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.

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...
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of another conifer tree resin components (abiic and levo-

pimaric acid derivatives maleopimaric acid) in the synthe-

sis of practically useful macrocyclic compound of several
topologies. The macrocyclic derivatives of isopimaric acid were unknown. Another type of macrocyclic com-

pounds was synthesized from tricyclic diterpenoids. The synthetic chemistry of tricyclic diterpenoids is a cur-

rently emerging area. In a series of macroheterocyclic deriv-

atives based on accessible labdane diterpenoid lambertian-
cid acid compounds with significant cytotoxicity to human

tumor cells, and also mercury(II) or zinc(II) ion com-
plexants have been identified. As a common synthetic
treatment to preparing macroheterocyclic diterpenoids the

Cu-catalyzed azide alkyne cycloaddition (CuAAC) reaction was successfully used. The 1,2,3-triazole rings resulting from the reaction can be employed as linkers or spacers. Additionally, their role in the manifestation of the results of preparation and spectral studies of chiral macrocyclic pimarane type diterpenoids from isopimaric acid.

Experimental

General

1H and 13C NMR spectra were recorded on Bruker AV-400
(1H: 400.13 MHz, 13C: 100.78 MHz), Bruker AV-300 (1H: 300.13
MHz, 13C: 75.48 MHz), Bruker AV-600 (1H: 600.30 MHz, 13C:
159.95 MHz) (Bruker BioSpin GmbH, Rheinstetten, Germany)
instruments. Deuterochloroform (CDCl3) was used as a solvent,
with residual CHCl3 (δH = 7.24 ppm) or CDCl3 (δC = 77.0 ppm).
In the description of the 1H and 13C NMR spectra, the atoms
nenumeration system given in macrocycle 8 was used. The IR spec-
tra were recorded by means of the KBr pellet (or film) technique
using a Bruker Vector-22 spectrometer. The UV spectra were obtained
from 200 to 260 nm by means of the KBr pellet technique.

The 13C NMR spectra, the assignments marked with the same
symbol *, # are interchangeable.

Supporting Information is available at https://macrorhet-
erocycles.isuict.ru/en/mhc200817s.

Synthesis

(1R, 4aR, 4bS, 7S, 10aR)-7-{(E)-2-(Methoxycarbonyl)
styryl}-1,4a,7-trimethyl-1,2,3,4,4a,5,6,7,8,10a-dode-
cahydropenanthrene-1-carboxylic acid (3, C28H34O3).
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 Ag2CO3
(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 CHCl3 (50 mL)
and washed with water (3 × 15 mL). The organic layer was

dried with MgSO4 and the solvent was removed under vacuum.
The resulting crude product was purified by column chromato-
graphy (eluting with petroleum ether-EtOAc, 1:1 to 1:10) to give the compound 3 (0.93 g, 86 %). White solid. M.p. 92.5 °C. [α]20
= +31.2 (c = 0.72 in CHCl3). ESI-HRMS (m/z): [M+H]+
calcd for C46H36O3: 436.2608, found 436.2606. IR (KBrs) νmax cm⁻1: 707
w, 752 m, 968 w, 1076 s, 1128 m, 1153 m, 1189 m, 1205 m, 1253 s,
1276 s, 1344 m, 1457 m, 1479 m, 1639 m, 1702 vs, 1722 vs, 2653
w, 2821 w, 2867 w, 2883 m, 2925 s, 2948 s, 2981 s, 3060 m, 3427
w. UV-Vis (ethanol) λmax (nm) : 299 (3.50), 255 (4.13), 209
(4.30). 1H NMR (CDCl3, 298 K) δ ppm: 0.90 (3H, s, CH3-17), 0.96
(3H, s, CH2-20), 1.11 (1H, m, H-1), 1.26 (3H, s, CH3-19), 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',6,6'), 1.60 (1H, m,
H-3), 1.75 (2H, m, H-9,9'), 1.76 (1H, dm J = 12.1 Hz, H-1), 1.85 (1H,
bd 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, CO2Me), 5.35 (1H, d J = 4.3 Hz, H-7), 6.06 (1H,
d J = 16.1 Hz, H-5, 10), 7.09 (1H, d J = 16.0 Hz, H-6, 16), 7.23 (1H,
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'). 13C NMR (CDCl3, 298 K)
δ ppm: 15.2 (C5), 16.9 (C9), 17.8 (C19), 19.9 (C21), 21.8 (C23),
25.0 (C34), 38.2 (C36), 36.7 (C37), 36.8 (C38), 44.8 (C3),
46.2 (C40), 46.2 (C41), 51.8 (C51), 51.9 (OMe), 121.0 (C12), 123.9
(C14), 126.3 (C16), 127.1 (C17), 128.1 (C18), 130.2 (C20), 131.8 (C24),
135.3 (C29), 135.9 (C30), 144.8 (C32), 167.9 (CO2Me), 185.4 (C95).

(1R, 4aR, 4bS, 7S, 10aR)-7-{((E)2-Carboxystyryl)-1,4a,7-
trimethyl-1,2,3,4,4a,5,6,7,8,10a-dodecahydropenanthrene-
1-carboxylic acid (4, C28H34O3).
A stirred solution of compound 3 (0.70 g, 1.63 mmol) in MeOH
(8 mL) was treated with 4 mL of 1 M KOH (1 M). The reaction mixture was heated to reflux for 6 h (control TLC).
HCl was added dropwise until pH 2, a white precipitate was formed and filtered. The solid was purified by column chromato-
graphy (CHCl3-MeOH, 1:1) to give the compound 4 (0.66 g, 96 %). White solid. M.p. 235.0 °C. [α]20
= +32.8 (c = 0.25 in CHCl3-MeOH, 3:1). ESI-HRMS (m/z): [M+H]+
calcd for C46H36O3: 422.2452: found 422.2450. IR (KBr) νmax cm⁻1: 464
m, 754 m, 796 m, 1078 vs, 1189 s, 1234 s, 1257 s, 1299 s, 1386
The reaction temperature was raised to ambient. The mixture was stirred vigorously for 15 min, and treated with oxalyl chloride (0.70 mL, 8.26 mmol) 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$_2$Cl$_2$ (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$_2$Cl$_2$ (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$_2$Cl$_2$ (10 mL) under a stream of argon treated with Et$_3$N (0.89 mL, 5.90 mmol) and then gradually with propargylamine 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. [a]$_{294}$ = +4.5 (c 0.13 in CHCl$_3$). HREMS (EI) (m/z): calculated for C$_{35}$H$_{44}$N$_2$: 496.3084, found 496.3082 [M]+. IR (film) $v_{max}$ cm$^{-1}$: 628 m, 661 m, 755 s, 968 m, 1024 m, 1052 m, 1120 w, 1157 w, 1201 w, 1257 m, 1272 m, 1348 m, 1363 m, 1384 m, 1444 m, 1458 m, 1475 m, 1518 s, 1567 w, 1598 w, 1625 s, 1708 s, 2485 w, 2848 s, 2865 s, 2923 s, 3085 w, 3305 v, 3500 s. UV-Vis (ethanol) $\lambda_{max}$ (nm) cm$^{-1}$: 205 (4.30), 254 (4.03). 1H NMR (CDCl$_3$, 298 K) $\delta$ 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$_2$-12, H-4'), 1.42 (2H, m, H-3'), 1.54 (4H, m, H-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, 201 (3H, m, H-9',1',1), 2.21 (1H, t, $J$ = 2.5 Hz, C=CH$_2$), 2.25 (1H, t, $J$ = 2.5 Hz, C=CH$_2$), 3.71 (1H, d, $J$ = 17.6, 4.8, 2.6 Hz, CH$_3$), 4.01 (1H, d, $J$ = 17.6, 4.8, 2.6 Hz, CH$_3$), 4.20 (1H, d, $J$ = 2.6 Hz, CH$_3$), 4.22 (1H, d, $J$ = 2.6 Hz, CH$_3$), 5.27 (1H, t, $J$ = 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) $\delta$ ppm: 15.23 (C), 17.18 (C), 17.98 (C), 19.83 (C), 21.77 (C), 24.73 (C), 29.51 (2CH$_3$CH), 35.06 (C), 36.19 (C), 36.79 (C), 37.01 (C), 38.65 (C), 45.63 (C), 46.17 (C), 46.20 (C), 51.85 (C), 71.43, 71.86 (2CH$_2$), 79.26, 79.76 (2CH$_2$), 121.14 (C), 122.71 (d, C), 126.66 (C), 126.82 ($^{15}$N), 127.82 ($^{13}$C), 130.33 ($^{13}$C), 133.83 (C), 135.11 ($^{15}$N), 136.30 (C), 145.87 (C), 168.81 (CON), 178.18 (CON).

General procedure for the synthesis of macroheterocycles 8a–a solution of 6 (0.50 g, 1.01 mmol) in CH$_2$Cl$_2$ (101 mL) was stirred; treated sequentially with diazide (7, 0.10 mmol), a solution of CuSO$_4$·5H$_2$O (0.10 g, 0.40 mmol) in H$_2$O (1.0 mL), and a solution of sodium ascorbate (0.40 g, 2.02 mmol) in H$_2$O (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$_4$·5H$_2$O (0.05 g, 0.20 mmol) in H$_2$O (1.0 mL), a solution of sodium ascorbate (0.20 g, 1.01 mmol) in H$_2$O (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$_2$O (3×50 mL), dried over MgSO$_4$, and evaporated in vacuo. The residue was chromatographed over a column of silica gel (eluents CHCl$_3$–MeOH) to afford 8.

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(2'S, 4'S, 4'R, 8'R, 8'a'R)-2'S, 4'B, 8'S-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-(1', 4'), 14(1, 4)-ditriazolo-1'-2', 8'-phanentrena-2(1', 2)-benzenacycloheptadecaphan-1-en-5, 17-dione (8b) (0.22 g, 34 %). White solid. M.p. 150.0 °C. [α]D 25 = +6.4 (c 0.67 in CHCl3). HRMS (EI) (m/z) calcld for C21H22N4O2: 350.1616, found 350.1618 [M]+. IR (film) νmax cm−1: 1654, 1640, 1595, 1554, 1504, 1459, 1446, 1428, 1427, 1228, 1114, 1101, 1053, 1042, 1021, 977, 801, 759, 731, 538, 501. UV-Vis (ethanol) λmax (lgε) nm: 263 (4.29), 295 (3.95). 1H NMR (CDCl3, 298 K) δ ppm: 0.86 (3H, s, СН3-11'), 1.19–1.40 (12H, m, H-12'), 1.50–1.63 (8H, m, H-3', 5', 10, 10, 12, 12, 1', 1'), 3.49 (1H, d, 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), 4.50–4.60 (3H, m, H, J = 11, 12), 5.10 (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, brs, NH-6), 7.01 (1H, brs, NH-6), 7.13 (1H, t, J = 7.1 Hz, H-2brn), 7.28 (1H, H, H, H-1brn), 7.43 (1H, d, J = 7.4 Hz, H-5brn), 7.60 (1H, H, H-14), 7.62 (1H, H, H-8), 8.04 CN (CDCl3, 298 K) δ ppm: 149.55 (C17'), 170.56 (C12'), 19.32 (C4'), 24.56 (C5'), 25.30 (C6'), 25.57 (C7'), 29.45 (C8'), 29.80 (C9'), 34.98 (C10'), 35.03 (C11'), 35.59 (C12), 36.70 (C13'), 38.64 (C14'), 45.02 (C15'), 45.70 (C16'), 46.11 (C17'), 49.70 (C18'), 49.93 (C19'), 51.60 (C20'), 120.74 (C21'), 121.77 (C22'), 122.71 (C23'), 128.81 (C24'), 128.86 (C25'), 127.12 (C26'), 127.90 (C27'), 130.31 (C28'), 133.86 (C29'), 135.54 (C30'), 136.51 (C31'), 144.21 (C32), 145.20 (C33), 145.17 (C34), 169.27 (CON), 178.82 (C35').

(2'S, 4'S, 4'R, 8'R, 8'a'R)-2'S, 4'B, 8'S-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-(1', 4'), 14(1, 4)-ditriazolo-1'-2', 8'-phanentrena-2(1', 2)-benzenacycloheptadecaphan-1-en-5, 17-dione (8e) (0.22 g, 33 %). White solid. M.p. 109.6 °C. [α]D 25 = +61.07 (c 0.57 in CHCl3). HRMS (EI) (m/z) calcld for C21H22N4O2: 350.1616, found 350.1618 [M]+. IR (film) νmax cm−1: 1654, 1640, 1595, 1554, 1504, 1459, 1446, 1428, 1427, 1228, 1114, 1101, 1053, 1042, 1021, 977, 801, 759, 731, 538, 501. UV-Vis (ethanol) λmax (lgε) nm: 263 (4.29), 295 (3.95). 1H NMR (CDCl3, 298 K) δ ppm: 0.73 (3H, s, СН3-11'), 0.78 (3H, s, СН3-12'), 1.03, 1.23 (8H, m, (1.23, s, СН3-12'), 1.50–1.63 (8H, m, H-12'), 1.50–1.63 (8H, m, H-12'), 1.71 (1H, H, H-8'a), 1.76, 1.78, 1.82 (3H, H, J = 5, 11'), 3.42–3.57 (2H, H, H-13'), 3.73 (1H, H, H-9'), 3.81 (1H, H, H-9'), 4.13 (1H, dd, J = 14.8, 5.2 Hz, H-13), 4.35 (4H, H, H, H-12), 4.49 (1H, d, J = 4.8 Hz, H-13), 4.50–4.73 (2H, H, H-15), 5.00 (1H, d, J = 2.9 Hz, H-10'), 5.96 (1H, H, 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-2brn), 7.22 (1H, H, H-1brn), 7.33 (1H, d, J = 7.8 Hz, H-6brn), 7.38 (1H, d, J = 7.2 Hz, H-5brn), 7.72 (1H, H, H-14), 7.75 (1H, H, H-8'), 178.82 (C35').

Crystallographic data for hydrate of 8d: C21H22N4O2·2H2O, monoclinic, P21, a = 15.492(4), b = 6.3464(7), c = 20.647(3), β, β, β, 111.299(4), V = 1891.6(4), Z = 2, Dcalc = 1.175 g·cm−3, μ(Mo-Ka) 0.077 mm−1, F(000) 720, (0 2 12 – 26.1 °), completeness (10 50) 99.4 %, colorless, (1.00 ± 0.04 mm−1, transmission 0.6419–0.8620, 36413 measured reflections in index range −18 ≤ h ≤ 18, −7 ≤ k ≤ 7, −25 ≤ l ≤ 25, 7163 independent (R = 0.055), 451 parameters 60 restraints, R = 0.0777 (for 4909 observed I > 2σ(I)). wR2 = 0.2364 (all data), GoOF = 1.023, largest diff. peak and hole 0.56 and −0.26 e·Å−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 F2 in anisotropic approximation (beside the atoms H) using the SHELXL20147 programs set[34] The H atoms positions were

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Dimeric compound 9 (0.17 g, 27 %). White solid. M.p. 153.8 °C. [α]D = +20.0 (c 0.1 in CHCl₃-MeOH, t = 1). ESI-HRMS (m/z): [M+Na]+ calcd. for C₇₆H₁₀₀N₁₆O₁₂ 351.80, found 351.810. [M+Na]+ calcd. for C₇₆H₁₀₀N₁₆O₁₁ 333.015, found 334.017. 1H NMR (CDCl₃, 75 m, 1051 m, 1135 w, 1157 m, 1216 m, 1241 m, 1267 m, 1301 m, 1338 m, 1367 m, 1444 m, 1463 m, 1519 m, 1598 s, 1641 m, 2865 m, 2923 s, 3380 s UV-Vis (ethanol) λmax (lgɛ) nm: 212 (3.95), 254 (3.12).

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-carbomethoxy 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 macrorayces. The reaction of compound 6 with 1,2-bis(2-azidoethoxy)ethane 7a (1 equiv.) in CH₂Cl₂-water medium in the presence of CuSO₄ 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 macroraycic compound 8a was isolated in the yield 70 % (Scheme 2). We found that the yield and composition

Scheme 1. Synthesis of N,N-bis(prop-2-yn-1-yl)-16-(2-carboxyphenyl)isopimarate 6.
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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)macrocyclic compound 8d (yield 34 %) and tetra(triazole)macrocyclic compound 9 (yield 27 %).

The composition and structure of the synthesized compounds were confirmed by IR, UV, 1H and 13C spectroscopy, mass-spectrometry data and mass-date. The 1H and 13C 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 1H NMR spectra of compounds 8a-d exhibited singlet signals for the H-5' proton ($\delta_H = 7.55–7.77$ 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-

![Figure 1](image)

**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)-styrène bridge from the diterpenoid moiety, triazole rings and ethylethoxyethyl, 1,6-, 1,5- or ethoxyethoxyethyl 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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