Last Step towards Macrocyclic Glycoterpenoids Having Isosteviol and Glucosamine Moieties


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 предшественниками 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 glycosaponoids having one or several diterpenoid moieties bonded with various carbohydrate residues, namely D-glucopyranose, glucuronic acid, or trehalose, have been reported. In continuation of these investigations 2-deoxy-2-amino-D-glucopyranose (glucosamine) was chosen as the next carbohydrate block for macrocyclic glycosaponoids. Glucosamine is the one of the most abundant monosaccharide units with their linkage modes found in mammalian oligosaccharides. N-Acetylglucosamine is an abundant hexasaccharide that as a monomer or as part of macromolecules plays multiple roles in eukaryotic cells. The literature has provided many examples of various glucosamine conjugates which exhibited anticancer, neuroprotective, anti-HIV-1, and antimalarial activities. Conjugating glucosamine to physicochemically active compounds has significantly reduced their hepatotoxic and immunotoxic effects. Herein, we report the first synthesis of diglycosides having two residues of glucosamine and 1, and two moieties of diterpenoid isosottiol (16-oxo-ent-beyeran-19-oic acid, \( \text{5} \)) which are the precursors of future macrocyclic glycosaponoids possessing glucosamine and isosottiol 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, Chrom-Lab Ltd, Russia), 18, 19 – with column chromatography on Kieselgel (0.060 – 0.200 mm, ACROS Organics).

All solvents were dried according to standard protocols. Iosotiol 5, diterpenoid diols 10, 11, diterpenoid diacids 12, 13 were prepared according to the literature. 3,4,6-Tri-O-acetyl-2-deoxy-2-[2,2,2-tricholroethoxy]carbonylemethyl]-l-D-glucopyranosyl bromide 4 was prepared according to the literature. 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\(_2\)Cl\(_2\) (75 ml) under argon. The reaction mixture was stirred for 15 hrs at room temperature, then mixture was diluted with CH\(_2\)Cl\(_2\), washed with 5 % NaHCO\(_3\) solution, water and brine, dried over Na\(_2\)SO\(_4\) and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (eluents – hexane:ethyl acetate in 5:1 mixture).

Diglycoside 14 (alpha-anomer). Yield: 20 %, white foam, \([\alpha]_20^{+22.2\circ} (c \ 1.40; \ CHCl\(_3\)). Found: %, C, 56.34; H, 6.97; Cl, 11.33; N, 1.49. Mass spectrum (MALDI TOF) m/z (%): 1899.5 [M+Na]+; 1915.6 [M+K]+. 

A flash chromatography on Silicagel KSKG (0.060 – 0.200 mm, was monitored by TLC on Sorbfil plates (Sorbfil, Russia). Spots were monitored by TLC on Sorbfil plates (Sorbfil, Russia). Spots were monitored by TLC on Sorbfil plates (Sorbfil, Russia). Spots were monitored by TLC on Sorbfil plates (Sorbfil, Russia). Spots were monitored by TLC on Sorbfil plates (Sorbfil, Russia). Spots were monitored by TLC on Sorbfil plates (Sorbfil, Russia). Spots were monitored by TLC on Sorbfil plates (Sorbfil, Russia). Spots were monitored by TLC on Sorbfil plates (Sorbfil, Russia). Spots were monitored by TLC on Sorbfil plates (Sorbfil, Russia). Spots were monitored by TLC on Sorbfil plates (Sorbfil, Russia). Spots were monitored by TLC on Sorbfil plates (Sorbfil, Russia). Spots were monitored by TLC on Sorbfil plates (Sorbfil, Russia). Spots were monitored by TLC on Sorbfil plates (Sorbfil, Russia). Spots were monitored by TLC on Sorbfil plates (Sorbfil, Russia). 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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]carbonylamin]-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 glucoterpenoids, diterpenoid diols 9, 10 and diterpenoid diacids 12, 13 were used. They were synthesized in 4th and 5th steps, respectively, by analogy with[20] (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 suberyl 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 groups 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 ZnCl2 (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 formula of glycoside 16 (C72H112Cl3NO19). 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 1H NMR spectrum of glycoside 17 has shown methylene protons of CHO 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 formula C77H120Cl3NO19Na and C77H120Cl3NO19K. The anomeric protons of diglycosides 14, 15, 17 have resonated in the 1H 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 bromine derivative 4 with diterpenoid diols 10 and 11 was carried out at room temperature in the presence of ZnCl2 afforded...
Scheme 2. Reagents and conditions: (i) NaBH₄, CH₂OH; (ii) Cl(O)C(CH₃)₂CH₂CH₂ClO, DMAP, DCC, CH₂Cl₂; (iii) SOCl₂; (iv) HO(CH₂)ₘCH₂CH₂OH, CH₂Cl₂; (v) CrO₃, H₂SO₄, acetone; (vi) bromide 4, ZnCl₂, CH₂Cl₂; (vii) bromide 4, TBAB, K₂CO₃, H₂O, CH₂Cl₂.
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\(\alpha\)-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 \(\beta\)-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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References


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