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Click Synthesis of Triazole–Linked Polyazamacrocycles through Selective Isopimaric Acid Transformations

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The first macrocyclic pimarane type diterpenoids containing fragments of 1,2,3-triazole and tricyclic diterpenoid isopimaric acid moieties were synthesized. The key step was the CuAAC reaction of various diazides with the dialkyne derivative obtained from 16-(carboxyphenyl)isopimaric acid. The molecular structure of the macrocyclic compound with 1,5-diazopentane unit was determined by single crystal X-ray diffraction analysis.

Keywords: Isopimaric acid, diterpenoids, dialkynes, diazides, CuAAC-reaction, macrocycles.

Синтез триазол–связанных полиазамакроциклов реакцией азид–алкинового циклоприсоединения диалкинильных производных изопимаровой кислоты

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Синтезированы первые макроциклические дитерпеноиды пимаранового типа, содержащие фрагменты 1,2,3-триазола и трициклического дитерпеноида изопимаровой кислоты. Ключевая стадия синтеза включала Cu-катализируемую реакцию 1,3-диполярного циклоприсоединения различных диазидов к диалкиновому производному 16-(карбоксифенил)изопимаровой кислоты. Молекулярная структура макроциклического соединения с 1,5-диазопентановым звеном подтверждена данными РСА.

Ключевые слова: Изопимаровая кислота, дитерпеноиды, диалкины, диазиды, CuAAC реакция, макрогетероциклы.

Introduction

Tricyclic pimarane type diterpenoid isopimaric acid **1** is widely found in nature firstly in the rosin of conifer trees.[1] The own biological activity,[2–4] low price, and chemical modification potential make this compound to be a valuable raw material for numerous applications.[5–9] So, derivatization of the 4th position of the isopimarane core with various substituent led to compounds with selective anticancer activity.[6–8] Polymerization of isopimaric acid derivatives was carried out to improve the functional properties of polymer products.[9] Despite the wide use

of another conifer tree resin components (abietic and levopimaric acid derivatives maleopimaric acid) in the synthesis of practically useful macrocyclic compound of several topologies[10–12] the macrocyclic derivatives of isopimaric acid were unknown. An another type of macrocyclic compounds was synthesized from tricyclic diterpenoids.[13,14,17,18] The synthetic chemistry of tricyclic diterpenoids is a currently emerging area. In a series of macroheterocyclic derivatives based on accessible labdane diterpenoid lambertianic acid[19–24] compounds with significant cytotoxicity to human tumor cells,[22] and also mercury(II)[21] or zinc(II) ion complexants have been identified.[24] As a common synthetic approach to preparing macroheterocyclic diterpenoids the Cu-catalyzed azide alkyne cycloaddition (CuAAC) reaction was successfully used.[25,26] The 1,2,3-triazole rings resulting from the reaction can be employed as linkers or spacers. Additionally, their role in the manifestation by the new compound of valuable biological activity also should be considered.[26,27] The research reported here presents the results of preparation and spectral studies of chiral macrocyclic pimarane type diterpenoids from isopimaric acid.

Experimental

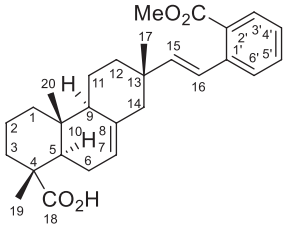
General

^{1}H and ^{13}C NMR spectra were registered on Bruker AV-400 (^{1}H: 400.13 MHz, ^{13}C: 100.78 MHz), Bruker AV-300 (^{1}H: 300.13 Mz, ^{13}C: 75.48 MHz), Bruker AV-600 (^{1}H: 600.30 MHz, ^{13}C: 150.95 MHz) (Bruker BioSpin GmbH, Rheinstetten, Germany) instruments. Deuterochloroform ($CDCl_3$) was used as a solvent, with residual $CHCl_3$ (δ_H = 7.24 ppm) or $CDCl_3$ (δ_C = 77.0 ppm). In the description of the ^{1}H and ^{13}C NMR spectra, the atoms numeration system given in macrocycle **8** was used. The IR spectra were recorded by means of the KBr pellet (or film) technique on a Bruker Vector-22 spectrometer. The UV spectra were obtained on an HP 8453 UV-Vis spectrometer (Hewlett-Packard, Waldbronn, Germany). The mass spectra were recorded on a Thermo Scientific DFS high-resolution mass spectrometer (evaporator temperature 240–270°C, EI ionization at 70 eV). The molecular weight of compound **9** in methanol solutions was determined by the HPLC MSD method on an Agilent 1100 Series LC/MSD instrument. Melting points were determined using termosystem Mettler Toledo FP900 (USA). The optical rotation was measured on a polarimeter PolAAr3005 in ethanol at 20–25 °C. XRD data for compound **8d** were obtained at room temperature on a Bruker Kappa Apex II CCD diffractometer with Mo Kα radiation (λ = 0.71073 Å) and a graphite monochromator.

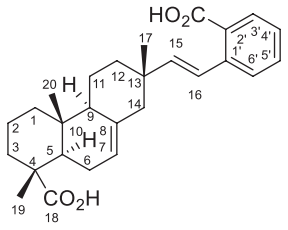
Reaction products were isolated by column chromatography on silica gel 60 (0.063–0.200 mm, Merck KGaA) and eluted with chloroform and chloroform-ethanol (100:1; to 25:l). The reaction progress and the purity of the obtained compounds were controlled by TLC on Silufol UV-254 plates (detection under UV light or by spraying with a 10 % aqueous solution of H_2SO_4, followed by heating to 100 °C). Isopimaric acid **1** was isolated from *Pinus sibirica R. Mayr* sap by the previously described method.[28] 1,2-Bis(2-azidoethoxy)ethane **7a**,[11] 1,6-diazidohexane **7b**,[29] 1-azido-2-(azidoethoxy)ethane **7c**[11] and 1,5-diazidopentane **7d**[30] are known compounds and were synthesized by reported methods. In the ^{13}C NMR spectra the assignments marked with the same symbols *, # are interchangeable.

The *Supporting Information* is available at *https://macroheterocycles.isuct.ru/en/mhc200817s.*

Synthesis

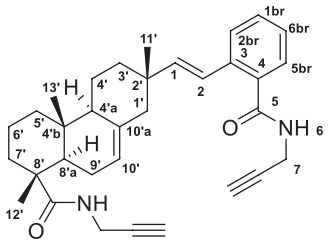


(1R,4aR,4bS,7S,10aR)-7-((E)-2-(Methoxycarbonyl) styryl)-1,4a,7-trimethyl-1,2,3,4,4a,4b,5,6,7,8,10,10a-dodecahydrophenanthrene-1-carboxylic acid (**3**, $C_{28}H_{36}O_4$). A solution of compound **1** (0.75 g, 2.48 mmol), methyl 2-iodobenzoate (0.64 g, 2.48 mmol), $Pd(OAc)_2$ (0.06 g, 0.25 mmol) and Ag_2CO_3 (0.68 g, 2.48 mmol) in *t*-BuOH (5 mL) was stirred at 80 °C for 6 h under argon. The mixture was diluted with $CHCl_3$ (50 mL) and washed with water (3 × 15 mL). The organic layer was dried with $MgSO_4$ and the solvent was removed under vacuum. The resulting crude product was purified by column chromatography (eluting with petroleum ether-Et_2O, from 1:10 to 1:1) to give the compound **3** (0.93 g, 86 %). White solid. M.p. 92.5 °C. $[\alpha]_D^{25}$ = +31.2 (*c* = 0.72 in $CHCl_3$). ESI-HRMS (*m/z*): [(M+H)$^+$ calcd. for $C_{28}H_{36}O_4$: 436.2608, found 436.2606. IR (KBr) ν_{max} cm^{-1}: 707 w, 752 m, 968 m, 1076 s, 1128 m, 1153 m, 1189 m, 1205 m, 1253 s, 1276 s, 1384 m, 1434 m, 1457 m, 1479 m, 1639 m, 1702 vs, 1722 vs, 2653 w, 2821 m, 2867 m, 2883 m, 2925 s, 2948 s, 2981 m, 3060 m, 3427 w. UV-Vis (ethanol) λ_{max} (lgε) nm: 299 (3.50), 255 (4.13), 209 (4.30). ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 0.90 (3H, s, CH_3-17), 0.96 (3H, s, CH_3-20), 1.11 (1H, m, H-1), 1.26 (3H, s, CH_3-19), 1.29 (1H, d *J* = 5.2, H-11), 1.35 (1H, dd *J* = 12.6, 3.3 Hz, H-12), 1.46 (1H, dd *J* = 12.6, 3.3 Hz, H-11), 1.53–1.63 (4H, m, H-2,2,6,12), 1.66 (1H, m, H-3), 1.75 (2H, m, H-9,3), 1.76 (1H, dm *J* = 12.1 Hz, H-1), 1.85 (1H, br.d *J* = 12.9 Hz, H-5), 1.95 (1H, m, H-6), 2.00, 2.03, 2.06 (2H, all m, H-14,14), 3.87 (3H, s, CO_2Me), 5.35 (1H, d *J* = 4.3 Hz, H-7), 6.06 (1H, d *J* = 16.1 Hz, H-15), 7.09 (1H, d *J* = 16.0 Hz, H-16), 7.23 (1H, m, H-4'), 7.41 (1H, dt *J* = 7.7, 1.0 Hz, H-5'), 7.51 (1H, d *J* = 7.7 Hz, H-6'), 7.84 (1H, dd *J* = 7.7, 1.1 Hz, H-3'). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 15.2 (C^{20}), 16.9 (C^{19}), 17.8 (C^2), 19.9 (C^{11}), 21.8 (C^{17}), 25.0 (C^6), 34.8 (C^{10}), 36.2 (C^{13}), 36.7 (C^{12}), 36.8 (C^3), 38.6 (C^1), 44.8 (C^5), 46.2 (C^4), 46.2 (C^{14}), 51.8 (C^9), 51.9 (OMe), 121.0 (C^7), 123.9 (C^{16}), 126.3 ($C^{4'}$), 127.1 ($C^{6'}$), 128.1 ($C^{2'}$), 130.2 ($C^{3'}$), 131.8 ($C^{5'}$), 135.3 (C^8), 139.9 ($C^{1'}$), 144.8 (C^{15}), 167.9 (CO_2Me), 185.4 (C^{18}).



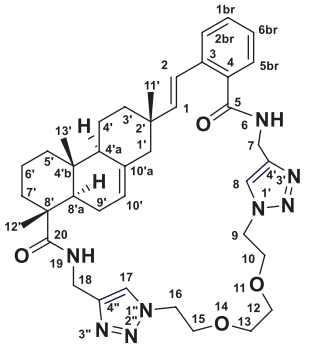
(1R,4aR,4bS,7S,10aR)-7-((E)-2-Carboxystyryl)-1,4a,7-trimethyl-1,2,3,4,4a,4b,5,6,7,8,10,10a-dodecahydrophenanthrene-1-carboxylic acid (**4**, $C_{27}H_{34}O_4$). A stirred solution of compound **3** (0.70 g, 1.63 mmol) in MeOH (8 mL) was treated with 4 mL KOH (1 M). The reaction mixture was heated to reflux for 6 h (control TLC). HCl was added dropwise until p*H* 2, a white precipitate was formed and filtered. The solid was purified by column chromatography ($CHCl_3$–MeOH, 1:1), to give the compound **4** (0.66 g, 96 %). White solid. M.p. 235.0 °C. $[\alpha]_D^{25}$ = + 32.8(*c* = 0.25 in $CHCl_3$:MeOH, 3:1). ESI-HRMS (*m/z*): [(M+H) $^+$] calcd for $C_{27}H_{34}O_4$: 422.2452: found 422.2450. IR (KBr) ν_{max} cm^{-1}: 464 m, 754 m, 796 m, 1078 vs, 1189 s, 1234 s, 1257 s, 1299 s, 1386

s, 1403 s, 1444 s, 1456 s, 1479 s, 1565 m, 1600 m, 1639 m, 1691 s, 2925 m, 2950 m, 3434 s. UV-Vis (ethanol) λ_{max} (lgε) nm: 299 (3.04), 255 (3.85), 209 (3.99), 205 (3.99). ^{1}H NMR ($CDCl_3$+CD_3OD, 298 K) δ_H ppm: 0.86 (3H, s, CH_3-17), 0.92 (3H, s, CH_3-20), 1.12 (1H, m, H-1), 1.21 (4H, s, CH_3-19, H-11), 1.39 (2H, m, H-12,11), 1.49–1.58 (4H, m, H-2,2,6,12), 1.60 (1H, m, H-3), 1.64 (1H, m, H-3), 1.75 (2H, m, H-1,9), 1.80 (1H, br.d *J* = 13.3 Hz, H-5), 1.92 (2H, m, H-6,14), 2.06 (1H, d *J* = 13.8 Hz, H-14), 5.30 (1H, d *J* = 4.6 Hz, H-7), 6.04 (1H, d *J* = 16.0 Hz, H-15), 7.09 (1H, d *J* = 16.0 Hz, H-16), 7.19 (1H, dt *J* = 7.8, 0.8 Hz, H-4'), 7.38 (1H, dt *J* = 7.8, 0.8 Hz, H-5'), 7.47 (1H, dd *J* = 7.8, 0.8 Hz, H-6'), 7.86 (1H, dd *J* = 7.8, 0.8 Hz, H-3'). ^{13}C NMR ($CDCl_3$+CD_3OD, 298 K) δ_C ppm: 15.1 (C^{20}), 17.0 (C^{19}), 17.8 (C^2), 19.8 (C^{11}), 21.9 (C^{17}), 24.9 (C^6), 34.8 (C^{10}), 36.2 (C^{13}), 36.6 (C^{12}), 36.9 (C^3), 38.6 (C^1), 44.8 (C^5), 45.8 (C^4), 46.1 (C^{14}), 51.7 (C^9), 120.9 (C^7), 123.9 (C^{16}), 126.2 ($C^{4'}$), 126.9 ($C^{6'}$), 128.3 ($C^{2'}$), 130.6 ($C^{3'}$), 131.9 ($C^{5'}$), 135.4 (C^8), 140.0 ($C^{1'}$), 144.6 (C^{15}), 171.3 (CO_2H), 183.0 (C^{18}).

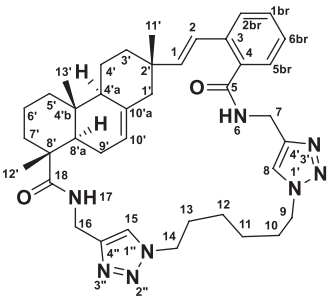


(1R,4aR,4bS,7S,10aR)-1,4a,7-Trimethyl-N-(prop-2-yn-1-yl)-7-((E)-2-(prop-2-yn-1-ylcarbamoyl)styryl)-1,2,3,4,4a,4b,5,6,7,8,10,10a-dodecahydrophenanthrene-1-carboxamide (**6**). A solution of compound **4** (0.50 g, 1.18 mmol) in anhydrous CH_2Cl_2 (10 mL) under a stream of argon was cooled in ice, stirred vigorously for 15 min, and treated with oxalyl chloride (0.70 mL, 8.26 mmol) in CH_2Cl_2 (10 mL), catalytic amount of DMF (two drops). The reaction temperature was raised to ambient. The mixture was stirred for 1 h. The solvent was vacuum distilled. The residue was treated with CH_2Cl_2 (10 mL). The solvent was removed again. This procedure was repeated four times. The residue afforded **4a** (0.54 g) was dissolved in anhydrous CH_2Cl_2 (15 mL) and under a stream of argon treated with Et_3N (0.89 mL, 5.90 mmol) and then gradually with propargyl amine hydrochloride (0.24 g, 2.60 mmol) and stirred at room temperature for 24 h. The solvent was removed in vacuum. Column chromatography of the residue over silica gel afforded compound **6** (0.54 g, 92 %). Using of 2.2 fold of oxalyl chloride (0.22 mL, 2.60 mmol) and increasing the reaction time in the first step to 24 h gave compounds **6** (0.18 g, 31 %) and **4** (0.30 g, 60 %). Increasing the excess of oxalyl chloride to 5 equiv. led to the isolation of **6** (0.26 g, 45 %) and **4** (0.25 g, 49 %). Colorless oil. $[\alpha]_D^{25}$ = +4.5 (c 0.13 in $CHCl_3$). HRMS (EI) (*m/z*): calcd. for $C_{33}H_{40}O_2N_2$: 496.3084, found 496.3082 $[M]^+$. IR (film) ν_{max} cm^{-1}: 628 m, 661 m, 755 s, 968 m, 1157 w, 1201 w, 1257 m, 1272 m, 1299 m, 1348 m, 1363 m, 1384 m, 1444 m, 1458 m, 1475 m, 1518 s, 1567 w, 1598 m, 1652 vs, 1708 m, 2848 m, 2865 m, 2923 s, 3058 w, 3305 s. UV-Vis (ethanol) λ_{max} (lgε) nm: 205 (4.30), 254 (4.03). ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 0.89 (3H, s, CH_3-11'), 0.95 (3H, s, CH_3-13'), 1.16 (1H, m, H-5'), 1.26 (4H, s, CH_3-12', H-4'), 1.42 (2H, m, H-3',4'), 1.56 (4H, m, H-6',6',9',3'), 1.66 (1H, m, H-7'), 1.76 (2H, m, H-7',5'), 1.82 (2H, m, H-8'a,4'a), 1.89, 1.98, 2.01 (3H, m, H-9',1',1'), 2.21 (1H, t *J* = 2.5 Hz, C≡CH), 2.25 (1H, t *J* = 2.5 Hz, C≡CH), 3.71 (1H, ddd *J* = 17.6, 4.8, 2.6 Hz, CH_2), 4.01 (1H, ddd *J* = 17.6, 4.8, 2.6 Hz, CH_2), 4.20 (1H, d *J* = 2.6 Hz, CH_2), 4.22 (1H, d *J* = 2.6 Hz, CH_2), 5.27 (1H, d *J* = 5.0 Hz, H-10'), 5.91 (1H, t *J* = 4.8, 4.4 Hz, NH), 6.04 (1H, t *J* = 4.0, 3.9 Hz, NH), 6.10 (1H, d *J* = 16.1 Hz, H-1), 6.60 (1H, d *J* = 16.1 Hz, H-2), 7.22 (1H, dd *J* = 7.4, 0.7 Hz, H-2br), 7.35 (1H, t *J* = 7.5 Hz, H-6br), 7.43 (1H, d *J* = 7.5 Hz, H-5br), 7.48 (1H, dd *J* = 7.6, 0.7 Hz, H-1br). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 15.23 ($C^{13'}$), 17.18 ($C^{12'}$), 17.98 ($C^{6'}$), 19.83 ($C^{4'}$), 21.77 ($C^{11'}$), 24.73 ($C^{9'}$), 29.51 (2*C*H$_2$C^{o}CH), 35.06 ($C^{4'b}$), 36.19 ($C^{2'}$), 36.79 ($C^{3'}$), 37.01 ($C^{7'}$), 38.65 ($C^{5'}$), 45.63 ($C^{8'a}$), 46.17 ($C^{8'}$), 46.20 ($C^{1'}$), 51.85 ($C^{4'a}$), 71.43, 71.86 (2C^o*C*H), 79.26, 79.76 (2*C*^{o}CH), 121.14 ($C^{10'}$), 122.71 (d, C^2), 126.66 (C^{5br}), 126.82 (C^{6br}), 127.82 (C^{2br}), 130.33 (C^{1br}), 133.83 (C^4), 135.11 ($C^{10'a}$), 136.30 (C^3), 145.87 (C^1), 168.81 (CON), 178.18 (CON).

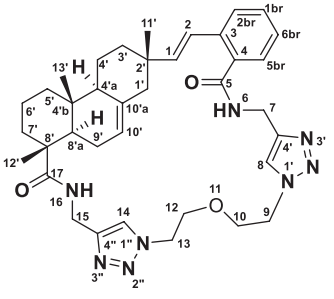
General procedure for the synthesis of macroheterocycles ***8a-d***. A solution of **6** (0.50 g, 1.01 mmol) in CH_2Cl_2 (101 mL) was stirred; treated sequentially with diazide (**7**, 0.10 mmol), a solution of $CuSO_4 \cdot 5H_2O$ (0.10 g, 0.40 mmol) in H_2O (1.0 mL), and a solution of sodium ascorbate (0.40 g, 2.02 mmol) in H_2O (1.0 mL); heated to 40 °C; stirred for 10 h; treated with diazide 7 (0.10 mmol); and refluxed for 10 h at 40 °C. This procedure was repeated three times. Then a solution of $CuSO_4 \cdot 5H_2O$ (0.05 g, 0.20 mmol) in H_2O (1.0 mL), a solution of sodium ascorbate (0.20 g, 1.01 mmol) in H_2O (1.0 mL), and diazide 7 (0.10 mmol) were added; heated to 40 °C; stirred for 10 h; treated with diazide 7 (0.10 mmol); and refluxed for 10 h at 40 °C. This procedure was repeated three times. The mixture was stirred at 40 °C for another 20 h. The organic layer was separated, washed with H_2O (3×50 mL), dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed over a column of silica gel (eluent $CHCl_3$–MeOH) to afford **8**.



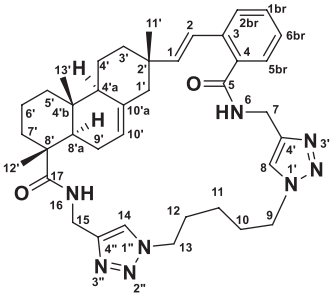
(2'S,4'aS,4'bR,8'R,8'aR)-2',4'b,8'-Trimethyl-1',2',3',4',4'a,4'b,5',6',7',8',8'a,9'-dodecahydro-8H,14H-11,14-dioxa-6,19-diaza-8-(4,1),17(1,4)-ditriazola-1-(2',8')-phenantrena-4(1,2)-benzenacycloicosaphan-1-en-5,20-dione (***8a***) (0.49 g, 70 %). White solid. M.p. 176.5 °C. $[\alpha]_D^{25}$ = -18.6 (c 0.18 in $CHCl_3$). HRMS (EI) (*m/z*): calcd. for $C_{39}H_{52}O_4N_8$: 696.4106, found 696.4093 $[M]^+$. IR (film) ν_{max} cm^{-1}: 754 m, 802 m, 970 m, 1024 m, 1052 m, 1120 s, 1261 s, 1365 m, 1382 m, 1459 m, 1521 s, 1598 m, 1643 s, 1720 s, 2854 m, 2865 s, 2923 vs, 3371 m. UV-Vis (ethanol) λ_{max} (lgε) nm: 253 (3.92). ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 0.80 (3H, s, CH_3-11'), 0.85 (3H, s, CH_3-13'), 0.95 (1H, t *J* = 6.4, 4.6 Hz, H-5'), 1.08–1.26 (6H, m, H-4',4',9',7') 1.28 (s, CH_3-12'), 1.44–1.52 (4H, m, H-3',6',6',7'), 1.67 (1H, dd *J* = 7.6, 0.9 Hz, H-4'a), 1.72–1.83 (4H, m, H-9',3',8'a, 5'), 1.96 (1H, d *J* = 12.0 Hz, H-1'), 1.98 (1H, d *J* = 11.8 Hz, H-1'), 3.51 (4H, m, 2H-12,13), 3.83 (4H, m, 2H-10,15), 4.22 (1H, dd *J* = 14.8, 5.0 Hz, H-18), 4.41–4.60 (5H, m, 2H-9,16, H-18), 4.71 (1H, m, H-7), 4.83 (1H, dd *J* = 15.6, 6.9 Hz, H-7), 5.14 (1H, m, H-10'), 6.03 (1H, d *J* = 16.1 Hz, H-1), 6.30 (1H, d *J* = 16.1 Hz, H-2), 6.54 (1H, d *J* = 4.3 Hz, NH-6), 6.63 (1H, d *J* = 4.6 Hz, NH-19), 7.21 (1H, d *J* = 7.1 Hz, H-2br), 7.32 (1H, t *J* = 7.1 Hz, H-6br), 7.39 (1H, m *J* = 7.0, 0.6 Hz, H-5br), 7.50 (1H, d *J* = 7.0 Hz, H-1br), 7.74 (1H, s, H-17), 7.77 (1H, s, H-8). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 15.24 ($C^{13'}$), 17.33 ($C^{12'}$), 17.97 ($C^{6'}$), 19.75 ($C^{4'}$), 22.77 ($C^{11'}$), 24.78 ($C^{9'}$), 34.86 ($C^{4'b}$), 35.06 (C^7), 35.17 ($C^{2'}$), 36.39 ($C^{3'}$), 36.54 ($C^{7'}$), 37.44 (C^{18}), 38.74 ($C^{5'}$), 44.02 ($C^{8'}$), 45.40 ($C^{8'a}$), 46.07 ($C^{1'}$), 50.26 ($C^{4'a}$), 50.74, 51.90 ($C^{9,16}$), 69.55, 69.91 ($C^{10,15}$), 70.66, 70.87 ($C^{12,13}$), 120.96 ($C^{10'}$), 121.95 (C^2), 122.84 (C^{17})*, 123.69 (C^8)*, 126.39 (C^{5br}), 126.85 (C^{6br}), 127.79 (C^{2br}), 130.07 (C^{1br}), 134.51 (C^3), 135.84 ($C^{10'a}$), 136.03 (C^4), 143.98 ($C^{4'}$), 145.22 ($C^{4''}$), 145.26 (C^1), 169.31 (CON), 178.91 (C^{20}).



(2'S,4'aS,4'bR,8'R,8'aR)-2',4'b,8'-Trimethyl-1',2',3',4',4'a,4'b,5',6',7',8',8'a,9'-dodecahydro-8H,14H-6,17-diaza-8-(4,1),15(1,4)-ditriazola-1-(2',8')-phenantrena-4(1,2)-benzenacycloocta-decaphan-1-en-5,18-dione (***8b***) (0.17 g, 26 %). White solid. M.p. 89.2 °C. $[\alpha]_D^{25}$ = +51.1 (c 0.13 in $CHCl_3$). HRMS (EI) (*m/z*): calcd. for $C_{39}H_{52}O_2N_8$: 664.4208, found 664.4188 $[M]^+$. IR (film) ν_{max} cm^{-1}: 754 vs, 970 m, 1051 m, 1157 m, 1216 m, 1236 m, 1259 m, 1267 m, 1297 m, 1367 m, 1384 m, 1444 m, 1461 m, 1519 s, 1598 m, 1641 vs, 1720 m, 2863 s, 2927 s, 3369 m. UV-Vis (ethanol) λ_{max} (lgε) nm: 252 (2.89). ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 0.85 (3H, s, CH_3-13'), 0.90 (3H, s, CH_3-11'), 1.06–1.34 (12H, m, (1.24, s, CH_3-12'), H-5',4',4',9',7',12,12,11,11), 1.49–1.52 (4H, m, H-3',6',6',7'), 1.66 (1H, m, H-4'a), 1.74–1.85 (8H, m, H-9',3',8'a,5',13,13,10,10), 1.89, 1.95, 2.01 (2H, m, H-1',1'), 4.19 (1H, dd *J* = 14.9, 5.0 Hz, H-16) 4.22–4.30 (3H, m, H-16,9,9), 4.38 (1H, m, H-14), 4.60–4.64 (2H, m, H-14,7), 4.68 (1H, dd *J* = 15.4, 5.5 Hz, H-7), 5.07 (1H, d *J* = 4.8 Hz, H-10'), 6.01 (1H, d *J* = 16.1 Hz, H-1), 6.53 (1H, d *J* = 16.1 Hz, H-2), 6.61 (1H, t *J* = 5.5 Hz, NH-6), 6.65 (1H, t *J* = 5.9 Hz, NH-17), 7.22 (1H, dd *J* = 7.3, 1.5 Hz, H-2br), 7.33 (1H, td *J* = 7.5, 1.1 Hz, H-1br), 7.36 (1H, d *J* = 7.0 Hz, H-6br), 7.54 (1H, d *J* = 1.5 Hz, H-5br), 7.55 (1H, s, H-15), 7.56 (1H, s, H-8). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 15.17 ($C^{13'}$), 17.12 ($C^{12'}$), 17.98 ($C^{6'}$), 19.64 ($C^{4'}$), 21.79 ($C^{11'}$), 24.56 ($C^{9'}$), 25.30 (C^{12})*, 25.57 (C^{11})*, 29.45 (C^{13})#, 29.80 (C^{10})#, 34.98 ($C^{4'b}$), 35.03 ($C^{7,16}$), 35.59 ($C^{2'}$), 36.70 ($C^{3'}$), 37.07 ($C^{7'}$), 38.64 ($C^{5'}$), 45.02 ($C^{8'}$), 45.70 ($C^{8'a}$), 46.11 ($C^{1'}$), 49.70 (C^{14})*, 49.93 (C^{9})*, 51.60 ($C^{4'a}$), 120.74 ($C^{10'}$), 121.77 (C^{2}), 122.71 (C^{8}), 122.81 (C^{15}), 126.86 (C^{5br}), 127.12 (C^{6br}), 127.90 (C^{2br}), 130.31 (C^{1br}), 133.86 (C^{3}), 135.54 ($C^{10'a}$), 136.51 (C^{4}), 144.21 ($C^{4'}$), 145.20 ($C^{4''}$), 145.17 (C^{1}), 169.27 (CON), 178.82 (C^{18}).



(2'S,4'aS,4'bR,8'R,8'aR)-2',4'b,8'-Trimethyl-1',2',3',4',4'a,4'b,5',6',7',8',8'a,9'-dodecahydro-8H,14H-11-oxa-6,16-diaza-8-(4,1),14(1,4)-ditriazola-1-(2',8')-phenantrena-2(1,2)-benzena-cycloheptadecaphan-1-en-5,17-dione (***8c***) (0.22 g, 33 %). White solid. M.p. 109.6 °C. $[\alpha]_D^{25}$ = +60.7 (c 0.57 in $CHCl_3$). HRMS (EI) (*m/z*): calcd for $C_{37}H_{48}O_3N_8$: 652.3844, found 652.3851 $[M]^+$. IR (film) ν_{max} cm^{-1}: 665 m, 754 s, 970 m, 1052 m, 1128 s,1157 m, 1201 m, 1218 m, 1236 m, 1270 m, 1305 m, 1365 m, 1384 m, 1427 m, 1446 m, 1459 m, 1475 m, 1519 s, 1598 m, 1641 vs, 2846 m, 2867 m, 2917 s, 3378 m. UV-Vis (ethanol) λ_{max} (lgε) nm: 253 (3.92). ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 0.73 (3H, s, CH_3-13'), 0.78 (3H, s, CH_3-11'), 1.01–1.23 (8H, m, (1.23, s, CH_3-12'), H-5', 4',4',9',7'), 1.41–1.49 (4H, m, H-3',6',6',7'), 1.56 (1H, m, H-4'a), 1.60–1.65 (2H, m, H-9',3'), 1.71 (1H, m, H-8'a), 1.76, 1.78, 1.82 (3H, m, H-5',1',1'), 3.42–3.57 (2H, m, H-13)*, 3.73 (1H, m, H-9)*, 3.81 (1H, m, H-9)*, 4.13 (1H, dd *J* = 14.8, 5.2 Hz, H-13), 4.35 (4H, m, H-12,10), 4.49 (1H, d *J* = 4.8 Hz, H-13), 4.59–4.73 (2H, m, H-15), 5.00 (1H, d *J* = 2.9 Hz, H-10'), 5.96 (1H, d *J* = 16.1 Hz, H-1), 6.15 (1H, d *J* = 16.1 Hz, H-2), 6.94 (1H, d *J* = 5.8 Hz, NH-6), 7.00 (1H, t *J* = 5.8 Hz, NH-16), 7.12 (1H, dd *J* = 7.4, 7.2 Hz, H-2br), 7.22 (1H, m, H-1br), 7.33 (1H, d *J* = 7.8 Hz, H-6br), 7.38 (1H, d *J* = 7.2 Hz, H-5br), 7.72 (1H, s, H-14), 7.75 (1H, s, H-8). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 15.01 ($C^{13'}$), 17.15 ($C^{12'}$), 17.75 ($C^{6'}$), 19.38 ($C^{4'}$), 22.46 ($C^{11'}$), 24.46 ($C^{9'}$), 34.74 ($C^{4'b}$), 34.89 (C^{7}), 35.20 (C^{15}), 36.18 ($C^{3'}$), 36.50 ($C^{7'}$), 38.34 ($C^{5'}$), 43.52 ($C^{8'}$), 45.57 ($C^{8'a}$), 45.96 ($C^{1'}$), 49.73 (C^{13})*, 50.45 ($C^{4'}$)*, 51.29 ($C^{4'a}$), 69.49 (C^{12})#, 69.57 (C^{10})#, 120.59 ($C^{10'}$), 121.38 (C^{2}), 122.46 (C^{8}), 123.91 (d, C^{14}), 125.85 (C^{5br}), 126.55 (C^{6br}), 127.31 (C^{2br}), 129.72 (C^{1br}), 134.49 (C^{3}), 135.48 ($C^{10'a}$), 135.89 (C^{4}), 144.44 (C^{1}), 144.59 ($C^{4'}$), 145.30 ($C^{4''}$), 169.56 (CON), 178.92 (C^{17}).



(2'S,4'aS,4'bR,8'R,8'aR)-2',4'b,8'-Trimethyl-1',2',3',4',4'a,4'b,5',6',7',8',8'a,9'-dodecahydro-8H,14H-6,16-diaza-8-(4,1),14(1,4)-ditriazola-1-(2',8')-phenantrena-2(1,2)-benzenacycloheptadecaphan-1-en-5,17-dione (***8d***) (0.22 g, 34 %). White solid. M.p. 150.0 °C. $[\alpha]_D^{25}$ = +6.4 (c 2.67 in $CHCl_3$). HRMS (EI) (*m/z*): calcd. for $C_{38}H_{50}O_2N_8$: 650.4051, found 650.4048 $[M]^+$. IR (film) ν_{max} cm^{-1}: 970 w, 1054 w, 1218 m, 1276 m, 1344 m, 1386 w, 1446 w, 1459 m, 1477 m, 1515 s, 1598 m, 1637 ws, 2865 m, 2919 s, 2931 m, 3351 m, 3442 m, 3529 m. UV-Vis (ethanol) λ_{max} (lgε) nm: 210 (4.29), 253 (3.95). ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 0.78 (6H, s, CH_3-13',11'), 1.04 (2H, m, H-5',11), 1.15–1.29 (8H, m, (1.20, s, CH_3-12'), H-4',4',9',7',11), 1.47 (5H, m, H-3',6',6',7',9'), 1.59, 1.64 (3H, m, H-4'a,8'a), 1.75–1.83 (8H, m, H-3',5',10,10,12,12,1',1'), 4.08 (1H, dd *J* = 14.6, 4.7 Hz, H-15), 4.15–4.20 (3H, m, H-9,9,15), 4.39 (1H, dd *J* = 13.3, 6.6 Hz, H-13), 4.50–4.64 (3H, m, H-7,7,13), 5.01 (1H, s, H-10'), 5.92 (1H, d *J* = 16.1 Hz, H-1), 6.28 (1H, d *J* = 16.1 Hz, H-2), 6.91 (1H, br.s, NH-6), 7.01 (1H, br.s, NH-16), 7.13 (1H, t *J* = 7.1 Hz, H-2br), 7.28 (2H, m, H-1br,6br), 7.43 (1H, d *J* = 7.4 Hz, H-5br), 7.60 (1H, s, H-14), 7.62 (1H, s, H-8). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 14.95 ($C^{13'}$), 17.00 ($C^{11'}$), 17.79 ($C^{6'}$), 19.36 ($C^{4'}$), 21.91 ($C^{12'}$), 22.67 (C^{11}), 24.35 ($C^{9'}$), 28.77 (C^{10})*, 29.08 (C^{12})*, 34.79 ($C^{4'b}$), 34.85 ($C^{7,15}$), 35.12 ($C^{2'}$), 36.37 ($C^{3'}$), 36.43 ($C^{7'}$), 38.35 ($C^{5'}$), 44.05 ($C^{8'}$), 45.55 ($C^{8'a}$), 45.91 ($C^{1'}$), 49.37 ($C^{9,13}$), 51.08 ($C^{4'a}$), 120.42 ($C^{10'}$), 121.73 (C^{2}), 122.14 ($C^{8,14}$), 122.98 (C^{5br}), 126.65 (C^{6br}), 127.57 (C^{2br}), 129.95 (C^{1br}), 133.98 (C^{3}), 135.55 ($C^{10'a}$), 136.06 (C^{4}), 144.55 ($C^{4'}$), 145.26 ($C^{4''}$), 145.40 (C^{1}), 169.27 (CON), 178.84 (C^{17}).

Crystallographic data for hydrate of ***8d***: $C_{38}H_{50}N_8O_2{\cdot}H_2O$, *M* 668.87, monoclinic, $P2_1$, *a* 15.494(2), *b* 6.3446(7), *c* 20.647(3) Å, *β* 111.299(4)º, *V* 1891.0(4) Å^3, *Z* 2, D_{calcd} 1.175 g·cm^{-3}, *μ*(Mo-*K*α) 0.077 mm^{-1}, F(000) 720, (θ 2.12 – 26.1°, completeness (θ 50º) 99.4 %), colorless, (1.00×0.18×0.04) mm^3, transmission 0.6419–0.8620, 36413 measured reflections in index range $-18 \le h \le 18$, $-7 \le k \le 7$, $-25 \le l \le 25$, 7163 independent (R_{int} 0.055), 451 parameters 60 restraintes, R_1 0.0777 (for 4909 observed $I > 2\sigma(I)$), wR_2 = 0.2364 (all data), GOOF 1.023, largest diff. peak and hole 0.56 and –0.26 e·A^{-3}. Absorption corrections were applied empirically using *SADABS* programs.[31] The structures were solved by direct methods using the *SHELX-97* programs set[32,33] and refined by full-matrix least-squares method against all F^2 in anisotropic approximation (beside the atoms H) using the *SHELXL2014*/7 programs set.[34] The H atoms positions were

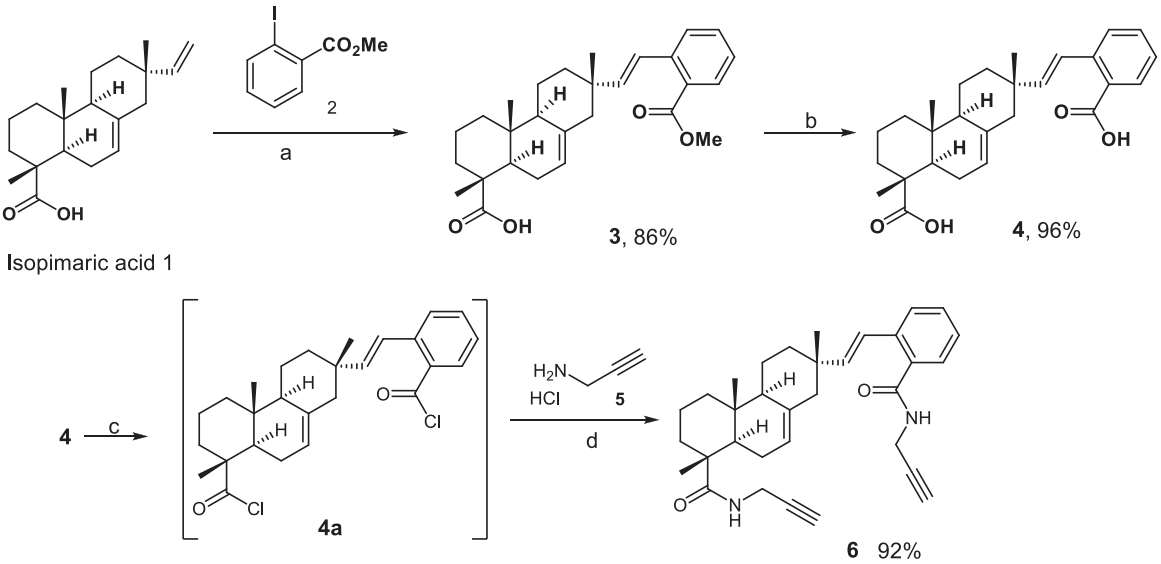
calculated with the riding model except of water hydrogens which were refined independently. The asymmetric unit of crystals includes 1:1 hydrate of compound **8d**.

Dimeric compound ***9*** (0.17 g, 27 %). White solid. M.p. 153.8 °C. $[\alpha]_D^{25}$ = +20.0 (c 0.1 in $CHCl_3$-MeOH, 1:1). ESI-HRMS (*m/z*): [(M+H)$^+$] calcd for $C_{76}H_{100}N_{16}O_4$: 1301.819, found 1301.810; [(M+Na)$^+$] calcd. for $C_{76}H_{100}N_{16}O_4$: 1323.801, found 1324.798. IR (film) ν_{max} cm^{-1}: 755 m, 970 m, 1051 m, 1135 w, 1157 m, 1216 m, 1241 m, 1267 m, 1301 m, 1338. m, 1367 m, 1384 m, 1444 m, 1463 m, 1519 m, 1598 m, 1641 m, 2865 m, 2923 s, 3380 s. UV-Vis (ethanol) λ_{max} (lgε) nm: 212 (3.95), 254 (3.12). ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 0.80, 0.82, 0.85 (12H, s, 2CH_3-13',12'), 1.04 (4H, m, 2H-5',11), 1.15–1.29 (16H, m, (1.25, 1.26, s, CH_3-11'), 2H-4',4',9',7',11), 1.49 (10H, m, 2H-3',6',6',7',9'), 1.74–1.89 (20H, m, 2H-4'a, 8'a,3',5',10,10,12,12,1',1'), 4.29 (10H, m, 2H-9,9,13,15,15), 4.44 (2H, m, 2H-13), 4.55 (1H, dd *J* = 15.1, 5.2 Hz, H-7), 4.60–4.68 (3H, m, 3H-7), 5.17 (2H, d dd *J* = 4.3 Hz, 2H-10'), 6.05 (2H, d *J* = 16.2 Hz, 2H-1), 6.43 (1H, d *J* = 16.0 Hz, H-2), 6.47 (1H, d *J* = 15.7 Hz, H-2), 6.85 (2H, m, 2NH-6), 6.94 (1H, t *J* = 5.4, 5.1 Hz, NH-16), 7.18 (3H, m, 2H-2br, NH-16), 7.32 (2H, m, 2H-1br), 7.40, 7.42, 7.46 (5H, m, H-5br,6br,14), 7.57, 7.59, 7.63 (1H, all s, H-14,8,8). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 15.19, 15.22 (2C$^{13'}$), 17.17, 17.19 (2C$^{11'}$), 18.00, 18.03 (2C$^{6'}$), 19.74, 19.77 (2C$^{4'}$), 21.93 (2C$^{12'}$), 22.98, 23.04 (2C^{11}), 24.69 (2C$^{9'}$), 29.10, 29.17 (2C^{10})*, 29.19, 29.21 (2C^{13})*, 35.02 (2C$^{4'b}$), 35.08, 35.14, 35.18, 35.30 (2C^{7,15}), 36.60 (2C$^{3'}$), 36.78, 36.82 (2C$^{7'}$), 38.60, 38.68 (2C$^{5'}$), 45.63, 45 (2C$^{8'}$), 45.78, 45.81 (2C$^{8'a}$), 46.13 (2C$^{1'}$), 49.54, 49.65, 49.67 (2C^{9,12}), 51.64, 51.81 (2C$^{4'a}$), 120.97, 121.09 (2C$^{10'}$), 122.13 (2C^2), 122.23, 122.28 122.60 (2C^{8,14}), 126.19, 126.24 (2C^{5br}), 126.71, 126.79 (2C^{6br}), 127.62 (2C^{2br}), 130.01, 130.07 (2C^{1br}), 134.49, 134.53 (2C^3), 135.34, 135.46 (2C$^{10'a}$), 135.92, 136.01 (2C^4), 144.51, 144.52 (C$^{4'}$), 144.98, 145.04 (C^1), 145.11, 145.18 (C$^{4''}$), 169.60, 169.63 (CON), 178.87, 179.01 (C^{17}).

Results and Discussion

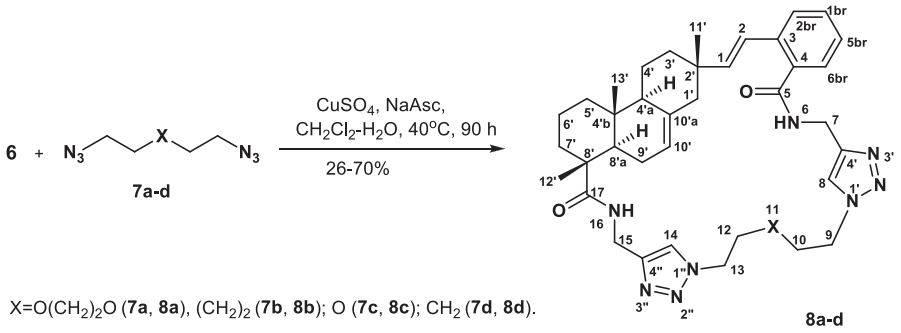
The synthetic route followed for the synthesis of the key compound - bis(prop-2-ynyl)amino)-derivatives of (*E*)-16-(2-carboxyphenyl)isopimaric acid **6** is outlined in Scheme 1. Firstly, we performed the preparation of isopimaric acid derivatives, modified at its terminal double bond. The functionalization of isopimaric acid **1** on the 16 position was carried out by palladium-catalyzed cross-coupling reaction with methyl ether of 2-iodobenzoic acid in the presence of silver carbonate. The subsequent (*E*)-16-aryl substituted derivative **3** was obtained in the yield of 86 % (Scheme 1). Accordingly, the 2-carbmethoxy group of 3 was hydrolyzed by reflux in aq. ethanol solution in the presence of potassium hydroxide under reflux in methanol. The synthesis of bis(prop-2-ynyl)amino derivatives of (*E*)-16-(2-carboxyphenyl)isopimaric acid **6** was achieved by the two-step reaction of the mentioned compound with an excess of oxalyl chloride (7 equiv.) followed by successive reaction of the bis-acid chloride derivative **4a** with propargyl amine hydrochloride **5** (7 equiv., gradually addition, 24 h, rt) in the presence of triethylamine and a catalytic amount of *N,N*-dimethylformamide. Compound **6** was isolated in the yield of 92 %. In spite of the ease of the synthesis of isopimaric acid *N*-propargyl amide by successive treatment with oxalyl chloride (1.99 equiv.) and amine **5** (1.87 equiv),[35] the transformation of 16-(2-carboxyphenyl) isopimaric acid **4** at two carboxyl function in the structure requires more excess of reagents and use of an additive – a catalytic amount of *N,N*-dimethylformamide. So, by using 5 equiv. of oxalyl chloride followed by addition of amine **5** (5 equiv.) the yield of compound **6** achieves only 45 % (compound **4** is additionally highlighted in the 42 % yield).

The CuAAC reaction of the terpenoid dialkyne **6** with diazides was used to prepare the 4,2'-connected macrocycles. The reaction of compound **6** with 1,2-bis(2-azidoethoxy) ethane **7a** (1 equiv.) in CH_2Cl_2-water medium in the presence of $CuSO_4$ and sodium ascorbate (AscNa) under high dilution conditions (0.01 M solution of **6**) with portion-wise adding of diazide proceeded smoothly. By stirring the reaction mixture at 40 °C over 90 h the full conversion of compound **6** was observed. After column chromatography on silica gel macrocyclic compound **8a** was isolated in the yield 70 % (Scheme 2). We found that the yield and composition



a: $Pd(OAc)_2$, Ag_2CO_3, *t*-BuOH, 80 °C, 6 h; b: KOH, MeOH:H_2O (1:1), heat, 6 h; c: $(COCl)_2$, CH_2Cl_2, Cat-DMF; d: Et_3N, CH_2Cl_2, 24 h.

Scheme 1. Synthesis of *N,N*-bis(prop-2-yn-1-yl)-16-(2-carboxyphenyl)isopimarate **6**.



Scheme 2. Synthesis of bis(triazole)macrocycles **8a-d**.

of the target macrocyclic compounds has been depended on the nature of the starting diazides. By performing the reaction of compound **6** with 1,6-diazidohexane **7b**, 1-azido-2-(2-azidoethoxy)ethane **7c**, or 1,5-diazidopentane **7d** the macroheterocyclic compounds **8b**, **8c** or **8d** were isolated in the yields 26, 33 or 34 % respectively. The reaction of dialkyne **6** with diazide **7d** was characterized by low selectivity. After column chromatography on silica gel two compounds were isolated: bis(triazole)macroheterocyclic compound **8d** (yield 34 %) and tetra(triazole)macrocyclic compound **9** (yield 27 %).

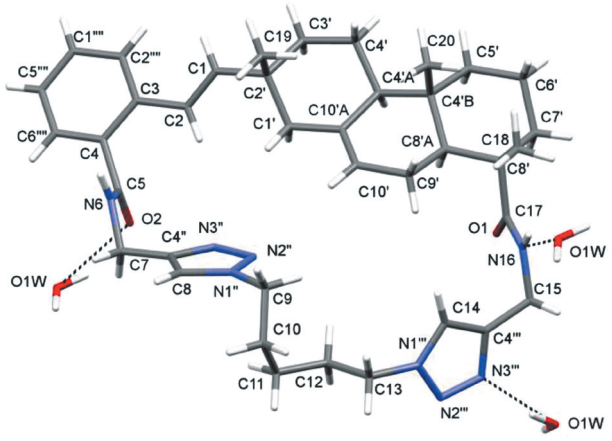


Figure 1. The molecular structure of (2'*S*,4'a*S*,4'b*R*,8'*R*,8'a*R*)-2',4'b,8'-trimethyl-1',2',3',4',4'a,4'b,5',6',7',8',8'a,9'-dodecahydro-8*H*,14*H*-6,16-diaza-8-(4,1),14(1,4)-ditriazola-1-(2-',8')-phenantrena-2(1,2)-benzenacycloheptadecaphan-1-en-5,17-dione **8d** with hydrogen bonded water molecules.

The composition and structure of the synthesized compounds were confirmed by IR, UV, ^{1}H and ^{13}C spectroscopy, mass-spectrometry 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 tricyclic diterpenoid skeleton and the corresponding substituent. Formation of the 1,2,3-triazole ring in compounds **8a-d** was confirmed by the NMR data. The ^{1}H NMR spectra of compounds **8a-d** exhibited singlet signals for the H-5' proton (δ_H = 7.55–7.77 ppm). The structure of **8d** was determined by the single crystal X-ray analysis (Figure 1). The analysis of the molecular geometries and intermolecular hydrogen bonding was performed using PLATON program.[36,37]

The cyclohexane rings in tricycle moiety adopt chair conformation while the *trans*-fused cyclohexene ring between them has a half-chair conformation with deviation of atoms C4'B and C8'A from the plane of the rest atoms of cycle equaling to 0.387 and 0.425 Å correspondingly. The double bond C1=C2 lies closely to plane of phenyl ring C1""C2""C3C4C6""C5"" with interplane angle 20.44º. The orientation of C5=O2 carbonyl group in contrast is almost perpendicular to phenyl moiety with torsion angle O2C5C4C6"" equaling to 78.3º and weak intramolecular hydrogen bond C7-H7A...O2. The C17=O1 carbonyl group has staggered orientation to the neighboring cyclohexane caused by intramolecular hydrogen bonds C8'A-H8'A...O1 and C7'-H7B'...O1 (Table 1).

Each molecule of the compound forms hydrogen bonds with 3 water molecules (Figure 1). This hydrogen bonds net-

Table 1. The parameters of hydrogen bonds for crystal hydrate of compound **8d**.

Intramolecular H-bonds	H…A (Å)	D…A (Å)	D-H…A (°)
C7-H7A...O2	2.40	2.78(3)	103
C8'A-H8'A...O1	2.42	2.872(6)	108
C7'-H7B'...O1	2.54	2.921(7)	104
intermolecular H-bonds			
O1W-H1WA...O2	2.3(1)	2.882(13)	131(11)
O1W-H1WB...N3'''	2.0(1)	2.854(10)	167(11)
N16-H16...O1W	2.12	2.911(9)	153

work determines crystal structure represented with columns of molecules along *b* axis packed into layers parallel to (*a*,*b*) plane. CCDC 2018836 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge *via http://www.ccdc.cam.ac.uk/cgi-bin/catreq.cgi*, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223 336 033; or e-mail: deposit@ccdc.cam.ac.uk.

Conclusions

In conclusion, we have achieved a practical synthesis of novel tricyclic diterpenoid-based macrocycles using a click-cycloaddition reaction protocol. The main features of the macrocyclic scaffolds are a (*E*)-styrene bridge from the diterpenoid moiety, triazole rings and ethylethoxyethyl, 1,6-, 1,5- or ethyloxyethyl units. The found conditions of the CuAAC reaction gave the possibility for selective formation of the bis(triazole) macrocycles with high overall yield. The composition and yield of the macroheterocycles in discussed here CuAAC-reaction were shown to be dependent on the nature of the starting diazides. The higher yield of the macrocycles incorporated two triazole moiety in the linker chain (isolated yield 70 %) was obtained in the reaction of the diterpenoid dialkyne with 1,2-bis-(2-azidoethoxy)ethane.

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