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Macrocyclic Derivatives of Isosteviol with Two Tetracyclic Diterpenoid Skeletons

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Abstract—Reaction of a diester based on 16-hydroxyisosteviol and sebacic acid with ditosylates of ethylene glycol, propane-1,2-diol, and octane-1,8-diol has led to new macrocycles containing two tetracyclic diterpenoid *ent*-beyerane skeletons.

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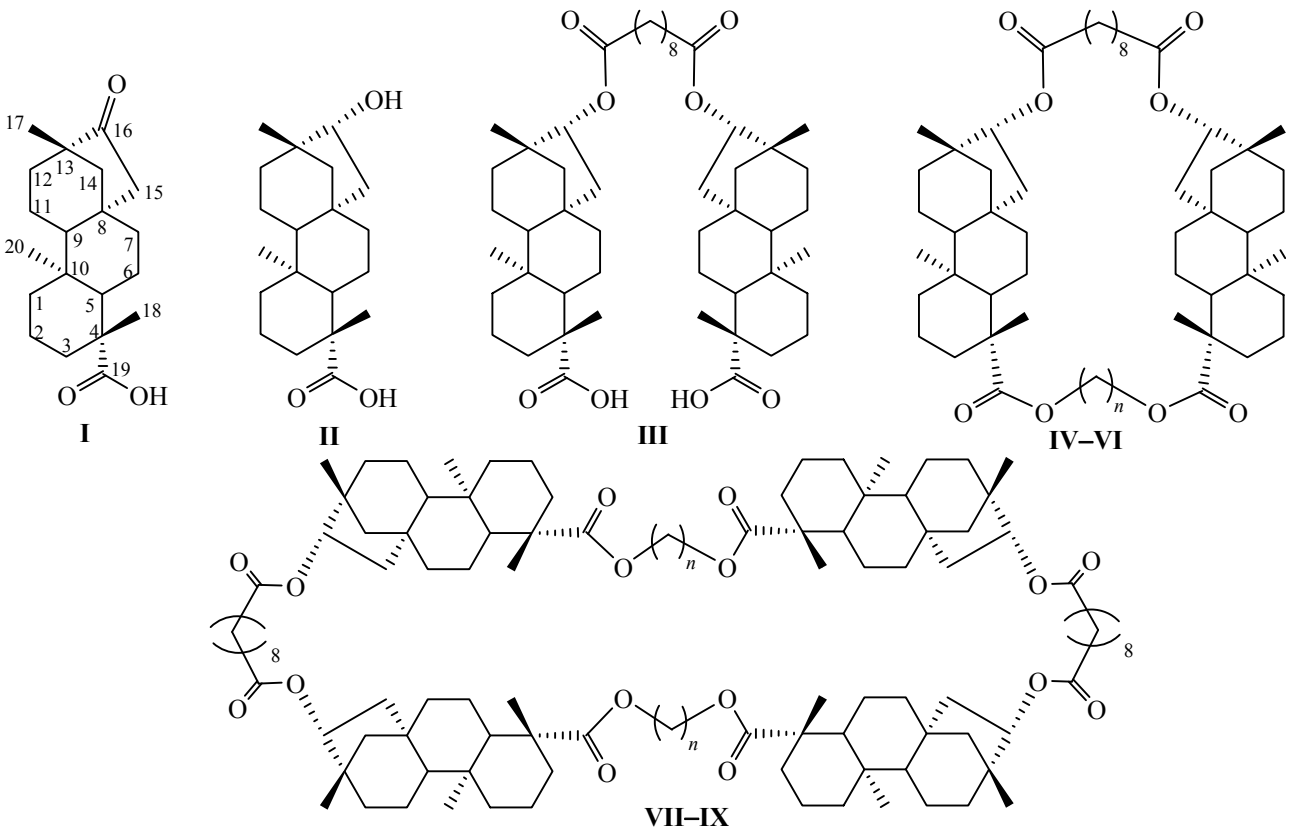
Over the last 15 years the number of publications on macrocyclic compounds has rapidly grown; however, papers reporting synthesis of macrocycles containing hydrocarbon fragments of terpenoid secondary metabolites have been a few among them. In particular, macrocycles derived from monoterpenes mirtenal [1], 3-karene [2, 3], and α-pinene [2, 3] as well as from diterpenoids isosteviol **I** (16-oxo-*ent*-

Scheme 1.



n = 8 (**IV, VII**), 6 (**V, VIII**), 2 (**VI, IX**).

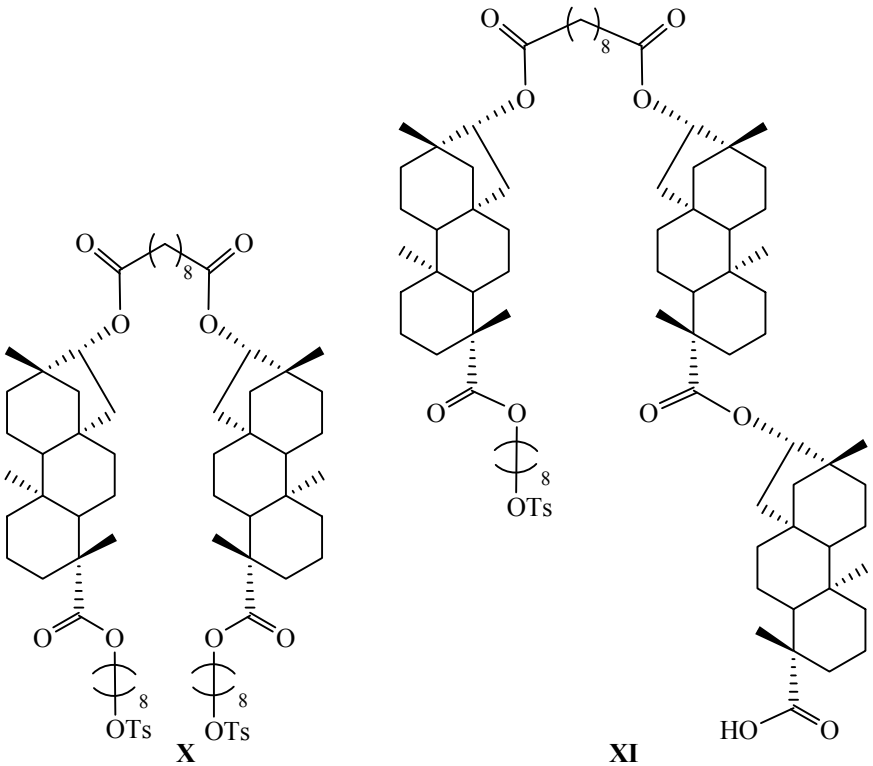
beyeran-19-oic acid) [4–7], steviol [8], and paclitaxel (Taxol trademark) [9, 10] have been described. However, the work in this line seems promising regarding the search for bioactive compounds. Indeed, macrocyclic derivatives of diterpenoids isosteviol [6], steviol [8], and paclitaxel [9, 10] showed higher biological activity than the corresponding parent compounds. In this work we report on the preparation of new macrocyclic derivatives of **I** with two isosteviol molecules covalently bound via diester linkers of varied length (Scheme 1).

Macrocyclic isosteviol derivatives were prepared in three stages. First, carbonyl group of **I** was reduced with sodium borohydride as described in [11]; compound **II** was thus obtained. The stereospecific reaction gave the C^{16}(*R*) epimer confirming the reports of [11–17]. In the second stage 16-hydroxyisosteviol **II** reacted with dichloroanhydride of sebacic acid to give the diacid **III** [6] that was subsequently transformed into the macrocycle via the reaction with ditosylates of diols of varied chain length similarly to [18].

The interaction of diacid **III** with octane-1,8-diol ditosylate gave a mixture of products. In particular, the low resolution MALDI mass spectrum of the reaction mixture contained peaks at *m*/*z* 939.7 $[M + Na]^+$ and 1856.4 $[M + Na]^+$ assigned to the ionized macrocycles **IV** and **VIII**, respectively. The weaker signals at *m*/*z* 1409.8 $[M + K]^+$ and 1414.8 $[M + Na]^+$ were assigned to trace amounts of **X** and **XI** byproducts. Other peaks could not be assigned (Scheme 2).

The major product of diacid **III** interaction with octane-1,8-diol ditosylate, binuclear macrocycle **IV**, was isolated in 86% yield. It was characterized with high resolution MALDI mass spectroscopy as well as with ^{1}H NMR spectroscopy. ^{1}H NMR spectrum of the macrocycle **IV** contained signals typical of isosteviol **I** and its derivatives (cf. [4–7, 11–16, 18, 19]), the signals of protons belonging to *ent*-beyerane skeleton ($C^{20}H_3$, $C^{17}H_3$, $C^{18}H_3$, and C^3H_{eq}), and the multiplet at 2.25–3.34 ppm assigned to the two $C^{16}OC(O)CH_2$ fragments of sebacic linker. This multiplet was found in the spectrum of **III** as well, at 2.22–2.43 ppm [19] (see table). Macrocyclization of diacid **III** was confirmed by appearance of the multiplet at 3.96–4.05 ppm in the spectrum of **IV**, assigned to ABX_2 spin systems of the two $C^{19}(O)OCH_2$ diester fragments of the linker binding the isosteviol fragments via their carboxylic groups. Protons of the $C^{19}(O)O(CH_2)_nO(O)C^{19'}$

Scheme 2.



X **XI**

Chemical shifts of characteristic proton signals of diacid **III** and binuclear macrocycles **IV**–**VI**

Proton	δ, ppm (*J*, Hz)			
	III	**IV**	**V**	**VI**
$C^{20}H_3$	0.76 s	0.71 s	0.70 s	0.71 s
$C^{17}H_3$	0.91 s	0.90 s	0.90 s	0.90 s
$C^{18}H_3$	1.21 s	1.16 s	1.15 s	1.16 s
C^3H_{eq}	2.14 d (*J* 13.72)	2.16 d (*J* 13.48)	2.17 d (*J* 13.02)	2.17 d (*J* 13.2)
$C^{16}OC(O)CH_2$	2.22–2.43 m	2.25–3.34 m	2.23–2.36 m	2.23–2.38 m
$C^{19}(O)OCH_2$	–	3.96–4.05 m	3.95–4.07 m	4.12–4.23 m
$C^{16}H$	4.63 dd (*J* 3.49, 10.31)	4.71 dd (*J* 4.13, 10.47)	4.69 dd (*J* 4.2, 10.54)	4.70 dd (*J* 4.2, 10.5)

diester linkers of the previously described isosteviol bisderivatives resonate in approximately the same region (cf. [20, 21]).

The major product of the interaction of diacid **III** with hexane-1,6-diol ditosylate, binuclear macrocycle **V**, was isolated in 36% yield and was characterized with high resolution MALDI mass spectroscopy and with ^{1}H NMR spectroscopy. The spectral features of **V** were similar to those of **IV**. In the course of the reaction a number of byproducts were formed. In particular, MALDI spectrum of the reaction mixture contained peaks at *m*/*z* of 1084.2 $[M + Na]^+$, 1618.4 $[M + Na]^+$, and 1717.2 $[M + Na]^+$ assigned to trace amounts of the ionized **XII**–**XIV** molecules. Moreover, the formation of tetranuclear macrocycle **VIII** was confirmed by appearance of the *m*/*z* = 1801 $[M + Na]^+$ signal in the low resolution MALDI spectrum. We failed to isolate **VIII** from the mixture (Scheme 3).

According to MALDI mass spectrometry data, the interaction of diacid **III** with ethylene glycol ditosylate gave binuclear macrocycle **VI** (*m*/*z* 855.5 $[M + Na]^+$, isolated in 25% yield), tetranuclear macrocycle **IX** (*m*/*z* 1688 $[M + Na]^+$), and two non-identified by-products. ^{1}H NMR spectral features of **VI** (in particular, chemical shifts of the $C^{20}H_3$, $C^{17}H_3$, $C^{18}H_3$, C^3H_{eq}, $C^{16}OC(O)CH_2$, $C^{19}(O)OCH_2$, and $C^{16}H$ protons) were in line with those of macrocycles **IV** and **V** (see Table) as well as with the published data [4–7, 11–16, 18–21].

To conclude, the reaction of diacid **III** with ditosylates of different diols yielded binuclear macrocyclic derivatives **IV**–**VI** of diterpenoid isosteviol (25–86%) and tetranuclear macrocycles **VII**–**IX** (not isolated). In **IV**–**VI**, the *ent*-beyerane hydrocarbon skeletons were connected via the diester linkers. Furthermore, the formation of a number of by products was detected by means of low resolution MALDI mass spectrometry; some of them was identified. Noteworthily, interaction of **III** with ethylene glycol ditosylate gave only two byproducts.

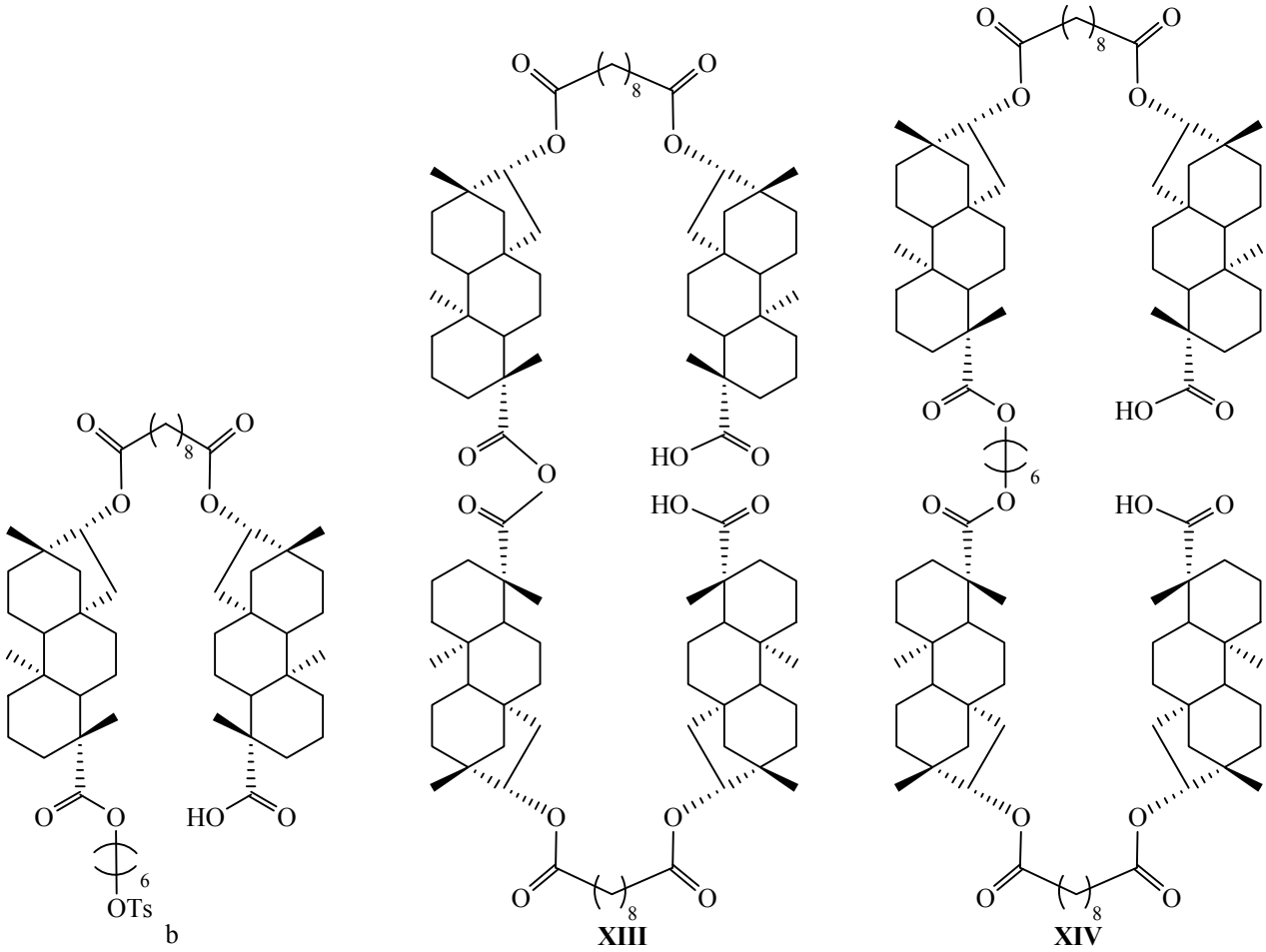
EXPERIMENTAL

IR spectra were registered using Vector 22 Bruker spectrometer at 400–4000 cm^{-1} from thin films. ^{1}H NMR spectra were recorded with Avance-400 Bruker spectrometer (400 MHz).

MALDI mass spectra of low and high resolution were registered on a time-of-flight mass spectrometer UltraFlex III TOF/TOF (Bruker Daltonik GmbH, Brehmen, Germany) in *m*/*z* range of 200–3000. The resulting high resolution spectrum was a sum of 100 spectra recorded at different sites of the specimen. The specimens were prepared as follows. A sample was dissolved in chloroform (10^{-3} mg/mL). The chloroform solutions of PEG-1500 and PEG-1000 of the same concentration were used as internal references. The matrix, 2,5-dihydroxybenzoic acid, was dissolved in methanol (5 mg/mL). The sample was applied by the "dried droplets" method. In particular, 0.3 μL of the matrix solution was applied at the Anchor Chip (Bruker Daltonik) target. After the solvent evaporation, 0.5 μL of the 1 : 1 mixture of solutions of the analyzed sample and PEG standards was applied. The data were processed using FlexAnalysis 3.0 software (Bruker Daltonik). Accuracy of the precisely determined masses was better than 3.4 ppm; the *m*/*z* values of monoisotopic peaks are given in the compounds descriptions below.

Melting points were determined using the Boetius microblock. Reaction completeness and the products purity were controlled by TLC (Silufol UV254 plates, Kavalier), the plates were developed with iodine

Scheme 3.



vapor. Individual compounds were isolated by flash chromatography (dry column, KSKG silica gel, fraction < 0.063 mm, Khromlab).

Isosteviol **I** was prepared according to [22] from Sweta sweetener (Stevian Biotechnology Corp.). 16-Hydroxyisosteviol **II** and diacid **III** were prepared according to [11] and [6], respectively. The physico-chemical properties of **I**–**III** coincided with published data.

Preparation of macrocycles (IV–VI) (general procedure). A solution of 0.25 mmol of the diol ditosylate in 15 mL of CH_3CN was added dropwise to a solution of 0.2 g (0.25 mmol) of diacid **III** in 50 mL of CH_3CN in the presence of 0.1 g (0.7 mmol) of K_2CO_3 at stirring, under an argon stream. The reaction mixture was refluxed during 12–35 h. Then the solvent was partially evaporated under reduced pressure, the residue was diluted with water and extracted with chloroform. The organic layer was dried over $MgSO_4$, the solvent was evaporated under reduced pressure, and the residue was purified by recrystallization or by chromatography on silica gel.

2,13,16,25-Tetraoxa-1,14(16,4α)-di(19-nor-*ent*-beyerane)cyclohexacosaphan-3,12,15,26-tetraone (IV). White crystals, recrystallized from petroleum-ether–diethyl ether–methylene chloride (1 : 1 : 0.5). Yield 0.22 g (86%), mp 145–150°C. IR spectrum, ν, cm^{-1}: 1728 (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.8–1.9 m [62H, *ent*-beyerane skeleton and two $(CH_2)_6$ linkers], 0.71 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, $C^{18}H_3$, $C^{18'}H_3$), 2.16 d (2H, C^3H_{eq}, $C^{3'}H_{eq}$, *J* 13.48), 2.25–3.34 m [4H, $C^{16}O(O)\cdot CCH_2$, $C^{16'}O(O)CCH_2$], 3.96–4.05 m [4H, $C^{19}(O)\cdot OC\underline{H}_2$, $C^{19'}(O)OCH_2$]. 4.71 dd (2H, $C^{16}H$, $C^{16'}H$, *J* 10.5, 4.1). Mass spectrum (MALDI), *m*/*z*: 939.6714 $[M + Na]^+$, 955.6420 $[M + K]^+$. Found, %: C 75.89; H 10.12. $C_{58}H_{92}O_8$. Calculated, %: C 75.94; H 10.11.

2,13,16,23-Tetraoxa-1,14(16,4α)-di(19-nor-*ent*-beyerane)cyclotetracosaphan-3,12,15,24-tetraone

(V). White powder, obtained chromatography on silica gel (petroleum-ether–ethyl acetate 20 : 1–5 : 1 as eluent). Yield 0.08 g (36%), mp 110–116°C. IR spectrum, ν, cm^{-1}: 1730 (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.8–1.95 m [58H, *ent*-beyerane skeleton, $(CH_2)_4$ and $(CH_2)_6$ linkers], 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 s (6H, $C^{18}H_3$, $C^{18'}H_3$), 2.17 d (2H, C^3H_{eq}, $C^{3'}H_{eq}$, *J* 13.02), 2.23–2.36 m [4H, $C^{16}O(O)CCH_2$, $C^{16'}O(O)CCH_2$], 3.95–4.07 m [4H, $C^{19}(O)OCH_2$, $C^{19'}(O)OCH_2$], 4.69 d. d (2H, $C^{16}H$, $C^{16'}H$, *J* 10.5, 4.2). Mass spectrum (MALDI), *m*/*z*: 911.6388 $[M + Na]^+$, 927.6096 $[M + K]^+$. Found, %: C 75.60; H 9.98. $C_{56}H_{88}O_8$. Calculated, %: C 75.63; H 9.97.

2,13,16,19-Tetraoxa-1,14(16,4α)-di(19-nor-*ent*-beyerane)cycloeicosaphan-3,12,15,20-tetraone (VI). White crystals, obtained chromatography on silica gel (petroleum-ether–ethyl acetate 20 : 1–5 : 1 as eluent). Yield 0.08 g (25%), mp 202–204°C. IR spectrum, ν, cm^{-1}: 1730 (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.8–1.95 m [50H, *ent*-beyerane skeleton and $(CH_2)_6$ linker], 0.71 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, $C^{18}H_3$, $C^{18'}H_3$), 2.17 d (2H, C^3H_{eq}, $C^{3'}H_{eq}$, *J* 13.2), 2.23–2.38 m [4H, $C^{16}O(O)CCH_2$, $C^{16'}O(O)CCH_2$], 4.12–4.23 m [4H, $C^{19}(O)OCH_2$, $C^{19'}(O)OCH_2$], 4.70 d. d (2H, $C^{16}H$, $C^{16'}H$, *J* 10.5, 4.2). Mass spectrum (MALDI), *m*/*z*: 855.5767 $[M + Na]^+$, 871.5455 $[M + K]^+$. Found, %: C 74.91; H 9.70. $C_{52}H_{80}O_8$. Calculated, %: C 74.96; H 9.68.

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