Study of alkaloids of the Siberian and Altai flora

12.* Synthesis of new lappaconitine derivatives containing olefinic substituents**

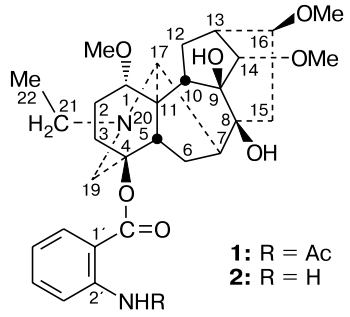
S. A. Osadchii, E. E. Shul´ts, E. V. Polukhina, M. M. Shakirov, and G. A. Tolstikov*

N. N. Vorozhtsov Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences, 9 prosp. Akad. Lavrent´eva, 630090 Novosibirsk, Russian Federation. Fax: +7 (383) 330 9752. E-mail: schultz@nioch.nsc.ru

Lappaconitine and *N*-deacetyllappaconitine derivatives containing bromine and iodine atoms in the aromatic moiety were synthesized. The Heck cross-coupling of these halides with ethyl acrylate or 2-methyl-5-vinylpyridine afforded new olefinated lappaconitine derivatives.

Key words: diterpene alkaloids, anthranilic acid, lappaconitine, *N*-deacetyllappaconitine, bromination, iodination, olefins, Heck reaction.

The diterpene alkaloid with the aconitane skeleton, *viz.*, lappaconitine (**1**), isolated from air-dried roots of northern wolfsbane *Aconitum septentrionale* Koelle and other plants of the Aconitum genus is the acting agent of the antiarrhythmic drug allapinine (lappaconitine hydrobromide).[2—9] *N*-Deacetyllappaconitine (**2**) exhibits the antiarrhythmic activity comparable to that of lappaconitine.[10] Lappaconitine was also found to have the psychotropic[11] and anesthetic[12] activities.



However, it should be noted that high toxicity of allapinine limits the use of this compound as an antiarrhythmic drug.[12,13] In this connection, the synthesis of new analogs of lappaconitine (**1**), which exhibit high specific physiological activity but have lower toxicity, is of considerable importance.

Modifications of the heterocyclic fragment of alkaloid **1** were documented.[14,15] The modification of the nitrogen-containing substituent in the aromatic moiety of the lappaconitine molecule was also described in the literature.[1,16] The replacement of the nitrogen-containing substituent in the aromatic ring with an unsaturated fragment[17] and oxidative bromination of compound **1** with a mixture of Br_2, $NaIO_4$, and AcOH giving rise to *N*-deethyl-5´-bromolappaconitine[18] were performed.

The aim of the present study was to develop procedures for the synthesis of new derivatives of lappaconitine (**1**) containing functionalized olefinic substituents in the aromatic fragment. The Heck reaction is a convenient procedure for the introduction of such fragments into the aromatic moiety.[19—22] However, to solve this problem, it was necessary to synthesize derivatives of lappaconitine (**1**) and *N*-deacetyllappaconitine (**2**) containing bromine or iodine atoms in the aromatic moiety.

It is known[23] that methyl *N*-acetylanthranilate is transformed into methyl 5-bromo-*N*-acetylanthranilate in 86% yield in the reaction with bromine in AcOH. Unfortunately, the extension of this method to lappaconitine (**1**) did not give the desired results, and compound **1** was quantitatively recovered from the reaction mixture. At the same time, we prepared 5´-bromolappaconitine (**3**) in 76% yield by the reaction in concentrated hydrochloric acid (the alkaloid : Br_2 molar ratio was 1 : 1.2) (Scheme 1). The reaction gave *N*-deacetyl-3´,5´-dibromolappaconitine (**4**) as a by-product (in 4% yield). Acidic hydrolysis of compound **3** afforded 5´-bromo-*N*-deacetyllappaconitine (**5**) in 81% yield.

Under analogous conditions, bromination of methyl *N*-acetylanthranilate produced the 5-bromo derivative in 93% yield.

According to the published data,[24] iodination of methyl anthranilate with ICl in AcOH gave methyl 5-iodoanthranilate (**6**) in 49% yield. The application of this procedure to *N*-deacetyllappaconitine (**2**) made it possible to prepare iodo derivative **7** in 74% yield (Scheme 2). Acetylation of iodide **7** with acetic anhydride gave rise to

* For Part 11, see Ref. 1.

** Dedicated to the memory of Academician V. A. Koptyug on the occasion of the 75th anniversary of his birth.

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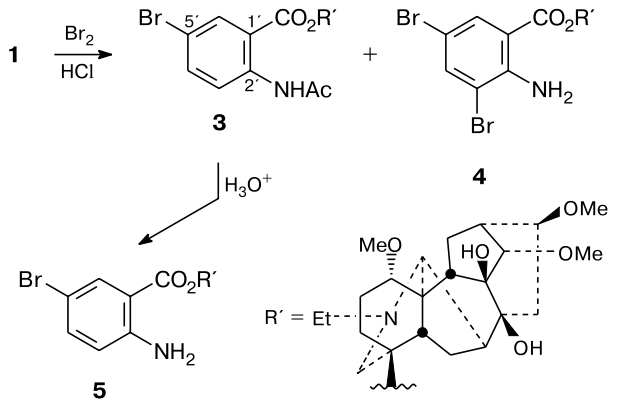
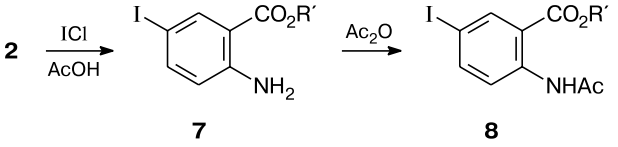
Scheme 1



5′-iodolappaconitine (**8**) in 96% yield. The corresponding acetamide **9** was prepared analogously from methyl 5-iodoanthranilate (**6**) in 97% yield. It should be noted that direct iodination of methyl *N*-acetylanthranilate afforded compound **9** in a yield as low as 37%.[25]

Scheme 2

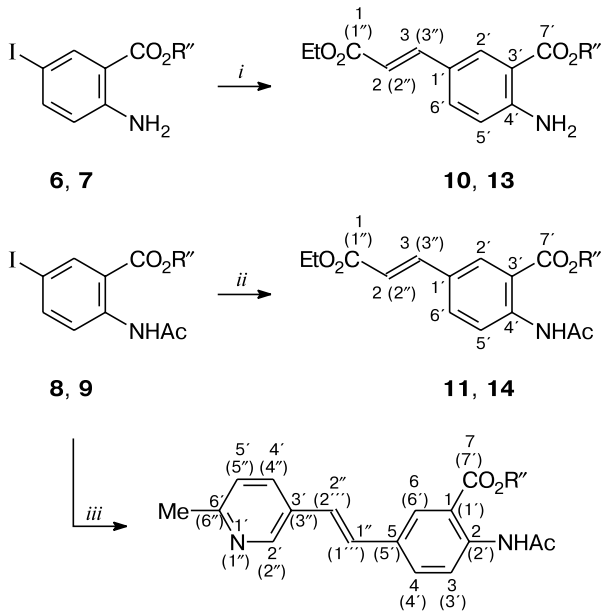


Preliminarily, we devised conditions for the Heck reaction using methyl 5-iodoanthranilate (**6**) and *N*-acetamide **9**. Ethyl acrylate and 2-methyl-5-vinylpyridine were used as olefinic counterparts. The latter compound was chosen because the known 5-ethyl-2-methylpyridine derivative, *viz.*, dimebon, is the promising antiarrhythmic drug.[26]

We found that the reaction of methyl 5-iodoanthranilate (**6**) with ethyl acrylate in DMF in the presence of $Pd(OAc)_2$ and tris(*o*-tolyl)phosphine, as well as triethylamine as a base, produced cinnamic derivative **10** in 63% yield (Scheme 3). Analogously, condensation of methyl 5-iodo-*N*-acetylanthranilate (**9**) with ethyl acrylate in the presence of bis(dibenzylideneacetone)palladium ($Pd(dba)_2$) gave product **11** in 71% yield. The Heck reaction of iodide **9** with 2-methyl-5-vinylpyridine in the presence of $Pd(dba)_2$, $P(o\text{-}Tol)_3$, and NEt_3 in DMF produced styrylpyridine derivative **12** in 72% yield.

The Heck reaction of 5′-iodo-*N*-deacetyllappaconitine (**7**) with ethyl acrylate ($Pd(dba)_2$, $P(o\text{-}Tol)_3$, and Et_3N in DMF) afforded compound **13** in 65% yield. Under the same conditions, the reaction of 5′-iodolappaconitine (**8**) produced ester **14** in higher yield (83%) (see Scheme 3). It should be noted that under the above-mentioned conditions, the conversion of 5′-bromolappaconitine (**3**) into the target product **14** was as low as ~30% (the ^1H NMR spectroscopic data for the reaction mixture). Condensation of iodide **8** with 2-methyl-5-vinylpyridine ($Pd(dba)_2$, $P(o\text{-}Tol)_3$, and Et_3N in DMF) afforded compound **15** in 86% yield.

Scheme 3



6, **9—12:** R″ = Me;
7, **8**, **13—15:** R″ = R′ (see Scheme 1)

Reagents and conditions: *i*. $CH_2{=}CHCO_2Et$, $Pd(OAc)_2$,$P(o\text{-}Tol)_3$, Et_3N, DMF. *ii*. $CH_2{=}CHCO_2Et$, $Pd(dba)_2$, $P(o\text{-}Tol)_3$, Et_3N, DMF. *iii*. 2-Methyl-5-vinylpyridine, $Pd(dba)_2$, $P(o\text{-}Tol)_3$, Et_3N, DMF.

Note. The atomic numbering for compounds **10—12** is given without parentheses; for compounds **13—15**, in parentheses.

It should be noted that the above-described transformation of lappaconitine at the aromatic fragment seems to be quite justified because the alternative synthesis of these compounds by acylation of lappaconine (tertiary alcohol) with the corresponding aromatic acid derivatives will most likely present difficulties (*cf.* Ref. 27).

To conclude, we synthesized functional olefinic derivatives of lappaconitine (**1**) and *N*-deacetyllappaconitine (**2**), which may be of interest as pharmacologically active compounds.

Experimental

Freshly distilled solvents and reagents of chemical purity grade were used. Lappaconitine (**1**) was isolated from air-dried roots of northern wolfsbane *Aconitum septentrionale* Koelle. Its physicochemical and spectroscopic characteristics have been

reported earlier.[14,15] *N*-Deacetyllappaconitine (**2**) was prepared by acidic hydrolysis of lappaconitine (**1**).[28] The reagents $Pd(OAc)_2$ [29] and $Pd(dba)_2$ [30] were synthesized according to known procedures.

Column chromatography was carried out with the use of Al_2O_3 (50—150 μm, TU 6-09-3916-75, Russia, Brockmann activity II). The chromatographic separation was visually monitored using UV irradiation, quartz columns, and the sorbent mixed with the K-35 luminophore (1 wt.%, TU 6-09-458-76, Russia). Preparative TLC with a nonfixed sorbent layer was performed with the use of silica gel (35—70 μm, Acros-Organics) mixed with 1 wt.% of the same luminophore. The plate size was 30×30 cm, and the thickness of the sorbent layer was 2 mm.

The melting points were determined on a Kofler apparatus. The IR spectra were recorded on a Vector 22 spectrometer in KBr pellets. The UV spectra were measured on a Specord UV—Vis spectrophotometer in ethanol ($c = 10^{-4}$ mol L^{-1}). The high-resolution mass spectra were obtained on a Finnigan MAT 8200 spectrometer (EI, 70 eV). The NMR spectra were recorded on Bruker AM-400 (400.13 MHz for ^1H and 100.61 MHz for ^{13}C) or Bruker AV-300 (300.13 MHz for ^1H and 75.47 MHz for ^{13}C) spectrometers for 10% solutions at 25 °C. The chemical shifts were measured relative to the residual signals of the solvent: $CHCl_3$ (δ_H 7.24 and δ_C 76.90), MeOH (δ_H 3.34 ($C\underline{H}_3$) and δ_C 49.00), and H_2O (δ_H 4.80). The multiplicities of the signals in the ^{13}C NMR spectra were determined using *J* modulation (JMOD) and proton off-resonance. The assignment of the signals for the carbon atoms of the aromatic rings in the ^{13}C NMR spectra of compounds **3—5**, **7**, **8**, and **13—15** was made with the use of the additive scheme[31] taking into account the chemical shifts of the corresponding carbon atoms of lappaconitine (**1**),[15] *N*-deacetyllappaconitine (**2**),[1] and methyl *N*-acetylanthranilate[32] and the increments of the bromine and iodine atoms[31] and the (*E*)-CH=CH—CO_2Et group.[17] The assignment of the signals in the ^1H and ^{13}C NMR spectra of compounds **10** and **12** was made using correlation 2D ^1H—^1H COSY and 2D ^{13}C—^1H spectroscopy (CH-COSY (125 Hz) and COLOC (10 Hz)) on a Bruker DRX-500 instrument (500.13 for ^1H and 125.76 MHz for ^{13}C). The chemical shifts of the signals for the carbon atoms of the aromatic fragments of compounds **10** and **12** were used to assign the signals for the carbon atoms of the analogous fragments in compounds **13** and **15**. The ^{13}C NMR spectroscopic data are given in Table 1. The assignment of the signals for the hydrogen atoms of the polycyclic moieties in compounds **3—5**, **7**, **8**, and **13—15** in the ^1H NMR spectra and the assignment of the signals for the carbon atoms of these moieties in the ^{13}C NMR spectra were made by comparing with the corresponding spectra of lappaconitine (**1**).[14] Since the assignment of all signals in the ^1H NMR spectra presents difficulties, only the characteristic signals are given for all the above-mentioned compounds.

The angles of optical rotation were measured on a Polamat A polarimeter (Carl Zeiss, λ = 578 nm). The specific rotation is expressed in (deg mL) (g dm)$^{-1}$. The concentrations of the solutions are given in g (100 mL)$^{-1}$.

Bromination of lappaconitine (1). Solution *A*. Powdered lappaconitine (**1**) (22.4 g, 38.3 mmol) was added portionwise with stirring to concentrated hydrochloric acid ($d = 1.19$, 57 mL). The process was accompanied by a weak exothermic effect and the gel formation. After stirring for 45 min, the gel was dissolved.

Solution *B*. Concentrated hydrochloric acid ($d = 1.19$, 45 mL) was poured with vigorous stirring into a weighed sample of Br_2 (7.38 g, 46.2 mmol). The solution *B* was added portionwise (~3 mL) to the solution *A* at 20—25 °C. A copious brownish nodular precipitate was obtained. After the addition of all bromine, the reaction mixture was vigorously shaken for ~1 h until the precipitate was dissolved. Then the mixture was diluted with water (350 mL). A 25% ammonia solution was added portionwise (3×50 mL) to the resulting solution with cooling (13—15 °C) to pH ~8 and the mixture was extracted with dichloromethane (5×50 mL). The extract was concentrated. The residue was dried at 60 °C (30 Torr) and extracted with boiling 95% EtOH (65 mL). After cooling of the extract, a crystalline product was obtained. After 3 h, the precipitate was filtered off and washed on a filter with a minimum amount of ethanol. **4β-(2-Acetylamino-5-bromobenzoyloxy)-20-ethyl-1α,14α,16β-trimethoxyaconitane-8,9-diol (3)** was obtained in a yield of 19.4 g (76%), m.p. 202—204 °C, $[\alpha]_{578}^{20}$ +40 (*c* 5.3, $CHCl_3$). Found (%): C, 57.55; H, 6.73; Br, 12.40; N, 4.41. $C_{32}H_{43}BrN_2O_8$. Calculated (%): C, 57.92; H, 6.53; Br, 12.04; N, 4.22. ^1H NMR ($CDCl_3$, 400.13 MHz), δ: 1.09 (t, 3 H, C(22)Me, $J = 7.0$ Hz); 1.51 (dd, 1 H, H_b(6), $J = 15.0$ Hz, $J = 8.0$ Hz); 1.82 (m, 1 H, H_b(3)); 2.17 (s, 3 H, NHCOC$\underline{H}_3$); 2.68 (dd, 1 H, H_a(6), $J = 15.0$ Hz, $J = 7.0$ Hz); 2.98 (s, 1 H, H(17)); 3.16 (dd, 1 H, H(1), $J = 10.0$ Hz, $J = 7.0$ Hz); 3.26, 3.27, and 3.37 (all s, 3 H each, C(1)OMe, C(16)OMe, and C(14)OMe, respectively); 7.54 (dd, 1 H, H(4′), $J = 9.0$ Hz, $J = 2.0$ Hz); 7.94 (d, 1 H, H(6′), $J = 2.0$ Hz); 8.56 (d, 1 H, H(3′), $J = 9.0$ Hz); 10.90 (s, 1 H, N$\underline{H}$COMe). IR, ν/cm^{-1}: 789; 837; 875; 899; 945; 968; 995; 1035; 1087; 1146; 1231; 1256; 1287; 1312; 1366; 1394; 1447; 1467; 1509; 1580; 1597; 1694, 1710 (NHC=O); 2819; 2927; 2962. UV, λ_{max}/nm (logε): 225 (4.40), 258 (4.17), 321 (3.65).

The precipitate that remained undissolved after refluxing in EtOH was dried and recrystallized from benzene. **4β-(2-Amino-3,5-dibromobenzoyloxy)-20-ethyl-1α,14α,16β-trimethoxyaconitane-8,9-diol (4)** was obtained in a yield of 0.97 g (4%), m.p. 255—260 °C (with decomp.), $[\alpha]_{578}^{20}$ +39 (*c* 3.1, $CHCl_3$). Found (%): C, 51.55; H, 5.80; Br, 22.49; N, 4.10. $C_{30}H_{40}Br_2N_2O_7$. Calculated (%): C, 51.44; H, 5.76; Br, 22.82; N, 4.00. ^1H NMR ($CDCl_3$, 400.13 MHz), δ: 1.09 (t, 3 H, C(22)Me, $J = 7.0$ Hz); 1.54 (dd, 1 H, H_b(6), $J = 15.0$ Hz, $J = 8.0$ Hz); 1.78 (m, 1 H, H_b(3)); 2.66 (dd, 1 H, H_a(6), $J = 15.0$ Hz, $J = 7.0$ Hz); 2.98 (s, 1 H, H(17)); 3.14 (dd, 1 H, H(1), $J = 10.0$ Hz, $J = 7.0$ Hz); 3.18, 3.20, and 3.30 (all s, 3 H each, C(1)OMe, C(16)OMe, and C(14)OMe, respectively); 6.28 (br.s, 2 H, NH_2); 7.63 and 7.80 (both d, 1 H each, H(3′), H(5′), $J = 2.0$ Hz). IR, ν/cm^{-1}: 993; 1033; 1077; 1122; 1150; 1226; 1264; 1363; 1448; 1532; 1565; 1603; 1689 (C=O); 2820; 2935. UV, λ_{max}/nm (logε): 229 (4.27), 251 (3.80), 356 (3.63).

Hydrobromide of base 3. A solution of 46% HBr (0.295 g, 1.70 mmol) in 95% EtOH (5.0 mL) was added dropwise with stirring to a solution of base **3** (1.11 g, 1.67 mmol) in CH_2Cl_2 (2.5 mL). The solvent was distilled of *in vacuo* at 50 °C (30 Torr). The resinous residue was triturated with diethyl ether (5 mL) and a crystalline colorless powder was obtained. The suspension in diethyl ether was kept for 15 h. The precipitate of the salt was filtered off, washed with diethyl ether, and dried in air. 5′-Bromolappaconitine hydrobromide was obtained in a yield of 1.25 g (100%), m.p. 208—210 °C (with decomp.), $[\alpha]_{578}^{20}$ +30 (*c* 5.6, H_2O). Found (%): Br (bromometric titration), 11.04. $C_{32}H_{43}BrN_2O_8 \cdot HBr$. Calculated (%): Br (ionic), 10.74.

Table 1. ^{13}C NMR spectra (100.61 MHz, $CDCl_3$) of lappaconitine derivatives **3—5**, **7**, **8**, and **13—15**

Atom	δ							
	3	**4**	**5**	**7**	**8**	**13**	**14**	**15***
C(1)	83.9	84.0	83.9	83.9	83.8	84.1	83.9	83.9
C(2)	26.7	26.6	26.5	26.5	26.5	26.7	26.6	26.6
C(3)	31.7	31.7	31.6	31.6	31.6	31.8	31.6	31.6
C(4)	85.5	84.2	83.3	83.4	84.6	83.4	85.2	84.8
C(5)	48.1	48.3	48.1	48.0	48.0	48.3	48.0	48.3
C(6)	24.0	23.9	23.7	23.7	23.8	23.8	23.9	24.0
C(7)	47.6	47.4	47.4	47.4	47.4	47.5	47.4	47.4
C(8)	75.5	75.5	75.2	75.2	75.3	75.4	75.3	75.3
C(9)	78.5	78.4	78.3	78.3	78.3	78.4	78.3	78.4
C(10)	49.8	49.7	49.6	49.6	49.7	49.7	49.7	49.7
C(11)	51.0	50.8	50.6	50.6	50.8	50.8	50.9	50.8
C(12)	26.1	26.1	25.9	25.9	26.0	26.1	26.0	26.0
C(13)	36.3	36.2	36.0	36.0	36.1	36.2	36.1	36.1
C(14)	90.0	90.0	89.8	89.8	89.9	90.0	89.9	89.9
C(15)	44.6	44.7	44.3	44.3	44.5	44.6	44.5	44.5
C(16)	82.8	82.8	82.6	82.6	82.7	82.8	82.7	82.7
C(17)	61.3	61.4	61.1	61.1	61.2	61.3	61.1	61.3
C(19)	55.4	55.4	55.3	55.3	55.3	55.5	55.3	55.3
C(21)	48.8	48.8	48.6	48.6	48.7	48.8	48.7	48.8
C(22)	13.3	13.4	13.2	13.2	13.3	13.3	13.3	13.4
C(1)OMe	56.4	56.4	56.1	56.1	56.4	56.3	56.3	56.3
C(14)OMe	57.8	57.8	57.6	57.6	57.8	57.7	57.7	57.7
C(16)OMe	56.0	56.0	55.7	55.8	56.0	55.9	55.9	55.9
C(1′)	117.3	113.7	112.8	113.6	117.4	122.5	128.3	130.9
C(2′)	140.6	146.4	149.1	149.6	141.0	131.9	131.4	140.9
C(3′)	121.9	110.9	118.1	118.5	121.9	111.3	115.7	120.4
C(4′)	136.9	138.7	136.1	141.7	142.7	151.9	142.8	131.0
C(5′)	114.6	106.3	106.8	75.5	85.4	117.1	117.6	115.8
C(6′)	133.2	132.9	133.1	139.1	138.9	133.1	132.4	129.5
C(7′)	166.1	165.5	165.9	165.7	165.8	166.7	166.7	167.0
$\underline{C}H_3CO$	25.3	—	—	—	25.3	—	25.4	25.4
$CH_3\underline{C}O$	168.8	—	—	—	168.8	—	168.9	168.8
C(1″)	—	—	—	—	—	167.3	166.7	—
C(2″)	—	—	—	—	—	113.9	120.4	147.7
C(3″)	—	—	—	—	—	144.1	142.8	129.7
C(4″)	—	—	—	—	—	—	—	132.7
C(5″)	—	—	—	—	—	—	—	123.0
C(6″)	—	—	—	—	—	—	—	157.2
C(6″)$\underline{C}H_3$	—	—	—	—	—	—	—	25.2
C(1‴)	—	—	—	—	—	—	—	128.0
C(2‴)	—	—	—	—	—	—	—	124.5
$OCH_2\underline{C}H_3$	—	—	—	—	—	14.2	14.1	—
$O\underline{C}H_2CH_3$	—	—	—	—	—	60.0	60.3	—

* 75.47 MHz.

^1H NMR (D_2O, 400.13 MHz), δ: 1.53 (t, 3 H, C(22)Me, J = 7.0 Hz); 2.37 (s, 3 H, NHCOMe); 3.51, 3.53, and 3.54 (all s, 3 H each, C(1)OMe, C(16)OMe, and C(14)OMe, respectively); 7.74 (dd, 1 H, H(4′), J = 9.0 Hz, J = 2.0 Hz); 7.82 (d, 1 H, H(3′), J = 9.0 Hz); 8.03 (d, 1 H, H(6′), J = 2.0 Hz). IR, ν/cm^{-1}: 965; 1039; 1084; 1130; 1134; 1256; 1287; 1307; 1394; 1464; 1505; 1579; 1599; 1636; 1689, 1702 (C=O); 2823; 2878; 2934; 3015. UV, λ_{max}/nm (logε): 226 (4.33), 258 (4.06), 324 (3.52).

4β-(2-Amino-5-bromobenzoyloxy)-20-ethyl-1α,14α,16β-trimethoxyaconitane-8,9-diol (5). A solution of 5′-bromolappaconitine (**3**) (3.32 g, 5 mmol) in 10% H_2SO_4 (11.3 mL) was heated at 95—98 °C for 5 h. The reaction mixture was cooled to 5 °C. A 25% ammonia solution cooled to 5 °C was added dropwise with stirring to pH ~8. The precipitate that formed was extracted with chloroform (3×15 mL). The extract was dried with anhydrous $MgSO_4$, concentrated to 35 mL, and chromatographed on Al_2O_3 (quartz column, the inner diameter was 3.5 cm,

the height of the sorbent layer was 15 cm) using chloroform as the eluent. The fraction of a solution of an UV-absorbing product was collected, and the solvent was removed. The residue was recrystallized from ethanol. Compound **5** was obtained in a yield of 2.52 g (81%), m.p. 255—257 °C (with decomp.). Found (%): C, 57.57; H, 6.84; Br, 13.00; N, 4.37. $C_{30}H_{41}BrN_2O_7$. Calculated (%): C, 57.97; H, 6.65; Br, 12.86; N, 4.51. ^{1}H NMR ($CDCl_3$, 400.13 MHz), δ: 1.03 (t, 3 H, C(22)Me, J = 7.0 Hz); 1.50 (dd, 1 H, H_b(6), J = 15.0 Hz, J = 8.0 Hz); 1.72 (m, 1 H, H_b(3)); 2.92 (s, 1 H, H(17)); 3.09 (dd, 1 H, H(1), J = 10.0 Hz, J = 7.0 Hz); 3.20, 3.23, and 3.33 (all s, 3 H each, C(1)OMe, C(16)OMe, and C(14)OMe, respectively); 3.36 (d, 1 H, H(14), J = 5.0 Hz); 3.48 (d, 1 H, H_a(19), J = 11.0 Hz); 5.71 (br.s, 2 H, NH_2); 6.44 (d, 1 H, H(3′), J = 9.0 Hz); 7.19 (dd, 1 H, H(4′), J = 9.0 Hz, J = 2.0 Hz); 7.73 (d, 1 H, H(6′), J = 2.0 Hz). IR, ν/ cm^{-1}: 945; 966; 1020; 1033; 1079; 1112; 1149; 1234; 1291; 1305; 1339; 1364; 1395; 1449; 1476; 1550; 1583; 1611; 1684 (C=O); 2819; 2932; 3372; 3495; 3538 (OH, NH). UV, λ_{max}/nm (logε): 222 (4.28), 258 (3.83), 352 (3.58).

Methyl 2-(acetylamino)-5-bromobenzoate. A solution of bromine (0.789 g, 4.93 mmol) in concentrated HCl (4.8 mL) was added dropwise with stirring to a solution of methyl *N*-acetylanthranilate (0.856 g, 4.44 mmol) in concentrated HCl (3.0 mL). The formation of the precipitate was observed. The mixture was shaken for 15 min and then diluted with water (27 mL). The precipitate that formed was filtered off, dried, and recrystallized from ethanol. The target bromo derivative was obtained in a yield of 1.12 g (93%) as colorless needle-like crystals, m.p. 134—135 °C (*cf.* lit. data[23]: m.p. 131—132 °C). High-resolution mass spectrum, found: m/z 270.98614 $[M]^+$. $C_{10}H_{10}BrNO_3$. Calculated: M = 270.98445. ^{1}H NMR ($CDCl_3$, 400.13 MHz), δ: 2.17 and 3.87 (both s, 3 H each, MeCO and MeO, respectively); 7.53 (dd, 1 H, H(4), J = 9.0 Hz, J = 2.0 Hz); 8.03 (d, 1 H, H(6), J = 2.0 Hz); 8.55 (d, 1 H, H(3), J = 9.0 Hz); 10.90 (br.s, 1 H, NH) (*cf.* lit. data[23]). ^{13}C NMR of the same solution (100.61 MHz), δ: 115.8 (C(1)), 140.3 (C(2)), 121.5 (C(3)), 136.9 (C(4)), 114.3 (C(5)), 132.8 (C(6)), 168.5 ($\underline{C}O_2CH_3$), 52.2 ($CO_2\underline{C}H_3$), 25.1 ($\underline{C}H_3CO$), 167.1 ($CH_3\underline{C}O$). IR, ν/cm^{-1}: 509; 528; 719; 791; 836; 971; 1094; 1237; 1259; 1290; 1312; 1362; 1394; 1430; 1515; 1583; 1600; 1684, 1701 (C=O); 2950; 3004; 3025; 3064; 3090; 3307 (NH). UV, λ_{max}/nm (logε): 226 (4.41), 257 (4.20), 319 (3.66).

4β-(2-Amino-5-iodobenzoyloxy)-20-ethyl-1α,14α,16β-trimethoxyaconitane-8,9-diol (7). *N*-Deacetyllappaconitine (**2**) (5.43 g, 10 mmol) was dissolved in glacial acetic acid (15 mL) at 50 °C. Iodine chloride (1.70 g, 10.5 mmol) was added dropwise with stirring to the solution at 20 °C. The reaction mixture was heated to 65 °C, stirred until the dark-colored resinous precipitate was completely dissolved (~30 min), then kept at 20 °C for 16 h, and diluted with water (45 mL). Then a 25% ammonia solution was added dropwise with stirring to pH ~8. The resulting mixture was extracted with chloroform (3×20 mL). The extract was dried with anhydrous $MgSO_4$. Compound **7** was isolated by chromatography as described above for compound **5**. The yield was 4.98 g (74%), m.p. 230—232 °C (with decomp., from EtOH). Found (%): C, 54.39; H, 6.29; I, 18.85; N, 4.20. $C_{30}H_{41}IN_2O_7$. Calculated (%): C, 53.89; H, 6.18; I, 18.98; N, 4.19. ^{1}H NMR ($CDCl_3$, 400.13 MHz), δ: 1.02 (t, 3 H, C(22)Me, J = 7.0 Hz); 1.49 (dd, 1 H, H_b(6), J = 15.0 Hz, J = 8.0 Hz); 1.72 (m, 1 H, H_b(3)); 2.59 (dd, 1 H, H_a(6), J = 15.0 Hz, J = 7.0 Hz); 2.91 (s, 1 H, H(17)); 3.08 (dd, 1 H, H(1), J = 10.0 Hz, J = 7.0 Hz); 3.19, 3.22, and 3.32 (all s, 3 H each, C(1)OMe, C(16)OMe, and C(14)OMe, respectively); 3.35 (d, 1 H, H(14), J = 5.0 Hz); 3.46 (d, 1 H, H_a(19), J = 11.0 Hz); 5.75 (br.s, 2 H, NH_2); 6.34 (d, 1 H, H(3′), J = 9.0 Hz); 7.34 (dd, 1 H, H(4′), J = 9.0 Hz, J = 2.0); 7.88 (d, 1 H, H(6′), J = 2.0 Hz). IR, ν/cm^{-1}: 944; 964; 992; 1019; 1033; 1077; 1148; 1236; 1291; 1305; 1336; 1364; 1396; 1472; 1545; 1576; 1608; 1682 (C=O); 2816; 2923; 3368, 3466, 3539 (OH, NH). UV, λ_{max}/nm (logε): 224 (4.20), 260 (3.83), 352 (3.42).

4β-(2-Acetylamino-5-iodobenzoyloxy)-20-ethyl-1α,14α,16β-trimethoxyaconitane-8,9-diol (8). A mixture of compound **7** (1.56 g, 2.33 mmol) and Ac_2O (2.3 mL, 2.48 g, 24.3 mmol) was heated with stirring at 100 °C for 10 min. The resulting solution was cooled and kept at 20 °C for 16 h. Then ice water (5 mL) and a 25% ammonia solution were successively added dropwise with stirring to pH ~8. The precipitate that formed was filtered off, washed with water (2×5 mL), dried, and dissolved in ethanol (3 mL). The solution was kept at 0 °C for 16 h. The precipitate that formed was filtered off and dried at 50—60 °C (3 Torr). The yield was 1.60 g (96%), colorless crystals, m.p. 183—185 °C. High-resolution mass spectrum, found: m/z 710.20740 $[M]^+$. $C_{32}H_{43}IN_2O_8$. Calculated: M = 710.20650. ^{1}H NMR ($CDCl_3$, 400.13 MHz), δ: 1.06 (t, 3 H, C(22)Me, J = 7.0 Hz); 1.48 (dd, 1 H, H_b(6), J = 15.0 Hz, J = 8.0 Hz); 1.79 (m, 1 H, H_b(3)); 2.32 (s, 3 H, $\underline{Me}CO$); 2.65 (dd, 1 H, H_a(6), J = 15.0 Hz, J = 7.0 Hz); 2.95 (s, 1 H, H(17)); 3.12 (dd, 1 H, H(1), J = 10.0 Hz, J = 7.0 Hz); 3.23, 3.25, and 3.34 (all s, 3 H each, C(1)OMe, C(16)OMe, and C(14)OMe, respectively); 3.38 (d, 1 H, H(14), J = 5.0 Hz); 3.48 (d, 1 H, H_a(19), J = 11.0 Hz); 7.69 (dd, 1 H, H(4′), J = 9.0 Hz, J = 2.0 Hz); 8.09 (d, 1 H, H(6′), J = 2.0 Hz); 8.40 (d, 1 H, H(3′), J = 9.0 Hz); 10.93 (s, 1 H, NH). IR, ν/cm^{-1}: 788; 834; 899; 995; 967; 1035; 1088; 1146; 1231; 1257; 1288; 1307; 1389; 1446; 1506; 1575; 1592; 1694, 1709 (C=O); 2818; 2926; 3519, 3482 (NH, OH). UV, λ_{max}/nm (logε): 229 (4.21), 261 (3.98), 324 (3.41).

Methyl 2-(acetylamino)-5-iodobenzoate (9). A solution of methyl 2-amino-5-iodobenzoate (**6**)[24] (0.734 g, 2.64 mmol) in Ac_2O (2.7 mL, 2.92 g, 28.6 mmol) was kept at 20 °C for 16 h. Then ice water (5.4 mL) was added with stirring to the reaction mixture. Crystals were filtered off and dried at 50—60 °C (3 Torr). Amide **9** was obtained in a yield of 0.820 g (97%) as colorless needle-like crystals, m.p. 132—133 °C (from EtOH) (*cf.* lit. data[25]: m.p. 110 °C (from EtOH)). High-resolution mass spectrum, found: m/z 318.97132 $[M]^+$. $C_{10}H_{10}INO_3$. Calculated: M = 318.97072. ^{1}H NMR ($CDCl_3$, 300.13 MHz), δ: 2.18 and 3.88 (both s, 3 H each, MeCO and MeO, respectively); 7.73 (dd, 1 H, H(4), J = 9.0 Hz, J =2.0 Hz); 8.25 (d, 1 H, H(6), J = 2.0 Hz); 8.44 (d, 1 H, H(3), J = 9.0 Hz); 10.91 (br.s, 1 H, NH). ^{13}C NMR of the same solution ($CDCl_3$, 75.47 MHz), δ: 116.3 (C(1)), 141.0 (C(2)), 122.1 (C(3)), 142.9 (C(4)), 84.6 (C(5)), 139.1 (C(6)), 167.2 ($\underline{C}O_2CH_3$), 52.5 ($CO_2\underline{C}H_3$), 25.4 ($\underline{C}H_3CO$), 168.8 ($CH_3\underline{C}O$). ^{1}H NMR (DMSO-d_6, 300.13 MHz), δ: 2.12 and 3.84 (both s, 3 H each, MeCO and MeO, respectively); 7.90 (dd, 1 H, H(4), J = 9.0 Hz, J = 2.0 Hz); 7.96 (d, 1 H, H(3), J = 9.0 Hz); 8.13 (d, 1 H, H(6), J = 2.0 Hz); 10.91 (br.s, 1 H, NH). The ^{1}H NMR spectroscopic data in DMSO-d_6 are consistent with the published data.[25] The difference in the ^{1}H NMR spectra recorded in $CDCl_3$ and DMSO-d_6 is, apparently, attributed to the difference in solvation. IR, ν/cm^{-1}: 790; 831; 950; 1089; 1186; 1234; 1259; 1289; 1306; 1387; 1430; 1511; 1578; 1596;

1685, 1708 (C=O); 2960; 3031; 3090; 3113; 3266 (NH). UV, λ_{max}/nm (log ε): 230 (4.36), 261 (4.16), 323 (354).

Ethyl 3-[(4-amino-3-methoxycarbonyl)phenyl]prop-2*E*-enoate (10). Methyl 5-iodoanthranilate (**6**)[24] (1.81 g, 6.54 mmol), DMF (13.4 mL), ethyl acrylate (4.0 mL, 3.68 g, 36.8 mmol), triethylamine (1.80 mL, 1.31 g, 12.9 mmol), tris(*o*-tolyl)phosphine (0.226 g, 0.742 mmol, 11 mol.%), and $Pd(OAc)_2$ (0.096 g, 0.428 mmol, 7.7 mol.%) (*cf.* lit. data[33]) were successively introduced with stirring in a reaction vessel. The reaction mixture was heated at 100 °C for 4 h under a stream of argon and then cooled to 25 °C. Dichloromethane (90 mL) and 10% H_2SO_4 (20 mL) were successively added with stirring to the reaction mixture. The organic layer was separated and dried with anhydrous $MgSO_4$. After removal of the solvent, the resinous residue was extracted with hexane (4×30 mL) under reflux. The crystals of compound **10** that formed upon storage of the extract were filtered off. The yield was 1.03 g (63%), m.p. 94—95 °C. High-resolution mass spectrum, found: *m/z* 249.10037 $[M]^+$. $C_{13}H_{15}NO_4$. Calculated: M = 249.10010. ^{1}H NMR ($CDCl_3$, 400.13 MHz), δ: 1.27 (t, 3 H, $C\underline{H}_3CH_2$, *J* = 7.0 Hz); 3.82 (s, 3 H, OMe); 4.19 (q, 2 H, $CH_3C\underline{H}_2$, *J* = 7.0 Hz); 6.10 (br.s, 2 H, NH_2); 6.18 (d, 1 H, H(2), *J* = 16.0 Hz); 6.60 (d, 1 H, H(5′), *J* = 9.0 Hz); 7.39 (dd, 1 H, H(6′), *J* = 9.0 Hz, *J* = 2.0 Hz); 7.52 (d, 1 H, H(3), *J* = 16.0 Hz); 7.95 (d, 1 H, H(2′), *J* = 2.0 Hz). ^{13}C NMR of the same solution (100.61 MHz), δ: 167.3 (C(1)), 113.8 (C(2)), 144.0 (C(3)), 122.4 (C(1′)), 132.4 (C(2′)), 110.0 (C(3′)), 151.8 (C(4′)), 116.9 (C(5′)), 132.6 (C(6′)), 167.8 (C(7′)), 14.1 ($CH_2\underline{C}H_3$), 60.0 ($\underline{C}H_2CH_3$), 52.2 ($CO_2\underline{C}H_3$). IR, ν/cm^{-1}: 827; 935; 956; 986; 1036; 1088; 1182; 1248; 1316; 1368; 1441; 1500; 1613, 1690 (C=O); 2905; 2957; 2988; 3334, 3437 (NH_2). UV, λ_{max}/nm (log ε): 227 (4.13), 330 (4.35).

Ethyl 3-[(4-acetylamino-3-methoxycarbonyl)phenyl]prop-2*E*-enoate (11). Condensation was carried out as described above for compound **10** starting from methyl 2-(acetylamino)-5-iodobenzoate (**9**) (0.583 g, 1.83 mmol), DMF (2.9 mL), ethyl acrylate 0.83 mL (0.76 g, 7.6 mmol), triethylamine (0.59 mL, 0.43 g, 4.3 mmol), tris(*o*-tolyl)phosphine (0.056 g, 0.183 mmol, 10 mol.%), and $Pd(dba)_2$ (0.053 g, 0.092 mmol, 5 mol.%). After cooling, the reaction mixture was kept for 16 h. The precipitate that formed was filtered off, dried at 80 °C (3 Torr), and extracted with dichloromethane. The extract was concentrated and compound **11** was obtained in a yield of 0.379 g (71%), m.p. 162—163 °C (from EtOH). High-resolution mass spectrum, found: *m/z* 291.11120 $[M]^+$. $C_{15}H_{17}NO_5$. Calculated: M = 291.11066. ^{1}H NMR ($CDCl_3$, 300.13 MHz), δ: 1.31 (t, 3 H, $C\underline{H}_3CH_2$, *J* = 7.0 Hz); 2.22 (s, 3 H, MeCO); 3.92 (s, 3 H, OMe); 4.24 (q, 2 H, $CH_3C\underline{H}_2$, *J* = 7.0 Hz); 6.36 (d, 1 H, H(2), *J* = 16.0 Hz); 7.57 (d, 1 H, H(3), *J* = 16.0 Hz); 7.64 (dd, 1 H, H(6′), *J* = 9.0 Hz, *J* = 2.0 Hz); 8.12 (d, 1 H, H(2′), *J* = 2.0 Hz); 8.70 (d, 1 H, H(5′), *J* = 9.0 Hz); 11.10 (br.s, 1 H, NH). ^{13}C NMR of the same solution (75.47 MHz), δ: 166.7 (C(1)), 120.5 (C(2)), 142.8 (C(3)), 128.5 (C(1′)), 130.8 (C(2′)), 114.8 (C(3′)), 142.8 (C(4′)), 117.9 (C(5′)), 133.5 (C(6′)), 14.3 ($CH_2\underline{C}H_3$), 60.5 ($\underline{C}H_2CH_3$), 25.5 ($\underline{C}H_3CO$), 168.1 ($CH_3\underline{C}O$), 52.5 ($CO_2\underline{C}H_3$), 169.1 (C(7′)). IR, ν/cm^{-1}: 751; 795; 854; 954; 981; 1013; 1036; 1088; 1181; 1208; 1238; 1280; 1305; 1321; 1339; 1368; 1415; 1442; 1478; 1524; 1589; 1634, 1703 (C=O); 2905; 2960; 2981; 3069; 3255 (NH). UV, λ_{max}/nm (log ε): 241 (4.22), 303 (4.38).

Methyl (*E*)-2-(acetylamino)-5-[2-(6-methylpyridin-3-yl)ethenyl]benzoate (12) was prepared as described above for compound **11** starting from iodide **9** (0.212 g, 0.665 mmol), DMF (1.05 mL), 2-methyl-5-vinylpyridine (0.198 g, 1.66 mmol), triethylamine (0.21 mL, 0.153 g, 1.51 mmol), tris(*o*-tolyl)phosphine (0.020 g, 0.067 mmol, 10 mol.%), and $Pd(dba)_2$ (0.020 g, 0.035 mmol, 5 mol.%). Compound **12** was obtained in a yield of 0.148 g (72%), m.p. 220—222 °C (from a CH_2Cl_2—EtOH mixture). High-resolution mass spectrum, found: *m/z* 310.13052 $[M]^+$. $C_{18}H_{18}N_2O_3$. Calculated: M = 310.13173. ^{1}H NMR ($CDCl_3$, 300.13 MHz), δ: 2.19 (s, 3 H, MeCO); 2.51 (s, 3 H, C(6′)Me); 3.90 (s, 3 H, CO_2Me); 6.98 and 7.01 (both d, 1 H each, AB system, H(2″) and H(1″), respectively, *J* = 16.5 Hz); 7.08 (d, 1 H, H(5′), *J* = 8.1 Hz); 7.61 (dd, 1 H, H(4), *J* = 8.8 Hz, *J* = 2.2 Hz); 7.66 (dd, 1 H, H(4′), *J* = 8.1 Hz, *J* = 2.3 Hz); 8.07 (d, 1 H, H(6), *J* = 2.2 Hz); 8.53 (d, 1 H, H(2′), *J* = 2.3 Hz); 8.66 (d, 1 H, H(3), *J* = 8.8 Hz); 11.00 (br.s, 1 H, NH). ^{13}C NMR of the same solution (75.47 MHz), δ: 130.9 (C(1)), 140.8 (C(2)), 120.3 (C(3)), 132.0 (C(4)), 114.7 (C(5)), 128.6 (C(6)), 147.6 (C(2′)), 129.6 (C(3′)), 132.7 (C(4′)), 123.0 (C(5′)), 157.3 (C(6′)), 127.8 (C(1″)), 124.6 (C(2″)), 24.0 ($\underline{C}H_3C(6')$), 25.3 ($\underline{C}H_3CO$), 168.8 ($CH_3\underline{C}O$), 52.2 ($CO_2\underline{C}H_3$), 168.3 ($\underline{C}O_2CH_3$). IR, ν/cm^{-1}: 791; 847; 985; 1088; 1203; 1227; 1239; 1280; 1302; 1336; 1369; 1415; 1439; 1485; 1519; 1589; 1681, 1706 (C=O); 2845; 2948; 3016; 3260 (NH). UV, λ_{max}/nm (log ε): 224 (3.94), 249 (3.96), 318 (4.22).

Ethyl 3-{4-amino-3-[(8,9-dihydroxy-20-ethyl-1α,14α,16β-trimethoxyaconit-4β-yloxy)carbonyl]phenyl}prop-2*E*-enoate (13) was prepared as described above for compound **11** starting from iodide **7** (0.545 g, 0.815 mmol), DMF (0.86 mL), ethyl acrylate (0.25 mL, 0.23 g, 2.3 mmol), triethylamine (0.21 mL, 0.153 g, 1.51 mmol), tris(*o*-tolyl)phosphine (0.020 g, 0.067 mmol, 8 mol.%), and $Pd(dba)_2$ (0.020 g, 0.035 mmol, 4 mol.%). After cooling, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and kept for 16 h. Then palladium black was filtered off. The filtrate was concentrated and the resinous residue was thoroughly dried at 100 °C (3 Torr) and dissolved in $CHCl_3$ (10 mL). The solution was extracted with 10% H_2SO_4 (3×5 mL). The acidic extract was filtered off and neutralized with stirring with a 25% ammonia solution to pH ~8. The precipitate that formed was extracted with chloroform (3×15 mL). The extract was dried with anhydrous $MgSO_4$, concentrated to 3 mL, and subjected to preparative TLC on a nonfixed layer of silica gel (Et_2O as the eluent). The sorbent zone exhibiting blue fluorescence under UV light was collected. The product was eluted from the sorbent with an Et_2O—MeOH mixture (9 : 1, v/v). Compound **13** was obtained as an amorphous powder in a yield of 0.339 g (65%). Found (%): C, 65.41; H, 7.46; N, 4.34. $C_{35}H_{48}N_2O_9$. Calculated (%): C, 65.60; H, 7.55; N, 4.37. ^{1}H NMR ($CDCl_3$, 400.13 MHz), δ: 1.07 (t, 3 H, C(22)Me, *J* = 7.0); 1.56 (dd, 1 H, H_b(6), *J* = 15.0 Hz, *J* = 8.0 Hz); 1.78 (m, 1 H, H_b(3)); 2.96 (s, 1 H, H(17)); 3.14 (dd, 1 H, H(1), *J* = 10.0, *J* = 7.0 Hz); 3.24, 3.26, and 3.36 (all s, 3 H each, C(1)OMe, C(16)OMe, and C(14)OMe, respectively); 3.40 (d, 1 H, H(14), *J* = 5.0 Hz); 3.52 (d, 1 H, H_a(19), *J* = 11.0 Hz); 4.20 (q, 2 H, $CO_2C\underline{H}_2CH_3$, *J* = 7.0 Hz); 6.02 (br.s, 2 H, NH_2); 6.15 (d, 1 H, H(2″), *J* = 16.0 Hz); 6.58 (d, 1 H, H(5′), *J* = 9.0 Hz); 7.41 (dd, 1 H, H(6′), *J* = 9.0 Hz, *J* = 2.0 Hz); 7.52 (d, 1 H, H(3″), *J* = 16.0 Hz); 7.81 (d, 1 H, H(2′), *J* = 2.0 Hz). IR, ν/cm^{-1}: 826; 893; 946; 967; 1036; 1088; 1159; 1201; 1269; 1299; 1368; 1426; 1450; 1466; 1501; 1614; 1688 (C=O); 2818; 2928; 3359, 3464 (NH, OH). UV, λ_{max}/nm (log ε): 226 (4.10), 331 (4.25).

Ethyl 3-{4-acetylamino-3-[(8,9-dihydroxy-20-ethyl-1α,14α,16β-trimethoxyaconit-4β-yloxy)carbonyl]phenyl}prop-2*E*-enoate (14) was prepared as described above for compound **13** starting from 5′-iodolappaconitine (**8**) (0.110 g, 0.155 mmol), DMF (0.5 mL), ethyl acrylate (0.07 mL, 0.064 g, 0.64 mmol), triethylamine (0.05 mL, 0.036 g, 0.36 mmol), tris(*o*-tolyl)phosphine (0.005 g, 0.016 mmol, 10 mol.%), and $Pd(dba)_2$ (0.005 g, 0.009 mmol, 6 mol.%). After preparative TLC (a nonfixed layer of silica gel; Et_2O as the eluent), the UV-absorbing sorbent zone was collected. The product was eluted from the sorbent with an Et_2O—MeOH mixture (9 : 1, v/v). Compound **14** was obtained as an amorphous powder in a yield of 0.088 g (83%). High-resolution mass spectrum, found: *m/z* 682.34747 $[M]^+$. $C_{37}H_{50}N_2O_{10}$. Calculated: M = 682.34652. ^1H NMR ($CDCl_3$, 400.13 MHz), δ: 1.05 (t, 3 H, C(22)Me, *J* = 7.0 Hz); 1.26 (t, 3 H, $CO_2CH_2C\underline{H}_3$, *J* = 7.0 Hz); 1.49 (dd, 1 H, $H_b(6)$, *J* = 15.0 Hz, *J* = 8.0 Hz); 2.16 (s, 3 H, MeCO); 2.65 (dd, 1 H, $H_a(6)$, *J* = 15.0 Hz, *J* = 7.0 Hz); 2.94 (s, 1 H, H(17)); 3.12 (dd, 1 H, H(1), *J* = 10.0 Hz, *J* = 7.0 Hz); 3.22, 3.23, and 3.33 (all s, 3 H each, C(1)OMe, C(16)OMe, and C(14)OMe, respectively); 3.37 (d, 1 H, H(14), *J* = 5.0 Hz); 3.48 (d, 1 H, $H_a(19)$, *J* = 11.0 Hz); 4.18 (q, 2 H, $CO_2C\underline{H}_2CH_3$, *J* = 7.0 Hz); 6.28 (d, 1 H, H(2″), *J* = 16.0 Hz); 7.52 (d, 1 H, H(3″), *J* = 16.0 Hz); 7.61 (dd, 1 H, H(6′), *J* = 9.0 Hz, *J* = 2.0 Hz); 7.91 (d, 1 H, H(2′), *J* = 2.0 Hz); 8.64 (d, 1 H, H(5′), *J* = 9.0 Hz); 11.08 (s, 1 H, NH). IR, ν/cm^{-1}: 1036; 1087; 1176; 1202; 1235; 1269; 1333; 1367; 1411; 1449; 1517; 1588; 1637; 1684, 1709 (C=O); 2819; 2928; 2983; 3256, 3308, 3394 (NH, OH). UV, λ_{max}/nm (logε): 229 (4.02), 246 (4.04), 303 (4.10).

(*E*)-4β-{2-(Acetylamino)-5-[2-(6-methylpyridin-3-yl)ethenyl]}benzoyloxy-20-ethyl-1α,14α,16β-trimethoxyaconitane-8,9-diol (15) was prepared as described above for compound **13** starting from 5′-iodolappaconitine (**8**) (0.580 g, 0.665 mmol), DMF (1.05 mL), 2-methyl-5-vinylpyridine (0.24 mL, 0.235 g, 1.96 mmol), triethylamine (0.21 mL, 0.153 g, 1.51 mmol), tris(*o*-tolyl)phosphine (0.020 g, 0.067 mmol, 10 mol.%), and $Pd(dba)_2$ (0.020 g, 0.035 mmol, 5 mol.%). After drying with anhydrous $MgSO_4$, the chloroform extract of the ammonia solution (pH ~8) was concentrated to dryness. The resinous residue was triturated with Et_2O (3 mL). Crystals of compound **15** were filtered off, m.p. 214—216 °C. The yield was 0.402 g (86%). Found (%): C, 67.91; H, 7.31; N, 5.88. $C_{40}H_{51}N_3O_8$. Calculated (%): C, 68.43; H, 7.33; N, 5.99. ^1H NMR ($CDCl_3$, 300.13 MHz), δ: 1.08 (t, 3 H, C(22)Me, *J* = 7.0 Hz); 1.57 (dd, 1 H, $H_b(6)$, *J* = 15.0 Hz, *J* = 8.0 Hz); 1.78 (m, 1 H, $H_b(3)$); 2.18 (s, 3 H, MeCO); 2.50 (s, 3 H, C(6″)Me); 2.72 (dd, 1 H, $H_a(6)$, *J* = 15.0 Hz, *J* = 7.0 Hz); 2.97 (s, 1 H, H(17)); 3.15 (dd, 1 H, H(1), *J* = 10.0 Hz, *J* = 7.0 Hz); 3.25, 3.26, and 3.36 (all s, 3 H each, C(1)OMe, C(16)OMe, and C(14)OMe, respectively); 3.40 (d, 1 H, H(14), *J* = 5.0 Hz); 3.55 (d, 1 H, $H_a(19)$, *J* = 11.0 Hz); 6.91 and 6.99 (both d, 1 H each, AB system, H(2″′) and H(1″′), respectively, *J* = 16.5 Hz); 7.08 (d, 1 H, H(5″), *J* = 8.1 Hz); 7.65 (dd, 1 H, H(4′), *J* = 8.8 Hz, *J* = 2.2 Hz); 7.71 (dd, 1 H, H(4″), *J* = 8.1 Hz, *J* = 2.3 Hz); 7.90 (d, 1 H, H(6′), *J* = 2.2 Hz); 8.52 (d, 1 H, H(2″), *J* = 2.3 Hz); 8.64 (d, 1 H, H(3′), *J* = 8.8 Hz); 11.01 (br.s, 1 H, NH). IR, ν/cm^{-1}: 839; 893; 946; 966; 997; 1035; 1086; 1115; 1147; 1211; 1234; 1276; 1299; 1332; 1367; 1413; 1450; 1465; 1515; 1588; 1685, 1700 (C=O); 2820; 2925; 3266, 3311, 3400 (NH, OH). UV, λ_{max}/nm (logε): 226 (4.00), 253 (4.05), 316 (4.23).

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