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SYNTHESIS OF METHYL MALEOPIMARATES WITH ADAMANTYL SUBSTITUENTS

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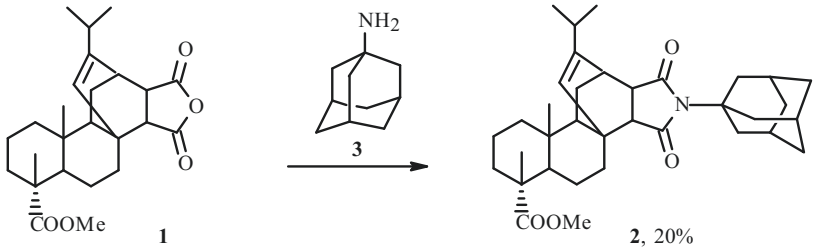
Conjugates with adamantyl substituents were synthesized as potentially biologically active compounds via the reaction of aminoadamantane with the anhydride of methyl maleopimarate (MMP) and with the N-*maleopimarimide-substituted acid chlorides of* α*-alanine,* β*-alanine, valine, and* γ*-aminobutyric acid.*

Keywords: methyl maleopimarate, aminoadamantane, amino acids, peptide bond.

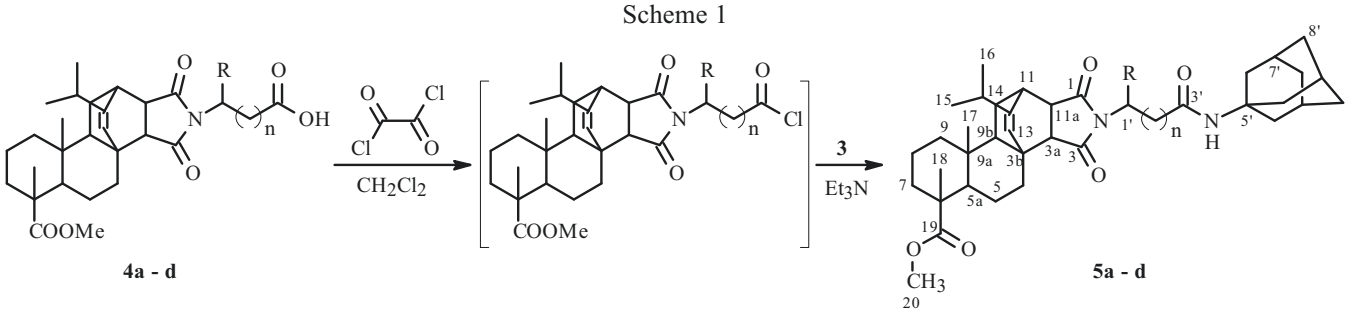
Methyl maleopimarate is produced via a Diels–Alder reaction from levopimaric acid and maleic anhydride and is considered a promising starting material for synthesizing compounds with anti-inflammatory, antiulcer, fungicidal, and other activities [1–4].

Practical applications of adamantane and its derivatives include antiviral drugs (rimantadine and amantadine). However, rimantadine and amantadine have suffered significant losses of antiviral potency against current flu A(H_3N_2) and A(H_1N_1) viruses because of their widespread use [5, 6]. This problem could be solved by placing additional functional groups on the adamantane carbocycle. This could increase the antiviral potency and diminish the resistance of the flu A strains. Amino acids introduced into rimantadine via peptide syntheses [7, 8] and also a derivative of the natural compound methyl maleopimarate (MMP) could act as such functional groups. Herein, syntheses of compounds containing an adamantyl substituent, a natural diterpene fragment, and a peptide bond formed in the key step are reported.

Condensation of MMP (**1**) with a two-fold excess of aminoadamantane (**3**) in DMF for 1.5 h led to **2** in 20% yield (Scheme 1). The conversion of MMP did not improve if a large excess of aminoadamantane was used and the reaction time was increased. MMP was recovered unchanged from the reaction mixture.



Scheme 1



4a, 5a: R = H, n = 1; **4b, 5b:** R = H, n = 2; **4c, 5c:** R = CH_3, n = 0; **4d, 5d:** R = $CH(CH_3)_2$, n = 0

Scheme 2

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Compounds **5a**–**d** were synthesized via condensation of MMP with β-alanine, γ-aminobutyric acid, α-alanine, and valine (**4a**–**d**) [8, 9] through the corresponding acid chlorides followed by reaction with aminoadamantane in the presence of Et_3N in CH_2Cl_2 (Scheme 2).

Compound **5a** exhibited a W-effect in the HMBC spectrum as a cross peak between the C-2′ methylene protons and quaternary adamantane C-5′ and a correlation of the NH proton resonating at δ 5.48 ppm with the ketone that appeared at δ 168.46 ppm.

Thus, the proposed convenient synthetic method for conjugates containing diterpene and pharmacophoric adamantyl substituents was based on the reaction of an amine with various acid chlorides to form a peptide bond in the key step.

EXPERIMENTAL

IR spectra were recorded from thin layers or in mineral oil on an IR-Prestige-21 FTIR spectrophotometer (Shimadzu). NMR spectra were obtained with TMS internal standard on a Bruker -AM 500 spectrometer at operating frequency 500.13 MHz (^1H) and 125.76 MHz (^{13}C). Resonances in NMR spectra of reaction products were assigned using homo- and heteronuclear 2D correlation COSY, NOESY, HSQC, and HMBC spectra. 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. Elemental analysis was performed using a EuroEA-3000 CHN analyzer. Melting points were determined on a Boetius apparatus. Reaction products were separated by column chromatography over Chemapol silica gel (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. Carboxylic acids **4a**–**d** were prepared by the literature method [10]. Et_3N was distilled from KOH. Aminoadamantane (**3**, 98%, abcr GmbH) was purchased.

Methyl 2-(12-Adamantyl)-12-isopropyl-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 (2). A mixture of methyl maleopimarate (**1**, 10 mmol) and aminoadamantane (**3**, 20 mmol) in DMF (50 mL) was refluxed for 1.5 h, cooled to room temperature, and treated with distilled H_2O. The resulting precipitate was filtered off, dissolved in CH_2Cl_2, and dried over $MgSO_4$. The product was chromatographed using $CHCl_3$–Me_2CO (9:1). Yield 20%, white powder, mp 121–123°C. IR spectrum (m.o., ν, cm^{-1}): 2961, 2882, 2854, 1716, 1683, 1456, 1367, 1330, 1124. ^1H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.60 (3H, s, CH_3-17), 0.93 (1H, m, Hax-9), 0.98 (3H, d, J = 6.8, CH_3-15), 1.01 (3H, d, J = 6.8, CH_3-16), 1.15 (3H, s, CH_3-18), 1.22 (1H, m, Heq-5), 1.30 (1H, m, Heq-10), 1.31 (1H, m, Heq-9), 1.38 (1H, m, H-9b), 1.40–1.50 (2H, m, H-8), 1.51 (1H, m, Hax-5), 1.53 (1H, m, Heq-7), 1.63 (6H, s, H-4′), 1.68 (1H, m, Hax-7), 1.70 (1H, m, Hax-10), 1.71 (1H, m, Hax-4), 1.75 (1H, m, H-5a), 1.88 (6H, s, H-2′), 1.99 (3H, s, CH_3-3′), 2.26 (1H, m, J = 6.8, H-14), 2.52 (1H, m, Heq-4), 2.73 (1H, d, J = 8.6, H-3a), 2.77 (1H, dd, J = 8.6, 2.9, H-11a), 3.10 (1H, s, H-11), 3.66 (3H, s, CH_3-20), 5.43 (1H, s, H-13). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 15.81 (C-17), 16.81 (C-18), 16.99 (C-8), 19.77 (C-15), 20.57 (C-16), 21.84 (C-5), 27.21 (C-10), 29.40 (C-3′), 32.59 (C-14), 35.61 (C-4), 35.67 (C-11), 36.41 (C-4′), 36.70 (C-7), 37.68 (C-9a), 38.00 (C-9), 40.45 (C-3b), 41.43 (C-2′), 45.66 (C-11a), 47.23 (C-6), 49.52 (C-5a), 51.56 (C-1′), 51.97 (C-20), 53.32 (C-3a), 55.22 (C-9b), 123.15 (C-13), 148.11 (C-12), 177.16 (C-3), 179.11 (C-1), 179.30 (C-19).

Method for Preparing 5a–d. A suspension of **4a**–**d** (10 mmol) in CH_2Cl_2 (100 mL) was stirred, treated dropwise with oxalyl chloride (50 mmol), and left over overnight. The solvent and excess of oxalyl chloride were distilled off. The resulting acid chlorides were used without further purification. A solution of **3** (10 mmol) in CH_2Cl_2 (40 mL) cooled to –5°C was stirred, treated dropwise with a small excess (12 mmol) of Et_3N and slowly dropwise with a cooled solution of the acid chloride, stirred at –5°C for 3 h, and evaporated. The residue was chromatographed over silica gel ($CHCl_3$–Me_2CO, 18:1 for **5a**–**5c** and petroleum ether–EtOAc, 6:1 for **5d**).

Methyl 2-[3′-(5′-Adamantylamino)-3′-oxopropyl]-12-isopropyl-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 (5a). Yield 75%, white powder, mp 224–226°C. IR spectrum (m.o., ν, cm^{-1}): 3360, 2920, 2881, 1726, 1694, 1527, 1462, 1377, 1239, 1164. ^1H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.59 (3H, s, CH_3-17), 0.92 (3H, d, J = 6.8, CH_3-15), 0.95 (3H, d, J = 6.8, CH_3-16), 0.98 (1H, m, Hax-9), 1.15 (3H, s, CH_3-18), 1.20 (1H, m, Heq-5), 1.25 (1H, m, Heq-10), 1.38–1.58 (2H, m, H_2-8), 1.41 (1H, m, H-9b), 1.44 (1H, m, Heq-9), 1.48 (1H, m, Hax-5), 1.55 (1H, m, Heq-7), 1.66 (6H, s, H-8′), 1.70 (1H, m, Hax-7), 1.73 (1H, m, Hax-10), 1.76 (1H, m, Hax-4), 1.78 (1H, m, H-5a), 1.96 (6H, s, H-6′), 2.06 (3H, s, CH_3-7′), 2.17 (1H, m, J = 6.8, H-14), 2.27

(2H, t, J = 7.6, H-2′), 2.44 (1H, d, J = 8.0, H-3a), 2.51 (1H, m, Heq-4), 2.80 (1H, dd, J = 8.0, 2.8, H-11a), 3.05 (1H, s, H-11), 3.59 (2H, t, J = 7.7, H-1′), 3.68 (3H, s, CH_3-20), 5.39 (1H, s, H-13), 5.48 (1H, s, NH-4′). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 15.68 (C-17), 16.67 (C-18), 16.97 (C-8), 19.89 (C-15), 20.37 (C-16), 21.68 (C-5), 23.26 (C-2′), 27.32 (C-10), 32.23 (C-14), 35.03 (C-4), 35.35 (C-11), 30.39 (C-3′), 36.64 (C-7), 51.73 (C-1′), 37.66 (C-9a), 38.03 (C-9), 40.79 (C-3b), 45.14 (C-11a), 47.11 (C-6), 50.98 (C-5′), 49.44 (C-5a), 52.06 (C-3a), 51.99 (C-20), 54.40 (C-9b), 123.91 (C-13), 147.13 (C-12), 176.52 (C-3), 177.59 (C-1), 179.31 (C-19), 172.63 (C-4′), 173.05 (C-6′).

Methyl 2-[4′-(6′-Adamantylamino)-4′-oxopropyl]-12-isopropyl-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 (5b). Yield 71%, white powder, mp 235–237°C. IR spectrum (m.o., ν, cm^{-1}): 3340, 2906, 2870, 1721, 1690, 1671, 1518, 1461, 1376, 1237, 1150. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.53 (3H, s, CH_3-17), 0.87 (3H, d, J = 6.8, CH_3-15), 0.90 (3H, d, J = 6.8, CH_3-16), 0.93 (1H, m, Hax-9), 1.10 (3H, s, CH_3-18), 1.14 (1H, m, Heq-5), 1.18 (1H, m, Heq-10), 1.38 (1H, m, H-9b), 1.40 (1H, m, Heq-9), 1.41–1.50 (2H, m, H-8), 1.43 (1H, m, Hax-5), 1.51 (1H, m, Heq-7), 1.63 (6H, s, H-9′), 1.66 (1H, m, Hax-7), 1.68 (1H, m, Hax-10), 1.70 (1H, m, Hax-4), 1.72 (1H, m, H-5a), 1.73 (2H, m, H-2′), 1.90 (2H, t, J = 7.2, H_2-3′), 1.94 (6H, s, H-7′), 2.00 (3H, s, CH_3-8′), 2.12 (1H, m, J = 6.8, H-14), 2.38 (1H, d, J = 8.0, H-3a), 2.43 (1H, m, Heq-4), 2.74 (1H, dd, J = 8.0, 2.8, H-11a), 3.01 (1H, s, H-11), 3.33 (2H, t, J = 5.6, H-1′), 3.62 (3H, s, CH_3-20), 5.35 (1H, s, H-13), 5.77 (1H, s, NH-4′). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 15.60 (C-17), 16.68 (C-18), 16.96 (C-8), 19.78 (C-15), 20.62 (C-16), 21.70 (C-5), 24.56 (C-2′), 27.43 (C-10), 29.34 (C-8′), 32.59 (C-14), 34.72 (C-3′), 35.22 (C-4), 35.64 (C-11), 36.30 (C-9′), 36.62 (C-7), 37.34 (C-1′), 37.62 (C-9a), 38.03 (C-9), 40.70 (C-3b), 41.47 (C-7′), 44.88 (C-11a), 47.05 (C-6), 49.43 (C-5a), 50.98 (C-5′), 51.73 (C-6′), 51.90 (C-20), 52.21 (C-3a), 54.17 (C-9b), 124.17 (C-13), 147.00 (C-12), 170.87 (C-4′), 177.77 (C-3), 178.82 (C-1), 179.10 (C-19).

Methyl 2-[3′-(5′-Adamantylamino)-1′-methyl-3′-oxoethyl]-12-isopropyl-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 (5c). Yield 84%, white powder, mp 248–250°C. IR spectrum (m.o., ν, cm^{-1}): 3361, 2916, 2864, 1720, 1690, 1672, 1531, 1460, 1378, 1240, 1149. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.52 (3H, s, CH_3-17), 0.86 (1H, m, Hax-9), 0.89 (3H, d, J = 6.8, CH_3-15), 0.91 (3H, d, J = 6.8, CH_3-16), 1.08 (3H, s, CH_3-18), 1.15 (1H, m, Heq-5), 1.18 (1H, m, Heq-10), 1.32 (1H, m, H-9b), 1.35–1.49 (2H, m, H-8), 1.36 (3H, m, CH_3-2′), 1.38 (1H, m, Heq-9), 1.44 (1H, m, Hax-5), 1.48 (1H, m, Heq-7), 1.58 (6H, s, H-8′), 1.61 (1H, m, Hax-7), 1.63 (1H, m, Hax-10), 1.66 (1H, m, Hax-4), 1.68 (1H, m, H-5a), 1.88 (6H, s, H-6′), 1.98 (3H, m, CH_3-7′), 2.12 (1H, m, J = 6.8, H-14), 2.37 (1H, d, J = 8.0, H-3a), 2.43 (1H, m, Heq-4), 2.79 (1H, dd, J = 8.0, 2.8, H-11a), 3.02 (1H, s, H-11), 3.60 (3H, s, CH_3-20), 4.42 (1H, m, H-1′), 5.33 (1H, s, H-13), 5.65 (1H, s, NH-4′). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 14.72 (C-2′), 15.60 (C-17), 16.67 (C-18), 16.95 (C-8), 19.81 (C-15), 20.58 (C-16), 21.67 (C-5), 27.34 (C-10), 29.28 (C-7′), 32.58 (C-14), 35.16 (C-4), 35.61 (C-11), 36.21 (C-8′), 36.55 (C-7), 37.60 (C-9a), 38.00 (C-9), 40.75 (C-3b), 41.19 (C-6′), 44.88 (C-11a), 47.04 (C-6), 49.39 (C-5a), 50.38 (C-1′), 51.86 (C-20), 52.05 (C-5′), 52.08 (C-3a), 54.20 (C-9b), 124.06 (C-13), 146.92 (C-12), 167.49 (C-3′), 172.63 (C-4′), 176.94 (C-3), 177.80 (C-1), 179.04 (C-19).

Methyl 2-{1′-[(8′-Adamantylamino)carbonyl]-2′-methylpropyl}-12-isopropyl-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 (5d). Yield 76%, white powder, mp 240–242°C. IR spectrum (m.o., ν, cm^{-1}): 3368, 2926, 2855, 1721, 1696, 1668, 1545, 1462, 1378, 1302, 1247, 1198, 1139. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.54 (3H, s, CH_3-17), 0.64 (3H, d, J = 5.8, CH_3-3′), 0.81 (1H, m, Hax-9), 0.88 (3H, d, J = 6.8, CH_3-15), 0.90 (3H, d, J = 6.8, CH_3-16), 0.92 (3H, m, CH_3-4′), 1.09 (3H, s, CH_3-18), 1.17 (1H, m, Heq-5), 1.20 (1H, m, Heq-10), 1.33–1.42 (2H, m, H_2-8), 1.35 (1H, m, H-9b), 1.41 (1H, m, Heq-9), 1.44 (1H, m, Hax-5), 1.47 (1H, m, Heq-7), 1.60 (6H, s, H-8′), 1.63 (1H, m, Hax-7), 1.65 (1H, m, Hax-10), 1.69 (1H, m, Hax-4), 1.72 (1H, m, H-5a), 1.87 (6H, s, H-6′), 1.99 (3H, s, CH_3-7′), 2.15 (1H, m, J = 6.8, H-14), 2.39 (1H, m, J = 7.6, H-2′), 2.41 (1H, d, J = 7.9, H-3a), 2.49 (1H, m, Heq-4), 2.79 (1H, dd, J = 7.9, 2.6, H-11a), 3.03 (1H, s, H-11), 3.62 (3H, s, CH_3-20), 3.92 (1H, m, H-1′), 5.31 (1H, s, H-13), 6.80 (1H, s, NH-6′). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 15.56 (C-17), 16.66 (C-18), 16.94 (C-8), 19.33 (C-4′), 19.43 (C-3′), 19.85 (C-15), 20.41 (C-16), 21.72 (C-5), 26.88 (C-2′), 27.41 (C-10), 29.26 (C-9′), 32.63 (C-14), 34.96 (C-11), 35.22 (C-4), 35.58 (C-7), 36.27 (C-10′), 37.60 (C-9a), 38.04 (C-9), 40.81 (C-3b), 41.38 (C-8′), 44.66 (C-11a), 47.04 (C-6), 49.41 (C-5a), 51.55 (C-7′), 51.70 (C-20), 51.87 (C-3a), 54.41 (C-9b), 65.35 (C-1′), 124.40 (C-13), 147.20 (C-12), 167.19 (C-5′), 178.19 (C-3), 178.47 (C-1), 179.03 (C-19).

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