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Synthetic Transformations of Higher Terpenoids: XVII.* Intramolecular Cyclization of *N*-Furfuryl Amides of the Labdane Series

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Abstract—16-(Benzylaminomethyl)lambertianic acid methyl ester reacts with 2-methylprop-2-enoyl chloride to give unsaturated amide which readily undergoes intramolecular [4+2]-cycloaddition with formation of terpenoid derivatives of 10-oxa-3-azatricyclo[5.2.1.$0^{1,5}$]decenone. Acetylation of lambertianic acid methyl ester with acetic anhydride occurs preferentially at the 2-position of the furan ring and is accompanied by migration of the exocyclic double bond. Reductive amination of 16-acetyl-15,16-epoxylabda-8(9),13,14-triene and subsequent reaction of the resulting amine with 2-methylprop-2-enoyl chloride give intramolecular cyclization products in high yield without isolation of intermediate furfurylacryloyl derivative. Reactions of methyl 16-(benzylaminomethyl)-15,16-epoxylabda-8(9),13,14- and -8(17),13,14-trien-18-oates with maleic anhydride lead to the formation of the corresponding 10-oxa-3-azatricyclo[5.2.1.$0^{1,5}$]dec-8-ene-6-carboxylic acid derivatives as mixtures of diastereoisomers.

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Intramolecular Diels–Alder reactions of *N*-alkenylfurfurylamines and furfurylacrylamides provide a convenient synthetic route to various 10-oxa-3-azatricyclo[5.2.1.$0^{1,5}$]decene or -undecene derivatives which can be regarded as epoxy derivatives of isoindole and isoquinoline. These reactions were widely used in the total syntheses of pharmacologically important compounds, such as penicillin antibiotic Avermectin [2], *exo*-δ-sultams [3], and various alkaloids (fused tetrahydro-β-carbolines and tetrahydroisoquinolines) [4, 5]. Published data on intramolecular [4+2]-cycloadditions in 2-alkenylfurans have been reviewed in [6], where considerable attention has been given to synthetic and mechanistic aspects of these reactions.

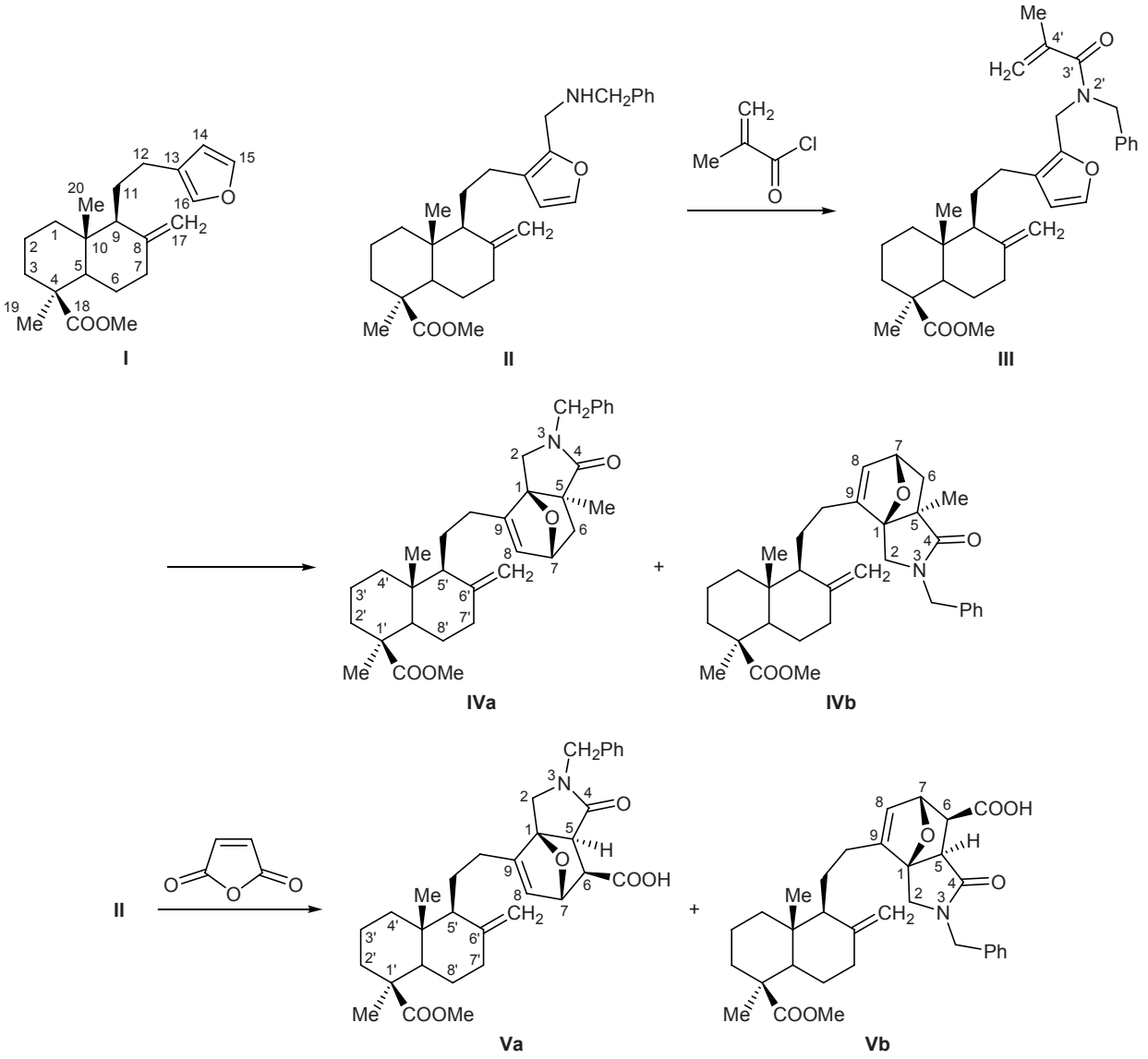
We previously studied intramolecular cyclization of quaternary ammonium salts obtained by reaction of allyl halides with 16-dialkylaminomethyl derivatives of lambertianic acid methyl ester (**I**) and proposed methods for the synthesis of labdane diterpenoids containing a 10-oxa-3-azatricyclo[5.2.1.$0^{1,5}$]decene fragment [7]. The goal of the present work was to develop procedures for the synthesis of oxatricyclic γ-lactams having a terpenoid fragment via intramolecular [4+2]-cycloaddition of *N*-furfuryl amides derived from accessible labdane diterpenoids.**

Acylation of methyl 16-(benzylaminomethyl)lambertianic acid methyl ester (**II**) [8] with 2-methylprop-2-enoyl chloride in chloroform in the presence of triethylamine (1.5 equiv) gave the corresponding methacrylic acid amide **III** in 64% yield. Compound **III** underwent intramolecular cyclization on heating in boiling benzene (8 h, TLC). Analysis of the reaction mixture showed that the products were exclusively *exo* adducts, diastereoisomeric methyl (1*R*,5*S*,7*R*)- and (1*S*,5*R*,7*S*)-5-{2-(3-benzyl-5-methyl-4-oxo-10-oxa-3-azatricyclo[5.2.1.$0^{1,5}$]dec-8-en-9-yl)ethyl}-1,4a-dimethyl-6-methylidenedecahydronaphthalene-1-carboxylates **IVa** and **IVb** (overall yield 75%, ratio 1:1; Scheme 1). The acylation of furfurylamine **II** with maleic anhydride under mild conditions (chloroform, 20°C) gave substituted 4-oxo-10-oxa-3-azatricyclo-

* For communication XVI, see [1].

** Atoms in the labdane fragment of compounds **II**, **III**, and **VI**–**IX** are numbered as shown for compound **I**. Atom numbering for compounds **IVb**, **Va**, **Vb**, **Xa**, **Xb**, **XIIa**, and **XIIb** is the same as shown for compound **IVa** in Scheme 1.

Scheme 1.

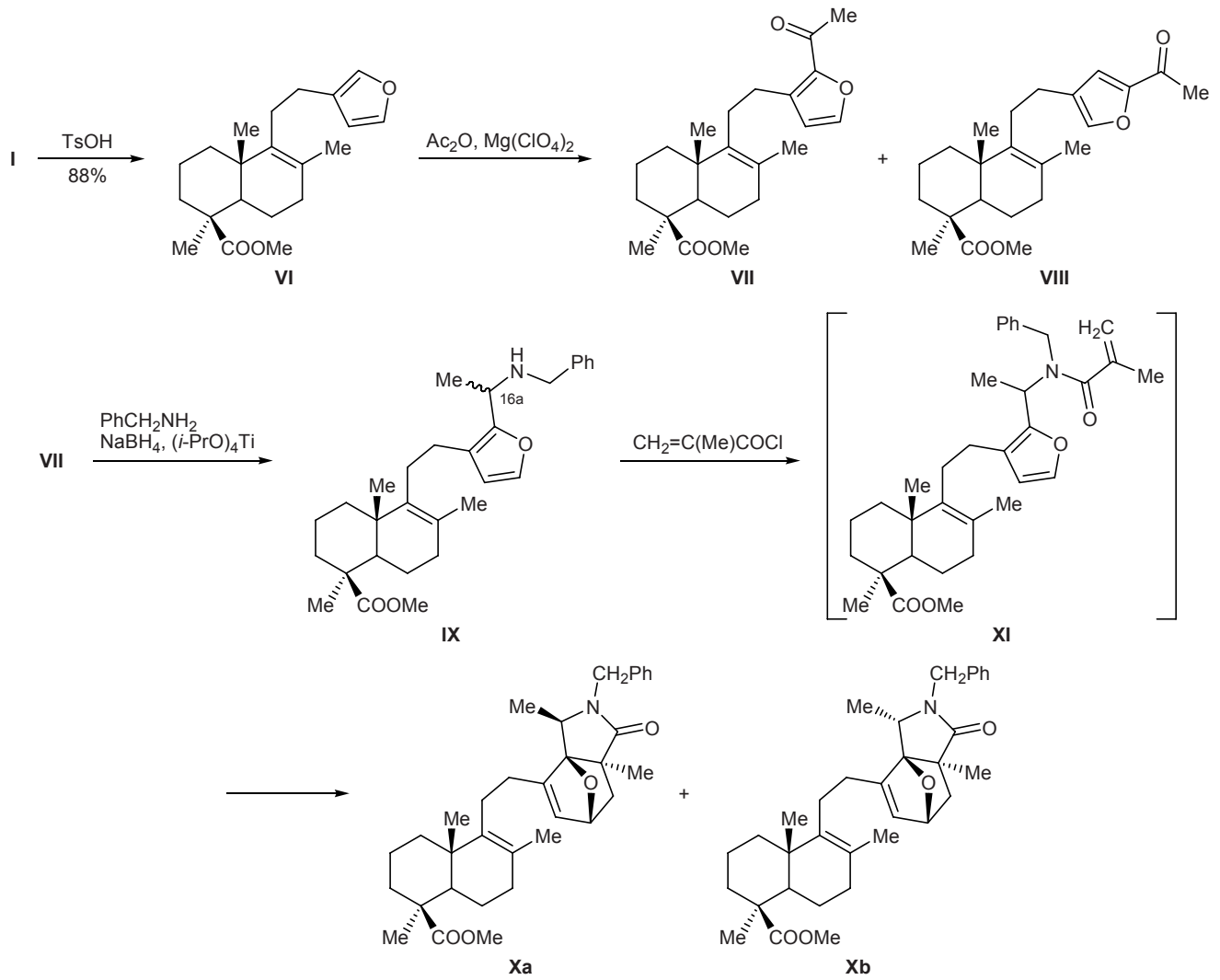


[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acids **Va** and **Vb** (yield 84%, mixture of diastereoisomers; Scheme 1).

Acetylation of lambertianic acid methyl ester (**I**) under standard conditions for acetylation of 3-methylfuran [9] was accompanied by migration of the exocyclic C=C bond in the terpene fragment to the 8(9)-position. The latter transformation was not complete, and a mixture of four compounds, 15- and 16-acetyl-substituted labdanoids having 8(17)- and 8(9)-double bonds, was formed. We found that treatment of lambertianic acid methyl ester (**I**) with *p*-toluenesulfonic acid in benzene smoothly afforded labda-8(9),13(16),14-triene derivative **VI** in 89% yield (Scheme 2). Acetylation of diterpenoid **VI** with acetic anhydride in the presence of $Mg(ClO_4)_2$ gave a mixture of 16- and 15-acetyl-substituted furanolabdanoids **VII** and **VIII** at a ratio of 1.6:1 in an overall yield of 68%. By column chromatography and subsequent recrystallization we succeeded in isolating terpenoid acetylfuran **VII** in 30% yield. Thus, the terpenoid moiety in the β-position of the furan ring forces the acetyl group to enter preferentially the nearest α-position. Analogous reaction direction was observed in the formylation of lambertianic acid methyl ester (**I**) [10].

Acetylfuran **VII** smoothly reacted with benzylamine in the presence of $NaBH_4$ and $Ti(OPr\text{-}i)_4$ [11] to produce 16-[1-(benzylamino)ethyl]-substituted furanolabdanoid **IX** (yield 81%) as a mixture of (16a*R*)- and (16a*S*)-diastereoisomers (Scheme 2). The reaction of furfurylamine **IX** with 2-methylprop-2-enoyl chloride

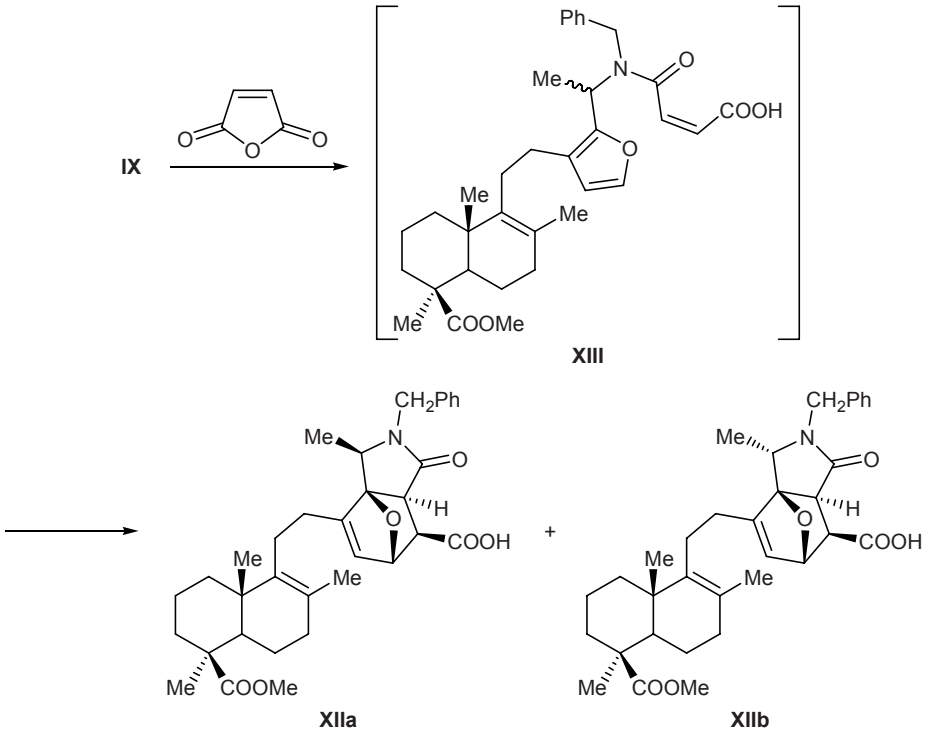
Scheme 2.



in chloroform in the presence of triethylamine at 0–20°C gave 86% of diastereoisomeric (1*R*,2*S*,5*S*,7*R*)- and (1*R*,2*R*,5*S*,7*R*)-2-methyl-10-oxa-3-azatricyclo-[5.2.1.0^{1,5}]decenones **Xa** and **Xb** at a ratio of 1 : 1 (Scheme 2). Intermediate methacrylamide **XI** was not isolated, but its formation was detected by ^{1}H NMR spectroscopy in 2 h after mixing the reactants. It is seen that α-methyl-substituted amide **VII** is more reactive than amide **III** in intramolecular cycloaddition. Diastereoisomeric adducts **Xa** and **Xb** differ by the configuration of the C^2 chiral center. Likewise, the acylation of amine **IX** with maleic anhydride smoothly afforded a mixture of equimolar amounts of diastereoisomeric (1*R*,2*S*,5*R*,6*R*,7*R*)- and (1*R*,2*R*,5*R*,6*R*,7*R*)-adducts **XIIa** and **XIIb** in an overall yield of 86%. As in the reaction of **IX** with 2-methylprop-2-enoyl chloride, we failed to isolate intermediate amide **XIII** (Scheme 3).

The structure of the isolated compounds was determined on the basis of their spectral parameters. Migration of the double C=C bond in labdanoids **VII**–**IX** from the 8(17)- to 8(9)-position leads to the appearance in their ^{1}H NMR spectra of an upfield singlet from protons in the 17-methyl group (δ 1.67 ppm for compound **VII**). In the ^{13}C NMR spectra, carbon atoms at the 8(9)-double bond resonated at δ_C 127.67 (C^8) and 138.17 ppm (C^9). Introduction of an acetyl group into the furan ring of compound **VI** gives rise to a singlet at δ 2.44 ppm in the ^{1}H NMR spectrum of **VII**. The ^{1}H NMR spectrum of a mixture of isomeric furfurylamines **IX** is characterized by the presence of doublet signals at δ 1.39 ppm (J = 7 Hz) from the methyl group and double set of singlets from the C^{17}H$_3$ (δ 1.57 and 1.60 ppm) and C^{20}H$_3$ methyl groups (δ 0.73 and 0.74 ppm). Signals from C^1, C^2, C^3, C^4, C^8, C^9, C^{11}, C^{16a}, C^{17}, and C^{20} in the ^{13}C NMR spec-

Scheme 3.



trum, as well as the signal from the methyl group on C^{16a} in the ^1H NMR spectrum, were also doubled.

The structure of adducts **IV**, **V**, **X**, and **XII** was established on the basis of the following data. Their ^1H NMR spectra contained signals from the 8-H protons as singlets or broadened singlets (J = 1.3–1.9 Hz). The 2-H protons in the spectra of **IVa**/**IVb** and **Va**/**Vb** resonated as doublets at δ 3.52–3.53 and 3.61–3.68 ppm, respectively (J = 13, 14 Hz). The doublets at δ 2.43 and 1.18 ppm (J = 11 Hz) in the spectrum of **IVa**/**IVb** were assigned to 6-H. The corresponding proton in **Va**/**Vb** gave a broadened singlet at δ 2.83 ppm and displayed couplings with 5-H and 7-H in the H,H-COSY spectrum (broadened singlet at δ 5.14 ppm). Adducts **Xa**/**Xb** and **XIIa**/**XIIb** characteristically showed in the ^1H NMR spectra doublet signals from the methyl group on C^2 in the oxazatricyclic fragment (δ 0.87/1.04 for **Xa**/**Xb** and 0.87/1.24 ppm for **XIIa**/**XIIb**; $J \approx 7$ Hz). The 5-H and 6-H protons in the spectrum of **XIIa**/**XIIb** resonated as doublets at δ 2.83 and 2.87 ppm, respectively (J = 8.2 Hz). Adducts **Xa**/**Xb** and **XIIa**/**XIIb** were characterized by enhanced diastereotopicity of the benzylic CH_2 protons at the nitrogen atom (δ 5.12/3.87 for **Xa**/**Xb** and 4.98/3.98 ppm for **XIIa**/**XIIb**). Signals from the corresponding protons in adducts **IVa**/**IVb** and **Va**/**Vb** appeared as doublets at δ 4.60/4.35 and 4.40/4.60 ppm, respectively. The stereoisomeric adducts were attributed to the *exo* series using NOE experiments, which make it possible to determine the conformation or relative configuration of chiral centers in solution [12]. The spectra of **XIIa**/**XIIb** showed NOEs between the 5-H, 6-H, and 7-H protons, indicating their *cis* arrangement. Interaction between the proton at the double bond and protons in the methyl group on C^5 in the spectra of both stereoisomers **Xa** and **Xb** confirms *exo* configuration of the oxanorbornene–pyrrolidine junction in their molecules [4]. In addition, the *exo*-stereoselectivity of the cyclization process is controlled by the length of the spacer connecting the reacting fragments [13, 14].

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were measured from solutions in $CDCl_3$ on Bruker AC-200 (200.13 MHz for ^1H and 50.32 MHz for ^{13}C), AV-300 (300.13 MHz for ^1H and 75.47 MHz for ^{13}C), AM-400 (400.13 MHz for ^1H and 100.78 MHz for ^{13}C), and DRX-500 spectrometers (500.13 MHz for ^1H and 125.76 MHz for ^{13}C). Signals in the NMR spectra were assigned using various proton–proton and carbon–proton shift correlation techniques (COSY, COLOC), as well as two-dimensional ^1H NOESY experiments (for compounds **V**, **IX**, **X**, **XII**). The mass spectra (electron impact, 70 eV)

were recorded on a Finnigan MAT-8200 high-resolution mass spectrometer (vaporizer temperature 270–300°C). The molecular weights and elemental compositions were determined from the high-resolution mass spectra. The IR spectra were obtained on a Vector-22 instrument from samples prepared as KBr pellets. The UV spectra were recorded on an HP 8453 UV-Vis spectrophotometer from solutions in ethanol with a concentration c of about 10^{-4} M. The melting points were determined on a Kofler hot stage. The optical rotations $[\alpha]_{580}^{20}$ were measured on a Polamat A polarimeter using chloroform or ethanol as solvent at room temperature (20–23°C). The progress of reactions was monitored by TLC on Silufol UV-254 plates; spots were visualized by spraying with a 10% aqueous solution of sulfuric acid. Silica gel (0.035–0.070 mm; from Acros Organic) was used for preparative column chromatography.

Methyl (1*S*,4a*R*,5*S*,8a*S*)-5-{2-(2-[*N*-benzyl-*N*-(2-methylprop-2-enoyl)aminomethyl]furan-3-yl)-ethyl}-1,4a-dimethyl-6-methylidenedecahydronaphthalene-1-carboxylate {methyl 16-[*N*-benzyl-*N*-(2-methylprop-2-enoyl)aminomethyl]-15,16-epoxylabda-8(17),13(16),14-trien-18-oate} (III). A solution of 1.0 g (2.24 mmol) of compound **II** and 0.23 g (2.24 mmol) of 2-methylprop-2-enoyl chloride in 30 ml of chloroform was cooled to 0°C, a solution of 0.34 g (3.36 mmol) of triethylamine in 10 ml of chloroform was added dropwise under stirring in an argon atmosphere, and the mixture was stirred for 6 h at room temperature and left overnight. The solvent was removed under reduced pressure, the residue was treated with 20 ml of diethyl ether, and the precipitate (triethylamine hydrochloride) was filtered off. The filtrate was evaporated under reduced pressure, and the residue was subjected to chromatography on silica gel using petroleum ether–diethyl ether (10:1) as eluent. Yield 0.74 g (64%), oily substance. IR spectrum, ν, cm^{-1}: 669 (C=C), 1217, 1718 (C=O). ^{1}H NMR spectrum, δ, ppm: 0.43 s (3H, $C^{20}H_3$), 0.88 m (1H, 1-H), 0.97 d.t (1H, 3-H, J = 13, 5 Hz), 1.13 s (3H, $C^{19}H_3$), 1.20 d.d (1H, 5-H, J = 13, 1.8 Hz), 1.46 m (3H, 2-H, 9-H, 11-H), 1.57 m (1H, 11-H), 1.71 t.d (1H, 1-H, J = 13, 3 Hz), 1.77 m (3H, 2-H, 6-H, 7-H), 1.93 d.m (1H, 6-H, ^2J = 13 Hz), 1.99 s (3H, 4-CH_3), 2.01 m (1H, 12-H), 2.11 d.m (1H, 3-H, ^2J = 13 Hz), 2.33 m (2H, 7-H, 12-H), 3.56 s (3H, OCH_3), 3.60 s (2H, 1′-H), 4.40 s (1H, 17-H), 4.46 d and 4.52 d (2H, C**H**$_2$Ph, J = 11 Hz), 4.77 s (1H, 17-H), 5.18 m (2H, 5′-H), 6.17 d (1H, 14-H, J = 1.2 Hz), 7.13 d (1H, 15-H, J = 1.2 Hz), 7.22 m and 7.28 m (5H, Ph). ^{13}C NMR spectrum, δ_C, ppm: 12.40 q (C^{20}), 19.72 t (C^2), 20.53 q (4-CH_3), 22.86 t (C^{12}), 24.24 t (C^{11}), 26.04 t (C^6), 28.57 q (C^{19}), 37.96 t (C^3), 38.47 t (C^7), 38.85 t (C^1), 39.92 s (C^4), 44.06 s (C^{10}), 45.23 t ($C^{1'}$), 50.89 q (OCH_3), 51.32 t (Ph**C**H$_2$), 54.89 d (C^9), 56.04 d (C^5), 106.31 t (C^{17}), 111.16 d (C^{14}), 115.47 t ($C^{5'}$), 123.41 s (C^{13}), 127.12 d ($C^{2''}$, $C^{6''}$), 127.29 d ($C^{4''}$), 128.41 d ($C^{3''}$, $C^{5''}$), 128.40 d (C^{15}), 136.17 s ($C^{1''}$), 140.36 s (C^{16}), 141.97 s ($C^{4'}$), 147.39 s (C^8), 172.66 s ($C^{3'}$), 177.45 s (C^{18}). Found, %: C 76.60; H 8.32; N 2.71. $C_{33}H_{43}NO_4$. Calculated, %: C 77.01; H 8.40; N 2.55.

Methyl (1*S*,4a*R*,5*S*,8a*S*)-5-{2-[(1*R*,5*S*,7*R*)- and (1*S*,5*R*,7*S*)-3-benzyl-5-methyl-4-oxo-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-en-9-yl]ethyl}-1,4a-dimethyl-6-methylidenedecahydronaphthalene-1-carboxylates (IVa/IVb). A solution of 0.60 g of compound **III** in 7 ml of benzene was heated for 10 h under reflux. The mixture was evaporated, and the residue was subjected to chromatography on silica gel using petroleum ether–diethyl ether (10:1) as eluent. Yield 0.41 g (75%), oily substance (mixture of diastereoisomers). ^{1}H NMR spectrum, δ, ppm: 0.46 s (6H, $C^{16'}H_3$), 0.99 m (4H, 2′-H, 4′-H), 1.02 s (6H, 5-CH_3), 1.14 s (6H, $C^{15'}H_3$), 1.18 m (2H, 6-H), 1.24 m (2H, 9′-H), 1.47 m (4H, 3′-H, 11′-H), 1.56 m (4H, 5′-H, 11′-H), 1.65–1.85 m (10H, 3′-H, 4′-H, 7′-H, 8′-H, 12′-H), 1.94 m (2H, 8′-H), 2.14 d.m (2H, 2′-H, ^2J = 13.1 Hz), 2.22 m (2H, 12′-H), 2.35 d.t (2H, 7′-H, J = 12, 3 Hz), 2.41 d and 2.43 d (1H each, 6-H, J = 11 Hz), 3.52 d (1H, 2-H, J = 13 Hz), 3.53 d (1H, 2-H, J = 14 Hz), 3.57 s (6H, OCH_3), 3.61 d (1H, 2-H, J = 14 Hz), 3.63 d (1H, 2-H, J = 13 Hz), 4.35 d (2H, C**H**$_2$Ph, J = 12 Hz), 4.37 s (2H, 13′-H), 4.60 d (2H, C**H**$_2$Ph, J = 12 Hz), 4.78 s (2H, 13′-H), 4.83 d (2H, 7-H, J = 1.9 Hz), 6.97 d (1H, 8-H, J = 1.9 Hz), 5.99 d (1H, 8-H, J = 1.9 Hz), 7.19 m (4H, 2″-H, 6″-H), 7.24 m (2H, 4″-H), 7.29 t (4H, 3″-H, 5″-H). ^{13}C NMR spectrum, δ_C, ppm: 12.36 q ($C^{16'}$), 19.74 t ($C^{3'}$), 20.09 q (5-CH_3), 20.88 t and 21.09 t (C^{11}), 26.03 t ($C^{8'}$), 27.31 t, 27.48 t ($C^{12'}$), 28.60 q ($C^{15'}$), 36.25 t (C^6), 37.98 t ($C^{2'}$), 38.49 t ($C^{7'}$), 38.99 t ($C^{4'}$), 40.15 s and 40.17 s ($C^{1'}$), 44.10 s ($C^{10'}$), 46.16 t and 46.24 t (C^2), 46.33 t and 46.34 t (Ph**C**H$_2$), 50.96 q (OCH_3), 52.10 s and 52.19 s (C^5), 55.26 d and 55.67 d ($C^{5'}$), 56.07 d ($C^{9'}$), 77.80 d (C^7), 91.91 s and 92.09 s (C^1), 106.01 t and 106.20 t ($C^{13'}$), 127.31 d ($C^{4''}$), 127.65 d ($C^{2''}$, $C^{6''}$), 127.82 d and 128.35 d (C^8), 128.58 d ($C^{3''}$, $C^{5''}$), 136.18 s ($C^{1''}$), 146.86 s and 147.17 s ($C^{6'}$), 147.56 s and 147.86 s (C^9), 177.43 s and 177.63 s (C^4), 177.65 s ($C^{14'}$). Found, %: C 77.15; H 8.42; N 2.61. $C_{33}H_{43}NO_4$. Calculated, %: C 77.01; H 8.40; N 2.55.

Methyl (1*S*,4a*R*,5*S*,8a*S*)-5-{2-[(1*R*,5*S*,6*R*,7*R*)- and (1*S*,5*R*,6*S*,7*S*)-3-benzyl-6-carboxy-4-oxo-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-en-9-yl]ethyl}-1,4a-dimethyl-6-ethylidenedecahydronaphthalene-1-carboxylates (Va/Vb). Maleic anhydride, 0.19 g (1.96 mmol), was added under stirring to a solution of 0.87 g (1.96 mmol) of furfurylamine **II** in 30 ml of benzene, the mixture was stirred for 48 h at 20°C and evaporated under reduced pressure, and the residue was subjected by chromatography on silica gel using chloroform as eluent. Yield 0.90 g (84%), oily substance (mixture of diastereoisomers). UV spectrum, λ_{max}, nm (logε): 258 (1.71), 264 (1.67). IR spectrum, ν, cm^{-1}: 692 (C=S), 1132, 1229, 1723 (C=O). ^{1}H NMR spectrum, δ, ppm: 0.45 s (6H, C$^{16'}$H$_3$), 0.97 m (2H, 4′-H), 1.00 m (2H, 2′-H), 1.14 s (6H, C$^{15'}$H$_3$), 1.24 m (2H, 9′-H), 1.45 m (2H, 3′-H, 11′-H), 1.52 m (4H, 5′-H, 11′-H), 1.73 m (4H, 4′-H, 8′-H), 1.81 m (6H, 3′-H, 7′-H, 12′-H), 1.95 m (2H, 8′-H), 2.14 d.m (2H, 2′-H, ^2J = 13.1 Hz), 2.22 m (2H, 12′-H), 2.35 m (2H, 7′-H), 2.83 br.s (2H, 6-H), 2.87 br.s (2H, 5-H), 3.50 d and 3.53 d (2H, 2-H, J = 13 Hz), 3.58 s (6H, OCH$_3$), 3.66 d and 3.68 d (2H, 2-H, J = 13 Hz), 4.33 s and 4.36 s (2H, 13′-H), 4.40 d and 4.60 d (4H, C**H**$_2$Ph, J = 12 Hz), 4.78 s (2H, 13′-H), 5.14 br.s (2H, 7-H), 5.94 d (1H, 8-H, J = 1.3 Hz), 5.96 d (1H, 8-H, J = 1.4 Hz), 7.21 m (4H, 2″-H, 6″-H), 7.26 m (2H, 4″-H), 7.30 m (2H, 3″-H, 5″-H). ^{13}C NMR spectrum, δ_C, ppm: 12.31 q and 12.38 q (C$^{16'}$), 19.70 t (C$^{3'}$), 20.79 t and 21.10 t (C$^{11'}$), 25.54 t (C$^{12'}$), 25.99 t (C$^{8'}$), 28.56 q and 28.58 q (C$^{15'}$), 37.92 t (C$^{2'}$), 38.41 t (C$^{7'}$), 38.98 t (C$^{4'}$), 40.10 s and 40.15 s (C$^{1'}$), 44.07 s (C$^{10'}$), 46.81 t and 46.82 t (CH$_2$), 46.93 t and 47.00 t (C^2), 47.19 d (C^6), 50.66 d and 50.72 d (C^5), 50.98 q (OCH$_3$), 55.28 d and 55.59 d (C$^{5'}$), 56.01 d (C$^{9'}$), 81.66 d and 81.70 d (C^7), 89.60 s and 89.68 s (C^1), 106.20 t and 106.24 t (C$^{13'}$), 127.58 d (C$^{4''}$), 127.77 d and 127.82 d (C$^{2''}$, C$^{6''}$), 127.99 d and 128.29 d (C^8), 128.69 d (C$^{3''}$, C$^{5''}$), 135.16 s and 135.18 s (C$^{1''}$), 147.42 s and 147.63 s (C$^{6'}$), 149.60 s and 149.81 s (C^9), 172.02 s and 172.09 s (C^4), 173.57 s (COOH), 177.42 s (C^{14}). Found, %: C 72.79; H 7.40; N 2.55. $C_{33}H_{46}NO_6$. Calculated, %: C 72.53; H 7.33; N 2.56.

Methyl (1*S*,4a*S*)-5-[2-(furan-3-yl)ethyl]-1,4a,6-trimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalene-1-carboxylate [methyl 15,16-epoxylabda-8(9),13(16),14-trien-18-oate] (VI). Lambertianic acid methyl ester (**I**), 1.00 g (3.02 mmol), was dissolved in 10 ml of benzene, 0.01 g (0.06 mmol) of anhydrous *p*-toluenesulfonic acid was added, the mixture was heated for 2 h under reflux, the solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel using petroleum ether as eluent. Yield 0.89 g (89%), oily substance, $[\alpha]_{580}$ = +23.4° (c = 3.1, EtOH). IR spectrum, ν, cm^{-1}: 669, 738, 775 (C=C), 1717 (C=O). ^{1}H NMR spectrum, δ, ppm: 0.76 s (3H, C^{20}H$_3$), 1.00 t.d (1H, 3-H, J = 12, 5 Hz), 1.19 s (3H, C^{19}H$_3$), 1.20 m (1H, 1-H), 1.32 d.d (1H, 5-H, J = 12.6, 2.8 Hz), 1.56 m (2H, 2-H), 1.61 s (3H, C^{17}H$_3$), 1.70 m (1H, 11-H), 1.85 m (1H, 7-H), 1.97 m (3H, 1-H, 7-H, 11-H), 2.07 m (1H, 6-H), 2.20 m (2H, 3-H, 6-H), 2.42 m (2H, 12-H), 3.61 s (3H, OCH$_3$), 6.27 s (1H, 14-H), 7.21 s (1H, 15-H), 7.33 s (1H, 16-H). ^{13}C NMR spectrum, δ_C, ppm: 17.72 q (C^{20}), 19.59 t (C^2), 19.77 q (C^{17}), 20.85 t (C^{11}), 25.72 t (C^{12}), 28.45 q (C^{19}), 28.93 t (C^6), 34.31 t (C^7), 37.21 t (C^1), 37.75 t (C^3), 39.58 s (C^4), 43.90 s (C^{10}), 51.09 q (OCH$_3$), 53.55 d (C^5), 110.81 d (C^{14}), 125.55 s (C^{13}), 127.34 s (C^8), 138.39 d (C^{15}), 138.86 s (C^9), 142.67 d (C^{16}), 178.08 s (C^{18}). Mass spectrum, m/z (I_{rel}, %): 330 [M]$^+$ (67), 189 (100), 175 (34), 147 (31), 133 (48), 121 (36), 119 (33), 55 (32), 41 (42). Found: [M]$^+$ 330.21972. $C_{21}H_{30}O_3$. Calculated: M 330.21948.

Methyl (1*S*,4a*S*)-5-[2-(2-acetylfuran-3-yl)ethyl]-1,4a,6-trimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalene-1-carboxylate [methyl 16-acetyl-15,16-epoxylabda-8(9),13(16),14-trien-18-oate] (VII). Compound **VI**, 1.00 g (3.00 mmol), was dissolved in 5 ml of acetic anhydride, 0.07 g of magnesium perchlorate was added under stirring at 20°C, and the mixture was stirred for 5 h and left overnight. It was then poured onto ice and extracted with chloroform (3×30 ml), the combined extracts were washed with a 5% aqueous solution of sodium carbonate (3×30 ml) and water (3×30 ml) and dried over MgSO$_4$, the solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel using petroleum ether–diethyl ether (10:1) as eluent. Crystallization of a mixture of compounds **VII** and **VIII**, 0.72 g (68%), from hexane gave 0.32 g (30%) of compound **VII**, mp 64–66°C (from hexane), $[\alpha]_{580}$ = +4.3° (c = 2.9, EtOH). UV spectrum: λ_{max} 275 nm (logε 4.05). IR spectrum, ν, cm^{-1}: 634, 775, 886, 1584 (C=C), 1676, 1720 (C=O). ^{1}H NMR spectrum, δ, ppm: 0.77 s (3H, C^{20}H$_3$), 1.00 t.d (1H, 3-H, J = 14, 5 Hz), 1.18 s (3H, C^{19}H$_3$), 1.23 m (1H, 1-H), 1.33 d.d (1H, 5-H, J = 12, 2 Hz), 1.53 d.t (1H, 2-H, J = 14, 3 Hz), 1.67 s (3H, C^{17}H$_3$), 1.68 m (1H, 2-H), 1.70 m (1H, 11-H), 1.89–1.96 m (4H, 1-H, 7-H, 11-H), 2.02 m (1H, 6-H), 2.18 m (1H, 3-H), 2.21 m (1H, 6-H), 2.44 s (3H, COCH$_3$), 2.83 d.d (2H, 12-H, J = 10, 2 Hz), 3.60 s

(3H, OCH_3), 6.43 d (1H, 14-H, J = 1.2 Hz), 7.38 d (1H, 15-H, J = 1.2 Hz). ^{13}C NMR spectrum, δ_C, ppm: 17.53 q (C^{20}), 19.45 q (C^{17}), 19.51 t (C^2), 20.67 t (C^{11}), 26.39 t (C^{12}), 26.80 q (CO**C**H_3), 28.27 t (C^6), 28.45 q (C^{19}), 34.20 t (C^7), 36.85 t (C^1), 37.57 t (C^3), 39.49 s (C^4), 43.71 s (C^{10}), 50.86 q (OCH_3), 53.37 d (C^5), 114.03 d (C^{14}), 127.67 s (C^8), 134.75 s (C^{13}), 138.17 s (C^9), 144.11 d (C^{15}), 147.96 s (C^{16}), 177.91 s (C^{18}), 188.70 s (**C**OCH_3). Mass spectrum, m/z (I_{rel}, %): 372 $[M]^+$ (6), 249 (32), 189 (30), 124 (100), 43 (29). $C_{23}H_{32}O_4$.

Methyl (1*S*,4a*S*)-5-{2-(2-[1-(benzylamino)ethyl]-furan-3-yl)ethyl}-1,4a,6-trimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalene-1-carboxylate [methyl (16a*RS*)-16-[1-(benzylamino)ethyl]-15,16-epoxy-labda-8(9),13(16),14-trien-18-oate] (IX). Compound **VII**, 1.00 g (2.70 mmol), was dissolved in 15 ml of anhydrous THF, 1.53 g (5.4 mmol) of Ti(OPr-*i*)$_4$ and 0.29 g (2.70 mmol) of benzylamine were added in succession under stirring in an argon atmosphere, the mixture was stirred for 8 h, 0.31 g (8.10 mmol) of $NaBH_4$ and 5 ml of ethanol were added in portions, and the mixture was additionally stirred for 8 h. When the reaction was complete, the mixture was poured into 20 ml of 2 M aqueous ammonia, and the precipitate was filtered off and washed with diethyl ether (3× 30 ml). The filtrate was combined with the washings, washed with a saturated aqueous solution of sodium chloride (3×30 ml) and water (3×30 ml) and dried over $MgSO_4$. The solvent was distilled off under reduced pressure, and the residue was subjected to column chromatography on silica gel using petroleum ether–diethyl ether (10:1) as eluent. Yield 1.04 g (81%), oily substance. UV spectrum, λ_{max}, nm (logε): 207 (4.20), 252 (2.55), 258 (2.56). IR spectrum, ν, cm^{-1}: 698 (C=C), 1140, 1229, 1727 (C=O). ^1H NMR spectrum, δ, ppm: 0.73 s and 0.74 s (3H, $C^{20}H_3$), 0.85 m (1H, 12-H), 0.88 t.d (1H, 3-H, J = 14, 5 Hz), 1.08 m (1H, 1-H), 1.18 s (3H, $C^{19}H_3$), 1.27 m (1H, 5-H), 1.39 d (3H, CH_3, J = 7 Hz), 1.47 m (1H, 12-H), 1.57 s and 160 s (3H, $C^{17}H_3$), 1.60–1.78 m (4H, 1-H, 2-H, 6-H, 12-H), 1.92–1.99 m (3H, 2-H, 6-H, 7-H), 2.11–2.20 m (2H, 7-H, 11-H), 2.26–2.36 m (2H, 3-H, 11-H), 3.52 d.d (1H, C**H**$_2$Ph, ^2J = 13 Hz), 3.61 s (3H, OCH_3), 3.64 d.d (1H, C**H**$_2$Ph), 3.86 m (1H, 16a-H), 6.03 d (1H, 14-H, J = 1.2 Hz), 7.18–7.27 m (5H, Ph), 7.28 d (1H, 15-H, J = 1.2 Hz). ^{13}C NMR spectrum, δ_C, ppm: 17.59 q and 17.60 q (C^{20}), 19.42 t and 19.47 t (C^2), 19.61 q and 19.65 q (C^{17}), 20.67 t (C^6), 20.84 q and 20.87 q (16a-CH_3), 25.16 t and 25.18 t (C^{11}), 28.26 q (C^{19}), 29.52 t (C^{12}), 34.15 t (C^7), 37.05 t and 37.08 t (C^1), 37.57 t and 37.58 t (C^3), 39.37 s and 39.38 s (C^4), 43.71 s (C^{10}), 48.49 d and 48.51 d (C^{16a}), 50.84 q (OCH_3), 51.23 t (CH_2Ph), 53.37 d (C^5), 110.81 d (C^{14}), 120.68 s (C^{13}), 126.61 d and 126.63 d ($C^{4'}$), 127.04 s and 127.07 s (C^8), 127.78 d and 127.82 d ($C^{2'}$, $C^{6'}$), 128.12 d and 128.14 d ($C^{3'}$, $C^{5'}$), 138.68 s and 138.70 s (C^9), 140.12 s and 140.14 s ($C^{1'}$), 140.48 d (C^{15}), 151.01 s (C^{16}), 177.75 s (C^{18}). Found, %: C 77.87; H 9.08; N 2.77. $C_{30}H_{41}NO_3$. Calculated, %: C 77.75; H 8.86; N 3.02.

Methyl (1*S*,4a*R*,8a*S*)-5-{2-[(1*R*,2*S*,5*S*,7*R*)- and (1*R*,2*R*,5*S*,7*R*)-3-benzyl-2,5-dimethyl-4-oxo-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-en-9-yl]ethyl}-1,4a,6-trimethyl-1,2,3,4,4a,7,8,8a-octahydronaphthalene-1-carboxylates (Xa/Xb). A solution of 1.00 g (2.16 mmol) of amine **IX** and 0.23 g (2.16 mmol) of 2-methylprop-2-enoyl chloride in 30 ml of chloroform was cooled to 0°C, a solution of 0.33 g (3.23 mmol) of triethylamine in 10 ml of chloroform was added dropwise under stirring in an argon atmosphere, and the mixture was allowed to warm up to room temperature, stirred for 6 h, and left overnight. The solvent was removed, 20 ml of diethyl ether was added to the residue, the precipitate of triethylamine hydrochloride was filtered off, the filtrate was evaporated under reduced pressure, and the residue was subjected to chromatography on silica gel using petroleum ether–diethyl ether (1:1) as eluent. Yield 0.96 g (84%), oily substance (mixture of diastereoisomers). UV spectrum, λ_{max}, nm (logε): 252 (2.64), 258 (2.64), 266 (2.59), 290 (2.38). IR spectrum, ν, cm^{-1}: 698 (C=C), 1149, 1229, 1694, 1727 (C=O). ^1H NMR spectrum, δ, ppm: 0.71 s (6H, $C^{16'}H_3$); 0.82 m (2H, 4′-H); 0.87 d (3H, 2-CH_3, J = 7 Hz); 0.94 m (2H, 2′-H); 1.04 d (3H, 2-CH_3, J = 7 Hz); 1.15 s (6H, $C^{14'}H_3$); 1.20 s (3H, 5-CH_3); 1.23 s (3H, 5-CH_3); 1.24 m (2H, 9′-H); 1.47 s and 1.48 s (6H, $C^{13'}H_3$); 1.40–1.47 m (6H, 4′-H, 7′-H, 8′-H); 1.62–1.77 m (6H, 3′-H, 7′-H, 11′-H); 1.92 m (4H, 8′-H, 11′-H); 2.02 m (2H, 12′-H); 2.16 m (2H, 2′-H); 2.46 d.d (2H, 6-H, J = 12, 4 Hz); 3.60 s (6H, OCH_3); 3.83 m (2H, 2-H); 3.87 d (2H, C**H**$_2$Ph, J = 12 Hz); 4.85 br.s (1H, 7-H); 4.86 br.s (1H, 7-H); 5.12 d (2H, C**H**$_2$Ph, J = 12 Hz); 6.04 d (2H, 8-H, J = 1.3 Hz); 7.22 m, 7.25 m, 7.30 m, and 7.33 m (10H, Ph). ^{13}C NMR spectrum, δ_C, ppm: 12.90 q (2-CH_3), 17.74 q ($C^{16'}$), 19.51 t ($C^{3'}$), 19.58 q ($C^{13'}$), 19.91 q (5-CH_3), 20.75 t ($C^{11'}$), 25.05 t ($C^{8'}$), 28.42 q ($C^{15'}$), 28.96 t ($C^{12'}$), 29.42 q (2-CH_3), 34.25 t ($C^{7'}$), 36.76 t ($C^{4'}$), 36.98 t (C^6), 37.64 t ($C^{2'}$), 39.58 s ($C^{1'}$), 43.10 t (CH_2Ph), 43.82 s ($C^{10'}$), 50.11 d (C^2), 51.10 q (OCH_3), 51.78 s ($C^{9'}$), 53.49 d and 53.55 d (C^5), 77.80 d (C^7),

94.57 s (C^1), 127.43 d ($C^{4''}$), 127.71 s ($C^{6'}$), 127.80 d ($C^{3''}$, $C^{5''}$), 128.53 d and 128.62 d (C^8), 128.76 d ($C^{2''}$, $C^{6''}$), 136.84 s ($C^{1''}$), 138.10 s ($C^{5'}$), 146.90 s (C^9), 172.40 s (C^4), 177.90 s ($C^{14'}$). Mass spectrum, *m*/*z* (I_{rel}, %): 531 $[M]^+$ (30), 440 (28), 283 (33), 189 (27), 109 (28), 91 (100), 69 (71), 43 (22), 41 (36). $C_{34}H_{45}NO_4$.

Methyl (1*S*,4a*R*,8a*S*)-5-{2-[(1*R*,2*S*,5*R*,6*R*,7*R*)- and (1*R*,2*R*,5*R*,6*R*,7*R*)-3-benzyl-6-carboxy-2-methyl-4-oxo-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-en-9-yl]-ethyl}-1,4a,6-trimethyl-1,2,3,4,4a,7,8,8a-octahydronaphthalene-1-carboxylates (XIIa/XIIb). Maleic anhydride, 0.21 g (2.16 mmol), was added under stirring to a solution of 1.0 g (2.16 mmol) of amine **IX** in 30 ml of chloroform, the mixture was stirred for 48 h at 20°C, the solvent was distilled off, and the residue was subjected to chromatography on silica gel using chloroform as eluent. The product was additionally recrystallized from hexane. Yield 0.96 g (86%), mp 64–66°C (mixture of diastereoisomers). IR spectrum, ν, cm^{-1}: 1167, 1229, 1695, 1724 (C=O), 3430 (OH). ^{1}H NMR spectrum, δ, ppm: 0.67 s (6H, $C^{16'}H_3$), 0.87 d (3H, 2-CH_3, *J* = 7 Hz), 0.93 t.d (2H, 2′-H, *J* = 13, 3 Hz), 1.02 d.d (2H, 9′-H, *J* = 12, 3 Hz), 1.14 s (6H, $C^{15'}H_3$), 1.18 m (2H, 4′-H), 1.24 d (3H, 2-CH_3, *J* = 7 Hz), 1.44 s (6H, $C^{13'}H_3$), 1.46 m (4H, 7′-H, 8′-H), 1.59–1.68 m (6H, 3′-H, 4′-H, 11′-H), 1.70 m (2H, 3′-H), 1.80–1.92 m (6H, 7′-H, 11′-H, 12′-H), 1.96–2.09 m (4H, 8′-H, 12′-H), 2.15 m (2H, 2′-H), 2.83 d (2H, 5-H, *J* = 8.2 Hz), 2.87 d (2H, 6-H, *J* = 8.2 Hz), 3.58 s (3H, OCH_3), 3.59 s (3H, OCH_3), 3.62 m (1H, 2-H, *J* = 7 Hz), 3.92 m (1H, 2-H, *J* = 7 Hz), 3.98 d (2H, C**H**$_2$Ph, *J* = 14 Hz), 4.98 d (2H, C**H**$_2$Ph, *J* = 14 Hz), 5.14 br.s (2H, 7-H), 6.00 br.s (2H, 8-H), 7.20 m (4H, 2″-H, 6″-H), 7.25 m (2H, 4″-H), 7.30 m (2H, 3″-H, 5″-H). ^{13}C NMR spectrum, δ_C, ppm: 12.71 q and 22.49 q (2-CH_3); 17.47 q ($C^{16'}$); 19.23 t ($C^{3'}$); 19.43 q and 19.48 q ($C^{13'}$); 20.47 t ($C^{11'}$); 25.25 t ($C^{8'}$); 27.14 t and 27.24 t ($C^{12'}$); 28.18 q ($C^{15'}$); 33.97 t ($C^{7'}$); 36.79 t and 36.86 t ($C^{4'}$); 37.38 t ($C^{2'}$); 39.24 s and 39.29 s ($C^{1'}$); 41.27 s ($C^{10'}$); 43.57 t and 43.80 t (**C**H_2Ph); 47.47 d and 47.51 d (C^6); 50.31 d (C^2); 50.96 q (OCH_3); 51.66 d (C^5); 53.17 d ($C^{9'}$); 81.29 d and 81.31 d (C^7); 92.08 s (C^1); 127.42 d, 127.43 d, and 127.54 d ($C^{3''}$, $C^{4''}$, $C^{5''}$); 127.75 s ($C^{6'}$); 128.64 d ($C^{2''}$, $C^{6''}$); 128.38 d and 128.73 d (C^8); 135.67 s ($C^{1'}$); 137.81 s ($C^{5'}$); 149.13 s (C^9); 172.40 s (C^4); 173.68 s (COOH); 177.78 s ($C^{14'}$). Found, %: C 74.29; H 7.75; N 2.29. $C_{34}H_{43}NO_6$. Calculated, %: C 74.05; H 7.80; N 2.54.

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