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Synthetic Transformations of Higher Terpenoids: VII.* Synthesis of Tetrahydro-β-carbolines of the Labdane Series**

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Abstract—Reductive amination of methyl 16-formyllambertianate with tryptamine, followed by Pictet–Spengler cyclization of the resulting diterpenoindole amine with formaldehyde, yields methyl 16-(1,2,3,4-tetrahydro-β-carbolin-2-ylmethyl)lambertianate. The reaction of formyl-substituted methyl labdatrienoates and labdadienoates with 2-(3-indolyl)ethylamines provides a convenient approach to 1-diterpeno-β-carbolines.

During the last decades, a vast series of natural terpenoids [2] has been intensely supplemented by metabolites of plant, microbial, and animal origin, whose molecules include various structural fragments attached to the main terpene skeleton through covalent bonds. The unique structure of many so-called mixed metabolites and their important biological activity makes them attractive as targets of the total synthesis and as models for the design of molecules having useful properties. Among such metabolites, nitrogen-containing and alkaloid-like compounds attract continuously increasing interest. Such compounds as indoloterpenes [3, 4] and adenine-containing diterpenes [5] demonstrate wide prospects of the application of nitrogen-containing mixed metabolites. The present article describes a convenient approach to β-carboline diterpenoids as potential models of such metabolites, which is based on the Pictet–Spengler reaction.

The first route to the above carbolines includes two-step transformation of methyl 16-formyllambertianate (**II**) [6]. Reductive amination of **II** with tryptamine in the presence of sodium tetrahydridoborate gives amine **III** in 87% yield. Condensation of **III** with formaldehyde leads to formation of β-carboline **IV** (Scheme 1). The structure of compounds **III** and **IV** follows from their spectral parameters. The mass spectrum of **IV** contains the molecular ion peak, *m*/*z* 514, and fragment ion peaks with *m*/*z* 184 (19%), 169 (25%), and 143 (100%), which are typical of β-carbolines [7]. The β-carboline fragment of **IV** gives rise to the following absorption bands in the UV spectrum, λ_{max}, nm: 228, 282, 290 sh. In the IR spectra of **III** and **IV** we observed absorption bands belonging to stretching vibrations of substituted indole nucleus (742, 1430, 1470, 1619, and 1636 cm^{-1}), furan ring (894, 1451, and 3086 cm^{-1}), carbonyl group (1722 cm^{-1}), and OH and NH groups (3242 cm^{-1}). The presence of a carboline fragment in molecule **IV** is characterized by the corresponding set of signals in the ^1H and ^{13}C NMR spectra (see table).

As an alternative route to terpenocarbolines we tried to accomplish direct reactions of diterpene aldehyde **II** with tryptamine and tryptophan methyl ester. In both cases the reactions were carried out in boiling benzene in the presence of *p*-toluenesulfonic acid. In the reaction with tryptamine we obtained 73% of a 1:1 mixture of diastereoisomeric labdanocarbolines which were isolated as *N*-benzoyl derivatives **V** and **VI**. Their steric structure was established on the basis of the NMR spectra.

The reaction of aldehyde **II** with L-tryptophan methyl ester gave an equimolar mixture of *cis*- and *trans*-labdanocarbolines which were isolated as amides **VII** and **VIII**. According to the data of [8–10], stereoisomeric 1,3-disubstituted β-carbolines are distinguished by the different signals from the $C^{1'}$, $C^{3'}$, $C^{4'}$, $C^{10'}$, and $C^{11'}$ atoms of the carboline fragment in

* For communication VI, see [1].

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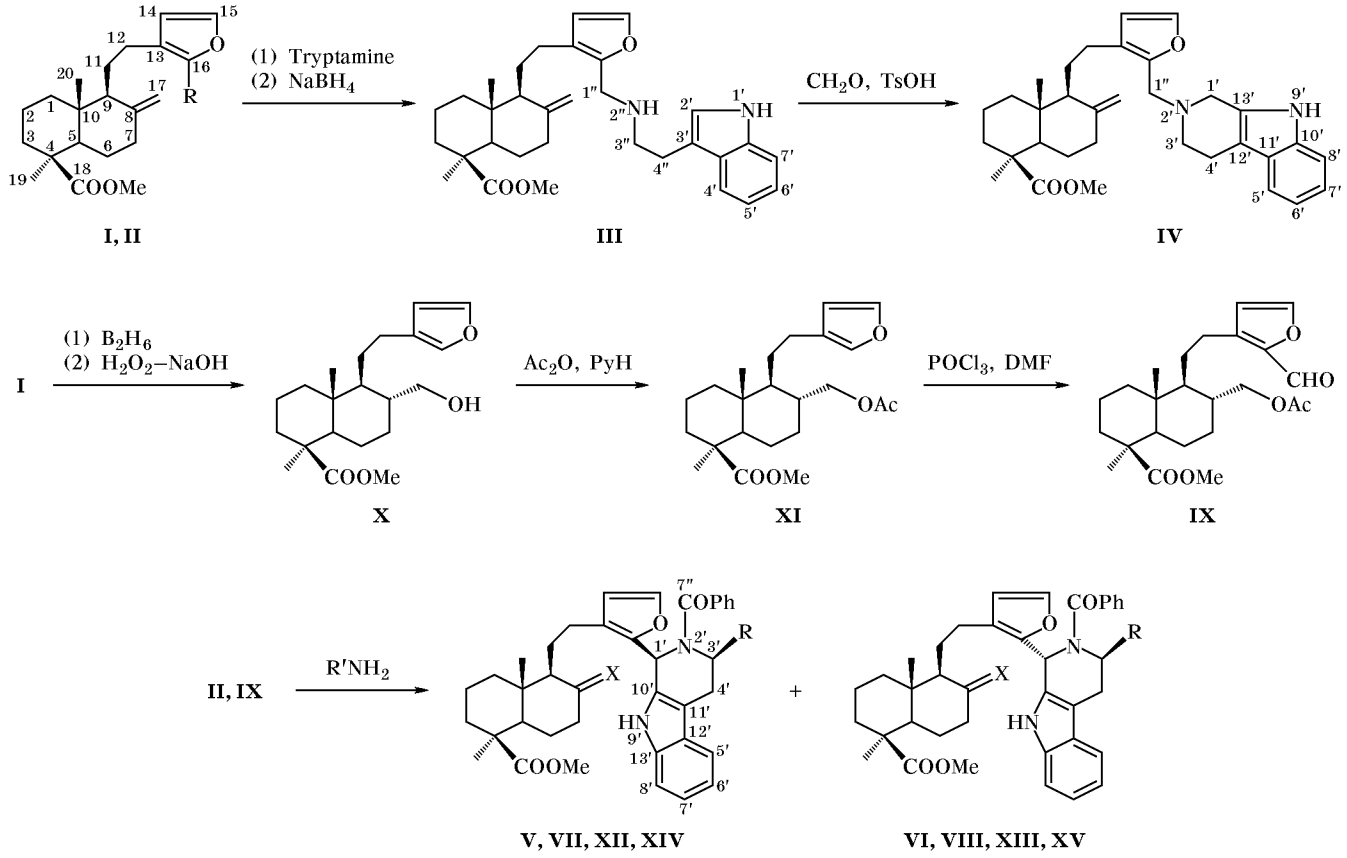
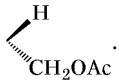
Scheme 1.



I, R = H; **II**, R = CHO; **V**, **VI**, **XII**, **XIII**, R = H, NH_2R' = tryptamine; **VII**, **VIII**, **XIV**, **XV**, R = CO_2Me, NH_2R' = tryptophan methyl ester; **V**–**VIII**, X = CH_2; **XII**–**XV**, X =  .

the ^{13}C NMR spectra. It was reliably established that the $C^{1'}$ and $C^{3'}$ signals of *trans* isomers are located in a stronger field while the $C^{4'}$, $C^{10'}$, and $C^{11'}$ signals are more downfield than the corresponding signals of *cis* isomers. Just these differences are observed in the ^{13}C NMR spectra of stereoisomers **VII** and **VIII**. In addition, the 1′-H signal in the ^1H NMR spectrum of *trans* isomer **VIII** is located in a stronger field, and the 3′-H signal, in a weaker field, as compared to analogous signals in the spectrum of *cis* isomer **VII**. These data are very consistent with those given in [9, 10]. Also, different positions of signals from the $C^{20}H_3$ protons, protons of the methoxycarbonyl group on $C^{3'}$, and protons at C^{17} should be noted: The more downfield signals belong to *trans* isomer **VIII**. The chemical shifts of $C^{1'}$, $C^{3'}$, $C^{10'}$, $C^{11'}$, and $C^{12'}$ of the carboline fragment in diastereoisomers **V** and **VI** differ by 1.0–2.5 ppm.

Thus, despite a sufficiently large size of aldehyde **II** molecule, the Pictet–Spengler reaction is not stereoselective, and possible stereoisomers are formed in equal amounts. Therefore, we synthesized aldehyde **IX** having an acetoxymethyl group on C^8 of the labdane skeleton. We expected this group to ensure stereocontrol of the cyclization. Compound **IX** was synthesized by successive treatment of methyl lambertianate (**I**) with B_2H_6 and H_2O_2 in NaOH, acetylation of alcohol **X** with acetic anhydride in pyridine, and formylation of **XI** according to Vilsmeier. The reaction with diborane at the $C^8{=}C^{17}$ double bond was stereoselective. By column chromatography on aluminum oxide we isolated pure 8-hydroxymethyl derivative **X** as a colorless oily substance in 68% yield. The structure of alcohol **X** follows from the ^1H NMR spectrum of acetate **XI**, which suggests *trans* arrangement of the 8-H and 9-H protons, δ(8-H) 2.01,

^{13}C NMR spectra of diterpeno-β-carbolines **IV**–**VIII**, **XII**, **XIV**, and **XV** in $CDCl_3$

Atom no.	Chemical shifts δ_C,[a] ppm							
	IV	**V**	**VI**	**VII**	**VIII**	**XII**	**XIV**	**XV**
1	38.91	38.51	38.97	40.11	40.32	39.15	38.85	39.14
2	19.80	19.76	19.83	19.74	19.78	18.88	18.75	18.77
3	38.01	38.74[a]	38.82[b]	38.75[c]	38.99[d]	38.11	38.08	38.14
4	40.07	40.18	40.14	40.07	40.32	38.31	37.93	38.07
5	56.09	56.08	55.77	55.16	56.07	56.99	56.86	57.55
6	26.12	26.11	26.11	26.11	25.18	29.77	29.63	29.36
7	38.59	37.99[a]	37.93[b]	38.10[c]	38.89[d]	19.30	20.08	21.11
8	147.72	147.39	147.35	147.15	147.95	35.47	35.66	36.34
9	54.99	56.08	55.89	53.32	53.88	52.41	52.02	52.44
10	44.16	44.14	44.12	44.09	44.14	43.77	43.75	43.60
11	23.32	22.80	23.62	23.10	23.83	25.98	25.86	27.03
12	24.41	24.72	24.45	24.28	24.16	22.83	23.23	23.43
13	123.21	122.06	122.00	122.15	122.23	122.23	123.34	123.20
14	111.10	111.06	111.70	111.13	111.83	111.97	110.99	111.60
15	141.25	141.92	141.90	142.85	141.58	141.29	141.48	141.62
16	146.82	147.39	147.01	147.89	148.01	146.15	147.42	147.98
17	106.39	106.11	107.35	105.99	106.32	63.62	63.44	63.72
18	177.45	177.52	177.62	177.54	177.61	176.88	176.92	176.96
19	28.61	28.67	28.63	28.58	28.72	28.86	28.54	28.64
20	12.50	12.48	12.52	12.40	12.50	14.07	13.82	13.89
OCH_3	50.94	50.98	51.04	50.99	50.94	51.10	50.86	50.93
3′-COO**C**H_3	–	–	–	53.88	55.91	–	56.53	56.85
3′-**C**$OOCH_3$	–	–	–	172.71	173.88	–	172.31	173.32
1′	49.44	53.02	50.98	52.28	50.99	52.22	52.56	50.88
3′	50.21	53.61	51.01	53.88	50.21	52.22	52.44	49.08
4′	20.94	19.84	20.25	19.01	19.92	19.84	19.28	20.13
5′	117.69	118.61	118.18	119.62	118.41	118.52	119.52	118.42
6′	118.99	119.53	119.24	119.56	119.79	119.73	119.02	119.28
7′	120.99	122.00	122.06	122.03	122.00	121.23	121.41	121.34
8′	110.59	111.71	111.06	111.82	110.93	111.03	112.93	112.03
10′	131.48	130.19	132.71	130.09	131.58	130.03	129.44	130.80
11′	107.79	106.39	107.42	105.90	107.54	108.20	107.02	108.53
12′	127.06	127.43	126.62	127.32	126.47	128.22	127.32	126.73
13′	135.96	136.15	136.07	135.53	136.07	136.59	136.01	136.42
1″	51.26	133.22	133.16	133.45	133.32	133.18	133.21	133.18
2″, 6″	–	126.61	126.32	126.70	126.41	126.43	126.91	126.35
3″, 5″	–	130.18	129.66	130.02	129.51	129.80	130.13	129.82
4″	–	132.44	132.21	132.42	132.56	132.23	132.36	132.13
Ph**C**=O	–	168.78	166.65	168.56	166.46	166.85	168.12	166.38

[a–d] Alternative assignment is possible.

δ(9-H) 1.19 ppm, $J_{8,9}$ = 4.9 Hz. The proton signals were unambiguously assigned using 2D H–H and 2D-C–H correlation techniques. The Vilsmeier reaction of **XI** smoothly yielded 78% of 16-formyl derivative **IX**. The overall yield of **IX** calculated on the initial methyl lambertianate was 42%.

Contrary to the expectations the reaction of aldehyde **IX** with tryptamine or L-tryptophan methyl ester was not stereoselective, and in both cases mixtures of diastereoisomers **XII**/**XIII** and *cis* and *trans* isomers **XIV**/**XV** were obtained at a ratio of 1 : 1. Compound **XII** was isolated in the pure state. The stereoisomers

were distinguished on the basis of the ^1H and ^{13}C NMR data (see table).

Thus the Pictet–Spengler reaction can be regarded as a promising route to 1- and 2-diterpeno-substituted β-carbolines. Interest in these compounds is explained by the fact that tetrahydro-β-carboline derivatives obtained from tryptophan (or 5-methoxytryptophan) act as monoaminooxidase A inhibitors and react with serotonin receptors in the central nervous system. Various β-carbolines can be used for studying inversion of the agonist–antagonist binding between pharmacophore and benzodiazepine receptors [11]. In addition, aminomethyl derivatives of lambertianic acid were recently shown [12] to exhibit neurotropic effect.

EXPERIMENTAL

The IR spectra were measured on a Vektor-22 instrument from samples pelleted with KBr. The UV spectra were recorded on a Specord spectrophotometer in ethanol ($c = 10^{-4}$ M). The mass spectra (70 eV) were run on a Finnigan MAT-8200 high-resolution mass spectrometer. The NMR spectra were obtained on Bruker AC-200 (200.13 and 50.32 MHz for ^1H and ^{13}C, respectively) and Bruker DRX-500 (500.13 and 125.76 MHz for ^1H and ^{13}C, respectively) instruments using $CDCl_3$, $CDCl_3$–CCl_4, or CCl_4 as solvent. The signals were assigned using different ^1H–^1H and ^1H–^{13}C correlation techniques (COSY, COLOC, CORRD). The optical rotations $[\alpha]_{580}$ were measured on a Polamat A polarimeter in ethanol at room temperature (20–23°C). The progress of reactions was monitored by TLC on Silufol UV-254 plates. The products were isolated by column chromatography on aluminum oxide.

The ^{13}C NMR spectra of compounds **IV**–**VIII**, **XII**, **XIV**, and **XV** are given in table. The elemental compositions of the products were consistent with the calculated values.

Methyl 16-{*N*-[2-(3-indolyl)ethyl]aminomethyl}-15,16-epoxy-8(17),13(16),14-labdatrien-18-oate $C_{32}H_{42}N_2O_3$ (III). A solution of 0.36 g (1 mmol) of aldehyde **II** [6] and 0.3 g (1.88 mmol) of tryptamine in 15 ml of benzene was kept for 18 h at room temperature. The solvent was removed, the residue was dissolved in 15 ml of MeOH, and 0.1 g (2.7 mmol) of $NaBH_4$ was added in small portions while stirring. When the reduction was complete (TLC), the solvent was distilled off, 15 ml of water was added to the residue, and the product was extracted into *tert*-butyl methyl ether. By column chromatography with petroleum ether–*t*-BuOMe (1 : 2) as eluent we isolated 0.44 g (87%) of amine **III** as an oily substance. $[\alpha]_{580}^{20}$ = +18° (*c* = 1, EtOH). IR spectrum, ν, cm^{-1}: 743, 780, 873, 1024, 1153, 1321, 1436, 1447, 1457, 1620, 1722, 1730, 3086, 3314, 3390. ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.43 s (3H, $C^{20}H_3$), 0.89 m (1H, 1-H), 0.98 m (1H, 3-H), 1.17 s (3H, $C^{19}H_3$), 1.20 m (1H, 5-H), 1.60 m (2H, 2-H, 9-H), 1.58–1.76 m (6H, 1-H, 2-H, 6-H, 7-H, 12-H), 1.98 (1H, 6-H), 2.10 d.t (1H, 3-H, *J* = 15.0, 8.5, 4.2), 2.20 d.d.d (1H, 11-H, *J* = 14.6, 7.5, 3.9), 2.45 m (2H, 7-H, 11-H), 2.93 m (2H, 3″-H), 3.03 m (2H, 4″-H), 3.58 s (3H, OCH_3), 3.76 s (2H, 1″-H), 4.51 s (1H, 17-H), 4.83 s (1H, 17-H), 6.13 d (1H, 14-H, *J* = 1.6), 7.0 t.d (1H, 6′-H, *J* = 7.3, 1.5), 7.10 t.d (1H, 5′-H, *J* = 7.3, 1.8), 7.21 d (1H, 15-H, *J* = 1.6), 7.28 t.d (1H, 8′-H, *J* = 7.8, 1.8), 7.49 t.d (1H, 7′-H, *J* = 7.9, 1.5), 7.90 br.s (1H, NH, halfwidth 8.0), 8.21 br.s (1H, NH, halfwidth 8.0). ^{13}C NMR spectrum, ($CDCl_3$), δ_C, ppm: 12.62 q (C^{20}), 19.91 t (C^2), 23.13 t (C^{11}), 24.39 t (C^{12}), 24.70 t ($C^{4''}$), 26.24 t (C^6), 28.78 q (C^{19}), 38.16 t (C^3), 38.67 t (C^7), 39.01 t (C^1), 40.15 s (C^4), 42.85 t ($C^{1''}$), 44.19 s (C^{10}), 48.13 t ($C^{3''}$), 51.03 q (OCH_3), 54.84 d (C^9), 56.19 d (C^5), 106.63 t (C^{17}), 109.98 s ($C^{3'}$), 111.11 d ($C^{7'}$), 111.23 d (C^{14}), 118.69 d ($C^{4'}$), 119.30 d ($C^{5'}$), 121.99 d ($C^{6'}$), 122.12 d ($C^{2'}$), 122.91 s (C^{13}), 127.23 s ($C^{3a'}$), 136.37 s ($C^{7a'}$), 141.66 d (C^{15}), 146.16 s (C^8), 147.64 s (C^{16}), 177.27 s (C^{18}). UV spectrum, λ_{max}, nm (log ε): 224 (4.16), 275 (3.26), 282 (3.52), 290 sh (3.02).

Methyl 16-(1,2,3,4-tetrahydro-β-carbolin-2-ylmethyl)-15,16-epoxy-8(17),13(16),14-labdatrien-18-oate $C_{33}H_{42}N_2O_3$ (IV). A mixture of 0.25 g (0.5 mmol) of compound **III**, 0.1 g (3.3 mmol) of powdered paraformaldehyde, and 0.086 g (0.5 mmol) of *p*-toluenesulfonic acid in 10 ml of benzene was refluxed for 1 h. When the reaction was complete, the mixture was washed with a 1% solution of ammonia and with water and evaporated. The residue was subjected to column chromatography on aluminum oxide to isolate 0.18 g (71%) of compound **IV**. mp 165–167°C (from petroleum ether–*t*-BuOMe). $[\alpha]_{580}^{20}$ = +25° (*c* = 5, $CHCl_3$). IR spectrum, ν, cm^{-1}: 742, 809, 894, 1150, 1302, 1430, 1451, 1470, 1619, 1636, 1722, 3086, 3242. ^1H NMR spectrum, $CDCl_3$, δ, ppm (*J*, Hz): 0.48 s (3H, $C^{20}H_3$), 0.91 d.d.d (1H, 1-H, *J* = 13.4, 8.3, 4.4), 0.95 d.d.d (1H, 3-H, *J* = 13.3, 8.3, 4.1), 1.15 s (3H, $C^{19}H_3$), 1.22 d.d (1H, 5-H, *J* = 12.5, 3.1), 1.42 m (1H, 2-H, ^2J = 14.1), 1.53 m (1H, 9-H), 1.66 m (1H, 12-H), 1.74 m (2H, 2-H, 12-H), 1.77 m (2H, 1-H, 6-H), 1.83 m (1H, 7-H), 1.92 d.q (1H, 6-H, *J* = 14.2, 12.6, 6.4, 3.1), 2.10 d.t (1H, 3-H, *J* = 13.3,

3.1), 2.22 m (1H, 11-H, J = 14.2, 8.1, 3.3), 2.36 d.d.d (1H, 7-H, ^2J = 14.2, J = 12.1, 3.1), 2.52 m (1H, 11-H), 2.74 m (2H, 4′-H), 2.81 m (2H, 3′-H), 3.50 s (2H, 1″-H), 3.56 s (3H, OCH_3), 3.62 s (2H, 1′-H), 4.53 s (1H, 17-H), 4.82 s (1H, 17-H), 6.20 d (1H, 14-H, J = 1.5), 6.98 t.d (1H, 6′-H, J = 7.3, 1.1), 7.01 t.d (1H, 7′-H, J 7.3, 1.1), 7.11 t.d (1H, 5′-H, J = 7.3, 1.1), 7.26 d (1H, 15-H, J = 1.5), 7.37 t.d (1H, 8′-H, J = 7.8, 1.5), 7.96 br.s (1H, NH, halfwidth 8.0). UV spectrum, λ_{max}, nm ($\log\varepsilon$): 228 (4.36), 282 (3.82), 290 sh (3.12). Mass spectrum, m/z (I_{rel}, %): 514 $[M]^+$ (34), 264 (8), 184 (19), 169 (25), 143 (100).

(8*R*)-15,16-Epoxy-17-hydroxy-8-methyl-13(16),-14-labdadien-18-oate $C_{21}H_{32}O_4$ (X). Freshly distilled BF_3–Et_2O, 1.5 ml (13.2 mmol), was added dropwise with stirring under argon to a solution of 3.3 g (10 mmol) of ester **I** and 0.8 g (21.6 mmol) of sodium tetrahydridoborate in 10 ml of anhydrous diethylene glycol dimethyl ether. The mixture was stirred for 1 h, and 2 ml of water was carefully added. After 15 min, 3.5 ml of a 2 N solution of NaOH was added, and 3.5 ml of 30% hydrogen peroxide was added dropwise (the mixture warmed up to 50°C). The mixture was stirred for 1 h and diluted with 50 ml of water, and the product was extracted into methylene chloride. The extract was washed with water (3 × 15 ml) and evaporated, and the residue was subjected to column chromatography to obtain 2.36 g (68%) of compound **X** as a colorless oily substance. $[\alpha]_{580}^{20}$ = +21° (c = 3.6, EtOH). ^{1}H NMR spectrum ($CDCl_3$–CCl_4), δ, ppm (J, Hz): 0.49 s (3H, $C^{20}H_3$), 0.80–1.08 m (3H, 1-H, 3-H, 5-H), 1.12 s (3H, $C^{19}H_3$), 1.18–1.22 m (2H, 6-H, 9-H), 1.40–1.50 m (2H, 7-H, 11-H), 1.6–1.8 m (5H, 2-H, 3-H, 7-H, 11-H), 1.90 m (1H, 6-H), 2.07 m (2H, 1-H, 8-H), 2.21 m (1H, 12-H, ^2J = 14.1), 2.51 m (1H, 12-H, ^2J = 14.1), 3.26 s (1H, OH), 3.44 m and 3.50 m (2H, 17-H), 3.56 s (3H, OCH_3), 6.16 d.d (1H, 14-H, J = 1.6, 0.6), 7.13 d (1H, 16-H, J = 0.6), 7.24 d (1H, 15-H, J = 1.6). ^{13}C NMR spectrum ($CDCl_3$–CCl_4), δ_C, ppm: 13.81 q (C^{20}), 18.93 t (C^2), 19.11 t (C^7), 23.03 t (C^{12}), 25.71 t (C^{11}), 28.62 q (C^{19}), 29.19 t (C^6), 37.96 t (C^3), 38.09 s (C^4), 38.91 d (C^8), 39.25 t (C^1), 43.75 s (C^{10}), 50.21 d (C^9), 50.94 q (OMe), 57.10 d (C^5), 60.69 t (C^{17}), 110.72 d (C^{14}), 124.84 s (C^{13}), 139.37 d (C^{15}), 142.48 d (C^{16}), 177.48 s (C^{18}). Acetylation of a 0.5-g portion of **X** with 2 ml of a 1:2 mixture of acetic anhydride and pyridine in 10 ml of benzene, followed by appropriate treatment gave 0.47 g (84%) of acetate **XI** as an oily substance. $[\alpha]_{580}^{20}$ = +16° (c = 2.8, EtOH). ^{1}H NMR spectrum, CCl_4, δ, ppm (J, Hz): 0.53 s (3H, $C^{20}H_3$), 0.85 d.d.d (1H, 1-H, J = 14.6, 6.6, 3.8), 0.97 d.d.d (1H, 3-H, ^2J = 15.0, J = 6.8, 2.5), 1.05 d.d (1H, 5-H, J = 10.2, 4.6), 1.11 s (3H, $C^{19}H_3$), 1.19 d.d.d (1H, 9-H, $J_{9,11}$ = 10.5, 2.8, $J_{8,9}$ = 4.9), 1.25–1.40 m (2H, 6-H, 7-H), 1.51 d.d (1H, 11-H, J = 14.4, 10.5), 1.67 d.d.d (1H, 11-H, ^2J = 14.4, J = 8.6, 2.8), 1.76 m (4H, 1-H, 2-H, 7-H), 1.90 d.d (1H, 6-H, J = 14.1, 3.6), 1.97 s (3H, CH_3), 2.01 m (1H, 8-H, $J_{8,17}$ = 10.5, $J_{8,9}$ = 4.9), 2.08 m (1H, 3-H), 2.40 m (1H, 12-H, ^2J = 14.2), 2.62 m (1H, 12-H, ^2J = 14.2), 3.57 s (3H, OCH_3), 4.00 t (1H, 17-H, J = 10.5, 10.6), 4.21 d (1H, 17-H, J = 10.6), 6.18 d.d (1H, 14-H, J = 1.8, 0.8), 7.18 d (1H, 16-H, J = 0.8), 7.22 d (1H, 15-H, J = 1.8).

(8*R*)-17-Acetoxy-15,16-epoxy-16-formyl-8-methyl-13(16),14-labdadien-18-oate $C_{24}H_{34}O_6$ (IX). Phosphoryl chloride, 1.5 g (10 mmol), was added to 20 ml of dimethylformamide on cooling to 0°C, and the mixture was left to stand for 2 h. Acetate **XI**, 3.0 g (7.7 mmol) was then added, the mixture was kept for 24 h, poured onto ice, and extracted with methylene chloride, and the extract was washed with a 5% solution of sodium acetate and with water and evaporated. The residue was subjected to chromatography on aluminum oxide to isolate 2.5 g (78%) of aldehyde **IX** as a colorless oily substance. $[\alpha]_{580}^{20}$ = +27° (c = 1.9, EtOH). ^{1}H NMR spectrum ($CDCl_3$–CCl_4), δ, ppm (J, Hz): 0.50 s (3H, $C^{20}H_3$), 0.85 d.d.d (1H, 1-H, J = 14.6, 6.6, 3.8), 0.97 d.d.d (1H, 3-H, ^2J = 14.2, J = 6.8, 2.5), 1.05 d.d (1H, 5-H, J = 10.2, 3.3), 1.11 s (3H, $C^{19}H_3$), 1.19 d.d.d (1H, 9-H, $J_{9,11}$ = 10.5, 2.8, $J_{8,9}$ = 4.9), 1.22 m (1H, 6-H), 1.35 d.d.d (1H, 7-H, J = 14.2, 4.8, 2.2), 1.51 d.d.d. (1H, 11-H, ^2J = 14.4, J = 10.5, 2.8), 1.65 d.d (1H, 11-H, J = 14.4, 3.6, 2.8), 1.76 m (4H, 7-H, 1-H, 2-H), 1.88 d.t (1H, 6-H, J = 14.6, 2.2), 1.97 s (3H, CH_3), 2.01 m (1H, 8-H, $J_{8,17}$ = 10.5, $J_{8,9}$ = 4.6), 2.07 m (1H, 3-H), 2.66 m (1H, 12-H, ^2J = 14.2), 2.67 m (1H, 12-H), 3.58 s (3H, OCH_3), 3.95 t (1H, 17-H, J = 10.5, 10.6), 4.20 d (1H, 17-H, ^2J = 10.6), 6.43 d (1H, 14-H, J = 1.8), 7.50 d (1H, 15-H, J = 1.8), 9.69 s (CHO). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 13.67 q (C^{20}), 18.59 t (C^2), 18.84 t (C^7), 22.81 t (C^{12}), 25.73 t (C^{11}), 20.83 q (17-CO**C**H_3), 28.42 q (C^{19}), 29.34 t (C^6), 34.83 d (C^8), 37.89 t (C^1), 37.71 s (C^4), 38.94 t (C^3), 43.54 s (C^{10}), 50.96 q (OCH_3), 51.47 d (C^9), 56.60 d (C^5), 63.02 t (C^{17}), 113.88 d (C^{14}), 138.02 s (C^{13}), 147.11 d (C^{15}), 148.25 s (C^{16}), 171.04 s (C=O), 177.39 s (C^{18}), 177.81 d (CHO). Mass spectrum, m/z (I_{rel}, %): 418 $[M]^+$ (23), 358 (14), 340 (16), 299 (14), 249 (28), 189 (56), 121 (89), 110 (100), 81 (68), 43 (68).

(1*R*)- and (1*S*)-16-(2-Benzoyl-1,2,3,4-tetrahydro-β-carbolin-1-yl)-15,16-epoxy-1-methyl-8(17),-13(16),14-labdatrien-18-oates $C_{39}H_{44}N_2O_4$ (V and VI). A solution of 0.36 g (1 mmol) of aldehyde **II**,

0.2 g (1.25 mmol) of tryptamine, and 0.006 g (0.03 mmol) of anhydrous *p*-toluenesulfonic acid in 15 ml of benzene was refluxed for 2 h. When the reaction was complete (TLC), 1 ml of pyridine and 0.2 g (1.43 mmol) of benzoyl chloride were added, and the mixture was left to stand at room temperature for 6 h, diluted with 10 ml of ether, and washed with water (3 × 10 ml). The solvent was removed, and the residue was subjected to chromatography using petroleum ether–diethyl ether (3 : 1) as eluent. A mixture of compounds **V** and **VI** was isolated. Yield 0.44 g (73%). mp 136–140°C (from petroleum ether–methylene chloride). ^{1}H NMR spectrum ($CDCl_3$–CCl_4), δ, ppm (*J*, Hz): 0.32 s ($C^{20}H_3$) (**V**), 0.48 s ($C^{20}H_3$) (**VI**), 0.90–1.05 m (2H, 1-H, 3-H), 1.11 s ($C^{19}H_3$) (**V**), 1.14 s ($C^{19}H_3$) (**VI**), 1.25–1.55 m (3H, 5-H, 2-H, 9-H), 1.60–1.80 m (5H, 1-H, 2-H, 6-H, 7-H, 12-H), 1.88 m (1H, 12-H), 1.98 m (1H, 6-H), 2.10 m (1H, 3-H, *J* = 15.0, 8.0, 4.0), 2.25 m (1H, 11-H), 2.45 m (2H, 7-H, 11-H), 2.90 m (2H, 4′-H), 3.40–3.60 m (2H, 3′-H), 3.56 s (OCH_3) (**V**), 3.63 s (OCH_3) (**VI**), 3.70 s (1H, 1′-H) (**VI**), 3.90 s (1H, 1′-H) (**V**), 4.45 s and 4.70 s (2H, 17-H) (**V**), 4.55 s and 4.88 s (2H, 17-H) (**VI**), 6.17 d (14-H, *J* = 1.6) (**V**), 6.25 d (14-H, *J* = 1.6) (**VI**), 7.06 t.d (1H, 6′-H, *J* = 7.6, 1.6), 7.17 m (1H, 7′-H, 5′-H), 7.22 d (1H, 15-H, *J* = 1.6), 7.30 d (1H, 8′-H, *J* = 7.4), 7.48 m (3H, 3″-H, 5″-H, 4″-H), 7.98 m (2″-H, 6″-H), 8.28 m and 8.72 m (1H, NH).

Methyl (1*S*,3*S*)- and (1*R*,3*S*)-16-(2-benzoyl-3-methoxycarbonyl-1,2,3,4-tetrahydro-β-carbolin-1-yl)-15,16-epoxy-8(17),13(16),14-labdatrien-18-oates $C_{41}H_{46}N_2O_6$ (VII and VIII). Following the above procedure, from 1 mmol of compound **II** and 1.25 mmol of L-tryptophan methyl ester we obtained 0.53 g (79%) of a mixture of isomers **VII** and **VIII**, mp 122–126°C. Recrystallization from petroleum ether gave pure *trans* isomer **VIII**. By evaporation of the mother liquor and subsequent recrystallization of the residue from CCl_4 we isolated *cis* isomer **VII**, mp 131–133°C. $[\alpha]_{580}^{20}$ = +21° (*c* = 2.0, EtOH). IR spectrum, ν, cm^{-1}: 701, 742, 893, 1160, 1320, 1408, 1449, 1475, 1598, 1643, 1722, 1744, 3077, 3359. ^{1}H NMR spectrum ($CDCl_3$–CCl_4), δ, ppm (*J*, Hz): 0.39 s (3H, $C^{20}H_3$), 0.90 m (1H, 1-H), 1.05 m (1H, 3-H), 1.19 s (3H, $C^{19}H_3$), 1.25–1.55 m (3H, 5-H, 2-H, 9-H), 1.60–1.80 m (5H, 1-H, 2-H, 6-H, 7-H, 12-H), 1.88 m (1H, 12-H, ^2J = 13.8), 1.98 d.d.d (1H, 6-H, *J* = 14.3, 12.8, 3.2), 2.10 d.t (1H, 3-H, *J* = 13.5, 8.0, 4.0), 2.25 m (1H, 11-H), 2.40 d.d.d (1H, 7-H, *J* = 14.2, 12.2, 3.4), 2.48 d.d.d (1H, 11-H, *J* = 14.2, 8.2, 3.4), 2.90 m (2H, 4′-H), 3.30 d.d (1H, 3′-H, *J* = 10.2, 3.8), 3.53 s (OCH_3), 3.54 s (3′-$COOCH_3$), 3.78 s (1H, 1′-H), 4.40 s (1H, 17-H), 4.80 s (1H, 17-H), 6.17 d (1H, 14-H, *J* = 1.6), 7.06 t.d (1H, 6′-H, *J* = 7.6, 1.6), 7.10 t.d (1H, 7′-H, *J* = 7.4, 1.3), 7.19 t.d (1H, 5′-H, *J* = 7.3, 1.1), 7.21 d (1H, 15-H, *J* = 1.6), 7.30 d (1H, 8′-H, *J* = 7.4), 7.51 m (3H, 3″-H, 5″-H, 4″-H), 7.86 m (2H, 2″-H, 6″-H), 8.08 br.s (1H, NH, halfwidth 8.4).

Compound **VIII**. mp 144–146°C. $[\alpha]_{580}^{20}$ = +29° (*c* = 2.2, EtOH). IR spectrum, ν, cm^{-1}: 700, 742, 786, 894, 1160, 1302, 1431, 1451, 1468, 1494, 1598, 1619, 1636, 1722, 3086, 3342. ^{1}H NMR spectrum ($CDCl_3$–CCl_4), δ, ppm (*J*, Hz): 0.59 s (3H, $C^{20}H_3$), 0.95 m (2H, 1-H, 3-H), 1.24 s (3H, $C^{19}H_3$), 1.20 m (1H, 5-H), 1.40–1.52 m (2H, 2-H, 9-H), 1.60–1.80 m (6H, 1-H, 2-H, 6-H, 7-H, 12-H), 1.92 m (1H, 6-H), 2.12 m (1H, 3-H), 2.25 m (1H, 11-H), 2.32 m (1H, 7-H), 2.45 m (1H, 11-H), 2.98 m (2H, 4′-H), 3.46 s (1H, 1′-H), 3.60 d.d (1H, 3′-H, *J* = 10.2, 2.5), 3.66 s (3′-$COOCH_3$), 3.57 s (OCH_3), 4.50 s (1H, 17-H), 4.92 s (1H, 17-H), 6.25 d (1H, 14-H, *J* = 1.6), 7.02 t and 7.04 t (2H, 6′-H, 7′-H, *J* = 8.2, 7.8), 7.18 d (1H, 5′-H, *J* = 8.2), 7.22 d (1H, 15-H, *J* = 1.6), 7.31 t.d (1H, 8′-H, *J* = 7.3, 1.1), 7.52 m (3H, 3″-H, 5″-H, 4″-H), 7.98 m (2H, 2″-H, 6″-H), 8.9 br.s (1H, NH, halfwidth 6.0). UV spectrum, λ_{max}, nm (log ε): 225 (4.26), 275 (3.63), 285 (3.42), 290 sh (3.12).

Methyl (1*R*,8*R*)- and (1*S*,8*R*)-17-acetoxy-16-(2-benzoyl-1,2,3,4-tetrahydro-β-carbolin-1-yl)-15,16-epoxy-13(16),14-labdadien-18-oates $C_{41}H_{42}N_2O_6$ (XII and XIII). Following the above procedure, from 1 mmol of aldehyde **IX** and 1.25 mmol of tryptamine we obtained 0.47 g (71%) of a mixture of compounds **XII** and **XIII** as an amorphous powder. Recrystallization from petroleum ether–acetone gave pure diastereoisomer **XII**, mp 126–128°C. $[\alpha]_{580}^{20}$ = +28° (*c* = 3.0, EtOH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.43 s (3H, $C^{20}H_3$), 0.90–1.05 m (2H, 1-H, 3-H), 1.14 s (3H, $C^{19}H_3$), 1.20 m (1H, 5-H), 1.35–1.55 m (3H, 2-H, 9-H, 11-H), 1.60–1.80 m (5H, 1-H, 2-H, 6-H, 7-H, 11-H), 2.02 s (3H, CH_3CO), 1.99 m (2H, 6-H, 8-H), 2.10 d.d.d (1H, 3-H, *J* = 14.8, 8.0, 3.4), 2.45 m (2H, 7-H, 12-H), 2.60 m (1H, 12-H, ^2J = 14.2), 2.90 m (2H, 4′-H), 3.40–3.60 m (2H, 3′-H), 3.61 s (3H, OCH_3), 3.70 s (1H, 1′-H), 3.86 m (2H, 17-H), 6.12 d (1H, 14-H, *J* = 1.6), 7.06 t.d (1H, 6′-H, *J* = 7.6, 1.6), 7.10 t.d (1H, 7′-H, *J* = 7.4, 1.3), 7.19 t.d (1H, 5′-H, *J* = 7.3, 1.1), 7.18 d (1H, 15-H, *J* = 1.6), 7.28 d (1H, 8′-H, *J* = 7.4), 7.52 m (3H, 3″-H, 4″-H, 5″-H), 7.92 m (2H, 2″-H, 6″-H), 9.20 br.s (NH, halfwidth 8.0).

Characteristic ^{1}H signals of isomer **XIII**: 0.56 s ($C^{20}H_3$), 1.19 s (3H, $C^{19}H_3$), 2.07 s (3H, CH_3CO), 3.50 s (1H, 1′-H), 3.66 s (3H, OCH_3), 3.98 m (2H,

17-H), 6.17 d (1H, 14-H), 7.22 d (15-H), 8.70 br.s (NH, halfwidth 8.2).

Methyl (1*S*,3*S*,8*R*)- and (1*R*,3*S*,8*R*)-17-acetoxy-16-(2-benzoyl-3-methoxycarbonyl-1,2,3,4-tetrahydro-β-carbolin-1-yl)-15,16-epoxy-13(16),14-labdadien-18-oates $C_{43}H_{50}N_2O_8$ (XIV and XV) were synthesized as described above from 0.42 g of aldehyde **IX** and 0.25 g (1.25 mmol) of L-tryptophan methyl ester. By column chromatography we isolated 0.56 g (78%) of a mixture of *cis* and *trans* isomers **XIV** and **XV**. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.49 s ($C^{20}H_3$) (**XIV**), 0.52 s ($C^{20}H_3$) (**XV**), 0.89 m (1H, 1-H), 0.95 m (1H, 3-H), 1.10 s and 1.13 s (3H, $C^{19}H_3$), 1.20–1.30 m (2H, 5-H, 11-H), 1.60–1.80 m (7H, 1-H, 2-H, 6-H, 7-H, 9-H, 11-H), 1.93 s and 1.97 s (3H, CH_3CO), 1.98 m (2H, 6-H, 8-H), 2.12 m (1H, 3-H), 2.25 m (1H, 7-H), 2.45 m (1H, 12-H), 2.79 m (1H, 12-H), 2.80–2.90 m (2H, 4′-H), 3.30–3.60 m (1H, 3′-H), 3.55 s (OCH_3), 3.69 s (3′-$COOCH_3$) (**XIV**), 3.63 s (OCH_3), 3.92 s (3′-$COOCH_3$) (**XIV**), 3.72 m (2H, 17-H) (**XV**), 3.70 s (1H, 1′-H) (**XV**), 3.88 m (2H, 17-H) (**XIV**), 3.90 s (1H, 1′-H) (**XIV**), 6.17 d (14-H, *J* = 1.6) (**XIV**), 6.22 d (14-H, *J* = 1.6) (**XV**), 7.00 t.d (1H, 6′-H, *J* = 7.6, 1.6), 7.11 t.d (1H, 5′-H, *J* = 7.3, 1.1), 7.18 t.d (1H, 7′-H, *J* = 7.4, 1.3), 7.22 d (1H, 15-H, *J* = 1.6), 7.30 d (1H, 8′-H, *J* = 7.4), 7.52 m (3H, 3″-H, 4″-H, 5″-H), 7.92 m (2H, 2″-H, 6″-H), 8.88 m and 9.40 m (1H, NH).

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