DOI 10.1007/s10600-015-1440-3
Chemistry of Natural Compounds, Vol. 51, No. 5, September, 2015

SYNTHESIS OF THE FIRST MACROCYCLIC GLYCOTERPENOID BASED ON TREHALOSE AND THE DITERPENOID ISOSTEVIOL

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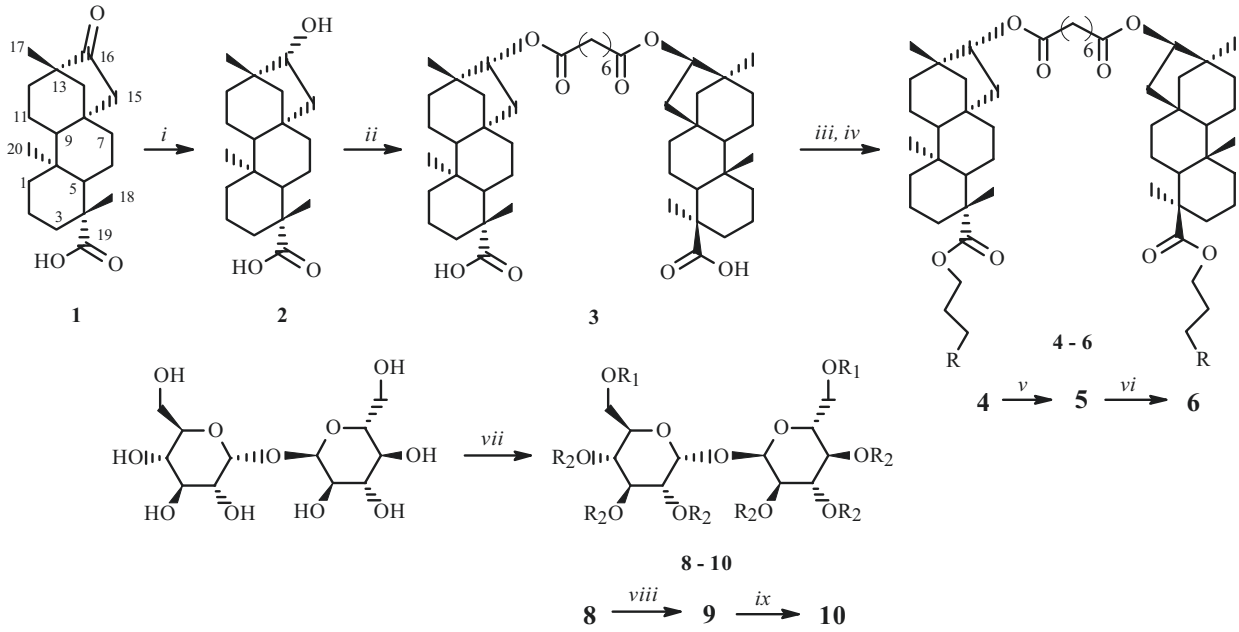
*A macrocyclic glycoterpenoid containing the diterpenoid dihydroisosteviol (16-hydroxy-*ent*-beyeran-19-oic acid) and α,α′-trehalose linked by an ester spacer was synthesized.*

Keywords: isosteviol, trehalose, diterpenoids, macrocycles, macrocyclic glycoterpenoids.

We recently reported the synthesis of a series of macrocyclic terpenoids constructed from one, two, and four molecules of the diterpenoid dihydroisosteviol **2** (16-hydroxy-*ent*-beyeran-19-oic acid) linked through polymethylene spacers containing esters, hydrazides, and hydrazonohydrazides [1, 2]. The present article is a continuation of our last publications on the synthesis of macrocyclic dihydroisosteviol derivatives [3, 4] and reports the synthesis of macrocycle **11** in which one of the spacers linking the diterpenoid **2** into the macrocyclic structure contains α,α′-trehalose **7**. We called it a macrocyclic glycoterpenoid in analogy with the literature [5] because it contained a carbohydrate moiety in addition to the terpenoid fragments.



4: R = CH_2OH; **5:** R = COOH; **6:** R = C(O)Cl
8: R_1 = Tr, R_2 = H; **9:** R_1 = Tr, R_2 = Ac; R_1 = H, R_2 = Ac

i. $NaBH_4$, CH_3OH; *ii*. $ClC(O)(CH_2)_6C(O)Cl$, DMAP, Py, CH_2Cl_2; *iii*. $SOCl_2$, 50°C; *iv*. $HO(CH_2)_4OH$, CH_2Cl_2, yield 60%; *v*. CrO_3, H_2SO_4, H_2O, Me_2CO, yield 88%; *vi*. $SOCl_2$, CH_2Cl_2, reflux; *vii*. Ph_3CCl, Py; *viii*. $(CH_3CO)_2O$, Py; *ix*. $FeCl_3·6H_2O$, CH_2Cl_2, H_2O, yield 60%

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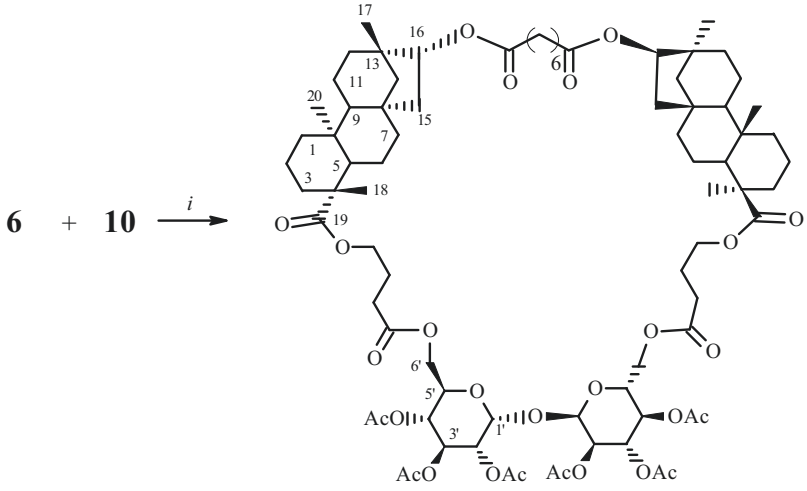
 0009-3130/15/5105-0886

The macrocycle was prepared by a convergent synthesis consisting of two branches, the terpene one leading to difunctionalized dihydroisosteviol derivative **6** (terpene precursor) and the carbohydrate one leading to hexaacetylated trehalose **10** (carbohydrate precursor). Covalent binding of precursors **6** and **10** in the last step afforded target macrocyclic glycoterpenoid **11**.



11

i. Et_3N, CH_2Cl_2, yield 7%

Precursor **6** was synthesized in six steps. First, the oxo group of the natural diterpenoid isosteviol **1** (16-oxo-*ent*-beyeran-19-oic acid) was reduced selectively and stereospecifically by a known method [6] into dihydroisosteviol **2** (100% *de*), two molecules of which were then bound covalently via a reaction with suberic acid dichloride as before [7]. The resulting diacid **3** was converted into the dichloride, which was then reacted *in situ* with a 30-fold excess of 1,4-butanediol. Then, diol **4** was isolated by column chromatography in 60% yield and oxidized by Jones reagent [8]. The order of addition of the reagents was atypical for this reaction [9], namely, slow addition of a dilute solution of **4** in Me_2CO to a solution of chromic acid. The constant deficiency of starting **4** in the reaction mixture avoided forming side macrocyclic products [9] and; therefore, column chromatography for working up the products. Diacid **5** was obtained in 88% yield. The dichloride **6** was used further as the terpene precursor.

2,2′,3,3′,4,4′-Hexa-*O*-acetyl-α,α'-trehalose (**10**) was synthesized by the known method [10]. First, the primary hydroxyls of trehalose (**7**) were protected with trityl groups. Then, the secondary hydroxyls of disaccharide **8** were acylated, after which the protecting groups were removed.

The last step of the convergent synthesis involved refluxing dichloride **6** and hexaacetylated trehalose **10** in CH_2Cl_2 at high dilution (10^{-4} M) in the presence of Et_3N. Macrocyclic glycoterpenoid **11** was isolated from the reaction mixture in 7% yield by column chromatography.

Only four natural macrocyclic glycoterpenoids (isolated from the sea hare *Syphonota geographica*) have been described in the literature [5, 11]. Synthetic macrocyclic glycoterpenoids had not been reported before our first publication [4] appeared.

EXPERIMENTAL

PMR spectra were recorded on an Avance-400 spectrometer (400 MHz, Bruker, Germany). MALDI mass spectra were obtained in linear mode using a Nd:YAG laser at 355 nm on an UltraFlex III TOF/TOF time-of-flight mass spectrometer (Bruker Daltonik GmbH, Bremen, Germany). Data were processed using the FlexAnalysis 3.0 program (Bruker Daltonik GmbH, Bremen, Germany). Masses were measured in the range *m*/*z* 200–6000 in positive-ion mode. The matrix was 2,5-dihydroxybenzoic acid (DHB) and *p*-nitroaniline (*p*-NA). Samples were dissolved in CH_2Cl_2 (10^{-3} M). The matrix solution in MeCN had a concentration of 10 mg/mL. Samples were deposited by the dried-drop method. Matrix solution (0.5 μL) was pipetted onto an Anchor Chip target (Bruker Daltonik GmbH, Bremen, Germany). After the solvent evaporated, the target was treated with analyte solution (0.5 μL). IR spectra were recorded in the range 400–4000 cm^{-1} on a Vector 22 Fourier-spectrometer (Bruker). Samples were studied as films. The course of reactions and purity of products were monitored by TLC on Sorbfil plates (OOO Imid, Krasnodar, Russia). Compounds were detected by treatment with H_2SO_4 solution (5%)

followed by heating to 120°C. Specific rotation was measured on a Model 341 polarimeter (PerkinElmer Inc., Waltham, USA) at wavelength 589 nm in a cell thermostatted at 20°C. Melting points were measured on a Boetius apparatus.

Isosteviol (**1**) was prepared by the literature method [12] from the sweetener Sweta (Stevian Biotechnology Corp.), mp 235°C (lit. 234–235°C [12], 231–234°C [13]). Its spectral data agreed with the literature [12]. Dihydroisosteviol (**2**) was synthesized by the literature method [6] from **1**, mp 199°C (lit. 198–200°C [6]). Diacid **3** was prepared from **2** by the literature method [7], mp 110°C (lit. 108–112°C [7]). 2,2′,3,3′,4,4′-Hexa-*O*-acetyl-α,α'-trehalose (**10**) was synthesized by the literature method [10], mp 95°C (lit. 102°C [10], 93–96°C [14]). Its spectral data agreed with the literature [10].

Bis[19-nor-4α(ω-hydroxybutyloxycarbonyl)-*ent*-beyeran-16-yl]-1,6-hexanedicarboxylate (4). Diacid **3** (1.3 g, 1.67 mmol) was treated with $SOCl_2$ (5 mL) and heated at 50°C for 2 h under Ar. The excess of $SOCl_2$ was vacuum distilled. The residue was treated with anhydrous CH_2Cl_2 and stirred. The solvent was distilled off. The residue was dried *in vacuo*. Yield 1.36 g (100%). IR spectrum (KBr, ν, cm^{-1}): 1732, 1796 (C=O).

A solution of 1,4-butanediol (4.5 g, 49.9 mmol) in anhydrous CH_2Cl_2 (10 mL) at 50°C under Ar was treated dropwise with a solution of freshly prepared **3** (1.36 g, 1.67 mmol) in anhydrous CH_2Cl_2 (50 mL), and refluxed for 4 h. The CH_2Cl_2 layer was separated, washed with H_2O (3 × 10 mL), and dried over $CaCl_2$. The solvent was removed. The residue was chromatographed over a dry column (petroleum ether–EtOAc eluent, 4:1, then 1:2) to afford diol **4** as a transparent oil. Yield 0.93 g (60%), $[\alpha]_D^{20}$ –54.0° (*c* 0.91, MeOH). PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.70 (6H, s, 2 × H_3-20); 0.90 (6H, s, 2 × H_3-17); 1.16 (6H, s, 2 × H_3-18); 0.83–1.90 [56H, m, *ent*-beyerane skeleton, $(CH_2)_4$ spacer, and two central $(CH_2)_2$ fragments of two 19-(O)O$(CH_2)_4$OH groups]; 2.16 (2H, d, J = 13.0, 2 × H_{eq}-3); 2.30 [4H, t, J = 7.4, 2 × 16-OC(O)CH_2]; 3.67 (4H, t, J = 6.2, 2 × CH_2OH); 3.95–4.04 [2H, m, 2 × 19-(O)OCH_A]; 4.06–4.13 [2H, m, 2 × 19-(O)OCH_B]; 4.71 (2H, dd, J = 10.5, 4.5, 2 × H-16). Mass spectrum: *m*/*z* 945.5 $[M + Na]^+$, 961.5 $[M + K]^+$; calcd 945.6 $[M + Na]^+$, 961.6 $[M + K]^+$. $C_{56}H_{90}O_{10}$.

Bis[19-nor-4α(ω-carboxypropyloxycarbonyl)-*ent*-beyeran-16-yl]-1,6-hexanedicarboxylate (5). A solution of CrO_3 (0.5 g, 5 mmol) in H_2SO_4 (38%, 5 mL) was cooled to 3°C and treated slowly dropwise with a solution of **4** (1.16 g, 1.26 mmol) in Me_2CO (50 mL) over 20 h. The precipitate was filtered off. The filtrate was concentrated *in vacuo* to 10 mL, poured into H_2O (100 mL), and extracted with Et_2O (5 × 20 mL). The Et_2O extract was washed with acidified H_2O (3 × 20 mL) and H_2O (3 × 20 mL) and dried over $CaCl_2$. The solvent was removed to afford diacid **5**. Yield 1.05 g (88%), mp 56–57°C, $[\alpha]_D^{20}$ –45° (*c* 0.24, MeOH). PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.69 (6H, s, 2 × H_3-20), 0.89 (6H, s, 2 × H_3-17); 1.16 (6H, s, 2 × H_3-18); 0.80–1.90 [48H, m, *ent*-beyerane skeleton, $(CH_2)_4$ spacer]; 1.94–2.01 (4H, m, 2 × 19-(O)O$CH_2C\mathit{H}_2$]; 2.15 (2H, d, J = 14.4, 2 × H_{eq}-3); 2.25–2.36 [4H, m, 2 × 16-OC(O)CH_2]; 2.40–2.53 [4H, m, 2 × 19-(O)O$CH_2CH_2CH_2$]; 3.99–4.06 [2H, m, 2 × 19-(O)OCH_A]; 4.09–4.15 [2H, m, 2 × 19-(O)OCH_B]; 4.73 (2H, dd, J = 10.5, 4.2, 2 × H-16). Mass spectrum: *m*/*z* 973.6 $[M + Na]^+$, 989.6 $[M + K]^+$; calcd 973.6 $[M + Na]^+$, 989.6 $[M + K]^+$. $C_{56}H_{86}O_{12}$.

2,11,14,19,22,25,30-Heptaoxa-1,12(16,4α)di(19-nor-*ent*-beyerane)-21,23(2,6)di(3,4,5-tri-*O*-acetyltetrahydropyran)cyclohentriacontaphane-3,10,13,18,26,31-hexaone (11). A solution of **5** (0.34 g, 0.36 mmol) in CH_2Cl_2 (8 mL) was treated with $SOCl_2$ (1 mL) and refluxed under Ar for 5 h. The excess of $SOCl_2$ was vacuum distilled. The residue was treated with CH_2Cl_2 and stirred. The solvent was distilled off. The residue was dried *in vacuo* to afford **6** (0.35 g, 100%). IR spectrum (KBr, ν, cm^{-1}): 1727, 1801 (C=O).

A solution of **10** (0.21 g, 0.36 mmol) in CH_2Cl_2 (250 mL) was treated with Et_3N (0.073 g, 0.72 mmol), refluxed under Ar, treated dropwise with a solution of freshly prepared **6** (0.35 g, 0.36 mmol) in CH_2Cl_2 (80 mL) over 4 h, refluxed for 10 h, washed with H_2O (3 × 60 mL), and dried over $CaCl_2$. The solvent was removed. The residue was chromatographed over silica gel (100/160) using CH_2Cl_2–MeOH (100:0.3 and 100:1). Yield 0.04 g (7.4%), mp 103–104°C, $[\alpha]_D^{20}$ 16.8° (*c* 0.78, CH_2Cl_2). PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.70 (6H, s, 2 × H_3-20), 0.90 (6H, s, 2 × H_3-17), 1.16 (6H, s, 2 × H_3-18), 0.80–1.90 [48H, m, *ent*-beyerane skeleton, $(CH_2)_4$ spacer], 1.95–2.00 [4H, m, 2 × 19-(O)O$CH_2C\mathit{H}_2$], 2.03 [6H, s, 2 × CH_3C(O)], 2.04 6H, s, 2 × CH_3C(O)], 2.08 [6H, s, 2 × CH_3C(O)], 2.15(2H, d, J = 14.5, 2 × H_{eq}-3), 2.27–2.34 [4H, m, 2 × 16-OC(O)CH_2], 2.44 [4H, t, J = 7.5, 2 × 19-(O)O$CH_2CH_2C\mathit{H}_2$], 3.91–4.11 [8H, m, 2 × 19-(O)OCH_2, 4 × H-6′], 4.21–4.30 (2H, m, 2 × H-5′), 4.75 (2H, dd, J = 10.5, 3.8, 2 ×H-16), 5.0–5.05 (4H, m, 2 × H-2′, 2 ×H-4′), 5.32 (2H, d, J = 3.8, 2 × H-1′), 5.50 (2H, t, J = 9.7, 2 × H-3′). Mass spectrum: *m*/*z* 1531.9 $[M + Na]^+$, 1547.8 $[M + K]^+$; calcd 1531.8 $[M + Na]^+$, 1547.7 $[M + K]^+$. $C_{80}H_{116}O_{27}$.

ACKNOWLEDGMENT

The work was sponsored by the Russian Science Foundation (Grant No. 14-50-00014).

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