Chemistry of Natural Compounds, Vol. 46, No. 3, 2010

SYNTHESIS AND MODIFICATION OF DITERPENOIDS WITH TWO DIHYDROQUINOPIMARIC ACID SKELETONS

I. E. Smirnova,[1] E. V. Tret′yakova,[1] O. B. Kazakova,[1]* L. V. Spirikhin,[1] G. A. Tolstikov,[1] V. E. Kataev,[2] and R. Z. Musin[2]

UDC 547.824:542.91:548.737

Diesters and diamides in which two dihydroquinopimaric acid carbon skeletons are covalently bonded through aliphatic spacers were synthesized.

Keywords: diterpenoids, dihydroquinopimaric acid, macrocycles.

The synthesis of compounds with several carbocyclic skeletons that form the basis of various isoprenoid natural metabolites has recently become one of the active areas of organic chemistry [1–3]. These derivatives, primarily higher terpenoids, are interesting because slight changes of their structures cause significant changes in the biological activity [4, 5]. The combination in a single molecule of several diterpenoid skeletons causes new properties to appear. Derivatives of podocarpic acid with two abietane skeletons are promising as potential liver X-receptor agonists [2]. Derivatives of the diterpenoid isosteviol with two *ent*-beyerane skeletons transport through a liquid $CHCl_3$ membrane amino acids [6] and iron cations [7] and exhibit antituberculosis activity [8]. The first macrocycles containing diterpenoid [9] or steroid [10] skeletons have been synthesized. Of these, macrocyclic taxanoids with anticancer activity greater than that of taxol have the most practical value [11].

One of the first important problems on the synthetic route to compounds with several skeletons is the development of methods for bonding them covalently. The simplest pathway is the acid chloride route that includes reaction of the acid chlorides of terpenoid acids with H-binucleophiles of various structures [8]. Herein we report the first synthesis of diesters and diamides containing two dihydroquinopimaric acid (DQPA) carbon skeletons (**1**).

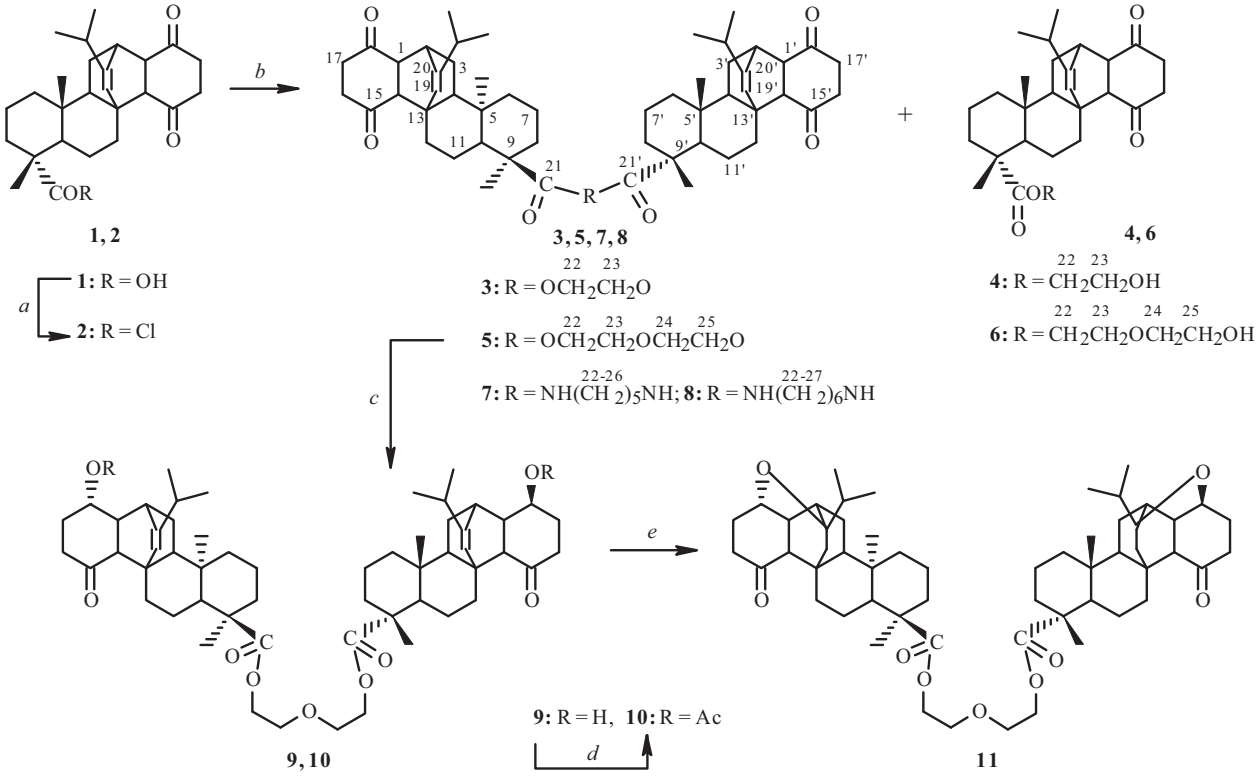
Reaction of DQPA chloride (**2**) with diols (ethyleneglycol, diethyleneglycol) and diamines (1,5-penta- and 1,6-hexamethylenediamines) in a 2:1 ratio by refluxing in $CHCl_3$ in the presence of Et_3N synthesized derivatives **3**–**8** in 29–65% yields after chromatographic purification (Scheme 1). The structures of the compounds were established by NMR spectroscopy and mass spectrometry. The NMR spectra of **3** and **5**–**8**, which contained two skeletons, showed one set of resonances of double intensity for the carbon skeleton. Characteristic resonances of C atoms C-21 and C-21′ at δ 177.8–178.5 ppm in the ^{13}C NMR spectra were indicative of the formation of ester and amide bonds in **3**–**8**.

Methylene resonances for the $–O–CH_2–CH_2–O–$ spacer in the skeleton of diester **3** were observed at δ_C 60.5 ppm (^{13}C NMR) and δ_H 2.81 ppm as a doublet of doublets (PMR). A doublet of triplets for the $–CH_2–CH_2OH$ resonance in the PMR spectrum at δ_H 4.40 ppm was indicative of the formation of monoester **4**. Resonances of the $–O–(CH_2)_2–O–(CH_2)_2–O–$ spacer in spectra of **5** were observed at δ 69.2 and 63.7 ppm (^{13}C NMR) and δ 3.65 and 4.23 ppm as triplets (PMR). In contrast with the ^{13}C NMR spectrum of **5**, that of **6** contained resonances of C-24 and C-25 at δ 72.2 and 61.5 ppm.

The electron-impact (EI) mass spectrum of **5** had a peak for the fragment ion $[M – CH_3]^+$ (*m*/*z* 879) in the heavy mass region. Other fragment ions with lower *m*/*z* values in the mass spectrum of **5** were apparently formed by successive decomposition under EI of the aforementioned ion. The base peak in the electrospray ionization (ESI) mass spectrum had *m*/*z* 917 and corresponded to $[M + Na]^+$.

1) Institute of Organic Chemistry, Ufa Scientific Center, Russian Academy of Sciences, 450054, Ufa, prosp. Oktyabrya, 71, Russia, fax: (3472) 35 60 66, e-mail: obf@anrb.ru; 2) A. E. Arbuzov Institute of Organic and Physical Chemistry, Kazan Scientific Center, Russian Academy of Sciences, 420088, Kazan, ul. Arbuzova, 8, Russia. Translated from Khimiya Prirodnykh Soedinenii, No. 3, pp. 324–327, May–June, 2010. Original article submitted September 23, 2009.

0009-3130/10/4603-0383



a. $(COCl)_2$, $CHCl_3$; *b*. $(CH_2OH)_2$ or $O(CH_2CH_2OH)_2$ or $NH_2(CH_2)_6NH_2CH_2Cl_2$; *c*. $NaBH_4$, MeOH; *d*. Ac_2O, Py; *e*. HCl, MeOH

Sheme 1

Resonances for methylene groups of the spacer in diamides **7** and **8** were observed at δ_C 39.6–24.2 ppm (^{13}C NMR) and at δ 3.14–3.35 as a multiplet (PMR).

Compound **5**, in which two DQPA skeletons were bonded by a diethyleneglycol spacer were modified at the C-18 and C-18′ positions. Reduction of **5** by $NaBH_4$ in MeOH produced the bishydroxy derivative **9**, which was characterized as the acetate **10**. The ^{13}C NMR spectrum of **11**, which was obtained from **9** by refluxing in the presence of HCl, exhibited characteristic resonances for the pairs C-18, C-18′ and C-20, C-20′ at δ 72.8 and 84.1 ppm, respectively.

Thus, we synthesized diesters and diamides in which two DQPA skeletons were covalently bonded through aliphatic spacers. The determination of the properties of the bis-derivatives as compared with the starting diterpenoids and the development of methods for converting them to macrocycles will be reported separately.

EXPERIMENTAL

^{13}C NMR and PMR spectra in $CDCl_3$ were recorded on a Bruker AM-300 spectrometer (75.5 and 300 MHz, respectively) with $SiMe_4$ internal standard. Melting points were determined on a Boetius microstage. Optical rotation was measured on a Perkin–Elmer 241 MC polarimeter in a 1-dm tube. EI mass spectra were obtained in a Trace MS Finnigan MAT instrument at 70 eV ionizing electron energy and ion-source temperature 200°C. Heating of the direct-probe vaporizer system was programmed from 40 to 400°C at 35°C/min. ESI mass spectra were obtained in a DFS Thermo Electron Corporation instrument (syringe pump, 1% solution in MeOH at flow rate 5 μL/min) in positive-ion mode at capillary potential 4.5 kV. TLC was performed on Silufol plates (Chemapol, Czech Rep.) using $CHCl_3$:MeOH (20:1). Compounds were detected by phosphotungstic acid solution (10%) in EtOH with subsequent heating to 100–120°C for 2–3 min. DQPA (**1**) and its acid chloride (**2**) were prepared by literature methods [12, 13].

Synthesis of 3–8. DQPA chloride (**2**, 1 mmol, 0.43 g) in dry CH_2Cl_2 (10 mL) was treated with diol (0.5 mmol, 0.02 mL ethyleneglycol or 0.025 mL diethyleneglycol) or diamine (0.5 mmol, 0.05 g 1,5-pentamethylenediamine or 0.05 g

1,6-hexamethylenediamine) and Et_2N (0.3 mL), refluxed for 12 h (TLC monitoring), washed with HCl solution (20 mL, 5%) and water (2 × 20 mL), and dried over $MgSO_4$. Solvent was vacuum distilled. The solid was purified by column chromatography over Al_2O_3 with elution by $CHCl_3$.

***Bis*-[(20-isopropyl-5,9-dimethyl-15,18-dioxopentacyclo[12.4.0.2^{2,13}.0^{5,10}.0^{4,13}]-eicos-19-en-5-carboxy]ethane (3).** Yield 0.39 g (43%), mp 102–105°C ($CHCl_3$), $[\alpha]_D^{20}$ +5.0° (*c* 0.1, $CHCl_3$), $C_{54}H_{74}O_8$.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.51 (6H, s, $2CH_3$), 0.68–0.79 (4H, m), 0.95 [6H, s, 2×CH($C\underline{H}_3$)$_2$], 1.01 [6H, s, 2×CH($C\underline{H}_3$)$_2$], 1.12 (6H, s, $2CH_3$), 1.15–2.00 (24H, m), 2.01–2.61 (14H, m), 2.81 (4H, dd, J_1 = 2.1, J_2 = 5.1, H-22, H-23), 3.11 (2H, br.s), 5.40 (2H, br.s, H-19, H-19′).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 208.0 (C-18, C-18′), 206.9 (C-15, C-15′), 177.8 (C-21, C-21′), 149.5 (C-20, C-20′), 126.2 (C-19, C-19′), 60.5 (C-22, C-23), 56.3 (2C), 54.8 (2C), 49.7 (2C), 46.9 (C-9, C-9′), 46.2 (2C), 41.5 (2C), 39.1 (2C), 39.0 (2C), 38.6 (2C), 38.3 (2C), 37.7 (2C), 37.3 (2C), 35.1 (2C), 33.1 (2C), 27.9 (2C), 22.4 (2C), 21.2 (2C), 20.3 (2C), 19.0 (2C), 17.0 (2C), 16.6 (2C).

9-Hydroxyethoxyethyl-[(20-isopropyl-5,9-dimethyl-15,18-dioxopentacyclo[12.4.0.2^{2,13}.0^{5,10}.0^{4,13}]-eicos-19-en-5-carboxylate (4). Yield 0.23 g (51%), mp 90–93°C ($CHCl_3$), $[\alpha]_D^{20}$ +43.0° (*c* 0.56, $CHCl_3$), $C_{28}H_{40}O_5$.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.65 (3H, s, CH_3), 0.71–0.89 (2H, m, 2CH), 0.91 [3H, d, J = 6.9, CH($C\underline{H}_3$)$_2$], 0.97 [3H, d, J = 6.9, CH($C\underline{H}_3$)$_2$], 1.09 (3H, s, CH_3), 1.11–1.72 (12H, m), 2.08–2.50 (6H, m), 2.75 (1H, br.s, H-12), 3.12 (1H, br.s), 4.11–4.31 (2H, m, H-22), 4.40 [2H, dt, J_1 = 2.3, J_2 = 5.7, $C\underline{H}_2$(23)OH], 5.30 (1H, br.s, OH), 5.49 (1H, br.s, H-19).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 209.5 (C-18), 207.9 (C-15), 177.8 (C-21), 149.1 (C-20), 125.4 (C-19), 62.3 (C-22), 60.4 (C-23), 60.0, 55.7, 54.7, 49.3 (C-9), 46.9, 41.1, 38.7, 38.2, 37.8, 37.6, 36.9, 36.5, 34.6, 32.8, 27.7, 21.7, 20.7, 19.8, 16.9, 16.6, 15.8.

***Bis*-[(20-isopropyl-5,9-dimethyl-15,18-dioxopentacyclo[12.4.0.2^{2,13}.0^{5,10}.0^{4,13}]-eicos-19-en-5-carboxy]ethoxyethane (5).** Yield 0.58 g (65%), mp 101–104°C ($CHCl_3$), $[\alpha]_D^{20}$ +5.5° (*c* 0.37, $CHCl_3$), $C_{56}H_{78}O_9$.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.56 (6H, s, 2×CH_3), 0.81–0.96 (4H, m), 0.98 [6H, s, 2×CH($C\underline{H}_3$)$_2$] and 1.03 [6H, s, 2×CH($C\underline{H}_3$)$_2$], 1.12 (6H, s, $2CH_3$), 1.12–1.81 (22H, m), 2.18–2.57 (12H, m), 2.67 (2H, dd, J_1 = 2.6, J_2 = 5.6, H-2, H-2′), 3.20 (2H, br.s), 3.65 (4H, t, J = 4.7, H-23, H-24), 4.23 (4H, t, J = 4.9, H-22, H-25), 5.51 (2H, br.s, H-19, H-19′).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 209.9 (C-18, C-18′), 208.9 (C-15, C-15′), 178.5 (C-21, C-21′), 149.6 (C-20, C-20′), 125.4 (C-19, C-19′), 69.2 (C-23, C-24), 63.7 (C-22, C-25), 60.7 (2C), 56.0 (2C), 54.9 (2C), 49.4 (2C), 47.1 (C-9, C-9′), 41.3 (2C), 39.0 (2C), 38.6 (2C), 38.0 (2C), 37.8 (2C), 37.1 (2C), 36.6 (2C), 34.8 (2C), 34.9 (2C), 27.9 (2C), 21.8 (2C), 20.8 (2C), 19.9 (2C), 17.1 (2C), 16.8 (2C), 16.0 (2C).

Mass spectrum (EI, 70 eV, *m*/*z*, I_{rel}, %): 879 (0.1) $[M - CH_3]^+$, 786 (0.15), 785 (0.25) $[C_{50}H_{73}O_7]^+$, 784 (0.22), 7835 (0.12), 674 (1.2), 673 (2.7) $[C_{45}H_{69}O_4]^+$, 672 (1.7), 671 (1.1), 257 (82.6) $[C_{17}H_{21}O_2]^+$, 133 (100) $[C_{10}H_{13}]^+$ (peaks of ions containing the most common isotopes are shown). Mass spectrum (ESI, *m*/*z*, I_{rel}, %): 917 (100) $[M + Na]^+$.

9-(2-Hydroxy-1-ethoxy)ethyl-[(20-isopropyl-5,9-dimethyl-15,18-dioxopentacyclo[12.4.0.2^{2,13}.0^{5,10}.0^{4,13}]-eicos-19-en-5-carboxylate (6). Yield 0.16 g (29%), mp 89–91°C ($CHCl_3$), $[\alpha]_D^{20}$ +54.0° (*c* 0.56, $CHCl_3$), $C_{30}H_{44}O_6$.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.67 (3H, s, CH_3), 0.73–0.94 (2H, m, 2CH), 0.95 [3H, d, J = 6.9, CH($C\underline{H}_3$)$_2$], 1.02 [3H, d, J = 6.9, CH($C\underline{H}_3$)$_2$], 1.12 (3H, s, CH_3), 1.15–1.83 (12H, m), 2.12–2.56 (6H, m), 2.76 (1H, br.s, H-12), 3.12 (1H, br.s), 3.57–3.65 (4H, m, H-23, H-24), 3.67 [2H, s, $C\underline{H}_2$(25)OH], 4.45 (2H, t, J = 6.5, H-22), 5.30 (1H, br.s, OH), 5.51 (1H, br.s, H-19).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 210.5 (C-18), 210.4 (C-15), 178.2 (C-21), 149.5 (C-20), 125.2 (C-19), 72.2 (C-24), 69.0 (C-23), 63.3 (C-22), 61.5 (C-25), 60.4, 55.8, 54.7, 49.0 (C-9), 46.9, 41.1, 38.7, 38.3, 37.7, 37.5, 36.8, 36.2, 34.4, 32.7, 27.7, 21.7, 20.6, 19.7, 16.7, 16.5, 15.7.

***N*,*N*′-*Bis*-[(20-isopropyl-5,9-dimethyl-15,18-dioxopentacyclo[12.4.0.2^{2,13}.0^{5,10}.0^{4,13}]-eicos-19-en-5-carboxy]-diaminopentane (7).** Yield 0.47 g (53%), mp 93–95°C ($CHCl_3$), $[\alpha]_D^{20}$ +4.3° (*c* 0.4, $CHCl_3$), $C_{57}H_{82}N_2O_6$.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.55 (6H, s, $2CH_3$), 0.60–0.98 (4H, m), 0.99 [6H, s, 2×CH($C\underline{H}_3$)$_2$], 1.05 [6H, s, 2×CH($C\underline{H}_3$)$_2$], 1.10 (6H, s, $2CH_3$), 1.12–1.87 (24H, m), 2.18–2.60 (12H, m), 2.78 (2H, dd, J_1 = 2.7, J_2 = 6.0, H-2, H-2′), 3.04 (2H, br.s), 3.13–3.34 (10H, m, $5CH_2$), 5.50 (2H, br.s, H-19, H-19′), 5.98 (2H, br.s, CON$\underline{H}$),

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 209.7 (C-18, C-18′), 208.7 (C-15, C-15′), 178.5 (2$\underline{C}$ONH), 149.3 (C-20, C-20′), 125.5 (C-19, C-19′), 60.6 (2C), 55.8 (2C), 54.8 (2C), 49.8 (2C), 46.6 (C-9, C-9′), 39.6 (2C), 38.8 (2C), 38.4 (2C), 38.0 (2C), 37.6 (2C), 36.9 (2C), 36.8 (2C), 34.7 (2C), 32.8 (2C), 31.8 (C), 29.5 (2C), 27.7 (2C), 24.2 (2C), 21.2 (2C), 20.7 (2C), 19.8 (2C), 17.1 (2C), 16.6 (2C), 15.9 (2C).

***N,N′-Bis*-[(20-isopropyl-5,9-dimethyl-15,18-dioxopentacyclo[12.4.0.2^{2,13}.0^{5,10}.0^{4,13}]-eicos-19-en-5-carboxy]-diaminohexane (8).** Yield 0.56 g (62%), mp 97–99°C ($CHCl_3$), $[\alpha]_D^{20}$ +5.2° (*c* 0.5, $CHCl_3$), $C_{58}H_{84}N_2O_6$.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.55 (6H, s, $2CH_3$), 0.70–0.98 (4H, m), 0.99 [6H, s, 2×CH($C\underline{H}_3$)$_2$], 1.04 [6H, s, 2×CH($C\underline{H}_3$)$_2$], 1.10 (6H, s, $2CH_3$), 1.13–1.85 (24H, m), 2.13–2.58 (12H, m), 2.80 (2H, dd, J_1 = 2.4, J_2 = 5.3, H-2, H-2′), 3.05 (2H, br.s), 3.14–3.35 (12H, m, $6CH_2$), 5.50 (2H, br.s, H-19, H-19′), 5.95 (2H, t, J = 5.2, CON$\underline{H}$).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 209.8 (C-18, C-18′), 208.8 (C-15, C-15′), 178.4 (2$\underline{C}$ONH), 149.5 (C-20, C-20′), 125.5 (C-19, C-19′), 60.6 (2C), 55.9 (2C), 54.8 (2C), 49.9 (2C), 46.6 (C-9, C-9′), 41.2 (2C), 39.6 (2C), 38.9 (2C), 38.4 (2C), 38.0 (2C), 37.7 (2C), 37.0 (2C), 36.9 (2C), 34.7 (2C), 32.9 (2C), 29.3 (2C), 27.8 (2C), 24.2 (2C), 21.2 (2C), 20.7 (2C), 19.8 (2C), 17.1 (2C), 16.7 (2C), 16.0 (2C).

***Bis*-[(20-isopropyl-5,9-dimethyl-15β-hydroxy,18-oxopentacyclo[12.4.0.2^{2,13}.0^{5,10}.0^{4,13}]-eicos-19-en-5-carboxy]ethoxyethane (9).** Compound **5** (1 mmol, 0.89 g) in $CHCl_3$:MeOH (20 mL, 1:1) was treated in portions with $NaBH_4$ (5 mmol, 0.2 g), stirred at room temperature for 2 h, washed with HCl solution (20 mL, 5%) and water (2 × 20 mL), and dried over $MgSO_4$. Solvent was vacuum distilled. The solid was purified by column chromatography over Al_2O_3 with elution by $CHCl_3$. Yield 0.78 g (87%), mp 102–104°C ($CHCl_3$), $[\alpha]_D^{20}$ +4.6° (*c* 1.8, $CHCl_3$), $C_{56}H_{82}O_9$.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.55 (6H, s, $2CH_3$), 0.79-0.96 (4H, m), 0.98 [6H, s, 2×CH($C\underline{H}_3$)$_2$], 1.03 [6H, s, 2×CH($C\underline{H}_3$)$_2$], 1.12 (6H, s, $2CH_3$), 1.25–1.95 (24H, m), 1.97–2.51 (14H, m), 2.75 (2H, br.s), 3.66 (4H, br.s, H-23, H-24), 3.89 (2H, br.s, H-18, H-18′), 4.12 (4H, br.s, H-22, H-25), 4.71 (2H, br.s, O$\underline{H}$), 5.51 (2H, br.s, H-19, H-19′).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 212.9 (C-15, C-15′), 178.1 (C-21, C-21′), 146.9 (C-20, C-20′), 125.2 (C-19, C-19′), 68.7 (C-23, C-24), 68.1 (C-18, C-18′), 63.1 (C-22, C-25), 54.9 (2C), 49.3 (2C), 48.1 (2C), 46.7 (C-9, C-9′), 40.3 (2C), 38.1 (2C), 37.7 (2C), 36.4 (2C), 36.1 (2C), 35.1 (2C), 34.9 (2C), 33.0 (2C), 30.1 (2C), 27.3 (2C), 21.8 (2C), 21.6 (2C), 21.3 (2C), 19.6 (2C), 17.0 (2C), 16.7 (2C), 15.7 (2C).

***Bis*-[(20-isopropyl-5,9-dimethyl-15-methylcarbonyloxy-18-oxopentacyclo[12.4.0.2^{2,13}.0^{5,10}.0^{4,13}]-eicos-19-en-5-carboxy]ethoxyethane (10).** Compound **8** (1 mmol, 0.89 g) in Py (10–15 mL) was treated with Ac_2O (0.6 mL), left at room temperature for 15 h, and poured into HCl solution (50 mL, 5%). The solid was filtered off, washed with water, dried in air, and purified by column chromatography over Al_2O_3 with elution by $CHCl_3$. Yield 0.91 g (93%), mp 105–107°C ($CHCl_3$), $[\alpha]_D^{20}$ +5.6° (*c* 0.25, $CHCl_3$), $C_{60}H_{86}O_{11}$.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.60 (6H, s, $2CH_3$), 0.62–0.98 (4H, m), 1.01 [6H, s, 2×CH($C\underline{H}_3$)$_2$] and 1.05 [6H, s, 2×CH($C\underline{H}_3$)$_2$], 1.30 (6H, s, $2CH_3$), 1.25–1.99 (24H, m), 2.05 (6H, s, $2C\underline{H}_3O$), 2.03–2.95 (14H, m), 3.12 (2H, br.s), 3.65 (4H, br.s, H-23, H-24), 4.12 (4H, br.s, H-22, H-25), 4.91 (2H, br.s, H-18, H-18′), 5.52 (2H, br.s, H-19, H-19′).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 210.9 (C-15, C-15′), 178.2 (2O$\underline{C}$OCH_3), 70.4 (C-18, C-18′), 147.2 (C-20, C-20′), 123.9 (C-19, C-19′), 68.9 (C-23, C-24), 63.3 (C-22, C-25), 61.6 (2C), 54.5 (2C), 49.1 (2C), 46.8 (C-9, C-9′), 44.4 (2C), 40.2 (2C), 38.0 (2C), 37.5 (2C), 36.3 (2C), 35.8 (2C), 35.0 (2C), 34.9 (2C), 32.7 (2C), 29.8 (2C), 23.6 (2O$\underline{C}$H3), 21.5 (2C), 21.2 (2C), 20.9 (2C), 19.3 (2C), 16.8 (2C), 16.6 (2C), 16.5 (2C), 15.5 (2C).

***Bis*-[(20-isopropyl-5,9-dimethyl-18-oxo-15-oxohexacyclo[12.4.0.2^{2,13}.0^{5,10}.0^{4,13}]-eicos-19-en-5-carboxy]ethoxyethane (11).** Compound **10** (1 mmol, 0.89 g) in $CHCl_3$:MeOH (20 mL, 1:1) was treated with conc. HCl (5 mL), refluxed for 12 h (TLC monitoring), washed with $NaHCO_3$ solution (20 mL, 5%) and water (2 × 20 mL), and dried over $MgSO_4$. Solvent was vacuum distilled. The solid was purified by column chromatography over Al_2O_3 with elution by $CHCl_3$. Yield 0.66 g (74%), mp 97–100°C ($CHCl_3$), $[\alpha]_D^{20}$ +3.8° (*c* 0.8, $CHCl_3$), $C_{56}H_{82}O_9$.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.57 (6H, s, $2CH_3$), 0.79–0.96 (4H, m), 0.98 [6H, s, 2×CH($C\underline{H}_3$)$_2$], 1.03 [6H, s, 2×CH($C\underline{H}_3$)$_2$], 1.12 (6H, s, $2CH_3$), 1.25–1.95 (24H, m), 1.97–2.51 (18H, m), 2.75 (2H, br.s), 3.65 (4H, br.s, H-23, H-24), 3.82 (2H, br.s, H-18, H-18′), 4.12 (4H, br.s, H-22, H-25).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 212.9 (C-15, C-15′), 178.3 (C-21, C-21′), 84.1 (C-20, C-20′), 72.8 (C-18, C-18′), 68.9 (C-23, C-24), 63.3 (C-22, C-25), 61.8 (2C), 55.4 (2C), 51.5 (2C), 49.9 (2C), 47.7 (2C), 46.7 (C-9, C-9′), 40.3 (2C), 38.1 (2C), 37.7 (2C), 36.4 (2C), 36.1 (2C), 35.1 (2C), 34.9 (2C), 33.0 (2C), 30.1 (2C), 27.3 (2C), 21.6 (2C), 21.3 (2C), 19.6 (2C), 17.0 (2C), 16.7 (2C), 15.7 (2C).

ACKNOWLEDGMENT

The work was supported financially by the Basic Research Program of the RAS Presidium "Development of Methods for Preparing Chemical Compounds and Creating New Materials."

REFERENCES

1. L.-H. Lin, L.-W. Lee, S.-Y. Sheu, and P.-Y. Lin, *Chem. Pharm. Bull.*, **52**, 1117 (2004).
2. W. Liu, S. Chen, J. Dropinski, L. Colwell, M. Robins, M. Szymonifka, N. Hayes, N. Sharma, K. MacNaul, M. Hernandez, C. Burton, C. P. Sparrow, J. G. Menke, and S. B. Singh, *Bioorg. Med. Chem. Lett.*, **15**, 4574 (2005).
3. V. A. Alfonsov, G. A. Bakaleynik, A. T. Gubaidullin, V. E. Kataev, G. I. Kovyljaeva, A. I. Konovalov, I. A. Litvinov, I. Yu. Strobykina, O. V. Andreeva, and M. G. Korochkina, *Mendeleev Commun.*, **5**, 177 (2000).
4. L. Huang, X. Yuan, C. Aiken, and C. Ho Chen, *Antimicrob. Agents Chemother.*, **4**, 663 (2004).
5. T. G. Tolstikova, I. V. Sorokina, G. A. Tolstikov, A. G. Tolstikov, and O. B. Flekhter, *Bioorg. Khim.*, **32**, 42 (2006) [*Russ. J. Bioorg. Chem.* (Engl. transl.), **32**, 37 (2006)].
6. V. E. Kataev, I. Yu. Strobykina, O. I. Militsina, M. G. Korochkina, O. V. Fedorova, I. G. Ovchinnikova, M. S. Valova, and G. L. Rusinov, *Tetrahedron Lett.*, **47**, 2137 (2006).
7. E. Kataev, O. I. Militsina, I. Yu. Strobykina, A. T. Gubaidullin, V. V. Zverev, O. I. Kataeva, O. V. Fedorova, M. S. Valova, and G. L. Rusinov, *J. Inclusion Phenom. Macrocyclic Chem.*, **60**, 51 (2008).
8. E. V. Kataev, O. I. Militsina, I. Yu. Strobykina, G. I. Kovylyaeva, R. Z. Musin, O. V. Fedorova, G. L. Rusinov, M. N. Zueva, G. G. Mordovskoi, and A. G. Tolstikov, *Khim.-farm. Zh.*, **40**, 12 (2006) [*Pharm. Chem. J.*, **40**, 473 (2006)].
9. I. Yu. Strobykina, B. F. Garifullin, G. I. Kovylyaeva, R. Z. Musin, A. T. Gubaidullin, and E. V. Kataev, *Zh. Obshch. Khim.*, **77**, 978 (2007) [*Russ. J. Gen. Chem.*, **77**, 1066 (2007)].
10. I. Ojima, S. Lin, T. Inoue, M. Miller, C. Borella, and X. Geng, *J. Am. Chem. Soc.*, **122**, 5343 (2000).
11. O. Shirota, S. Sekita, M. Satake, H. Morita, K. Takeya, and H. Itokawa, *Chem. Pharm. Bull.*, **52**, 739 (2004).
12. W. Herz, R. C. Blackstone, and M. G. Nair, *J. Org. Chem.*, **32**, 2992 (1967).
13. O. B. Flekhter, I. E. Smirnova, E. V. Tret′yakova, G. A. Tolstikov, O. V. Savinova, and E. I. Boreko, *Bioorg. Khim.*, **35**, 424 (2009) [*Russ. J. Bioorg. Chem.* (Engl. transl.), **35**, 385 (2009)].