Study of alkaloids of the Siberian and Altai flora
13.* Synthesis of alkynyllappaconitines

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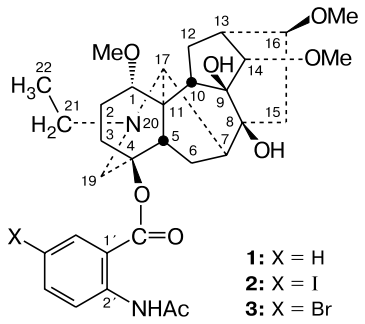
The Sonogashira coupling of 5´-iodolappaconitine with prop-2-yn-1-ol, 2-methylbut-3-yn-2-ol, phenylacetylene, and 5-ethynylpyrimidine gave new lappaconitine derivatives containing an alkynyl fragment.

Key words: diterpenes, alkaloids, lappaconitine, iodoarenes, alkynes, Sonogashira reaction, cross-coupling, alkynylation.

A diterpene alkaloid with the aconitane skeleton, lappaconitine (**1**), is the active substance of the drug allapinin of antiarrhythmic action.[2] Modification of the lappaconitine molecule by introducing a bromine atom into the aromatic fragment gave a drug with a higher antiarhythmic activity.[3] In order to extend the range of functional derivatives of lappaconitine for bioscreening, in this work we synthesized its alkynyl-substituted derivatives.

In view of our most recent results on the synthesis and modification of 5´-iodolappaconitine, *viz.*, 4β-[2-(*N*-acetylamino)-5-iodobenzoyloxy]-1α,14α,16β-trimethoxy-20-ethylaconitane-8,9-diol (**2**), and its brominated analog **3**,[1] we considered the Sonogashira reaction (palladium-catalyzed cross-coupling of terminal alkynes with aryl halides) to be a convenient method for the introduction of alkynyl group into the lappaconitine molecule.[4—6] It is noteworthy that acetylene derivatives of various structural types, including nitrogen-containing compounds are considered as efficient anticancer agents.[7—10]

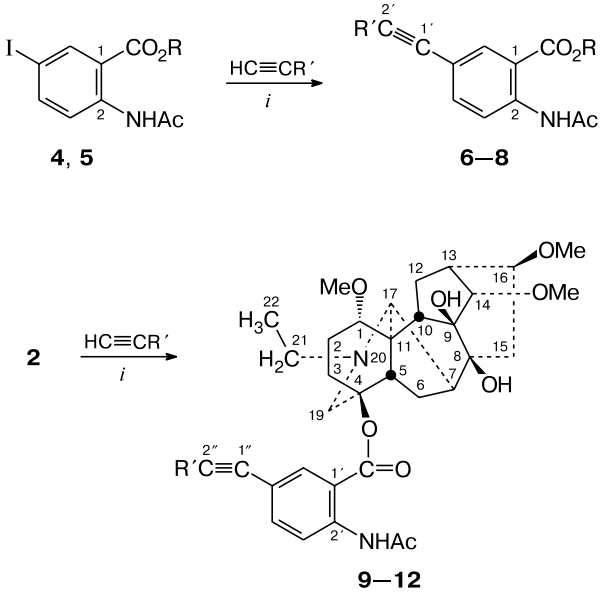


1: X = H
2: X = I
3: X = Br

We optimized the cross-coupling conditions by studying the reactions of alkynes with model compounds, namely, methyl and ethyl 2-(*N*-acetylamino)-5-iodobenzoates (**4** and **5**, respectively), and then carried out this reaction for 5´-iodolappaconitine (**2**).

Model aryl iodides **4** and **5** were found to smoothly react with prop-2-yn-1-ol, 2-methylbut-3-yn-2-ol,

Scheme 1



i. $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, C_6H_6.

R = Me (**4**, **6**, **7**), Et (**5**, **8**); R´ = CH_2OH (**6**, **9**), CMe_2OH (**7**, **10**), Ph (**8**, **11**), 5-pyrimidyl (**12**)

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phenylacetylene, and 5-ethynylpyrimidine in benzene in the presence of catalytic amounts of $(Ph_3P)_2PdCl_2$, CuI, and triethylamine as the base (Scheme 1). This gave arylacetylenes **6—8** (yields 63—82%). The extension of this procedure to 5′-iodolappaconitine resulted in modified alkaloids **9—12** (yields 67—76%).

Note that the use of 5′-bromolappaconitine (**3**) instead of its iodine-containing analog **2** proved inefficient (*cf.* Ref. 5). Thus the reaction of aryl bromide **3** with phenylacetylene results in an incomplete conversion (~33%) and the target product **11** is difficult to separate from the unreacted starting compound **3**.

To conclude, on the basis of the Sonogashira reaction we prepared a number of alkynyl derivatives of lappaconitine (**1**), which may be of interest as pharmacologically active compounds.

Experimental

"Pure" grade I_2, CuI, and PPh_3; the BAU activated carbon (Russia), commercial prop-2-yn-1-ol (Merck), 2-methylbut-3-yn-2-ol (Fluka), and phenylacetylene (Aldrich) were used. 5-Ethynylpyrimidine,[11] $Pd(PPh_3)_2Cl_2$,[12] methyl 2-(*N*-acetylamino)-5-iodobenzoate (**4**), 5′-iodolappaconitine (**2**), and 5′-bromolappaconitine (**3**)[1] were prepared by reported procedures. Analytical TLC was carried out on 7.5×2.5 cm glass plates with a sorbent layer (0.04 g cm^{-2}), namely, type G silica gel with gypsum (10—40 μm (Sigma)) containing 1 wt.% of the luminophore K-35 (TU 6-09-458-76, Russia) and 1% Na_2CO_3, which were prepared as described previously;[13] the mixture components were visualized under UV light and by iodine vapor. Iodoaromatic compounds **2** and **4** were visualized by exposing the plate to UV light for 5 min, which resulted in brown spots. Preparative chromatography was carried out using Al_2O_3 (50—150 μm, TU 6-09-3916-75, Russia), Brockman activity II, and silica gel (35—70 μm, Acros Organics). The separation and elution were visually monitored in the UV light. For this purpose, the sorbents were mixed with the luminophore K-35 (1 wt.%). Melting points were determined on a Kofler stage. IR spectra were measured on a Vector 22 spectrometer in KBr pellets; UV spectra were recorded on a Specord UV—Vis spectrophotometer in ethanol ($c = 10^{-4}$ mol L^{-1}). High resolution (HR) mass spectra were measured on a Finnigan MAT instrument, design 8200 (EI, 70 eV). Elemental analysis was carried out on a CHN-analyzer (model 1106, Carlo Erba, Italy). NMR spectra were recorded on Bruker AM-400 (400.13 (^{1}H) and 100.61 MHz (^{13}C)) and Bruker AV-300 (300.13 (^{1}H) and 75.47 MHz (^{13}C)) instruments for 10% solutions in $CDCl_3$ at 25 °C. The chemical shifts were referred to the residual signals of the solvent ($CHCl_3$): δ_H 7.24 and δ_C 76.90. The signal multiplicity in the ^{13}C NMR spectra was determined in the *J*-modulation mode (JMOD) and with proton off-resonance. The carbon signals of the aromatic rings in the ^{13}C NMR spectra of compounds **9** and **10** were assigned by the additive scheme[14] considering the chemical shifts of the respective carbon atoms of lappaconitine (**1**)[15] and methyl 2-(*N*-acetylamino)benzoate[16] and the increments of the —C≡C—CH_2OH group calculated using the carbon chemical shifts of the aromatic rings in benzene (δ_C 128.7) and 1-phenylprop-1-yn-3-ol[17] (δ_C 122.6 (C(1)), 131.6 (C(2), C(6)), 128.2 (C(3), C(5)) and 128.2 (C(4))). The ^{1}H NMR signals and the ^{13}C NMR signals for the polycyclic core of compounds **9—12** were assigned by comparison with the signals in the spectra of lappaconitine (**1**)[15] as the parent compound. Due to the complexity of assignment of all signals in the ^{1}H NMR spectra, only characteristic signals are given for these compounds.

Ethyl 2-(*N*-acetylamino)-5-iodobenzoate (5). Iodine (1.02 g, 4 mmol) and HIO_3 (0.44 g, 2.5 mmol) were added to a stirred mixture of ethyl 2-(*N*-acetylamino)benzoate (2.07 g, 10 mmol) in 30% H_2SO_4 (1 mL) and AcOH (3 mL). The mixture was heated to 80 °C, kept under these conditions until the iodine color disappeared (4 h), cooled, neutralized with a saturated solution of $NaHCO_3$, and extracted with chloroform (3×15 mL). The extract was dried ($MgSO_4$), filtered through an Al_2O_3 layer (2×1 cm), and concentrated. The residue (3.1 g) was recrystallized from hexane to give 2.6 g (78%) of iodide **5**, m.p. 144—146 °C. HR MS, found: *m/z* 332.98627 $[M]^+$. $C_{11}H_{12}INO_3$. Calculated: M = 332.98637. ^{1}H NMR (400.13 MHz), δ: 1.44 (t, 3 H, C$\underline{H}_3$CH$_2$, *J* = 7 Hz); 2.24 (s, 3 H, MeCO); 4.40 (q, 2 H, MeC$\underline{H}_2$O, *J* = 7 Hz); 7.81 (dd, 1 H, H(4), *J* = 9 Hz, *J* = 2 Hz); 8.33 (d, 1 H, H(6), *J* = 2 Hz); 8.52 (d, 1 H, H(3), *J* = 9 Hz); 11.20 (br.s, 1 H, NH). IR (KBr), ν/cm^{-1}: 791, 960, 1096, 1236, 1258, 1295, 1367, 1446, 1519, 1580; 1679, 1701 (C=O); 2901, 2935; 3352, 3437 (NH). UV (EtOH), λ_{max}/nm (logε): 230 (4.43), 262 (4.25), 323 (3.64).

Methyl 2-(*N*-acetylamino)-5-(3-hydroxyprop-1-ynyl)benzoate (6) was prepared by a modified procedure.[18] Methyl 2-(*N*-acetylamino)-5-iodobenzoate (**4**) (1.60 g, 5 mmol), CuI (19 mg, 0.10 mmol, 2 mol.%), $Pd(PPh_3)_2Cl_2$ (13 mg, 0.02 mmol, 0.4 mol.%), and PPh_3 (13 mg, 0.05 mmol, 1 mol.%) were charged under argon into a reaction vessel equipped with a reflux condenser, and benzene (25 mL) was added. Then triethylamine (4 mL, 2.90 g, 29 mmol) and a solution of prop-2-yn-1-ol (0.6 mL, 582 mg, 10.4 mmol) in benzene (15 mL) were successively added with stirring. The mixture was heated for 5 h at 60—65 °C in an argon flow, cooled to 25 °C, and left for 16 h without stirring. The solution was decanted off from the resinous precipitate, the precipitate was washed with benzene (3×3 mL), and the combined solutions were concentrated *in vacuo*. The residue was kept at 60 °C (3 Torr), dissolved in chloroform (10 mL), and subjected to column chromatography (quartz column) on silica gel (a 20×2 cm sorbent layer) containing 1 wt.% luminophore K-35 (chloroform as the eluent). The fraction with blue fluorescence on the sorbent under UV light was collected. Evaporation of the solvent gave 1.01 g (82%) of the crystals of compound **6**, m.p. 142—143 °C (from MeOH). HR MS, found: *m/z* 247.08381 $[M]^+$. $C_{13}H_{13}NO_4$. Calculated: M = 247.08445. ^{1}H NMR (300.13 MHz), δ: 2.18 (s, 3 H, MeCO); 3.11 (br.s, 1 H, OH); 3.85 (s, 3 H, OMe); 4.42 (s, 2 H, C(3′)H_2); 7.45 (dd, 1 H, H(4), *J* = 9 Hz, *J* = 2 Hz); 7.99 (d, 1 H, H(6), *J* = 2 Hz); 8.56 (d, 1 H, H(3), *J* = 9 Hz); 11.02 (br.s, 1 H, NH). ^{13}C NMR (75.47 MHz), δ: 25.2 ($\underline{C}H_3CO$); 51.0 (C(3′)); 52.3 (OMe); 83.8, 87.5 (C(1′), C(2′)); 114.5 (C(1)); 116.7 (C(5)); 119.9 (C(3)); 134.0 (C(6)); 137.2 (C(4)); 140.9 (C(2)); 167.9 (COO); 169.2 (Me$\underline{C}$O). IR (KBr), ν/cm^{-1}: 790, 840, 908, 957, 997, 1040, 1090, 1241, 1295, 1324, 1371, 1404, 1440, 1515, 1592; 1681, 1698 (C=O); 2220 (C≡C); 2853, 2935, 2955; 3269, 3301, 3434 (NH, OH). UV (EtOH), λ_{max}/nm (logε): 234 (4.35), 272 (4.25), 280 (4.25), 325 (3.59).

Methyl 2-(*N*-acetylamino)-5-(3-hydroxy-3-methylbut-1-ynyl)benzoate (7) was prepared in a similar way from methyl 2-(*N*-acetylamino)-5-iodobenzoate (**4**) (1.60 g, 5 mmol), 2-methylbut-3-yn-2-ol (0.90 mL, 0.78 g, 9.2 mmol), CuI (11 mg), $Pd(PPh_3)_2Cl_2$ (21 mg), PPh_3 (20 mg), triethylamine (4.0 mL), and benzene (40 mL). The reaction mixture was heated for 5 h at 60—65 °C in an argon flow (TLC monitoring ($CHCl_3$)). The precipitate was filtered off, washed with benzene (3×2 mL), and dried to give 1.01 g (88%) of triethylammonium iodide, m.p. 180—181 °C. The combined benzene solutions were concentrated *in vacuo* and the resinous residue was kept at 60 °C (3 Torr) and dissolved in a chloroform—ethyl acetate (1 : 1 v/v) mixture (10 mL), and the solution was subjected to column chromatography on Al_2O_3 (quartz column, a 20×2 cm sorbent layer) containing 1 wt.% luminophore K-35 (AcOEt as the eluent). The fraction with blue fluorescence on the sorbent under UV light was collected to give 1.03 g (75%) of crystalline compound **7**, m.p. 135—136 °C. HR MS, found: *m/z* 275.11531 $[M]^+$. $C_{15}H_{17}NO_4$. Calculated: M = 275.11575. ^{1}H NMR (400.13 MHz), δ: 1.56 (s, 6 H, Me_2C); 2.18 (s, 3 H, MeCO); 2.74 (br.s, 1 H, OH); 3.87 (s, 3 H, OMe); 7.46 (dd, 1 H, H(4), J = 9 Hz, J = 2 Hz); 8.00 (d, 1 H, H(6), J = 2 Hz); 8.59 (d, 1 H, H(3), J = 9 Hz); 11.02 (br.s, 1 H, NH). ^{13}C NMR (75.47 MHz), δ: 25.3 ($\underline{C}H_3CO$); 31.3 (($\underline{C}H_3)_2C$); 52.3 (OMe); 65.2 (C(3′)); 80.6, 93.8 (C(1′), C(2′)); 114.4 (C(1)); 116.8 (C(5)); 119.9 (C(3)); 133.9 (C(6)); 137.2 (C(4)); 140.9 (C(2)); 167.9 (COO); 169.2 ($CH_3\underline{C}O$). IR (KBr), ν/cm^{-1}: 568, 792, 845, 962, 1090, 1129, 1153, 1176, 1197, 1238, 1303, 1321, 1383, 1397, 1436, 1527, 1597; 1673, 1687 (C=O); 2228 (C≡C); 2952, 2988; 3262, 3345, 3400 (NH, OH). UV (EtOH), λ_{max}/nm (logε): 234 (4.37), 272 (4.28), 280 (4.27), 326 (3.65).

Ethyl 2-(*N*-acetylamino)-5-(phenylethynyl)benzoate (8). A mixture of ethyl 2-(*N*-acetylamino)-5-iodobenzoate (**5**) (1.00 g, 3 mmol), CuI (7 mg, 0.04 mmol, 1.3 mol.%), $Pd(PPh_3)_2Cl_2$ (15 mg, 0.02 mmol, 0.7 mol.%), and phenylacetylene (0.40 g, 3.9 mmol) in triethylamine (2 mL) and benzene (20 mL) was stirred for 2 h at 65 °C in an argon flow. The mixture was cooled, filtered through a silica gel layer (1.5×1 cm) and washed with benzene (30 mL), and the filtrate was concentrated *in vacuo*. Activated carbon (~100 mg) and benzene (10 mL) were added to the residue (0.9 g), the mixture was refluxed until the organic product dissolved, the hot suspension was filtered, and the filtrate was concentrated until crystals started to appear. Cooling gave 0.58 g (63%) of compound **8**, m.p. 152—152.5 °C. HR MS, found: *m/z* 307.11730 $[M]^+$. $C_{19}H_{17}NO_3$. Calculated: M = 307.11714. ^{1}H NMR (300.13 MHz), δ: 1.42 (t, $C\underline{H}_3CH_2$, J = 7 Hz); 2.22 (s, 3 H, MeCO); 4.38 (q, 2 H, $MeC\underline{H}_2O$, J = 7 Hz); 7.32—7.35 (m, 3 H, o-H_{Ph}, p-H_{Ph}); 7.50—7.55 (m, 2 H, m-H_{Ph}); 7.65 (dd, 1 H, H(4), J = 9 Hz, J = 2 Hz); 8.18 (d, 1 H, H(6), J = 2 Hz); 8.70 (d, 1 H, H(3), J = 9 Hz); 11.12 (br.s, 1 H, NH). ^{13}C NMR (75.47 MHz), δ: 14.3 ($CH_2\underline{C}H_3$); 25.7 ($\underline{C}H_3CO$); 61.7 ($\underline{C}H_2Me$); 88.3, 89.3 (C(1)′, C(2′)); 115.1 (C(1)); 117.3 (C(5)); 120.3 (C(3)); 123.1 (*ipso*-C_{Ph}); 127.5 (p-C_{Ph}); 128.4 (o-C_{Ph}); 134.2 (C(6)); 137.3 (C(4), m-C_{Ph}); 141.3 (C(2)); 167.8 (COO); 169.1 ($CH_3\underline{C}O$). IR (KBr), ν/cm^{-1}: 754, 792, 855, 1024, 1083, 1236, 1294, 1326, 1369, 1401, 1477, 1515, 1588; 1683, 1703 (C=O); 2206 (C≡C); 2905, 2981; 3251, 3307, 3440 (NH). UV (EtOH), λ_{max}/nm (logε): 200 (1.63), 224 (1.53), 245 (1.17), 296 (1.96).

4β-[2-(*N*-Acetylamino)-5-(3-hydroxyprop-1-ynyl)benzoyloxy]-1α,14α,16β-trimethoxy-20-ethylaconitane-8,9-diol (9). Benzene (2 mL) was added in an argon flow to a mixture of 5′-iodolappaconitine (**2**) (355 mg, 0.500 mmol), CuI (2 mg, 0.01 mmol, 2 mol.%), $Pd(PPh_3)_2Cl_2$ (7 mg, 0.01 mmol, 2 mol.%), and PPh_3 (7 mg, 0.03 mmol, 0.6 mol.%). Then triethylamine (0.4 mL, 290 mg, 2.9 mmol) and a solution of prop-2-yn-1-ol (0.1 mL, 97 mg, 1.7 mmol) in benzene (2 mL) were added successively with stirring. The mixture was heated for 4 h at 60—65 °C in an argon flow, cooled to 25 °C, and concentrated *in vacuo*. The residue was dried at 60 °C (3 Torr), and chloroform (10 mL) and water (5 mL) were added with stirring. The organic layer was separated and the aqueous layer was extracted with chloroform (2×10 mL). The combined organic solutions were extracted with 10% H_2SO_4 (3×7 mL). A 25% solution of ammonia was added with stirring to the acidic aqueous extract to pH ~8 and the precipitate formed was extracted with chloroform (3×15 mL). The extract was dried with $MgSO_4$, concentrated to 3 mL, and subjected to preparative TLC with a loose Al_2O_3 layer containing 1 wt.% luminophore K-35 (2 mm thick sorbent layer, 60 cm long starting band, ether as the eluent). The sorbent band with blue fluorescence under UV radiation was collected. The product was eluted from the sorbent with methanol. After removal of methanol, the residue was triturated with ether (5 mL) to give 230 mg (72%) of crystalline compound **9**, m.p. 178—180 °C. Found (%): C, 65.42; H, 7.38; N, 4.09. $C_{35}H_{46}N_2O_9$. Calculated (%): C, 65.81; H, 7.26; N, 4.39. ^{1}H NMR (400.13 MHz), δ: 1.05 (t, 3 H, $C(22)H_3$, J = 7 Hz); 1.48 (dd, 1 H, $H_b(6)$, J = 15 Hz, J = 8 Hz); 1.76 (m, 1 H, $H_b(3)$); 2.15 (s, 3 H, COMe); 2.93 (s, 1 H, H(17)); 3.09 (dd, 1 H, H(1), J = 10 Hz, J = 7 Hz); 3.21, 3.24, 3.34 (all s, 3 H each, C(1)OMe, C(16)OMe, C(14)OMe, respectively); 3.37 (d, 1 H, H(14), J = 5 Hz); 3.46 (d, 1 H, $H_a(19)$, J = 11 Hz); 4.41 (s, 2 H, $C\underline{H}_2OH$); 7.43 (dd, 1 H, H (4′), J = 9 Hz, J = 2 Hz); 7.87 (d, 1 H, H(6′), J = 2 Hz); 8.55 (d, 1 H, H(3′), J = 9 Hz); 11.20 (s, 1 H, NH). ^{13}C NMR (100.61 MHz), δ: 13.3 (C(22)); 23.9 (C(6)); 25.3 ($\underline{C}H_3CO$); 26.0 (C(12)); 26.6 (C(2)); 31.6 (C(3)); 36.1 (C(13)); 44.3 (C(15)); 47.5 (C(7)); 48.1 (C(5)); 48.7 (C(21)); 49.7 (C(10)); 50.8 (C(11)); 51.0 (C(3″)); 55.2 (C(19)); 55.9 (16-OMe); 56.2 (1-OMe); 57.7 (14-OMe); 61.3 (C(17)); 75.3 (C(8)); 78.4 (C(9)); 82.8 (C(16)); 83.8 (C(1)); 83.9 (C(2″)); 85.1 (C(4)); 87.4 (C(1″)); 89.9 (C(14)); 115.5 (C(1)′); 116.6 (C(5′)); 119.9 (C(3′)); 134.0 (C(6′)); 137.1 (C(4′)); 141.2 (C(2′)); 166.5 (COO); 168.9 ($Me\underline{C}O$). IR (KBr), ν/cm^{-1}: 793, 945, 966, 993, 1035, 1088, 1116, 1146, 1232, 1293, 1323, 1382, 1448, 1510, 1587; 1685, 1705 (C=O); 2230 (C≡C); 2816, 2928; 3317, 3464 (NH, OH). UV (EtOH), λ_{max}/nm (logε): 232 (4.35), 273 (4.20), 281 (4.20), 326 (3.60).

4β-[2-(*N*-Acetylamino)-5-(3-hydroxy-3-methylbut-1-ynyl)benzoyloxy]-1α,14α,16β-trimethoxy-20-ethylaconitane-8,9-diol (10) was prepared similarly to compound **9** from 5′-iodolappaconitine (**2**) (711 mg, 1 mmol), 2-methylbut-3-yn-2-ol (0.20 mL, 168 mg, 2 mmol), CuI (2 mg), $Pd(PPh_3)_2Cl_2$ (4 mg), PPh_3 (4 mg), triethylamine (1.0 mL), and benzene (8.0 mL). The mixture was heated for 4 h at 60—65 °C in an argon flow with TLC monitoring (AcOEt as the eluent). The precipitate was filtered off, washed with benzene (3×2 mL), and dried to give 220 mg (96%) of triethylammonium iodide, m.p. 180—181 °C. The combined benzene solutions were concentrated *in vacuo* and the residue was kept at 60 °C (3 Torr) and then treated as described for compound **9** to give 509 mg (76%) of the crystals of **10**, m.p. 172—174 °C (from Et_2O). Found (%): C, 66.80; H, 7.30; N, 4.14. $C_{37}H_{50}N_2O_9$. Calculated (%):

C, 66.64; H, 7.56; N, 4.20. ^{1}H NMR (400.13 MHz), δ: 1.10 (t, 3 H, C(22)H_3, J = 7 Hz); 1.54 (dd, 1 H, H_b(6), J = 15 Hz, J = 8 Hz); 1.59 (s, 6 H, Me_2C); 1.83 (m, 1 H, H_b(3)); 2.18 (s, 3 H, COMe); 2.69 (dd, 1 H, H_a(6), J = 15 Hz, J = 7 Hz); 2.99 (s, 1 H, H(17)); 3.17 (dd, 1 H, H(1), J = 10 Hz, J = 7 Hz); 3.26, 3.28, 3.38 (all s, 3 H each, C(1)OMe, C(16)OMe, C(14)OMe, respectively); 3.41 (d, 1 H, H(14), J = 5 Hz); 3.53 (d, 1 H, H_a(19), J = 11 Hz); 7.48 (dd, 1 H, H(4′), J = 9 Hz, J = 2 Hz); 7.88 (d, 1 H, H(6′), J = 2 Hz); 8.60 (d, 1 H, H(3′), J = 9 Hz); 11.05 (s, 1 H, NH). ^{13}C NMR (75.47 MHz), δ: 13.3 (C(22)); 24.0 (C(6)); 25.4 ($\underline{C}H_3CO$); 26.1 (C(12)); 26.6 (C(2)); 31.3 (($\underline{C}H_3)_2C$); 31.6 (C(3)); 36.2 (C(13)); 44.6 (C(15)); 47.5 (C(7)); 48.1 (C(5)); 48.8 (C(21)); 49.7 (C(10)); 50.9 (C(11)); 55.4 (C(19)); 55.9 (16-OMe); 56.3 (1-OMe); 57.8 (14-OMe); 61.3 (C(17)); 65.3 (C(3″)); 75.4 (C(8)); 78.4 (C(9)); 80.8, 93.8 (C(1″), C(2″)); 82.7 (C(16)); 83.9 (C(1)); 85.1 (C(4)); 89.9 (C(14)); 115.5 (C(1′)); 116.7 (C(5′)); 120.0 (C(3′)); 133.7 (C(6′)); 137.2 (C(4′)); 141.2 (C(2′)); 166.7 (COO); 168.9 (Me$\underline{C}$O). IR (KBr), ν/cm^{-1}: 792, 943, 966, 1021, 1147, 1255, 1294, 1321, 1368, 1452, 1511, 1586; 1683, 1693 (C=O); 2233 (C≡C); 2819, 2929, 2975; 3400 (NH, OH). UV (EtOH), λ_{max}/nm (logε): 232 (4.45), 273 (4.31), 281 (4.31), 327 (3.68).

4β-[2-(*N*-Acetylamino)-5-(phenylethynyl)benzoyloxy]-1α,14α,16β-trimethoxy-20-ethylaconitane-8,9-diol (11). Triethylamine (2 mL) and a solution of phenylacetylene (71 mg, 0.70 mmol) in benzene (2 mL) were successively added with stirring in an argon flow to a mixture of 5′-iodolappaconitine (**2**) (355 mg, 0.500 mmol), CuI (2 mg, 0.01 mmol, 2 mol.%), $Pd(PPh_3)_2Cl_2$ (7 mg, 0.01 mmol, 2 mol.%), and benzene (3 mL). The mixture was heated for 3.5 h at 65 °C in an argon flow, cooled to 25 °C, diluted with benzene (35 mL), and washed with 25% ammonia (3×15 mL). The organic layer was separated, dried with $MgSO_4$, and passed through an Al_2O_3 layer (1.5×1.5 cm), which was washed with chloroform (15 mL), and the filtrate was concentrated *in vacuo*. Activated carbon (~50 mg) and benzene (5 mL) were added to the residue (0.29 g), the mixture was refluxed until the organic product dissolved, the hot suspension was filtered, the filtrate was evaporated until crystals started to form. Then hexane (5 mL) was added to give 0.23 g (67%) of compound **11**, m.p. 192—195 °C. Found (%): C, 69.63; H, 7.56; N, 3.88. $C_{40}H_{48}N_2O_8$. Calculated (%): C, 70.15; H, 7.06; N, 4.09. ^{1}H NMR (400.13 MHz), δ: 1.09 (t, 3 H, C(22)H_3, J = 7 Hz); 1.52 (dd, 1 H, H_b(6), J = 15 Hz, J = 8 Hz); 1.78 (m, 1 H, H_b(3)); 2.20 (s, 3 H, COMe); 3.01 (s, 1 H, H(17)); 3.19 (dd, 1 H, H(1), J = 10 Hz, J = 7 Hz); 3.29, 3.31, 3.40 (all s, 3 H each, C(1)OMe, C(16)OMe, C(14)OMe, respectively); 3.57 (d, 1 H, H(14), J = 5 Hz); 3.60 (d, 1 H, H_a(19), J = 11 Hz); 7.36—7.38 (m, 3 H, *o*-H_{Ph}, *p*-H_{Ph}); 7.56—7.59 (m, 2 H, *m*-H_{Ph}); 7.65 (dd, 1 H, H(4′), J = 9 Hz, J = 2 Hz); 8.06 (d, 1 H, H(6′), J = 2 Hz); 8.72 (d, 1 H, H(3′), J = 9 Hz); 11.20 (s, 1 H, NH). ^{13}C NMR (100.61 MHz), δ: 13.6 (C(22)); 24.2 (C(6)); 25.6 ($\underline{C}H_3CO$); 26.2 (C(12)); 26.8 (C(2)); 31.6 (C(3)); 36.3 (C(13)); 44.8 (C(15)); 47.6 (C(7)); 48.4 (C(5)); 49.0 (C(21)); 49.8 (C(10)); 51.1 (C(11)); 55.5 (C(19)); 56.2 (16-OMe); 56.7 (1-OMe); 57.9 (14-OMe); 61.6 (C(17)); 76.5 (C(8)); 78.4 (C(9)); 82.8 (C(16)); 84.2 (C(1)); 85.2 (C(4)); 88.5, 89.2 (C(1″), C(2″)); 90.1 (C(14)); 115.5 (C(1′)); 117.2 (C(5′)); 120.2 (C(3′)); 133.8 (*p*-C_{Ph}); 134.0 (*o*-C_{Ph}, C(6′)); 137.3 (*m*-C_{Ph}, C(4′)); 141.8 (C(2′)); 166.8 (COO); 169.0 (Me$\underline{C}$O). IR (KBr), ν/cm^{-1}: 757, 945, 967, 1021, 1084, 1116, 1144, 1256, 1291, 1332, 1399, 1444, 1510, 1584; 1688, 1705 (C=O); 2208 (C≡C); 2816, 2928; 3317, 3464 (NH). UV (EtOH), λ_{max}/nm (logε): 225 (4.26), 232 (4.25), 246 (4.18), 254 (4.14), 295 (4.32).

4β-{2-(*N*-Acetylamino)-5-[(5-pyrimidyl)ethynyl]benzoyloxy}-1α,14α,16β-trimethoxy-20-ethylaconitane-8,9-diol (12). Triethylamine (2 mL) and a solution of 5-ethynylpyrimidine (73 mg, 0.70 mmol) in benzene (2 mL) were successively added with stirring in an argon flow to a mixture of 5′-iodolappaconitine (**2**) (355 mg, 0.500 mmol), CuI (2 mg, 0.01 mmol, 2 mol.%), $Pd(PPh_3)_2Cl_2$ (7 mg, 0.01 mmol, 2 mol.%), and benzene (3 mL). The mixture was heated for 3 h at 80 °C in an argon flow, cooled to 25 °C, diluted with benzene (35 mL), and washed with 25% ammonia (3×15 mL). The organic layer was separated, dried with $MgSO_4$, and passed through an Al_2O_3 layer (1.5×1.5 cm), which was washed with chloroform (15 mL), and the filtrate was concentrated *in vacuo*. The residue (0.33 g) was recrystallized from a benzene—hexane mixture with activated carbon as in the case of compound **11** to give 0.23 g (67%) of compound **12**, m.p. 199—201 °C. HR MS, found: m/z 686.33025 $[M]^+$. $C_{38}H_{46}N_4O_8$. Calculated: M = 686.33154. ^{1}H NMR (400.13 MHz), δ: 1.12 (t, 3 H, C(22)H_3, J = 7 Hz); 1.60 (dd, 1 H, H_b(6), J = 15 Hz, J = 8 Hz); 1.98 (m, 1 H, H_b(3)); 2.24 (s, 3 H, COMe); 3.01 (s, 1 H, H(17)); 3.19 (dd, 1 H, H(1), J = 10 Hz, J = 7 Hz); 3.30, 3.40, 3.44 (all s, 3 H each, C(1)OMe, C(16)OMe, C(14)OMe, respectively); 3.56 (d, 1 H, H(14), J = 5 Hz); 3.63 (d, 1 H, H_a(19), J = 11 Hz); 7.64 (dd, 1 H, H(4′), J = 9 Hz, J = 2 Hz); 8.06 (d, 1 H, H(6′), J = 2 Hz); 8.72 (d, 1 H, H(3′), J = 9 Hz); 8.88 (s, 2 H, pyrimidine H(4) and H(6)); 9.10 (s, 1 H, pyrimidine H(2)); 11.20 (s, 1 H, NH). ^{13}C NMR (100.61 MHz), δ: 13.4 (C(22)); 24.1 (C(6)); 25.5 ($\underline{C}H_3CO$); 26.3 (C(12)); 26.7 (C(2)); 31.7 (C(3)); 36.3 (C(13)); 44.9 (C(15)); 47.5 (C(7)); 48.4 (C(5)); 49.7 (C(21), C(10)); 51.0 (C(11)); 55.9 (C(19)); 56.0 (16-OMe); 56.4 (1-OMe); 57.9 (14-OMe); 61.4 (C(17)); 75.6 (C(8)); 78.5 (C(9)); 82.2, 95.2 (C(1″), C(2″)); 82.8 (C(16)); 84.0 (C(1)); 85.4 (C(4)); 90.1 (C(14)); 115.5 (C(1′)); 119.7 (C(5′)); 120.3 (C(3′)); 134.2 (C(6′)); 137.3 (C(4′)); 142.2 (C(2′)); 156.6 (pyrimidine C(4) and C(6)); 158.5 (pyrimidine C(2)); 166.0 (COO); 169.0 (Me$\underline{C}$O). IR (KBr), ν/cm^{-1}: 719, 945, 1035, 1085, 1146, 1258, 1292, 1332, 1367, 1414, 1508, 1584; 1690, 1705 (C=O); 2210 (C≡C); 2819, 2928; 3325, 3455 (NH). UV (EtOH), λ_{max}/nm (logε): 232 (4.14), 257 sh (3.93), 283 sh (4.03), 304 (4.08).

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