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Synthesis of Macroheterocyclic Compounds with a Furan Bridge Possessing Structural Fragments of 1,2,3–Triazoles and Natural Diterpenoids

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Derivatives of natural diterpenoid lambertianic acid containing alkyne and dialkyne substituent in the furan ring were obtained. 1,2,3-Triazole-incarporated furan bridged macrocycles have been prepared by 1,3-dipolar cycloaddition of methyl 15,16-bis[(prop-2-yn-1-yloxy)methyl]lambertianate with various diazides in the presence of Cu(II)/sodium ascorbate in methylene chloride/water reaction medium.

Keywords: Lambertianic acid, labdanoid alkynes, azides, click chemistry, macroheterocycles.

Синтез макрогетероциклических соединений с фурановым мостиком, содержащих фрагменты 1,2,3–триазолов и природных дитерпеноидов

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Получены производные дитерпеноида ламбертиановой кислоты, содержащие ацетиленовые заместители в фурановом кольце. Реакцией 1,3-диполярного циклоприсоединения метил-15,16-бис[(проп-2-ин-1-илокси) метил]ламбертианата с различными диазидами в присутствии Cu(II)/аскорбат натрия в системе хлористый метилен-вода синтезированы триазолсодержащие макрогетероциклы с фурановым мостиком.

Ключевые слова: Ламбертиановая кислота, лабданоидные алкины, азиды, CuAAC реакция, макрогетероциклы.

Introduction

Natural and synthetic macrocyclic molecules are interesting compounds for various application in supramolecular chemistry,[1] material science[2] and in the biological science.[3] Owing to the prominent characteristics, such as chiral rigid skeletons, multiplete chemical reaction sites and unique amphiphilicity steroidal compounds (especially bile acid and its derivatives) are increasingly used as building blocks in supramolecular chemistry, especially in recognition and assembly,[4] because their special characteristics offer a diversity of spacer, different sized cavities, varied binding sites, and unique spatial structure arrangement, as well as biological activity and biocompatibility.[5] With similar structural properties as the biogenic homologue of steroids, triterpenoids (18β-glycyrrhetinic acid, oleanolic acid) have also started to emerge in recognition and assembly systems, thus attracting more and more attention from organic and material scientists.[6-8] Among the synthesized macrocyclic steroidal dimers the compounds with good inverse recognition properties,[9] as well as cytotoxic hormone receptor modulating activities[10] were obtained. Glycyrrhetinic acid-tweezer receptors with excellent selectivity and affinity for Hg^{2+} ion,[11] and stable cyclic dimer based on oleanolic acid with remarkable binding ability to F^- ion[7] were reported. In the series of macrocyclic diterpenoids from isosteviol[12,13] and steviol,[14] compounds with excellent antituberculosis activity were found.[14] Macrocyclic derivatives of diterpenoid paclitaxel exhibited cytotoxicity against pancreatic cell lines expressing multidrug-resistant genes.[15]

In recent years, Cu^I catalyzed azide-alkyne cycloaddition (CuAAC) received much attention as a method for construction of steroid/triterpenoid-based functional molecules. In view of the specific chemical properties of the formed by this method 1,4-disubstituted 1,2,3-triazoles (stable to metabolic degradation, capable of hydrogen bonding, favorable in the solubility and binding of bimolecular targets because of its relative planarity and strong dipole characteristics[16]) triazole connecting macrocycles represent a challenging class of molecules with promising therapeutic potential.

During our previous investigation we demonstrated the possibility to synthesize the macrocyclic compounds based on labdane diterpenoids[17] using CuAAC reaction. In this work we describe the synthesis of compounds, possessing structural fragments of 1,2,3-triazoles and labdanoids with a furan bridge *via* the CuAAC reaction of a new diacetylenic derivatives – methyl-15,16-epoxy-15,16-bis(propinyloxymethyl)labdatriene with diazides.

The development of approaches to macroheterocyclic compounds with a furan bridge produce independent interest because of the high cytotoxicity of macrocyclic diterpenes and C_4-norditerpenes of 14-membered cembranoids and polycyclic cembranoids.[18]

Experimental

NMR spectra were acquired on Bruker AV-400 (^{1}H: 400.13 MHz, ^{13}C: 100.78 MHz) or Bruker AV-600 (^{1}H: 600.30 MHz, ^{13}C: 150.95 MHz) (Bruker BioSpin GmbH, Rheinstetten, Germany) instruments, using tetramethylsilane (TMS) as an internal standard. In the description of the ^{1}H and ^{13}C-NMR spectra, the labdane skeleton atoms numeration system given in structure **1** was used. The IR spectra were recorded by means of the KBr pellet technique on a Bruker Vector-22 spectrometer. The UV spectra were obtained on an HP 8453 UV-Vis spectrometer (Hewlett-Packard, Waldbronn, Germany). Mass spectra were recorded on a DFS spectrometer (Thermo Scientific, evaporator temperature 240-270 °C). The melting points were determined on a Stuart SMF-38 melting point apparatus (Bibby Scientific, Staffordshire, UK) and are uncorrected. Elemental analysis was carried out on a Carlo-Erba 1106 analysis instrument. Molecular weights were determined on a VP Osmometer K 7000 (Knauer, Germany). The optical rotation was measured on a polarimeter PolAAr3005 in ethanol at 20-25 °C. Elemental, spectral and analytical investigations were carried out at Collective Chemical Service center of Siberian Branch of the Russian Academy of Sciences.

Reaction products were isolated by column chromatography on silica gel 60 (0.063–0.200 mm, Merck KGaA) and eluted with chloroform and chloroform-ethanol (100:1; to 25:l). The reaction progress and the purity of the obtained compounds were monitored by TLC on Silufol UV-254 plates (detection under UV light or by spraying with a 10 % aqueous solution of H_2SO_4, followed by heating to 100 °C).

Lambertianic acid **1** was isolated from the soft resin of Siberian pine Pinus sibirica R. Mayr by known method.[19] Methyl-16-formyllabdatrienoate **2**,[20] methyl 16-(propynyloxymethyl) lambertianate **3**,[17] diazidopentane **4**,[21] 1,10-diazidodecane **5**,[22] 1-azido-2-(2-azidoethoxy)ethane **6**,[23] and 1,2-bis(2- azidoethoxy) ethane **7**[23] are known compounds and were prepared by the reported methods. Chemicals used – $POCl_3$, $NaBH_4$, NaH, 80 % solution of propargyl bromide in PhMe, $CuSO_4 \cdot 5H_2O$ – were purchased from Sigma-Aldrich (St. Louis, MO, USA) or Alfa Aesar (GmbH, Karlsruhe, Germany). Solvents (dichloromethane, acetonitrile, DMF, MeOH, *i*-propanol) were purified by standard methods and distilled in a stream of argon just before use.

*(1S,4aR,5S,8aR)-Methyl-5-(2-{5-formyl-2-[(prop-2-yn-1-yloxy) methyl]furan-3-yl}ethyl)-1,4a-dimethyl-6-methylenedecahydronaphthalene-1-carboxylate (**8**).* Compound **3** (1.00 g, 2.51 mmol) was dissolved in 15 mL of dimethylformamide, phosphoryl chloride (0.45 mL, 5.02 mmol) was added dropwise under stirring at 20 °C, and the mixture was left to stand for 48 h at 20 °C. The mixture was then poured into ice water (40 mL), a saturated aqueous solution of sodium acetate (20 mL) was added, the organic phase was separated, and the aqueous phase was extracted with chloroform (3×30 mL). The combined extracts were washed with 5 % aqueous solution of sodium carbonate (3×30 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was subjected to chromatography on silica gel (petroleum ether-diethyl ether, 4:1) to isolate 0.98 g (100 %) of compound **8** as an oily substance. Mass spectrum, *m/z* (I_{rel}, %): 426 (7.8), 358 (21), 357 (87), 325 (11), 311 (13), 310 (19), 297 (36), 189 (28), 187 (10), 181 (11), 175 (17), 161 (10), 149 (16), 133 (12), 123 (13), 122 (11), 121 (100), 199 (19), 109 (16), 107 (27), 105 (20), 95 (15), 93 (25), 91 (30), 81 (32), 79 (21), 77 (13), 67 (15), 55 (17), 41 (18). MS (EI, 70 eV) found: 426.2403. $C_{26}H_{34}O_5$. calcd. 426.2401. UV (EtOH) λ_{max} nm (lgε): 289 (4.04). IR ν cm^{-1}: 669 w, 756 m, 891 w, 988 w, 1028 w, 1078 m, 1155 s, 1229 m, 1317 w, 1352 w, 1381 w, 1447 m, 1466 m, 1528 m, 1645 w, 1684 w, 1720 s, 2118 m, 2847 m, 2872 m, 2945 s, 3078 w, 3269 m, 3302 w, 3424 w. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 9.55 (1H, s, CHO), 7.06 (1H, s, $C^{14}H$), 4.87 (1H, s, $C^{17}H$), 4.53 (1H, s, $C^{17}H$), 4.50 (2H, s, C^1H_2), 4.13 (2H, d, *J*=2.4 Hz, C^3H_2), 3.55 (3H, s, OCH_3), 2.57 (1H, m, $C^{12}H$), 2.45 (1H, t, *J*=2.4 Hz, C^5H), 2.37 (1H, t.d, *J*=12.4 Hz, *J*=3.1 Hz, C^7H), 2.31 (1H, m, $C^{12}H$), 2.10 (1H, d.m, *J*=12.9 Hz, C^3H), 1.94 (1H, m, C^6H), 1.67-1.85 (5H, m, C^1H, C^2H, C^6H, C^7H, $C^{11}H$), 1.57 (1H, m, $C^{11}H$), 1.53 (1H, m, C^9H), 1.44 (1H, m, C^2H), 1.21 (1H, d.d, *J*=12.4 Hz, *J*=2.7 Hz, C^5H), 1.12 (3H, s, $C^{19}H_3$), 0.96 (1H, d.t, *J*=13.3 Hz, *J*=4.0 Hz, C^3H), 0.91 (1H, d.t, *J*=13.3 Hz, *J*=3.5 Hz, C^1H), 0.45 (3H, s, $C^{20}H_3$). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 177.9

(CHO), 177.6 (C^{18}), 151.9 (C^{16})*, 151.8 (C^{15})*, 147.6 (C^{8}), 127.3 (C^{13}), 122.0 (C^{14}), 106.5 (C^{17}), 78.9 ($C^{4'}$), 75.3 ($C^{5'}$), 61.3 ($C^{1'}$), 57.5 ($C^{3'}$), 56.2 (C^{5}), 54.9 (C^{9}), 51.1 (OCH_3), 44.2 (C^{4}), 40.2 (C^{10}), 39.0 (C^{1}), 38.6 (C^{7}), 38.1 (C^{3}), 28.7 (C^{19}), 26.2 (C^{6}), 24.4 (C^{11}), 22.9 (C^{12}), 19.9 (C^{2}), 12.6 (C^{20}).

*(1S,4aR,5S,8aR)-Methyl-5-(2-{5-(hydroxymethyl)-2-[(prop-2-yn-1-yloxy)methyl]furan-3-yl}ethyl)-1,4a-dimethyl-6-methylenedecahydronaphthalene-1-carboxylate (**9**)*. $NaBH_4$ (0.89 g, 23.44 mmol) was added portion wise to a solution of aldehyde **8** (1.00 g, 2.34 mmol) in 15 mL of *i*-propanol under stirring at 20 °C. After stirring for 24 h at 20 °C the mixture was diluted with water, and extracted with chloroform (3×30 mL). The combined extract was washed with water (3×30 mL), dried over $MgSO_4$, filtered and evaporated. The residue was subjected to column chromatography on silica gel (petroleum ether-diethyl ether, 2:1) to isolate 1.00 g (97 %) of compound **9** as an oily substance. $[\alpha]_D$ + 40.39° (c 3.61; $CHCl_3$). Mass spectrum, *m/z* (I_{rel}, %): 428 (4), 372 (12), 357 (24), 341 (12), 249 (11), 193 (13), 189 (36), 188 (10), 181 (15), 180 (14), 178 (22), 173 (15), 161 (13), 150 (24), 149 (19), 147 (10), 133 (16), 133 (11), 125 (15), 124 (45), 123 (10), 122 (13), 121 (100), 199 (22), 109 (22), 107 (31), 105 (27), 95 (20), 93 (32), 91 (32), 83 (10), 81 (44), 79 (27), 77 (17), 67 (21), 55 (27), 53 (12), 43 (15), 41 (26), 39 (15). MS (EI, 70 eV) found: 428.2551. $C_{26}H_{36}O_5$. calcd. 428.2557. UV (EtOH) λ_{max} nm (lgε): 228 (3.84), 289 (3.31). IR (KBr) ν cm^{-1}: 667 w, 756 m, 889 w, 984 w, 1070 m, 1155 s, 1229 m, 1383 w, 1447 m, 1466 m, 1528 m, 1643 w, 1682 w, 1722 s, 1761 m, 2118 m, 2849 m, 2874 m, 2945 s, 3078 w, 3306 w, 3433 w. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 6.14 (1H, s, C^{14}H), 4.88 (1H, s, C^{17}H), 4.56 (1H, s, C^{17}H), 4.54 (2H, s, $C^{1'}H_2$), 4.44 (2H, s, $C^{1''}H_2$), 4.11 (2H, d, *J*=2.3 Hz, $C^{3'}H_2$), 3.59 (3H, s, OCH_3), 2.52 (1H, m, C^{12}H), 2.43 (1H, t, *J*=2.3 Hz, $C^{5'}$H), 2.40 (1H, m, C^{7}H), 2.25 (1H, m, C^{12}H), 2.13 (1H, d.m, *J*=13.2 Hz, C^{3}H), 1.96 (1H, m, C^{6}H), 1.67, 1.76, 1.82, 1.88 (5H, all m, C^{1}H, C^{2}H, C^{6}H, C^{7}H, C^{11}H), 1.57 (2H, m, C^{11}H, C^{9}H), 1.47 (1H, m, C^{2}H), 1.26 (1H, d.d, *J*=12.4 Hz, *J*=2.8 Hz, C^{5}H), 1.15 (3H, s, $C^{19}H_3$), 1.00 (1H, d.t, *J*=13.2 Hz, *J*=3.9 Hz, C^{3}H), 0.96 (1H, d.t, *J*=14.2 Hz, *J*=2.7 Hz, C^{1}H), 0.47 (3H, s, $C^{20}H_3$). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 177.6 (C^{18}), 153.8 (C^{16}), 147.7 (C^{8}), 146.0 (C^{15}), 125.9 (C^{13}), 109.4 (C^{14}), 106.4 (C^{17}), 79.4 ($C^{4'}$), 74.7 ($C^{5'}$), 61.1 ($C^{1'}$), 57.5 ($C^{1''}$), 56.6 ($C^{3'}$), 56.1 (C^{5}), 54.9 (C^{9}), 51.0 (OCH_3), 44.2 (C^{4}), 40.1 (C^{10}), 38.9 (C^{1}), 38.6 (C^{7}), 38.1 (C^{3}), 28.7 (C^{19}), 26.2 (C^{6}), 24.5 (C^{11}), 23.2 (C^{12}), 19.8 (C^{2}), 12.5 (C^{20}).

By carrying out this reaction in methanol *(1S,4aR,5S,8aR)-methyl 5-(2-{5-(dimethoxymethyl)-2-[(prop-2-yn-1-yloxy)methyl]furan-3-yl}ethyl)-1,4a-dimethyl-6-methylenedecahydronaphthalene-1-carboxylate (**10**)* was obtained in the yield 98 %. Oily substance. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 6.24 (1H, s, C^{14}H), 5.32 (1H, s, C*H*$(OCH_3)_2$), 4.84 (1H, s, C^{17}H), 4.53 (1H, s, C^{17}H), 4.40 (2H, s, $C^{1'}H_2$), 4.05 (2H, d, *J*=2.2 Hz, $C^{3'}H_2$), 3.54 (3H, s, OCH_3), 3.29 (6H, s, $CH(OCH_3)_2$), 2.49 (1H, m, C^{12}H), 2.39 (1H, t, *J*=2.2 Hz, $C^{5'}$H), 2.35 (1H, m, C^{7}H), 2.21 (1H, m. C^{12}H), 2.09 (1H, d.m, *J*=12.6 Hz, C^{3}H), 1.92 (1H, m, C^{6}H), 1.65, 1.74, 1.85 (5H, all m, C^{1}H, C^{2}H, C^{6}H, C^{7}H, C^{11}H), 1.53 (2H, m, C^{11}H, C^{9}H), 1.42 (1H, m, C^{2}H), 1.21 (1H, d.d, *J*=12.2 Hz, *J*=2.7 Hz, C^{5}H), 1.11 (3H, s, $C^{19}H_3$), 0.95 (1H, d.t, *J*=13.3 Hz, *J*=3.8 Hz, C^{3}H), 0.91 (1H, d.t, *J*=14.2 Hz, *J*=3.5 Hz, C^{1}H), 0.43 (3H, s, $C^{20}H_3$). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 177.4 (C^{18}), 146.2 (C^{8}), 150.3 (C^{16}), 147.6 (C^{15}), 125.5 (C^{13}), 111.1 (C^{14}), 106.3 (C^{17}), 97.8 [*C*H$(OCH_3)_2$], 79.3 ($C^{4'}$), 74.6 ($C^{5'}$), 60.9 ($C^{1'}$), 56.5 ($C^{3'}$), 56.0 (C^{5}), 54.8 (C^{9}), 52.6, 52.7 (OCH_3), 50.9 (OCH_3), 44.0 (C^{4}), 39.9 (C^{10}), 38.9 (C^{1}), 38.5 (C^{7}), 37.9 (C^{3}), 28.6 (C^{19}), 26.1 (C^{6}), 24.4 (C^{11}), 23.2 (C^{12}), 19.7 (C^{2}), 12.4 (C^{20}).

*(1S,4aR,5S,8aR)-Methyl-5-(2-{2,5-bis[(prop-2-yn-1-yloxy)methyl]furan-3-yl}ethyl)-1,4a-dimethyl-6-methylenedecahydronaphthalene-1-carboxylate (**11**)*. A) To a stirred solution of compound **9** (1.00 g, 2.2 mmol) in 10 mL of acetonitrile a dispersion of sodium hydride in mineral oil (0.17 g, 4.3 mmol) was added at 0 °C portionwise. The mixture was stirred for 30 min, and a solution of propargyl bromide in toluene (0.48 mL, 4.3 mmol) was added. The reaction mixture was warmed to ambient temperature and stirred for additional 4 h, then poured on 50 g of ice, and extracted with chloroform (3×50 mL). The combined extracts were washed with water (3×50 mL), dried over $MgSO_4$, filtered and evaporated. The residue was subjected to column chromatography on silica gel. Eluting with a mixture of petroleum ether– diethyl ether, 10:1 gave 0.73 g (73 %) of compound **11** as an oily substance. B) To a stirred solution of compound **9** (1.00 g, 2.2 mmol) in 10 mL of DMF a dispersion of sodium hydride in mineral oil (0.17 g, 4.3 mmol) was added at 0 °C. The mixture was stirred for 30 min, and a solution of propargyl bromide in toluene (0.48 mL, 4.3 mmol) was added. The reaction mixture was warmed to ambient temperature and stirred for additional 4 h then poured on 50 g of ice, and extracted with chloroform (3×50 mL). The combined extracts were washed with water (7×50 mL), dried over $MgSO_4$ and evaporated. By column chromatography of the residue on silica gel (petroleum ether-diethyl ether, 10:1 as an eluent) compounds **11** (0.37 g, yield 34 %) and **12** (0.24 g, yield 23 %) were successively isolated.

Compound 11. $[\alpha]_D$ + 16.00° (c 0.20; $CHCl_3$). Mass spectrum, *m/z* (I_{rel}, %): 466 (5), 411 (18), 397 (26), 341 (17), 231 (23), 218 (16), 216 (29), 189 (27), 181 (14), 173 (20), 162 (40), 161 (14), 149 (16), 133 (18), 131 (14), 121 (100), 119 (23), 117 (13), 109 (26), 107 (33), 105 (32), 97 (15), 95 (26), 93 (31), 91 (38), 85 (41), 83 (64), 81 (46), 79 (28), 77 (19), 71 (14), 69 (23), 67 (23), 57 (20), 55 (34), 53 (13), 46 (16), 43 (19), 41 (40), 39 (35). MS (EI, 70 eV) found: 466.2711. $C_{29}H_{38}O_5$. calcd. 466.2714. UV (EtOH) λ_{max} nm (lgε): 230 (4.00). IR (KBr) ν cm^{-1}: 635 w, 671 w, 822 m, 889 w, 988 w, 1030 w, 1074 m, 1155 s, 1229 m, 1352 w, 1383 w, 1445 m, 1464 m, 1643 w, 1684 w, 1722 s, 1761 m, 2116 m, 2849 m, 2945 s, 3078 w, 3292 w. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 6.20 (1H, s, C^{14}H), 4.86 (1H, s, C^{17}H), 4.54 (1H, s, C^{17}H), 4.47 (2H, s, $C^{1'}H_2$)*, 4.42 (2H, s, $C^{1''}H_2$)*, 4.12 (2H, d, *J*=2.4 Hz, $C^{3'}H_2$)**, 4.08 (2H, d, *J*=2.4 Hz, $C^{3''}H_2$)**, 3.56 (3H, s, OCH_3), 2.50 (1H, m, C^{12}H), 2.43 (1H, t, *J*=2.4 Hz, $C^{5'}$H)*, 2.41 (1H, t, *J*=2.4 Hz, $C^{5''}$H)*, 2.37 (1H, m, C^{7}H), 2.24 (1H, m, C^{12}H), 2.11 (1H, d.m, *J*=12.4 Hz, C^{3}H), 1.93 (1H, m, C^{6}H), 1.65, 1.74, 1.84 (5H, all m, C^{1}H, C^{2}H, C^{6}H, C^{7}H, C^{11}H), 1.55 (2H, m, C^{11}H, C^{9}H), 1.45 (1H, m, C^{2}H), 1.23 (1H, d.d, *J*=12.4 Hz, *J*=3.0 Hz, C^{5}H), 1.13 (3H, s, $C^{19}H_3$), 0.98 (1H, d.t, *J*=13.2 Hz, *J*=4.0 Hz, C^{3}H), 0.93 (1H, d.t, *J*=13.4 Hz, *J*=3.8 Hz, C^{1}H), 0.45 (3H, s, $C^{20}H_3$). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 177.6 (C^{18}), 150.4 (C^{16}), 147.7 (C^{8}), 146.8 (C^{15}), 125.8 (C^{13}), 111.8 (C^{14}), 106.4 (C^{17}), 79.4 ($C^{4'}$)*, 79.2 ($C^{4''}$)*, 74.8 ($C^{5'}$)**, 74.6 ($C^{5''}$)**, 63.2 ($C^{1'}$)*, 61.1 ($C^{1''}$)*, 56.8 ($C^{3'}$)**, 56.7 ($C^{3''}$)**, 56.1 (C^{5}), 54.9 (C^{9}), 51.0 (OCH_3), 44.2 (C^{4}), 40.0 (C^{10}), 38.9 (C^{1}), 38.6 (C^{7}), 38.0 (C^{3}), 28.7 (C^{19}), 26.2 (C^{6}), 24.5 (C^{11}), 23.2 (C^{12}), 19.8 (C^{2}), 12.5 (C^{20}).

(1S,4aR,5S,8aR)-Methyl-5-(2-{5-[(formyloxy)methyl)-2-((prop-2-yn-1-yloxy)methyl]furan-3-yl}ethyl)-1,4a-dimethyl-6-methylenedecahydronaphthalene-1-carboxylate (***12***). Mass spectrum, *m/z* (I_{rel}, %): 456 (1), 357 (16), 189 (31), 181 (16), 173 (14), 161 (15), 133 (16), 121 (100), 119 (22), 109 (23), 107 (33), 105 (26), 95 (18), 93 (27), 91 (28), 81 (37), 79 (24), 67 (16), 55 (21), 41 (24), 39 (16). MS (EI, 70 eV) found: 456.2507. calcd. for $C_{27}H_{36}O_6$. 456.2506. UV (EtOH) λ_{max} nm (lgε): 228 (2.98), 284 (2.28). IR (KBr) ν cm^{-1}: 667 w, 756 m, 891 w, 934 w, 986 w, 1030 m, 1074 m, 1155 s, 1228 m, 1360 m, 1383 w, 1447 m, 1464 m, 1645 w, 1722 s, 1761 m, 2849 m, 2874 m, 2946 s, 3290 w, 3429 w. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 8.06 (1H, s, CH_2OCHO), 6.28 (1H, s, C^{14}H), 5.07 (2H, s, CH_2OCHO), 4.88 (1H, s, C^{17}H), 4.55 (1H, s, C^{17}H), 4.44 (2H, s, $C^{1'}H_2$), 4.12 (1H, d, *J*=2.3 Hz, $C^{3'}$H), 4.10 (1H, d, *J*=2.3 Hz, $C^{3'}$H), 3.58 (3H, s, OCH_3), 2.51 (1H, m, C^{12}H), 2.43 (1H, t, *J*=2.4 Hz, $C^{5'}$H), 2.40 (1H, m, C^{7}H), 2.25 (1H, m, C^{12}H), 2.13 (1H, d.m, *J*=12.6 Hz, C^{3}H), 1.95 (1H, m, C^{6}H), 1.67, 1.74, 1.78, 1.85 (5H, all m, C^{1}H, C^{2}H, C^{6}H, C^{7}H, C^{11}H), 1.58 (2H, m, C^{11}H, C^{9}H), 1.49 (1H, m, C^{2}H), 1.25 (1H, d.d, *J*=12.1 Hz, *J*=2.5 Hz, C^{5}H), 1.15 (3H, s, $C^{19}H_3$), 0.99 (1H, d.t, *J*=13.4 Hz, *J*=4.3 Hz, C^{3}H), 0.95 (1H, d.t, *J*=13.9 Hz, *J*=4.0 Hz, C^{1}H), 0.47 (3H, s, $C^{20}H_3$). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 177.6 (C^{18}), 160.4 (CHO), 148.2 (C^{16}), 147.8 (C^{8}), 147.3 (C^{15}), 126.1 (C^{13}), 112.8 (C^{14}), 106.4 (C^{17}), 79.3 ($C^{4'}$), 74.8 ($C^{5'}$), 61.1 ($C^{1'}$), 57.5 (CH_2), 56.9 ($C^{3'}$), 56.1 (C^{5}), 54.9 (C^{9}), 51.1 (OCH_3), 44.2 (C^{4}), 40.1 (C^{10}), 39.0 (C^{1}), 38.6 (C^{7}), 38.1 (C^{3}), 28.7 (C^{19}), 26.2 (C^{6}), 24.6 (C^{11}), 23.2 (C^{12}), 19.9 (C^{2}), 12.6 (C^{20}).

*Reaction of methyl ester (15,16-((prop-2-yn-1-yloxy)methyl)-15,16-epoxy-8(9),13(16),14-labdatrienoate (**11**) with 1,5-*

diazidopentane (4). A) A solution of the diacetylene **11** (0.50 g, 1.07 mmol) in CH_2Cl_2 (20 mL) and a solution of $CuSO_4 \cdot 5H_2O$ (0.11 g, 0.43 mmol) in water (0.5 mL), and sodium ascorbate (0.21 g, 1.07 mmol) in water (0.5 mL) were mixed, and the 1,5-diazidopentane **4** (0.17 g, 1.07 mmol) was added with stirring at ambient temperature. The temperature was raised to 40 °C and stirring was continued for 10 h. The cooled mixture was diluted with water (10 mL), the organic phase was separated, washed with water (3×50 mL), dried over $MgSO_4$ and filtered. The solvent was evaporated, the residue was subjected to column chromatography on silica gel (eluent chloroform-methanol, 50:1) to isolate 0.058 g (7 %) of diazide **13**, 0.086 g (13 %) of macroheterocyclic compound **14**, 0.279 g (42%) of cyclic dimer **15** and 0.133 g (20 %) of cyclic trimer **16**. B) A solution of the diacetylene **11** (0.50 g, 1.07 mmol) in CH_2Cl_2 (107 ml) and a solution of $CuSO_4 \cdot 5H_2O$ (0.11 g, 0.43 mmol) in water (0.5 mL), and sodium ascorbate (0.21 g, 1.07 mmol) in water (0.5 mL) were mixed, and the 1,5-diazidopentane **4** (0.17 g, 1.07 mmol) was added with stirring at ambient temperature. The temperature was raised to 40 °C and stirring was continued for 90 h. The cooled mixture was diluted with water (10 mL), the organic phase was separated, washed with water (3×50 mL), dried over $MgSO_4$, filtered and evaporated. Column chromatography on silica gel (eluent chloroform-methanol, 50:1) gave 0.452 g (68 %) of compound **14** and 0.08 g (12 %) of compound **15**.

(1S,4aR,5S,8aR)-Methyl-5-{2-[2,5-bi{[(1-(5-azidopentyl)-1H-1,2,3-triazol-4-yl]methoxy}methyl)furan-3-yl]ethyl}-1,4a-dimethyl-6-methylenedecahydronaphthalene-1-carboxylate (***13***), oily substance. $[\alpha]_D$ + 18.45° (c 1.03; $CHCl_3$). Found: C 60.77, H 7.34, N 20.78%. $C_{39}H_{58}N_{12}O_5$. requires C 60.44, H 7.54, N 21.69 %. UV (EtOH) λ_{max} nm (lgε): 216 (4.14), 283 (3.33). IR (KBr) ν cm^{-1}: 1049 m, 1093 m, 1136 s, 1155 m, 1229 m, 1333 m, 1358 m, 1379 w, 1452 m, 1464 m, 1645 w, 1681 w, 1720 s, 1759 m, 2097 s, 2849 m, 2870 s, 2943 s, 3140 s, 3327 s. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 7.54 (1H, s, $C^{5''}H$)*, 7.52 (1H, s, $C^{5'}H$)*, 6.21 (1H, s, $C^{14}H$), 4.85 (1H, s, $C^{17}H$), 4.65 (2H, s, $C^{4''}CH_2$)*, 4.61 (2H, s, $C^{4'}CH_2$)*, 4.53 (1H, s, $C^{17}H$), 4.46 (2H, s, $C^{16}CH_2$)*, 4.42 (2H, s, $C^{15}CH_2$)*, 4.32 (2H, d.d, *J*=7.9 Hz, *J*=4.7 Hz, $CH_2N^{1'}$)**, 4.33 (2H, d.d, *J*=7.9 Hz, *J*=4.7 Hz, $CH_2N^{1''}$)**, 3.58 (3H, s, OCH_3), 3.25 (4H, t, *J*=6.8 Hz, $2CH_2N_3$), 2.60 (1H, m, $C^{12}H$), 2.37 (1H, d.t, *J*=12.8 Hz, *J*=2.7 Hz, C^7H), 2.21 (1H, m, $C^{12}H$), 2.11 (1H, d.m, *J*=12.8 Hz, C^3H), 1.91 (5H, m, $CH_2CH_2N^{1'}$, $CH_2CH_2N^{1''}$, C^6H), 1.85 (1H, d.d, *J*=12.8 Hz, *J*=4.3 Hz, C^7H), 1.75 (2H, m, C^2H, C^6H), 1.67 (1H, m, C^1H), 1.60 (5H, m, $2CH_2CH_2N_3$, $C^{11}H$), 1.56 (1H, m, C^9H), 1.53 (1H, m, $C^{11}H$), 1.45 (1H, m, C^2H), 1.38 (4H, m, $2CH_2$), 1.24 (1H, d.d, *J*=12.8 Hz, *J*=3.2 Hz, C^5H), 1.14 (3H, s, $C^{19}H_3$), 0.98 (1H, d.t, *J*=13.6 Hz, *J*=4.0 Hz, C^3H), 0.95 (1H, d.t, *J*=13.3 Hz, *J*=4.7 Hz, C^1H), 0.45 (3H, s, $C^{20}H_3$). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 177.6 (C^{18}), 150.7 (C^{16}), 147.9 (C^8), 147.2 (C^{15}), 145.0 ($C^{4''}$)*, 144.9 ($C^{4'}$)*, 125.5 (C^{13}), 122.5 ($C^{5''}$)*, 122.4 ($C^{5'}$)*, 111.6 (C^{14}), 106.3 (C^{17}), 64.3 (CH_2C^{16}), 63.5 ($CH_2C^{4''}$)*, 63.4 ($CH_2C^{4'}$)*, 62.3 (CH_2C^{15}), 56.1 (C^5), 55.0 (C^9), 51.1 (OCH_3), 51.0 ($2CH_2N_3$), 49.9 ($CH_2N^{1'}$, $CH_2N^{1''}$), 44.2 (C^4), 40.1 (C^{10}), 38.9 (C^1), 38.6 (C^7), 38.1 (C^3), 29.8 ($CH_2CH_2N^{1'}$, $CH_2CH_2N^{1''}$), 28.7 (C^{19}), 23.7 ($2CH_2CH_2N_3$), 26.2 (C^6), 24.6 (C^{11}), 23.7 ($2CH_2$), 23.3 (C^{12}), 19.9 (C^2), 12.6 (C^{20}).

(1S,4aR,5S,8aR)-Methyl-5-(2-(3,10,25-trioxa-13,14,15,21,22,23-hexaazatetracyclo[19.2.1.1^{5,8}.1^{12,15}]hexacosa-1(24),5,7,12(26),13,22-hexaen-6-yl)ethyl)-1,4a-dimethyl-6-methylenedecahydronaphthalene-1-carboxylate ***(14)***, oily substance. $[\alpha]_D$+31.25° (c 0.58; $CHCl_3$). Found: C 65.51, H 7.62, N 12.99%. [*M*] 639. $C_{34}H_{48}N_6O_5$. requires C 65.78, H 7.79, N 13.54%. [*M*] 620. UV (EtOH) λ_{max} nm (lgε): 216 (4.08), 282 (3.38). IR (KBr) ν cm^{-1}: 754 w, 775 w, 822 w, 891 w, 986 w, 1049 m, 1067 m, 1092 m, 1155 m, 1229 m, 1333 w, 1362 w, 1383 w, 1449 m, 1464 m, 1531 w, 1547 w, 1654 w, 1720 s, 2870 m, 2945 s, 3080 s, 3140 s, 3400 s. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 7.38 (1H, s, $C^{25}H$)*, 7.37 (1H, s, $C^{24}H$)*, 6.23 (1H, s, C^7H), 4.90 (1H, s, $C^{11'}H$), 4.59 (2H, s, $C^{11}H_2$)*, 4.58 (1H, s, $C^{11'}H$), 4.54 (2H, s, C^2H_2)*, 4.48 (2H, s, C^9H_2), 4.44 (2H, s, C^4H_2), 4.31 (4H, t, *J*=6.0 Hz, $C^{16}H_2$, $C^{20}H_2$), 3.59 (3H, s, OCH_3), 2.53 (1H, m, $C^{10'}H$), 2.41 (1H, d.m, *J*=11.5 Hz, $C^{7'}H$), 2.25 (1H, m, $C^{10''}H$), 2.13 (1H, d.m, *J*=13.2 Hz, $C^{2'}H$), 1.68-1.98 (10H, m, $C^{9'}H$, $C^{4'}H$, $C^{3'}H$, $C^{8'}H$, $C^{7'}H$, $C^{8''}H$, $C^{17}H_2$, $C^{19}H_2$), 1.58 (1H, m, $C^{5'}H$), 1.57 (1H, m, $C^{9''}H$), 1.48 (1H, m, $C^{3''}H$), 1.19, 1.22 (2H, all m, $C^{18}H_2$), 1.26 (1H, d.d, *J*=12.2 Hz, *J*=2.8 Hz, $C^{8a'}H$), 1.15 (3H, s, $C^{13'}H_3$), 0.99 (1H, d.t, *J*=13.3 Hz, *J*=4.0 Hz, $C^{2''}H$), 0.96 (1H, d.t, *J*=11.0 Hz, *J*=2.4 Hz, $C^{4''}H$), 0.48 (3H, s, $C^{14'}H_3$). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 177.5 ($C^{12'}$), 150.4 (C^8), 147.6 ($C^{6'}$), 146.8 (C^5), 144.9 (C^1)*, 144.9 (C^{12})*, 125.2 (C^6), 122.5 (C^{24}, C^{25}), 111.5 (C^7), 106.2 ($C^{11'}$), 63.7 (C^9), 62.5 (C^{11})*, 62.3 (C^2)*, 61.4 (C^4), 55.9 ($C^{8a'}$), 54.8 ($C^{5''}$), 50.9 (OCH_3), 49.9 (C^{16}, C^{20}), 44.0 ($C^{1''}$), 39.9 ($C^{4a'}$), 38.8 ($C^{4''}$), 38.4 ($C^{7''}$), 37.9 ($C^{2''}$), 28.7 (C^{19}, C^{17}), 28.5 ($C^{13''}$), 26.0 ($C^{8''}$), 24.4 ($C^{9''}$), 23.0 (C^{18}), 23.0 ($C^{10''}$), 19.7 ($C^{3''}$), 12.4 ($C^{14''}$).

*Dimeric compound **15***, oily substance. $[\alpha]_D$+26.41° (c 0.62; $CHCl_3$). Found: C 65.64, H 7.48, N 12.99%. [*M*] 1258. $C_{68}H_{96}N_{12}O_{10}$. requires C 65.78, H 7.79, N 13.54%. [*M*] 1240. UV (EtOH) λ_{max} nm (lgε): 216 (4.07), 282 (3.41). IR (KBr) ν cm^{-1}: 755 w, 777 w, 819 w, 891 w, 985 w, 1047 m, 1067 m, 1089 m, 1156 m, 1229 m, 1331 w, 1367 w, 1382 w, 1449 m, 1459 m, 1532 w, 1547 w, 1655 w, 1720 s, 2871 m, 2943 s, 3081 s, 3140 s, 3405 s. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 7.59, 7.59 (2H, all s, $2C^{5''}H$)*, 7.56, 7.57 (2H, all s, $2C^{5'}H$)*, 6.20 (2H, s, $2C^{14}H$), 4.88 (2H, s, $2C^{17}H$), 4.64 (4H, s, $2C^{4''}CH_2$)*, 4.60 (4H, s, $2C^{4'}CH_2$)*, 4.54 (2H, s, $2C^{17}H$), 4.47 (4H, s, $2C^{15}CH_2$)*, 4.43 (4H, s, $2C^{16}CH_2$)*, 4.29 (8H, t, *J*=7.0 Hz, $2CH_2N^{1'}$, $2CH_2N^{1''}$)*, 3.59 (6H, s, $2OCH_3$), 2.51 (2H, m, $2C^{12}H$), 2.39 (2H, d.m, *J*=12.4 Hz, $2C^7H$), 2.23 (2H, m, $2C^{12}H$), 2.12 (2H, d.m, *J*=13.4 Hz, $2C^3H$), 1.94 (2H, m, $2C^6H$), 1.89 (8H, t, *J*=7.0 Hz, $2CH_2CH_2N^{1'}$, $2CH_2CH_2N^{1''}$), 1.84 (2H, m, $2C^7H$), 1.66, 1.73, 1.77 (8H, all m, $2C^{11}H$, $2C^1H$, $2C^2H$, $2C^6H$), 1.56 (4H, m, $2C^9H$, $2C^{11}H$), 1.46 (2H, m, $2C^2H$), 1.30 (4H, m, $2CH_2$), 1.25 (2H, d.d, *J*=12.9 Hz, *J*=3.0 Hz, $2C^5H$), 1.14 (6H, s, $2C^{19}H_3$), 0.99 (2H, d.t, *J*=13.4 Hz, *J*=4.0 Hz, $2C^3H$), 0.95 (2H, d.t, *J*=12.6 Hz, *J*=3.8 Hz, $2C^1H$), 0.46 (6H, s, $2C^{20}H_3$). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 177.5 ($2C^{18}$), 150.6 ($2C^{15}$), 147.7 ($2C^8$), 146.9 ($2C^{16}$), 144.8 ($2C^{4'}$)*, 144.6 ($C^{4''}$)*, 125.3 (s, $2C^{13}$), 122.6 ($2C^{5''}$)*, 122.4 ($2C^{5'}$)*, 111.5 ($2C^{14}$), 106.2 ($2C^{17}$), 64.2 ($2CH_2C^{15}$), 63.2 ($2CH_2C^{4'}$)*, 63.1 ($2CH_2C^{4''}$)*, 62.1 ($2CH_2C^{16}$), 55.9 ($2C^5$), 54.8 ($2C^9$), 50.9 ($2OCH_3$), 49.6 ($2CH_2N^{1'}$, $2CH_2N^{1''}$), 44.0 ($2C^4$), 39.9 ($2C^{10}$), 38.8 ($2C^1$), 38.5 ($2C^7$), 37.9 ($2C^3$), 29.4 ($6CH_2$), 28.6 ($2C^{19}$), 26.0 ($2C^6$), 24.4 ($2C^{11}$), 23.1 ($2C^{12}$), 19.7 ($2C^2$), 12.4 ($2C^{20}$).

*Trimeric compound **16***, oily substance. $[\alpha]_D$ + 26.41° (c 0.62; $CHCl_3$). Found: C 65.63, H 7.85, N 13.28%. [*M*] 1774. $C_{102}H_{144}N_{18}O_{15}$ requires C 65.78, H 7.79, N 13.54%. [*M*] 1860. UV (EtOH) λ_{max} nm (lgε): 216 (4.07), 282 (3.41). IR (KBr) ν cm^{-1}: 756 w, 777 w, 821 w, 892 w, 985 w, 1049 m, 1066 m, 1089 m, 1155 m, 1228 m, 1332 w, 1366 w, 1382 w, 1449 m, 1459 m, 1533 w, 1548 w, 1654 w, 1720 s, 2871 m, 2942 s, 3082 s, 3139 s, 3405 s. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 7.55 (3H, s, $3C^{5''}H$)*, 7.52 (3H, s, $3C^{5'}H$)*, 6.21 (3H, s, $3C^{14}H$), 4.85 (3H, s, $3C^{17}H$), 4.63 (6H, s, $3C^{4''}CH_2$)*, 4.59 (6H, s, $3C^{4'}CH_2$)*, 4.52 (3H, s, $3C^{17}H$), 4.46 (6H, s, $3C^{15}CH_2$)*, 4.42 (6H, s, $3C^{16}CH_2$)*, 4.29 (12H, t, *J*=5.6 Hz, $3CH_2N^{1'}$, $3CH_2N^{1''}$)*, 3.57 (9H, s, $3OCH_3$), 2.50 (3H, m, $3C^{12}H$), 2.37 (3H, d.m, *J*=11.6 Hz, $3C^7H$), 2.21 (3H, m, $3C^{12}H$), 2.11 (3H, d.m, *J*=12.9 Hz, $3C^3H$), 1.90 (15H, m, $3CH_2CH_2N^{1'}$, $3CH_2CH_2N^{1''}$, $3C^6H$), 1.81 (3H, m, $3C^7H$), 1.68, 1.72, 1.75 (12H, all m, $3C^{11}H$, $3C^1H$, $3C^2H$, $3C^6H$), 1.55 (3H, m, $3C^9H$), 1.52 (3H, m, $3C^{11}H$), 1.46 (3H, m, $3C^2H$), 1.32 (6H, m, $3CH_2$), 1.24 (3H, d.d, *J*=12.1 Hz, *J*=2.7 Hz, $3C^5H$), 1.13 (9H, s, $3C^{19}H_3$), 0.98 (3H, d.t, *J*=13.4 Hz, *J*=3.8 Hz, $3C^3H$), 0.95 (3H, d.t, *J*=13.4 Hz, *J*=3.0 Hz, $3C^1H$), 0.45 (9H, s, $3C^{20}H_3$). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 177.7 ($3C^{18}$), 150.8 ($3C^{15}$), 147.9 ($3C^8$), 147.2 ($3C^{16}$), 145.0 ($3C^{4'}$)*, 144.9 ($3C^{4''}$)*, 125.5 ($3C^{13}$), 122.2, 122.3 ($3C^{5''}$)*, 122.0, 122.1 ($3C^{5'}$)*, 111.7 ($3C^{14}$), 106.4 ($3C^{17}$), 64.4 ($3CH_2C^{15}$), 63.4 ($3CH_2C^{4''}$)*, 63.3 ($3CH_2C^{4'}$)*, 62.3 ($3CH_2C^{16}$), 56.1 ($3C^5$), 55.0 ($3C^9$), 51.1 ($3OCH_3$), 49.8 ($3CH_2N^{1'}$, $3CH_2N^{1''}$), 44.2 ($3C^4$), 40.1 ($3C^{10}$), 39.0 ($3C^1$), 38.6 ($3C^7$), 38.1 ($3C^3$), 29.6 ($9CH_2$), 28.7 ($3C^{19}$), 26.2 ($3C^6$), 24.6 ($3C^{11}$), 23.3 ($3C^{12}$), 19.9 ($3C^2$), 12.6 ($3C^{20}$).

*Reaction of dialkynyl labdatrienoate **11** with 1,10-diazidodecane **(5)**.* Diazide **5** (0.24 g, 1.07 mmol), was added to a mixture of a solution of compound **11** (0.50 g, 1.07 mmol) in dichloromethane

(107 mL), a solution of $CuSO_4 \cdot 5H_2O$ (0.11 g, 0.43 mmol) in H_2O (0.5 mL) and a solution of sodium ascorbate (0.21 g, 1.07 mmol) in H_2O (0.5 mL) with stirring. The temperature was raised to 40 °C and stirring was continued for 90 h. The cooled mixture was diluted with water (10 mL), the organic phase was separated, washed with water (3×50 mL), and dried over $MgSO_4$. The solvent was evaporated, the residue was subjected to chromatography on silica gel (eluent chloroform-methanol, 100:2) to isolate 0.394 g (53 %) of compound **17** and 0.220 g (30 %) of dimeric compound **18**.

*(1S,4aR,5S,8aR)-Methyl-5-(2-{3,10,30-trioxa-13,14,15,26,27,28-hexaazatetracyclo[24.2.1.1^{5,8}.1^{12,15}]heptriaconta-1(29),5,7,12(31),13,27-hexaen-6-yl}ethyl)-1,4a-dimethyl-6-methylenedecahydronaphthalene-1-carboxylate (**17**)*, oily substance. Found: C 67.48, H 8.54, N 11.78%. [*M*] 720. $C_{39}H_{58}N_6O_5$. requires C 67.80, H 8.46, N 12.16%. [*M*] 691. UV (EtOH) λ_{max} nm (lgε): 221 (4.09), 285 (3.11). IR (KBr) ν cm^{-1}: 667 w, 754 w, 822 w, 891 w, 922 w, 964 w, 1051 m, 1072 m, 1153 m, 1229 m, 1333 w, 1360 w, 1449 m, 1464 m, 1558 m, 1643 w, 1682 w, 1720 s, 2855 m, 2930 m, 3078 s, 3136 s. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 7.55 (1H, s, C^{30}H)*, 7.52 (1H, s, C^{29}H)*, 6.21 (1H, s, C^{7}H), 4.88 (1H, s, C$^{11'}$H), 4.58 (2H, d, *J*=1.6 Hz, C^{2}H$_2$)*, 4.61 (2H, d, *J*=1.6 Hz, C^{11}H$_2$)*, 4.54 (1H, s, C$^{11'}$H), 4.46 (2H, s, C^{9}H$_2$), 4.42 (2H, s, C^{4}H$_2$), 4.30 (4H, t, *J*=6.4 Hz, C^{16}H$_2$, C^{25}H$_2$, *J* 6.4), 3.57 (3H, s, OCH$_3$), 2.51 (1H, m, C$^{10'}$H), 2.38 (1H, d.m, *J*=11.8 Hz, C$^{7'}$H), 2.23 (1H, m, C$^{10''}$H), 2.11 (1H, d.m, *J*=12.4 Hz, C$^{2'}$H), 1.94 (1H, m, C$^{8''}$H), 1.86 (5H, m, C$^{7''}$H, C^{17}H$_2$, C^{24}H$_2$), 1.76 (1H, m, C$^{8''}$H), 1.73 (2H, m, C$^{4''}$H, C$^{3'}$H), 1.67 (1H, m, C$^{9''}$H), 1.56 (1H, m, C$^{5'}$H), 1.54 (1H, m, C$^{9''}$H), 1.45 (1H, m, C$^{3''}$H), 1.20 (13H, s, C$^{8a'}$H, C^{18}H$_2$, C^{19}H$_2$, C^{20}H$_2$, C^{21}H$_2$, C^{22}H$_2$, C^{23}H$_2$), 1.13 (3H, s, C$^{13'}$H$_3$), 0.97 (2H, m, C$^{4''}$H, C$^{2''}$H), 0.46 (3H, s, C$^{14''}$H$_3$). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 177.6 (C$^{12'}$), 150.7 (C^8), 147.8 (C$^{6'}$), 147.2 (C^5), 144.8, 144.6 (C^1, C^{12}), 125.4 (C^6), 122.5 (C^{29}, C^{30}), 111.6 (C^7), 106.3 (C$^{11'}$), 64.5 (C^9), 63.9, 63.8 (C^2, C^{11}), 62.3 (C^4), 56.0 (C$^{8a'}$), 54.9 (C$^{5''}$), 51.0 (OCH$_3$), 50.2 (C^{16}, C^{25}), 44.2 (C$^{1'}$), 40.1 (C$^{4a'}$), 38.9 (C$^{4''}$), 38.6 (C$^{7''}$), 38.0 (C$^{2''}$), 29.8 (C^{19}, C^{22}), 28.7 (C$^{13''}$), 28.3 (C^{18}, C^{23}), 28.2 (C^{20}, C^{21}), 26.2 (C$^{8''}$), 25.7 (C^{17}, C^{24}), 24.5 (C$^{9''}$), 23.3 (C$^{10''}$), 19.8 (C$^{3''}$), 12.5 (C$^{14''}$).

*Dimeric compound **18***, oily substance. Found: C 67.91, H 8.54, N 13.22%. [*M*] 1450. $C_{78}H_{116}N_{12}O_{10}$. requires C 67.80, H 8.46, N 12.16%. [*M*] 1382. UV (EtOH) λ_{max} nm (lgε): 220 (4.33), 285 (3.35). IR (KBr) ν cm^{-1}: 665 w, 756 w, 820 w, 891 w, 922 w, 988 w, 1051 m, 1074 m, 1092 m, 1136 m, 1153 m, 1229 m, 1333 w, 1362 w, 1450 m, 1464 m, 1549 m, 1643 w, 1682 w, 1722 s, 1765 w, 2855 m, 2930 m, 3076 s, 3136 s. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 7.54 (2H, s, 2C$^{5''}$H)*, 7.51 (2H, s, 2C$^{5''}$H)*, 6.21 (2H, s, 2C^{14}H), 4.85 (2H, s, 2C^{17}H), 4.65 (4H, s, 2C$^{4''}$CH$_2$)*, 4.61 (4H, s, 2C$^{4'}$CH$_2$)*, 4.53 (2H, s, 2C^{17}H), 4.46 (4H, s, 2C^{15}CH$_2$), 4.42 (4H, s, 2C^{16}CH$_2$), 4.30 (4H, t, *J*=6.9 Hz, 2CH$_2$N$^{1'}$)*, 4.30 (4H, t, *J*=6.9 Hz, 2CH$_2$N$^{1''}$)*, 3.58 (6H, s, 2OCH$_3$), 2.50 (2H, m, 2C^{12}H), 2.38 (2H, d.m, *J*=10.4 Hz, 2C^{7}H), 2.22 (2H, m, 2C^{12}H), 2.12 (2H, d.m, *J*=12.9 Hz, 2C^{3}H), 1.95 (2H, m, 2C^{6}H), 1.85 (10H, m, 2C^{7}H, 4CH$_2$), 1.76, 1.72 (6H, all m, 2C^{1}H, 2C^{2}H, 2C^{6}H), 1.65 (2H, m, 2C^{11}H), 1.56 (4H, m, 2C^{9}H, 2C^{11}H), 1.46 (2H, m, 2C^{2}H), 1.20 (26H, s, 12CH$_2$, 2C^{5}H), 1.14 (6H, s, 2C^{19}H$_3$), 0.98 (2H, d.t, *J*=13.2 Hz, *J*=4.0 Hz, 2C^{3}H), 0.95 (2H, d.t, *J*=13.4 Hz, *J*=3.6 Hz, 2C^{1}H), 0.45 (6H, s, 2C^{20}H$_3$). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 177.7 (2C^{18}), 150.7 (2C^{15}), 147.8 (2C^8), 147.1 (2C^{16}), 144.9, 144.7 (2C$^{4'}$, C$^{4''}$), 125.4 (2C^{13}), 122.4, 122.3 (2C$^{5'}$, 2C$^{5''}$), 111.6 (2C^{14}), 106.3 (2C^{17}), 64.3 (2*C*H$_2$C^{15}), 63.5, 63.3 (2*C*H$_2$C$^{4'}$, 2*C*H$_2$C$^{4''}$), 62.2 (2*C*H$_2$C^{16}), 56.0 (2C^5), 54.9 (2C^9), 51.1 (2OCH$_3$), 50.2 (2CH$_2$N$^{1'}$, 2CH$_2$N$^{1''}$), 44.2 (2C^4), 40.1 (2C^{10}), 38.9 (2C^1), 38.6 (2C^7), 38.0 (2C^3), 28.8 (4CH$_2$), 29.2 (4CH$_2$), 30.2 (4CH$_2$), 28.7 (2C^{19}), 26.4 (4CH$_2$), 26.2 (2C^6), 24.5 (2C^{11}), 23.2 (2C^{12}), 19.8 (2C^2), 12.6 (2C^{20}).

*Reaction of dialkynyl labdatrienoate **11** with 1-azido-2-(2-azidoethoxy)ethane (**6**).* 1-azido-2-(2-azidoethoxy)ethane **5** (0.17 g, 1.07 mmol) was added to a mixture of compound **11** (0.50 g, 1.07 mmol) in dichloromethane (107 mL) and solutions of $CuSO_4 \cdot 5H_2O$ (0.11 g, 0.43 mmol) in H_2O (0.5 mL) and sodium ascorbate (0.21 g, 1.07 mmol) in H_2O (0.5 mL) with stirring. The temperature was raised to 40 °C and stirring was continued for 90 h. The cooled mixture was diluted with water (10 mL), the organic phase was separated, washed with water (3×50 mL), dried over $MgSO_4$ and filtered. The solvent was evaporated, the residue was subjected to chromatography on silica gel (eluent chloroform-methanol, 50:1) to isolate 0.255 g (38 %) of compound **19**, 0.154 g (23 %) of dimeric compound **20** and 0.174 g (26 %) of trimeric compound **21**.

*(1S,4aR,5S,8aR)-Methyl-5-(2-{3,10,18,25-tetraoxa-13,14,15,21,22,23-hexaazatetracyclo[19.2.1.1^{5,8}.1^{12,15}]hexacosa-1(24),5,7,12(26),13,22-hexaen-6-yl}ethyl)-1,4a-dimethyl-6-methylenedecahydronaphthalene-1-carboxylate (**19**),* oily substance. $[\alpha]_D$ +14.85° (c 3.07; $CHCl_3$). Found: C 63.95, H 7.67, N 12.98%. [*M*] 624. $C_{33}H_{46}N_6O_6$. requires C 63.65, H 7.45, N 13.49%. [*M*] 622. UV (EtOH) λ_{max} nm (lgε): 221 (4.04), 280 (2.61). IR (KBr) ν cm^{-1}: 754 w, 820 w, 891 w, 955 w, 988 w, 1049 m, 1072 m, 1109 m, 1134 m, 1153 m, 1229 m, 1333 w, 1360 w, 1450 m, 1464 m, 1558 w, 1643 w, 1720 s, 2855 m, 2870 m, 2945 s, 3078 s, 3142 s. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 7.47 (1H, s, C^{25}H)*, 7.46 (1H, s, C^{24}H)*, 6.23 (1H, s, C^{7}H), 4.89 (1H, s, C$^{11''}$H), 4.58 (2H, s, C^{11}H$_2$)*, 4.55 (1H, s, C$^{11''}$H), 4.51 (2H, s, C^{2}H$_2$)*, 4.49 (2H, d, *J*=3.1 Hz, C^{9}H$_2$), 4.47 (4H, m, C^{16}H$_2$, C^{20}H$_2$), 4.44 (2H, s, C^{4}H$_2$), 3.78 (4H, q, *J*=4.7 Hz, C^{17}H$_2$, C^{19}H$_2$), 3.57 (3H, s, OCH$_3$), 2.52 (1H, m, C$^{10''}$H), 2.39 (1H, t.d, *J*=12.8 Hz, *J*=3.2 Hz, C$^{7''}$H), 2.24 (1H, m, C$^{10''}$H), 2.11 (1H, d.m, *J*=13.0 Hz, C$^{2''}$H), 1.95 (1H, d.m, *J*=13.0 Hz, C$^{8''}$H), 1.86 (1H, d.t, *J*=12.8 Hz, *J*=4.7 Hz, C$^{7''}$H), 1.76 (1H, m, C$^{8''}$H), 1.74 (2H, m, C$^{4''}$H, C$^{3''}$H), 1.67 (1H, m, C$^{9''}$H), 1.57 (1H, m, C$^{5''}$H), 1.54 (1H, m, C$^{9''}$H), 1.46 (1H, m, C$^{3''}$H), 1.24 (1H, d.d, *J*=12.7 Hz, *J*=3.2 Hz, C^{8a}H), 1.13 (3H, s, C$^{13''}$H$_3$), 0.98 (1H, d.t, *J*=13.0 Hz, *J*=3.8 Hz, C$^{2''}$H), 0.95 (1H, d.t, *J*=13.0 Hz, *J*=3.0 Hz, C$^{4''}$H), 0.46 (3H, s, C$^{14''}$H$_3$). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 177.6 (C$^{12'}$), 150.7 (C^8), 147.7 (C$^{6''}$), 147.2 (C^5), 144.9 (C^{12}, C^1), 125.4 (C^6), 123.5 (C^{24})*, 123.6 (C^{25})*, 111.8 (C^7), 106.4 (C$^{11''}$), 69.5 (C^{19}, C^{17}), 63.8 (C^9), 62.6 (C^{11})*, 62.3 (C^2)*, 61.4 (C^4), 56.1 (C$^{8a'}$), 54.9 (C$^{5''}$), 51.1 (OCH$_3$), 50.3 (C^{16}, C^{20}), 44.2 (C$^{1'}$), 40.1 (C$^{4a'}$), 38.9 (C$^{4''}$), 38.6 (C$^{7''}$), 38.1 (C$^{2''}$), 28.7 (C$^{13''}$), 26.2 (C$^{8''}$), 24.6 (C$^{9''}$), 23.2 (C$^{10''}$), 19.8 (C$^{3''}$), 12.6 (C$^{14''}$).

*Dimeric compound **20***, oily substance. $[\alpha]_D$ +30.53° (c 0.57; $CHCl_3$). Found: C 63.81, H 7.67, N 13.58%. [*M*] 1302. $C_{66}H_{92}N_{12}O_{12}$. requires C 63.65, H 7.45, N 13.49%. [*M*] 1244. UV (EtOH) λ_{max} nm (lgε): 222 (4.45), 280 (3.31). IR (KBr) ν cm^{-1}: 754 w, 818 w, 891 w, 920 w, 988 w, 1049 m, 1069 m, 1134 m, 1151 m, 1227 m, 1333 w, 1360 w, 1449 m, 1462 m, 1547 m, 1558 w, 1643 w, 1720 s, 1763 w, 2855 m, 2870 m, 2932 m, 2945 s, 3078 s, 3144 s. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 7.42 (2H, s, 2C$^{5''}$H)*, 7.41, 7.40 (2H, all s, 2C$^{5''}$H)*, 6.18 (2H, s, 2C^{14}H), 4.85 (2H, s, 2C^{17}H), 4.58 (4H, d, *J*=5.4 Hz, 2C$^{4''}$CH$_2$)*, 4.56 (4H, d, *J*=3.8 Hz, 2C$^{4'}$CH$_2$)*, 4.51 (2H, s, 2C^{17}H), 4.43 (4H, d, *J*=3.2 Hz, 2C^{15}CH$_2$)*, 4.40 (8H, m, 2CH$_2$N$^{1'}$, 2CH$_2$N$^{1''}$), 4.39 (4H, s, 2C^{16}CH$_2$), 3.73 (8H, t, *J*=4.6 Hz, 4CH$_2$O), 3.57 (6H, s, 2OCH$_3$), 2.48 (2H, m, 2C^{12}H), 2.37 (2H, d.m, *J*=11.8 Hz, 2C^{7}H), 2.19 (2H, m, 2C^{12}H), 2.10 (2H, d.m, *J*=13.4 Hz, 2C^{3}H), 1.95 (2H, d.m, *J*=12.0 Hz, 2C^{6}H), 1.81 (2H, d.t, *J*=14.0 Hz, *J*=3.2 Hz, 2C^{7}H), 1.71, 1.75 (6H, all m, 2C^{1}H, 2C^{2}H, 2C^{6}H), 1.63 (2H, m, 2C^{11}H), 1.54 (4H, m, 2C^{9}H, 2C^{11}H), 1.46 (2H, m, 2C^{2}H), 1.23 (2H, d.d, *J*=12.4 Hz, *J*=2.7 Hz, 2C^{5}H), 1.13 (6H, s, 2C^{19}H$_3$), 0.97 (2H, d.t, *J*=13.4 Hz, *J*=4.3 Hz, 2C^{3}H), 0.94 (2H, d.t, *J*=13.4 Hz, *J*=3.8 Hz, 2C^{1}H), 0.44 (6H, s, 2C^{20}H$_3$). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 177.6 (2C^{18}), 150.70, 150.72 (2C^{15}), 147.7 (2C^8), 147.08, 147.11 (2C^{16}), 144.7 (2C$^{4'}$)*, 144.56, 144.59 (C$^{4''}$)*, 125.29, 125.32 (2C^{13}), 123.90, 123.93 (2C$^{5''}$)*, 123.80, 123.83 (2C$^{5'}$)*, 111.53, 111.56 (2C^{14}), 106.3 (2C^{17}), 69.10, 69.12 (2CH$_2$O), 69.1 (2CH$_2$O), 64.26, 64.30 (2*C*H$_2$C^{15}), 63.3 (2*C*H$_2$C$^{4'}$)*, 63.2 (2*C*H$_2$C$^{4''}$)*, 62.1 (2*C*H$_2$C^{16}), 55.9 (2C^5), 54.9 (2C^9), 51.1 (2OCH$_3$), 49.9 (2CH$_2$N$^{1'}$, 2CH$_2$N$^{1''}$), 44.1 (2C^4), 40.1 (2C^{10}), 38.9 (2C^1), 38.6 (2C^7), 37.9 (2C^3), 28.7 (2C^{19}), 26.1 (2C^6), 24.5 (2C^{11}), 23.2 (2C^{12}), 19.8 (2C^2), 12.5 (2C^{20}).

Trimeric compound **21**, oily substance. $[\alpha]_D$+25.48° (c 2.74; $CHCl_3$). Found: C 63.48, H 7.75, N 13.66%. [*M*] 1788. $C_{99}H_{138}N_{18}O_{18}$. requires C 63.65, H 7.45, N 13.49%. [*M*] 1866. UV (EtOH) λ_{max} nm (lgε): 221 (4.44), 280 (3.35). IR (KBr) ν cm^{-1}: 756 w, 820 w, 893 w, 922 w, 988 w, 1051 m, 1069 m, 1134 m, 1151 m, 1229 m, 1335 w, 1360 w, 1450 m, 1464 m, 1643 w, 1664 w, 1720 s, 1761 w, 2856 m, 2870 m, 2930 m, 2947 s, 3078 s, 3142 s. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 7.53

(6H, s, 3C$^{5'}$H, 3C$^{5''}$H), 6.19 (3H, s, 3C^{14}H), 4.83 (3H, s, 3C^{17}H), 4.57 (6H, d, *J*=3.8 Hz, 3C$^{4''}$CH$_2$)*, 4.55 (6H, d, *J*=3.8 Hz, 3C$^{4'}$CH$_2$)*, 4.50 (3H, s, 3C^{17}H), 4.42 (18H, s, 3CH$_2$N$^{1'}$, 3CH$_2$N$^{1''}$, 3CH$_2$C^{15}), 4.39 (6H, s, 3C^{16}CH$_2$), 3.74 (12H, s, 6CH$_2$O), 3.55 (9H, s, 3OCH$_3$), 2.47 (3H, m, 3C^{12}H), 2.35 (3H, d.m, *J*=11.3 Hz, 3C^{7}H), 2.19 (3H, m, 3C^{12}H), 2.09 (3H, d.m, *J*=12.9 Hz, 3C^{3}H), 1.93 (3H, d.m, *J*=11.8 Hz, 3C^{6}H), 1.81 (3H, d.t, *J*=14.5 Hz, *J*=3.2 Hz, 3C^{7}H), 1.70, 1.73 (9H, all m, 3C^{1}H, 3C^{2}H, 3C^{6}H), 1.63 (3H, m, 3C^{11}H), 1.53 (6H, m, 3C^{11}H, 3C^{9}H), 1.44 (3H, m, 3C^{2}H), 1.23 (3H, d.d, *J*=12.4 Hz, *J*=2.7 Hz, 3C^{5}H), 1.12 (9H, s, 3C^{19}H$_3$), 0.96 (3H, d.t, *J*=12.9 Hz, *J*=3.2 Hz, 3C^{3}H), 0.94 (3H, d.t, *J*=11.8 Hz, *J*=3.8 Hz, 3C^{1}H), 0.43 (9H, s, 3C^{20}H$_3$). ^{13}C NMR (CDCl$_3$, 298 K) δ_C ppm: 177.6 (3C^{18}), 150.6 (3C^{15}), 147.8 (3C^{8}), 147.0 (3C^{16}), 144.71, 144.72, 144.6 (3C$^{4'}$, 3C$^{4''}$), 125.4 (3C^{13}), 123.7, 123.8, 123.56, 123.59 (3C$^{5'}$, 3C$^{5''}$), 111.6 (3C^{14}), 106.3 (3C^{17}), 69.2 (6CH$_2$O), 64.2 (3*C*H$_2$C^{15}), 63.2, 63.1 (3*C*H$_2$C$^{4'}$, 3*C*H$_2$C$^{4''}$), 62.1 (3CH$_2$C^{16}), 55.9 (3C^{5}), 54.9 (3C^{9}), 51.0 (3OCH$_3$), 49.8 (3CH$_2$N$^{1'}$, 3CH$_2$N$^{1''}$), 44.1 (3C^{4}), 40.0 (3C^{10}), 38.9 (3C^{1}), 38.6 (3C^{7}), 37.9 (3C^{3}), 28.6 (3C^{19}), 26.1 (3C^{6}), 24.5 (3C^{11}), 23.2 (3C^{12}), 19.8 (3C^{2}), 12.5 (3C^{20}).

*Reaction of compound **11** with 1,2-bis(2-azidoethoxy)ethane (**7**)*. Diazide **7** (0.21 g, 1.07 mmol), was added to a mixture of a solution of compound **11** (0.50 g, 1.07 mmol) in dichloromethane (107 mL), a solution of $CuSO_4 \cdot 5H_2O$ (0.11 g, 0.43 mmol) in H_2O (0.5 mL) and a solution of sodium ascorbate (0.21 g, 1.07 mmol) in H_2O (0.5 mL) with stirring. The temperature was raised to 40 °C and stirring was continued for 90 h. The cooled mixture was diluted with water (10 mL), the organic phase was separated, washed with water (3×50 mL), dried over $MgSO_4$ and filtered. The solvent was evaporated, the residue was subjected to column chromatography on silica gel (eluent chloroform-methanol, 50:1) to isolate 0.229 g (32 %) of compound **22**, 0.071 g (10 %) of dimeric compound **23**, and 0.221 g (31 %) of trimeric compound **24**.

*(1S,4aR,5S,8aR)-Methyl-5-(2-{3,10,18,21,28-pentaoxa-13,14,15,24,25,26-hexaazatetracyclo-[22.2.1.1^{5,8}.1^{12,15}]nonacosa-1(27),5,7,12(29),13,25-hexaen-6-yl}ethyl)-1,4a-dimethyl-6-methylene decahydronaphthalene-1-carboxylate (**22**),* oily substance. Found: C 63.32, H 7.88, N 13.02%. [*M*] 654. $C_{35}H_{50}N_6O_7$. requires C 63.04, H 7.56, N 12.60. [*M*] 666. UV (EtOH) λ_{max} nm (lgε): 221 (4.06), 285 (2.75). IR (KBr) ν cm^{-1}: 665 w, 754 w, 822 w, 893 w, 922 w, 988 w, 1051 m, 1072 m, 1136 m, 1150 m, 1227 m, 1333 w, 1358 w, 1450 m, 1464 m, 1553 m, 1643 w, 1682 w, 1720 s, 2870 m, 2945 m, 3080 s, 3142 s. ^{1}H NMR (CDCl$_3$, 298 K) δ_H ppm: 7.67, 7.66 (both s, 1H, C^{28}H and C^{27}H), 6.04 (1H, s, C^{7}H), 4.87 (1H, s, C$^{11'}$H), 4.70 (2H, s, C^{2}H$_2$)*, 4.65 (2H, s, C^{11}H$_2$)*, 4.51 (1H, s, C$^{11'}$H), 4.46 (4H, m, C^{17}H$_2$, C^{22}H$_2$), 4.45 (2H, s, C^{9}H$_2$), 4.40 (2H, s, C^{4}H$_2$), 3.76 (4H, m, C^{16}H$_2$, C^{23}H$_2$), 3.57 (3H, s, OCH$_3$), 3.50 (4H, s, C^{20}H$_2$, C^{19}H$_2$), 2.39 (2H, m, C$^{10'}$H, C$^{7'}$H), 2.12 (2H, m, C$^{2'}$H, C$^{10'}$H), 1.94 (1H, d.m, *J*=12.1 Hz, C$^{8'}$H), 1.86 (1H, d.t, *J*=12.1 Hz, *J*=4.0 Hz, C$^{7'}$H), 1.70-1.78 (3H, m, C$^{8'}$H, C$^{4'}$H, C$^{3'}$H), 1.67 (1H, m, C$^{9'}$H), 1.60 (2H, m, C$^{5'}$H, C$^{9'}$H), 1.45 (1H, m, C$^{3'}$H), 1.21 (1H, d.d, *J*=12.0 Hz, *J*=2.7 Hz, H$^{8a'}$), 1.13 (3H, s, C$^{13'}$H$_3$), 0.97 (1H, d.t, *J*=13.7 Hz, *J*=3.4 Hz, C$^{2'}$H), 0.91 (1H, d.t, *J*=13.7 Hz, *J*=4.0 Hz, C$^{4'}$H), 0.44 (3H, s, C$^{14'}$H$_3$). ^{13}C NMR (CDCl$_3$, 298 K) δ_C ppm: 177.7 (C$^{12'}$), 150.6 (C^{8}), 147.7 (C$^{6'}$), 147.1 (C^{5}), 144.9 (C^{1}, C^{12}), 125.2 (C^{6}), 123.8, 123.7 (C^{28}, C^{27}), 111.4 (C^{7}), 106.4 (C$^{11'}$), 69.2 (C^{17}, C^{22}), 69.9 (C^{19}, C^{20}), 64.6 (C^{9}), 64.1 (C^{11}), 63.9 (C^{2}), 62.3 (C^{4}), 56.0 (C$^{8a'}$), 54.9 (C$^{5'}$), 51.1 (OCH$_3$), 50.0 (C^{16}, C^{23}), 44.2 (C$^{1'}$), 40.1 (C$^{4a'}$), 38.9 (C$^{4'}$), 38.6 (C$^{7'}$), 38.0 (C$^{2'}$), 28.7 (C$^{13'}$), 26.2 (C$^{8'}$), 24.4 (C$^{9'}$), 23.1 (C$^{10'}$), 19.8 (C$^{3'}$), 12.6 (C$^{14'}$).

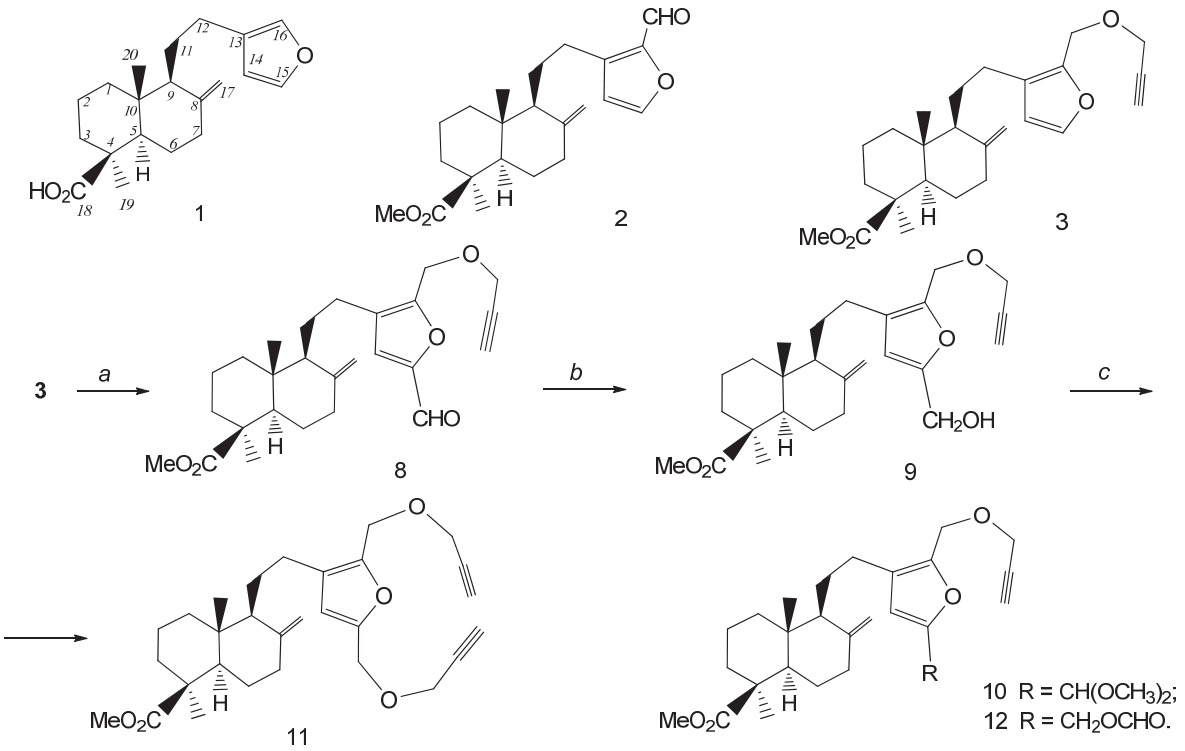
*Dimeric compound **23**,* oily substance. Found: C 62.98, H 7.82, N 12.67%. [*M*] 1267. $C_{70}H_{100}N_{12}O_{14}$. requires C 63.04, H 7.56, N 12.60%. [*M*] 1332. UV (EtOH) λ_{max} nm (lgε): 221 (4.05), 285 (2.76). IR (KBr) ν cm^{-1}: 665 w, 755 w, 822 w, 894 w, 919 w, 987 w, 1052 m, 1072 m, 1137 m, 1149 m, 1228 m, 1331 w, 1354 w, 1453 m, 1467 m, 1553 m, 1645 w, 1720 s, 2870 m, 2946 m, 3080 s, 3143 s. ^{1}H NMR (CDCl$_3$, 298 K) δ_H ppm: 7.70, 7.70 (2H, all s, 2C$^{5''}$H)*, 7.68, 7.68 (2H, all s, 2C$^{5'}$H)*, 6.18 (2H, s, 2C^{14}H), 4.87 (2H, s, 2C^{17}H), 4.61 (4H, d, *J*=2.0 Hz, 2C$^{4''}$CH$_2$)*, 4.58 (4H, d, *J*=2.0 Hz, 2C$^{4'}$CH$_2$)*, 4.53 (2H, s, 2C^{17}H), 4.44 (8H, m, 4CH$_2$O), 4.41 (4H, s, 2C^{15}CH$_2$)*, 4.39 (4H, s, 2C^{16}CH$_2$), 3.75 (8H, m, 2CH$_2$N$^{1'}$, 2CH$_2$N$^{1''}$), 3.59 (6H, s, 2OCH$_3$), 3.49 (8H, s, 2OCH$_2$CH$_2$O), 2.49 (2H, m, 2C^{12}H), 2.39 (2H, d.m, *J*=11.6 Hz, 2C^{7}H), 2.20 (2H, m, 2C^{12}H), 2.12 (2H, d.m, *J*=13.2 Hz, 2C^{3}H), 1.95 (2H, m, 2C^{6}H), 1.82 (2H, m, *J*=3.2 Hz, 2C^{7}H), 1.73-1.77 (6H, all m, 2C^{1}H, 2C^{2}H, 2C^{6}H), 1.67 (2H, m, 2C^{11}H), 1.55 (4H, m, 2C^{9}H, 2C^{11}H), 1.49 (2H, m, 2C^{2}H), 1.26 (2H, d.d, *J*=12.0 Hz, *J*=2.6 Hz, 2C^{5}H), 1.15 (6H, s, 2C^{19}H$_3$), 0.99 (2H, d.t, *J*=13.0 Hz, *J*=3.6 Hz, 2C^{3}H), 0.96 (2H, m, 2C^{1}H), 0.46 (6H, s, 2C^{20}H$_3$). ^{13}C NMR (CDCl$_3$, 298 K) δ_C ppm: 177.7 (2C^{18}), 150.7 (2C^{15}), 147.7 (2C^{8}), 147.13, 147.16 (2C^{16}), 144.68, 144.72, 144.51, 144.56 (2C$^{4'}$, 2C$^{4''}$), 125.4 (2C^{13}), 123.9, 123.8 (2C$^{5'}$, 2C$^{5''}$), 111.62, 111.64 (2C^{14}), 106.4 (2C^{17}), 70.2 (2O*C*H$_2$*C*H$_2$O), 69.3 (4CH$_2$O), 64.3, 64.4 (2*C*H$_2$C^{15}), 63.62, 63.65, 63.54, 63.57 (2*C*H$_2$C$^{4'}$, 2*C*H$_2$C$^{4''}$), 62.2, 62.3 (2*C*H$_2$C^{16}), 56.1 (2C^{5}), 55.1 (2C^{9}), 51.1 (2OCH$_3$), 50.03, 50.05 (2CH$_2$N$^{1'}$, 2CH$_2$N$^{1''}$), 44.2 (2C^{4}), 40.2 (2C^{10}), 39.0 (2C^{1}), 38.7 (2C^{7}), 38.1 (2C^{3}), 28.8 (2C^{19}), 26.2 (2C^{6}), 24.6 (2C^{11}), 23.3 (2C^{12}), 19.9 (2C^{2}), 12.6 (2C^{20}).

*Trimeric compound **24**,* oily substance. Found: C 62.93, H 7.34, N 12.35%. [*M*] 1893. $C_{105}H_{150}N_{18}O_{21}$. requires C 63.04, H 7.56, N 12.60%. [*M*] 1998. UV (EtOH) λ_{max} nm (lgε): 221 (4.03), 286 (2.74). IR (KBr) ν cm^{-1}: 667 w, 755 w, 822 w, 894 w, 920 w, 990 w, 1049 m, 1071 m, 1137 m, 1149 m, 1228 m, 1334 w, 1358 w, 1451 m, 1465 m, 1555 m, 1644 w, 1721 s, 2870 m, 2946 m, 3078 s, 3143 s. ^{1}H NMR (CDCl$_3$, 298 K) δ_H ppm: 7.55, 7.65, 7.67 (6H, all s, 3C$^{5''}$H, 3C$^{5'}$H), 6.19 (3H, s, 3C^{14}H), 4.84 (3H, s, 3C^{17}H), 4.61 (6H, s, 3C$^{4''}$CH$_2$)*, 4.57 (6H, s, 3C$^{4'}$CH$_2$)*, 4.51 (3H, s, 3C^{17}H), 4.43 (18H, s, 3C^{15}CH$_2$, 6CH$_2$O), 4.39 (6H, s, 3C^{16}CH$_2$), 3.76 (12H, s, 3CH$_2$N$^{1'}$, 3CH$_2$N$^{1''}$), 3.58 (9H, s, 3OCH$_3$), 3.49 (12H, s, 3OC*H*$_2$*C*H$_2$O), 2.47 (3H, m, 3C^{12}H), 2.36 (3H, d.m, *J*=10.8 Hz, 3C^{7}H), 2.19 (3H, m, 3C^{12}H), 2.10 (3H, d.m, *J*=13.4 Hz, 3C^{3}H), 1.94 (3H, m, 3C^{6}H), 1.83 (3H, m, 3C^{7}H), 1.71-1.78 (9H, m, 3C^{1}H, 3C^{2}H, 3C^{6}H), 1.65 (3H, m, 3C^{11}H), 1.54 (6H, m, 3C^{9}H, 3C^{11}H), 1.45 (3H, m, 3C^{2}H), 1.24 (3H, d.d, *J*=12.0 Hz, *J*=2.2 Hz, 3C^{5}H), 1.13 (9H, s, 3C^{19}H$_3$), 0.97 (3H, d.t, *J*=12.9 Hz, *J*=3.2 Hz, 3C^{3}H), 0.94 (3H, d.t, *J*=12.9 Hz, *J*=2.7 Hz, 3C^{1}H), 0.44 (9H, s, 3C^{20}H$_3$). ^{13}C NMR (CDCl$_3$, 298 K) δ_C ppm: 177.66, 177.68, 177.70 (3C^{18}), 150.67, 150.69, 150.72 (3C^{15}), 147.81, 147.84 (3C^{8}), 147.05, 147.06, 147.09 (3C^{16}), 144.7, 144.8, 144.6, 144.7 (3C$^{4'}$, 3C$^{4''}$), 125.43, 125.45 (3C^{13}), 123.8, 123.9, 123.6, 123.7 (3C$^{5'}$, 3C$^{5''}$), 111.62, 111.64, 111.65 (3C^{14}), 106.3 (3C^{17}), 70.3 (3O*C*H$_2$*C*H$_2$O), 69.3 (6CH$_2$O), 64.26, 64.29 (3*C*H$_2$C^{15}), 63.39, 63.40, 63.42, 63.27, 63.29, 63.30 (3*C*H$_2$C$^{4'}$, 3*C*H$_2$C$^{4''}$), 62.21, 62.24, 62.25 (3*C*H$_2$C^{16}), 56.0 (3C^{5}), 55.0 (3C^{9}), 51.1 (3OCH$_3$), 50.1, 50.05 (t, 3*C*H$_2$N$^{1'}$, 3*C*H$_2$N$^{1''}$), 44.2 (3C^{4}), 40.1 (3C^{10}), 38.9 (3C^{1}), 38.6 (3C^{7}), 38.0 (3C^{3}), 28.2 (3C^{19}), 26.2 (3C^{6}), 24.5 (3C^{11}), 23.3 (3C^{12}), 19.8 (3C^{2}), 12.5 (3C^{20}).

Results and Discussion

The synthetic route followed for the synthesis of the key compound – labdanoid diacetylenic derivatives **11** is outlined in Scheme 1. Vilsmeier-Haack formylation of compound **3** gave its 15-formyl derivative **8** which was converted to the compound **9** by treatment with sodium borohydride in *i*-propanol. By reduction of **8** in methanol the compound **10** was obtained exclusively. The reaction of 15-hydroxymethyl labdatrinoate **9** with propargyl bromide in DMF in the presence of sodium hydride resulted in formation of diacetylenic derivatives **11** (yield 34 %) and compound **12** (yield 23 %). Compound **11** was obtained in 75 % yield by reaction of compound **9** with propargyl bromide in acetonitrile.

The terpenoid dialkyne **11** was reacted with 1 equivalent of 1,5-diazidopentane **4** in CH_2Cl_2-water medium (20:1; 0.05 M solution of **11**) in the presence of $CuSO_4$ and sodium ascorbate in conditions used in our previous studies.[24] By performing the reaction at 40 °C over 10 h the full conversion of compound **11** was observed. After column chromatography on silica gel four compounds were isolated: diazide **13** (7 %), macroheterocyclic compound **14** (13 %), cyclic dimer **15** (42%) and cyclic trimer



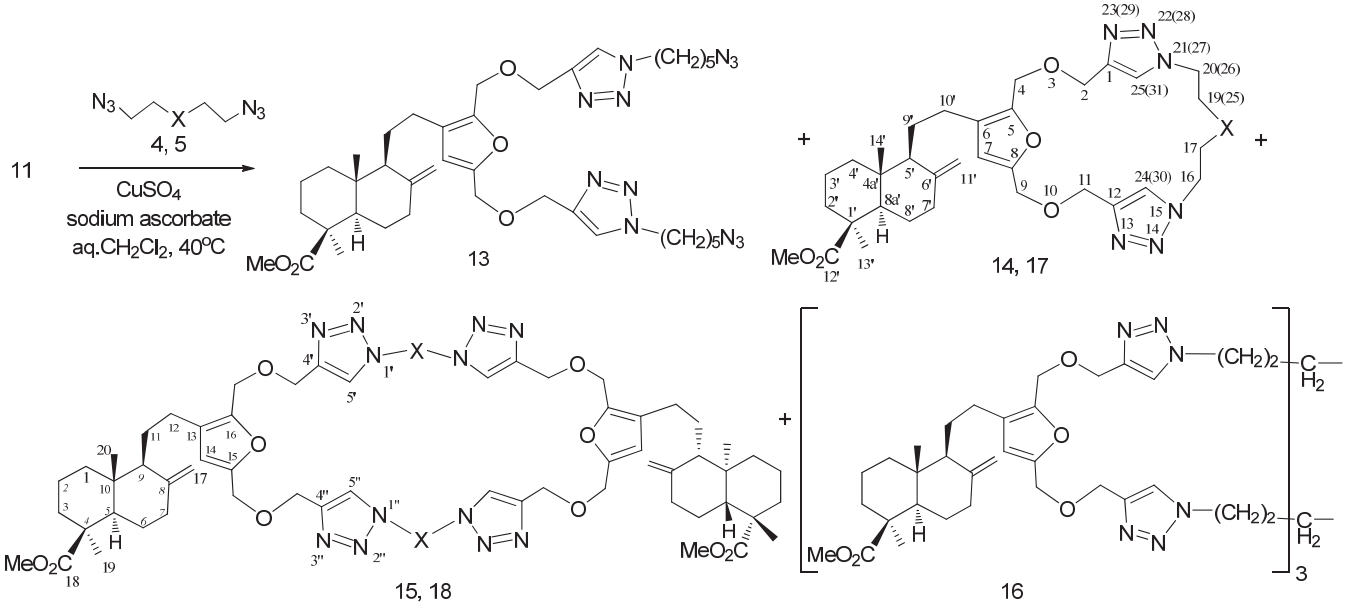
Reagents and Reaction Conditions: (a): $POCl_3$, DMF, AcONa, 20 °C, 48 h; (b): $NaBH_4$, i-PrOH, 20 °C, 24 h; (c) $BrCH_2C{\equiv}CH$, NaH, CH_3CN, 0 °C, then rt, 4 h.

Scheme 1.

16 (20 %) (Scheme 2). Dilution of the reaction mixture with methylene chloride (0.01 M solution) improved the yield of the target compound **14** to 68 %. Additionally, dimeric compound **15** was also isolated in the yield 12 %.

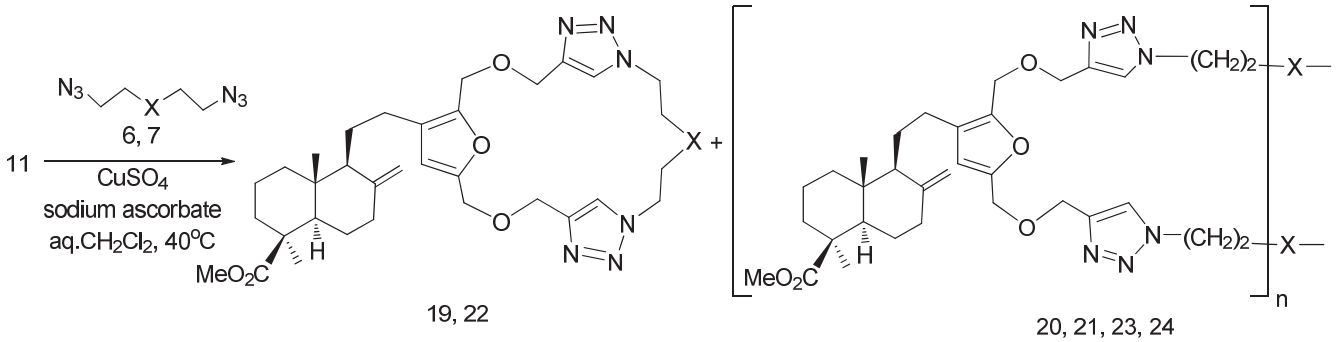
Reaction of dialkyne **11** (0.01 M solution in methylene chloride) with 1,10-diazidodecane (**5**) in the presence of $CuSO_4$ and sodium ascorbate resulted in the formation of a mixture of compound **17** and dimeric compound **18** isolated in 53 % and 30 % yield after column chromatography.

By using of the mentioned CuAAC conditions for reacting of diterpenoid dialkyne **11** with 1-azido-2-(2-azidoethoxy)ethane **6** the compound **19** was isolated in the yield 38 % (Scheme 3). Cyclodimer **20** and cyclotrimer **21** were also isolated in the yield 22 % and 26 % respectivelly.



X = $C^{18}H_2$ (**4**, **14**, **15**); $CH_2^{(19)}CH_2^{(20)}CH_2^{(21)}CH_2^{(22)}CH_2^{(23)}CH_2^{(24)}$ (**5**, **17**, **18**)

Scheme 2.



X = O (**6**, **19**, **20**, **21**); $O(CH_2)_2O$ (**7**, **22**, **23**, **24**); n = 2 (**20**, **23**); 3 (**21**, **24**).

Scheme 3.

Comparable results were obtained in the reaction of dialkyne **11** with 1,2-bis(2-azidoethoxy)ethane (**7**); macrocyclic derivatives **22**, **23** and **24** were obtained in the yield of 32 %, 10 % and 31 % after column chromatography.

The composition and structure of the synthesized compounds were confirmed by IR, UV, ^{1}H, and ^{13}C spectroscopy, mass-spectrometry, elemental analysis data and mass-date for dimeric and trimeric compounds. The ^{1}H and ^{13}C NMR spectra of all synthesized compounds agree with their structure and contain the set of characteristic signals of labdanoid skeleton and the corresponding substituent. Formation of the 1,2,3-triazole ring in compounds **13-24** was confirmed by the NMR data. The ^{1}H NMR spectra exhibited singlet signals for the H-5' proton (δ=7.37–7.68 ppm). The ^{13}C NMR signals of the C4-',5' carbon atoms were observed in the region of 144.6–145.9 ppm and 122.3–124.0 ppm, respectively. Macrocyclic **14**, **19** and cyclodimeric compounds **15**, **20** with a 5-membered linker between triazole rings possess greatly different in the shifts of the H-5 proton in the triazole ring. A shift around 0.2 ppm was observed for the signal of H-5 atom in the ^{1}H NMR spectra of compound **15**, **20** compared with compounds **14**, **19**.

Conclusions

As a result, we have elaborated bi-, tetra- and hexa-(1,2,3-triazol)containing furan bridged macrocyclic compounds using CuAAC reaction of diacetylenic derivatives of easily available methyl lambertianate with various diazides. The yield and composition of the target macrocyclic compounds were shown to be dependent on the nature of the starting diazides, better yield of bi(1,2,3-triazol)containing furan bridged macrocyclic compound being observed in the case of 1,5-diazidopentane and 1,10-diazidodecane.

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