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SYNTHESIS OF 1,2,3-TRIAZOLE DERIVATIVES FROM 2,3-DIENOATES OF METHYL MALEOPIMARATE

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Hybrid compounds based on N*-maleopimarimides containing a triazole-ring pharmacophore were prepared via 1,3-dipolar cycloaddition of methyl-2-azidoacetate to allenoates.*

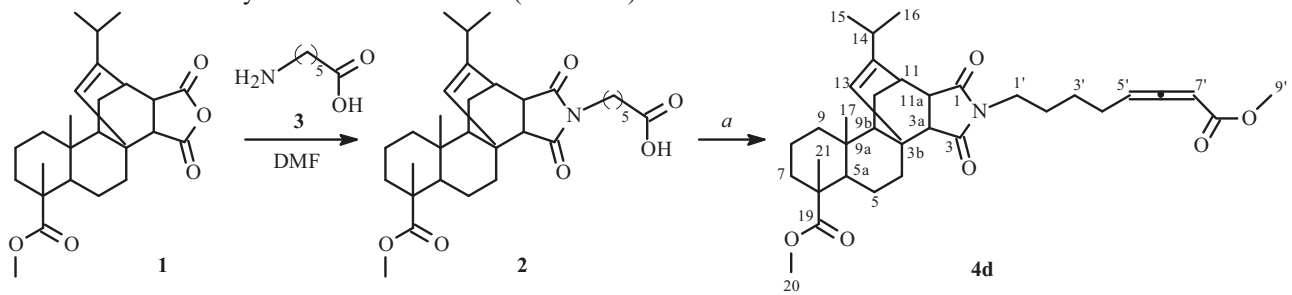
Keywords: 1,3-dipolar cycloaddition, methyl maleopimarate, 1,2,3-traizoles, allenoates.

Derivatives of 1,2,3-triazoles are known for their antibacterial, anti-allergic, anti-inflammatory, antimicrobial, antitumor, and anticonvulsant properties and are highly attractive for designing protective agents, plant growth regulators, and drugs [1].

Triazoles exhibit biological activity because they are isosteres of key biomolecular functional groups such as a peptide bond [–C(=O)NH–] and a carboxylic acid [–C(=O)OH] [2]. The 1,2,3-triazole ring plays an important role in increasing biological activity due to a moderate dipole moment, the ability to form H-bonds, the resistance to redox reactions, and the robustness and stability of the heterocyclic ring to acid and alkaline hydrolysis [3].

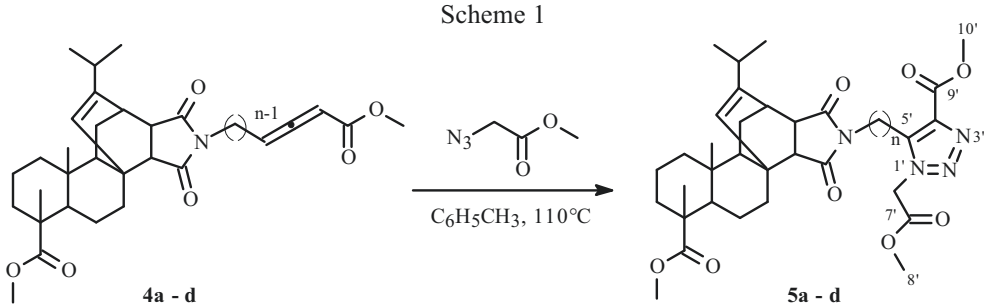
Herein, the synthesis of new triazole derivatives containing methyl maleopimarate (**1**, MMP), which is known to have anti-inflammatory and anti-ulcer activity [4, 5], is reported.

Allenoate **4d**, which was synthesized from adduct **2** that was in turn obtained via condensation of **1** with *ω*-aminocaproic acid (**3**) (Scheme 1), and allenoates **4a**–**c** [6], which were prepared previously by us, were refluxed in toluene with methyl-2-azidoacetate for 10 h to synthesize triazoles **5a**–**d** (Scheme 2).



a. 1. $SOCl_2$, C_6H_6; 2. Et_3N, $Ph_3P{=}CHCO_2Me$

Scheme 1



5a: n = 1 (58%); **5b:** n = 2 (51%)
5c: n = 3 (47%); **5d:** n = 5 (40%)

Scheme 2

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The structure of **4d** was elucidated by spectral methods. The PMR contained characteristic resonances for the two olefinic protons of the allene group at δ 5.56 and 5.58 ppm. The ^{13}C NMR spectrum had characteristic resonances for the allene C atoms at δ 88.12 and 94.82 ppm and a resonance for the central quaternary C atom at weak field of δ 212.30 ppm.

The yields of the triazoles were <20% using the standard method for preparing triazoles [7] using an equimolar amount of the azide. However, the yield of the desired products could be more than doubled if a two-fold excess of methyl-2-azidoacetate was used (Scheme 2). In all instances, allenoates **4a**–**d** were incompletely converted.

The structures of the synthesized compounds were elucidated by spectral methods. IR spectra of **5a**–**d** exhibited absorption bands characteristic of triazoles at ~1575 cm^{-1} [8]. The NMR spectrum in HMBC mode of **5a** gave cross peaks for the C-1″ methylene protons with imide C atoms C-1 and C-3 and quaternary C atoms C-4′ and C-5′ of the triazole-ring double bond. The methylene C-6′ protons (N–CH_2) on the triazole ring resonated as two doublets at 5.25 and 5.39 ppm and coupled with C-5′ and C-7′ of the ester. The lack of correlation of the C-6′ methylene with C-4′ agreed with the structure of **5a**. Analogous cross peaks in HMBC mode were observed for **5b**–**d**.

Thus, we prepared for the first time 1,2,3-triazole derivatives based on **1**, which are of interest as biologically active compounds.

EXPERIMENTAL

IR spectra were recorded from thin layers or mineral-oil mulls on an IR-Prestige-21 instrument (Fourier Transform Spectrophotometer, Shimadzu). NMR spectra were taken with TMS internal standard on a Bruker-AM 500 spectrometer at operating frequency 500.13 MHz (^1H) and 125.76 MHz (^{13}C). Homo- and heteronuclear two-dimensional COSY, NOESY, HSQC, and HMBC correlations were used for correct assignment of NMR resonances of the reaction products. The course of reactions was monitored using TLC on Sorbfil PTSKh-AF-A plates with detection by UV light, I_2 vapor, and spraying plates with ninhydrin solution followed by heating at 100–120°C. Mass spectra were measured on an LCMS-2010EV LC-MS (Shimadzu) with chemical ionization at atmospheric pressure (APCI). Elemental analysis used a EURO EA-3000 CHN analyzer. Melting points were determined on a Boetius apparatus. Reaction products were isolated by column chromatography over Chemapol silica gel of particle size 40/100 and 100/160 μm.

Elemental analyses of all compounds agreed with those calculated.

Methyl maleopimarate (**1**) was synthesized by the published method [9]. Its physicochemical characteristics agreed with those in the literature. Acid **2** and allenes **4a**–**d** were prepared by the described method [6]. Methyl-2-azidoacetate was synthesized as before [10].

1′-[12-Isopropyl-6-(methoxycarbonyl)-6,9a-dimethyl-1,3-dioxo-3,3a,4,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-3b,11-ethenonaphtho[2,1-*e*]isoindol-2(1*H*)-yl]hexanoic Acid (2). Yield 96%, white powder, mp 121°C. IR spectrum (m.o., ν, cm^{-1}): 1692, 1717, 1768, 1777, 3262. ^1H NMR spectrum (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.55 (3H, s, CH_3-17), 0.92 (3H, d, J = 6.8, CH_3-15), 0.94 (3H, d, J = 6.8, CH_3-16), 0.99 (1H, m, Hax-9), 1.12 (3H, s, CH_3-18), 1.17 (1H, m, Heq-5), 1.21 (2H, m, H-3′), 1.24 (1H, m, Heq-10), 1.27 (2H, m, H-2′), 1.40 (1H, m, H-9b), 1.42 (2H, m, H-4′), 1.44 (1H, m, Heq-9), 1.52–1.60 (2H-gem, m, H-8), 1.53 (1H, m, Hax-5), 1.55 (1H, m, Heq-7), 1.58 (1H, m, Hax-10), 1.63 (1H, m, Hax-4), 1.66 (1H, m, Hax-7), 1.71 (1H, m, H-5a), 2.14 (1H, m, J = 6.8, H-14), 2.28 (2H, t, J = 7.3, H-5′), 2.40 (1H, d, J = 8.0, H-3a), 2.45 (1H, m, Heq-4), 2.75 (1H, dd, J = 8.0, 2.9, H-11a), 3.02 (1H, m, H-11), 3.29 (1H, t, J = 7.3, H-1′), 3.64 (3H, s, CH_3-20), 5.28 (1H, s, H-13). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 15.59 (C-17), 16.68 (C-18), 16.97 (C-8), 19.79 (C-15), 20.60 (C-16), 21.70 (C-5), 24.03 (C-4′), 26.19 (C-3′), 27.44 (C-10), 32.55 (C-14), 33.69 (C-2′), 35.21 (C-4), 35.58 (C-11), 36.64 (C-7), 37.61 (C-9a), 38.00 (C-5′), 38.05 (C-9), 40.67 (C-3b), 44.86 (C-11a), 47.08 (C-6), 49.47 (C-5a), 51.92 (C-20), 52.20 (C-3a), 53.27 (C-1′), 54.17 (C-9b), 124.23 (C-13), 146.88 (C-12), 177.38 (C-3), 178.63 (C-1), 179.12 (C-6′), 179.20 (C-19). Mass spectrum (APCI), *m/z* (I_{rel}, %): 528 [MH^+, 100], 526 [$(M - H)^-$, 14], $C_{31}H_{45}NO_6$. Calcd M 527.

Methyl-12-isopropyl-2-(8′-methoxy-8′-oxoocta-5′,6′-dien-1′-yl)-6,9a-dimethyl-1,3-dioxo-1,2,3,3a,4,5,5a,6,7,8,9,9a,9b,10,11,11a-hexadecahydro-3b,11-ethenonaphtho[2,1-*e*]isoindole-6-carboxylate (4d). Yield 70%, transparent oil. IR spectrum (m.o., ν, cm^{-1}): 1695, 1767, 1960. ^1H NMR spectrum (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.57 (3H, s, CH_3-17), 0.89 (3H, d, J = 6.8, CH_3-15), 0.93 (3H, d, J = 6.8, CH_3-16), 0.96 (1H, m, Hax-9), 1.12 (3H, s, CH_3-18), 1.18 (1H, m, Heq-5), 1.22 (1H, m, Heq-10), 1.35 (1H, m, H-9b), 1.42 (1H, m, Heq-9), 1.47–1.53 (2H-gem, m, H-8), 1.46 (1H, m, Hax-5), 1.50 (1H, m, Heq-7), 1.53 (1H, m, Hax-10), 1.60 (1H, m, Hax-4), 1.63 (1H, m, Hax-7), 1.67 (1H, m, H-5a), 1.72 (2H, m, H-3′), 1.75 (2H, m, H-2′), 2.10 (1H, m, J = 6.8, H-14), 2.15 (2H, m, H-4′), 2.38 (1H, d, J = 8.0, H-3a), 2.47 (1H, m,

Heq-4), 2.75 (1H, dd, J = 8.0, 2.9, H-11a), 3.03 (1H, s, H-11), 3.30 (2H, t, J = 7.1, H-1′), 3.65 (3H, s, CH_3-20), 3.70 (3H, s, H-9′), 5.37 (1H, s, H-13), 5.56 (1H, s, H-7′), 5.58 (1H, t, J = 7.6, H-5′). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 15.63 (C-17), 16.73 (C-18), 17.03 (C-8), 19.83 (C-15), 20.63 (C-16), 21.76 (C-5), 25.82 (C-3′), 26.87 (C-2′), 27.11 (C-4′), 27.53 (C-10), 32.58 (C-14), 35.28 (C-4), 35.63 (C-11), 36.71 (C-7), 37.67 (C-9a), 37.86 (C-1′), 38.14 (C-9), 40.71 (C-3b), 44.92 (C-11a), 47.13 (C-6), 49.53 (C-5a), 51.90 (C-20), 51.96 (C-9′), 52.28 (C-3a), 54.24 (C-9b), 88.12 (C-5′), 94.82 (C-7′), 124.32 (C-13), 146.94 (C-12), 166.47 (C-8′), 177.31 (C-3), 178.49 (C-1), 179.14 (C-19), 212.30 (C-6′). Mass spectrum (APCI), *m/z* (I_{rel}, %): 566 [MH^+, 100], $C_{34}H_{47}NO_6$. Calcd M 565.

Method for Preparing Triazoles 5a–d. Allene (0.01 mol) and azide (0.02 mol) in toluene (15 mL) were refluxed for 10 h. The reaction mixture was evaporated. The residue was chromatographed over silica gel (petroleum ether–EtOAc, 1:1).

Methyl (3a*R*,3b*S*,5a*R*,6*R*,9a*R*,9b*R*,11*R*,11a*R*)-12-Isopropyl-2-{[4′-(methoxycarbonyl)-1′-(2′-methoxy-2′-oxoethyl)-1′*H*-1′,2′,3′-triazol-5′-yl]methyl}-6,9a-dimethyl-1,3-dioxohexadecahydro-3b,11-ethenonaphtho[2,1-*e*]isoindole-6-carboxylate (5a). Yield 58%, yellow oil. IR spectrum (ν, cm^{-1}): 1223, 1388, 1438, 1591, 1703, 2253. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.52 (3H, s, H-17), 0.73 (3H, d, J = 6.8, CH_3-15), 0.80 (3H, d, J = 6.8, CH_3-16), 0.89 (1H, m, Hax-9), 1.10 (3H, s, CH_3-18), 1.15 (1H, m, Heq-5), 1.21 (1H, m, Heq-10), 1.36 (1H, m, H-9b), 1.41 (1H, m, Heq-9), 1.43–1.51 (2H-gem, m, H-8), 1.48 (1H, m, Hax-5), 1.51 (1H, m, Heq-7), 1.62 (1H, m, Hax-10), 1.65 (1H, m, Hax-4), 1.69 (1H, m, Hax-7), 1.72 (1H, m, H-5a), 2.04 (1H, m, J = 6.8, H-14), 2.41 (1H, d, J = 8.1, H-3a), 2.44 (1H, m, Heq-4), 2.74 (1H, dd, J = 8.1, 2.1, H-11a), 2.97 (1H, s, H-11), 3.62 (3H, s, CH_3-20), 3.76 (3H, s, CH_3-10′), 3.92 (3H, s, CH_3-8′), 4.80, 4.89 (2H, d, J = 15.2, H-1″), 5.25, 5.39 (2H, d, J = 18.2, H-6′), 5.41 (1H, s, H-13). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 15.50 (C-17), 16.66 (C-18), 16.93 (C-8), 19.87 (C-15), 20.43 (C-16), 21.63 (C-5), 27.44 (C-10), 29.77 (C-1″), 32.45 (C-14), 35.18 (C-4), 35.28 (C-11), 36.61 (C-7), 37.59 (C-9a), 38.01 (C-9), 40.64 (C-3b), 44.90 (C-11a), 47.04 (C-6), 49.39 (C-5a), 49.72 (C-6′), 51.90 (C-20), 52.22 (C-3a), 52.40 (C-8′), 53.16 (C-10′), 53.97 (C-9b), 124.39 (C-13), 135.70 (C-5′), 138.10 (C-4′), 147.19 (C-12), 160.99 (C-9′), 166.55 (C-7′), 176.71 (C-3), 177.71 (C-1), 179.10 (C-19). Mass spectrum (APCI), *m/z* (I_{rel}, %): 625 [MH^+, 100], 623 [$(M - H)^-$, 100], $C_{33}H_{44}N_4O_8$. Calcd M 624.

Methyl (3a*R*,3b*S*,5a*R*,6*R*,9a*R*,9b*R*,11*R*,11a*R*)-12-Isopropyl-2-{2″-[4′-(methoxycarbonyl)-1′-(2′-methoxy-2′-oxoethyl)-1′*H*-1′,2′,3′-triazol-5′-yl]ethyl}-6,9a-dimethyl-1,3-dioxohexadecahydro-3b,11-ethenonaphtho[2,1-*e*]isoindole-6-carboxylate (5b). Yield 51%, yellow oil. IR spectrum (m.o., ν, cm^{-1}): 1377, 1405, 1442, 1690, 1724, 1754. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.57 (3H, s, CH_3-17), 0.88 (3H, d, J = 6.8, CH_3-15), 0.92 (3H, d, J = 6.8, CH_3-16), 0.95 (1H, m, Hax-9), 1.12 (3H, s, CH_3-18), 1.18 (1H, m, Heq-5), 1.22 (1H, m, Heq-10), 1.39 (1H, m, H-9b), 1.42 (1H, m, Heq-9), 1.41–1.49 (2H-gem, m, H-8), 1.46 (1H, m, Hax-5), 1.52 (1H, m, Heq-7), 1.64 (1H, m, Hax-10), 1.68 (1H, m, Hax-4), 1.71 (1H, m, Hax-7), 1.74 (1H, m, H-5a), 2.14 (1H, m, J = 6.8, H-14), 2.41 (1H, d, J = 8.0, H-3a), 2.48 (1H, m, Heq-4), 2.77 (1H, dd, J = 8.0, 2.8, H-11a), 3.00 (2H, dd, J = 8.0, H-1″), 3.02 (1H, s, H-11), 3.57 (2H, m, H-2″), 3.65 (3H, s, CH_3-20), 3.80 (3H, s, CH_3-8′), 3.95 (3H, s, CH_3-10′), 5.22 (2H, s, H-6′), 5.37 (1H, s, H-13). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 15.56 (C-17), 16.69 (C-18), 16.97 (C-8), 20.03 (C-15), 20.67 (C-16), 21.52 (C-2″), 21.68 (C-5), 27.51 (C-10), 32.62 (C-14), 35.20 (C-1″), 35.35 (C-4), 35.59 (C-11), 36.64 (C-7), 37.63 (C-9a), 38.06 (C-9), 40.66 (C-3b), 44.94 (C-11a), 47.07 (C-6), 48.77 (C-6′), 49.43 (C-5a), 51.93 (C-20), 52.18 (C-3a), 52.34 (C-10′), 53.23 (C-8′), 54.00 (C-9b), 124.40 (C-13), 137.12 (C-4′), 138.95 (C-5′), 147.04 (C-12), 161.33 (C-9′), 166.33 (C-7′), 176.92 (C-3), 178.11 (C-1), 179.12 (C-19). Mass spectrum (APCI), *m/z* (I_{rel}, %): 639 [MH^+, 100], 637 [$(M - H)^-$, 100], $C_{34}H_{46}N_4O_8$. Calcd M 638.

Methyl (3a*R*,3b*S*,5a*R*,6*R*,9a*R*,9b*R*,11*R*,11a*R*)-12-Isopropyl-2-{3″-[4′-(methoxycarbonyl)-1′-(2′-methoxy-2′-oxoethyl)-1′*H*-1′,2′,3′-triazol-5′-yl]propyl}-6,9a-dimethyl-1,3-dioxohexadecahydro-3b,11-ethenonaphtho[2,1-*e*]isoindole-6-carboxylate (5c). Yield 47%, yellow oil. IR spectrum (ν, cm^{-1}): 1374, 1402, 1436, 1695, 1722, 1758. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.54 (3H, s, CH_3-17), 0.83 (3H, d, J = 6.6, CH_3-15), 0.90 (3H, d, J = 6.6, CH_3-16), 0.93 (1H, m, Hax-9), 1.10 (3H, s, CH_3-18), 1.16 (1H, m, Heq-5), 1.21 (1H, m, Heq-10), 1.37 (1H, m, H-9b), 1.40 (1H, m, Heq-9), 1.40–1.49 (2H-gem, m, H-8), 1.45 (1H, m, Hax-5), 1.50 (1H, m, Heq-7), 1.63 (1H, m, Hax-10), 1.68 (1H, m, Hax-4), 1.72 (1H, m, Hax-7), 1.75 (1H, m, H-5a), 1.77 (2H, m, H-2″), 2.11 (1H, m, J = 6.6, H-14), 2.43 (1H, d, J = 8.1, H-3a), 2.47 (1H, m, Heq-4), 2.76 (1H, dd, J = 8.1, 2.7, H-11a), 2.82 (2H, t, J = 7.8, H-3″), 2.99 (1H, s, H-11), 3.34 (2H, m, H-1″), 3.63 (3H, s, CH_3-20), 3.76 (3H, s, CH_3-10′), 3.90 (3H, s, CH_3-8′), 5.12 (2H, s, H-6″), 5.33 (1H, s, H-13). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 15.56 (C-17), 16.68 (C-18), 16.96 (C-8), 19.97 (C-15), 20.66 (C-16), 20.78 (C-3″), 21.69 (C-5), 25.93 (C-2″), 27.48 (C-10), 32.60 (C-14), 35.20 (C-4), 35.51 (C-11), 36.63 (C-7), 37.48 (C-1″), 37.60 (C-9a), 38.05 (C-9), 40.62 (C-3b), 44.91 (C-11a), 47.06 (C-6), 48.84 (C-6′), 49.42 (C-5a), 51.92 (C-20), 52.01 (C-8′), 52.26 (C-3a), 53.20 (C-10′), 54.03 (C-9b), 124.33 (C-13), 136.28 (C-4′), 142.23 (C-5′), 146.99 (C-12), 161.44 (C-9′), 166.13 (C-7′), 177.40 (C-3), 178.48 (C-1), 179.13 (C-19). Mass spectrum (APCI), *m/z* (I_{rel}, %): 653 [MH^+, 100], 651 [$(M - H)^-$, 100], $C_{35}H_{48}N_4O_8$. Calcd M 652.

Methyl (3a*R*,3b*S*,5a*R*,6*R*,9a*R*,9b*R*,11*R*,11a*R*)-12-Isopropyl-2-{5″-[4′-(methoxycarbonyl)-1′-(2′-methoxy-2′-oxoethyl)-1′*H*-1′,2′,3′-triazol-5′-yl]pentyl}-6,9a-dimethyl-1,3-dioxohexadecahydro-3b,11-ethenonaphtho[2,1-*e*]isoindole-6-carboxylate (5d). Yield 40%, yellow oil. IR spectrum (ν, cm^{-1}): 1244, 1373, 1401, 1437, 1693, 1721, 1755. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.55 (3H, s, CH_3-17), 0.87 (3H, d, J = 6.6, CH_3-15), 0.91 (3H, d, J = 6.6, CH_3-16), 0.94 (1H, m, Hax-9), 1.11 (3H, s, CH_3-18), 1.15 (1H, m, Heq-5), 1.18 (2H, m, H-2″), 1.23 (1H, m, Heq-10), 1.37 (1H, m, H-9b), 1.42 (1H, m, Heq-9), 1.47–1.55 (2H-gem, m, H-8), 1.48 (1H, m, Hax-5), 1.51 (1H, m, Heq-7), 1.54 (2H, m, H-3″), 1.57 (1H, m, Hax-10), 1.60 (1H, m, Hax-4), 1.63 (1H, m, Hax-7), 1.66 (2H, m, H-4″), 1.73 (1H, m, H-5a), 2.11 (1H, m, J = 6.8, H-14), 2.38 (1H, d, J = 8.1, H-3a), 2.45 (1H, m, Heq-4), 2.73 (1H, dd, J = 8.1, 2.9, H-11a), 2.88 (2H, t, J = 8, H-5″), 3.00 (1H, s, H-11), 3.28 (2H, t, J = 7.1, H-1″), 3.63 (3H, s, CH_3-20), 3.77 (3H, s, CH_3-10′), 3.92 (3H, s, CH_3-8′), 5.15 (2H, s, H-6′), 5.30 (1H, s, H-13). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 15.63 (C-17), 16.72 (C-18), 17.00 (C-8), 19.84 (C-15), 20.63 (C-16), 21.09 (C-2″), 21.76 (C-5), 22.93 (C-5″), 26.14 (C-3″), 27.28 (C-4″), 27.51 (C-10), 32.59 (C-14), 35.27 (C-4), 35.62 (C-11), 36.70 (C-7), 37.48 (C-1″), 37.66 (C-9a), 38.09 (C-9), 40.69 (C-3b), 44.90 (C-11a), 47.12 (C-6), 48.74 (C-6′), 49.48 (C-5a), 51.96 (C-20), 52.00 (C-10′), 52.26 (C-3a), 53.15 (C-8′), 54.18 (C-9b), 124.26 (C-13), 136.12 (C-4′), 143.23 (C-5′), 146.94 (C-12), 161.73 (C-8′), 166.31 (C-7′), 177.63 (C-3), 178.64 (C-1), 179.23 (C-19). Mass spectrum (APCI), *m/z* (I_{rel}, %): 681 [MH^+, 100], 679 [$(M - H)^-$, 100], $C_{37}H_{52}N_4O_8$. Calcd M 680.

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