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OPEN-CHAIN AND MACROCYCLIC POLYETHYLENEGLYCOL ESTERS OF THE DITERPENOID ISOSTEVIOL

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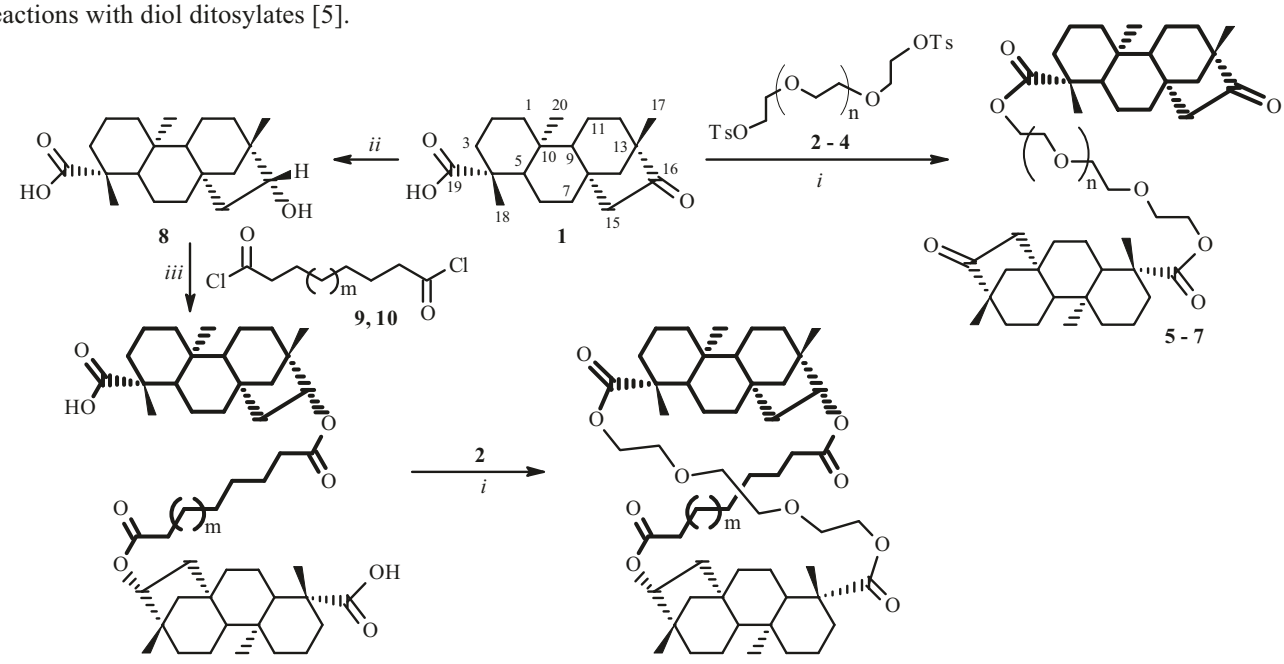
*Open-chain and macrocyclic derivatives of the diterpenoid isosteviol (16-oxo-*ent*-beyeran-19-oic acid) in which two isosteviol molecules were connected by polyethyleneglycol spacers were synthesized for the first time.*

Keywords: isosteviol, diterpenes, diterpenoids, beyerane, macrocycles, macrocyclic derivatives, polyethyleneglycol.

The number of publications on chemical transformations of the *ent*-beyerane diterpenoid isosteviol (**1**, 16-oxo-*ent*-beyeran-19-oic acid), which is obtained by acid hydrolysis of *Stevia rebaudiana* glycosides, has risen dramatically during the last five years [1]. Greater than 150 isosteviol derivatives have been reported [2]. We previously synthesized open-chain dinuclear isosteviol derivatives in which two *ent*-beyerane moieties were connected by polymethylene spacers with terminal esters via the reactions of isosteviol chloride with diols and of 16-dihydroisosteviol (**8**) with dibasic carboxylic acid chlorides [3, 4]. Recently, two of these dinuclear derivatives, i.e., diacids **11** and **12**, were transformed into dinuclear macrocycles in which two isosteviol *ent*-beyerane moieties were connected by diester spacers of different polymethylene chain lengths via reactions with diol ditosylates [5].



2, 5: n = 1; **3, 6:** n = 2; **4, 7:** n = 3
9, 11, 13: m = 1; **10, 12, 14:** m = 3
i. CH_3CN, K_2CO_3; *ii*. $NaBH_4$, CH_3OH; *iii*. CH_2Cl_2, DMAP, Py

Scheme 1

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Herein we report the synthesis of analogs of the aforementioned isosteviol derivatives in which the polymethylene spacers were replaced by polyethyleneglycol (PEG) spacers. Open-chain dinuclear derivatives **5**–**7** were obtained by reacting **1** with polyethyleneglycol ditosylates **2**–**4** in refluxing MeCN in the presence of K_2CO_3 under an inert atmosphere (Scheme 1). Macrocyclic dinuclear derivatives **13** and **14** were synthesized by reacting triethyleneglycol ditosylate (**2**) with diacids **11** and **12**, which were prepared by reacting 16-dihydroisosteviol (**8**) with suberic (**9**) and sebacic (**10**) acid chlorides using the literature methods [4, 6]. Compound **8** was prepared by selective reduction of the oxo-group of **1** by $NaBH_4$ in MeOH as before [7].

The literature describes only a few derivatives of natural products that were functionalized by PEG chains. These were derivatives of estradiol [8], cholesterol [9], betulinic acid [10], and the diterpenoid phorbol [11]. They all exhibited one type of biological activity or another. The properties of isosteviol PEG esters **5**–**7**, **13**, and **14** will be reported separately.

EXPERIMENTAL

PMR spectra were recorded on a Bruker Avance-400 instrument. MALDI mass spectra were obtained on an UltraFlex III TOF/TOF time-of-flight mass spectrometer (Bruker Daltonik GmbH, Germany). Data were processed using the flexAnalysis 3.0 programs (Bruker Daltonik GmbH, Germany). The matrix was *p*-nitroaniline. Melting points were determined on a Boetius melting-point apparatus. The course of reactions was monitored by TLC on Silufol UV254 plates (Kavalier, Czechoslovakia). Compounds were detected using I_2 vapor. Flash chromatography was performed over a dry column of KSKG silica gel (fraction <0.063 mm, Khromlab Ltd.).

Isosteviol (**1**) was obtained from the sweetener Sweta (Stevian Biotechnology Corp., Malaysia) by the literature method [12] (mp 233°C, lit. [1] mp 231–233°C). We used commercial triethyleneglycol (grade A, Vekton) and tetraethyleneglycol (99%, abcr GmbH & Co.). PEG ditosylates **2**–**4** were prepared by the literature method [13] {triethyleneglycol ditosylate (**2**), mp 80°C, lit. [13] mp 80–81°C; tetraethyleneglycol ditosylate (**3**), oil, *m*/*z* 502 (theor. *m*/*z* 502.13); pentaethyleneglycol ditosylate (**4**), oil, *m*/*z* 546 (theor. *m*/*z* 546.16)}. Diacid **11** was synthesized analogously as before [4], mp 111°C (lit. [4] mp 108–112°C); diacid **12**, also as before [6], mp 109°C (lit. [4] mp 105–110°C).

General Method for Preparing 5–7. Isosteviol (**1**, 1 mmol) and PEG ditosylate (0.5 mmol) were dissolved with heating in MeCN (30 mL) under a stream of Ar, treated with K_2CO_3 (0.5 mmol), and refluxed for 15 h. The precipitate was filtered off. The solvent was evaporated at reduced pressure. The residue was chromatographed over silica gel (petroleum ether–EtOAc eluent, 5:1–1:1).

3,6-Dioxaoctane-1,8-diyl-*bis*(16-oxo-*ent*-beyeran-19-oate) (5). Yield 77%, mp 127–129°C, $[\alpha]_D^{20}$ –76° (*c* 0.19; MeOH + CH_2Cl_2). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.71 (6H, s, H_3-20, 20′), 0.97 (6H, s, H_3-17, 17′), 1.19 (6H, s, H_3-18, 18′), 0.87–1.93 (36H, m, *ent*-beyerane skeleton), 2.19 (2H, d, J = 13.3, H_{eq}-3, 3′), 2.62 (2H, dd, J = 18.6, 3.7, H_α-15, 15′), 3.59–3.62 (4H, br.s, spacer -OCH_2CH_2O-), 3.65–3.70 (4H, m, 19-(O)OCH_2CH_2, 19′-(O)OCH_2CH_2), 4.14–4.22 (4H, m, 19-(O)OCH_2, 19′-(O)OCH_2). Mass spectrum (MALDI-TOF): *m/z* (exp) 773.66 $[M + Na]^+$, *m/z* (theor) 773.50 $[M + Na]^+$; *m/z* (exp) 789.62 $[M + K]^+$, *m/z* (theor) 789.47 $[M + K]^+$. $C_{46}H_{70}O_8$.

3,6,9-Trioxaundecane-1,11-diyl-*bis*(16-oxo-*ent*-beyeran-19-oate) (6). Yield 68%, mp 85–88°C, $[\alpha]_D^{20}$ –78.3° (*c* 0.69; CH_2Cl_2). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.71 (6H, s, H_3-20, 20′), 0.97 (6H, s, H_3-17, 17′), 1.20 (6H, s, H_3-18, 18′), 0.85–1.92 (36H, m, *ent*-beyerane skeleton), 2.19 (2H, d, J = 13.5, H_{eq}-3, 3′), 2.62 (2H, dd, J = 18.6, 3.7, H_α-15, 15′), 3.59–3.65 (8H, m, spacers 2(-OCH_2CH_2O-)), 3.66–3.70 (4H, m, 19-(O)OCH_2CH_2, 19′-(O)OCH_2CH_2), 4.14–4.22 (4H, m, 19-(O)OCH_2, 9′-(O)OCH_2). Mass spectrum (MALDI-TOF): *m/z* (exp) 817.52 $[M + Na]^+$, *m/z* (theor) 817.52 $[M + Na]^+$. $C_{48}H_{74}O_9$.

3,6,9,12-Tetraoxatetradecane-1,14-diyl-*bis*(16-oxo-*ent*-beyeran-19-oate) (7). Yield 72%, oil, $[\alpha]_D^{20}$ –75.5° (*c* 0.64; CH_2Cl_2). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.70 (6H, s, H_3-20, 20′), 0.95 (6H, s, H_3-17, 17′), 1.18 (6H, s, H_3-18, 18′), 0.86–1.90 (36H, m, *ent*-beyerane skeleton), 2.17 (2H, d, J = 13.3, H_{eq}-3, 3′), 2.60 (2H, dd, J = 18.6, 3.7, H_α-15, 15′), 3.60–3.62 (8H, m, spacers 2(-OCH_2CH_2O-)), 3.62–3.64 (4H, m, spacer -OCH_2CH_2O-), 3.64–3.68 (4H, m, 19-(O)OCH_2CH_2, 9′-(O)OCH_2CH_2), 4.14–4.21 (4H, m, 19-(O)OCH_2, 19′-(O)OCH_2). Mass spectrum (MALDI-TOF): *m/z* (exp) 861.50 $[M + Na]^+$, *m/z* (theor) 861.55 $[M + Na]^+$. $C_{50}H_{78}O_{10}$.

Method for Preparing 13 and 14. Diacid **11** or **12** (0.26 mmol) and **2** (0.26 mmol) were dissolved with heating in MeCN (50 mL) under a stream of Ar, treated with K_2CO_3 (0.52 mmol), and refluxed for 25 h. The precipitate was filtered off.

The solvent was evaporated at reduced pressure. The residue was chromatographed over silica gel (petroleum ether–EtOAc eluent, 15:1–1:1).

2,11,14,17,20,23-Hexaoxa-1,12(16,4α)di(19-nor-*ent*-beyerane)tetracosaphane-3,10,13,24-tetraone (13). Yield 72%, mp 144–145°C, $[\alpha]_D^{20}$ –102.5° (*c* 0.60; CH_2Cl_2). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.72 (6H, s, H_3-20, 20′), 0.90 (6H, s, H_3-17, 17′), 1.16 (6H, s, H_3-18, 18′), 1.17–1.92 (46H, m, *ent*-beyerane skeleton, spacer $(CH_2)_4$), 2.16 (2H, d, J = 13.1, H_{eq}-3, 3′), 2.28 (4H, t, J = 7.1, 16-OC(O)CH_2, 16′-OC(O)CH_2), 3.49–3.62 (4H, m, spacer -OCH_2CH_2O-), 3.63–3.76 (4H, m, 19-(O)OCH_2CH_2, 19′-(O)OCH_2CH_2), 4.02–4.08 (2H, m, 19-(O)OCH_A, 9′-(O)OCH_A), 4.34–4.40 (2H, m, 19-(O)OCH_B, 19′-(O)OCH_B), 4.66 (2H, dd, J = 10.6, 4.1, H-16, 16′). Mass spectrum (MALDI-TOF): *m/z* (exp) 915.56 $[M + Na]^+$, *m/z* (theor) 915.60 $[M + Na]^+$. $C_{54}H_{84}O_{10}$.

2,13,16,19,22,25-Hexaoxa-1,14(16,4α)di(19-nor-*ent*-beyerane)hexacosaphane-3,12,15,26-tetraone (14). Yield 11%, mp 181–183°C, $[\alpha]_D^{20}$ –38.8° (*c* 1.17; CH_2Cl_2). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.72–1.92 (50H, m, *ent*-beyerane skeleton, spacer $(CH_2)_6$), 0.72 (6H, s, H_3-20, 20′), 0.91 (6H, s, H_3-17, 17′), 1.17 (6H, s, H_3-18, 18′), 2.17 (2H, d, J = 13.7, H_{eq}-3, 3′), 2.26–2.32 (4H, m, 16-OC(O)CH_2, 16′-OC(O)CH_2), 3.53–3.62 (4H, m, spacer -OCH_2CH_2O-), 3.65–3.76 (4H, m, 19-(O)OCH_2CH_2, 19′-(O)OCH_2CH_2), 4.04–4.11 (2H, m, 19-(O)OCH_A, 19′-(O)OCH_A), 4.25–4.32 (2H, m, 19-(O)OCH_B, 19′-(O)OCH_B), 4.68 (2H, dd, J = 10.6, 4.4, H-16, 16′). Mass spectrum (MALDI-TOF): *m/z* (exp) 943.64 $[M + Na]^+$, *m/z* (theor) 943.63 $[M + Na]^+$. $C_{56}H_{88}O_{10}$.

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