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SYNTHESIS OF MACROCYCLES WITH ONE AND MORE *ent*-BEYERANE SKELETONS BASED ON THE DITERPENOID ISOSTEVIOL

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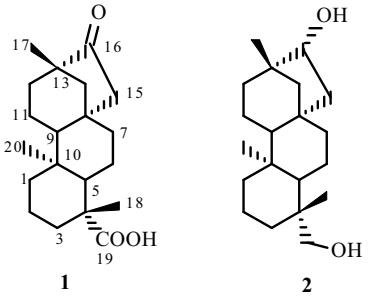
Macrocycles with one and more ent-*beyerane skeletons were prepared by the reaction of 16,19-dihydroxy-* ent-*beyerane with several dibasic carboxylic acid chlorides. The structures of the synthesized compounds, namely, the number of* ent-*beyerane skeletons in the macrocycle, depended on the length of the polymethylene chain in the acid chloride. The molecular structures of two of the synthesized macrocycles were established by x-ray crystal structures.*

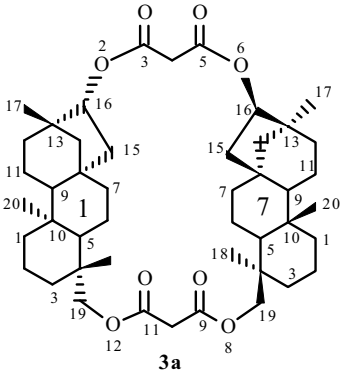
Keywords: macrocycles, diterpenoids, beyeranes, isosteviol.

The number of publications on the synthesis of macrocyclic compounds has risen dramatically in the last 20 years. The interest in them is due to their ability to act as host molecules, often exhibiting highly selective molecular recognition of guests (ions) [1–3]. Native macrocycles isolated from plants or marine organisms were also described in the literature [4–7]. However, these compounds have little practical value despite their biological activity because they are isolated in minimal quantities from natural sources. In this respect synthetic macrocycles obtained from biologically active metabolites isolated from natural sources in tangible quantities are much more promising. Several such compounds are known, for example, synthetic macrocycles based on bile acids [8] and mono- [9, 10] and diterpenoids [11–14]. It is noteworthy that the first macrocycles containing two diterpenoid skeletons were obtained as side products from the synthesis of compounds in which two isosteviol (16-oxo-*ent*-beyeran-19-oic acid) diterpenoid molecules (**1**) were joined by diester and anhydride spacers [14]. In order to synthesize macrocycles based on this diterpenoid, we used a more rational approach, the so-called acid-chloride approach, which consisted of the reaction of fully reduced isosteviol, diol **2**, with dibasic carboxylic acid chlorides. As it turned out, the structures of the products depended on that of the starting acid chloride, namely, on the length of the hydrocarbon chain between the C(O)Cl groups.

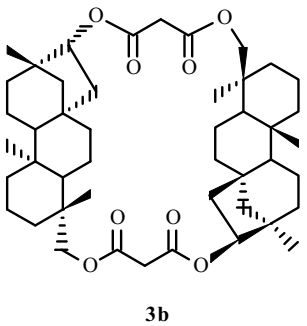


1

2



3a



3b

The reaction of **2** (16,19-dihydroxy-*ent*-beyerane) with malonic acid dichloride gave in 9% yield a product with a molecular ion that corresponded to the mass of macrocycle **3**. According to PMR data this macrocycle was not a pure compound but a mixture of the head-to-head **3a** and head-to-tail **3b** isomers. This was indicated by the presence of not a single multiplet

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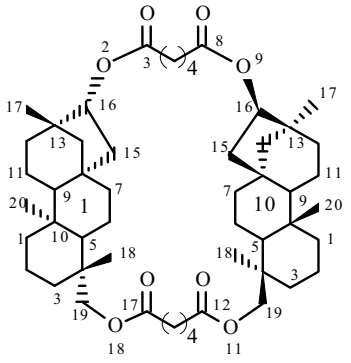
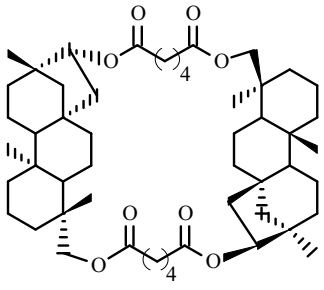
for the resonance of the C^{19} protons (4.4–5 ppm), as would be found for only one macrocycle **3**, but two multiplets (4.41–4.46 and 4.94–4.99 ppm) separated from each other by 0.5 ppm and corresponding to resonances of $C^{19}H_2$ protons in **3a** and **3b**. The malonate protons of **3a** and **3b** differed less. Their AB spin system formed a multiplet at 3.31–3.39 ppm. The presence in the PMR spectrum of not three characteristic singlets for the resonances of C^{20}, C^{18}, and C^{17} methyl protons at 0.9–1.0 ppm, as would be found for one isomer, but four, two of which were broadened, also provided evidence that the obtained product was a mixture of two structural isomers. This indicated that two nonequivalent *ent*-beyerane hydrocarbon skeletons were present. Isomeric macrocycles **3a** and **3b** could not be separated.

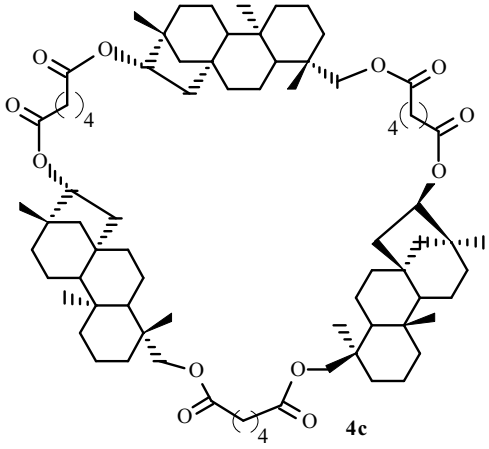
The IR spectrum of the product from reaction of **2** and adipic acid chloride lacked a characteristic band for OH vibrations (3350 cm^{-1}) and had a band for ester vibrations (1730 cm^{-1}). This indicated that a macrocycle had formed. The EI mass spectrum of the product showed a strong peak for a molecular ion with *m*/*z* 832, corresponding to macrocycle **4**. By analogy with **3**, it was assumed that head-to-head **4a** and head-to-tail **4b** isomer were formed. However, MALDI mass spectrometry revealed another two compounds in the product mix. These appeared as peaks for molecular ions with *m*/*z* 1272 $[M + Na]^+$ and 1703 $[M - 2H + K]^+$ and corresponded to macrocycles **4c** and **4d**. Thus, according to the EI and MALDI mass spectrometric results, the reaction product of **2** with adipic acid chloride was a mixture of **4a**–**4d**, each of which could exist theoretically as a set of head-to-head and head-to-tail isomers. The absence in the EI mass spectrum of peaks for molecular ions of the macrocycles with three (**4c**) and four (**4d**) *ent*-beyerane skeletons was probably explained by the fact that these compounds did not vaporize under the EI experimental conditions. Therefore, they were not detected.



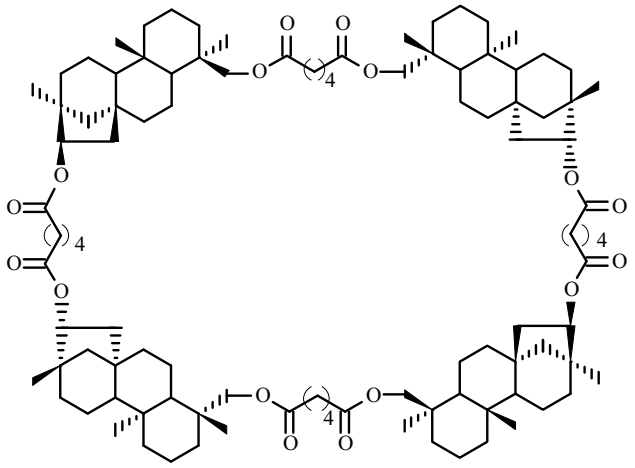
4a



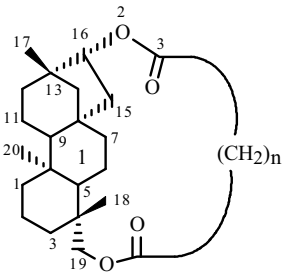
4b



4c



4d



5 - 11

5: n = 6; **6:** n = 8; **7:** n = 10; **8:** n = 5
9: n = 4; **10:** n = 3; **11:** n = 2

Substantial differences in the chemical structures of the reaction products of **2** with suberic, sebacic, and 1,10-decanedicarboxylic acids, which were obtained in yields of 14, 26, and 45%, respectively, with respect to those from the reactions with malonic and adipic acids (macrocycles **3** and **4**, respectively), were already observed in TLC data (Silufol, hexane:benzene:Et_2O, 3:3:2). The R_f value for the first of the three aforementioned products (0.67, 0.69, and 0.80, respectively) was greater than those of **3** and **4** (0.36 and 0.31, respectively). Like in the previous instances, the disappearance in the IR spectra of the products of characteristic bands for OH vibrations (3350 cm^{-1}) and the presence of bands for ester vibrations (1730 cm^{-1}) provided proof that the macrocycles had formed. Based on EI mass spectrometric data, they were assigned macrocyclic structures **5**–**7**. This was confirmed by x-ray crystal structure analyses for **5** and **6**. Figure 1 shows their molecular structures.

TABLE 1. Total Energy (E, kcal/mol) of Macrocycles with One *ent*-Beyerane Skeleton and Polymethylene Spacers with Different Numbers (n) of Methylene Units from MM+ Molecular Mechanics Data (HyperChem 5.0)

Macrocycle	**5**	**6**	**7**	**8**	**9**	**10**	**11**
n	6	8	10	5	4	3	2
E	61	61	64	70	74	78	86

TABLE 2. Crystal Data for **5** and **6** and X-ray Structure Experimental Conditions

Parameter	Compound	
	5	**6**
Empirical formula	$C_{28}H_{44}O_4$	$C_{30}H_{48}O_4$
System	Monoclinic	Orthorhombic
Space group	$P2_1$	$P\ 2_12_12_1$
a, Å	9.184 (1)	11.271 (6)
b, Å	8.870 (1)	12.650 (7)
c, Å	16.009 (2)	19.57 (1)
β, deg	101.192 (1)	90
V, Å^3	1279.4 (2)	2790 (3)
Z	2	4
M	444.63	472.68
d_{calc}, g/cm^3	1.154	1.125
Absorption coefficient, μ, cm^{-1}	0.75	0.72
Radiation (λ,Å)	0.71073	0.71073
Range of θ, deg	$2.26 \le \theta \le 27.85$	$2.08 \le \theta \le 28.00$
Measured reflections	11402	13564
Number of observed reflections with $I > 2\ \sigma$ (I)	4901	2696
Final agreement factors	R = 0.0379	R = 0.048
	R_W = 0.0984	R_W = 0.1155
Fitting parameter	1.053	0.926
Number of refined parameters	292	310
Number of independent reflections (R_{int})	3212 (0.0406)	3728 (0.0471)

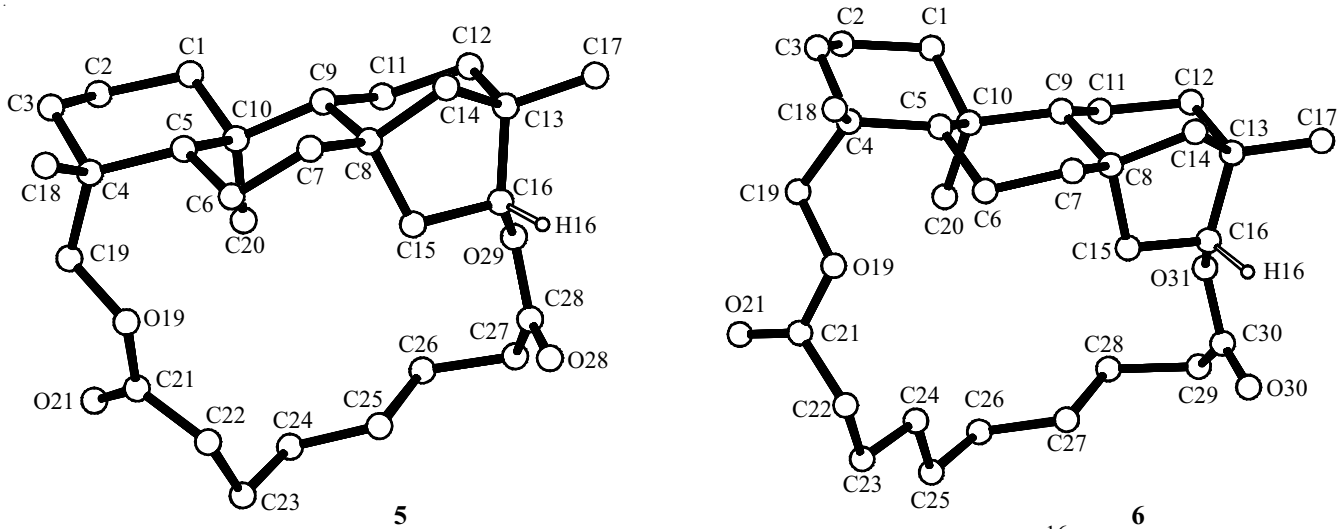


Fig. 1. Molecular structures of **5** and **6** from x-ray crystal structures. The H atom on C^{16} only is shown.

The principal difference of **5**-**7** from **3** and **4** was the fact that they contained only one *ent*-beyerane skeleton, atoms C^{16} and C^{19} of which were closed by the ester spacer. In order to explain the reason for the different courses of the reactions of the dibasic carboxylic acid chlorides with **2**, the total energies of the actual macrocycles (**5**–**7**) and model (**8**–**11**) compounds that differed in the number of methylene units (n) in the diester spacer joining C^{16} and C^{19} of *ent*-beyerane were calculated using MM in the HyperChem program [15]. Table 1 presents the results. It can be seen that the energies of **5** and **6** with

polymethylene spacers with n = 6 and 8 were identical and practically did not differ from the energy of **7** (n = 10). Decreasing the length of the diester spacer by only one methylene (changing from **5** to **8**) increased the total molecule energy by 9 kcal/mol (Table 1). This indicated that steric strain had appeared in it. Decreasing the length of the diester spacer further on going from **8** to **11** caused an even greater increase of the energy (Table 1). This indicated that the steric strain of the macrocycle increased due to the mismatch of the sizes (lengths) of its *ent*-beyerane skeleton and the diester spacer joining its border atoms C^{16} and C^{19}.

Thus, the structures of the macrocycles that were newly synthesized by the reaction of **2** and dibasic carboxylic acid chlorides were determined by the length of the polymethylene chain in the latter. Malonic and adipic acid chlorides reacted to form macrocycles containing two and more *ent*-beyerane skeletons. Suberic, sebacic, and 1,10-decanedicarboxylic acid chlorides formed macrocycles with one *ent*-beyerane skeleton.

EXPERIMENTAL

X-ray crystal structure analyses of **5** and **6** were performed on a Bruker SMART Apex II diffractometer (graphite monochromator, λ Mo Kα = 0.71073 Å) with semi-empirical absorption calculation using the SADABS program [16]. The structures were solved by direct methods using the SHELXS method [17]. Nonhydrogen atoms were refined isotropically and then anisotropically using the SHELXL-97 program [18]. Hydrogen atoms were placed in calculated positions and refined using a rider model. Table 2 presents the crystal parameters and x-ray structure experiment conditions. All calculations were performed using WinGX [19] and APEX2 [20] programs. Figure 1 were plotted using the PLATON program [21].

The x-ray crystal structure data for **5** and **6** were deposited in the Cambridge Crystallographic Data Centre (Nos. 794880 and 794879) as cif-files and can be obtained at the address: www.ccdc.cam.uk/conts/retrieving.html or deposit@ccdc.cam.ac.uk.

IR spectra were recorded on a UR-20 spectrophotometer (Carl Zeiss, Jena, GDR) in the range 400–3600 cm^{-1} and on a Vector 22 Fourier-spectrometer (Bruker, Germany) in the range 400–4000 cm^{-1}. Samples were prepared as emulsions in mineral oil and as KBr pellets.

Mass spectra were obtained on an MX-1310 instrument with ionizing potential 60 eV, electron-collector current 30 μA, and direct introduction of compounds into the ion source at 120°C. The vaporizer ampul was heated to 120–250°C. Matrix-assisted laser-desorption/ionization (MALDI) mass spectra were obtained in an Ultraflex III MALDI TOF time-of-flight mass spectrometer (Bruker, Germany). The matrix was 2,5-dihydroxybenzoic acid. PMR spectra were taken on an Avance 600 instrument (Bruker, Germany). Column chromatography was performed on silica gel (Chemapol). Reaction mixtures were analyzed by TLC on Silufol UV-254 plates (Kavalier, Czechoslovakia).

Isosteviol (**1**) was synthesized by the literature method [22] from Sweta sweetener (Stevian Biotechnology Corp.), mp 235°C (lit. mp 234–235°C [22] and 231–234°C [23]). Spectral parameters agreed with those published [22].

19,16-Dihydroxy-*ent*-beyerane (2). A solution of **1** (0.3 g, 1 mmol) in Et_2O was treated with $LiAlH_4$ (0.04 g, 1.2 mmol) until **1** was fully converted according to TLC. The reaction mixture was heated for 2 h, diluted with HCl solution (10%) until the pH was 2, and extracted with Et_2O. The organic layer was washed with H_2O and dried over $CaCl_2$. The Et_2O was removed to afford crystalline **2** that was recrystallized twice from MeOH. Yield 50%, mp 154–156°C (MeOH). IR spectrum (KBr, ν, cm^{-1}): 1026 (C–O), 1062 (C–O), 1454, 3318 (>CH–OH). PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.76–1.90 (20H, m, *ent*-beyerane skeleton), 0.89 (3H, s, H_3-20), 0.90 (3H, s, H_3-17), 0.95 (3H, s, H_3-18), 3.40 (H, d, J_{AB} = 10.8, H_A-19), 3.75 (1H, d, J_{AB} = 10.8, H_B-19), 3.85 (H, dd, $J_{15\alpha,16}$ = 10.6, $J_{15\beta,16}$ = 4.7, H-16). Mass spectrum (EI, 60 eV, *m*/*z*): found: 306.3 $[M]^+$; calcd 306.26 $[M]^+$ ($C_{20}H_{34}O_2$).

General Method for Synthesizing 3–6. A solution of **2** (1-3 mmol) in CCl_4 (100 mL) containing freshly calcined molecular sieves (4 Å) was treated dropwise with an equimolar amount of dibasic carboxylic acid chloride and heated to complete the reaction. The course of the reaction was monitored by TLC (petroleum ether:EtOAc, 1:1). The solvent was distilled off. The dry solid was dissolved in benzene and chromatographed over silica gel (benzene eluent).

2,6,8,12-Tetraoxa-1,7(16,19)di(*ent*-beyerane)cyclododecaphane-3,5,9,11-tetraone (3). Yield 9%, mp 229–231°C, $[\alpha]_D^{20}$ –96° (*c* 0.22, $CHCl_3$). IR spectrum (KBr, ν, cm^{-1}): 757, 1003, 1225, 1310, 1455, 1730 (CO–O–CH_2), 2848, 2925 (C–H). PMR spectrum (600 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.8–1.90 (40H, m, *ent*-beyerane skeleton), 0.91 (6H, s, H_3-20), 0.93 (6H, s, H_3-17), 0.95 (6H, s, H_3-18), 3.36 [4H, m, C(O)CH_2], 3.90 (2H, dd, $J_{15\alpha,16}$ = 10.8, $J_{15\beta,16}$ = 5.7, H-16), 4.43 (2H, m, H_A-19), 4.96 (2H, m, H_B-19). Mass spectrum (EI, 60 eV, *m*/*z*): found: 748.5 $[M]^+$; calcd 748.49 $[M]^+$ ($C_{46}H_{68}O_8$).

2,6,11,18-Tetraoxa-1,10(16,19)di(*ent*-beyerane)cyclooctadecaphane-3,8,12,17-tetraone (4). Yield 25%, mp 255–258°C. IR spectrum (KBr, ν, cm^{-1}): 973, 1035, 1132, 1158, 1457, 1646, 1733 (CO–O–CH_2), 2828 (C–H). PMR spectrum (600 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.72–1.85 (40H, m, *ent*-beyerane skeleton), 0.86 (6H, s, H_3-20), 0.90 (6H, s, H_3-17), 0.92 (6H, s, H_3-18), 2.30 [6H, m, $(CH_2)_3$], 2.38 [2H, m, C(O)CH_2], 3.75 (2H, d, J_{AB} = 11.22, H_A-19), 4.29 (2H, d, J_{AB} = 11.22, H_B-19), 4.75 (2H, dd, $J_{15\alpha,16}$ = 9.9, $J_{15\beta,16}$ = 4.2, H-16). Mass spectrum (MALDI-TOF, *m*/*z*): found: 856 $[M + Na]^+$; calcd 832.59 $[M]^+$ ($C_{52}H_{80}O_8$).

2,11-Dioxa-1(16,19)-*ent*-beyeranecycloundecaphane-3,10-dione (5). Yield 14%, mp 197–199°C. IR spectrum (KBr, ν, cm^{-1}): 1057, 1095, 1152, 1198, 1244, 1292, 1349, 1371, 1459, 1730 (CO–O–CH_2), 2848, 2929, 2955 (C–H). PMR spectrum (600 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.9–1.9 (20H, m, *ent*-beyerane skeleton), 0.82 (3H, s, H_3-20), 0.97 (3H, s, H_3-17), 1.05 (3H, s, H_3-18), 1.98 [H, m, C(O)CH_2], 2.04 [H, m, C(O)CH_2], 2.12 [H, m, C(O)CH_2], 2.35 (2H, m, CH_2), 2.53 [H, m, C(O)CH_2], 3.40 (H, d, J_{AB} = 12.16, H_A-19), 4.67 (2H, d, J_{AB} = 12.16, H_B-19), 4.86 (2H, dd, $J_{15\alpha,16}$ = 10.78, $J_{15\beta,16}$ = 3.9, H-16). Mass spectrum (EI, 60 eV, *m*/*z*): found: 444.3 $[M]^+$; calcd 444.32 $[M]^+$ ($C_{28}H_{44}O_4$).

2,13-Dioxa-1(16,19)-*ent*-beyeranecyclotridecaphane-3,12-dione (6). Yield 26%, mp 158–161°C, $[\alpha]_D^{20}$ –105° (*c* 0.45, $CHCl_3$). IR spectrum (KBr, ν, cm^{-1}): 1001, 1154, 1185, 1249, 1340, 1460, 1731 (CO–O–CH_2), 2849, 2928 (C–H). PMR spectrum (600 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.81–1.8 (20H, m, *ent*-beyerane skeleton), 0.87 (3H, s, H_3-20), 0.92 (3H, s, H_3-17), 1.25 (3H, s, H_3-18), 2.17–2.26 [2H, m, C(O)CH_2], 2.36 [H, m, C(O)CH_2], 2.45 [H, m, C(O)CH_2], 3.56 (H, d, J_{AB} = 11.98, H_A-19), 4.39 (H, d, J_{AB} = 11.98, H_B-19), 4.86 (H, dd, $J_{15\alpha,16}$ = 9.4, $J_{15\beta,16}$ = 4.6, H-16). Mass spectrum (EI, 60 eV, *m*/*z*): found: 472.4 $[M]^+$; calcd 472.36 $[M]^+$ ($C_{30}H_{48}O_4$).

2,15-Dioxa-1(16,19)-*ent*-beyeranecyclopentadecaphane-3,14-dione (7). Yield 45%, mp 115–118°C, $[\alpha]_D^{20}$ –78.5° (*c* 0.88, $CHCl_3$). IR spectrum (KBr, ν, cm^{-1}): 969, 999, 1032, 1170, 1224, 1344, 1372, 1462, 1732 (CO–O–CH_2), 2851, 2925 (C–H). PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.81–1.85 (20H, m, *ent*-beyerane skeleton), 0.91 (3H, s, H_3-20), 0.92 (3H, s, H_3-17), 0.97 (3H, s, H_3-18), 2.30 [3H, m, C(O)CH_2], 2.38 [H, m, C(O)CH_2], 3.75 (H, d, J_{AB} = 11.89, H_A-19), 4.22 (H, d, J_{AB} = 11.89, H_B-19), 4.86 (H, dd, $J_{15\alpha,16}$ = 7.6, $J_{15\beta,16}$ = 7.6, H-16). Mass spectrum (EI, 60 eV, *m*/*z*): found: 500.4 $[M]^+$; calcd 500.39 $[M]^+$ ($C_{32}H_{52}O_4$).

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