Chemistry of Natural Compounds and Bioorganic Chemistry

Study of alkaloids of the Siberian and Altai flora. 2.* Diterpene alkaloids from *Delphinium retropilosum*

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A number of known allied diterpene alkaloids were isolated from *Delphinium retropilosum* Sambuk, a species growing in the Altai Territory. The main one was methyllycaconitine, possessing valuable pharmacological properties.

Key words: diterpene alkaloids; *Delphinium*; methyllycaconitine.

Diterpene alkaloids (**1**—**8**) produced by the Ranunculaceae family are natural compounds of high practical value.[2] Thus alkaloids with an aconitane skeleton structure, *viz.*, methyllycaconitine (**1**) and lappaconitine (**9**), are the active principles of such pharmaceuticals as mellictine, known as curariform medicine, and allapinine, effective against arrhythmia.[3]

The interest in methyllycaconitine recently increased due to revelation of its high affinity and selectivity of binding with nicotinic acetylcholine neuroreceptors. Due to these remarkable properties, methyllycaconitine could be used in the diagnostics of Alzheimer disease; the search for active insecticides among derivatives of the alkaloid is also promising.[4—6]

It is known[7,8] that methyllycaconitine is produced by plants of the genus *Delphinium* (larkspur). Until recently, one of the species of larkspur widespread in Kazakhstan (*D. dictyocarpum* DC, aboveground part)[2,9] and cultivated forms of *D. elatum* L. (seeds)[10] were considered as the most available sources of this alkaloid. However, the study of the alkaloid composition of plants of the genus *Delphinium* growing in the regions of Siberia and Altai has not received much attention.

It has been recently determined[11] that roots of *D. retropilosum* contain methyllycaconitine **1** and elasine (**4**) as the major components (13 and 2%, respectively, of the total amount of alkaloids) and delretine (**5**) and licoctonine (**7**) as minor components. Alkaloids of the aboveground part are mainly represented by elasine **4** (up to 60% of total amount) and by traces of delretine **5**. It should be noted that the period of plant collection has not been mentioned in the paper cited; the plant was named *D. retropilosum* L. instead *D. retropilosum* Sambuk.

In order to find reliable sources of diterpene alkaloids under discussion we attempted to isolate them from woolly larkspur (*D. retropilosum* Sambuk) growing

* For Part 1, see Ref. 1.

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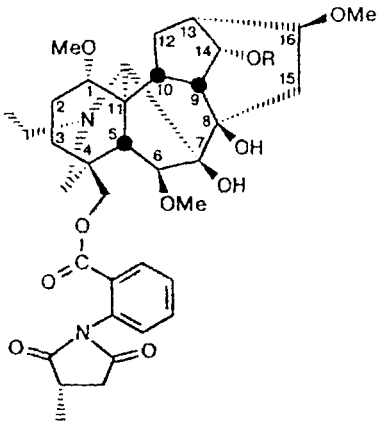

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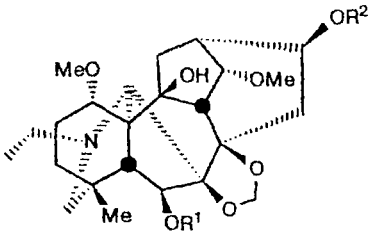

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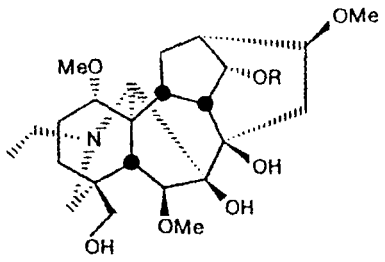

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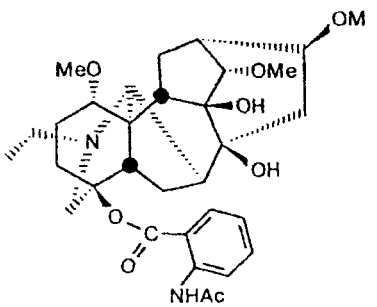

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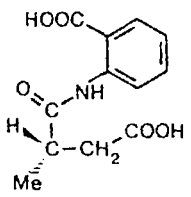
in Altai Territory. This plant forms a thicket of mighty perennial bushes in meadow areas at mountain streams, tributaries of Upper Ob' Basin.[12] Plant specimens were collected in August and September, 1997; the height of the aboveground part of the plants was up to 250 cm and the weight of the crude root system was up to 1.5 kg. The total yield of alkaloids from dried roots collected in September (fruiting stage) was 1.02%. Methyllycaconitine **1** and nudicauline (**2**) were isolated as the major components (54 and 28%, respectively, of the total amount of bases) and deacetylnudicauline (**3**) as a minor component (5%). Extraction of a dried aboveground part collected in August afforded a mixture of alkaloids in an overall yield of 0.27%. The major components of the mixture were elasine **4**, delretine **5**, and methyllycaconitine **1** (42, 19, and 13%, respectively, of the total amount of bases).

As was expected, hydrolysis of a mixture of alkaloids from the roots led to licoctonine **7** and delectinine **8** and to a mixture of *N*-(3-carboxy-2*S*-methylpropionyl)- (**10**) and *N*-(3*S*-carboxy-3-methylpropionyl)anthranilic acids (**11**) in the ratio of ~55 : 45. Alkaline hydrolysis of a mixture of alkaloids from the aboveground part gave licoctonine **7** and a novel deacetylelasine (**6**) and a mixture of acids (**10** : **11** ≈ 55 : 45). It is evident that deacetylelasine **6** is formed from elasine **4** and delretine **5** with 1α,5*R*,6β,9*S*,14α,16β-configuration.[13] Hence, deacetylelasine **6** has the same configuration.



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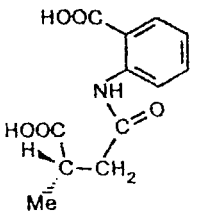

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There are literature data[5] about the formation of a mixture of acids **10** and **11** as a result of hydrolysis of methyllycaconitine **1**; however, spectral data of these compounds have not been reported. In the earlier papers,[9,10] structures of acids isolated after hydrolysis of **1** were not determined. We assigned non-overlapping signals of the isomers **10** and **11** in the ^{13}C NMR spectrum of their mixture. Thus the doublet signals at δ 39.8 and 36.3 were assigned to the C(2′) atom of compound **10** and the C(3′) atom of compound **11**, respectively, since the downfield shift effect of the amide group is larger than that of the carboxy group.[14] On the same basis, the first of two triplet signals at δ 38.0 and 41.9 was assigned to C(3′) of compound **10** and the second, to C(2′) of compound **11**.

Acid hydrolysis of a mixture of **10** and **11** (*cf.* Ref. 10) has led to the expected methylsuccinic (**12**) and anthranilic acids (**13**).

The set of alkaloids isolated (**1**—**8**) allows one to use HPLC (see Ref. 15) for identification of bases in roots

and the aboveground part of the plant, as well as those that form after alkaline hydrolysis of a mixture of bases. Alkaloids **1**—**5** were found in a mixture of bases isolated from both roots of the September collection and the aboveground part of the August collection. Alkaloids **6**—**8** were found among products obtained after alkaline hydrolysis of a total mixture of bases isolated from roots of the September collection as well as from the aboveground part of the August collection.

Thus, a series of known diterpene alkaloids including methyllycaconitine **1** were isolated from woolly larkspur (*Delphinium retropilosum* Sambuk), which grows in Altai Territory. After alkaline hydrolysis of a total mixture of alkaloids, a set of the corresponding bases including a novel deacetylelasine **6** were obtained.

Experimental

Analytical TLC was performed on glass plates with a layer of sorbent prepared as described below. A sorbent (100 g, *A*: neutral alumina 5/40 μm, Chemapol, Czechoslovakia; *B*: silica gel G, 10/40 μm, Sigma, USA) containing 1 wt. % of luminophore K-35 (TU 6-09-1458-76, Russia) was suspended in a solution of Na_2CO_3; the suspension was applied onto glass plates and dried. 100 g of sorbent *A* was mixed with 150 mL of 2% aq. Na_2CO_3, and 100 g of sorbent *B* was mixed with 300 mL of 1% aq. Na_2CO_3. Zones of alkaloids on dried plates were detected under UV light or following exposure to iodine vapor. Preparative TLC was performed on Al_2O_3 (50—250 μm, TU 6-09-3916-75, Russia) activated at 250 °C for 6 h and then deactivated to activity II by adding 3% of water[16] and mixed with luminophore K-35 (1 wt.% of alumina).

HPLC was performed with an analytical liquid chromatograph Milichrom-1 (Nauchpribor, Orlovskoe PO, Russia). Chromatographic conditions: a steel column 2×75 mm packed with Separon C18 or Lichrospher C18; operation pressure in the column 5.2 MPa; temperature ~20 °C; eluent, acetonitrile—0.1 *M* aq. tris(hydroxymethyl)aminomethane (1 : 1, v/v); 100 $\mu L \cdot min^{-1}$; UV-detector (220 nm); time constant 0.3 s. Samples with the concentration of compounds to be tested 3—5 $mg \cdot mL^{-1}$ were analyzed as acetonitrile solutions (4—6 μL). Retention times of compounds **6**, **8**, **4**, **3**, **7**, **5**, **2**, **1**, and **9** were 2.43, 2.59, 3.40, 4.26, 4.60, 5.29, 5.87, 6.27, and 8.60 min, respectively.

IR spectra were recorded with a Specord M-80 spectrometer; UV spectra were measured with a Specord UV-VIS spectrophotometer. Mass spectra (EI) were recorded with a Finnigan MAT 8200 spectrometer. Melting points were determined with a Kofler hot-plate apparatus.

Optical rotations were measured with a Polamat A polarimeter. ^1H and ^{13}C NMR spectra were recorded with a Bruker AC-200 instrument (^1H, 200.13 MHz; ^{13}C, 50.32 MHz) for solutions in $CDCl_3$ at 25 °C. Chemical shifts are given relative to the signal of the solvent (δ_H 7.24 and δ_C 76.90). Multiplicity of signals in ^{13}C NMR spectra was determined using standard JMOD and off-resonance proton irradiation techniques. Assignment of signals in the NMR spectra of compound **6** were made using different types of proton-proton, carbon-proton, and carbon-carbon correlations. 2D NMR spectra $^1H—^1H$ (COSY), $^{13}C—^1H$ (COSY 125 Hz, COLOC 7 Hz), and $^{13}C—^{13}C$ (INADEQUATE) were recorded with a Bruker DRX 500 instrument (^1H, 500.13 MHz; ^{13}C, 125.76 MHz) using standard Bruker programs.

Plants of *D. retropilosum* Sambuk were collected in meadow areas at mountain streams, tributaries of Chernyi Anui River near Lutaevo Settlement, Soloneshnenskii District, Altai Territory, in August and September, 1997. Roots with etiolated radical necks and the aboveground part were studied.

Isolation of alkaloids. Dried and crushed roots of the September collection placed into a calico bag were refluxed in acetone for 6 h (2 L of solvent per 1 kg of roots). The extraction was repeated 4 times. The combined acetone extract from 13.1 kg of roots was concentrated, and the residue (320 g) was extracted with benzene (1×500 mL, 4×50 mL) with stirring. The combined extract was kept for 16 h, then decanted to remove a resinous precipitate, and extracted with 10% aq. H_2SO_4 (1×930 mL, 2×250 mL). The combined acidic fraction was cooled (5 °C) and adjusted to pH 9 with 25% aq. ammonia. The precipitate was separated and extracted with benzene (4×100 mL). Benzene was evaporated, and the residual mixture of alkaloids was dried (3 Torr, 60—70 °C) to give an amorphous solid (133.2 g, 1.02 wt.% of dried roots).

In a similar way, a mixture of alkaloids (7.4 g, 0.27%) was isolated from the dried aboveground part of plants of the August collection (2.7 kg).

Separation of alkaloids. A mixture of alkaloids from roots (1.23 g) was subjected to preparative TLC on Al_2O_3 (nonfixed layer, thickness 2 mm). A solution of the mixture in 2-propanol (~0.3 $g \cdot mL^{-1}$) was applied onto plates (0.1—0.2 g per 10 cm of the starting line). The eluent was 2-propanol—ether, 1 : 9 (v/v). Nudicauline **2** (0.34 g, 28%), methyllycaconitine **1** (0.66 g, 54%), and deacetylnudicauline 3 (0.06 g, 5%) were eluted with a mixture of 2-propanol—ether (1 : 1, v/v) from chromatographic zones with R_f 0.8, 0.4, and 0.1, respectively.

Methyllycaconitine **1** (0.15 g) was isolated by preparative TLC from a mixture of alkaloids from the aboveground part (1.18 g). The residue after concentration of the eluate of a chromatographic zone with R_f 0.8 was subjected to repeated preparative TLC on Al_2O_3 (acetone—ether, 1 : 2, v/v). Delretine 5 (0.22 g) and elasine **4** (0.50 g, amorphous solid) were eluted with acetone from zones with R_f 0.6 and R_f 0.2, respectively. Thus, compounds **1**, **4**, and **5** were isolated from a mixture of alkaloids from the aboveground part in 13, 42, and 19% yields, respectively.

Alkaline hydrolysis of a mixture of alkaloids from roots. A mixture of alkaloids (12.63 g) from roots was added to a solution of KOH (4.04 g) in methanol (81 mL), and the resultant mixture was refluxed for 45 min. From the resulting solution, 65 mL of the solvent was distilled off (bath temperature, 85—87 °C), and the residue was concentrated *in vacuo* (3 Torr). Chloroform (100 mL) and water (20 mL) were added to the residue with careful stirring (to avoid formation of emulsion). The aqueous layer was separated and extracted with chloroform (2×10 mL). Combined organic fractions were dried ($MgSO_4$), and the solvent was evaporated under reduced pressure to give a residual mixture of bases as an amorphous solid (8.65 g).

A portion of the residue (1.30 g) was dissolved in 2-propanol and subjected to preparative TLC on Al_2O_3 (2-propanol—ether, 1 : 4, v/v). Delectine **8** (0.34 g) and licoctonine **7** (0.62 g) were isolated from zones with R_f 0.17 and 0.56, respectively.

To isolate pure licoctonine monohydrate, the remaining mixture of bases (7.35 g) was dissolved in ether (10 mL) and water (1 mL) was added to the solution. The mixture was shaken vigorously and then kept for 16 h. A microcrystalline precipitate (6.15 g) was filtered off and recrystallized from boiling 70% ethanol (15 mL) to give licoctonine monohydrate **7** (2.38 g) containing traces of delectinine **8** (according to analytical TLC data).

The aqueous layer after extraction with chloroform was adjusted to pH 4 with 10% H_2SO_4. The precipitated oil solidified after 1 h. The product was filtered off, dried, and treated with boiling acetone. The hot mixture was filtered to remove the admixture of water-soluble salts, and the filtrate was concentrated. The solid residue was suspended in chloroform, then filtered off, and dried to give a mixture of acids **10** and **11** (2.95 g), m.p. 161—163 °C (*cf.* Ref. 16), $[\alpha]^{20}_{578}$ −1.6° (*c* 3.5, EtOH). According to earlier data,[10] hydrolysis of methyllycaconitine **1** with $[\alpha]^{20}_{D}$ +49.1° (*c* 2, EtOH) led to acids **10** and **11** with $[\alpha]^{24}_{D}$ −7.0° (*c* 2, EtOH).

Alkaline hydrolysis of a mixture of alkaloids from the aboveground part was carried out as described above. Treatment of a mixture of alkaloids (3.25 g) gave a mixture of bases (2.90 g, amorphous solid). A portion of the residue (1.30 g) was subjected to preparative TLC on Al_2O_3 as described above for the separation of a similar mixture of bases from roots. Licoctonine **7** (0.21 g) and deacetylelasine **6** (0.69 g) were isolated from chromatographic zones with R_f 0.56 and 0.43, respectively. A mixture of acids **10** and **11** (0.17 g) was isolated from the aqueous layer after extraction with chloroform followed by treatment with dilute H_2SO_4 to pH 4.

Acid hydrolysis of a mixture of acids 10 and 11. A mixture of acids **10** and **11** (1.56 g) in 10% HCl (20 mL) was refluxed for 1.5 h (*cf.* Ref. 10). The resulting solution was concentrated under reduced pressure at 80 °C, and the residue was dried (3 Torr, 80 °C). The crystalline residue was extracted with ether (6×5 mL). Methylsuccinic acid **12** (0.74 g, 90%) was isolated from the extract, m.p. 113—114 °C, $[\alpha]^{20}_{578}$ −2.0° (*c* 3, water), lit. data[10]: m.p. 114 °C, $[\alpha]^{23}_{D}$ −8.8° (*c* 2, water). ^{1}H NMR data agree with those reported earlier.[17] The residue, insoluble in ether, gave anthranilic acid **13** (0.77 g, 90%) after recrystallization from water, m.p. 146—147 °C, identified by comparison with an authentic sample.

Characteristics of the obtained specimens. Methyllycaconitine 1,[5,18] amorphous solid.[10] ^{1}H and ^{13}C NMR data are identical with those reported in Ref. 19. $[\alpha]^{20}_{578}$ +48.0° (*c* 4.4, EtOH). Lit. data: $[\alpha]^{20}_{D}$ +48.1° (*c* 2, EtOH),[18] +49.1° (EtOH).[19]

Nudicauline 2, amorphous solid.[20] ^{1}H and ^{13}C NMR data are identical with those reported in Ref. 20 (cf. Ref. 7b, p. 527). $[\alpha]^{20}_{578}$ +46.9° (*c* 5.4, $CHCl_3$). Lit. data[20]: $[\alpha]^{20}_{D}$ +47.0° ($CHCl_3$).

Deacetylnudicauline 3, amorphous solid.[21] ^{1}H NMR data are identical with those reported in Ref. 20.

Elasine 4, amorphous solid[13] or crystals with m.p. 116—118 °C (hexane).[11] ^{1}H and ^{13}C NMR data are identical with those reported in Refs. 11, 13. $[\alpha]^{20}_{578}$ −61.0° (*c* 1.9, $CHCl_3$). Lit. data[13]: $[\alpha]^{20}_{D}$ −55.7° (*c* 0.51, $CHCl_3$).

Delretine 5, m.p. 216—219 °C (hexane). Lit. data: m.p. 219.5—221.5 °C[13]; 216—219 °C (hexane).[11] ^{1}H and ^{13}C NMR data are identical with those reported in Refs. 11, 13. $[\alpha]^{20}_{578}$ −17.8° (*c* 1.8, $CHCl_3$).

Deacetylelasine 6 (20-ethyl-1,14-dimethoxy-4-methyl-7,8-methylenedioxy-1α,5*R*,6β,9*S*,14α,16β-aconitane-6,10,16-triol), m.p. 115—117 °C ($CHCl_3$), $[\alpha]^{20}_{578}$ −40.8° (*c* 2.6, $CHCl_3$). ^{1}H NMR spectrum (500.13 MHz, $CDCl_3$), δ: 0.89 (s, 3 H, $H_3C(18)$); 0.99 (t, 3 H, $NCH_2C\underline{H}_3$, J = 7 Hz); 1.11 and 1.52 (both ddd, 2 H, $H_2C(3)$, J = 13 Hz, J = 5 Hz, and J = 2.5 Hz); 1.45 (s, 1 H, HC(5), half-width 4 Hz); 1.67 (ddd, 1 H, J = 16.5 Hz, J = 8.5 Hz, and J = 1 Hz) and 2.55 (dd, 1 H, J = 16.5 Hz, and J = 8.5 Hz) ($H_2C(15)$); 1.67 (dd, 1 H, J = 16.5 Hz, and J = 2.5 Hz) and 2.49 (d, 1 H, J = 16.5 Hz) ($H_2C(12)$); 1.95—2.01 and 2.06—2.14 (m, 2 H, $H_2C(2)$); 2.23 (dd, 1 H, J = 11.5 Hz, and J = 2.5 Hz) and 2.62 (d, 1 H, J = 11.5 Hz) ($H_2C(19)$); 2.43 (td, 1 H, HC(13), J = 5 Hz, and J = 2.5 Hz); 2.59 and 2.71 (both dq, 2 H, $NC\underline{H}_2CH_3$, J = 13 Hz, and J = 7 Hz); 3.14 (d, 1 H, HC(17), J = 2.5 Hz); 3.19 (s, 3 H, $O(1)CH_3$); 3.42 (s, 3 H, $O(14)CH_3$); 3.55—3.60 (m, 3 H, HC(1), HC(9), and HC(16)); 4.19 (s, 1 H, HC(6), half-width 2.5 Hz); 4.24 (td, 1 H, HC(14), J = 5 Hz, and J = 1 Hz); 5.00 and 5.11 (both s, 1 H, OCH_2O); 2.57, 3.30, and 3.78 (all br. s, 3×1 H, 3 OH, the signals were assigned by analysis of their shifts after addition of CD_3OD). ^{13}C NMR spectrum ($CDCl_3$, 125.76 MHz), δ: 13.78 (q, $NCH_2\underline{C}H_3$); 25.3 (q, C(18)); 26.2 (t, C(2)); 33.7 (s, C(4)); 36.5 (t, C(3)); 36.9 and 36.7 (both t, C(12), C(15)); 39.8 (d, C(13)); 48.1 (d, C(9)); 50.3 (t, $N\underline{C}H_2CH_3$); 51.0 (d, C(5)); 55.2 (s, C(11)); 55.4 (q, $O(1)CH_3$); 57.0 (t, C(19)); 58.1 (q, $O(14)CH_3$); 63.5 (d, C(17)); 71.5 (d, C(16)); 76.9 (d, C(1)); 79.9 (d, C(6)); 80.9 (s, C(8) or C(10)); 82.2 (d, C(14)); 82.7 (s, C(10) or C(8)); 93.0 (t, OCH_2O); 93.1 (s, C(7)). IR spectrum (CCl_4), ν/cm^{-1}: 975, 1050, 1060, 1088, 1100, 1125, 1205, 1455, 2887, 2937, 2975, 3400—3550 (broad band). UV spectrum (EtOH), λ_{max}/nm (lgε): smooth decrease in absorption from 208 (3.23) to 250 (2.70). Mass spectrum, found: mol. weight 451.2581. $C_{24}H_{37}NO_7$. Calculated: mol. weight 451.2570.

Licoctonine 7, amorphous solid.[10] ^{1}H and ^{13}C NMR data are identical with those reported in Refs. 4, 6a, and 22. Licoctonine monohydrate, crystals with 138—143 °C (dec.), $[\alpha]^{20}_{578}$ +52.5° (*c* 3.9, EtOH). Lit. data[10]: m.p. 143 °C (dec.), $[\alpha]^{20}_{D}$ +53.2° (*c* 2, EtOH).

Delectinine 8, amorphous solid[20] or crystals with m.p. 167—169 °C (acetone—hexane).[23] ^{1}H and ^{13}C NMR data for obtained amorphous delectinine **8** are identical with those reported in Refs. 23 and 24. $[\alpha]^{20}_{578}$ +41.6° (*c* 1.5, $CHCl_3$). Lit. data[23]: $[\alpha]^{20}_{D}$ +42.0° (*c* 0.67, $CHCl_3$).

Mixture of 2-[(2*S*)-3-carboxy-2-methylpropionyl]aminobenzoic (10) and 2-[(3*S*)-3-carboxy-3-methylpropionyl]aminobenzoic acid (11). ^{1}H NMR spectrum (200.13 MHz, acetone-d_6), δ: 1.25 and 1.29 (both d, 3 H, CH_3 groups of isomers, J = 7 Hz); 2.4—2.6 (m, 2 H) and 2.8—3.0 (m, 4 H), CH—CH_2 groups of both isomers; 7.11 (td, 2 H, HC(5), J = 7 Hz, and J = 1 Hz); 7.56 (td, 2 H, HC(4), J = 1 Hz); 8.08 (m, 2 H, HC(6)); 8.68 (dd, 1 H, HC(3), J = 8 Hz, and J = 1 Hz); 8.70 (dd, 1 H, HC(3), J = 8 Hz, and J = 1 Hz), signals for the protons of C_6H_4 groups of both isomers. ^{13}C NMR spectrum of the same solution (50.32 MHz), δ: isomer **10**: 18.0 (q, (2′-CH_3); 38.0 (t, C(3′)); 39.8 (d, C(2′)); isomer **11**: 17.3 (q, (3′-CH_3); 36.3 (d, C(3′)); 41.9 (t, C(2′)); overlapping signals of isomers **10** and **11**: 116.0 (s, C(1)); 120.7, 123.1, 132.1, 135.1 (all d, C-3—C-6); 142.8 and 143.0 (both s, C(2)); and signals for the C atoms of the C=O groups of both isomers: 170.4, 170.5, 170.7, 173.4, 174.8, 176.9 (all s). The ratio of acids **10** : **11** ≈ 55 : 45 (found from the ratio of intensity of the 2′-CH_3 signal of isomer **10** to intensity of the 3′-CH_3 signal of isomer **11** in ^{13}C NMR spectrum under conditions of the off-resonance decoupling experiment). Signals in ^{1}H and ^{13}C NMR spectra were assigned using spectral data of an analog, licoctoninic acid.[4]

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