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Synthesis of Novel Labdanoid–Based Macroheterocycles Using Click–Cycloaddition Reaction Protocol

Yurii V. Kharitonov,[a,b] Makhmut M. Shakirov,[a] and Elvira E. Shults[a,b@]

[a]*Novosibirsk Institute of Organic Chemistry Siberian Branch, Russian Academy of Sciences, 630090 Novosibirsk, Russia*
[b]*Novosibirsk State University, 630090 Novosibirsk, Russia*
[@]*Corresponding author E-mail: schultz@nioch.nsc.ru*

A convenient synthetic method to diterpenoid dialkyne 18-propargyloxy-16-[(prop-2-yn-1-yloxi)methyl]labda-8(17),13,15-triene in the common yield of 34 % from the natural plant diterpenoid lambertianic acid was developed. 1,2,3-Triazolyl containing macroheterocyclic compounds with an integrated diterpenoid fragment have been prepared by CuAAC reaction of the labdanoid dialkyne with organic diazides.

Keywords: Diterpenoids, lamberianic acid, dialkynes, diazides, CuAAC-reaction, macrocycles.

Синтез новых макрогетероциклических соединений на основе лабданоидов посредством Cu–катализируемой реакции азид–алкинового циклоприсоединения

Ю. В. Харитонов,[a,b] М. М. Шакиров,[a] Э. Э. Шульц[a,b@]

[a]*Новосибирский институт органической химии им. Н.Н. Ворожцова СО РАН, 630090 Новосибирск, Россия*
[b]*Новосибирский национальный исследовательский государственный университет, 630090 Новосибирск, Россия*
[@]*E-mail: schultz@nioch.nsc.ru*

На основе растительного дитерпеноида ламбертиановой кислоты разработан удобный способ получения дитерпеноидного диацетилена 18-пропаргилокси-16-[(проп-2-ин-1-илокси)метил]лабда-8(17),13,15-триена с общим выходом 34 %. Си-Катализируемой реакцией 1,3-диполярного циклоприсоединения (CuAAC-реакцией) указанного лабданоидного диалкина с органическими диазидами синтезированы триазолсодержащие макрогетероциклы с интегрированным лабданоидным фрагментом.

Ключевые слова: Дитерпеноиды, ламертиановая кислота, диалкины, диазиды, CuAAC реакция, макрогетероциклы.

Introduction

The impact of macrocyclic structures on modern medicinal chemistry is demonstrated by the diverse structures that display significant biological properties.[1,2] The prevalence of macrocyclic structures in natural products[3] and synthetic derivatives[4,5] has stimulated the development of elegant and efficient syntheses, particularly when applied to the search for new drugs,[1] or construction of new materials.[6]

In recent reports several macrocyclic compounds from plant diterpenoids have been synthesized and investigated. Macrocyclic diterpenoids from isosteviol and steviol were studied as compounds with excellent antituberculosis activity,[7] as well as novel supramolecular affinity materials.[8] A group of C_1-symmetry chiral 22-crown-6 ethers bearing maleopimaric acid (the Diels-Alder adducts of tricyclic diterpenoid levopimaric acid with maleic anhydride) exhibited good chiral recognition and showed different complementary towards the chiral quests.[9-10]

Macrocyclic derivatives of diterpenoid paclitaxel possessed higher potency than paclitaxel against several human breast, ovary and colon cancer cell lines.[11] As a member of the diterpenoids family, furanolabdanoid lambertianic acid 1 could be considered an ideal scaffold for receptors, due to its low toxicity and biocompatibility.[12,13] In recent years the copper(I)-catalyzed azide alkyne cycloaddition (CuAAC), the most frequently used "click" reaction, have emerged as efficient methodologies for the construction of a range of different macrocyclic structures for different purposes.[14-16] CuAAC has been utilized as an efficient protocol to close macrocycles of different sizes by the formation of 1,4-triazoles.[14-17] During our previous investigation we demonstrated the possibility for construction of macrocyclic compounds on the furan ring of lambertianic acid derivatives. Furanolabdanoid with 1,2,3-triazole-incorporated macrocycles at C-16 position[18] and furan bridged macrocyclic compounds[19] were obtained and characterized. Chiral macrocyclic compounds connected on the 16 and 17-positions by 1,2,3-triazole rings with methylene, ethyloxyethyl or ethylethoxyethyl units with selectivity and affinity for Hg^{2+} ion were obtained.[20] Macroheterocyclic compounds, connected in the 16,17-positions of decaline core of the labdanoid with selective cytotoxicity were also synthesized.[21] In this report, we describe a practical approach for rapid access to a labdanoid-based macrocyclic skeleton connected on the 16,18-positions by 1,4-substituted triazoles with methylene or oxamethylene units.

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 lambertianic acid 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. The molecular weights of compounds **10-12** in methanol solutions were determined by the HPLC MSD method on an Agilent 1100 Series LC/MSD instrument. A solution was directly injected into the solvent (MeOH) flow. The samples were ionized by means of electrostatic spraying at atmospheric pressure (APIES).The solvent flow rate was 0.3 mL·min^{-1}; the flowrate of the drying gas (nitrogen) was 10 L·min^{-1}, and its temperature was 340 °C. Molecular weight of compound **13** was determined on a VP Osmometer K 7000 (Knauer, Germany). The optical rotation was measured on a polarimeter PolAAr3005 on ethanol at 20–25 °C purification of chemicals, specific experimental preparative methods and characterization of new compounds. 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 25:1). 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** and methyl lambertianate **2** were isolated from the soft resin of Siberian pine Pinus sibirica R. Mayr by method.[22] 1,10-Diazidodecane **8**,[23] 1-azido-2-(2-azidoethoxy) ethane **9**[24] are known compounds and were prepared by the reported methods. Chemicals used – $LiAlH_4$, $POCl_3$, $NaBH_4$, NaH, 80 % solution of propargyl bromide in PhMe, sodium ascorbate, $CuSO_4 \cdot 5H_2O$ – 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.

(4S,9S,10R)-18-(Prop-2-yn-1-yloxy)-15,16-epoxy-8(17),13(16),14(15)-labdatriene (**4**). To a stirred solution of compound **3**[25] (0.50 g, 1.60 mmol) in DMF (10 ml) a dispersion of sodium hydride in mineral oil (0.26 g, 6.41 mmol) was added at 0 °C. The mixture was stirred for 30 min, and a solution of propargyl bromide in toluene (0.35 ml, 4.3 mmol) was added. The reaction mixture was warmed to ambient temperature and stirred for additional 20 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. The residue was subjected to chromatography on silica gel (petroleum ether-diethyl ether, 4:1 as an eluent) to isolate 0.37 g (67 %) of compound **4** as a colorless oily substance. $[\alpha]_D$+38.57° (c 2.86; $CHCl_3$). Found: C 79.99, H 9.54 %. $C_{23}H_{32}O_2$. Calc. C 81.13, H 9.47 %. IR (KBr) ν_{max} cm^{-1}: 459 w, 561 w, 600 m, 631 m, 665 m, 725 w, 779 m, 822 w, 874 m, 891 m, 939 m, 958 m, 982 m, 1024 s, 1093 s, 1163 m, 1194 m, 1261 m, 1358 m, 1371 m, 1383 m, 1408 w, 1444 s, 1468 m, 1500 m, 1643 m, 1722 m, 1767 m, 2116 w, 2848 s, 2868 s, 2931 s, 3078 m, 3304 s. UV-Vis (EtOH) λ_{max} (lgε) nm: 220 (3.59). ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 7.34 (1H, d, *J*=1.1 Hz, C^{15}H), 7.19 (1H, s, C^{16}H), 6.26 (1H, d, *J*=1.1 Hz, C^{14}H), 4.86 (1H, s, C^{17}H), 4.57 (1H, s, C^{17}H), 4.10 (1H, d.d, *J*=16.1 Hz, *J*=2.2 Hz, CH_2), 4.06 (1H, d.d, *J*=16.1 Hz, *J*=2.2 Hz, CH_2), 3.60 (1H, d, *J*=8.6 Hz, C^{18}H), 3.23 (1H, d, *J*=8.6 Hz, C^{18}H), 2.55 (1H, m, C^{12}H), 2.40 (1H, d.d.d, *J*=12.9 Hz, *J*=4.8 Hz, *J*=2.7 Hz, C^{7}H), 2.38 (1H, t, *J*=2.2 Hz, ≡CH), 2.24 (1H, m, C^{12}H), 1.94 (1H, d.t, *J*=12.9 Hz, *J*=4.8 Hz, C^{6}H), 1.71–1.86 (4H, m, C^{1}H, C^{6}H, C^{7}H, C^{11}H), 1.64 (1H, m, C^{9}H), 1.46–1.62 (3H, m, C^{2}H, C^{11}H, C^{3}H), 1.34 (1H, m, C^{2}H), 1.19 (1H, d.d, *J*=12.9 Hz, *J*=2.2 Hz, C^{5}H), 0.97 (3H, s, C$^{19}H_3$), 1.01 (1H, d.t, *J*=12.9 Hz, *J*=3.2 Hz, C^{3}H), 0.94 (1H, d.t, *J*=12.4 Hz, *J*=4.3 Hz, C^{1}H), 0.69 (3H, s, C$^{20}H_3$). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 147.95 (C^8), 142.55 (C^{16}), 138.56 (C^{15}), 125.40 (C^{13}), 110.86 (C^{14}), 106.40 (C^{17}), 80.32 (*C*≡CH), 73.83 (C≡*CH*), 72.57 (C^{18}), 58.38 (CH_2), 56.20 (C^5)^{a*}, 56.03 (C^9)^a, 39.39 (C^1), 38.84 (C^7), 38.52 (C^4), 37.91 (C^{10}), 36.05 (C^3), 27.79 (C^{19}), 24.46 (C^{11}), 24.07 (C^6), 23.46 (C^{12}), 19.01 (C^2), 15.26 (C^{20}),

(4S,9S,10R)-16-Formyl-18-(prop-2-yn-1-yloxy)-15,16-epoxy-8(17),13(16),14(15)-labdatriene (**5**). Compound **4** (0.50 g, 1.47 mmol) was dissolved in DMF (15 ml), phosphoryl chloride (0.27 ml, 2.94 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 was 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 as an eluent) to isolate 0.48 g (89 %) of compound **5** as a colorless oily substance. $[\alpha]_D$+36.23° (c 0.86; $CHCl_3$). Found: C 77.98, H 8.75 %. $C_{24}H_{32}O_3$. Calc.: C 78.22, H 8.75 %. IR (KBr) ν_{max} cm^{-1}: 644 w, 667 w, 756 s, 854 m, 889 s, 982 m, 1045 m, 1092 m, 1153 s, 1204 m, 1229 s, 1333 w, 1383 m, 1449 m, 1466 m, 1643 m, 1674 m, 1722 s, 2847 s, 2876 s, 2945 s, 2988 s, 3078 m. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 9.65 (1H, s, CHO), 7.55 (1H, d, *J*=1.4 Hz, C^{15}H), 6.43 (1H, d, *J*=1.4 Hz, C^{14}H), 4.87 (1H, s, C^{17}H),

4.57 (1H, s, C^{17}H), 4.07 (1H, d.d, *J*=15.9 Hz, *J*=2.2 Hz, CH_2), 4.01 (1H, d.d, *J*=15.9 Hz, *J*=2.2 Hz, CH_2), 3.54 (1H, d, *J*=8.7 Hz, C^{18}H), 3.20 (1H, d, *J*=8.7 Hz, C^{18}H), 2.84 (1H, m, C^{12}H), 2.64 (1H, m, C^{12}H), 2.37 (1H, m, C^{7}H), 2.35 (1H, t, *J*=2.2 Hz, ≡CH), 1.88 (1H, d.t, *J*=12.7 Hz, *J*=5.2 Hz, C^{6}H), 1.67–1.82 (4H, m, C^{1}H, C^{6}H, C^{7}H, C^{11}H), 1.61 (2H, m, C^{9}H, C^{11}H), 1.44–1.48 (2H, m, C^{2}H, C^{3}H), 1.32 (1H, m, C^{2}H), 1.13 (1H, d.d, *J*=12.9 Hz, *J*=2.0 Hz, C^{5}H), 0.94 (1H, m, C^{3}H), 0.92 (3H, s, C^{19}H_3), 0.89 (1H, d.t, *J*=13.1 Hz, *J*=4.9 Hz, C^{1}H), 0.65 (3H, s, C^{20}H_3). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 177.34 (CHO), 148.47 (C^{16}), 147.59 (C^{8}), 147.34 (C^{15}), 128.70 (C^{13}), 113.93 (C^{14}), 106.62 (C^{17}), 80.28 (*C*≡CH), 73.79 (C≡*CH*), 72.59 (C^{18}), 58.38 (CH_2), 56.20 (C^{5})^{a}, 55.90 (C^{9})^{a}, 39.44 (C^{1}), 38.83 (C^{7}), 38.42 (C^{4}), 37.88 (C^{10}), 36.02 (C^{3}), 27.74 (C^{19}), 24.46 (C^{11}), 24.14 (C^{6}), 23.28 (C^{12}), 18.95 (C^{2}), 15.22 (C^{20}).

(4S,9S,10R)-16-Hydroxymethyl-18-(prop-2-yn-1-yloxy)-15,16-epoxy-8(17),13(16),14(15)-labdatriene (**6**). $NaBH_4$ (0.26 g, 6.79 mmol) was added portion wise to a solution of aldehyde **5** (0.50 g, 1.36 mmol) in *i*-propanol (15 ml) 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 as an eluent) to isolate 0.46 g (91 %) of compound **6** as a colorless oily substance. $[\alpha]_D$+26.23° (c 0.77; $CHCl_3$). Found: C 77.74, H 9.11 %. $C_{24}H_{34}O_3$. Calc.: C 77.80, H 9.25 %. IR (KBr) ν_{max} cm^{-1}: 631 m, 665 m, 756 m, 891 s, 959 m, 982 m, 1020 m, 1094 s, 1142 m, 1263 m, 1358 m, 1371 m, 1379 m, 1443 m, 1508 w, 1643 m, 2116 w, 2849 s, 2868 s, 2932 s, 3078 w, 3304 m, 3441 m. UV-Vis (EtOH) λ_{max} (lgε) nm: 219 (3.81). ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 7.32 (1H, d, *J*=1.6 Hz, C^{15}H), 6.23 (1H, d, *J*=1.6 Hz, C^{14}H), 4.87 (1H, s, C^{17}H), 4.57 (1H, s, C^{17}H), 4.51 (2H, s, C*H*$_2$OH), 4.09 (1H, d.d, *J*=15.7 Hz, *J*=2.2 Hz, CH_2), 4.03 (1H, d.d, *J*=15.7 Hz, *J*=2.2 Hz, CH_2), 3.57 (1H, d, *J*=8.9 Hz, C^{18}H), 3.21 (1H, d, *J*=8.9 Hz, C^{18}H), 2.52 (1H, m, C^{12}H), 2.39 (1H, m, C^{7}H), 2.36 (1H, t, *J*=2.2 Hz, ≡CH), 2.29 (1H, m, C^{12}H), 1.91 (1H, d.t, *J*=12.5 Hz, *J*=5.3 Hz, C^{6}H), 1.70–1.83 (4H, m, C^{1}H, C^{6}H, C^{7}H, C^{11}H), 1.60 (1H, m, C^{9}H,), 1.46, 1.50, 1.55 (3H, all m, C^{2}H, C^{3}H, C^{11}H), 1.34 (1H, m, C^{2}H), 1.15 (1H, d.d, *J*=12.9 Hz, *J*=2.4 Hz, C^{5}H), 0.97 (1H, m, C^{3}H), 0.94 (3H, s, C^{19}H_3), 0.91 (1H, m, C^{1}H), 0.66 (3H, s, C^{20}H_3). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 149.27 (C^{16}), 148.08 (C^{8}), 141.84 (C^{15}), 122.87 (C^{13}), 111.51 (C^{14}), 106.58 (C^{17}), 80.38 (*C*≡CH), 73.82 (C≡*CH*), 72.70 (C^{18}), 58.48 (CH_2), 56.24 (C^{5})^{a}, 55.65 (C^{9})^{a}, 55.27 (CH_2OH), 39.43 (C^{1}), 38.86 (C^{7}), 38.55 (C^{4}), 37.97 (C^{10}), 36.08 (C^{3}), 27.80 (C^{19}), 24.54 (C^{11}), 24.46 (C^{6}), 23.01 (C^{12}), 19.05 (C^{2}), 15.34 (C^{20}).

(4S,9S,10R)-16-((Prop-2-yn-1-yloxy)methyl)-18-propargyloxy-15,16-epoxy-8(17),13(16),14(15)-labdatriene (**7**). To a stirred solution of compound **6** (0.50 g, 1.35 mmol) in acetonitrile (10 ml) a dispersion of sodium hydride in mineral oil (0.22 g, 5.41 mmol) was added at 0 °C. The mixture was stirred for 30 min, and asolution of propargyl bromide in toluene (0.30 ml, 2.70 mmol) was added. The reaction mixture was warmed to ambient temperature and stirred for additional 20 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. The residue was subjected to chromatography on silica gel (petroleum ether-diethyl ether, 4:1 as an eluent) to isolate 0.35 g (63 %) of compound **7** as a colorless oily substance. $[\alpha]_D$ +22.22° (c 1.26; $CHCl_3$). Found: C 79.70, H 8.80 %. $C_{27}H_{36}O_3$. Calc.: C 79.37, H 8.88 %. IR (KBr) ν_{max} cm^{-1}: 573 w, 633 m, 665 m, 743 m, 893 m, 937 m, 1024 m, 1078 s, 1092 s, 1144 m, 1261 m, 1354 m, 1443 m, 1506 w, 1643 m, 2116 w, 2849 s, 2963 s, 3078 w, 3298 s. UV-Vis (EtOH) λ_{max} (lgε) nm: 221 (3.94). ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 7.33 (1H, s, C^{15}H), 6.24 (1H, s, C^{14}H), 4.86 (1H, s, C^{17}H), 4.58 (1H, s, C^{17}H), 4.47 (2H, m C$^{1'}$$H_2$), 4.10 (2H, m C$^{3'}$$H_2$), 4.09 (1H, d, *J*=16.1 Hz, CH_2), 4.05 (1H, d, *J*=16.1 Hz CH_2), 3.57 (1H, d, *J*=8.7 Hz, C^{18}H), 3.21 (1H, d, *J*=8.7 Hz, C^{18}H), 2.54 (1H, m, C^{12}H), 2.43 (1H, t, *J*=2.2 Hz, C$^{5'}$H), 2.38 (1H, m, C^{7}H), 2.37 (1H, t, *J*=2.2 Hz, ≡CH), 2.29 (1H, m, C^{12}H), 1.92 (1H, d.t, *J*=12.1 Hz, *J*=4.0 Hz, C^{6}H), 1.71–1.82 (4H, m, C^{1}H, C^{6}H, C^{7}H, C^{11}H), 1.59 (1H, m, C^{9}H,), 1.45, 1.53, 1.57 (3H, all m, C^{2}H, C^{3}H, C^{11}H), 1.33 (1H, m, C^{2}H), 1.16 (1H, d.d, *J*=12.1 Hz, *J*=2.7 Hz, C^{5}H), 0.94 (4H, s, C^{19}H_3, C^{3}H), 0.91 (1H, m, C^{1}H), 0.66 (3H, s, C^{20}H_3). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 147.96 (C^{8}), 146.23 (C^{16}), 142.27 (C^{15}), 125.10 (C^{13}), 111.45 (C^{14}), 106.51 (C^{17}), 80.35 (*C*≡C*H*), 79.49 (C$^{4'}$), 74.59 (C$^{5'}$), 73.82 (C≡*CH*), 72.66 (C^{18}), 61.02 (C$^{1'}$), 58.45 (CH_2), 56.60 (C$^{3'}$), 56.21 (C^{5})^{a}, 55.76 (C^{9}) ^{a}, 39.40 (C^{1}), 38.83 (C^{7}), 38.54 (C^{4}), 37.94 (C^{10}), 36.06 (C^{3}), 27.78 (C^{19}), 24.51 (C^{11}), 24.51 (C^{6}), 23.13 (C^{12}), 19.03 (C^{2}), 15.30 (C^{20}).

Reaction of dialkynyl labdatrienoate **7** *with 1,10-diazidodecane* **8**. A solution of diacetylene **7** (0.50 g, 1.23 mmol) in CH_2Cl_2 (123 ml) and solutions of $CuSO_4 \cdot 5H_2O$ (0.12 g, 0.49 mmol) in water (1.0 ml), and sodium ascorbate (0.61 g, 3.06 mmol) in water (1.0 ml) were mixed, and 1,10-diazidodecane **8** (0.027 g, 0.12 mmol) was added with stirring at ambient temperature. The temperature was raised to 40 °C and stirring was continued for 10 h. The reaction mixture was added to 0.027 g (0.12 mmol) of 1,10-diazidodecane **8** and heated at 40 °C for 10 h, repeated this procedure 8 times. 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 0.10 g (12 %) of compound **10** and 0.30 g (36 %) of compound **11**.

Compound **10**, oily substance. $[\alpha]_D$+23.84° (c 0.34; $CHCl_3$). MS (EI, 70 eV) found: 632.4417 $[C_{37}H_{56}N_6O_3]^+$. $C_{37}H_{56}N_6O_3$. Calcd. 632.4408. IR (KBr) ν_{max} cm^{-1}: 665 w, 754 s, 891 m, 1049 s, 1082 s, 1142 m, 1219 m, 1335 w, 1367 m, 1448 m, 1464 m, 1506 w, 1641 w, 1720 w, 1759 w, 2094 w, 2854 s, 2928 s, 3078 w, 3134 w. UV-Vis (EtOH) λ_{max} (lgε) nm: 216 (4.12). ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 7.42 (1H, s, C^{36}H)^{a}, 7.41 (1H, s, C^{35}H)^{a}, 7.31 (1H, d, *J*=1.6 Hz, C^{38}H), 6.20 (1H, d, *J*=1.6 Hz, C^{37}H), 4.74 (1H, s, C^{39}H), 4.61 (1H, s, C^{17}H), 4.66 (2H, s, C^{2}H, C^{17}H), 4.57 (1H, s, C^{39}H)^{a}, 4.56 (1H, s, C^{2}H)^{a}, 4.40 (2H, s, C^{4}H_2), 4.37 (1H, d, *J*=6.5 Hz, C^{31}H)^{b}, 4.33 (1H, d, *J*=6.5 Hz, C^{31}H)^{b}, 4.29 (2H, t, *J*=7.0 Hz, C^{22}H_2, *J* 7.0)^{b}, 3.36 (1H, d, *J*=9.1 Hz, C^{15}H), 3.17 3.36 (1H, d, *J*=9.1 Hz, C^{15}H), 2.45 (1H, m, C^{7}H), 2.23 (2H, m, C^{7}H, C^{11}H), 1.61–1.84 (9H, m, C$^{3'}$H, C^{12}H, C^{11}H, C^{8}H, C^{12}H, 2CH_2), 1.54 (2H, m, C^{9}H, C^{8}H), 1.48–1.57 (2H, m, C$^{2'}$H, C$^{1'}$H), 1.33 (1H, m, C$^{2'}$H), 1.19, 1.23, 1.25 (12H, all m, 6CH_2), 1.16 (1H, d.d, *J*=12.9 Hz, *J*=2.7 Hz, C^{13}H), 0.92 (1H, m, C$^{1'}$H), 0.89 (3H, s, C^{40}H_3), 0.87 (1H, m, C$^{3'}$H), 0.51(3H, s, C$^{5'}$$H_3$). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 148.06 (C^{10}), 146.94 (C^{5}), 146.94 (C^{18})^{a}, 146.02 (C^{1})^{a}, 142.02 (C^{38}), 124.32 (C^{6}), 121.96 (C^{36}), 121.89 (C^{35}), 111.58 (C^{37}), 106.37 (C^{39}), 72.50 (C^{15}), 64.56 (C^{17})^{a}, 63.87 (C^{2})^{a}, 62.31 (C^{4}), 56.05 (C^{13})^{b}, 55.42 (C^{9})^{b}, 50.12 (C^{22}, C^{31}), 39.32 (C$^{3'}$), 38.76 (C^{11}), 38.57 (C^{14}), 37.87 (C$^{4'}$), 36.48 (C$^{1'}$), 30.18 (CH_2), 30.07 (CH_2), 29.18 (CH_2), 28.95 (CH_2), 28.90 (CH_2), 28.76 (CH_2), 28.04 (C^{40}), 26.12 (2CH_2), 24.68 (C^{8}), 24.36 (C^{12}), 23.00 (C^{7}), 19.02 (C$^{2'}$), 15.09 (C$^{5'}$).

Dimeric compound **11**, oily substance. ESI-HRMS (*m/z*): $[(M+H)^+]$ calcd for $C_{74}H_{113}N_{12}O_6$: 1265.89, found 1265.89; $[(M+Cl)^+]$ calcd for $C_{74}H_{112}N_{12}O_6Cl$: 1299.850, found 1299.852. IR (KBr) ν_{max} cm^{-1}: 727 m, 752 m, 891 m, 1020 m, 1049 s, 1093 s, 1140 m, 1227 m, 1265 m, 1340 m, 1371 m, 1410 m, 1466 m, 1641 m, 1759 m, 2096 w, 2854 s, 2928 s, 3080 w, 3140 m. UV-Vis (EtOH) λ_{max} (lgε) nm: 216 (3.95), 280 (2.94). ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 7.49 (2H, s, 2C$^{5''}$H)^{a}, 7.44 (2H, s, 2C$^{5'}$H)^{a}, 7.31 (2H, d, *J*=1.6 Hz, 2C^{15}H), 6.22 (2H, d, *J*=1.6 Hz, 2C^{16}H), 4.82 (2H, s, 2C^{17}H), 4.61 (4H, s, 4CH_2C$^{4''}$)^{b}, 4.54 (4H, s, 4CH_2C$^{4'}$)^{b}, 4.55 (2H, s, 2C^{17}H), 4.44 (4H, s, 2C^{16}CH_2), 4.30 (8H, m, 4CH_2N$^{1'}$, 4CH_2N$^{1''}$), 3.52 (2H, d, *J*=9.1 Hz, 2C^{18}H), 3.21 (2H, d, *J*=9.1 Hz, 2C^{18}H), 2.52 (2H, m, 2C^{12}H), 2.36 (4H, m, 2C^{12}H, 2C^{7}H), 1.65–1.86 (18H, m, 2C^{1}H, 2C^{7}H, 2C^{11}H, 2C^{6}H_2, 4CH_2), 1.48–1.58 (8H, m, 2C^{2}H, 2C^{3}H, 2C^{9}H, 2C^{11}H), 1.38 (2H, m, 2C^{2}H), 1.28 (24H, m, 12CH_2), 1.12 (2H, d.d, *J*=12.4 Hz, *J*=2.2 Hz, 2C^{5}H), 0.92 (8H, s, 2C^{3}H, C^{19}H_3), 0.87 (2H, m, 2C^{1}H), 0.59 (6H, s, C^{20}H_3). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 147.97 (2C^{8}), 146.73 (2C^{16}), 145.90 (2C$^{4''}$)^{a},145.05 (2C$^{4'}$)^{a}, 142.10 (2C^{15}), 124.62 (2C^{13}), 122.18 (2C$^{5''}$)^{b},121.83 (2C$^{5'}$)^{b}, 111.43 (2C^{14}), 106.48 (2C^{17}), 73.07 (2C^{18}), 65.09 (2C$^{4''}$CH_2)^{c}, 63.52 (2C$^{4'}$CH_2)^{c}, 62.19 (2C^{16}CH_2),

56.15 ($2C^5$)[d], 55.75 ($2C^9$)[d], 50.26 ($2N^{1''}C$)[e], 50.24 ($2N^{1'}C$)[e], 39.39 ($2C^1$), 38.82 ($2C^7$), 38.53 ($2C^4$), 38.13 ($2C^{10}$), 36.14 ($2C^3$), 30.27 ($2CH_2$), 30.24 ($2CH_2$), 29.20 ($2CH_2$), 29.18 ($2CH_2$), 28.88 ($4CH_2$), 27.86 ($2C^{19}$), 26.40 ($4CH_2$), 24.55 ($2C^{11}$), 24.43 ($2C^6$), 23.15 ($2C^{12}$), 19.05 ($2C^2$), 15.28 ($2C^{20}$).

Reaction of dialkynyl labdatrienoate **7** *with 1-azido-2-(2-azidoethoxy)ethane* **9**. A solution of diacetylene **7** (0.50 g, 1.23 mmol) in CH_2Cl_2 (123 ml) and solutions of $CuSO_4{\cdot}5H_2O$ (0.12 g, 0.49 mmol) in water (1.0 ml), and sodium ascorbate (0.61 g, 3.06 mmol) in water (1.0 ml) were mixed, and the 1-azido-2-(2-azidoethoxy)ethane **9** (0.019 g, 0.12 mmol) was added with stirring at ambient temperature. The temperature was raised to 40 °C and stirring was continued for 10 h. The reaction mixture was added 0.019 g (0.12 mmol) 1-azido-2-(2-azidoethoxy)ethane **9** (and heated at 40 °C for 10 h, repeated this procedure 8 times. 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 0.089 g (12 %) of compound **12** and 0.092 g (12 %) of compound **13**.

Compound **12**, oily substance. $[\alpha]_D$ + 28.97° (c 0.86; $CHCl_3$). MS (EI, 70 eV) found: 608.3679 $[C_{33}H_{48}N_6O_5]^+$. $C_{33}H_{48}N_6O_5$. calcd. 608.3681. IR (KBr) ν_{max} cm^{-1}: 665 w, 754 s, 810 w, 893 m, 1049 s, 1084 s, 1136 s, 1223 m, 1263 m, 1335 w, 1360 m, 1450 m, 1641 w, 1722 w, 1757 w, 2866 s, 2928 s, 3078 w, 3140 w. UV-Vis (EtOH) λ_{max} (lgε) nm: 217 (4.00). ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 7.57 (1H, s, $C^{34}H$)[a], 7.45 (1H, s, CH^{33})[a], 7.25 (1H, d, *J*=1.6 Hz, $C^{36}H$), 6.17 (1H, d, *J*=1.6 Hz, $C^{35}H$), 4.78 (1H, s, $C^{37}H$), 4.65 (2H, d, *J*=10.2 Hz, $C^{17}H_2$), 4.61 (2H, d, *J*=12.4 Hz, C^2H_2), 4.58 (1H, s, $C^{37}H$), 4.52 (2H, s, C^4H_2), 4.40-4.53 (4H, m, $C^{22}H_2$, $C^{29}H_2$), 3.79, 3.83 (8H, both m, $C^{23}H_2$, $C^{25}H_2$, $C^{26}H_2$, $C^{28}H_2$), 3.27 (1H, d, *J*=9.1 Hz, $C^{15}H$), 3.18 д (1H, d, *J*=9.1 Hz, $C^{15}H$), 2.52 (1H, m, C^7H), 2.34 (1H, m, $C^{11}H$), 2.06 (1H, m, C^7H), 1.89 (1H, d.t, *J*=12.6 Hz, *J*=4.3 Hz, $C^{12}H$), 1.44-1.78 (8H, m, $C^{3'}H$, $C^{12}H$, $C^{11}H$, C^9H, $C^{1'}H$, $C^{2'}H$, C^8H_2), 1.27 (1H, m, $C^{2'}H$), 1.13 (1H, d.d, *J*=12.4 Hz, *J*=1.6 Hz, $C^{13}H$), 0.96 (4H, s, $C^{38}H_3$, $C^{1'}H$), 0.91 (1H, m, $C^{3'}H$), 0.41 (3H, s, $C^{5'}H_3$). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 148.41 (C^{10}), 147.32 (C^5), 145.83 (C^{18})[a], 145.58 (C^1)[a], 141.45 (C^{36}), 125.22 (C^6), 123.03 (C^{34})[b], 122.84 (C^{33})[b], 112.75 (C^{35}), 106.30 (C^{37}), 72.77 (C^{15}), 69.56 ($2CH_2O$), 68.78 ($2CH_2O$), 64.21 (C^{17})[c], 63.87 (C^2)[c], 63.20 (C^4), 56.58 (C^{13}), 55.90 (C^9), 49.60 (C^{29})[d], 49.22 (C^{22})[d], 39.45 ($C^{3'}$), 38.85 (C^{11}), 38.54 (C^{14}), 37.63 ($C^{4'}$), 36.67 ($C^{1'}$), 28.30 (C^{38}), 26.62 (C^8), 24.81 (C^{12}), 24.35 (C^7), 19.03 ($C^{2'}$), 14.85 ($C^{5'}$).

Dimeric compound **13**, oily substance. Found: 65.03, H 8.05, N 12.89 %. [*M*] 1189. $C_{36}H_{56}N_6O_3$. requires C C 65.11, H 7.95, N 13.80 %. [*M*] 1216. IR (KBr) ν_{max} cm^{-1}: 665 w, 754 s, 893 w, 1051 s, 1088 s, 1122 s, 1136 s, 1223 m, 1358 m, 1369 m, 1450 m, 1464 m, 1643 m, 1714 m, 1759 m, 2868 s, 2928 s, 3078 w, 3144 w. UV-Vis (EtOH) λ_{max} (lgε) nm: 217 (4.36), 278 (3.29). ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 7.50, 7.51 (2H, both s, $2C^{5''}H$)[a], 7.44, 7.46 (2H, both s, $2C^{5'}H$)[a], 7.31 (2H, s, $2C^{15}H$), 6.22 (1H, s, $2C^{14}H$), 4.82 (4H, m, $2CH_2C^{4'}$)[b], 4.77 (2H, s, $2C^{17}H$), 4.59 (4H, m, $2CH_2C^{4''}$)[b], 4.45, 4.53 (14H, both m, $2CH_2N^{1'}$, $2CH_2N^{1''}$, $2CH_2C^{16}$, $2C^{17}H$), 3.79 (16H, m, $8CH_2O$), 3.53 (2H, m, $2C^{18}H$), 3.22 (2H, m, $2C^{18}H$), 2.52 (2H, m, $2C^{12}H$), 2.35 (2H, m, $2C^7H$), 2.25 (2H, m, $2C^{12}H$), 1.88 (2H, m, $2C^6H$), 1.38–1.76 (16H, m, $2C^1H$, $2C^6H$, $2C^7H$, $2C^9H$, $2C^3H$, $2C^2H$, $2C^{11}H_2$), 1.27 (2H, m, $2C^2H$), 1.12 (2H, d, *J*=12.4 Hz, $2C^5H$), 0.93 (8H, s, $2C^{19}H_3$, $2C^3H$), 0.87 (2H, m, $2C^1H$), 0.59 (6H, s, $3C^{20}H_3$). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 147.96, 147.98 ($2C^8$), 146.69, 146.71 ($2C^{16}$), 145.92, 145.93 ($2C^{4''}$)[a], 145.09 ($2C^{4'}$)[a], 142.09 ($2C^{15}$), 124.66 ($2C^{13}$), 123.40, 123.45 ($2C^{5''}$)[b], 122.99, 123.04 ($2C^{5'}$)[b], 111.46 ($2C^{14}$), 106.50 ($2C^{17}$), 73.18 ($2C^{18}$), 69.42 ($4CH_2O$), 69.36 ($4CH_2O$), 64.88, 64.92 ($2CH_2C^{4''}$)[c], 63.30, 63.32 ($2CH_2C^{4'}$)[c], 62.23 ($2CH_2C^{16}$), 56.13, 56.21 ($2C^5$), 55.78, 55.81 ($2C^9$), 49.96 ($2CH_2N^{1'}$, $2CH_2N^{1''}$), 39.40 ($2C^1$), 38.82 ($2C^7$), 38.54 ($2C^4$), 38.15 ($2C^{10}$), 36.14 ($2C^3$), 27.89 ($2C^{19}$), 24.56 ($2C^{11}$), 24.47 ($2C^6$), 23.18 ($2C^{12}$), 19.06 ($2C^2$), 15.29 ($2C^{20}$).

*In the describing the ^{1}H and ^{13}C NMR spectral signals marked with the same letter may be exchanged within the spectrum of the same compound.

Results and Discussion

The synthetic route followed for the synthesis of the key compound – labdanoid 16,18-diacetylene **5** from methyl lambertianate **2** is outlined in Scheme 1. Accordingly, the C-4 carbmethoxyl group was reduced to yield the alcohol **3**.[25] The reaction of compound **3** with propargyl bromide in DMF in the presence of sodium hydride resulted in the formation of acetylenic derivatives **4** (yield 67 %). Vilsmeier-Haack formylation of compound **4** proceeds selectively and gave the 16-formyl derivatives **5** (yield 89 %) which was converted to the compound **6** (yield 91 %) by treatment with sodium borohydride in *i*-propanol. Then the alcohol **6** was alkylated with propargyl bromide giving the corresponding labdanoid dialkyne **7** (yield 63 %). It is worth pointing out that starting dialkyne **7** could be obtained in a gram scale in good overall yields over the three steps, and required only a few column chromatography purification.

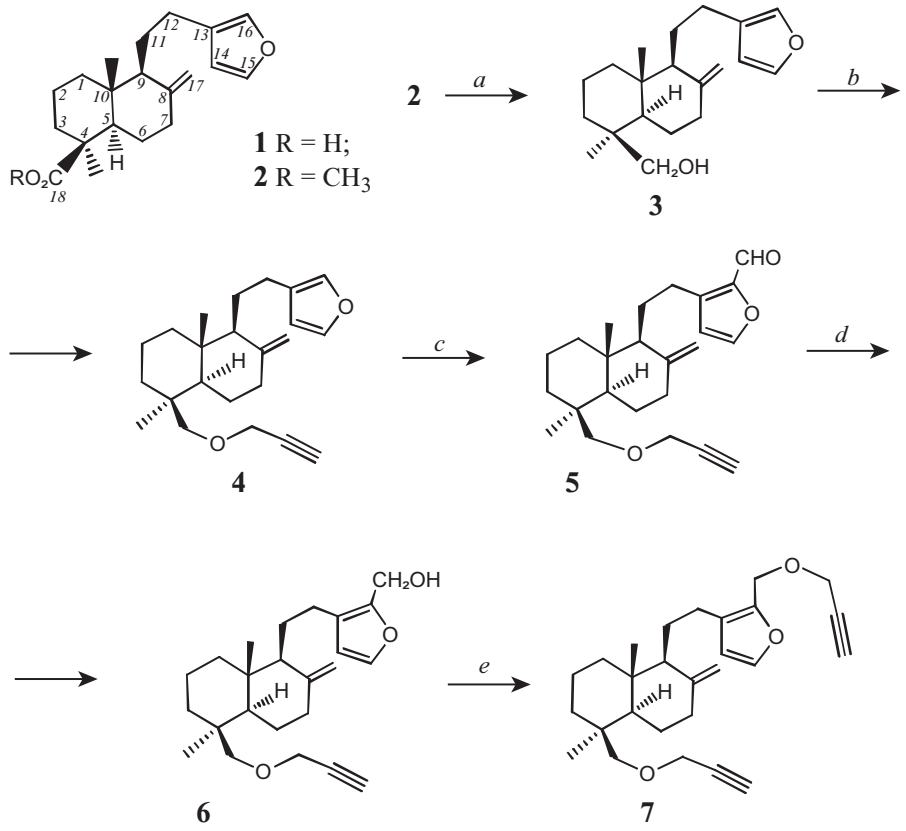
The CuAAC reaction of terpenoid dialkyne **7** with diazides **8**, **9** was used to prepare the 16,18-connected bis(triazole) macrocycles. By performing the reaction of compound **7** with 1,10-diazidodecane **8** (1 equiv, portionwise addition) in CH_2Cl_2-water medium (20:1; 0.01 M solution of **7**) in the presence of $CuSO_4$ and sodium ascorbate under high dilution conditions the full conversion of compound **7** was observed after the heating about of 90 h. After column chromatography on silica gel two compounds were isolated: bis(triazole) macroheterocyclic compound **10** (yield 12 %) and tetra(triazole) macrocycle **11** (yield 36 %) (Scheme 2).

The yield and composition of the target macrocyclic compounds were shown to be dependent on the nature of the starting diazides Reaction of dialkyne **7** (0.01 M solution in methylene chloride) with 1-azido-2-(2-azidoethoxy) ethane **9** in the above conditions was more selective in the formation of the macrocyclic compound **12**. After column chromatography each bis- and tetra(triazole) macrocyclic compounds **12** and **13** were isolated in 12 % yield.

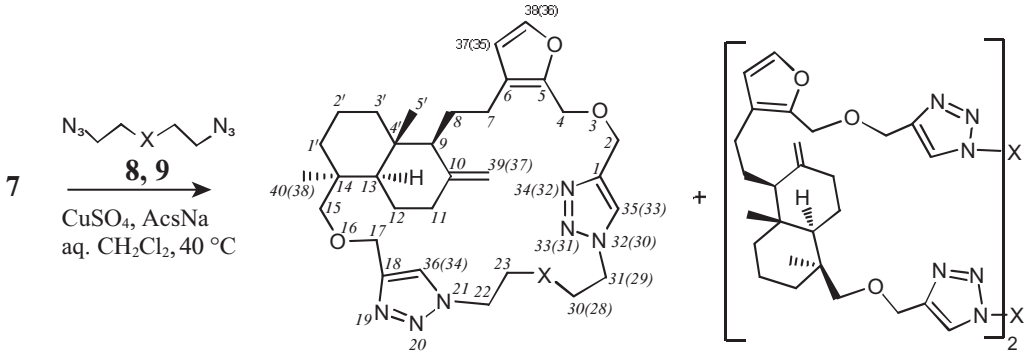
The composition and structure of the synthesized compounds were confirmed by IR, UV, ^{1}H and ^{13}C spectroscopy, mass-spectrometry, elemental analysis data and mass-date. The ^{1}H and ^{13}C NMR spectra of all synthesized compounds agree with their structure and contain the set of characteristic signals of labdanoid skeleton and the corresponding substituent. Formation of the 1,2,3-triazole ring in compounds **10-13** was confirmed by the NMR data. The ^{1}H NMR spectra exhibited singlet signals for the H-5' proton (δ=7.31–7.57 ppm). The ^{13}C NMR signals of the C-4',5' carbon atoms were observed in the region of 145.0–146.9 ppm and 121.8–123.5 ppm, respectively. These data confirmed the formation of 1,4-disubstituted 1*H*-1,2,3-triazoles in the CuAAC reaction.[26]

Conclusions

In conclusion, we have achieved a synthesis of novel labdanoid-based macrocycles using the click-cycloaddition reaction protocol. The present protocol offered the opportunity to explore structural diversity by variation of the diazide structures and leaves room for further exploration of



Scheme 1. Synthesis of the key labdanoid dialkyne **7**. Reagents and reaction conditions: a) $LiAlH_4$, THF, 60 °C, 4h; b) $BrCH_2C{\equiv}CH$, NaH, DMF, 0 °C, then rt, 20 h; c) $POCl_3$, DMF, AcONa, 20 °C, 48 h; d) $NaBH_4$, *i*-PrOH, 20 °C, 24 h; e) $BrCH_2C{\equiv}CH$, NaH, CH_3CN, 0 °C, then rt, 24 h.



X = $C^{24}H_2C^{25}H_2C^{26}H_2C^{27}H_2C^{28}H_2C^{29}H_2$ (**8, 10,11**); $O^{24}C^{25}H_2C^{26}H_2O^{27}$ (**9, 12, 13**)

Scheme 2. Synthesis of bis(triazole) macrocycles (**10**,**12**), tetra(triazole) macrocycles (**11**,**13**).

structural and biological functional diversity in these novel macrocyclic scaffolds.

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