39	NI	13
D-**6b**	OH	Me	7	NI	5.2	8	14
L-**6b**	OH	Me	7	105	NI	87	210
D-**6c**	OH	Me	9	NI	25	16	25
D-**6d**	OH	Me	11	NI	35	5.8	8.7

NI: no inhibition $<10^{-3}$ M.

[a] All compounds did not show any notable inhibitory activity against α-glucosidase, β-glucosaminidase, and α-mannosidase.

Compared to the corresponding derivatives[2] of the α-anomers, DL-**5a–f** possessed about one tenth of the inhibitory activity against α-fucosidase and the potential was actually thought to be mainly due to the β-L-fucose-mimicking enantiomers, as verified by assaying L-**5b–d** and L-**5f** newly prepared.

It is interesting to note that compounds DL-**5a–f** possess very strong activity toward both β-galactosidase and β-glucosidase, showing marked cross-reactivities with both enzymes as observed for aminocyclopentitol glycosidase inhibitors.[14,15] Their high potential could be demonstrated to be largely attributable to the respective D-enantiomers, that is, *N*-alkyl-6-deoxy-5a-carba-β-D-galactopyranosylamines. In fact, the L-enantiomers, *N*-alkyl-5a-carba-β-L-fucopyranosylamines had decreased activity toward these two enzymes as shown for L-**5b–d** and L-**5f**, displaying rather potent cross-reactivities with both α-fucosidase and β-galactosidase. Among the six derivatives, compound DL-**5d**, actually D-**5d**, was the strongest inhibitor of β-galactosidase: $K_i < 4.5$ nM. Furthermore, compound DL-**5e** was demonstrated to be a very potent inhibitor, possessing characteristic pH-dependent activity against β-glucosidase: K_i 0.39 μM at pH 5.5; K_i 0.057 μM at pH 6.8. These results would indicate that optically active D-**5e** is an effective β-glucosidase inhibitor fully compatible with results for isofagomine[16] (K_i 0.11 μM, at pH 6.8) and calystegine[17] (K_i 0.75 μM, pH independent). Thus, N-substituted 6-deoxy-5a-carba-β-D-galactopyranosylamines may be promising lead compounds for new carba-sugar-type β-galactosidase and β-glucosidase inhibitors. The inhibitory potential of 5a-carba-glycosylamines and derivatives appears to be comparable to those of structurally related 4-amino-5-(hydroxymethyl)cyclopentane-1,2,3-triols.[15] It may probably depend on close resemblance between the structures of 5a-carba-hexopyranosylamine and those of ground states of the corresponding substrates. However, in the case of 5a-carba-hexopyranosylamines, the configuration of the 4-hydroxyl function seems to be very important for the generation of activity, although it is difficult to explain rationally the fact that, the corresponding β-*gluco* isomers, the 4-epimers of D-**5b**, had rather decreased[3] the activity toward β-glucosidase, in spite of close resemblance of the substrate structures.

It is noteworthy that the free bases L-**3** and D-**4**[18] were found to be not very strong but selective inhibitors against α-fucosidase and α-galactosidase, corresponding to the respective stereochemistry of the substrates (Table 2). As demonstrated for *N*-octyl derivative D-**6b**, *N*-alkyl-5a-carba-β-D-galactopyranosylamines are moderate α- and β-galactosidases, and β-glucosidase inhibitors, so that the N-substituents and the hydrophobic area conferred by the 5-methyl branching on the carbocyclic ring are likely to control and enhance binding to the active sites of enzymes. The L-enantiomers, as indicated by L-**6b**, almost lacked inhibitory activity against all enzymes.

Newly prepared carba-disaccharide-type compounds **19** and **22** only showed inhibitory activity (IC_{50} 3.9 and 39 μM) against α-fucosidase, suggesting selectivity along the lines observed for L-**3**. Since, the former compound was initially designed for the purpose of providing a synthetic precursor for N-linked *N*-acetyl-5a′-carba-lactosaminide derivatives, it is promising that this kind of disaccharide mimic may give selective α-fucosidase inhibition through further chemical modification.

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}. ^{1}H NMR spectra were recorded for solutions in deuteriochloroform and deuteriomethanol with internal tetramethylsilane (TMS) as a reference with a JEOL JNM LAMBDA-300 (300 MHz) instrument. Mass spectra were determined with HITACHI M-8000 ion trap mass spectrometer. 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 °C under diminished pressure.

Unless otherwise noted, when both racemic and optically active compounds were prepared, the processing for the later were only described.

4.2. 3,4-Di-*O*-acetyl-1,5-anhydro-6-bromo-2,6-dideoxy-5a-carba-D-*xylo*-hex-1-enitol (D-8) and 3,4-di-*O*-acetyl-1,5-anhydro-2,6-dideoxy-5a-carba-D-*xylo*-hex-1-enitol [(1*S*,2*S*,3*R*)-1,2-di-*O*-acetyl-3-methylcyclohex-5-ene-1,2-diol] (D-9)

(a) 3,4-Di-*O*-acetyl-2,6-dibromo-2,6-dideoxy-5a-carba-L-β-glucopyranosyl bromide[6] (L-**7**, 46.2 g, 0.10 mol) was dissolved in acetic acid (370 mL), to which zinc powder (33.5 g, 0.51 atom) was added. The suspension was stirred vigorously for 2 h at 80 °C. Formation of two components was observed by TLC (1:6 EtOAc/hexane). Excess zinc dust and precipitates were removed by filtration, and the filtrate was co-evaporated with toluene. The products were fractionated over a silica gel column (500 g, 1:10 EtOAc/hexane) to give D-**9** (7.0 g, 32%) and D-**8** (17.8 g, 59%) as a colorless syrup. Data for D-**8**: TLC: R_f 0.28 (1:6 EtOAc/hexane). The compound was characterized by comparison with an authentic racemate.[6]

Data for D-**9**: TLC: R_f 0.37 (1:6 EtOAc/hexane); $[\alpha]_D^{22}$ +12 (*c* 1.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.80 (m, 1H, H-1), 5.44–5.51 (m, 2H, H-2, H-3), 4.94 (dd, 1H, $J_{3,4} = 7.8$ Hz, $J_{4,5} = 11.0$ Hz, H-4), 2.27 [ddd, 1H, $J_{1,5a(eq)} = J_{5,5a(eq)} = 4.3$ Hz, $J_{5agem} = 13.8$ Hz, H-5a(eq)], 2.04 and 2.08 (2s, each 3H, 2 × Ac), 1.89–2.04 [m, 2H, H-5a(ax)], 0.97 (d, 3H, $J_{5,6} = 6.3$ Hz, H-6); ITMS-ESI (positive mode): *m/z* 235 $[M+Na]^+$, 251 $[M+K]^+$.

(b) To a solution of D-**8** (0.10 g, 0.34 mmol) in toluene (8.0 mL) were added in turn AIBN (8 mg, 0.048 mmol) and tributyltinhydride (0.27 mL, 1.0 mmol), and the mixture was stirred for 10 min at 120 °C. The reaction mixture was evaporated to dryness, and the residue was chromatographed on a silica gel column (7.0 g, hexane → 1:10 EtOAc/hexane) to give D-**9** (62 mg, 86%).

4.3. 3-*O*-Benzoyl-1,5-anhydro-2,6-dideoxy-4-*O*-mesyl-5a-carba-D-*xylo*-hex-1-enitol [(1*S*,2*S*,3*R*)-1-*O*-benzoyl-2-*O*-mesyl-3-methylcyclohex-5-ene-1,2-diol] (D-10)

A solution of D-**9** (0.94 g, 4.4 mmol) in methanol (5.0 mL) was treated with 1 M methanolic sodium methoxide (1.0 mL) for 1 h at room temperature, and, after neutralization with Amberlite IR-120B (H^+) resin, concentrated to dryness. The residual diol was dissolved in dry pyridine (6.0 mL) and a solution was stirred at −15 °C, to which a solution of benzoyl chloride (0.62 mL, 5.3 mmol) in pyridine (3 mL) was added dropwise for 0.5 h. The mixture was stirred for 15 h at 0 °C. TLC (1:10 MeOH/$CHCl_3$) showed disappearance of the diol and formation of a new component. To the reaction mixture were added mesyl chloride (1.0 mL, 12.9 mmol) and a catalytic amount of DMAP under stirring at 0 °C, and then the mixture was stirred for 17 h at room temperature. Formation of one major and one minor components was detected by TLC. After the reaction was quenched by addition of methanol at 0 °C, the mixture was diluted with EtOAc (150 mL). The solution was washed thoroughly with 1 M hydrochloric acid, saturated aqueous $NaHCO_3$, and water, and dried. The organic layer was evaporated and the residue was chromatographed on a silica gel (100 g, 1:7 EtOAc/hexane) to afford D-**10** (0.87 g, 64%) as a colorless syrup: $[\alpha]_D^{22}$ +144 (*c* 0.67, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.44–8.11 (m, 5H, Ph), 5.87 [dddd, 1H, $J_{1,3}$ = 2.0 Hz, $J_{1,5a(ax)}$ = $J_{1,5a(eq)}$ = 4.9 Hz, $J_{1,2}$ = 10.0 Hz, H-1], 5.77 (ddd, 1H, $J_{1,3}$ = 2.0 Hz, $J_{2,3}$ = 3.5 Hz, $J_{3,4}$ = 7.8 Hz, H-3), 5.62 [dddd, 1H, $J_{2,5a(ax)}$ = $J_{2,5a(eq)}$ = 1.8 Hz, $J_{2,3}$ = 3.5 Hz, $J_{1,2}$ = 10.0 Hz, H-2], 4.83 (dd, 1H, $J_{3,4}$ = 7.8 Hz, $J_{4,5}$ = 11.2 Hz, H-4), 2.91 (s, 3H, Ms), 2.40 [ddd, 1H, $J_{1,5a(eq)}$ = $J_{5,5a(eq)}$ = 4.9 Hz, $J_{5a gem}$ = 17.8 Hz, H-5a(eq)], 2.19 [dddd, 1H, $J_{5,5a(eq)}$ = 4.9 Hz, $J_{5,6}$ = 6.3 Hz, $J_{5,5a(ax)}$ = 10.0 Hz, $J_{4,5}$ = 11.2 Hz, H-5], 2.03 [m, 1H, H-5a(ax)], 1.20 (d, 3H, $J_{5,6}$ = 6.3 Hz, H-6); ITMS-ESI (positive mode): *m/z* 333 $[M+Na]^+$, 349 $[M+K]^+$.

4.4. 1,5-Anhydro-2,6-dideoxy-5a-carba-L-*lyxo*-hex-1-enitol [(1*S*,2*R*,3*R*)-3-methylcyclohex-5-ene-1,2-diol] (L-11)

A mixture of D-**10** (0.87 g, 2.8 mmol) and sodium benzoate (2.0 g, 14 mmol) in 90% aqueous DMF (13 mL) was stirred for 15 h at 110 °C. After cooling, the mixture was diluted with ethyl acetate (150 mL) and the solution was washed with water. The organic layer was evaporated and the residue was treated with 1 M methanolic sodium methoxide (2 mL) in methanol (4 mL) for 3 h at room temperature. After neutralization with Amberlite IR-120B (H^+) resin, the mixture was evaporated and the residue was chromatographed on a silica gel column (30 g, 1:2 EtOAc/hexane) to give L-**11** (0.34 g, 93%) as a syrup: $[\alpha]_D^{22}$ +29 (*c* 0.99, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.73 (br d, 1H, $J_{1,2}$ = 10.3 Hz, H-1), 5.47 (br d, 1H, $J_{1,2}$ = 10.3 Hz, H-2), 4.19 (br s, 1H, H-3), 3.77 (br s, 1H, H-4), 3.36 (br s, 2H, 2 × OH), 1.75–1.92 (m, 3H, H-5, 2 × H-5a), 1.03 (d, 3H, $J_{5,6}$ = 6.3 Hz, H-6); ITMS-ESI (positive mode): *m/z* 151 $[M+Na]^+$.

4.5. 1,5-Anhydro-3,4-*O*-cyclohexylidene-2,6-dideoxy-5a-carba-L-*lyxo*-hex-1-enitol (L-12)

A mixture of the triol L-**11** (2.00 g, 15.6 mmol), 1,1-dimethoxycyclohexane (10 mL), $TsOH \cdot H_2O$ (0.53 g, 3 mmol), and DMF (40 mL) was stirred for 2 h at room temperature. The mixture was then neutralized with triethylamine and evaporated to dryness. The product was purified with a silica gel column (20 g, 1:100 EtOAc/hexane) to give L-**12** (2.83 g, 85%) as a syrup, TLC: R_f 0.47 (1:10 EtOAc/hexane); $[\alpha]_D^{24}$ +37 (*c* 0.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.71 [br ddd, 1H, $J_{1,5a(ax)}$ = 2.0 Hz, $J_{1,5a(eq)}$ = 2.4 Hz, $J_{1,2}$ = 6.1 Hz, H-1], 5.51 (br d, 1H, $J_{1,2}$ = 6.1 Hz, H-2), 4.44 (m, 1H, H-3), 4.08 (br d, 1H, $J_{4,5}$ = 5.2 Hz, H-4), 1.77–1.85 (m, 2H, 2 × H-5a), 1.75 (br dd, 1H, $J_{4,5}$ = 5.2 Hz, $J_{5,6}$ = 6.3 Hz, H-5), 1.42 (m, 10H, C_6H_{10}), 1.05 (d, 3H, $J_{5,6}$ = 6.3 Hz, Me); ITMS-APCI (positive mode): *m/z* 209 $[M+H]^+$.

4.6. 1,2-Anhydro-3,4-*O*-cyclohexylidene-5a-carba-α-L-fucopyranose (L-13)

To a stirred suspension of compound L-**12** (2.83 g, 13.3 mmol) and a mixture of 1 M aqueous NaH_2PO_4 (1.0 mL) and 1 M aqueous Na_2HPO_4 (1.0 mL) in dichloromethane (42 mL), was added *m*CPBA (2.98 g, 17.2 mmol), and it was agitated vigorously for 3 h at 0 °C. The mixture was then diluted with chloroform (600 mL), and the solution was thoroughly washed successively with saturated aqueous sodium thiosulfate, sodium hydrogen carbonate, and water, dried, and evaporated. The residue was chromatographed on a silica gel column (30 g, 1:80 → 1:60 EtOAc/hexane) to give the epoxide L-**13** (1.57 g, 90%) as a crystalline solid, TLC: R_f 0.67 (1:10 EtOAc/hexane); $[\alpha]_D^{24}$ +19 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 4.31 (br d, 1H, $J_{3,4}$ = 5.6 Hz, H-3), 3.98 (br d, 1H, $J_{3,4}$ = 5.6 Hz, H-4), 3.23 (br s, 1H, H-1), 2.97 (br d, 1H, $J_{2,3}$ = 3.2 Hz, H-2), 1.84 (m, 3H, H-5, 2 × H-5a), 1.25–1.78 (m, 10H, C_6H_{10}), 1.04 (d, 3H, $J_{5,6}$ = 4.4 Hz, Me); ITMS-APCI (positive mode): *m/z* 225 $[M+H]^+$.

4.7. *N*-Hexyl-5a-carba-β-DL-fucopyranosylamine (DL-5a)

A mixture of the epoxide DL-**13** (50 mg, 0.22 mmol), hexylamine (28.7 μL, 0.22 mmol), and 2-propanol (0.5 mL) was heated in a sealed tube for four days at 120 °C, and then evaporated. The residue was chromatographed on a silica gel column (5.0 g, 100:1 → 20:1 $CHCl_3$/MeOH) to give the protected amine DL-**14a** (47 mg, 66%). It was treated with 80% aqueous acetic acid (1.0 mL) for 2 h at 80 °C, and the mixture was evaporated. The product was purified on a column of Dow-

ex-50W × 2 (H^+) resin (1.0 g, 1% aqueous NH_3) to give the amine DL-**5a** (16 mg, 92%) as a white powder, TLC: R_f 0.57 (5:1 $CHCl_3$/MeOH); ^1H NMR (300 MHz, CD_3OD): δ 3.80 (br s, 1H, H-1), 3.59 (dd, 1H, $J_{1,2} = J_{2,3} = 9.5$ Hz, H-2), 3.43 (br d, 1H, $J_{2,3} = 9.5$ Hz, H-3), 2.75 (dt, 1H, $J = 7.1$ Hz, $J_{gem} = 11.0$ Hz, NHCH_2), 2.39–2.51 (m, 2H, NHCH_2, H-1), 1.59–1.70 [m, 2H, H-5, H-5a(eq)], 1.45–1.51 (m, 2H, $NHCH_2CH_2$), 1.29–1.36 [m, 7H, $(CH_2)_3CH_3$, H-5a(ax)], 1.04 (d, 3H, $J_{5,6} = 6.5$ Hz, H-6), 0.88 (t, 3H, $J = 6.6$ Hz, CH_2CH_3); ITMS-ESI (positive mode): *m/z* 246 $[M+H]^+$.

4.8. *N*-Octyl-5a-carba-β-L-fucopyranosylamine (L-5b)

A mixture of the epoxide L-**13** (50 mg, 0.22 mmol), octylamine (36.1 μL, 0.22 mmol), and 2-propanol (0.5 mL) was heated in a sealed tube for four days at 120 °C, and then evaporated. The residue was chromatographed on a silica gel column (5.0 g, 100:1 → 20:1 $CHCl_3$/MeOH) to give the protected amine L-**14b** (47 mg, 66%). It was treated with 80% aqueous acetic acid (1.0 mL) for 3 h at 80 °C, and evaporated. The product was purified on a column of Dowex-50W × 2 (H^+) resin (1.0 g, 1% aqueous NH_3) to give the amine L-**5b** (33 mg, ~100%) as a white powder, TLC: R_f 0.58 (5:1 $CHCl_3$/MeOH); $[\alpha]_D^{24}$ +21 (*c* 1.4, MeOH); ^1H NMR (300 MHz, CD_3OD): δ 3.80 (br s, 1H, H-4), 3.59 (dd, 1H, $J_{1,2} = J_{2,3} = 9.5$ Hz, H-2), 3.21 (br d, 1H, $J_{2,3} = 9.5$ Hz, H-3), 2.75 (dt, 1H, $J = 7.1$ Hz, $J_{gem} = 11.0$ Hz, NHCH_2), 2.39–2.51 (m, 2H, H-1, NHCH_2), 1.59–1.70 [m, 2H, H-5, H-5a(eq)], 1.29–1.36 [m, 7H, $(CH_2)_3CH_3$, H-5a(ax)], 1.04 (d, 3H, $J_{5,6} = 6.5$ Hz, H-6), 0.88 (t, 3H, $J = 6.6$ Hz, CH_2CH_3); ITMS-ESI (positive mode): *m/z* 274 $[M+H]^+$.

4.9. *N*-Decyl-5a-carba-β-L-fucopyranosylamine (L-5c)

A mixture of the epoxide L-**13** (50 mg, 0.22 mmol), decylamine (42.9 μL, 0.22 mmol), and 2-propanol (0.5 mL) was heated in a sealed tube for eight days at 120 °C, and then evaporated. The residue was chromatographed on a silica gel column (5.0 g, 100:1 → 20:1 $CHCl_3$/MeOH) to give the protected amine L-**14c** (53 mg, 88%). It was treated with 80% aqueous acetic acid (1.0 mL) for 3 h at 80 °C, and evaporated. The product was purified on a column of Dowex-50W × 2 (H^+) resin (1.0 g, 1% aqueous NH_3) to give the amine L-**5c** (24 mg, ~100%) as a white powder, TLC: R_f 0.60 (5:1 $CHCl_3$/MeOH), $[\alpha]_D^{24}$ +1.4 (*c* 0.8, MeOH); ^1H NMR (300 MHz, CD_3OD): δ 3.61 (br s, 1H, H-4), 3.45 (dd, 1H, $J_{2,3} = 9.3$ Hz, $J_{1,2} = 9.5$ Hz, H-2), 3.21 (br d, 1H, $J_{2,3} = 9.3$ Hz, H-3), 2.73 (dt, 1H, $J = 7.3$ Hz, $J_{gem} = 11.5$ Hz, NHCH_2), 2.46–2.60 (m, 2H, H-1, NHCH_2), 1.45–1.57 [m, 4H, $NHCH_2CH_2$, H-5, H-5a(eq)], 1.21–1.34 [m, 15H, $(CH_2)_7CH_3$, H-5a(ax)], 1.05 (d, 3H, $J_{5,6} = 6.3$ Hz, Me); ITMS-ESI (positive mode): *m/z* 302 $[M+H]^+$.

4.10. *N*-Dodecyl-5a-carba-β-L-fucopyranosylamine (L-5d)

A mixture of the epoxide L-**13** (50 mg, 0.22 mmol), dodecylamine (40.0 μL, 0.22 mmol), and 2-propanol (0.5 mL) was heated in a sealed tube for 10 days at 120 °C, and then evaporated. The residue was chromatographed on a silica gel column (5.0 g, 80:1 → 20:1 $CHCl_3$/MeOH) to give the protected amine L-**14d** (68 mg, 93%). It was treated with 80% aqueous acetic acid (1.0 mL) for 4 h at 80 °C, and evaporated. The product was purified on a column of Dowex-50W × 2 (H^+) resin (1.0 g, 1% aqueous NH_3) to give the amine L-**5d** (35 mg, 69%) as a white powder, TLC: R_f 0.69 (5:1 $CHCl_3$/MeOH); $[\alpha]_D^{24}$ +0.2 (*c* 1.4, $CHCl_3$); ^1H NMR (300 MHz, CD_3OD): δ 3.70 (br s, 1H, H-4), 3.48 (dd, 1H, $J_{2,3} = 9.6$ Hz, $J_{1,2} = 9.7$ Hz, H-2), 3.29 (dd, 1H, $J_{3,4} = 3.0$ Hz, $J_{2,3} = 9.6$ Hz, H-3), 2.69 (dt, 1H, $J = 7.3$ Hz, $J_{gem} = 11.2$ Hz, NHCH_2), 2.36–2.51 (m, 2H, H-1, NHCH_2), 1.49–1.66 [m, 4H, H-5, H-5a(eq), $NHCH_2CH_2$], 1.28–1.40 [m, 19H, $(CH_2)_9CH_3$, H-5a(ax)], 1.01 (d, 3H, $J_{5,6} = 6.6$ Hz, H-6), 0.89 (t, 3H, $J = 6.6$ Hz, CH_2CH_3); ITMS-ESI (positive mode): *m/z* 330 $[M+H]^+$.

4.11. *N*-(2-Phenylethyl)-5a-carba-β-DL-fucopyranosylamine (DL-5e)

A mixture of the epoxide DL-**13** (50 mg, 0.22 mmol), 2-phenylethylamine (27.5 μL, 0.22 mmol), and 2-propanol (0.5 mL) was heated in a sealed tube for five days at 120 °C, and then evaporated. The residue was chromatographed on a silica gel column (5.0 g, 100:1 → 20:1 $CHCl_3$/MeOH) to give the protected amine DL-**14e** (55 mg, 72%). It was treated with 80% aqueous acetic acid (1.0 mL) for 3 h at 80 °C, and evaporated. The product was purified on a column of Dowex-50W × 2 (H^+) resin (1.0 g, 1% aqueous NH_3) to give the amine DL-**5e** (10 mg, 50%) as a white powder, TLC: R_f 0.60 (5:1 $CHCl_3$/MeOH); ^1H NMR (300 MHz, CD_3OD): δ 7.16–7.31 (m, 5H, Ph), 3.69 (br s, 1H, H-4), 3.50 (dd, 1H, $J_{2,3} = 9.6$ Hz, $J_{1,2} = 9.7$ Hz, H-2), 3.30 (br d, 1H, $J_{2,3} = 9.6$ Hz, H-3), 2.82–3.06 [m, 4H, $NH(CH_2)_2$], 2.53 [ddd, 1H, $J_{1,5a(eq)} = 2.2$ Hz, $J_{1,2} = 9.7$ Hz, $J_{1,5a(ax)} = 11.9$ Hz, H-1], 1.59–1.68 [m, 2H, H-5, H-5a(eq)], 1.39 [m, 1H, H-5a(ax)], 1.02 (d, 3H, $J_{5,6} = 6.6$ Hz, H-6); ITMS-ESI (positive mode): *m/z* 266 $[M+H]^+$.

4.12. *N*-(4-Phenylbutyl)-5a-carba-β-L-fucopyranosylamine (L-5f)

A mixture of the epoxide L-**13** (50 mg, 0.22 mmol), 4-phenylbutylamine (34.5 μL, 0.22 mmol), and 2-propanol (0.5 mL) was heated in a sealed tube for six days at 120 °C, and then evaporated. The residue was chromatographed on a silica gel column (5.0 g, 100:1 → 20:1 $CHCl_3$/MeOH) to give the protected amine L-**14f** (55 mg, 66%). It was treated with 80% aqueous acetic acid (1.0 mL) for 3 h at 80 °C, and evaporated. The product was purified on a column of Dowex-50W × 2 (H^+) resin (1.0 g, 1% aqueous NH_3) to give the amine L-**5f** (10 mg, 54%) as a white powder, TLC: R_f 0.60 (5:1 $CHCl_3$/MeOH); $[\alpha]_D^{24}$ +0.4 (*c* 1.5, CD_3OD); ^1H NMR (300 MHz, $CDCl_3$): δ 7.04–7.17 (m, 5H, Ph), 3.60 (br s, 1H, H-4), 3.38 (dd, 1H, $J_{1,2} = 9.3$ Hz, $J_{2,3} = 9.5$ Hz, H-2), 3.18 (br d, 1H, $J_{2,3} = 9.5$ Hz, H-3), 2.29–2.69 [m, 5H, $NH(CH_2)_2$, H-1], 1.45–1.62 [m, 6H, $(CH_2)_2Ph$, H-5, H-5a(eq)], 1.24 [br dd, 1H, $J_{1,5a(ax)} = 8.7$ Hz, $J_{5agem} = 12.6$ Hz, H-5a(ax)], 0.92 (d, 3H, $J_{5,6} = 6.5$ Hz, H-6); ITMS-ESI (positive mode): *m/z* 294 $[M+H]^+$.

4.13. *N*-Butyl-6-*O*-benzyl-3,4-*O*-isopropylidene-5a-carba-β-D-galactopyranosylamine (D-16a)

A mixture of 1,2-anhydro-6-*O*-benzyl-3,4-*O*-isopropylidene-5a-carba-α-D-galactopyranose[9] D-**15** (53 mg, 0.18 mmol), butylamine (18 μL, 0.18 mmol), and 2-propanol was heated in a sealed tube for two days at 120 °C, and then evaporated to dryness. The products were chromatographed on a silica gel column (7 g, $CHCl_3$ → 20:1 $CHCl_3$/MeOH) to give the amine D-**16a** (25 mg, 38%) as a syrup, together with D-**15** (13 mg, 25%) recovered, $[\alpha]_D^{24}$ −3.8 (*c* 0.26, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27–7.35 (m, 5H, Ph), 4.54 (s, 2H, CH_2Ph), 4.29 (dd, 1H, $J_{4,5}$ = 4.2 Hz, $J_{3,4}$ = 4.5 Hz, H-4), 3.89 (dd, 1H, $J_{3,4}$ = 4.5 Hz, $J_{2,3}$ = 7.6 Hz, H-3), 3.47 and 3.64 (dd, each 1H, $J_{5,6}$ = 7.3 Hz, J_{6gem} = 9.0 Hz, H-6a, H-6b), 3.41 (dd, 1H, $J_{2,3}$ = 7.6 Hz, $J_{1,2}$ = 10.7 Hz, H-2), 2.68 (br s, 1H, OH), 2.46 and 2.77 (2dt, each 1H, J = 7.2 Hz, J_{gem} = 11.1 Hz, NHCH_2), 2.32 [ddd, 1H, $J_{1,5a(eq)}$ = 3.1 Hz, $J_{1,2}$ = 10.7 Hz, $J_{1,5a(ax)}$ = 11.6 Hz, H-1], 2.05–2.17 (m, 1H, H-5), 1.97 [ddd, 1H, $J_{1,5a(eq)}$ = 3.1 Hz, $J_{5,5a(eq)}$ = 3.4 Hz, J_{5agem} = 12.5 Hz, H-5a(eq)], 1.35 and 1.49 (2s, each 3H, CMe_2), 1.25–1.52 (m, 4H, H-2′, H-3′), 1.14 [ddd, 1H, $J_{1,5a(ax)}$ = 11.6 Hz, $J_{5,5a(ax)}$ = 12.2 Hz, J_{5agem} = 12.5 Hz, H-5a(ax)], 0.91 (t, 3H, $J_{3',4'}$ = 7.2 Hz, CH_2CH_3); ITMS-ESI (positive mode): *m/z* 364 $[M+H]^+$.

4.14. *N*-Octyl-6-*O*-benzyl-3,4-*O*-isopropylidene-5a-carba-β-D-galactopyranosylamine (D-16b) and *N*-octyl-5a-carba-β-D-galactopyranosylamine (D-6b)

A mixture of the epoxide D-**15** (98 mg, 0.34 mmol), octylamine (50 μL, 0.30 mmol), and 2-propanol was heated in a sealed tube for two days at 120 °C, and then evaporated to dryness. The products were chromatographed on a silica gel column (10 g, 60:1 $CHCl_3$/MeOH) to give the protected amine D-**16b** (73 mg, 51%) as a syrup and D-**15** (41 mg, 42%) recovered. Compound D-**16b** (73 mg, 0.17 mmol) was treated with acetic anhydride (0.36 mL) and pyridine (0.73 mL) overnight at room temperature.

The reaction mixture was evaporated, the residue was diluted with ethyl acetate (20 mL), and the solution was washed with 1 M hydrochloric acid, saturated aqueous $NaHCO_3$, and water, dried, and evaporated. The residue was chromatographed on silica gel (9 g, 2:3 EtOAc/hexane) to give the *N*,*O*-acetyl derivative (70 mg, 82%) of D-**16b**.

Hydrolysis of the *N*,*O*-acetyl derivative (70 mg, 0.14 mmol) with 1 M hydrochloric acid for 6 h at 100 °C gave, after chromatography on Dowex-50W × 2 (H^+) resin with 1% methanolic ammonia as eluent, the amine D-**6b** (38 mg, 71%) as a white powder, $[\alpha]_D^{24}$ −36 (*c* 0.44, MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ 3.97 (br s, 1H, H-4), 3.63 (dd, 1H, $J_{1,2}$ = 7.3 Hz, $J_{2,3}$ = 10.7 Hz, H-2), 3.50 (dd, 1H, $J_{3,4}$ = 6.3 Hz, $J_{2,3}$ = 10.7 Hz, H-3), 3.28 and 3.51 (2dd, each 1H, $J_{5,6}$ = 2.7 Hz, J_{6gem} = 9.5 Hz, H-6a, H-6b), 2.47 and 2.71 (2dt, each 1H, $J_{1',2'}$ = 7.5 Hz, J_{gem} = 11.1 Hz, NHCH_2), 2.41 [br dd, 1H, $J_{1,2}$ = 7.3 Hz, $J_{1,5a(ax)}$ = 9.6 Hz, H-1], 1.73 [ddd, 1H, $J_{1,5a(eq)}$ = 3.0 Hz, $J_{5,5a(eq)}$ = 3.5 Hz, J_{5agem} = 12.2 Hz, H-5a(eq)], 1.49–1.66 (m, 3H, H-5, H-2′), 1.24–1.46 [m, 11H, H-5a(ax), $(CH_2)_5CH_3$], 0.89 (t, 3H, $J_{7',8'}$ = 6.6 Hz, CH_2CH_3); ITMS-ESI (positive mode): *m/z* 290 $[M+H]^+$.

4.15. 1,2-Anhydro-6-*O*-benzyl-3,4-*O*-isopropylidene-5a-carba-α-L-galactopyranose (L-15)

This compound was prepared from 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-5a-carba-D-*xylo*-hex-1-enitol: $[\alpha]_D^{23}$ +22 (*c* 0.7, $CHCl_3$); ITMS-ESI (positive mode); *m/z* 293 $[M+Na]^+$, 309 $[M+K]^+$, according to the standard four-step reactions,[9] $[\alpha]_D^{23}$ +28 (*c* 0.8, $CHCl_3$); ITMS-APCI (positive mode): *m/z* 291 $[M+H]^+$.

4.16. *N*-Octyl-6-*O*-benzyl-3,4-*O*-isopropylidene-5a-carba-β-L-galactopyranosylamine (L-16b)

A mixture of the epoxide L-**15** (52 mg, 0.19 mmol), octylamine (30.2 μL, 0.19 mmol), and 2-propanol (0.5 mL) was heated in a sealed tube for six days at 120 °C, and then evaporated to dryness. The residue was chromatographed on a silica gel column (8.0 g, 50:1 → 10:1 $CHCl_3$/MeOH) to give the amine L-**16b** (50 mg, 63%) as a pale yellow syrup, TLC: R_f 0.58 (1:3 EtOH/toluene); $[\alpha]_D^{24}$ +10.6 (*c* 0.79, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26–7.35 (m, 5H, Ph), 4.54 (br s, 1H, H-4), 4.28 (dd, 1H, $J_{4,5}$ = 3.9 Hz, $J_{3,4}$ = 4.4 Hz, H-4), 3.89–3.93 (m, 1H, H-3), 3.62–3.67 (m, 1H, H-6a), 3.45–3.51 (m, 2H, H-2, H-6b), 2.51 and 2.82 (2dt, each 1H, J = 4.1 Hz, J_{gem} = 11.0 Hz, NHCH_2), 2.39 [br dd, 1H, $J_{1,5a(eq)}$ = 3.2 Hz, $J_{1,2}$ = 8.5 Hz, H-1], 2.13 [br dd, 1H, $J_{4,5}$ = $J_{5,5a(eq)}$ = 3.9 Hz, H-5], 1.99 [br dd, 1H, $J_{1,5a(eq)}$ = 3.2 Hz, $J_{5,5a(eq)}$ = 3.9 Hz, H-5a(eq)], 1.35 and 1.49 [2s, each 3H, CMe_2], 1.18–1.32 [m, 11 H, $(CH_2)_5CH_3$, H-5a(ax)], 0.88 (t, 3H, J = 6.5 Hz, CH_2CH_3); ITMS-ESI (positive mode): *m/z* 420 $[M+H]^+$.

4.17. *N*-Decyl-6-*O*-benzyl-3,4-*O*-isopropylidene-5a-carba-β-D-galactopyranosylamine (D-16c)

A mixture of the epoxide D-**15** (54 mg, 0.18 mmol), decylamine (40 μL, 0.20 mmol), and 2-propanol was heated in a sealed tube for two days at 120 °C, and then evaporated to dryness. The products were chromatographed on a silica gel column (8 g, $CHCl_3$ → 25:1 $CHCl_3$/MeOH) to give the amine D-**16c** (49 mg, 60%) as a syrup, $[\alpha]_D^{20}$ −4.2 (*c* 0.85, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30–7.35 (m, 5H, Ph), 4.54 (s, 2H, CH_2Ph), 4.29 (dd, 1H, $J_{4,5}$ = 4.2 Hz, $J_{3,4}$ = 4.5 Hz, H-4), 3.90 (dd, 1H, $J_{3,4}$ = 4.5 Hz, $J_{2,3}$ = 7.7 Hz, H-3), 3.47 and 3.64 (dd, each 1H, $J_{5,6}$ = 7.5 Hz, J_{6gem} = 8.5 Hz, H-6a, H-6b), 3.44 (dd, 1H, $J_{2,3}$ = 7.7 Hz, $J_{1,2}$ = 10.4 Hz, H-2), 3.29 (br s, 1H, OH), 2.48 and 2.78 (2dt, each 1H, J = 7.3 Hz, J_{gem} = 11.2 Hz, NHCH_2), 2.35 [ddd, 1H, $J_{1,5a(eq)}$ = 2.9 Hz, $J_{1,2}$ = 10.4 Hz, $J_{1,5a(ax)}$ = 11.4 Hz, H-1], 2.05–2.18 (m, 1H, H-5), 1.98 [ddd, 1H, $J_{1,5a(eq)}$ =2.9 Hz, $J_{5,5a(eq)}$ = 3.4 Hz, J_{5agem} = 12.5 Hz, H-5a(eq)], 1.35 and 1.49 (2s, each 3H, CMe_2), 1.10–1.52 [m, 17H, H-5a(ax), H-2′, H-9′], 0.88 (t, 3H, $J_{9',10'}$ = 6.5 Hz, CH_2CH_3); ITMS-ESI (positive mode): *m/z* 448 $[M+H]^+$.

4.18. *N*-Dodecyl-6-*O*-benzyl-3,4-*O*-isopropylidene-5a-carba-β-D-galactopyranosylamine (D-16d)

A mixture of the epoxide D-**15** (48 mg, 0.17 mmol), dodecylamine (31 mg, 0.17 mmol), and 2-propanol was heated in a sealed tube for two days at 120 °C, and then evaporated to dryness. The products were chromatographed on a silica gel column (8 g, $CHCl_3 \rightarrow$ 25:1 $CHCl_3$/MeOH) to give the amine D-**16d** (58 mg, 74%) as a syrup, $[\alpha]_D^{24}$ −4.1 (*c* 0.33, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29–7.35 (m, 5H, Ph), 4.54 (s, 2H, CH_2Ph), 4.29 (dd, 1H, $J_{4,5}$ = 4.2 Hz, $J_{3,4}$ = 4.5 Hz, H-4), 3.90 (dd, 1H, $J_{3,4}$ = 4.5 Hz, $J_{2,3}$ = 7.6 Hz, H-3), 3.47 and 3.64 (dd, each 1H, $J_{5,6}$ = 7.2 Hz, J_{6gem} = 9.0 Hz, H-6a, H-6b), 3.38 (dd, 1H, $J_{2,3}$ = 7.6 Hz, $J_{1,2}$ = 10.7 Hz, H-2), 2.22 (br s, 1H, OH), 2.45 and 2.76 (2dt, each 1H, J = 7.2 Hz, J_{gem} = 11.1 Hz, NHCH_2), 2.30 [ddd, 1H, $J_{1,5a(eq)}$ = 3.1 Hz, $J_{1,2}$ = 10.7 Hz, $J_{1,5a(ax)}$ 12.2 Hz, H-1], 2.05–2.17 (m, 1H, H-5), 1.98 [ddd, 1H, $J_{1,5a(eq)}$ = 3.1 Hz, $J_{5,5a(eq)}$ = 3.4 Hz, J_{5agem} = 12.5 Hz, H-5a(eq)], 1.44–1.46 (m, 2H, H-2′), 1.35 and 1.49 (2s, each 3H, CMe_2), 1.25 [br m, 18H, $(CH_2)_9CH_3$], 1.12 [ddd, 1H, $J_{1,5a(ax)}$ = 12.2 Hz, $J_{5,5a(ax)}$ = 12.2 Hz, J_{5agem} = 12.5 Hz, H-5a(ax)], 0.88 (t, 3H, $J_{11',12'}$ = 6.7 Hz, CH_2CH_3); ITMS-ESI (positive mode): *m/z* 476 $[M+H]^+$.

4.19. *N*-Butyl-5a-carba-β-D-galactopyranosylamine (D-6a)

A mixture of D-**16a** (14 mg, 40 μmol) and 80% aqueous acetic acid (2 mL) was stirred for 16 h at 80 °C, and then evaporated to dryness. The residue was hydrogenated in ethanol (2 mL) in the presence of 10% Pd/C under atmospheric pressure of hydrogen for 3 h at room temperature. A catalyst was removed by filtration, and the filtrate was evaporated. The residual product was chromatographed on a column of Dowex-50W × 2 (H^+) resin (0.9 g, 1% methanolic NH_3) to give the amine D-**6a** (8.6 mg, 93%) as a white powder, $[\alpha]_D^{20}$ +20 (*c* 0.42, MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ 3.97 (br, 1H, H-4), 3.63 (dd, 1H, $J_{1,2}$ = 7.3 Hz, $J_{2,3}$ = 10.7 Hz, H-2), 3.50 (dd, 1H, $J_{3,4}$ = 6.3 Hz, $J_{2,3}$ = 10.7 Hz, H-3), 3.28 and 3.51 (dd, 1H, $J_{5,6}$ = 2.7 Hz, J_{6gem} = 9.5 Hz, H-6a, H-6b), 2.47 and 2.71 (2dt, each 1H, J = 7.5 Hz, J_{gem} = 11.1 Hz, NHCH_2), 2.41 [br dd, 1H, $J_{1,2}$ = 7.3 Hz, $J_{1,5a(ax)}$ = 9.6 Hz, H-1], 1.73 [ddd, 1H, $J_{1,5a(eq)}$ = 3.0 Hz, $J_{5,5a(eq)}$ = 3.5 Hz, J_{5agem} = 12.2 Hz, H-5a(eq)], 1.49–1.66 (m, 3H, H-5, H-2′), 1.24–1.46 [m, 11H, H-5a(ax), $(CH_2)_5CH_3$], 0.89 (t, 3H, $J_{7',8'}$ = 6.6 Hz, CH_2CH_3); ITMS-ESI (positive mode): *m/z* 234 $[M+H]^+$.

4.20. *N*-Octyl-5a-carba-β-L-galactopyranosylamine (L-6b)

A mixture of L-**16b** (52 mg, 0.19 mmol) and 80% aqueous acetic acid (1.0 mL) was stirred for 2 h at 80 °C, and then evaporated to dryness. The residue was dissolved in ethanol (1.0 mL) and the solution was hydrogenated in the presence of a catalytic amount of 10% Pd–C in the atmospheric pressure of hydrogen for 2 h at room temperature. The product was chromatographed on a silica gel column (3 g, 50:1 → 10:1 $CHCl_3$/MeOH) to give the amine L-**6b** (14.5 mg, 62%) as a pale yellow syrup, TLC: R_f 0.28 (1:2 EtOH/toluene); $[\alpha]_D^{24}$ +37 (*c* 0.89, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.97 (br s, 1H, H-4), 3.64 (dd, 1H, $J_{5,6a}$ = 7.4 Hz, J_{gem} = 10.4 Hz, H-6a), 3.47–3.55 (m, 2H, H-3, H-6b), 3.27–3.34 (m, 1H, H-2), 2.72 (dt, 1H, J = 3.9 Hz, J_{gem} = 11.3 Hz, NHCH_2), 2.39–2.53 (m, 2H, H-1, NHCH_2), 1.71–1.78 (m, 1H, H-5), 1.47–1.63 [m, 3H, $NHCH_2CH_2$, H-5a(eq)], 1.32 [m, 11H, $(CH_2)_5CH_3$, H-5a(ax)], 0.89 (t, 3H, J = 6.4 Hz, CH_2CH_3); ITMS-APCI (positive mode): *m/z* 290 $[M+H]^+$.

4.21. *N*-Decyl-5a-carba-β-D-galactopyranosylamine (D-6c)

A mixture of D-**16c** (38 mg, 86 μmol) and 80% aqueous acetic acid (2 mL) was stirred for 4 h at 80 °C, and then evaporated to dryness. The residue was hydrogenated in ethanol (2 mL) in the presence of 10% Pd/C under atmospheric pressure of hydrogen for 3 h at room temperature. A catalyst was removed by filtration, and the filtrate was evaporated. The residual product was chromatographed on a column of Dowex-50W × 2 (H^+) resin (2.7 g, 1% methanolic NH_3) to give the amine D-**6c** (20 mg, 73%) as a white powder, $[\alpha]_D^{24}$ ~0 (*c* 0.28, MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ 3.97 (br, 1H, H-4), 3.52 (dd, 1H, $J_{1,2}$ = 9.0 Hz, $J_{2,3}$ = 9.2 Hz, H-2), 3.50 and 3.64 (dd, each 1H, $J_{5,6}$ = 7.2 Hz, J_{6gem} = 10.6 Hz, H-6), 3.29 (dd, 1H, $J_{3,4}$ = 2.8 Hz, $J_{2,3}$ = 9.2 Hz, H-3), 2.48 and 2.72 (2dt, each 1H, J = 7.1 Hz, J_{gem} = 13.3 Hz, NHCH_2), 2.43 [ddd, 1H, $J_{1,5a(eq)}$ = 3.1 Hz, $J_{1,2}$ = 9.0 Hz, $J_{1,5a(ax)}$ = 11.2 Hz, H-1], 1.74 [ddd, 1H, $J_{1,5a(eq)}$ = 3.1 Hz, $J_{5,5a(eq)}$ = 3.7 Hz, J_{5agem} = 12.2 Hz, H-5a(eq)], 1.57–1.67 (m, 1H, H-5), 1.52 (br t, 1H, $J_{2',3'}$ = 6.2 Hz, H-2′), 1.24–1.37 [m, 15H, $(CH_2)_7CH_3$, H-5a(ax)], 0.89 (t, 3H, $J_{9',10'}$ = 6.6 Hz, CH_2CH_3); ITMS-ESI (positive mode): *m/z* 318 $[M+H]^+$.

4.22. *N*-Dodecyl-5a-carba-β-D-galactopyranosylamine (D-6d)

A mixture of D-**16d** (49 mg, 0.12 mmol) and 80% aqueous acetic acid (2 mL) was stirred for 16 h at 80 °C, and then evaporated to dryness. The residue was hydrogenated in ethanol (2 mL) in the presence of 10% Pd/C under atmospheric pressure of hydrogen for 3 h at room temperature. A catalyst was removed by filtration, and the filtrate was evaporated. The residual product was chromatographed on a column of Dowex-50W × 2 (H^+) resin (3.6 g, 1% methanolic NH_3) to give the amine D-**6d** (25 mg, 69%) as a white powder, $[\alpha]_D^{24}$ −45 (*c* 0.17, MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ 3.97 (br, 1H, H-4), 3.47–3.55 (m, 2H, H-2, H-6), 3.64 (dd, 1H, $J_{5,6}$ = 7.2 Hz, J_{6gem} = 10.6 Hz, H-6), 3.29 (dd, 1H, $J_{3,4}$ = 2.8 Hz, $J_{2,3}$ = 9.5 Hz, H-3), 2.48 and 2.72 (2dt, each 1H, J = 7.4 Hz, J_{gem} = 11.4 Hz, NHCH_2), 2.42 [ddd, 1H, $J_{1,5a(eq)}$ = 3.1 Hz, $J_{1,2}$ = 9.5 Hz, $J_{1,5a(ax)}$ = 9.8 Hz, H-1], 1.74 [ddd, 1H, $J_{1,5a(eq)}$ = 3.1 Hz, $J_{5,5a(eq)}$ = 3.5 Hz, J_{5agem} = 12.2 Hz, H-5a(eq)], 1.57–1.67 (m, 1H, H-5), 1.52 (br t, 2H, $J_{2',3'}$ = 6.2 Hz, H-2′), 1.28–1.36 [m, 19H, $(CH_2)_9CH_3$, H-5a(ax)], 0.89 (t, 3H,

$J_{11',12'} = 6.7$ Hz, CH_2CH_3); ITMS-ESI (positive mode): *m/z* 346 $[M+H]^+$.

4.23. 3,4-*O*-Cyclohexylidene-5a-carba-β-L-fucopyranosyl azide (L-17)

A mixture of the epoxide L-**13** (152 mg, 0.66 mmol) and sodium azide (650 mg, 25 molar equiv) in DMF (3.0 mL) was stirred for two days at 110 °C. The reaction mixture was then diluted with ethyl acetate (60 mL), and the solution was washed with saline and water, dried, and evaporated to dryness. The residue was chromatographed on silica gel (18 g, 1:6 ethyl acetate/hexane) to give L-**17** (174 mg, 98%) as a solid, TLC: R_f 0.58 (1:3 ethyl acetate/hexane); $[\alpha]_D^{24}$ −3.1 (*c* 0.39, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.07 (t, 1H, $J_{4,5} = 3.9$ Hz, $J_{3,4} = 4.7$ Hz, H-4), 3.89 (dd, 1H, $J_{3,4} = 4.7$ Hz, $J_{2,3} = 7.4$ Hz, H-3), 3.51 (dd, 1H, $J_{2,3} = 7.4$ Hz, $J_{1,2} = 10.3$ Hz, H-2), 3.25 [ddd, 1H, $J_{1,5a(eq)} = 4.0$ Hz, $J_{1,5a(ax)} = 8.0$ Hz, $J_{1,2} = 10.3$ Hz, H-1], 2.78 (s, 1H, O*H*), 2.14 (s, 3H, Ac), 1.93 [dddd, 1H, $J_{5,5a(eq)} = 3.4$ Hz, $J_{4,5} = 3.9$ Hz, $J_{5,6} = 6.8$ Hz, $J_{5,5a(ax)} = 9.0$ Hz, H-5], 1.37–1.96 [m, 12H, C_6H_{10}, 2 × H-5a], 1.15 (d, 3H, $J_{5,6} = 6.8$ Hz, Me); ITMS-APCI (positive mode): *m/z* 268 $[M+H]^+$.

Data for the 2-*O*-acetyl derivative: TLC: R_f 0.40 (1:5 ethyl acetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.01 (dd, 1H, $J_{2,3} = 7.8$ Hz, $J_{1,2} = 10.7$ Hz, H-2), 4.08 (dd, 1H, $J_{3,4} = J_{4,5} = 4.0$ Hz, H-4), 3.96 (dd, 1H, $J_{3,4} = 4.0$ Hz, $J_{2,3} = 7.8$ Hz, H-3), 3.28 [ddd, 1H, $J_{1,5a(eq)} = 3.9$ Hz, $J_{1,5a(ax)} = 8.0$ Hz, $J_{1,2} = 10.7$ Hz, H-1], 2.14 (s, 3H, Ac), 1.79 [ddd, 1H, $J_{1,5a(eq)} = J_{5,5a(eq)} = 4.0$ Hz, $J_{1,2} = 10.7$ Hz, H-5a(eq)], 1.63 [m, 2H, H-5, H-5a(ax)], 1.19–2.01 (m, 10H, C_6H_{10}), 1.17 (d, 3H, $J_{5,6} = 6.3$ Hz, Me).

4.24. 5a-Carba-β-L-fucopyranosylamine (L-3)

A solution of L-**17** (250 mg, 0.94 mmol) in ethanol (5 mL) was hydrogenolyzed in the presence of a catalytic amount of 10% Pd/C for 4 h at room temperature. The product was O-decyclohexylidenated similarly to give, after purification by acid resin column to give the amine L-**3** (109 mg, 72%) as a white powder, $[\alpha]_D^{24}$ −2.2 (*c* 0.29, MeOH); ^{1}H NMR (300 MHz, D_2O): δ 3.77 (br s, 1H, H-4), 3.40 (m, 2H, H-2, H-3), 2.78 (m, 1H, H-1), 1.71 (m, 1H, H-5), 1.62 [ddd, 1 H, $J_{1,5a(eq)} = J_{5,5a(eq)} = 4.0$ Hz, $J_{5agem} = 12.7$ Hz, H-5a(eq)], 1.30 [ddd, 1H, $J_{1,5a(ax)} = J_{5,5a(ax)} = J_{5agem} = 12.7$ Hz, H-5a(ax)], 0.92 (d, 3H, $J_{5,6} = 6.8$ Hz, H-6); ITMS-APCI (positive mode): *m/z* 162 $[M+H]^+$.

4.25. 1,6-Anhydro-2-azido-4-(5a-carba-β-L-fucopyranos-1-yl)amino-2,4-dideoxy-β-D-glucopyranose (19)

A mixture of L-**3** (11.8 mg, 0.07 mmol) and 1,6:3,4-dianhydro-2-azido-2-deoxy-β-D-galactopyranose[12] (**18**, 18.6 mg, 0.11 mmol) in 2-propanol (1 mL) was heated for two weeks at 120 °C, and then evaporated to dryness. The residue was chromatographed on a silica gel (2.0 g, 1:10 MeOH/$CHCl_3$) to give the amine **19** (22.5 mg, 93%) as a syrup: $[\alpha]_D^{24}$ −37 (*c* 0.18, MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ 5.38 (br s, 1H, H-1), 4.44 (br d, 1H, H-5), 4.09 (br d, 1H, H-6a), 3.82 (br s, 1H, H-3), 3.61–3.67 (m, 2H, H-6b, H-4′), 3.52 (br s, 1H, H-2), 3.17–3.35 (m, 2H, H-2′, H-3′), 2.66 (br s, 1H, H-4), 2.46–2.54 (m, 1H, H-1′), 1.51–1.74 (m, 2H, H-5′, H-5a′eq), 1.05 (dd, 1H, $J_{gem} = 13.4$ Hz, $J_{5,5a'ax} = 12.0$ Hz, H-5a′ax), 0.82 (d, 3H, $J_{5,6} = 6.6$ Hz, H-6); ITMS-APCI (positive mode): *m/z* 331 $[M+H]^+$.

Compound **19** (11.4 mg) was converted into the acetyl derivative by treatment with acetic anhydride (0.5 mL) and pyridine (1.0 mL) for 10 h at room temperature. The product was chromatographed on a silica gel (1.0 g, 1:7 acetone/hexane) to give the tetra-*O*-acetyl derivative **20** (13.5 mg, 78%) as a colorless syrup: ^{1}H NMR (300 MHz, CD_3OD): δ 5.44 (br s, 1H, H-1), 5.31 (br s, 1H, H-4′), 5.19 (dd, 1H, $J_{1',2'} = J_{2',3'} = 10.0$ Hz, H-2′), 4.83 (br s, 1H, H-2), 4.56 (br s, 1H, H-5), 4.09 (br d, 1H, $J_{gem} = \sim 7.0$ Hz, H-6a), 3.82 (br dd, 1H, H-6b), 3.51 (br s, 1H, H-3), 3.02–3.10 (m, 1H, H-1′), 2.71 (br s, 1H, H-4), 2.14, 2.12, 2.09, and 1.97 (4s, each 3H, 4 × Ac), 1.75–1.82 [m, 2H, H-5, H-5a(eq)], 1.48–1.55 [m, 1H, H-5a(ax)], 0.93 (d, 3H, $J_{5,6} = 6.6$ Hz, H-6); ITMS-APCI (positive mode): *m/z* 499 $[M+H]^+$.

4.26. *N*-(5a-Carba-β-L-fucopyranos-1-yl)-3,4-*O*-cyclohexylidene-5a-carba-β-L-fucopyranosylamine (21)

A mixture of L-**3** (13.2 mg, 0.08 mmol) and L-**13** (28.2 mg, 0.12 mmol) in 2-propanol (1 mL) was heated in a sealed tube for three weeks at 120 °C, and then evaporated to dryness. The residual product was eluted from a column of silica gel (1.5 g, 1:10 MeOH/$CHCl_3$) to give **21** (12.9 mg, 40%) as a colorless syrup: ^{1}H NMR (300 MHz, CD_3OD): δ 3.99–4.02 (m, 1H, H-4′), 3.73–3.78 (br d, 1H, $J_{3',4'} = 4.4$ Hz, H-3′), 3.60 (br s, 1H, H-4), 3.20–3.37 (m, 3H, H-2, H-3, H-2′), 2.37–2.48 (m, 2H, H-1, H-1′), 1.79–1.85 (m, 1H, H-5′), 1.26–1.68 [m, 13H, C_6H_{10}, H-5, H-5a(eq), H-5a′eq], 1.16–1.22 (m, 1H, H-5a′ax), 1.12 [br d, 1H, $J_{5,5a(ax)} = 4.1$ Hz, H-5a(ax)], 1.01 (d, 3H, $J_{5',6'} = 6.8$ Hz, H-6′), 0.92 (d, 3H, $J_{5,6} = 6.6$ Hz, H-6).

4.27. *N*-(5a-Carba-β-L-fucopyranosyl)-5a-carba-β-L-fucopyranosylamine (22)

Compound **21** (42 mg, 0.11 mmol) was treated with 80% aqueous acetic acid (0.5 mL) for 5 h at 80 °C, and then co-evaporated with ethanol and toluene. The residue was chromatographed on a column of Dowex-50W × 2 (H^+) (1.0 g, 1% aqueous NH_3) to give **22** (12.2 mg, ~100%) as a white powder: $[\alpha]_D^{24}$ +16 (*c* 0.38, MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ 3.68 (br s, 2H, H-4, H-4′), 3.46 (dd, 2H, $J_{1,2} = J_{1',2'} = 9.3$ Hz, $J_{2,3} = J_{2',3'} = 9.7$ Hz, H-2, H-2′), 3.32 (dd, 2H, $J_{3,4} = J_{3',4'} = 2.5$ Hz, $J_{2,3} = J_{2',3'} = 9.7$ Hz, H-3, H-3′), 2.80 (ddd, 2H, $J_{1,5a(eq)} = J_{1',5a'eq} = 3.9$ Hz, $J_{1,2} = J_{1',2'} = 9.3$ Hz, $J_{1,5a(ax)} = J_{1',5a'ax} = 12.2$ Hz, H-1, H-1′), 1.57–1.69 [m, 4H, H-5, H-5′, H-5a(eq), H-5a′eq], 1.22 [br dd, 2H, $J_{1,5a(ax)} = J_{1',5a'ax} = 12.2$ Hz, $J_{5a(ax),5a(eq)} = J_{5a'ax,5a'eq} = 12.4$ Hz, H-5a(ax), H-5a′ax], 0.84 (d, 6H, $J_{5,6} = J_{5',6'} = 6.6$ Hz, H-6, H-6′); ITMS-ESI (positive mode): *m/z* 306 $[M+H]^+$.

4.28. Biological assay

(a) Determination of IC_{50}: the IC_{50} values were determined for all inhibitors and correspond to the inhibition concentration required for 50% inhibition of the enzyme in our experimental conditions. α-Fucosidase (bovine kidney) was assayed using *p*-nitrophenyl α-L-fucopyranoside (4 mM) as a substrate at pH 5.5 (30 mM CH_3COONa) at 37 °C. α-Galactosidase (green coffee beans) was assayed using *p*-nitrophenyl α-D-galactopyranoside as a substrate at pH 6.8 (20 mM, phosphate buffer) at 27 °C. β-Galactosidase (bovine liver) assayed similarly using *p*-nitrophenyl β-galactopyranoside at 37 °C. α-Glucosidase (Baker's yeast) was assayed similarly using *p*-nitrophenyl α-D-glucopyranoside (4 mM) as a substrate at pH 5.5 (30 mM CH_3COONa) at 27 °C. β-Glucosidase (almond) was assayed similarly using *p*-nitrophenyl β-D-glucopyranoside (4 mM) as a substrate at pH 5.5 (30 mM CH_3COONa) at 27 °C. β-Glucosaminidase (bovine kidney) was assayed using *p*-nitrophenyl *N*-acetyl-β-D-glucosaminide (4 mM) as a substrate at pH 5.5 (30 mM CH_3COONa) at 37 °C. α-Mannosidase was assayed using *p*-nitrophenyl α-D-mannopyranoside (4 mM) as a substrate at pH 5.5 (30 mM CH_3COONa) at 27 °C.

Test compound was added to each reaction mixture described above and it was incubated for 1 h at 27 or 37 °C. After 1 h, the reaction was quenched by addition of three volumes of aqueous 0.2 M sodium carbonate, and the absorbance of the liberated *p*-nitrophenol was measured at 410 nm. The percentage inhibition was calculated by the formula $BA \times 100$, where A is the *p*-nitrophenol liberated by the enzyme without an inhibitor and B is that with an inhibitor.

(b) Determination of K_i: the K_i values were determined for especially potent inhibitors using Dixon graphical method. The effects of pH on the inhibition were investigated for DL-**5e** and reference inhibitor calystegin C,[17] at pH 5.5 and 6.8, in order to compare their K_i values with those reported for isofagomine.[16] The following substrate concentrations were applied: 4, 2, 1, and 0.5 mM, and the inhibitor concentrations: 0.25, 0.1, 0.05, and 0.025 $\mu g\,mL^{-1}$ or 0.025, 0.01, 0.005, and 0.0025 $\mu g\,mL^{-1}$.

Acknowledgements

The authors would like to thank Drs. A. Takahashi and A. Tomoda (Hokko Chemical Industry, Co. Ltd, Atsugi, Japan) for the biological assays, Prof. Naoki Asano (Hokuriku University, Kanazawa, Japan) for providing us with a sample of calystegine, Prof. Yoshiyuki Suzuki (International University of Health and Welfare, Otawara, Japan) for helpful discussions, and Ms. Miki Kanto for her assistance in preparing this manuscript.

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Bioorganic & Medicinal Chemistry Letters 14 (2004) 5183–5188

Synthesis of 5a-carba-hexopyranoses and hexopyranosylamines, as well as 5a,5a′-dicarbadisaccharides, from 3,8-dioxatricyclo[4.2.1.$0^{2,4}$]nonan-9-ol: glycosidase inhibitory activity of N-substituted 5a-carba-β-gluco- and β-galactopyranosylamines, and derivatives thereof

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Received 10 May 2004; accepted 26 July 2004

Abstract—Since glycosidase and glycosyltransferase inhibitors, composed of carba-sugars, have recently attracted much attention, it is desirable to develop effective preparative routes for provision of new carba-sugar derivatives of potential biological interest. 1,2:3,6-Dianhydro-5a-carba-α-glucopyranose was here chosen for study of synthetic utility, and demonstrated to be a promising intermediate for supplying several carba-β-glycosylamines and N-linked dicarba-oligosaccharides. An N-linked 5a,5a′-dicarbalactose derivative obtained here was found to be a strong α-galactosidase inhibitor (IC_{50} 1.2 μM, green coffee beans).

1. Introduction

In recent years, glycosidase and glycosyltransferase inhibitors, of carba-glycosylamine[1] and N-linked carba-disaccharide types,[2] have attracted much attention, stimulating us to develop efficient preparative routes for different carba-sugars of biological interest. We here chose 1,2:3,6-dianhydro-5a-carba-α-DL-glucopyranose† (**2a**), (1*SR*,2*RS*,4*SR*,6*SR*,9*RS*)-3,8-dioxatricyclo[4.2.1.$0^{2,4}$]-nonan-9-ol, for examination of its potential as a synthetic intermediate with general application for further demands of glycobiology. Compound **2a** was first prepared[3] as a precursor for synthesis of β-validamine and its 6-amino-6-deoxy derivative, a branched-chain analogue of 2-deoxystreptamine. Recently, this compound was successfully utilized as an intermediate for synthesis of 5a-carba-sugars, especially fucose-type validamines.[4] The present communication describes a further investigation of the potential of **2a** as a key compound for several biologically interesting 5a-carba-sugars (Fig. 1).

Advantageous chemical features of **2a** are as follows: the 3,6-anhydro bridge plays a role both in protecting the 3- and 6-hydroxyl groups and in causing 5a-carba-α-glucopyranose to adopt the 1C conformation. The anhydro ring is easily opened by conventional acetolysis or bromination with HBr–AcOH. Furthermore, the 1,2-epoxide group is reactive toward common nucleophiles, being cleaved at C-1 with high regioselectivity. The 4-hydroxyl group of **2a** is readily oxidized to give rise to the ketone **4**, which can be reduced to regenerate **2a**. The 4-sulfonates **3f** and **3i** do not undergo nucleophilic displacement even with strong nucleophiles and also remain unchanged under acetolysis to open the 3,6-anhydro ring.

2. Results and discussion

2.1. Improved synthesis of 1,2:3,6-dianhydro-5a-carba-α-D-glucopyranose (2a)

Initially the dianhydride **2a** was prepared from 2,3,4-tri-*O*-acetyl-6-bromo-6-deoxy-5a-carba-β-glucopyranosyl

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† In this paper, the nomenclature of carba-sugar derivatives follows the IUPAC-IUB Recommendations 1996 (*Carbohydr. Res.* **1997**, *297*, 1).

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doi:10.1016/j.bmcl.2004.07.091

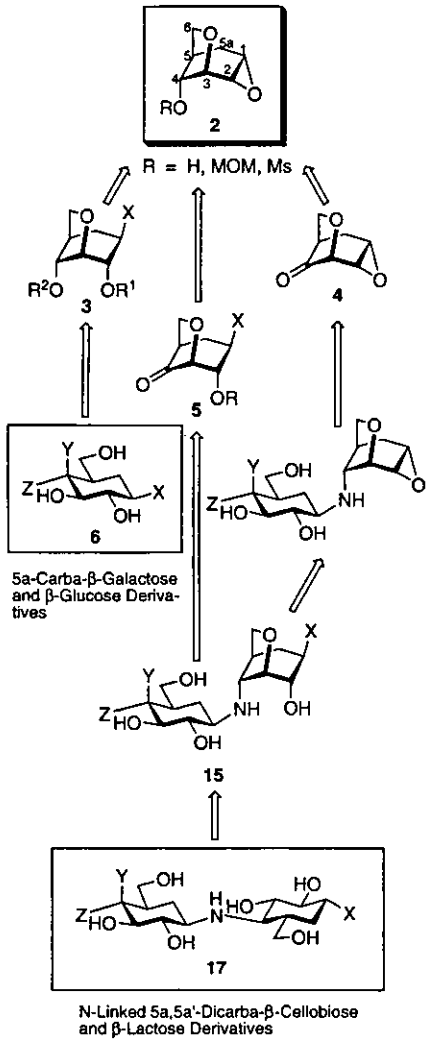
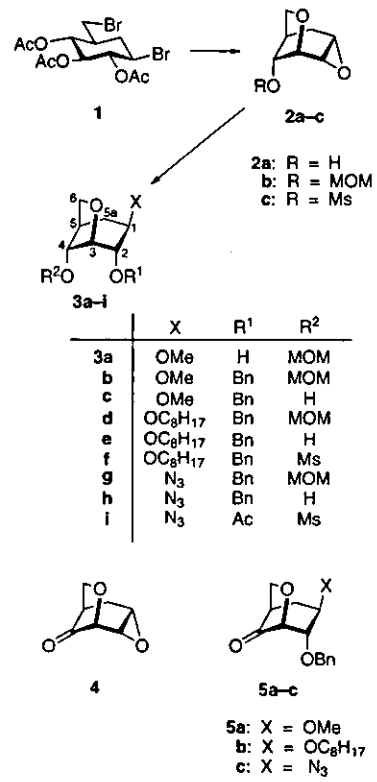


Figure 1. Possible synthetic routes to 5a-carba-β-galacto- and β-glucopyranose derivatives, and N-linked 5a,5a'-dicarbadisaccharides from 1,2:3,6-dianhydro-5a-carba-α-glucopyranose: X = NHR, OR, etc.; Y, Z = OH, NH_2, etc.



	X	R^1	R^2
3a	OMe	H	MOM
b	OMe	Bn	MOM
c	OMe	Bn	H
d	OC_8H_{17}	Bn	MOM
e	OC_8H_{17}	Bn	H
f	OC_8H_{17}	Bn	Ms
g	N_3	Bn	MOM
h	N_3	Bn	H
i	N_3	Ac	Ms

Scheme 1. Preparation of 1,2:3,6-dianhydro-5a-carba-α-glucopyranose and its transformation into synthetic intermediates.

bromide[5] (**1**) by treatment with an excess of methanolic sodium methoxide for 2 h at reflux temperature, and the major product **2a** was isolated as the acetate in 65% yield, accompanied by the methyl ether generated by cleavage of the 1,2-anhydro ring with a methoxide ion (Scheme 1). In this work, compound[6] **2a** was obtained directly as pure crystals in 89% by treatment of **1** with 3 molar equiv of solid sodium methoxide in methanol at 0–5 °C for 3 h. Compound **2a** was readily transformed into the protected derivatives: the methoxymethyl ether **2b** and mesylate **2c**.

2.2. Synthesis of 3,6-anhydro-5a-carba-β-glucopyranose derivatives

Treatment of **2b** with methanolic sodium methoxide (5 molar equiv) for 20 h at reflux temperature gave the methyl ether **3a** (75%), which was conventionally exposed to benzyl bromide–NaH in DMF (3 molar equiv) at room temperature to afford the benzyl ether[7] **3b** (95%). Subsequent removal of a methoxymethyl group of **3b** under the influence of THF and 12 M HCl at room temperature gave the 4-OH unprotected derivative **3c** (~100%). Similarly, the octyl ether was readily obtained from **2b** by treatment with a slight excess of sodium octoxide in octanol for 2 days at reflux temperature, and the product was isolated[8] as the benzyl ether **3d** (28% over-all yield), which was also converted into the 4-hydroxy compound **3e** (83%). Azidolysis of **2b** with sodium azide (3 molar equiv) in 80% aqueous DMF at 120 °C proceeded smoothly and the resulting sole azide was isolated as the benzyl ether **3g** (86% over-all yield), which was similarly converted into the 4-hydroxy compound **3h** (91%). Compounds **2a**, **3c**, **3e**, and **3h** were found to be oxidized with DMSO/Ac_2O to afford the respective ketones[9] **4** and **5a–c** in ~80% yields, which were used as acceptors for reductive amination with carba-glycosylamines, affording N-linked 5a,5a'-dicarbadisaccharides. When compound **2c** was treated with sodium azide (3 molar equiv) in DMF at 120 °C, this gave, after acetylation, the azido mesylate **3i** (64%), showing that the 4-mesyloxyl group is unreactive toward strong nucleophiles. Removal of the 3,6-anhydro bridges of **3f** and **3i** would be expected to provide useful precursors for the preparation of 5a-carba-β-galactopyranose derivatives.

2.3. Synthesis of alkyl 5a-carba-β-gluco- and β-galactopyranosides

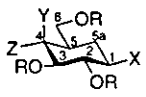
Conventional acetolysis of **3d** and **3f** with AcOH/Ac_2O/H_2SO_4 (40:20:1) at 80 °C gave carba-glucopyranoside derivatives **6a** (96%) and **6c** (81%), respectively.

O-Deacetylation of **6a** gave octyl 5a-carba-β-glucopyranoside[10] **6b** (84%). On the other hand, nucleophilic substitution of the 4-mesyloxyl group of **6c** with potassium acetate (5 molar equiv) readily proceeded in DMF in the presence of 18-crown-6 ether at 110 °C to give[8] a sole tetra-*O*-acetyl derivative **6d** (44%), which was O-deacetylated under Zemplén conditions to give octyl 5a-carba-β-galactopyranoside[10] **6e** (85%). In this reaction, formation of other products, initiated by neighboring participation of the 3-acetoxyl group, was not observed. The present synthesis significantly improved the preceding routes[10] to **6b** and **6e**, thus constituting a practical synthetic regimen for alkyl 5a-carba-galacto and glucopyranosides. Very recently some alkyl 5a-carba-glycopyranosides have actually been applied[11] as potent primers for biocombinatorial synthesis[12] (Scheme 2).

Acetolysis of compound **3i** produced[8,13] the mesylate **6f** (26%) and the acetate **6g** (5%). The latter appeared to be formed by further acetolysis of **6f** in situ. In fact, nucleophilic substitution of **6f** with sodium acetate in DMF gave **6g** (71%). Conventional O-deacetylation of **6g** followed by hydrogenolysis in ethanol in the presence of Raney nickel afforded, after purification over a column of Dowex-50W × 2 (H^+) resin with methanolic 5% ammonia, 5a-carba-β-galactopyranosylamine (**6h**, 85%), which was transformed into the *N*-acetyl derivative **6i** (~100%) (Scheme 3).

2.4. Synthesis of *N*-alkyl 3,6-anhydro-5a-carba-β-glucosylamines and derivatives thereof

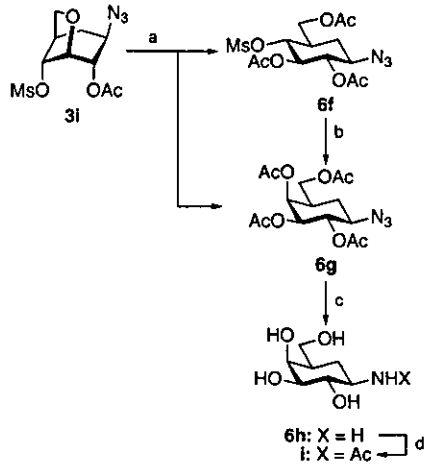
Direct nucleophilic cleavage of the 1,2-anhydro ring of **2a** with alkyl and phenylalkyl-amines was attempted in order to prepare N-substituted derivatives **7a–f**, from which corresponding 5a-carba-β-glucopyranosylamines might be obtainable (Scheme 4). Treatment with a molar equivalent of butylamine in 2-propanol in a sealed tube for 4 days at 120 °C resulted in preferential cleavage at C-1 to give, after purification by silica gel chromatography, *N*-butyl-3,6-anhydro-5a-carba-β-glucopyranosylamines[14] **7a** (78%). Similarly, by use of hexyl, octyl, decyl, dodecyl, benzyl, and 2-phenylethyl-amines, the corresponding N-substituted 3,6-anhydrides **7b–g** were synthesized in 98%, 97%, 38%,[8] 94%, 76%, and 83% yields, respectively.



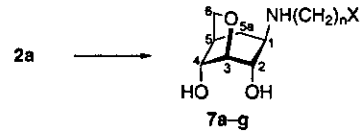
6a–i

	X	Y	Z	R
6a	OC_8H_{17}	H	OAc	Ac
b	OC_8H_{17}	H	OH	H
c	OC_8H_{17}	H	OMs	Ac
d	OC_8H_{17}	OAc	H	Ac
e	OC_8H_{17}	OH	H	H
f	N_3	H	OMs	Ac
g	N_3	OAc	H	Ac
h	NH_2	OH	H	H
i	NHAc	OH	H	H

Scheme 2. Synthesis of 5a-carba-β-galacto- and β-glucopyranose derivatives.



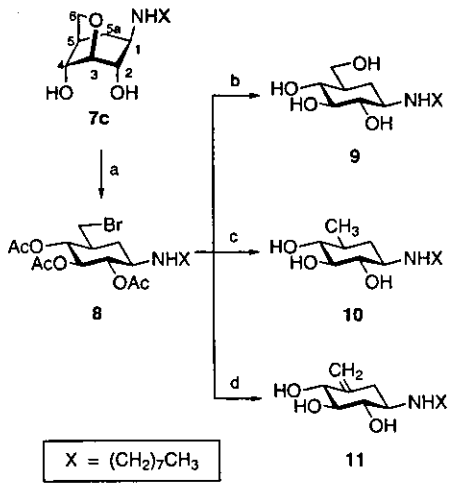
Scheme 3. Synthesis of 5a-carba-β-galactopyranosylamine and derivative. Reagents and conditions: (a) $AcOH/Ac_2O/H_2SO_4$ (40:20:1), 120 °C; (b) NaOAc, DMF, 110 °C; (c) NaOMe, MeOH; H_2, EtOH, Raney Ni; (d) Ac_2O, MeOH.



7a–g

	n	X
7a	3	Me
b	5	Me
c	7	Me
d	9	Me
e	11	Me
f	1	Ph
g	2	Ph

Scheme 4. Structures of several N-substituted 3,6-anhydro-5a-carba-β-glucopyranosylamines.

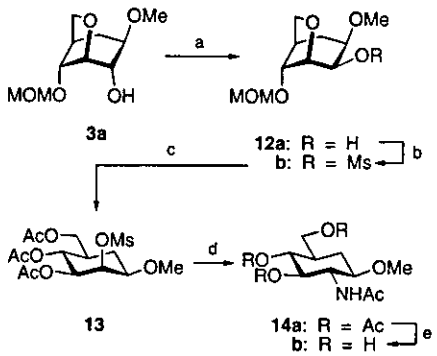


Scheme 5. Synthesis of some *N*-octyl-5a-carba-β-glucopyranosylamine derivatives. Reagents and conditions: (a) 30% HBr–AcOH, 85 °C; (b) Conventional acetolysis of 7c or NaOAc, aq 80% 2-methoxyethanol, reflux; NaOMe, MeOH; (c) Bu_3SnH, AIBN, toluene; NaOMe, MeOH; (d) NaOAc, DMF, reflux; NaOMe, MeOH.

The *N*-octyl derivative **7c** was chosen, as an example, for possible further chemical transformation (Scheme 5). Thus, it was first acetylated and then treated with 30% HBr–AcOH at 85 °C, resulting in the opening of the 3,6-anhydro ring with a bromide ion to give the 6-bromo-6-deoxy derivative **8**, which was debrominated with tributyltin hydride in toluene in the presence of AIBN, followed by hydrolysis with 4 M hydrochloric acid, to afford *N*-octyl-6-deoxy-5a-carba-β-glucopyranosylamine **10** on acid resin chromatography with methanolic ammonia (25% over-all yield). Dehydrobromination of **8** was effected by treatment with sodium acetate (10 molar equiv) in DMF at reflux temperature to give the 6-deoxy-5-eno derivative **11** (~20% over-all yield). *N*-Octyl-5a-carba-β-galactopyranosylamine **9** was prepared in ~50% over-all yield by acetolysis of **7c** followed by hydrolysis with 4 M hydrochloric acid and purification over an acid resin column, in order to supply a sample for biological assays (Table 1) for enzyme-inhibitory activity to compare the three structurally related compounds **9**, **10**, and **11**. Alternatively, starting from the mesylate **2c**, a series of 5a-carba-β-galactopyranosylamine derivatives would be generated through amination and subsequent acetolysis, followed by 4-epimerization.

2.5. Synthesis of alkyl 2-acetamido-2-deoxy-5a-carba-β-glucopyranoside

Oxidation of **3a** with Ac_2O–DMSO and successive reduction with L-selectride gave preferentially the 2-epimer **12a** (59%), which was then transformed into the mesylate **12b** (91%). Acetolysis of **12b** gave methyl 3,4,6-tri-*O*-acetyl-2-*O*-mesyl-5a-carba-β-mannopyranoside (**13**, 82%). Similarly, methyl 5a-carba-β-mannopyranoside could be obtained from **12a**. Compound **13** was then subjected to azidolysis (NaN_3, 5 molar equiv) in DMF at 120 °C, giving a sole azide, which was similarly hydrogenolyzed in ethanol containing acetic anhydride, followed by acetylation, to give the penta-*N*,*O*-acetyl derivative[15] **14a** (52%), O-deacetylation of which afforded methyl 2-acetamido-2-deoxy-5a-carba-β-D-glucopyranoside **14b** (81%). This sequence could be generally utilized for the preparation of alkyl 5a-carba-β-mannosides and *N*-acetyl-5a-carba-β-glucosaminides (Scheme 6).

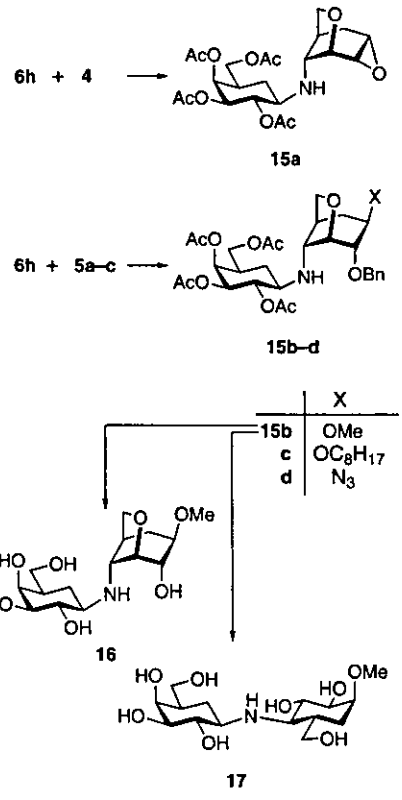


Scheme 6. Synthesis of methyl 2-acetamido-2-deoxy-5a-carba-β-glucopyranoside. Reagents and conditions: (a) Ac_2O, DMSO; L-selectride, THF; (b) MsCl, pyridine; (c) conventional acetolysis; (d) NaN_3, DMF, 120 °C; H_2, MeOH, Raney Ni, Ac_2O; (e) NaOMe, MeOH.

2.6. Synthesis of imino-linked 5a,5a′-dicarbalactose derivatives

Reductive amination of the ketones **4** and **5a–c** with 5a-carba-hexopyranosylamines has been demonstrated to proceed readily in stereoselective fashion, affording N-linked β(1→4)-5a,5a′-dicarbadisaccharide derivatives containing 3,6-anhydro-5a-carba-glucopyranose residues (Scheme 7).

5a-Carba-β-galactopyranosylamine **6h** was first converted into the hydrochloride under the influence of an equimolar amount of 1 M hydrochloric acid, and then subjected to reductive coupling with the ketone **4**. Thus, reaction of **4** (2 molar equiv) and the hydrochloride of **6h** was conducted in aqueous methanol in the presence of sodium cyanoborohydride (2 molar equiv) and anhydrous magnesium sulfate for 19 h at reflux temperature. The product could successfully be isolated as the tetra-*O*-acetyl derivative **15a** (47%). Similar coupling of **5a–c** with **6h** produced the respective 5a,5a′-dicarbadisaccharide derivatives **15b–d** in 60%, 41%, and 50% yields, respectively. O-Deacetylation of **15b** gave N-linked methyl 3,6-anhydro-5a,5a′-dicarba-β-D-lactoside[16] **16** (91%). Acetolysis of **15b** and subsequent deprotection would provide[17] 5a,5a′-dicarba-β-lactose **17**.



Scheme 7. Synthesis of some 5a,5a′-dicarbalactose derivatives.

Table 1. Inhibitory activity of some 5a-carba-hexopyranosylamine derivatives against three glycosidases

Compd	IC_{50} (M)		
	α-Galactosidase (green coffee beans)	β-Galactosidase (bovine liver)	β-Glucosidase (rat intestine)
6h	2.8	NI	130
6i	NI	NI	14
9	NI	10	NI
10	NI	18	NI
11	NI	30	NI
16	1.2	NI	NI

NI: No inhibition $<10^{-3}$ M.

2.7. Glycosidase inhibitory activity

Some of the new compounds synthesized underwent preliminary assay for enzyme-inhibitory activity against six glycosidases[18] (Table 1). Interestingly, 5a-carba-β-galactopyranosylamine (**6h**) was shown to be a good inhibitor of α-galactosidase rather than β-galactosidase, while its *N*-acetyl derivative **6i** exhibited moderate inhibition.[19] Seven *N*-alkyl and phenylalkyl-3,6-anhydro-5a-carba-β-glucopyranosylamines **7a–g** did not show any inhibitory activity against the six enzymes. In view of the structural relationship between substrates and enzyme inhibitors, *N*-octyl-β-gluopyranosylamine **9**, and its 6-deoxy and 6-deoxy-5-eno derivatives (**10** and **11**) can be considered to be model compounds for discussion regarding the hydrophobic nature of the region around substituents at C-5. The products are all moderate β-galactosidase inhibitors, being not α- nor β-glucosidase inhibitors, and substantial structural change around C-5 did not appreciably alter the activity.

Very interestingly, the N-linked dicarbalactose derivative **16** has been demonstrated to be a strong and specific α-galactosidase inhibitor (green coffee beans). As expected,[20] N-alkylation of **6h** much improved[21] the inhibitory potential toward α- and β-galactosidases, and β-glucosidase. However, its characteristic specificity as a α-galactosidase inhibitor completely disappeared. Hydrophobic spacer *N*-alkyl chains seemed to enhance its affinity for other enzymes, independent of specific recognition owing to structural mimicking dependent on the carba-galactopyranose residue. Therefore, in chemical modification of **6h**, the N-linked dicarbadisaccharide **16** might hopefully be a lead compound for development of specific α-galactosidase inhibitors of this kind.

Acknowledgements

The authors sincerely thank Drs. Atsushi Takahashi and Akihiro Tomoda (Hokko Chemical Industry Co. Ltd) for the biological assays, and Ms. Miki Kanto for her assistance in preparing this manuscript.

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6. Compound **2a**: $[\alpha]_D^{20} - 68$ (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 4.62 (d, 1H, $J_{1,2} = 8.7$ Hz, H-1), 4.26 (dd, 1H, $J_{3,4} = 5.1$ Hz, $J_{2,3} = 8.3$ Hz, H-3), 4.20 (dd, 1H, $J_{3,4} = J_{4,5} = 5.1$ Hz, H-4), 4.15 (ddd, 1H, $J_{5a(exo),6exo} = 1.8$ Hz, $J_{5,6exo} = 5.4$ Hz, $J_{gem} = 8.8$ Hz, H-6*exo*), 3.83 (d, 1H, $J_{gem} = 8.8$ Hz, H-6*endo*), 3.41 (br s, 1H, H-2), 3.32–3.35 (m, 1H, H-1), 2.46–2.52 (m, 1H, H-5), 2.03–2.32 [m, 1H, H-5a(*exo*)], 1.99 [ddd, 1H, $J_{1,5a(endo)} = 2.0$ Hz, $J_{5,5a(endo)} = 4.2$ Hz, $J_{gem} = 16.1$ Hz, H-5a(*endo*)].
7. Compound **3b**: ^1H NMR (300 MHz, $CDCl_3$): δ 7.26–7.35 (m, 5H, Ph), 4.66 and 4.74 (ABq, each 1H, $J_{gem} = 6.7$ Hz, OCH_2), 4.64 (s, 2H, OCH_2), 4.20 (dd, 1H, $J_{3,4} = J_{4,5} = 4.9$ Hz, H-4), 4.11 (dd, 1H, $J_{2,3} = 2.0$ Hz, $J_{3,4} = 4.9$ Hz, H-3), 3.87 (ddd, 1H, $J_{5,6exo} = 3.2$ Hz, $J_{5a(exo),6exo} = 4.4$ Hz, $J_{gem} = 8.1$ Hz, H-6*exo*), 3.79 (d, 1H, $J_{gem} = 8.1$ Hz, H-6*endo*), 3.69 (ddd, 1H, $J_{1,2} = 3.7$ Hz, $J_{1,5a(endo)} = J_{1,5a(exo)} = 4.9$ Hz, H-1), 3.55 (ddd, 1H, $J_{2,3} = 2.0$ Hz, $J_{1,2} = 3.7$ Hz, H-2), 3.35, and 3.39 (2 s, each 3H, 2 × OMe), 2.50 [dddd, 1H, $J_{5a(exo),6exo} = 3.2$ Hz, $J_{1,5a(endo)} = 4.9$ Hz, $J_{5,5a(exo)} = 6.1$ Hz, $J_{gem} = 14.4$ Hz, H-5a(*exo*)], 2.50 (dddd, 1H, $J_{5,5a(endo)} = J_{5,6exo} = 4.4$ Hz, $J_{4,5} = 4.9$ Hz, $J_{5,5a(exo)} = 6.1$ Hz, H-5), 1.57 [ddd, 1H, $J_{5,5a(endo)} = 4.4$ Hz, $J_{1,5a(endo)} = 4.9$ Hz, $J_{gem} = 14.4$ Hz, H-5a(*endo*)].
8. The reaction conditions have not been optimized yet.
9. Compound **4**: ^1H NMR (300 MHz, $CDCl_3$) data for **4**; δ 4.32 (ddd, 1H, $J_{5a(eq),6exo} = 2.1$ Hz, $J_{5,6exo} = 4.9$ Hz, $J_{gem} = 8.5$ Hz, H-6*exo*), 4.18 (d, 1H, $J_{2,3} = 3.4$ Hz, H-3), 4.03 (d, 1H, $J_{gem} = 8.5$ Hz, H-6*endo*), 3.60 (dd, 1H, $J_{2,3} = 3.4$ Hz, $J_{1,2} = 3.7$ Hz, H-2), 3.27 (ddd, 1H, $J_{1,5a(endo)} = 1.2$ Hz, $J_{1,2} = 3.7$ Hz, $J_{1,5a(exo)} = 4.0$ Hz, H-1), 2.60 (ddd, 1H, $J_{5,5a(exo)} = 2.0$ Hz, $J_{5,6exo} = 4.9$ Hz, $J_{5,5a(endo)} = 6.8$ Hz, H-5), 2.44–2.48 [m, 1H, H-5a(*endo*)], 2.26 [ddd, 1H, $J_{5,5a(exo)} = 2.0$ Hz, $J_{1,5a(exo)} = 4.0$ Hz, $J_{gem} = 15.1$ Hz, H-5a(*exo*)]; for **5a**: δ 7.27–7.37 (m, 5H, Ph), 4.56 and 4.66 (ABq, each 1H, $J_{gem} = 11.8$ Hz, OCH_2), 4.37 (d, 1H, $J_{gem} = 7.8$ Hz, H-6*endo*), 4.15 (dd, 1H, $J_{2,3} = 4.9$ Hz, $J_{1,2} = 5.0$ Hz, H-2), 4.06 (ddd, 1H, $J_{5a(exo),6exo} = 2.9$ Hz, $J_{5,6exo} = J_{gem} = 7.8$ Hz, H-6*exo*), 3.95 (d, 1H, $J_{2,3} = 4.9$ Hz, H-3), 3.40 (ddd, 1H, $J_{1,5a(exo)} = 2.0$ Hz, $J_{1,5a(endo)} = 4.4$ Hz, $J_{1,2} = 5.0$ Hz, H-1), 3.38 (s, 3H, OMe), 2.49 (ddd, 1H, $J_{5,5a(endo)} = 3.4$ Hz, $J_{5,5a(exo)} = 3.7$ Hz, $J_{5,6exo} = 7.8$ Hz, H-5), 2.34–2.37 (m, 2H, H-5a,5a).
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13. Exhaustive acetolysis of **3i** is likely to give **6g** selectively; however, prolonged heating of intermediate **6f** and/or **6g**