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Last Step towards Macrocyclic Glycoterpenoids Having Isosteviol and Glucosamine Moieties

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Dedicated to Academician of the Russian Academy of Sciences O.G. Sinyashin on the occasion of his 60th birthday

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The first diglycosides possessing two glucosamine residues and two moieties of diterpenoid isosteviol have been synthesized. They are the precursors of future macrocyclic glycoterpenoids possessing glucosamine and isosteviol moieties.

Keywords: Terpenoids, isosteviol, glucosamine, glycoconjugates, glycoterpenoids.

Последний шаг на пути к макроциклическим гликотерпеноидам, содержащим изостевиольный и глюкозаминовый фрагменты

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Синтезированы первые дигликозиды на основе глюкозамина и дитерпеноида изостевиола. Они являются прекурсорами будущих макроциклических гликотерпеноидов, содержащих глюкозаминовый и изостевиольный фрагменты.

Ключевые слова: Терпеноиды, изостевиол, глюкозамин, гликоконъюгаты, гликотерпеноиды.

Introduction

Recently the first syntheses of open chain and macrocyclic glycoterpenoids having one or several diterpenoid moieties bonded with various carbohydrate residues, namely D-glucopyranose[1,2], glucuronic acid[3-5] or trehalose[6,7] have been reported. In continuation of these investigations 2-deoxy-2-amino-D-glucopyranose (glucosamine) was chosen as the next carbohydrate block for macrocyclic glycoterpenoids. Glucosamine is the one of the most abundant monosaccharide units with their linkage modes found in mammalian oligosaccharides.[8,9] *N*-Acetylglucosamine is an abundant hexose that as a monomer or as part of macromolecules plays multiple roles in eukaryotic cells.[10,11] The literature has provided many examples of various glucosamine conjugates[12-18] which exhibited anticancer,[13,14] neuroprotective,[15] anti-HIV-1,[16] and antimalarial[17] activities. Conjugating glucosamine to biologically active compounds has significantly reduced their hepatotoxic and immunotoxic effects.[18] Herein, we report the first synthesis of diglycosides having two residues of glucosamine **1**, and two moieties of diterpenoid isosteviol (16-oxo-*ent*-beyeran-19-oic acid, **5**) which are the precursors of future macrocyclic glycoterpenoids possessing glucosamine and isosteviol moieties.

Experimental

General

NMR experiments were carried out with Avance-400 (Bruker) spectrometer in $CDCl_3$ at 400 MHz at 30 °C. MALDI mass spectra were measured on DYNAMO MALDI TOF instrument (Thermo BioAnalysis, Santa Fe, New Mexico). Samples were prepared as 0.1 % solutions of compounds in an appropriate solvent. The matrix was *p*-nitroaniline (Acros). The completeness of the reaction and the purity of the compounds were monitored by TLC on Sorbfil plates (Sorbfil, Russia). Spots were detected by treatment with the 5 % solution of sulfuric acid, followed by heating up to 120 °C.

Isolation of individual substances **14–17** was performed with a flash chromatography on Silicagel KSKG (0.060–0.200 mm, Crom-Lab Ltd, Russia), **18**, **19** – with column chromatography on Kiesegel (0.060–0.200 mm, ACROS Organics).

All solvents were dried according to standard protocols. Isosteviol **5**, diterpenoid diols **10**, **11**, diterpenoid diacids **12**, **13** were prepared according to the literature.[7,19] 3,4,6-Tri-*O*-acetyl-2-deoxy-2-[(2,2,2-trichloroethoxy)carbonylamino]-α-D-glucopyranosyl bromide **4** was prepared according to the literature.[20] The physicochemical properties of these compounds agreed with those published.

Synthesis

*General procedure for synthesis of diglycosides **14–17**.* $ZnCl_2$ (4.9 mmol) was added to a solution of diol **10** or **11** (2.4 mmol) and bromide **4** (5.4 mmol) in CH_2Cl_2 (75 ml) under argon. The reaction mixture was stirred for 15 hrs at room temperature, then mixture was diluted with CH_2Cl_2, washed with 5 % $NaHCO_3$, water and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (eluent – hexane:ethyl acetate as 5:1 mixture).

*Diglycoside **14** (α-anomer).* Yield: 20 %, white foam, $[\alpha]_D^{20}$ +22.2° (*c* 1.40; CH_2Cl_2). Found, %: C, 56.34; H, 6.97; Cl, 11.33; N, 1.47. $C_{88}H_{130}Cl_6N_2O_{28}$. Calculated, %: C, 56.32; H, 6.98; Cl, 11.33; N, 1.49. Mass spectrum (MALDI TOF) *m/z* (%): 1899.5 $[M+Na]^+$; 1915.6 $[M+K]^+$. ^{1}H NMR (400 MHz, $CDCl_3$, 30 °C) δ_H ppm: 0.70 (s, 6H, $C^{20}H_3$, $C^{20'}H_3$), 0.90 (s, 6H, $C^{17}H_3$, $C^{17'}H_3$), 1.17 (s, 6H, $C^{18}H_3$, $C^{18'}H_3$), 0.83–1.89 (m, 58H, *ent*-beyeran skeleton, 2 linkers $(CH_2)_2$ and linker $(CH_2)_6$), 2.00 (s, 6H, CH_3CO, $C'H_3CO$), 2.03 (s, 6H, CH_3CO, $C'H_3CO$), 2.09 (s, 6H, CH_3CO, $C'H_3CO$), 2.16 (d, 2H, *J*=13.0 Hz, C^3H_{eq}, $C^{3'}H_{eq}$), 2.30 (t, 4H, *J*=7.4 Hz, $C^{16}OC(O)CH_2$, $C^{16'}OC(O)CH_2$), 3.44–3.52 (m, 2H, $C^{19}OC(O)(CH_2)_3CH_A$, $C^{19'}OC(O)(CH_2)_3CH_A$), 3.70–3.78 (m, 2H, $C^{19}OC(O)(CH_2)_3CH_B$, $C^{19'}OC(O)(CH_2)_3CH_B$), 3.93–4.01 (m, 4H, H^5, $H^{5'}$, H^2, $H^{2'}$), 4.03–4.17 (m, 6H, H^6, $H^{6'}$, $C^{19}(O)OCH_2$, $C^{19'}OC(O)CH_2$), 4.27 (dd, 2H, *J*=12.4, 4.6 Hz, H^6, $H^{6'}$), 4.64 (d, 2H, *J*=12.1 Hz, OCH_ACCl_3), 4.72 (dd, 2H, *J*=10.5, 4.2 Hz, $C^{16}H$, $C^{16'}H$), 4.81 (d, 2H, *J*=12.1 Hz, OCH_BCCl_3), 4.88 (d, 2H, *J*=3.4 Hz, H^1, $H^{1'}$), 5.10 (t, 2H, *J*=9.9 Hz, H^4, $H^{4'}$), 5.24 (t, 2H, *J*=9.9 Hz, H^3, $H^{3'}$), 5.29 (d, 2H, *J*=9.8 Hz, 2 NH).

*Diglycoside **15** (α-anomer).* Yield: 22 %, white foam, $[\alpha]_D^{20}$ +17.7° (*c* 2.05; CH_2Cl_2). Found, %: C, 57.14; H, 7.19; Cl, 11.03; N, 1.44. $C_{92}H_{138}Cl_6N_2O_{28}$. Calculated, %: C, 57.17; H, 7.20; Cl, 11.01; N, 1.45. Mass spectrum (MALDI TOF) *m/z* (%): 1955.2 $[M+Na]^+$; 1971.1 $[M+K]^+$. ^{1}H NMR (400 MHz, $CDCl_3$, 30 °C) δ_H ppm: 0.70 (s, 6H, $C^{20}H_3$, $C^{20'}H_3$), 0.89 (s, 6H, $C^{17}H_3$, $C^{17'}H_3$), 1.16 (s, 6H, $C^{18}H_3$, $C^{18'}H_3$), 0.81–1.89 (m, 66 H, *ent*-beyeran skeleton, 2 linkers $(CH_2)_4$ and linker $(CH_2)_6$), 1.99 (s, 6H, CH_3CO, $C'H_3CO$), 2.02 (s, 6H, CH_3CO, $C'H_3CO$), 2.09 (s, 6H, CH_3CO, $C'H_3CO$), 2.15 (d, 2H, *J*=12.8 Hz, C^3H_{eq}, $C^{3'}H_{eq}$), 2.30 (t, 4H, *J*=7.4 Hz, $C^{16}OC(O)CH_2$, $C^{16'}OC(O)CH_2$), 3.41–3.49 (m, 2H, $C^{19}OC(O)(CH_2)_5CH_A$, $C^{19'}OC(O)(CH_2)_5CH_A$), 3.65–3.73 (m, 2H, $C^{19}OC(O)(CH_2)_5CH_B$, $C^{19'}OC(O)(CH_2)_5CH_B$), 3.90– 3.99 (m, 4H, H^5, $H^{5'}$, H^2, $H^{2'}$), 4.00–4.15 (m, 6H, H^6, $H^{6'}$, $C^{19}(O)OCH_2$, $C^{19'}OC(O)CH_2$), 4.26 (dd, 2H, *J*=12.3, 4.6 Hz, H^6, $H^{6'}$), 4.63 (d, 2H, *J*=12.1 Hz, OCH_ACCl_3), 4.70 (dd, 2H, *J*=10.5, 4.2 Hz, $C^{16}H$, $C^{16'}H$), 4.79 (d, 2H, *J*=12.1 Hz, OCH_BCCl_3), 4.87 (d, 2H, *J*=3.5 Hz, H^1, $H^{1'}$), 5.09 (t, 2H, *J*=9.8 Hz, H^4, $H^{4'}$), 5.24 (t, 2H, *J*=9.8 Hz, H^3, $H^{3'}$), 5.37 (d, 2H, *J*=9.9 Hz, 2 NH).

*Glycoside **17** (α-anomer).* Yield: 9 %, white foam, $[\alpha]_D^{20}$ -2.3° (*c* 0.75; CH_2Cl_2). Found, %: C, 62.95; H, 8.21; Cl, 7.23; N, 0.94. $C_{77}H_{120}Cl_3NO_{19}$. Calculated, %: C, 62.91; H, 8.23; Cl, 7.23; N, 0.95. Mass spectrum (MALDI TOF) *m/z* (%): 1492.6 $[M+Na]^+$; 1508.5 $[M+K]^+$. ^{1}H NMR (400 MHz, $CDCl_3$, 30 °C) δ_H ppm: (s, 6H, $C^{20}H_3$, $C^{20'}H_3$), 0.89 (s, 3H, $C^{17}H_3$), 0.90 (s, 3H, $C^{17'}H_3$), 0.82–1.90 (m, 66H, *ent*-beyeran skeleton, 2 linkers $(CH_2)_4$ and linker $(CH_2)_6$), 1.15 (s, 3H, $C^{18}H_3$), 1.16 (s, 3H, $C^{18'}H_3$), 2.00 (s, 3H, CH_3CO), 2.03 (s, 3H, CH_3CO), 2.09 (s, 3H, CH_3CO), 2.16 (d, 2H, *J*=13.1 Hz, C^3H_{eq}, $C^{3'}H_{eq}$), 2.30 (t, 4H, *J*=7.4 Hz, $C^{16}OC(O)CH_2$, $C^{16'}OC(O)CH_2$), 3.42–3.49 (m, 1H, $C^{19}OC(O)(CH_2)_5CH_A$), 3.62 (t, 2H, *J*=6.8 Hz, $C^{19}OC(O)(CH_2)_5CH_2OH$), 3.66 – 3.74 (m, 1H, $C^{19}OC(O)(CH_2)_5CH_B$), 3.91–4.15 (m, 7H, H^2, H^5, H^6, $C^{19}(O)OCH_2$, $C^{19'}OC(O)CH_2$), 4.26 (dd, 1H, *J*=12.4, 4.5 Hz, H^6), 4.62–4.73 (m, 3H, OCH_ACCl_3, $C^{16}H$, $C^{16'}H$), 4.80 (d, 1H, *J*=12.2 Hz, OCH_BCCl_3), 4.88 (d, 1H, *J*=3.6 Hz, H^1), 5.10 (t, 1H, *J*=9.6 Hz, H^4), 5.25 (t, 1H, *J*=9.9 Hz, H^3), 5.38 (d, 1 H, *J*=9.7 Hz, NH).

*General procedure for synthesis of **18**, **19**.* A solution of diacids **12** or **13** (0.2 mmol) in CH_2Cl_2 (5 ml) was added dropwise to a stirred solution of bromide **4** (0.48 mmol) in CH_2Cl_2 (5 ml) and H_2O (5 ml) in the presence of K_2CO_3 (0.6 mmol) and TBAB (0.1 mmol) under argon. The mixture was vigorously stirred for 48 hrs, then mixture was diluted with CH_2Cl_2. The aqueous layer was shaken with CH_2Cl_2. The combined CH_2Cl_2 layers were washed with water and dried with Na_2SO_4, the solvent was removed under reduced pressure, and then a precipitate was purified by silica gel column chromatography (eluent – hexane:ethyl acetate mixture from 5:1 to 1:1).

*Diglycoside **18** (β-anomer).* Yield: 38 %, white foam, $[\alpha]_D^{20}$ -14.3° (*c* 1.0; CH_2Cl_2). Found, %: C, 55.81; H, 6.84; Cl,

10.94; N, 1.50. $C_{90}H_{130}Cl_6N_2O_{30}$. Calculated, %: C, 55.93; H, 6.78; Cl, 11.01; N, 1.45. Mass spectrum (MALDI TOF) *m/z* (%): 1954.6 $[M+Na]^+$; 1972.4 $[M+K]^+$. ^{1}H NMR (400 MHz, $CDCl_3$, 30 °C) δ_H ppm: 0.67 (s, 6H, $C^{20}H_3$, $C^{20'}H_3$), 0.88 (s, 6H, $C^{17}H_3$, $C^{17'}H_3$), 1.14 (s, 6H, $C^{18}H_3$, $C^{18'}H_3$), 0.80–1.90 (m, 58H, *ent*-beyeran skeleton, 2 linkers $(CH_2)_3$ and linker $(CH_2)_4$), 2.01 (s, 6H, CH_3CO, $C'H_3CO$), 2.02 (s, 6H, CH_3CO, $C'H_3CO$), 2.07 (s, 6H, CH_3CO, $C'H_3CO$), 2.13 (d, 2H, J=12.8 Hz, C^3H_{eq}, $C^{3'}H_{eq}$), 2.26–2.38 (m, 8H, $C^{16}OC(O)CH_2$, $C^{16'}OC(O)CH_2$, $C^{19}(O)O(CH_2)_4CH_2$, $C^{19'}OC(O)(CH_2)_4CH_2$), 3.80–3.85 (m, 2H, H^2 or H^5, $H^{2'}$ or $H^{5'}$), 3.88–4.09 (m, 8H, H^2 or H^5, $H^{2'}$ or $H^{5'}$, C19(O)OCH_2, $C^{19'}OC(O)CH_2$), 4.28 (dd, 2H, J=12.5, 4.4 Hz, H^6, $H^{6'}$), 4.60–4.80 (m, 6H, 2 CH_2CCl_3, $C^{16}H$, $C^{16'}H$), 5.09 (t, 2H, J=9.7 Hz, H^4, $H^{4'}$), 5.28 (t, 2H, J=9.7, H^3, $H^{3'}$), 5.69 (d, 2H, J=9.1 Hz, 2 NH), 5.77 (d, 2H, J=8.8 Hz, H^1, $H^{1'}$).

*Diglycoside **19** (β-anomer).* Yield: 28 %, white foam, $[\alpha]_D^{20}$ -16.8° (*c* 1.60; CH_2Cl_2). Found, %: C, 56.19; H, 6.78; Cl, 10.99; N, 1.38. $C_{92}H_{134}Cl_6N_2O_{30}$. Calculated, %: C, 56.35; H, 6.89; Cl, 10.85; N, 1.43. Mass spectrum (MALDI TOF) *m/z* (%): 1982.4 $[M+Na]^+$; 1998.4 $[M+K]^+$. ^{1}H NMR (400 MHz, $CDCl_3$, 30 °C) δ_H ppm: 0.69 (s, 6H, $C^{20}H_3$, $C^{20'}H_3$), 0.90 (s, 6H, $C^{17}H_3$, $C^{17'}H_3$), 1.15 (s, 6H, $C^{18}H_3$, $C^{18'}H_3$), 0.80–1.85 (m, 62H, *ent*-beyeran skeleton, 2 linkers $(CH_2)_3$ and linker $(CH_2)_6$), 2.02 (s, 6H, CH_3CO, $C'H_3CO$), 2.03 (s, 6H, CH_3CO, $C'H_3CO$), 2.08 (s, 6H, CH_3CO, $C'H_3CO$), 2.14 (d, 2H, J=12.8 Hz, C^3H_{eq}, $C^{3'}H_{eq}$), 2.29–2.42 (m, 8H, $C^{16}OC(O)CH_2$, $C^{16'}OC(O)CH_2$, $C^{19}(O)O(CH_2)_4CH_2$, $C^{19'}OC(O)(CH_2)_4CH_2$), 3.81–3.85 (m, 2H, H^2 or H^5, $H^{2'}$ or $H^{5'}$), 3.91–4.09 (m, 8H, H^2 or H^5, $H^{2'}$ or $H^{5'}$, C19(O)OCH_2, $C^{19'}OC(O)CH_2$), 4.30 (dd, 2H, J=12.4, 4.3 Hz, H^6, $H^{6'}$), 4.67–4.77 (m, 6H, 2 CH_2CCl_3, $C^{16}H$, $C^{16'}H$), 5.11 (t, 2H, J=10.0 Hz, H^4, $H^{4'}$), 5.28 (t, 2H, J=10.0 Hz, H^3, $H^{3'}$), 5.59 (d, 2H, J=8.6 Hz, 2 NH), 5.78 (d, 2H, J=8.6 Hz, H^1, $H^{1'}$).

Results and Discussion

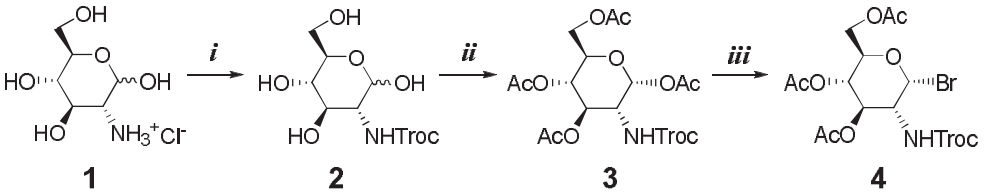
By analogy with the literature,[20] commercially available glucosamine hydrochloride **1** was converted to 3,4,6-tri-*O*-acetyl-2-deoxy-2-[(2,2,2-trichloroethoxy)carbonylamino]-α-D-glucopyranosyl bromide **4** (Scheme 1) which seemed to be suitable glycosyl-donor for reactions with alcohols and carboxylic acids. As the aglycon of target diglycosides as well as the diterpenoid component of future macrocyclic glycoterpenoids, diterpenoid diols **9**, **10** and diterpenoid diacids **12**, **13** were used. They were synthesized in 4th and 5th steps, respectively, by analogy with[7] (Scheme 2).

At the first step, isosteviol **5** was converted to dihydroisosteviol **6** by treatment with sodium tetrahydridoborate, and two molecules of this isosteviol derivative were bonded by the reaction with suberoyl or sebacoyl chlorides afforded diterpenoid diacids **7** and **8** (Scheme 2). Then these diterpenoid diacids were converted to their acid chlorides which *in situ* were reacted with butane-1,4-diol or hexane-1,6-diol provided diterpenoid diols **9–11**. At the 5th step the hydroxy grops of diols **9** and **11** were oxidized with Jones' reagent afforded diterpenoid diacids **12**, **13** in 88 %, and 90 % yields, respectively (Scheme 2).

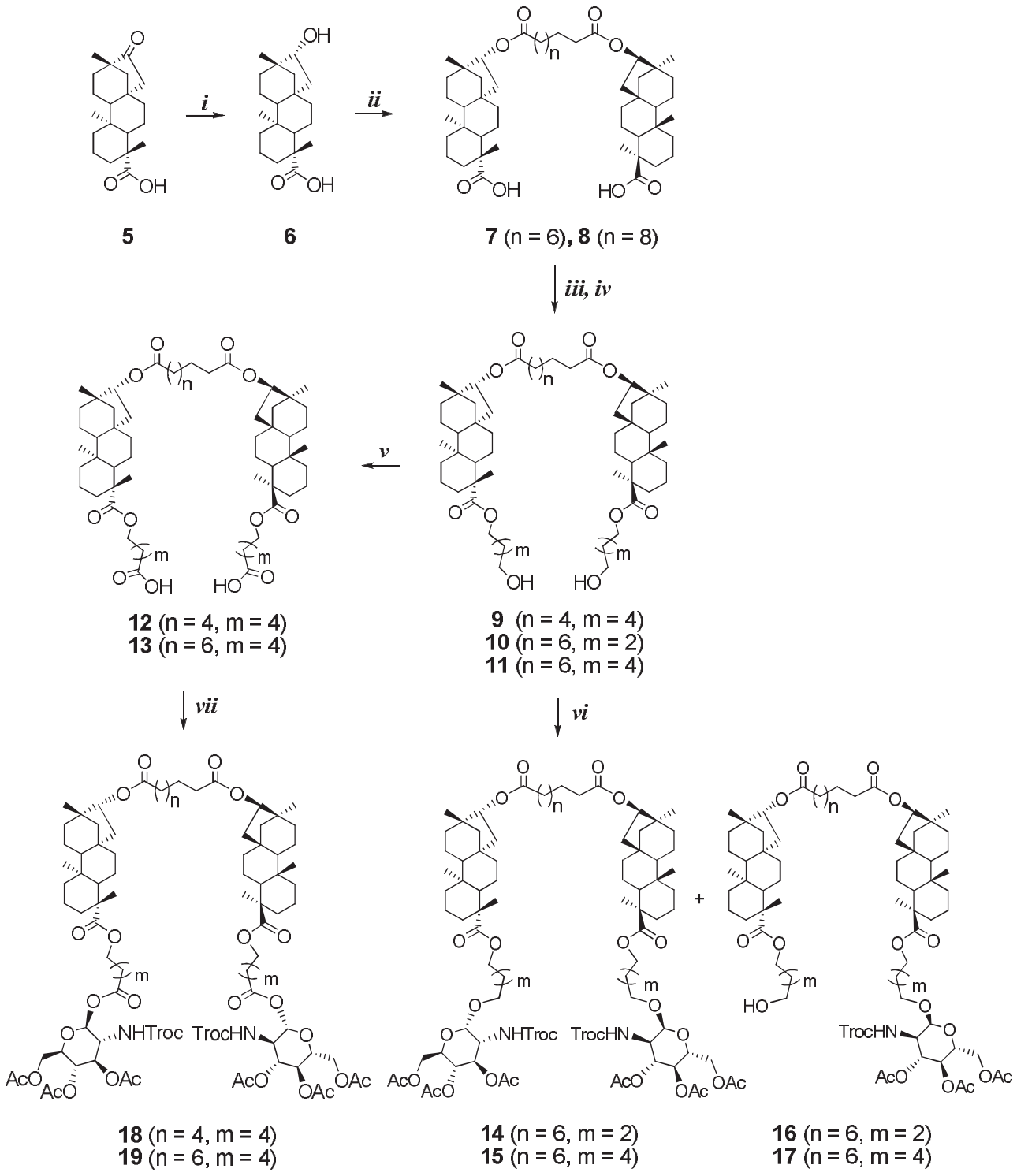
Diglycosides containing glucosamine residues and isosteviol moieties were synthesized by the reaction of bromide **4** with both diterpenoid diols **10**, **11**, and diterpenoid diacids **12**, **13**. By analogy with the literature,[21] bromide **4** was treated with diterpenoid diols **10** and **11** in the presence of $ZnCl_2$ (Scheme 2). The reactions have provided diglycosides **14** and **15** in 20 % and 22 % yields, respectively. Besides, by-products of monosubstitution were formed in both cases. The reaction of bromide **4** with diterpenoid diol **10** has afforded glycoside **16** which was observed only in the MALDI spectrum that demonstrated the peak of molecular ion $[M+Na]^+$ (*m/z*=1436.4) corresponding to the molecular formulae of glycoside **16** ($C_{73}H_{112}Cl_3NO_{19}$). The reaction of bromide **4** with diterpenoid diol **11** has provided glycoside **17** isolated by a flash chromatography in 9 % yield (Scheme 2). In contrast to diglycosides **14** and **15**, the ^{1}H NMR spectrum of glycoside **17** has shown methylene protons of CH_2OH group as a triplet at 3.62 ppm. The MALDI spectrum of glycoside **17** has exhibited the peaks of molecular ions $[M+Na]^+$ (*m/z*=1492.6), $[M+K]^+$ (*m/z*=1508.5) corresponding to molecular formulae $C_{77}H_{120}Cl_3NO_{19}Na$ and $C_{77}H_{120}Cl_3NO_{19}K$. The anomeric protons of diglycosides **14**, **15**, **17** have resonated in the ^{1}H NMR spectrum as single doublets at 4.88, 4.87, 4.88 ppm with vicinal coupling constants of 3.4, 3.5, 3.6 Hz, respectively. All these indicate that diglycosides **14**, **15**, **17** have α-orientation of the glycoside bonds. Reactions of bromide **4** with diterpenoid diacids **12** and **13** were carried out under the condition of heterogeneous catalysis by TBAB in a water–chloroform mixture provided exclusively the products of disubstitution, namely, diglycosides **18** and **19** isolated by column chromatography in 38 % and 28 % yields, respectively (Scheme 2). It should be noted that in contrast to diglycosides **14** and **15**, the anomeric protons of diglycosides **18** and **19** were shifted downfield and appeared at 5.77 and 5.78 ppm, respectively, as doublets with vicinal coupling constants of 8.8 and 8.6 Hz, indicating β-orientation of the glycoside bonds.

Conclusions

In conclusion, four before unknown diglycosides **14**, **15**, **18**, **19** containing two glucosamine residues and two isosteviol moieties were synthesized. It should be noted that the reaction of glucosamine bromo derivative **4** with diterpenoid diols **10** and **11** was carried out at room temperature in the presence of $ZnCl_2$ afforded



Scheme 1. Reagents and conditions: (i) $NaHCO_3$, TrocCl, H_2O; (ii) Ac_2O, Py; (iii) 33 % HBr, AcOH, CH_2Cl_2.



Scheme 2. Reagents and conditions: (i) $NaBH_4$, CH_3OH; (ii) $Cl(O)C(CH_2)_nCH_2CH_2C(O)Cl$, DMAP, DCC, CH_2Cl_2; (iii) $SOCl_2$; (iv) $HO(CH_2)_mCH_2CH_2OH$, CH_2Cl_2; (v) CrO_3, H_2SO_4, acetone; (vi) bromide **4**, $ZnCl_2$, CH_2Cl_2; (vii) bromide **4**, TBAB, K_2CO_3, H_2O, CH_2Cl_2.

α-diglycosides **14** and **15**, whereas the reaction of bromide **4** with diterpenoid diacids **12** and **13** was carried out under the condition of heterogeneous catalysis by TBAB led to diglycosides **18** and **19** having β-orientation of glycoside bonds.

One can see that the interaction of deprotected amino groups of glucosamine residues of diglycosides **14**, **15**, **18**, **19** with bielectrophilic reagents will lead to their macrocyclization, and macrocyclic glycoterpenoids analogous to already known macrocycles[4-7] will be obtained. These reactions are currently being studied and will be reported soon.

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