ISSN 1070-3632, Russian Journal of General Chemistry, 2007, Vol. 77, No. 6, pp. 1066–1068. © Pleiades Publishing, Ltd., 2007.
Original Russian Text © I.Yu. Strobykina, B.F. Garifullin, G.I. Kovylyaeva, R.Z. Musin, A.T. Gubaidullin, V.E. Kataev, 2007, published in Zhurnal Obshchei Khimii, 2007, Vol. 77, No. 6, pp. 978–980.

First Synthetic Macrocyclic Compounds in the Series of *ent*-Beyerane Diterpenoids

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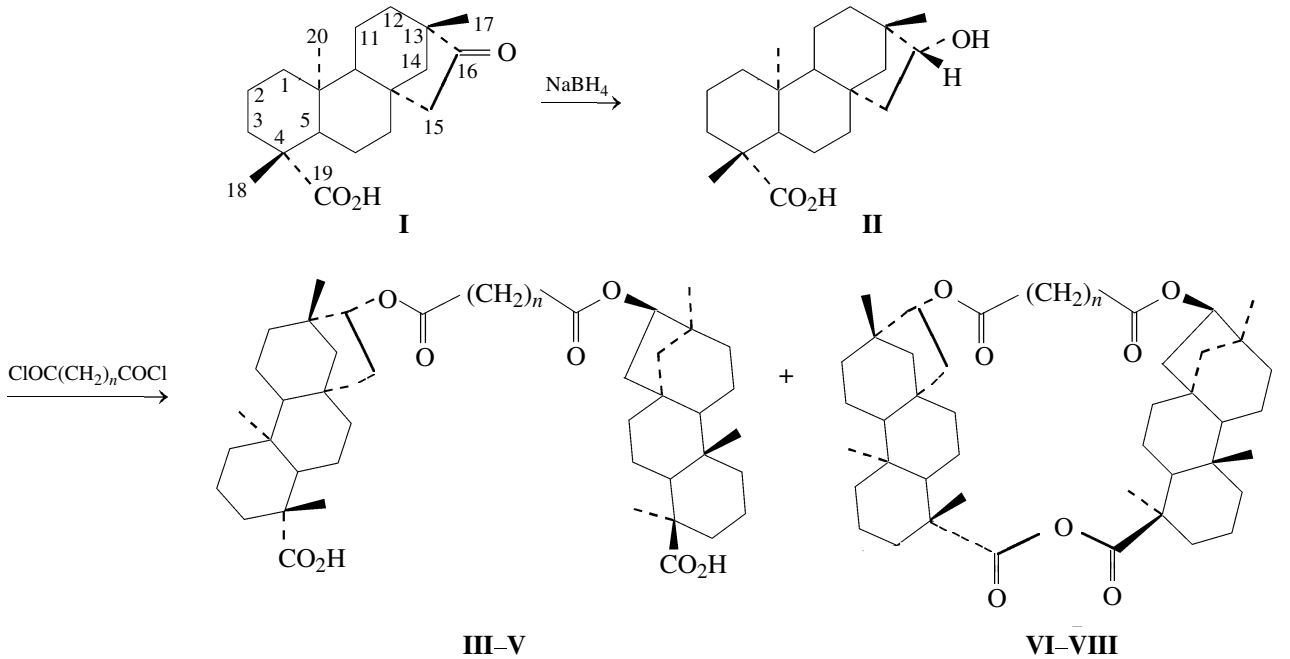
Received January 11, 2007

Abstract — New macrocyclic compounds were synthesized by reaction of 16-hydroxy-*ent*-beyeran-19-oic acid (derivative of the diterpenoid isosteviol with reduced ketone group) with adipic, suberic, and sebacic acid chlorides.
DOI: 10.1134/S1070363207060205

We previously [1] synthesized diesters **III**–**V** from diterpenoid isosteviol (**I**, *ent*-16-oxobeyeran-19-oic acid) and adipic, suberic, and sebacic acid chlorides. Analysis of the reaction mixtures by thin-layer chromatography revealed the presence of trace amounts of weakly polar products with R_f 0.9 (diesters **III**–**V** had an R_f value of 0.7, petroleum ether–diethyl ether–benzene, 1 : 1 : 1). In the present work we succeeded in isolating these minor products in 4–6% yield by column chromatography on silica gel.



I **II**

III–V **VI–VIII**

III, **VI**, n = 4; **IV**, **VII**, n = 6; **V**, **VIII**, n = 8.

The IR spectra of the isolated compounds lacked absorption bands typical of carboxylic acids (stretching vibrations of the carbonyl group at 1697 cm^{-1} and OH group at 2700–3000 cm^{-1}), but bands at 990 and 1800 cm^{-1} were present, which may be assigned to carboxylic acid anhydrides. In the MALDI-TOF spectra of each product we observed a peak with an *m/z* value corresponding to the molecular weight of diester

III–**V** minus 18 (water molecule). These data led us to presume that the minor products have the structure of macrocyclic assemblies **VI**–**VIII** in which two *ent*-beyerane fragments are linked through an anhydride bridge between the C^4 atoms. The structure of compound **VIII** was proved by the X-ray diffraction data (see figure). As far as we know, compounds **VI**–**VIII** are the first representatives of synthetic macrocycles of the *ent*-beyerane series.

EXPERIMENTAL

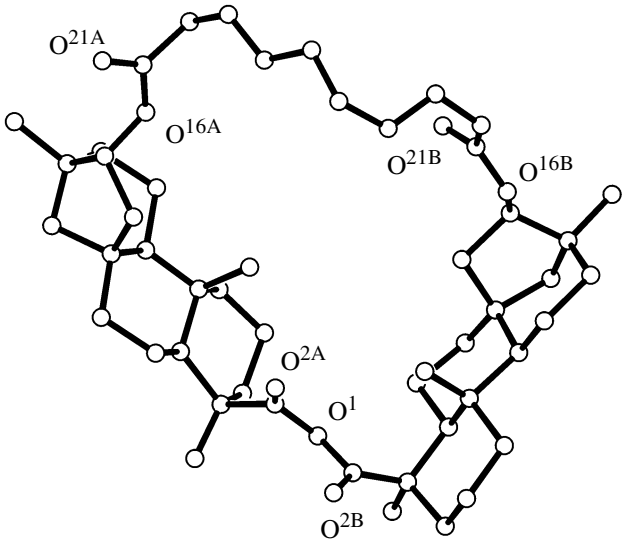
X-ray analysis of a single crystal of compound **VIII** was performed on an Enraf–Nonius CAD-4 automatic four-circle diffractometer (CuK_α irradiation, λ = 1.54184 Å, graphite monochromator; $\theta/2\theta$ scanning, scan range $4.2 \le \theta \le 78.4°$, scan angle $\omega = 1.2 + 0.35 \tan\theta$; variable scan rate, 1 to 16.4 deg min^{-1} by θ). The complete set of crystallographic data for compound **VIII** (coordinates of atoms and crystal structure parameters) was deposited to the Cambridge Crystallographic Data Center (entry no. CCDC 627 872).

The IR spectra were recorded on a Bruker Vector 22 spectrometer with Fourier transform in the frequency range from 400 to 4000 cm^{-1}; samples were prepared as KBr pellets. The mass spectra (matrix-assisted laser desorption/ionization, MALDI) were obtained on a DYNAMO MALDI TOF time-of-flight mass spectrometer (Thermo Bioanalysis Finnigan, USA; pulse UV laser, λ = 337 nm; dihydroxybenzoic acid matrix); a sample was prepared by the "dried drop" technique: a mixture of a solution of dihydroxybenzoic acid in ethanol (1 wt%) and a solution of compound **VI**–**VIII** in methanol (0.1 wt%) was applied to an appropriate support and dried at 40°C.

The ^1H NMR spectra were measured on an Avance 600 instrument. Silica gel (Chemapol) was used for column chromatography. The reaction mixtures were analyzed by thin-layer chromatography on Silufol UV-254 plates.

Compounds **VI**–**VIII** were obtained according to the procedure described in [1] and were isolated by column chromatography on silica gel using petroleum ether–diethyl ether–benzene (1 : 1 : 1) as eluent. Isosteviol (**I**) was synthesized by acid hydrolysis of the glycoside extract from *Stevia rebaudiana Bertoni* as reported in [2] and was reduced to hydroxy acid **II** according to the known procedure [3]. The properties of diesters **III**–**V** were consistent with the data of [1].

2,9,12-Trioxa-1,10(16,4)di(*ent*-19-norbeyerana)-cyclotridecaphane-3,8,11,13-tetraone (VI). Yield 0.01 g (5%). IR spectrum, ν, cm^{-1}: 1377 m, 1458 s, 1729 s (O–C–O), 1801 s (CO–O–CO). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.8–1.9 m (42H, beyerane skeleton) 0.79 s (6H, $C^{20}H_3$); 0.90 s (6H, $C^{17}H_3$); 1.26 s (6H, $C^{18}H_3$); 2.18 d.d (2H, 3-H_{eq}); 2.33 m (4H, $COCH_2$); 4.65 d.d (2H, 16-H, *J* = 10.8, 4.4). Mass spectrum (MALDI-TOF): *m/z* 865 [*M* + Cs]$^+$. $C_{46}H_{68}O_7$. Calculated: *M* 732.



Structure of the molecule of compound **VIII** in crystal according to the X-ray diffraction data. Hydrogen atoms are not shown; only oxygen atoms are marked.

2,11,14-Trioxa-1,12(16,4)di(*ent*-19-norbeyerana)cyclopentadecaphane-3,10,13,15-tetraone (VII). Yield 0.02 g (6%). IR spectrum, ν, cm^{-1}: 1370 m, 1458 s, 1734 s (O–C–O), 1804 s (CO–O–CO). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.7–2.0 m (42H, beyerane skeleton), 0.71 s (6H, $C^{20}H_3$); 0.80 s (6H, $C^{17}H_3$); 1.25 s (6H, $C^{18}H_3$); 2.21 d (2H, 3-H_{eq}); 2.30 m (4H, $COCH_2$); 4.73 d.d (2H, 16-H, *J* = 10.6, 4.1). Mass spectrum (MALDI-TOF), *m/z*: 760 [*M*]$^+$, 783 [*M* + Na]$^+$, 799 [*M* + K]$^+$. $C_{48}H_{72}O_7$. Calculated: *M* 760.

2,13,16-Trioxa-1,14(16,4)di(*ent*-19-norbeyerana)cycloheptadecaphane-3,12,15,17-tetraone (VIII). Yield 0.01 g (4%). IR spectrum, ν, cm^{-1}: 1380 m, 1464 s, 1734 s (O–C–O), 1804 s (CO–O–CO). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.85–2.0 m (42H, beyerane skeleton), 0.82 s (6H, $C^{20}H_3$); 0.97 s (6H, $C^{17}H_3$); 1.37 s (6H, $C^{18}H_3$); 2.19 d (2H, 3-H_{eq}); 4.75 d.d (2H, 16-H, *J* = 10.45, 4.63). Mass spectrum (MALDI-TOF), *m/z*: 811 [*M* + Na]$^+$, 827 [*M* + K]$^+$. $C_{50}H_{76}O_7$. Calculated: *M* 788.

ACKNOWLEDGMENTS

This study was performed under financial support by the Russian Foundation for Basic Research (project nos. 04-03-32133, 05-03-33008).

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