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Synthesis and antituberculosis activity of the first macrocyclic glycoterpenoids comprising glucosamine and diterpenoid isosteviol

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ABSTRACT

The first macrocyclic glycoterpenoids comprising glucosamine and diterpenoid isosteviol moieties were synthesized and evaluated for inhibition activity against *Mycobacterium tuberculosis* H37Rv.

1. Introduction

An increasing number of studies have been devoted to the isolation, purification, and structural elucidation of natural macrocyclic glycosides. Among them a first place is occupied by resin glycosides (or else fatty acid glycosides) which contain saturated fatty acids mainly jalapinolic acid (11(*S*)-hydroxyhexadecanoic acid) and convolvulinolic acid (11(*S*)-hydroxytetradecanoic acid) as the aglycon [1]. A carbohydrate portion of resin glycosides is typically composed of two [1b,c,e] to five [1a,b,g,h] monosaccharides as D-glucose, D-fucose, L-rhamnose, and D-quinovose. Many resin glycosides have cytotoxic [1a-c,e,i], antibacterial [1b,i], and antifungal [1i] effects. Perhaps one can single out from the rank of resin glycosides the macrocyclic glycolipids isolated from the plant *Cerastium glomeratum*, named glomerasides [1j], and glycolipids isolated from different microorganisms, e.g. cycloviracins [1i], and macroviracins [1d,i]. Glomerasides were found to be unique 1,6-cyclic esters with 17-, 18- or 19-membered ring formed by D-glucose and 9(*R*)-, 10(*R*)- or 11(*R*)-hydroxydocosanoic acid [1j]. Cycloviracins own C_2-symmetrical macrodilactone core functionalized with two long side polymethylene chains having several D-glucopyranose residues [1i]. Macroviracins are 42- to 46-membered macrodilactones composed of a glucopyranosyl C_{22} or C_{24} fatty acid dimer and a long side polymethylene chain attached to the core [1d,i]. Both groups of glycolipids exhibit a powerful antiviral activity [1d,i]. The following large group of macrocyclic glycosides contains phenols [1d,2], polyphenols [1d] or flavonoids [1d] as the aglycon. Among them cyclic dimers of 4-(glycosyloxy)benzoates with two and four sugar residues showed inhibitory activity against α- and β-glucosidases, lipoxygenase, and antioxidant potential [1d,2c]. Some polyphenols containing macrocyclic glycosides demonstrated inhibitory activity against HIV-1 enzymes and have shown an antimicrobial activity against human bacterial pathogens as well [1d]. The literature has provided several examples of the macrocyclic glycosides having a terpenoid moiety as the aglycon [1b,i,3]. These are glycosides urceolide [3a] and parkinsenes A-E [3b] which have some monoterpenoid acids as the aglycon as well as D-glucose [3a], D-fucose

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[3b], D-quinovose [3b], and D-apiose [3a] as the glycon. The aglycon of the macrocyclic glycosides of the syphonoside series is diterpenoid clerodane and the glycon is D-glucopyranose [3c,d]. The macrocyclic glycosides lobatosides A-E are 34-membered macrocycles which are composed of triterpenoid oleanolic acid as the aglycon, and four or five monosaccharides (D-glucose, D-galactose, and L-arabinofuranose) [1b,i]. All above mentioned macrocyclic terpenoid glycosides have demostrated one or another type of biological activity. Monoterpene glycosides showed significant analgesis, anti-inflammatory, hepatoprotective, and hypoglycemic activities [3b]. Diterpenoid glycoside syphonoside was able to inhibit high density induced apoptosis [3c]. Lobatoside E belonging to the macrocyclic triterpenoid glycosides (saponins) demonstrated a high potency to inhibit the growth of tumor cells [1i].

As far as we had reported on the synthesis of a large range of macrocycles constituted by one, two or four molecules of diterpenoid steviol or isosteviol [4], the aboremention publications about naturally occurring macrocyclic terpenoid glycosides (or else macrocyclic glycoterpenoids [3c]) gave us the impetus to synthesize macrocyclic derivatives of diterpenoid isosteviol that would also have carbohydrate residues. Recently the first synthesis of macrocyclic glycoterpenoids composed of diterpenoid isosteviol and monosaccharid (α,α′-trehalose or D-glucuronic acid) residues have been reported [5]. In continuation of these studies, herein we describe the first synthesis of macrocyclic glycoterpenoids comprising glucosamine and isosteviol moieties. Their antituberculosis activities were also evaluated.

2. Results and discussion

Diterpenoid isosteviol **1** (16-oxo-*ent*-beyeran-19-oic acid [6]) obtained by acid hydrolysis of commercially available sweetener Sweta [7] and commercially available glucosamine hydrochloride **3** were used as starting compounds for the synthesis of target macrocyclic glycoterpenoids. General strategy for their synthesis consists of four stages and it is shown in Scheme 1. In the first stage, two isosteviol molecules are coupled with a linker attached to the atoms C16 of *ent*-beyerane skeletons and carboxylic groups are functionalized by ω-hydroxypolymethylene chains that afford a terpenoid precursor **2**. In the second stage hydroxyl and amine groups of glucosamine hydrochloride **3** are protected and anomeric center is brominated that give a carbohydrate precursor **4**. In the next stage terpenoid and carbohydrate precursors are coupled to afford diglycoside **5** which undergoes macrocyclization in the final stage to provide a target macrocyclic glycoterpenoid **6**.

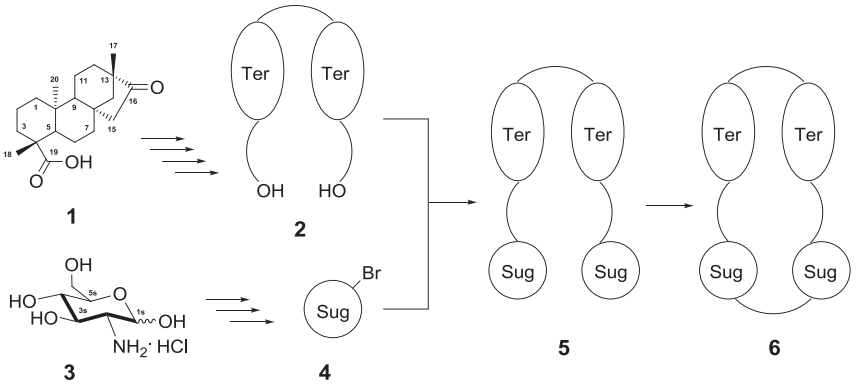
2.1. Chemistry

2.1.1. Synthesis of starting materials

To obtain terpenoid precursors, initially the 16-oxo group in isosteviol **1** was chemo- and stereoselectively reduced with sodium borohydride by analogy with described procedure [8] to give dihydroisosteviol **7** (100% *de*). Then two molecules of dihydroisosteviol **7** were coupled with each other by the reaction with sebacyl dichloride to afford the binuclear derivative of isosteviol **8** [4a,9]. This compound was choosen as the intermediate in the pathway towards terpenoid precursors because it had exhibited the highest antitubercular activity in the series of binuclear isosteviol derivatives [4f]. According to the X-ray crystal structure data [4f] diacid **8** has the maximum folding, sandwich-like structure. Then diacid **8** was converted to its bis-acyl chloride that was involved in the reactions with 1,4-butandiol and 1,6-hexanediol to afford terpenoid precursors **9** and **10** [5d] in 56% and 60% yields (Scheme 2).

To prepare carbohydrate precursor **13** (Scheme 3), according to the known procedure [10], the amine group of glucosamine hydrochloride **3** was protected by 2,2,2-trichloroethoxycarbonyl (Troc) group to give glucosamine derivative **11** which was per-*O*-acetylated, and then monosaccharide **12** was treated with 33% HBr in AcOH in CH_2Cl_2 to afford glycosyl-donor **13**. It is to be noted that exactly Troc group was chosen for the protection of amine group of glucosamine for two reasons. Firstly, N-Troc-protected glucosamine derivatives is more reactive than benzylidene or N-phthalyl-protected derivatives [11]. Secondly, the selective removal of the Troc group takes place in a rather mild conditions under which acetate groups of glucosamine residues and ester groups of linkers are not affected [12].

In the next stage diglycosides **5** (Scheme 1) containing glucosamine residues and isosteviol moieties were synthesized by the reaction of bromide **13** with both terpenoid precursors **9** and **10**. By analogy with the literature [13] bromide **13** was treated with diterpenoid diols **9** and **10** in the presence of $ZnCl_2$ (Scheme 4). The reactions provided diglycosides **14** and **15** in 20% and 22% yields, respectively. It is worth noting that both reactions led to the formation of α-glycosides. This was proved by the fact that the anomeric protons in diglycoside **14** resonated in the ^1H NMR spectrum as a doublet at 4.88 ppm with a vicinal coupling constant of 3.4 Hz, and the anomeric protons in diglycoside **15** resonated as a doublet at 4.87 ppm with a vicinal coupling constant of 3.5 Hz. The reason is the amazing property of the Lewis acid $ZnCl_2$ to manifest itself as the stereoselective activator of the classical Koenigs-Knorr reaction [13]. In both reactions glycosides **16** and **17** formed as the byproducts (Scheme 4). Glycoside **16** was detected in the reaction



Scheme 1. General strategy for the synthesis of macrocyclic glycoterpenoids. Designations: **Ter** means terpenoid (isosteviol moiety), **Sug** means carbohydrate (glucosamine residue).