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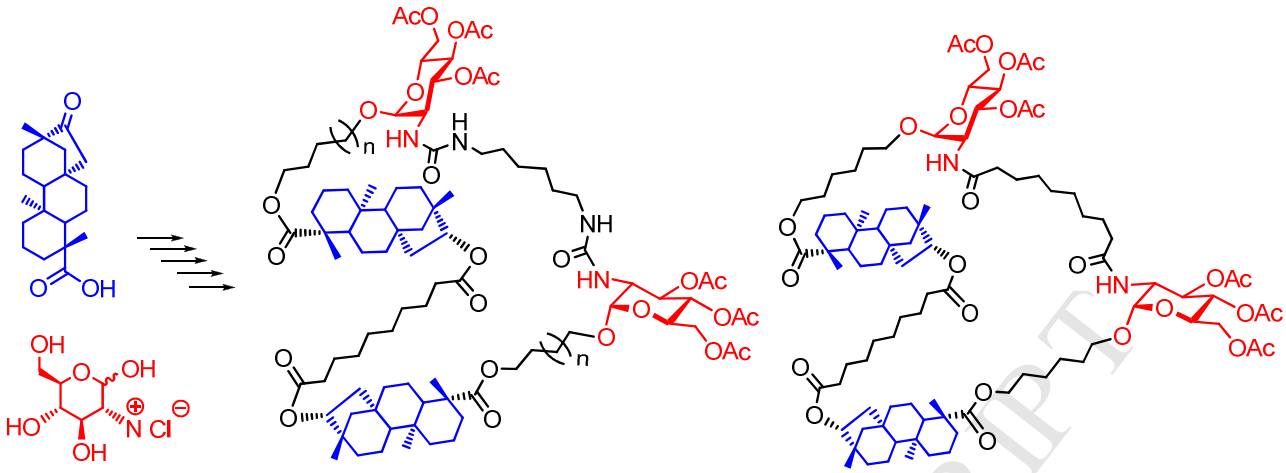

Synthesis and antituberculosis activity of the first macrocyclic glycoterpenoids comprising glucosamine and diterpenoid isosteviol

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

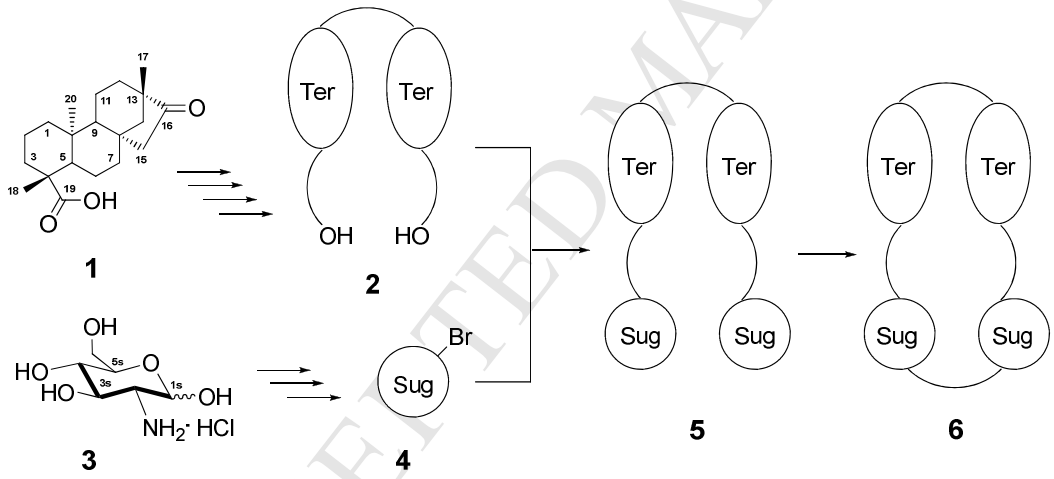
1. Introduction

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,[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 aborementioned 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**.



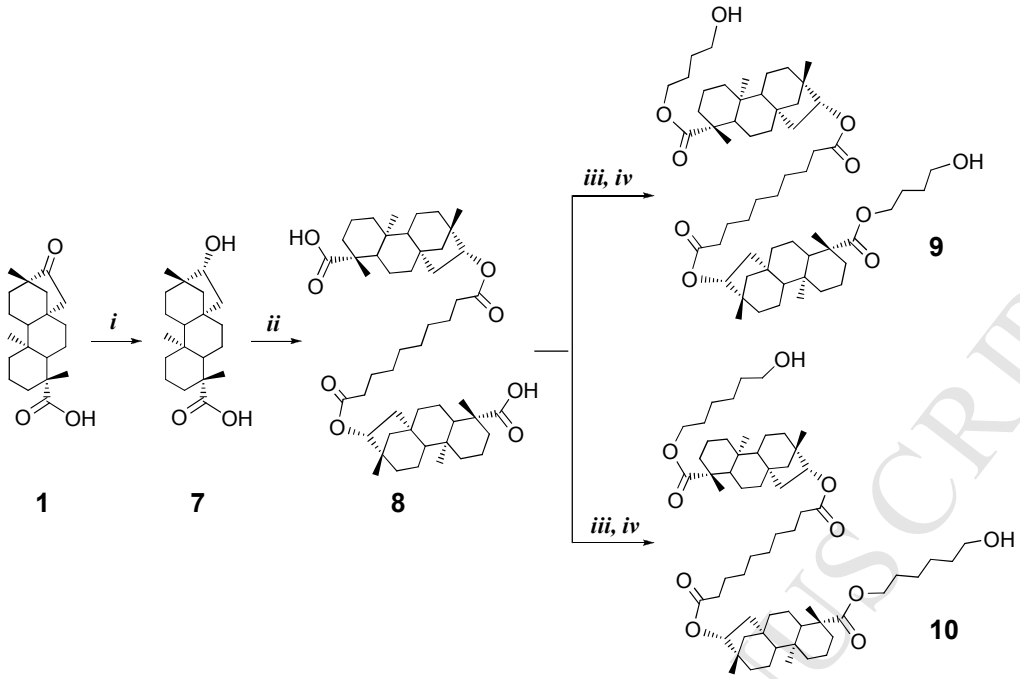
Scheme 1. General strategy for the synthesis of macrocyclic glycoterpenoids. Designations: **Ter** means terpenoid (isosteviol moiety), **Sug** means carbohydrate (glucosamine residue).

2.1. Chemistry

2.1.1. Synthesis of starting materials

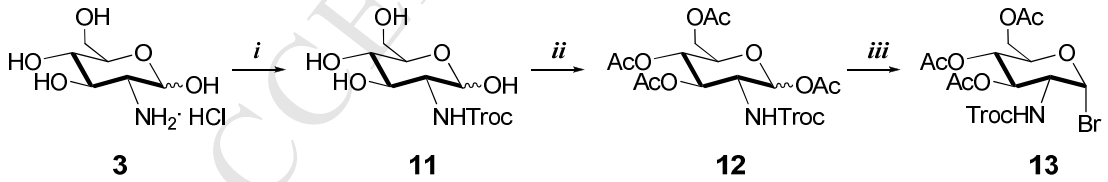
To obtain terpenoid precursors, initially the 16-oxo group in isosteviol **1** was chemo- and stereoselectively reduced with sodium borohydride by analogy with described procedure[8] to give dihydroisosteviol **7** (100% *de*). Then two molecules of dihydroisosteviol **7** were coupled with each other 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 binucleur 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. *Reagents and conditions*: (i) $NaBH_4$, CH_3OH; (ii) $ClC(O)(CH_2)_8C(O)Cl$, CH_2Cl_2, DMAP; (iii) $SOCl_2$, 50°C; (iv) $HO(CH_2)_nOH$, CH_2Cl_2 (n = 4 or 6).

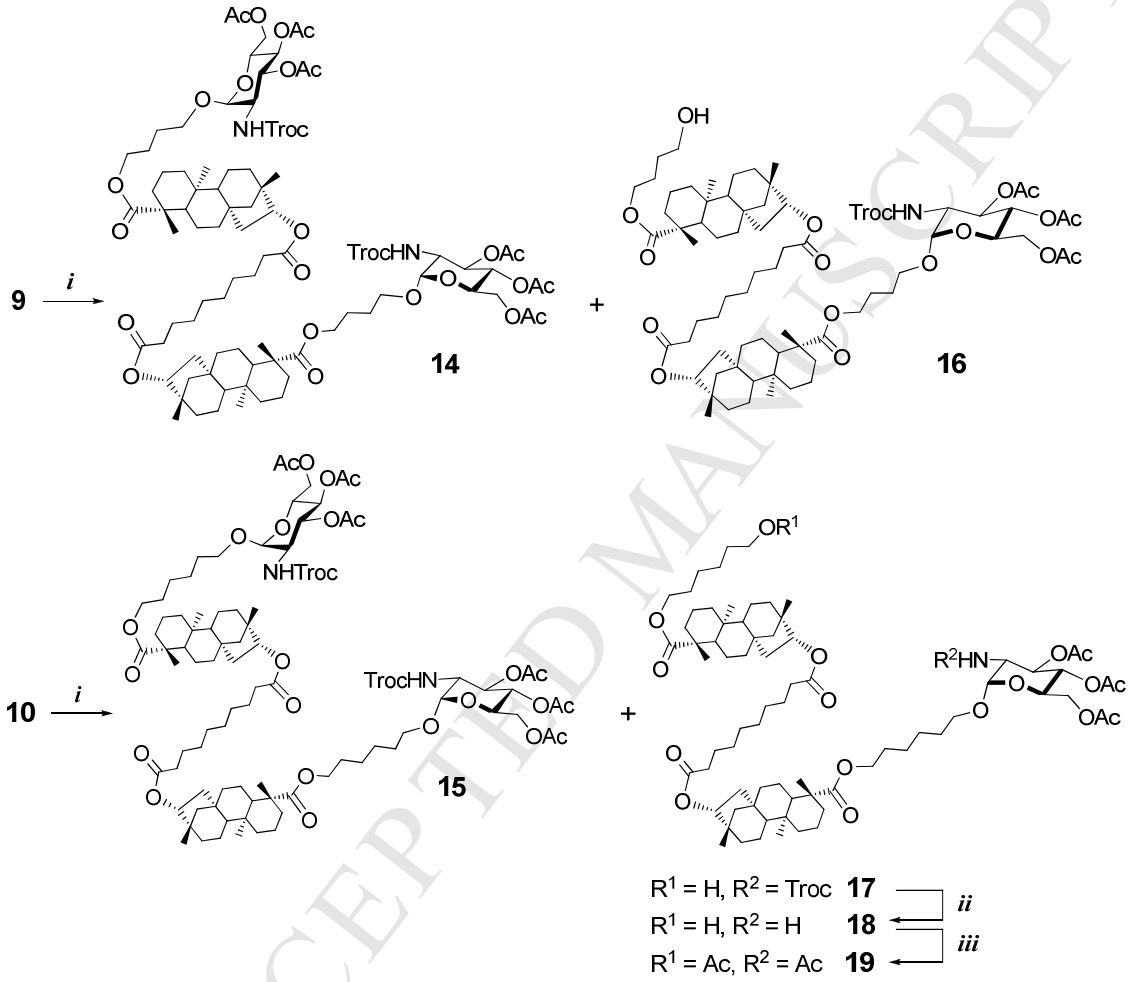
To prepare carbohydrate precursor **13** (Scheme 3), according to the known procedure,[10] the amine group of glucosamine hydrochloride **3** was protected by 2,2,2-trichloroethoxycarbonyl (Troc) group to give glucosamine derivative **11** which was per-*O*-acetylated, and then monosaccharide **12** 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]



Scheme 3. *Reagents and conditions*: (i) $NaHCO_3$, TrocCl, H_2O; (ii) Ac_2O, Py; (iii) 33% HBr, AcOH, CH_2Cl_2.

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 mixture by MALDI mass spectroscopy which revealed the peaks at 1436.9, $[M+Na]^+$ (calcd. 1436.7 $[M+Na]^+$ for $C_{73}H_{112}Cl_3NNaO_{19}$), and *m/z* 1452.9, $[M+K]^+$ (calcd. 1452.7 $[M+K]^+$ for $C_{73}H_{112}Cl_3KNO_{19}$). Glycoside **17** was obtained in 9% yield after flash chromatography. In contrast to diglycosides **14** and **15**, the ^1H NMR spectrum of glycoside **17** showed methylene protons of the terminal CH_2OH group as a triplet at 3.62 ppm with a coupling constant 6.8 Hz. The MALDI spectrum of glycoside **17** exhibited the peaks at *m/z* 1493.1, $[M+Na]^+$, and at *m/z* 1509.1, $[M+K]^+$ corresponding to molecular formulae $C_{77}H_{120}Cl_3NNaO_{19}$ and $C_{77}H_{120}Cl_3KNO_{19}$.

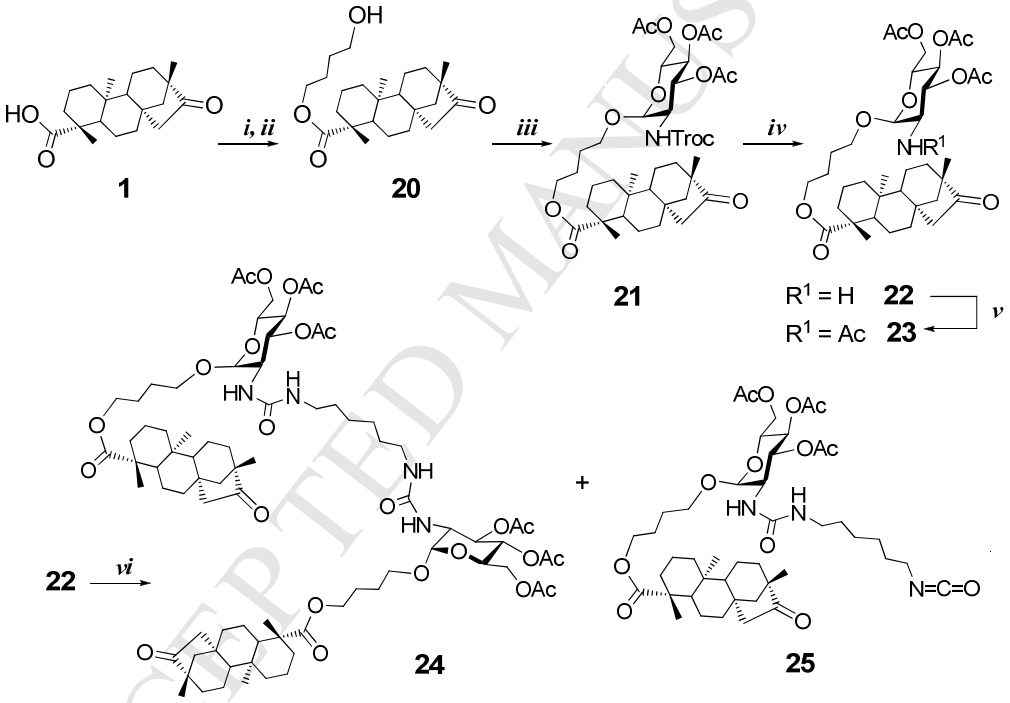


Scheme 4. *Reagents and conditions*: (i) bromide **13**, $ZnCl_2$, CH_2Cl_2; (ii) Zn, AcOH; (iii) Ac_2O, Et_3N, CH_2Cl_2

2.1.2. Synthesis of macrocyclic glycoterpenoids

For closing diglycosides **14** and **15** in target macrocycles it was necessary to remove Troc groups and then to bind the amine groups by a suitable linker. Previously, during the synthesis of macrocyclic derivatives of isosteviol by closing diacid **8** it was found that the yield of forming macrocycle appeared to depend on the length of a linker which have to bind the carboxylic groups of diacid **8**.[4f] The maximum yield was achieved by using 1,8-octanediol as a linker, that is, the length of a linker between two ester groups in the formed macrocycle should equal eight methylene groups.[4f] Therefore sebacic acid chloroanhydride and 1,6-diisocyanatohexane were chosen as linkers for macrocyclization of diglycosides **14** and **15**. Beforehand we tested macrocyclization of glucosamine residues with 1,6-diisocyanatohexane in glycoside **21** which was obtained from

ketoalcohol **20**[5d] in 40% yield (Scheme 5). As noted above, since $ZnCl_2$ was used as the catalytic activator of Koenigs-Knorr reaction, glycoside **21** had α-orientation of the glycoside bond. This followed from the anomeric proton signal in the ^{1}H NMR spectrum which appeared as a single doublet at 4.87 ppm with a vicinal coupling constant of 3.6 Hz. The amine group of glycoside **21** was deprotected by zinc dust in acetic acid[12] to provide free amine **22** which then was involved in the reaction with 1,6-diisocyanatohexane according to described procedure[14] which afforded diglycoside **24** in 13% yield, and glycoside **25** in 19% yield (Scheme 5). Following spectral data confirmed the formation of diglycoside **24**. Its MALDI spectrum showed peaks at *m/z* 1523.8, $[M+H]^+$, (calc. *m/z* 1523.9, $[M+H]^+$, $C_{80}H_{123}N_4O_{24}$), *m/z* 1545.6, $[M+Na]^+$, (calc. *m/z* 1545.8, $[M+Na]^+$, $C_{80}H_{122}N_4NaO_{24}$), and *m/z* 1561.6, $[M+K]^+$, (calc. *m/z* 1561.8, $[M+K]^+$, $C_{80}H_{122}KN_4O_{24}$). The IR spectrum of diglycoside **24** demonstrated absorption bands at 1561, 1641, 3367, 3412 cm^{-1} which are typical to ureic moieties. The ^{1}H NMR spectrun of diglycoside **24** indicated the presence of ureic protons as a doublet at 4.90 ppm with a coupling constant of 5.7 Hz, and a triplet at 5.24 ppm with a coupling constant of 5.7 Hz. The MALDI spectrum of glycoside **25** showed peaks at *m/z* 846.7, $[M+H]^+$, (calc. *m/z* 846.5, $[M+H]^+$, $C_{44}H_{68}N_3O_{13}$), *m/z* 868.7, $[M+Na]^+$, (calc. *m/z* 868.5, $[M+Na]^+$, $C_{44}H_{67}N_3NaO_{13}$), and *m/z* 884.7, $[M+K]^+$, (calc. *m/z* 884.4, $[M+K]^+$, $C_{44}H_{67}KN_3O_{13}$). The IR and ^{1}H NMR spectra of glycoside 25 were similar to the spectra of diglycoside **24**.



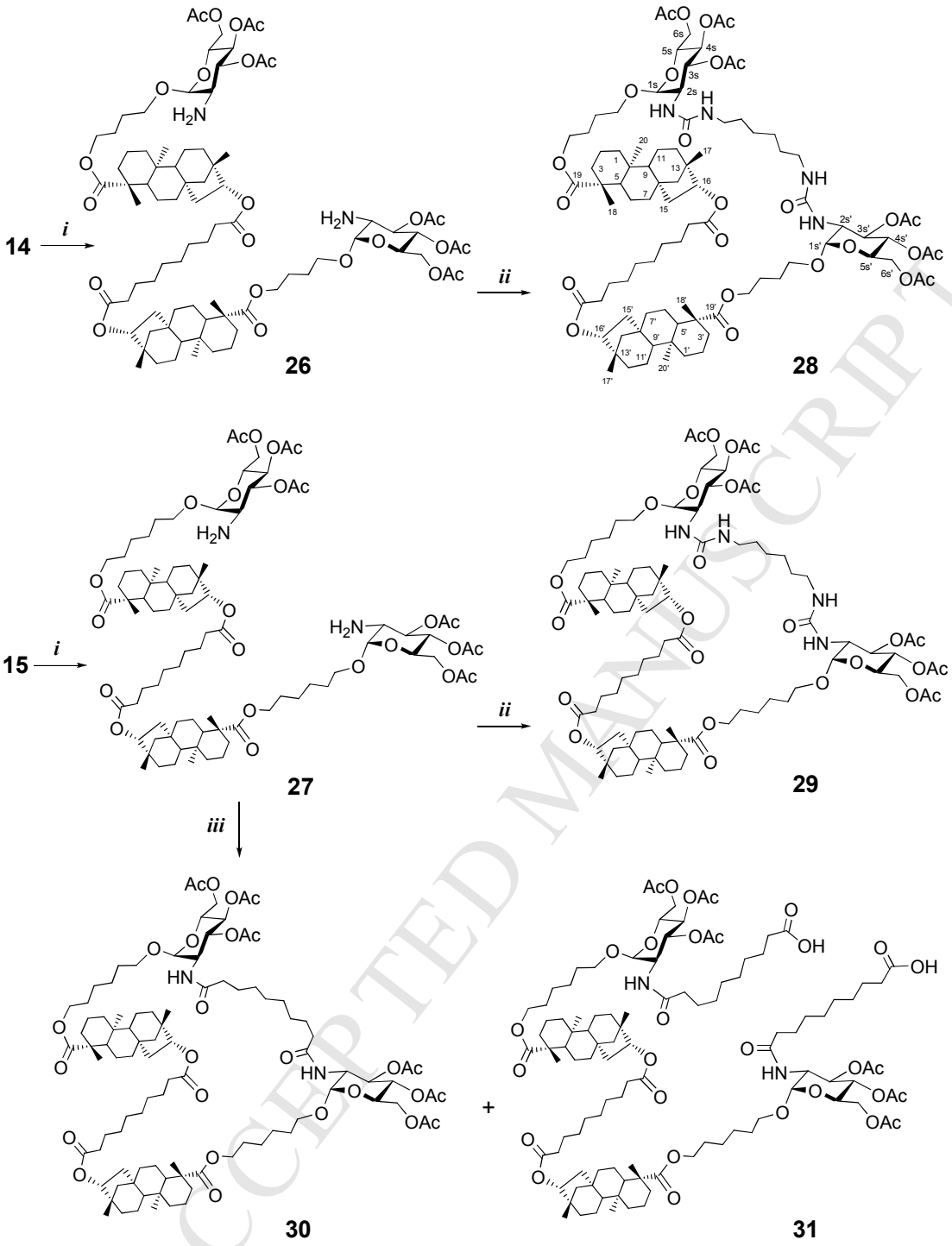
Scheme 5. *Reagents and conditions* (i) $SOCl_2$, 50 °C; (ii) $HO(CH_2)_nOH$, CH_2Cl_2; (iii) bromide **13**, $ZnCl_2$, CH_2Cl_2; (iv) Zn, AcOH; (v) Ac_2O, Et_3N, CH_2Cl_2; (vi) $OCN(CH_2)_6NCO$, CH_2Cl_2.

The tested approach to the macrocyclization of glucosamine residues with 1,6-diisocyanatohexane linker was then used for the synthesis of target macrocyclic glycoterpenoids. Troc protective groups in diglycosides **14** and **15** were removed by zinc dust in acetic acid[12] to give diamines **26** and **27** in good yields (96% and 87%). As a rule, free amines formed after removing Troc protective groups were used without further purification in next steps.[15] However, one of the diamines obtained, namely diamine **27**, has been isolated. Its MALDI spectrum showed peaks at *m/z* 1582.1, $[M+H]^+$, (calc. *m/z* 1582.0, $[M+H]^+$, $C_{86}H_{136}N_2O_{24}$), *m/z* 1604.1, $[M+Na]^+$, (calc. *m/z* 1603.9, $[M+Na]^+$, $C_{86}H_{136}N_2NaO_{24}$), and *m/z* 1620.1, $[M+K]^+$ (calc. *m/z* 1619.9, $[M+K]^+$, $C_{86}H_{136}KN_2O_{24}$). In the ^{1}H NMR spectrum of diamine **27** the anomeric protons resonated as a doublet at 4.85 ppm with a vicinal coupling constant of 3.2 Hz indicating α-orientation of the glycoside bonds. The reactions of diamines **26** and **27** with 1,6-diisocyanatohexane afforded the target macrocyclic glycoterpenoids

28 and **29** (Scheme 6) in 40% and 15% yields. The MALDI spectrum of macrocycle **28** showed peaks at *m/z* 1694.3, $[M+H]^+$, (calc. *m/z* 1694.0, $[M+H]^+$, $C_{90}H_{141}N_4O_{26}$), *m/z* 1716.3, $[M+Na]^+$, (calc. *m/z* 1716.0, $[M+Na]^+$, $C_{90}H_{140}N_4NaO_{26}$), and *m/z* 1732.2, $[M+K]^+$, (calc. *m/z* 1731.9, $[M+K]^+$, $C_{90}H_{140}KN_4O_{26}$). The MALDI spectrum of macrocycle **29** showed peaks at *m/z* 1750.7, $[M+H]^+$, (calc. *m/z* 1751.0, $[M+H]^+$, $C_{94}H_{149}N_4O_{26}$), and *m/z* 1772.7, $[M+Na]^+$, (calc. *m/z* 1773.0, $[M+Na]^+$, $C_{94}H_{148}N_4NaO_{26}$). The ^{1}H NMR spectra of macrocycles **28** and **29** displaed the methylene protons of the ureidic moieties $NHC(O)NHCH_2$ as multiplets at 3.02-3.24 ppm, and ureidic moieties own protons appeared as dublets at 4.92 ppm (^3J = 10 Hz) and 4.96 ppm (^3J = 10 Hz), as well as multiplets at 5.40-5.47 ppm and 5.21-5.30 ppm. Diglycoside **27** was also involved in the reaction with sebacic acid chloroanhydride to give macrocyclic glycoterpenoid **30** in 23% yield (Scheme 6). The MALDI spectrum of macrocycle **30** showed peaks at *m/z* 1771.1, $[M+Na]^+$, (calc. *m/z* 1771.0, $[M+Na]^+$, $C_{96}H_{150}N_2NaO_{26}$), and 1787.1, $[M+K]^+$, (calc. *m/z* 1787.0, $[M+K]^+$, $C_{96}H_{150}KN_2O_{26}$). The ^{1}H NMR spectrum of macrocycle **30** showed the amidic protons as a doublet at 5.82 ppm with a vicinal constant of 9.3 Hz. The anomeric protons of macrocyclic glycoterpenoids **28**-**30** resonated as dublets at 4.83, 4.84, 4.83 ppm with coupling constants 3.4, 3.5, 3.6 Hz, respectively, that confirmed α-orientation of the glycoside bonds. It is to be noted that diacid **31** was formed simultaneously with macrocycle **30** and was isolated in 20% yield after column chromatography. The MALDI spectrum of glycoterpenoid **31** showed peaks at *m/z* 1973.2, $[M+Na]^+$, (calc. *m/z* 1973.2, $[M+Na]^+$, $C_{106}H_{168}N_2O_{30}Na$), and *m/z* 1989.3 $[M+K]^+$, (calc. *m/z* 1989.1, $C_{106}H_{168}N_2O_{30}K$).

2.2. Antituberculosis activity

Since both glucosamine[16] and isosteviol[17] included in the target macrocyclic glycoterpenoids **28**-**30** are biologically active molecules, there is no doubt that macrocycles **28**-**30** should have also a broad spectrum of biological activity. As we have previously studied the ability of some glycoterpenoids based on isosteviol and trehalose **32**-**34**,[5d] as well as glucuronic acid **35**, **36**[5e] (Fig. 1) to inhibit the in vitro growth of *M. tuberculosis* H37Rv,[5d,e] the target macrocyclic glycoterpenoids **28**-**30** as well as some of their precursors **19**, **23**, **24**, and byproduct **31** were also screened against *M. tuberculosis* H37Rv. The obtained values of minimum inhibitory concentration (MIC) are presented in Table 1. To analyse the data obtained, MIC values found for isosteviol **1**,[9] diacid **8**,[9] glycoconjugates of isosteviol and trehalose **32**-**34**,[5d] glycocnjugates of isosteviol and glucuronic acid **35**, **36**,[5e] 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-glucopyranose **37,**[21] as well as antitubercular drugs isoniazid and pyrazinamide are also presented in Table 1. The comparison of MIC values indicates that antituberculosis activity of target macrocycles **28**-**30**, their precursors **19**, **24**, and diglycoside **31** is almost the same. Macrocyclic glycoterpenoids **34**[5d] and **36**,[5e] as well as their precursors **32**[5d] and **35**[5e] showed a similar activity. One can see that antituberculosis activities of isosteviol glycoconjugates **19**, **24**, **28**-**32**, **34**-**36** are 19-13-fold lower than the activity of antitubercular drug isoniazid in control experiments, but, at the same time, these compounds appeared to be 8-17-fold better inhibitors than antitubercular drug pyrazinamide whose MIC equals 101.5 μM.[18] Several important conclusions can be drawn from an examination of Table 1. Firstly, the binding of two molecules of isosteviol **1** (MIC 157 μM) with 1,8-octanedioate linker increases its antituberculosis activity by 2.5 times (MIC for diacid **8** equals 62 μM). The functionalization of isosteviol **1** with 3,4,6-tri-*O*-acetyl-glucosamine moiety increases its antituberculosis activity by 9 times (MIC for glycoside **23** equals 17.4 μM). The functionalization of isosteviol **1** with several 3,4,6-tri-*O*-acetyl-glucosamine moieties increases its antituberculosis activity already by 22 times. This is another confirmation of the known fact that glycosylation of bioactive compounds enhances their activity.[19] By the way, the antituberculosis activity of glucosamine itself, or rather, its derivative **37** (MIC 16.2 μM), was not changed after it had been coupled with isosteviol to afford glycoside **23** (MIC 17.4 μM). Secondly, the antituberculosis activity of macrocyclic glycoterpenoids investigated does not depend on the presence (or absence) of nitrogen-containig functional groups. Thus MIC values for nitrogen-containig macrocyclic



Scheme 6. *Reagents and conditions* (i) Zn, AcOH; (ii) $OCN(CH_2)_6NCO$, CH_2Cl_2 (iii) $ClOC(CH_2)_8COCl$, CH_2Cl_2.

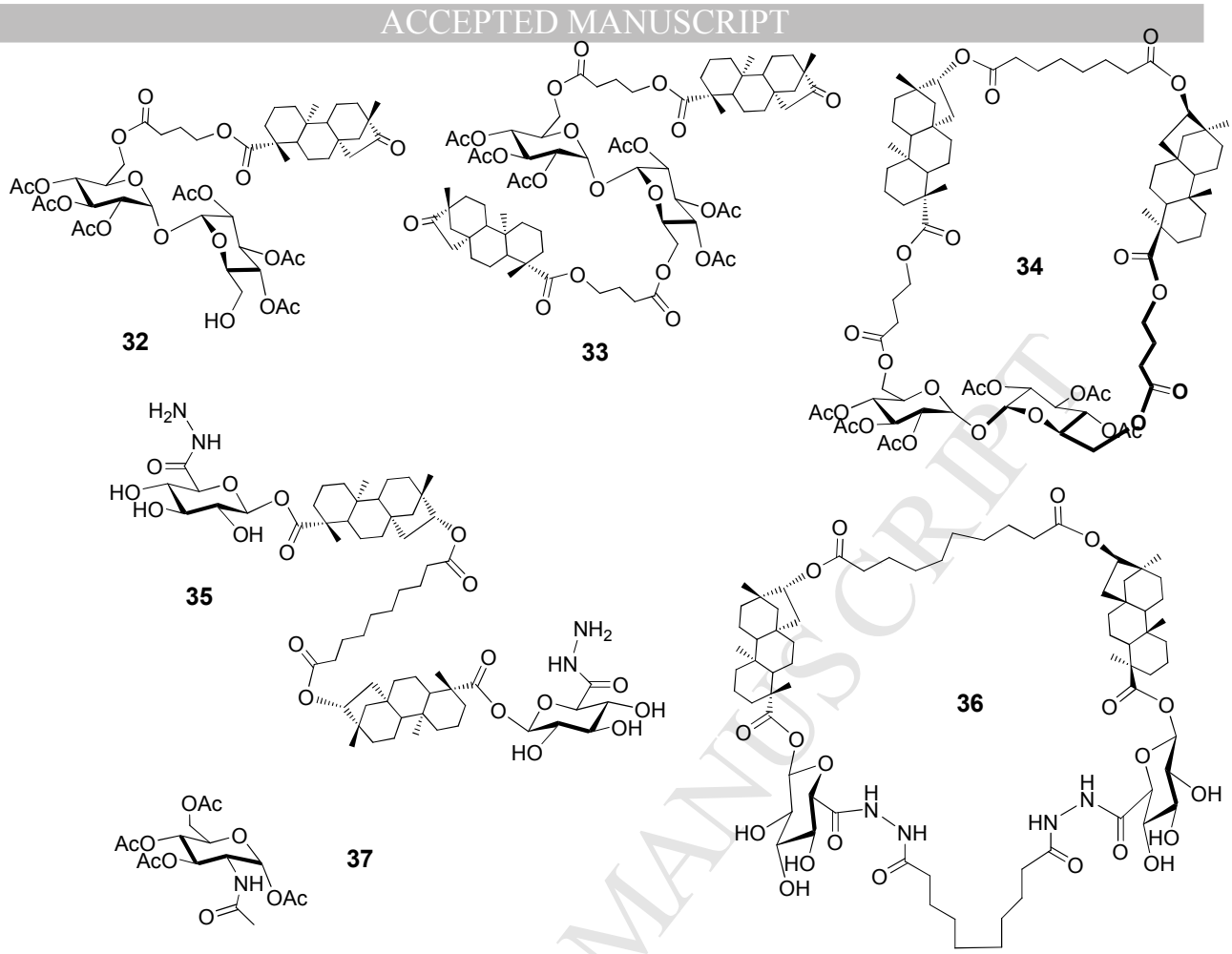


Fig. 1. Glycoterpenoids which have already been synthesized and have been subjected to biological evaluation as antituberculosis agents.[5d,e]

Table 1
In vitro inhibitory activities against the growth of *M. tuberculosis* H37Rv

Compound	MIC (μM)	Compound	MIC (μM)
1	157.0[9]	**31**	6.4
8	62.0[9]	**32**	12.7[5d]
19	9.1	**33**	0.3[5d]
23	17.4	**34**	8.3[5d]
24	8.2	**35**	10.5[5e]
28	7.4	**36**	9.2[5e]
29	7.1	**37**	16.2
30	7.2	pyrazinamide	101.5[10]
		isoniazid	0.7

glycoterpenoids **28**-**30**, **36** and the MIC value for macrocyclic glycoterpenoid **34** which has no nitrogen atoms are almost the same. The striking conclusion that has been already marked[5d] is that

glycoconjugate of trehalose and isosteviol **33** which has no nitrogen atoms showed the same antituberculosis activity as antitubercular drug isoniazid in control experiment. This is all the more surprising that both isosteviol **1**,[9] and trehalose[20] are poor inhibitors of the growth of *M. tuberculosis* H37Rv.[9,20] Of course, this unexpected finding requires a careful study.

3. Conclusions

We have proposed for the first time a synthetic approach to macrocyclic glycoterpenoids containing glucosamine and isosteviol moieties. The target macrocycles **28**-**30** as well as some of their precursors **19**, **23**, **24** were examined for the ability to inhibit the in vitro growth of *M. tuberculosis* H37Rv. All compounds tested showed moderate tuberculostatic activity. MIC values for them were within range of 6.4-17.4 μM while MIC value for antitubercular drug isoniazid (reference compound in experiment) was 0.7 μM.

4. Experimental

4.1. Chemistry

4.1.1. General

NMR experiments were carried out with Avance-400 or Avance-500 (Bruker) spectrometers in $CDCl_3$ at 400 or 500 MHz at 30 ºC. 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). IR spectra of the compounds **24**, **25** were recorded with Bruker Vector-22 Fourier spectrometer in the wavenumber range from 400 to 4000 cm^{-1}. Melting points of substances were determined on a BOETIUS compact heating table. Optical rotations were determined on a Perkin-Elmer 341 polarimeter (concentration *c* is given as g/100 mL) (PerkinElmer, Inc, USA) at 20 °C, λ = 589 nm. The completeness of the reactions 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 ºC. The isolation of individual substances **19**, **21**, **23-25**, **28**, **29**–**31** was performed with a flash chromatography on Silicagel KSKG (< 0.063 mm, Crom-Lab Ltd, Russia). All solvents were dried according to standard protocols. Isosteviol **1**,[7] dihydroisosteviol **7**,[8] diacid **8**,[4a,9] diols **9, 10**,[5d] compounds **13**,[10] **20,**[5d] and **37**[21] were prepared according to the literature.[4a,5d,7,8,9,10,21] The physicochemical properties of these compounds agreed with those published. Sweetener Sweta was obtained from Stevian Biotechnology Corporation Sdn Bhd (Malaysia), glucosamine hydrochloride **3** were purchased from abcr GmbH&Co.

4.1.2. Synthesis of compounds

*4.1.2.1. General procedure for the synthesis of diglycosides (**14**-**17**)*

$ZnCl_2$ (2 equiv) was added to a solution of diol **9** or **10** (1 equiv) and bromide **13** (2.2-2.5 equiv) in CH_2Cl_2 under argon. The reaction mixture was stirred for 15 h at room temperature, then 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 (hexane/EtOAc = 5/1).

*4.1.2.1.1. Bis{19-[3',4',6'-tri-O-acetyl-2'-deoxy-2'-(2",2",2"-trichloroethoxycarbonyl)amino-α-D-glucopyranosyl-oxybutyl-4-oxycarbonyl]-ent-beyeran-16-yl}-1,8-octanedioat (**14**)*

This compound was prepared as a white foam in 20% yield (0.37 g). $[\alpha]_D^{20}$ +22.2 (*c* 1.40, CH_2Cl_2); Anal. Calcd for $C_{88}H_{130}Cl_6N_2O_{28}$: C, 56.32; H, 6.98; Cl, 11.33; N, 1.49. Found: C, 56.44; H, 6.97; Cl, 11.37; N, 1.49; ^{1}H NMR (400 MHz, $CDCI_3$): δ 0.70 (s, 6H, $C^{20}H_3$, $C^{20'}H_3$), 0.90 (s, 6H, $C^{17}H_3$, $C^{17'}H_3$), 1.18 (s, 6H, $C^{18}H_3$, $C^{18'}H_3$), 0.83–1.89 (m, 58H, *ent*-beyerane skeleton, two $(CH_2)_2$ linkers and $(CH_2)_6$ linker), 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, $C^{1s}OCH_2$, $C^{1s'}OCH_2$), 3.70–3.78 (m, 2H, $C^{1s}OCH_2$, $C^{1s'}OCH_2$), 3.93–4.01 (m, 4H, H-5s, H-5s', H-2s, H-2s'), 4.03–4.17 (m, 6H, H-6s, H-6s', $C^{19}(O)OCH_2$, $C^{19'}(O)OCH_2$), 4.27 (dd, 2H, *J* = 12.4, 4.6 Hz, H-6s, H-6s'), 4.64 (d, 2H, *J* = 12.1 Hz, 2 OCH_2CCl_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, 2 OCH_2CCl_3), 4.89 (d, 2H, *J* = 3.4 Hz, H-1s, H-1s'), 5.10 (t, 2H, *J* = 9.9 Hz, H-4s, H-4s'), 5.24 (t, 2H, *J* = 9.9 Hz, H-3s, H-3s'), 5.29 (d, 2H, *J* = 9.8 Hz, 2 NH) ppm; MALDI-TOF MS *m/z* calcd for $C_{88}H_{130}Cl_6N_2O_{28}Na$ $[M+Na]^+$ 1899.7, found 1899.5; calcd for $C_{88}H_{130}Cl_6N_2O_{28}K$ $[M+K]^+$ 1915.6, found 1915.6.

*4.1.2.1.2. Bis{19-[3',4',6'-tri-O-acetyl-2'-deoxy-2'-(2",2",2"-trichloroethoxycarbonyl)amino-α-D-glucopyranosyl-oxyhexyl-6-oxycarbonyl]-ent-beyeran-16-yl}-1,8-octanedioat (**15**)*

This compound was prepared as a white foam in 22% yield (0.52 g). $[\alpha]_D^{20}$ +17.7 (*c* 2.05, CH_2Cl_2); Anal. Calcd for $C_{92}H_{138}Cl_6N_2O_{28}$: C, 57.17; H, 7.20; Cl, 11.01; N, 1.45. Found: C, 57.14; H, 7.19; Cl, 11.03; N, 1.44; ^{1}H NMR (400 MHz, $CDCl_3$): δ 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*-beyerane skeleton, two $(CH_2)_4$ linkers and $(CH_2)_6$ linker), 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, $C^{1s}OCH_2$, $C^{1s'}OCH_2$), 3.65–3.73 (m, 2H, $C^{1s}OCH_2$, $C^{1s'}OCH_2$), 3.90–3.99 (m, 4H, H-5s, H-5s', H-2s, H-2s'), 4.00–4.15 (m, 6H, H-6s, H-6s', $C^{19}(O)OCH_2$, $C^{19'}(O)OCH_2$), 4.26 (dd, 2H, *J* = 12.3, 4.6 Hz, H-6s, H-6s'), 4.64 (d, 2H, *J* = 12.1 Hz, 2 OCH_2CCl_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, 2 OCH_2CCl_3), 4.87 (d, 2H, *J* = 3.5 Hz, H-1s, H-1s'), 5.09 (t, 2H, *J* = 9.8 Hz, H-4s, H-4s'), 5.24 (t, 2H, *J* = 9.8 Hz, H-3s, H-3s'), 5.37 (d, 2H, *J* = 9.9 Hz, 2 NH) ppm; MALDI-TOF MS *m/z* calcd for $C_{92}H_{138}Cl_6N_2O_{28}Na$ $[M+Na]^+$ 1955.7, found 1955.7; calcd for $C_{92}H_{138}Cl_6N_2O_{28}K$ $[M+K]^+$ 1971.7, found 1971.7.

*4.1.2.1.3. O-{19-[3',4',6'-tri-O-acetyl-2'-deoxy-2'-(2",2",2"-trichloroethoxycarbonyl)amino-α-D-glucopyranosyl-oxyhexyl-6-oxycarbonyl]-ent-beyeran-16-yl}-O'-[19-(6'-hydroxyhexyloxycarbonyl)-ent-beyeran-16-yl]-1,8-octanedioat (**17**)*

This compouns was prepared as a white foam in 9% yield (0.16 g). $[\alpha]_D^{20}$ -2.3 (*c* 0.75, CH_2Cl_2); Anal. Calcd for $C_{77}H_{120}Cl_3NO_{19}$: C, 62.91; H, 8.23; Cl, 7.23; N, 0.95. Found: C, 62.95; H, 8.21; Cl, 7.25; N, 0.94; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.70 (s, 6H, $C^{20}H_3$, $C^{20'}H_3$), 0.89 (s, 3H, $C^{17}H_3$), 0.90 (s, 3H, $C^{17'}H_3$), 1.15 (s, 3H, $C^{18}H_3$), 1.16 (s, 3H, $C^{18'}H_3$), 0.82–1.90 (m, 66H, *ent*-beyerane skeleton, two $(CH_2)_4$ linkers, and $(CH_2)_6$ linker), 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, $C^{1s}OCH_2$), 3.62 (t, 2H, *J* = 6.8 Hz, $C^{19}OC(O)(CH_2)_5CH_2OH$), 3.66–3.74 (m, 1H, $C^{1s}OCH_2$), 3.91–4.15 (m, 7H, H-2s, H-5s, H-6s, $C^{19}(O)OCH_2$, $C^{19'}(O)OCH_2$), 4.26 (dd, 1H, *J* = 12.4, 4.5 Hz, H-6s), 4.62–4.73 (m, 3H, OCH_2CCl_3, $C^{16}H$, $C^{16'}H$), 4.80 (d, 1H, *J* = 12.2 Hz, OCH_2CCl_3), 4.88 (d, 1H, *J* = 3.6 Hz, H-1s), 5.10 (t, 1H, *J* = 9.6 Hz, H-4s), 5.25 (t, 1H, *J* = 9.9 Hz, H-3s), 5.39 (d, 1 H, *J* = 9.7 Hz, NH) ppm; MALDI-TOF MS *m/z* calcd for $C_{77}H_{120}Cl_3NO_{19}Na$ $[M+Na]^+$ 1492.7, found 1493.1; calcd. for $C_{77}H_{120}Cl_3NO_{19}K$ $[M+K]^+$ 1508.7, found 1509.1.

*4.1.2.2. O-{19-[3',4',6'-tri-O-acetyl-2'-deoxy-2'-acetamido-α-D-glucopyranosyl-oxyhexyl-6-oxycarbonyl]-ent-beyeran-16-yl}-O'-[19-(6'-acetoxyhexyloxycarbonyl)-ent-beyeran-16-yl]-1,8-octanedioat (**19**)*

To a solution of monoglycoside **17** (0.12 g, 0.08 mmol) in AcOH (6 mL) Zn powdered (0.048 g, 0.8 mmol) was added under argon. The reaction mixture was stirred for 3 h at room temperature, then was concentrated under reduced pressure. The residue diluted with CH_2Cl_2, washed with 5% $NaHCO_3$ and water and brine, dried over Na_2SO_4, and concentrated under reduced pressure to give glicoside **18** (0.1 g, 95 %) which was used without further purification in the next step.

Glycoside **18** 0.10 g (0.08 mmol) was dissolved in CH_2Cl_2 (6 mL), then Et_3N (0.068 mL, 0.49 mmol) and Ac_2O (1 mL, 7.7 mmol) were added. The reaction mixture was stirred for 2 h at room temperature, then diluted with CH_2Cl_2, washed with sat. $NaHCO_3$ and 1.0 M HCl, dried over Na_2SO_4, and concentrated under reduced pressure. Silica gel flash chromatography (eluent – hexane/EtOAc = 5/1) of the residue afforded compound **19** in 57% yield (0.06 g) as a colourless oil. $[\alpha]_D^{20}$ +10.2 (*c* 1.00, CH_2Cl_2); Anal. Calcd for $C_{78}H_{123}NO_{19}$: C, 67.95; H, 8.99; N, 1.02. Found: C, 67.91; H, 8.96; N, 1.03; ^{1}H NMR (400 MHz, $CDCI_3$): δ 0.70 (s, 6H, $C^{20}H_3$, $C^{20'}H_3$), 0.90 (s, 6H, $C^{17}H_3$, $C^{17'}H_3$), 1.15, 1.16 (2s, 6H, $C^{18}H_3$, $C^{18'}H_3$), 0.78 - 1.90 (m, 66 H, *ent*-beyerane skeleton, two $(CH_2)_4$ linkers, and $(CH_2)_6$ linker), 1.95 (s, 3H, CH_3CO, $C'H_3CO$), 2.01 (s, 3H, CH_3CO, $C'H_3CO$), 2.03 (s, 3H, CH_3CO, $C'H_3CO$), 2.04 (s, 3H, CH_3CO, $C'H_3CO$), 2.09 (s, 3H, CH_3CO, $C'H_3CO$), 2.15 (d, 2H, *J* = 13.1 Hz, C^3H_{eq}, $C^{3'}H_{eq}$), 2.30 (td, *J* = 7.4, 2.4 Hz, 4H, $C^{16}OC(O)CH_2$, $C^{16'}OC(O)CH_2$), 3.39–3.49 (m, 2H, $C^{1s}OCH_2$, $C^{1s'}OCH_2$), 3.61–3.71 (m, 2H, $C^{1s}OCH_2$, $C^{1s'}OCH_2$), 3.91–4.14 (m, 6H, H-5s, H-6s, $C^{19}(O)OCH_2$, $C^{19'}(O)OCH_2$), 4.24 (dd, 1H, *J* = 12.3, 4.5 Hz, H-6s), 4.32–4.37 (m, 1H, H-2s), 4.71 (td, 2H, *J* = 9.8, 4.4 Hz, $C^{16}H$, $C^{16'}H$), 4.83 (d, 1H, *J* = 3.6 Hz, H-1s), 5.11 (t, 1H, *J* = 9.5 Hz, H-4s), 5.21 (t, 1H, *J* = 9.5 Hz, H-3s), 5.78 (d, 1H, *J* = 9.5 Hz, NH) ppm; MALDI-TOF MS *m/z* calcd for $C_{78}H_{123}NO_{19}Na$ $[M+Na]^+$ 1400.9, found 1400.9; calcd for $C_{78}H_{123}NO_{19}K$ $[M+K]^+$ 1416.8, found 1416.9.

*4.1.2.3. 4-[3',4',6'-tri-O-acetyl-2'-deoxy-2'-(2",2",2"-trichloroethoxycarbonyl)amino-α-D-glucopyranosyl]-butyl-16-oxo-ent-beyeran-19-oat (**21**)*

To a solution of ketoalcohol **20** (0.40 g, 1.02 mmol) and bromide **13** (0.71 g, 1.30 mmol) in CH_2Cl_2 (15 mL) $ZnCl_2$ (0.21 g, 1.54 mmol) was added under argon. The reaction mixture was stirred for 30 h at room temperature, then 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 (hexane/EtOAc = 3/1) to give glycoside **21** in 58% yield (0,47 g) as a colourless oil. $[\alpha]_D^{20}$ +1.0 (*c* 0.47, CH_2Cl_2); Anal. Calcd for $C_{39}H_{56}Cl_3NO_{13}$: C, 54.90; Cl, 12.47; H, 6.62; N, 1.64. Found: C, 55.11; Cl, 12.52; H, 6.59; N, 1.63; ^{1}H NMR (400 MHz, $CDCI_3$): δ 0.69 (s, 3H, $C^{20}H_3$), 0.94 (s, 3H, $C^{17}H_3$), 1.18 (s, 3H, $C^{18}H_3$), 0.80–1.90 (m, 22H, *ent*-beyerane skeleton and $(CH_2)_2$ linker), 1.97 (s, 3H, CH_3CO), 2.00 (s, 3H, CH_3CO), 2.06 (s, 3H, CH_3CO), 2.16 (d, 1H, C^3H_{eq}, *J* = 13.3 Hz), 2.59 (dd, 1H, C^{15} H_α, *J* = 18.6, 3.7 Hz), 3.42–3.49 (m, 1H, $C^{1s}OCH_2$), 3.68–3.75 (m, 1H, $C^{1s}OCH_2$), 3.89-3.95 (m, 1H, H-5s), 3.99 – 4.10 (m, 4H, H-6s, H-2s, $C^{19}(O)OCH_2$), 4.24 (dd, 1H, H-6s, *J* = 12.3, 4.5 Hz), 4.63 (d, 1H, OCH_2CCl_3, *J* = 12.1 Hz), 4.76 (d, 1H, OCH_2CCl_3, *J* = 12.1 Hz), 4.87 (d, 1H, H-1s, *J* = 3.6 Hz), 5.07 (t, 1H, H-4s, *J* = 9.8 Hz), 5.21 (t, 1H, H-3s, *J* = 9.7 Hz), 5.27 (d, 1H, NH, *J* = 9.7 Hz) ppm; MALDI-TOF MS *m/z* calcd for $C_{39}H_{56}Cl_3NO_{13}Na$ $[M+Na]^+$ 876.3, found 876.4; calcd for $C_{39}H_{56}Cl_3NO_{13}K$ $[M+K]^+$ 892.2, found 892.4.

*4.1.2.4. 4-(3',4',6'-tri-O-acetyl-2'-deoxy-2'-amino-α-D-glucopyranosyl)-butyl-16-oxo-ent-beyeran-19-oat (**22**)*

To a solution of glycoside **21** (0.47 g, 0.55 mmol) in AcOH (12 mL) Zn powdered (1.2 g, 18 mmol) was added under argon. The reaction mixture was stirred for 1 h at room temperature, then was concentrated under reduced pressure. The residue diluted with CH_2Cl_2, washed with saturated solution $NaHCO_3$, dried over Na_2SO_4, and concentrated under reduced pressure to give glycoside **22** in 92% yield (0.34 g) as a colourless oil. Anal. Calcd for $C_{36}H_{55}NO_{11}$: C. 63.79; H, 8.18; N, 2.07. Found: C, 63.44; H, 8.21; N, 2.05. ^{1}H NMR (400 MHz, $CDCI_3$): δ 0.71 (s, 3H, $C^{20}H_3$), 0.97 (s, 3H, $C^{17}H_3$), 1.20 (s, 3H, $C^{18}H_3$), 0.83–1.96 (m, 22H, *ent*-beyerane skeleton and $(CH_2)_2$ linker), 2.01 (s, 3H, CH_3CO), 2.07 (s, 3H, CH_3CO), 2.08 (s, 3H, CH_3CO), 2.19 (d, 1H, C^3H_{eq}, *J* = 13.2 Hz), 2.61 (dd, 1H, $C^{15}H_\alpha$, *J* = 18.5, 3.7 Hz), 2.93 (dd, 1H, H-2s, *J* = 10.2, 3.6 Hz), 3.43–3.52 (m, 1H, $C^{1s}OCH_2$), 3.71–3.79 (m, 1H, $C^{1s}OCH_2$), 3.92–3.99 (m, 1H, H-5s), 4.00–4.13 (m, 3H, H-6s, $C^{19}(O)OCH_2$), 4.28 (dd, 1H, H-6s, *J* = 12.2, 4.6 Hz), 4.86 (d, 1H, H-1s, *J* = 3.6 Hz), 4.95 (t, 1H, H-4s, *J* = 9.8 Hz,), 5.11 (t, 1H, H-3s, *J* = 9.8 Hz) ppm; MALDI-TOF MS *m/z* calcd for $C_{36}H_{56}NO_{11}$ $[M+H]^+$ 678.4; found 678.4; calcd for $C_{36}H_{55}NO_{11}Na$ $[M+Na]^+$ 700.4; found 700.4.

*4.1.2.5. 4-[3',4',6'-tri-O-acetyl-2'-deoxy-2'-acetamido-α-D-glucopyranosyl]-butyl-16-oxo-ent-beyeran-19-oat (**23**)*

The mixture of Et_3N (0.16 mL, 1.16 mmol) and Ac_2O (2.4 mL, 18.29 mmol) was added to a solution of amine **22** (0.13 g, 0.19 mmol) in CH_2Cl_2 (5 mL) under argon. The reaction mixture was stirred for 2 h at room temperature, then diluted with CH_2Cl_2, washed with sat. $NaHCO_3$ and 1.0 M HCl, dried over Na_2SO_4, and concentrated under reduced pressure. Silica gel flash chromatography (hexane/EtOAc = 1/1) of the residue afforded glycoside **23** in 73% yield (0.10 g) as a colorless oil. $[\alpha]_D^{20}$ +16.4 (*c* 0.65, CH_2Cl_2); Anal. Calcd for $C_{38}H_{57}NO_{12}$: C, 63.40; H, 7.98; N, 1.95. Found: C, 63.54; H, 7.95; N, 1.96.01; ^{1}H NMR (400 MHz, $CDCI_3$) : δ 0.72 (s, 3H, $C^{20}H_3$), 0.97 (s, 3H, $C^{17}H_3$), 1.21 (s, 3H, $C^{18}H_3$), 0.86–1.93 (m, 22H, *ent*-beyerane skeleton and $(CH_2)_2$ linker), 1.96 (s, 3H, CH_3CO), 2.01 (s, 3H, CH_3CO), 2.02 (s, 3H, CH_3CO), 2.09 (s, 3H, CH_3CO), 2.19 (d, 1H, C^3H_{eq}, *J* = 13.2 Hz), 2.63 (dd, 1H, $C^{15}H_\alpha$, *J* = 18.5, 3.7 Hz), 3.41–3.49 (m, 1H, $C^{1s}OCH_2$), 3.70–3.78 (m, 1H, $C^{1s}OCH_2$), 3.88–3.94 (m, 1H, H-5s), 4.01–4.15 (m, 3H, H-6s, $C^{19}(O)OCH_2$), 4.24 (dd, 1H, H-6s, *J* = 12.3, 4.5 Hz), 4.31–4.38 (m, 1H, H-2s), 4.84 (d, 1H, H-1s, *J* = 3.6 Hz), 5.11 (t, 1H, H-4s, *J* = 9.7 Hz,), 5.19 (t, 1H, H=3s, *J* = 9.8 Hz), 5.83 (d, 1H, NH, *J* = 9.4 Hz) ppm; MALDI-TOF MS *m/z* calcd for $C_{38}H_{57}NO_{12}Na$ $[M+Na]^+$ 742.4, found 742.3; calcd for $C_{38}H_{57}NO_{12}K$ $[M+K]^+$ 758.4, found 758.3.

*4.1.2.6. The synthesis of compounds (**24**) and (**25**)*

A solution of 1,6-diisocyanatohexane (0.024 g, 0.14 mmol) in CH_2Cl_2 (1 mL) was added in portions during 1 h to a solution of amine **22** (0.21 g, 0.29 mmol) in CH_2Cl_2 (10 mL) under argon. The reaction mixture was stirred for 40 h at room temperature, then washed with water, and dried over Na_2SO_4. The residue was purified by silica gel flash chromatography (hexane/EtOAc = 5/1) to give diglycoside **24** and glycoside **25**.

*4.1.2.6.1. 1,6-Bis[2'-(16"-oxo-ent-beyeran-19"-carboxybutyl-6"'-oxy)-4',5'-diacetoxy-6'-methylacetoxy-tetrahydropyran-3'-ureidyl]hexane (**24**)*

This compound was prepared in 13% yield (0.06 g) as a colorless oil. $[\alpha]_D^{20}$ +27.7 (*c* 1.95, CH_2Cl_2); Anal. Calcd for $C_{80}H_{122}N_4O_{24}$: C, 63.06; H, 8.07; N, 3.68. Found: C, 63.27; H, 8.05; N, 3.70; IR (film); ν 1561, 1641 [NHC(O)], 1726 [C(O)O], 1746 [$CH_3C(O)O$], 3367, 3412 см$^{-1}$ (NH); ^{1}H NMR (400 MHz, $CDCI_3$) : δ 0.72 (s, 6H, $C^{20}H_3$, $C^{20'}H_3$), 0.97 (s, 6H, $C^{17}H_3$, $C^{17'}H_3$), 1.21 (s, 6H, $C^{18}H_3$, $C^{18'}H_3$), 0.87–1.90 [m, 52H, *ent*-beyerane skeleton, two $(CH_2)_2$ linkers, and $(CH_2)_4$ linker), 1.99 (s, 6H, CH_3CO, $C'H_3CO$), 2.00 (s, 6H, CH_3CO, $C'H_3CO$), 2.08 (s, 6H, CH_3CO, $C'H_3CO$), 2.16 (d, 2H, C^3H_{eq}, $C^{3'}H_{eq}$, *J* = 13.1 Hz), 2.64 (dd, 2H, C^{15} H_α, $C^{15'}$ H_α, *J* = 18.5, 3.5 Hz), 3.00–3.21 (m, 4H, $2C(O)NHCH_2$), 3.36–3.45 (m, 2H, $C^{1s}OCH_2$, $C^{1s'}OCH_2$), 3.73–3.82 (m, 2H, $C^{1s}OCH_2$, $C^{1s'}OCH_2$), 3.87–3.95 (m, 2H, H-2s, H-2s'), 4.04–4.26 (m, 10H, 2H-6s, 2H-6s', H-5s, H-5s', $C^{19}(O)OCH_2$, $C^{19'}(O)OCH_2$), 4.82 (d, 2H H-1s, H-1s', *J* = 3.5 Hz), 4.90 (d, 2H 2 NHC(O), *J* = 9.9 Hz), 5.05–5.19 (m, 4H, H-4s, H-4s', H-3s, H-3s'), 5.24 (t, 2H, 2 $C(O)NHCH_2$ *J* = 5.7 Hz) ppm; MALDI-TOF MS *m/z* calcd for $C_{80}H_{123}N_4O_{24}$ $[M+H]^+$ 1523.9, found 1523.8; calcd for $C_{80}H_{122}N_4O_{24}Na$ $[M+Na]^+$ 1545.8, found 1545.6; calcd for $C_{80}H_{122}N_4O_{24}K$ $[M+K]^+$ 1561.8, found 1561.6.

*4.1.2.6.2. 4'-[3",4",6"-tri-O-acetyl-2"-deoxy-2"-(ureidyl-6"'-isocyanatohexane)-α-D-glucopyranosyl]-butyl-16-oxo-ent-beyeran-19-oat (**25**)*

This compound was prepared in 19% yield (0.005 g) as a colorless oil. Anal. Calcd for $C_{44}H_{67}N_3O_{13}$: C, 62.47; H, 7.98; N, 4.97. Found: C, 62.51; H, 8.01; N, 4.95; IR (film); ν 1561, 1641]NHC(O)], 1726 [C(O)O], 1746 [$CH_3C(O)O$], 2272 (NCO), 3364, 3408 см$^{-1}$ (NH); ^{1}H NMR (400 MHz, $CDCI_3$) : δ 0.74 (s, 3H, $C^{20}H_3$), 0.98 (s, 3H, $C^{17}H_3$), 1.23 (s, 3H, $C^{18}H_3$), 0.87–1.90 (m, 30 H, *ent*-beyerane skeleton, $(CH_2)_2$ linker, and $(CH_2)_4$ linker), 2.01 (s, 3H, CH_3CO), 2.04 (s, 3H, CH_3CO), 2.09 (s, 3H, CH_3CO), 2.18 (d, 1H, C^3H_{eq}, *J* = 13.5 Hz), 2.65 (dd, 1H, C^{15} H_α, *J* = 18.5, 3.7 Hz), 3,03–3.24 (m, 2H, $C(O)NHCH_2$), 3.28 (t, 2H, CH_2NCO, *J* = 6.6), 3.36–3.43 (m, 1H,

$C^{1s}OCH_2$), 3.76–3.84 (m, 1H, $C^{1s}OCH_2$), 3.87–3.93 (m, 1H, H-2s), 4.03–4.26 (m, 5H, 2 H-6s, H-5s, $C^{19}(O)OCH_2$), 4.83 (d, 1H H-1s, J = 3.6 Hz), 4.87 (d, 1H, NHC(O), J = 9.8 Hz), 5.07–5.17 (m, 2H, H-3s, H-4s), 5.18–5.22 [m, 1H, $C(O)NHCH_2$] ppm; MALDI-TOF MS *m/z* calcd for $C_{44}H_{68}N_3O_{13}$ $[M+H]^+$ 846.5, found 846.7; calcd for $C_{44}H_{67}N_3O_{13}Na$ $[M+Na]^+$ 868.5, found 868.7; calcd for $C_{44}H_{67}N_3O_{13}K$ $[M+K]^+$ 884.4, found 884.7.

*4.1.2.7. The general procedure for the synthesis of diamines (**26**, **27**)*

To a solution of diglycoside **14** or **15** (1 equiv) in AcOH was added Zn powdered (100 equiv) under argon. The reaction mixture was stirred for 3 h at room temperature, then was concentrated under reduced pressure. The residue was diluted with CH_2Cl_2, washed with 5% $NaHCO_3$ and water and brine, dried over Na_2SO_4, and concentrated under reduced pressure.

*4.1.2.7.1. Bis{19-[3',4',6'-tri-O-acetyl-2'-deoxy-2'-amino-α-D-glucopyranosyl-oxybutyl-4-oxycarbonyl]-ent-beyeran-16-yl}-1,8-octanedioat (**26**)*

This compound was prepared as a white foam in 96% yield (0.11 g) and was used without further purification in the next step.

*4.1.2.7.2. Bis{19-[3',4',6'-tri-O-acetyl-2'-deoxy-2'-amino-α-D-glucopyranosyl-oxyhexyl-6-oxycarbonyl]-ent-beyeran-16-yl}-1,8-octanedioat (**27**)*

This compound was prepared as a white foam in 87% yield (0.13 g). Anal. Calcd for $C_{86}H_{136}N_2O_{24}$: C, 65.29; H, 8.66; N, 1.77. Found: C, 65.53; H, 8.69; N, 1.78; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 0.70 (s, 6H, $C^{20}H_3$, $C^{20'}H_3$), 0.90 (s, 6H, $C^{17}H_3$, $C^{17'}H_3$), 1.16 (s, 6H, $C^{18}H_3$, $C^{18'}H_3$), 0.81–1.89 [m, 66 H, *ent*-beyerane skeleton, two $(CH_2)_4$ linkers, and $(CH_2)_6$ linker), 2.02 (s, 6H, CH_3CO, $C'H_3CO$), 2.07 (s, 6H, CH_3CO, $C'H_3CO$), 2.08 (s, 6H, CH_3CO, $C'H_3CO$), 2.15 (d, 2H, J = 13.5 Hz, C^3H_{eq}, $C^{3'}H_{eq}$), 2.30 (t, 4H, J = 7.4 Hz, $C^{16}OC(O)CH_2$, $C^{16'}OC(O)CH_2$), 2.93 (dd, 2H, J = 10.2, 3.3 Hz, H-2s, H-2s'), 3.40–3.49 (m, 2H, $C^{1s}OCH_2$), $C^{1s'}OCH_2$), 3.66–3.75 (m, 2H, $C^{1s}OCH_2$, $C^{1s'}OCH_2$), 3.89–4.13 (m, 8H, H-6s, H-6s', $C^{19}(O)OCH_2$, $C^{19'}(O)OCH_2$, H-5s, H-5s'), 4.28 (dd, 2H, J = 12.3, 4.7 Hz, H-6s, H-6s'), 4.72 (dd, 2H, J = 10.5, 4.2 Hz, $C^{16}H$, $C^{16'}H$), 4.85 (d, 2H, J = 3.2 Hz, H-1s, H-1s'), 4.95 (t, 2H, J = 9.8 Hz, H-4s, H-4s'), 5.12 (t, 2H, J = 9.7 Hz, H-3s, H-3s') ppm; MALDI-TOF MS *m/z* calcd for $C_{86}H_{137}N_2O_{24}$ $[M+H]^+$ 1582.0, found 1582.1; calcd for $C_{86}H_{136}N_2O_{24}Na$ $[M+Na]^+$ 1603.9, found 1604.1; calcd for $C_{86}H_{136}N_2O_{24}K$ $[M+K]^+$ 1619.9, found 1620.1.

*4.1.2.8. General procedure for the synthesis of macrocycles (**28**, **29**)*

1,6-Diisocyanatohexane (1 equiv) was added to a solution of diglycoside **26** or **27** (1 equiv) in CH_2Cl_2 under argon. The reaction mixture was stirred for 40 h at room temperature, then was concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (hexane/EtOAc = 5/1).

*4.1.2.8.1. 2,13,16,20,35,40-Hexaoxa-22,24,31,33-tetraaza-1,14(16α,4α)di(19-nor-ent-beyeran)-21,34(1,2)di(3',4',6'-tri-O-acetyl-2'-deoxy-α-D-glucopyranosyl)cyclohentetracontaphan-3,12,15,23,32,41-hexaon (**28**)*

This compound was prepared in 39.5% yield (0.05 g) as a white powder. Mp 106-108 °C (hexane/EtOAc); $[\alpha]_D^{20}$ +17.5 (*c* 0.83, CH_2Cl_2); Anal. Calcd for $C_{90}H_{140}N_4O_{26}$: C, 63.81; H, 8.33; N, 3.31. Found: C, 63.77; H, 8.35; N, 3.32; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 0.69 (s, 6H, $C^{20}H_3$, $C^{20'}H_3$), 0.90, 0.92 (2s, 6H, $C^{17}H_3$, $C^{17'}H_3$), 1.20 (s, 6H, $C^{18}H_3$, $C^{18'}H_3$), 0.81–1.90 (m, 58H, *ent*-beyerane skeleton, two $(CH_2)_2$ linkers, and $(CH_2)_6$ linker), 1.99 (s, 6H, CH_3CO, $C'H_3CO$), 2.00 (s, 6H, CH_3CO, $C'H_3CO$), 2.09 (s, 6H, CH_3CO, $C'H_3CO$), 2.13–2.19 (m, 2H, C^3H_{eq}, $C^{3'}H_{eq}$), 2.27–2.36 (m, 4H, $C^{16}OC(O)CH_2$, $C^{16'}OC(O)CH_2$), 3.02–3.24 (m, 4H, $2C(O)NHCH_2$,), 3.36–3.44 (m, 2H, $C^{1s}OCH_2$, $C^{1s'}OCH_2$), 3.74–3.82 (m, 2H, $C^{1s}OCH_2$, $C^{1s'}OCH_2$), 3.87–3.95 (m, 2H, H-2s, H-2s'), 4.03–4.27 (m, 10 H, 2 H-6s, 2 H-6s', $C^{19}(O)OCH_2$, $C^{19'}(O)OCH_2$, H-5s, H-5s'), 4.66 (dd, 2H, J = 10.6, 4.4 Hz, $C^{16}H$, $C^{16'}H$), 4.83 (d, 2H, J = 3.4 Hz, H-1s, H-1s'), 4.92 [d, 2H, J = 10.0 Hz, 2

NHC(O)], 5.06–5.18 (m, 4H, H-4s, H-4s', H-3s, H-3s'), 5.40–5.47 (m, 2H, 2 C(O)N*H*CH_2) ppm; MALDI-TOF MS *m/z* calcd for $C_{90}H_{141}N_4O_{26}$ $[M+H]^+$ 1694.0, found 1694.3; calcd for $C_{90}H_{140}N_4O_{26}Na$ $[M+Na]^+$ 1716.0, found 1716.3; calcd for $C_{90}H_{140}N_4O_{26}K$ $[M+K]^+$ 1731.9, found 1732.2.

*4.1.2.8.2. 2,13,16,23,38,45-Tetraoxa-25,27,34,36-tetraaza-1,14(16α,4α)di(19-nor-ent-beyeran)-24,37(1,2)di(3',4',6'-tri-O-acetyl-2'-deoxy-α-D-glucopyranosyl)cyclohexatetracontaphan-3,12,15,26,35,46-hexaon (**29**)*

This compound was prepared in 14.5% yield (0.03 g) as a white powder. Mp 110-111 °C (hexane/EtOAc); $[\alpha]_D^{20}$ +16.7 (*c* 1.05, CH_2Cl_2); Anal. Calcd for $C_{94}H_{148}N_4O_{26}$: C, 64.51; H, 8.52; N, 3.20. Found: C, 64.55; H, 8.49; N, 3.19; ^{1}H NMR (500 MHz, $CDCI_3$) : δ 0.69 (s, 6H, $C^{20}H_3$, $C^{20'}H_3$), 0.90 (s, 6H, $C^{17}H_3$, $C^{17'}H_3$), 1.16 (s, 6H, $C^{18}H_3$, $C^{18'}H_3$), 0.84–1.88 (m, 66 H, *ent*-beyerane skeleton, two $(CH_2)_4$ linkers, and $(CH_2)_6$ linker), 1.99 (s, 6H, CH_3CO, $C'H_3CO$), 2.00 (s, 6H, CH_3CO, $C'H_3CO$), 2.08 (s, 6H, CH_3CO, $C'H_3CO$), 2.15 (d, 2H, *J* = 13.5 Hz, C^3H_{eq}, $C^{3'}H_{eq}$), 2.27–2.35 (m, 4H, $C^{16}OC(O)CH_2$, $C^{16'}OC(O)CH_2$), 3.04–3.20 (m, 4H, 2C(O)NHCH_2), 3.37–3.44 (m, 2H, $C^{1s}OCH_2$, $C^{1s'}OCH_2$), 3.60–3.68 (m, 2H, $C^{1s}OCH_2$, $C^{1s'}OCH_2$), 3.89–4.03 (m, 4H, H-2s, H-2s', H-5s, H-5s'), 4.07–4.24 (m, 8H, 2 H-6s, 2 H-6s', $C^{19}(O)OCH_2$, $C^{19'}(O)OCH_2$), 4.66 (dd, 2H, *J* = 10.3, 4.1 Hz, $C^{16}H$, $C^{16'}H$), 4.84 (d, 2H, *J* = 3.5 Hz, H-1s, H-1s'), 4.96 [d, 2H, *J* = 10.0 Hz, 2 NHC(O)], 5.08 (t, 2H, *J* = 9.7 Hz, H-4s, H-4s'), 5.16 (t, 2H, *J* = 9.7 Hz, H-3s, H-3s'), 5.21–5.30 (m, 2 C(O)N*H*CH_2) ppm; MALDI-TOF MS *m/z* calcd for $C_{94}H_{149}N_4O_{26}$ $[M+H]^+$ 1751.0, found 1750.7; calcd for $C_{94}H_{148}N_4O_{26}Na$ $[M+Na]^+$ 1773.0, found 1772.7.

*4.1.2.9. Synthesis of macrocycle (**30**) and diglycoside (**31**)*

A solution of sebacyl dichloride (0. 012 g, 0.05 mmol) in CH_2Cl_2 (3 mL) was added to a solution of diglycoside **27** (0.08 g, 0.05 mmol) and pyridine (0.008 g, 0.1 mmol) in CH_2Cl_2 (5 mL) under argon. The reaction mixture was stirred for 8 h at room temperature, then diluted with CH_2Cl_2, washed with 0.1 M HCl and water, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc = 1/1) to give macrocycle **30** and diglycoside **31**.

*4.1.2.9.1. 2,13,16,23,38,45-Hexaoxa-25,36-diaza-1,14(16α,4α)di(19-nor-ent-beyeran)-24,37(1,2)di(3',4',6'-tri-O-acetyl-2'-deoxy-α-D-glucopyranosyl)cyclohexatetracontaphan-3,12,15,26,35,46-hexaon (**30**)*

This compound was prepared in 23% yield (0.02 g) as a white foam. $[\alpha]_D^{20}$ +13.8 (*c* 0.53, CH_2Cl_2); Anal. Calcd for $C_{96}H_{150}N_2O_{26}$: C, 65.95; H, 8.65; N, 1.60. Found: C, 66.01; H, 8.62; N, 1.60; ^{1}H NMR (500 MHz, $CDCI_3$) : δ 0.70 (s, 6H, $C^{20}H_3$, $C^{20'}H_3$), 0.91 (s, 6H, $C^{17}H_3$, $C^{17'}H_3$), 1.16 (s, 6H, $C^{18}H_3$, $C^{18'}H_3$), 0.80–1.89 [m, 78H, *ent*-beyerane skeleton, two $(CH_2)_4$ linkers, and two $(CH_2)_6$ linkers), 2.00 (s, 6H, CH_3CO, $C'H_3CO$), 2.03 (s, 6H, CH_3CO, $C'H_3CO$), 2.09 (s, 6H, CH_3CO, $C'H_3CO$), 2.10–2.19 (m, 6H, C^3H_{eq}, $C^{3'}H_{eq}$, 2 NHC(O)CH_2), 2.28–2.33 (m, 4H, $C^{16}OC(O)CH_2$, $C^{16'}OC(O)CH_2$,), 3.39–3.47 (m, 2H, $C^{1s}OCH_2$, $C^{1s'}OCH_2$), 3.65–3.71 (m, 2H, $C^{1s}OCH_2$, $C^{1s'}OCH_2$), 3.91–4.12 (m, 8H, $C^{19}(O)OCH_2$, $C^{19'}(O)OCH_2$, H-6s, H-6s', H-5s, H-5s'), 4.24 (dd, 2H, *J* = 12.4, 4.5 Hz, H-6s, H-6s'), 4.32–4.38 (m, 2H, H-2s, H-2s'), 4.68 (dd, 2H, *J* = 10.2, 4.4 Hz, $C^{16}H$, $C^{16'}H$), 4.83 (d, 2H, *J* = 3.6 Hz, H-1s, H-1s'), 5.11 (t, 2H, *J* = 9.9 Hz, H-4s, H-4s'), 5.21 (t, 2H, *J* = 10.0 Hz, H-3s, H-3s'), 5.82 (d, 2H, *J* = 9.3 Hz, 2 NH) ppm; MALDI-TOF MS *m/z* calcd for $C_{96}H_{150}N_2O_{26}Na$ $[M+Na]^+$ 1771.0, found 1771.1; calcd for $C_{96}H_{150}N_2O_{26}$ K 1787.0, found 1787.1.

*4.1.2.9.2. Bis{19-[8-carboxy-2-octylacetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-glucopyranosyl-oxyhexyl-6-oxycarbonyl]-ent-beyeran-16-yl}-1,8-octanedioat (**31**)*

This compound was prepared in 20% yield (0.01 g) as a white foam. $[\alpha]_D^{20}$ +4.4 (*c* 1.06, CH_2Cl_2/MeOH = 3/1); Anal. Calcd for $C_{106}H_{168}N_2O_{30}$: C, 65.27; H, 8.68; N, 1.44. Found: C, 65.05; H, 8.70; N, 1.45; ^{1}H NMR (400 MHz, $CDCI_3$) : δ 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, $C^{18}H_3$, $C^{18'}H_3$), 0.81–1.90 [m, 90H, *ent*-beyerane skeleton, two $(CH_2)_4$ linkers and three $(CH_2)_6$ linkers), 2.01 (s, 6H, CH_3CO, $C'H_3CO$), 2.03 (s, 6H, CH_3CO, $C'H_3CO$), 2.09 (s, 6H, CH_3CO, $C'H_3CO$), 2.11–2.20 (m, 6H, C^3H_{eq}, $C^{3'}H_{eq}$, 2 NHC(O)CH_2), 2.28–2.37 (m, 8H, $C^{16}OC(O)CH_2$, $C^{16'}OC(O)CH_2$, 2 CH_2COOH), 3.38–3.47 (m, 2H, $C^{1s}OCH_2$, $C^{1s'}OCH_2$), 3.64–3.72 (m, 2H, $C^{1s}OCH_2$, $C^{1s'}OCH_2$), 3.90–4.12 (m, 8H, $C^{19}(O)OCH_2$, $C^{19'}(O)OCH_2$, H-6s, H-6s', H-5s, H-5s'), 4.24 (dd, 2H, J = 12.3, 4.1 Hz, H-6s, H-6s'), 4.33–4.39 (m, 2H, H-2s, H-2s'), 4.70 (dd, 2H, J = 10.5, 4.2 Hz, $C^{16}H$, $C^{16'}H$), 4.83 (d, 2H, J = 3.4 Hz, H-1s, H-1s'), 5.11 (t, 2H, J = 9.8 Hz, H-4s, H-4s'), 5.21 (t, 2H, J = 9.5 Hz, H-3s, H-3s'), 5.81 (d, 2H, J = 9.1 Hz, 2 NH) ppm; MALDI-TOF MS *m/z* calcd for $C_{106}H_{168}N_2O_{30}Na$ $[M+Na]^+$ 1973.2, found 1973.2; calcd for $C_{106}H_{168}N_2O_{30}K$ $[M+K]^+$ 1989.1, found 1989.3.

4.2. In vitro assays

Compounds **19**, **23**, **24**, **28**-**31** were tested for antituberculosis activity by the vertical diffusion method on a *Novaya* solid nutrient medium using H37Rv laboratory strain as a test culture. The nutrient medium was placed in 5 mL test tubes and inoculated with 0.1 mL of test culture diluted to a turbidity of 10 units, and the test tubes were incubated for 24 h to grow *M. tuberculosis*. The test tubes were then set vertically, and 0.3 mL of a solution of compounds **19**, **23**, **24**, **28**-**31** in aqueous EtOH with a concentration of 12.5, 6.2, 3.1, 1.5, 0.7, 0.35, or 0.1 μg/mL was added dropwise (test solutions were prepared by serial decimal dilutions of the initial solution of 100 μg of compounds tested in the mixture of 5 mL of 96% ethanol and 5 mL of sterile distilled water). The test tubes were incubated for 10 days at 37 °C under sterile conditions, and the zone of bacterial growth inhibition was measured. An inhibition zone of longer than 10 mm indicated tuberculostatic activity. Antitubercular drug isoniazid which was used as a control inhibited the in vitro growth of *M. tuberculosis* at MIC 0.1 μg/mL (0.7 μM).

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Appendix: Supplementary information

Supplementary information to this article can be found online at …

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