Study of alkaloids of the Siberian and Altai flora
10.* Synthesis of *N*(20)-deethyllappaconitine derivatives

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Efficient procedures were developed for *N*-deethylation of lappaconitine to give *N*(20)-deethyllappaconitine. Alkyl derivatives of *N*(20)-deethyllappaconitine, including labeled lappaconitine, and *N*(20)-acetoxy-*N*(20)-deethyllappaconitine were prepared for the first time. The assignments of the signals for the carbon atoms in the ^{13}C NMR spectra of lappaconitine and related lappaconine were refined using $^{13}C—^{13}C$ 2D INADEQUATE and 2D $^{13}C—^{1}H$ correlation experiments.

Key words: diterpenoid alkaloids, lappaconitine, *N*(20)-deethylation, *N*(20)-deethyllappaconitine derivatives, labeled lappaconitine.

One of the most readily available diterpenoid alkaloids, *viz.*, lappaconitine (**1**), exhibits pronounced antiarrhythmic activity. Lappaconitine hydrobromide (allapinine) is used as an antiarrhythmic drug.[2] However, diterpenoid alkaloids possessing antiarrhythmic properties are generally highly toxic.[3] Hence, there is a need to prepare new compounds possessing high specific physiological activity but lower toxicity.

It is believed that the biological activity of lappaconitine is associated with its chemical structure and, primarily, with the presence of the 3-azabicyclo[3.3.1]nonane fragment. In this connection, it is of interest to synthesize compounds retaining this fragment and bearing various substituents at the N(20) atom and to study their biological activities.

The pharmacodynamics of drugs is investigated with the use of radioactively labeled samples, which allows one to determine the distribution of microamounts of these compounds in organisms and follow their metabolic pathways. To our knowledge, the synthesis of labeled lappaconitine has not been described. Such a compound can be prepared by the transformation of unlabeled lappaconitine into *N*(20)-deethyllappaconitine followed by ethylation of the latter with ^{14}C- or ^{3}H-labeled bromo- or iodoethane.

The aim of the present study was to develop procedures for *N*-deethylation of lappaconitine and to synthesize derivatives modified at the N(20) atom.

We developed an efficient three-step scheme for the transformation of lappaconitine **1** into *N*(20)-deethyllappaconitine (**4**) (Scheme 1, path *a*—*b*—*c*) involving oxidation of the former with *m*-chloroperbenzoic acid to give *N*-oxide (**2**)[4] followed by thermolysis yielding the corresponding hydroxylamine **3**[5] and reduction of the latter with Zn dust in AcOH giving rise to secondary amine **4**. In each step, only one product was formed in 85, 94, and 75% yields, respectively. As a result, *N*(20)-deethylation product **4** was prepared in a total yield of 60% with respect to lappaconitine **1**. Acylation of hydroxylamine **3** with acetic anhydride in the presence of K_2CO_3 afforded *N*(20)-acetoxy-*N*(20)-deethyllappaconitine (**5**).

Tertiary amines containing the methylene groups at the α position with respect to the nitrogen atom can be converted into secondary amines under the action of *N*-bromosuccinimide in an aqueous medium[7] (*cf.* lit.[8]) and other oxidants.[9,10] We found that the known procedure[7] as applied to lappaconitine **1** gave rise to *N*(20)-deethyllappaconitine (**4**) in 58% yield (see Scheme 1, path *d*).

Treatment of lappaconitine **1** with a mixture of $NaIO_4$, Br_2, and AcOH afforded *N*(20)-deethyl-5´-bromolappaconitine[11] (*cf.* lit.[12]).

Recently, *N*(20)-deethyllappaconitine has been isolated from Chinese monkshood (*Aconitum sinomontanum*) and called sinomontanine A.[13]

The secondary amine **4** serves as a key compound for subsequent chemical transformations involving the heterocyclic nitrogen atom. For example, we synthesized for the first time a series of *N*(20)-deethyllappaconitine derivatives based on amine **4**.

Treatment of *N*(20)-deethyllappaconitine **4** with an excess of bromo- or iodoethane followed by alkalization

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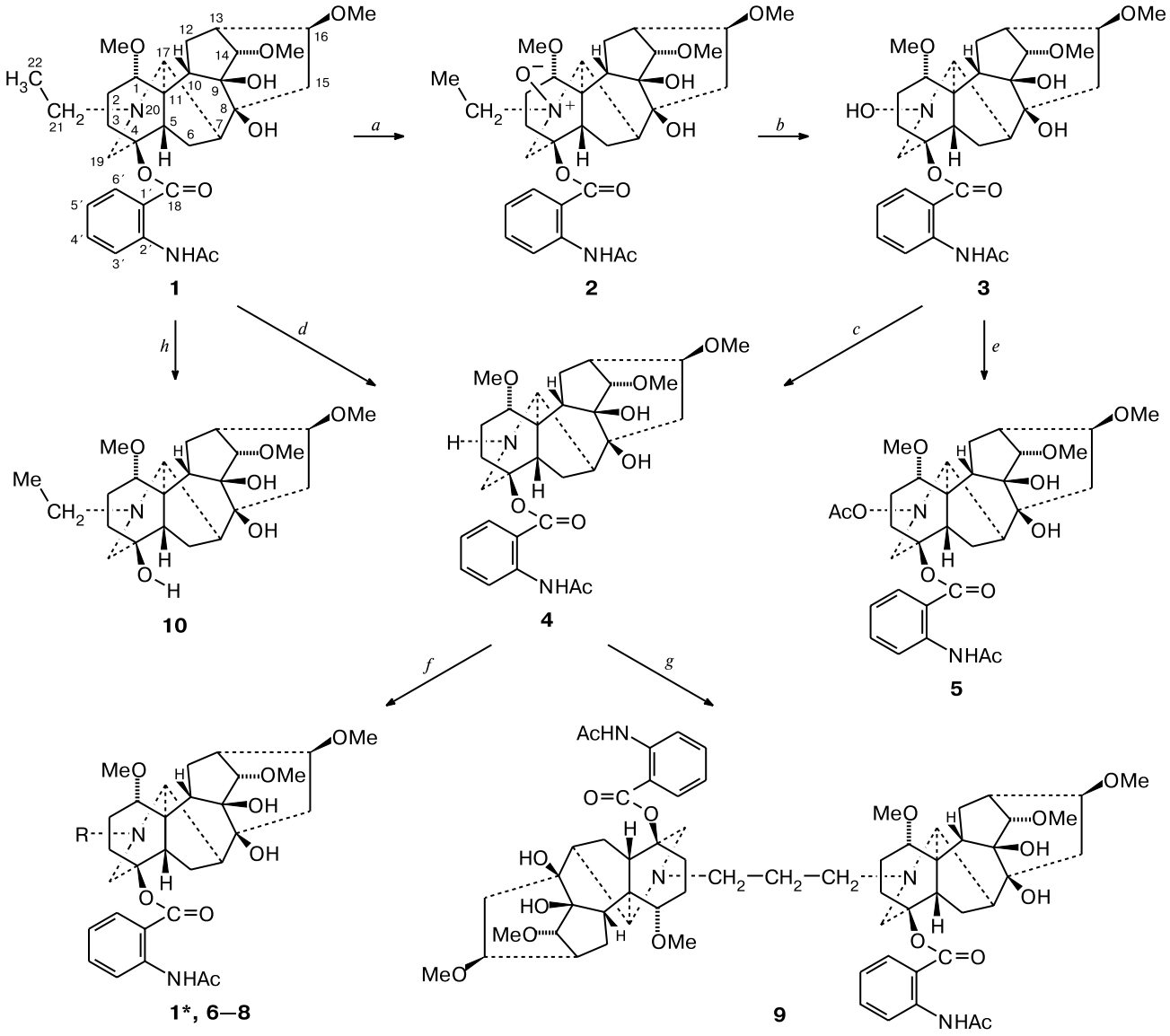
Scheme 1



Reagents and conditions: *a*. *cf*. lit.[4]; *b*. *cf*. lit.[5]; *c*. Zn, AcOH, 20 °C, 5 h; *d*. NBS, H_2O, 50 °C, 1 h; *e*. Ac_2O, K_2CO_3, $CHCl_3$, 20 °C, 48 h; *f*. $MeCD_2Br$, 20 °C, 96 h (for **1***); MeI, K_2CO_3, MeCN, Ar, 40—45 °C, 48 h (for **6**); CH_2=$CHCH_2Br$, K_2CO_3, DMF, Ar, 90—95 °C, 4 h (for **7**); CH_2=CHCN, EtOH, Et_3N, Ar, 70—80 °C, 48 h (for **8**); *g*. $Br(CH_2)_3Br$, K_2CO_3, DMF, Ar, 70 °C, 4.5 h; *h*. *cf*. lit.[6]

afforded "synthetic" lappaconitine **1** identical to the starting lappaconitine in specific optical rotation, melting point, IR and ^1H and ^{13}C NMR spectra. Evidently, this procedure can be used for the preparation of labeled lappaconitine **1** containing both stable (^{13}C and ^2H) and radioactive (^{14}C and ^3H) isotopes, analogously to the preparation of deuterium-labeled aconitine and mesaconitine.[14] As an example, we synthesized [21,21-$^2H_2$]-lappaconitine (**1***).

Due to fragmentation, the abundance of the molecular ion peak in the mass spectrum of [21,21-$^2H_2$]-lappaconitine appeared to be insufficient for the high-accuracy determination of *m/z*. The *m/z* for the most abundant fragmentation ion (407.2637) corresponds to elimination of the protonated *N*-acetylanthraniloyloxy fragment ($C_9H_9NO_3$). The same fragment was eliminated from lappaconitine[15] whose most abundant peak is observed at *m/z* 405.

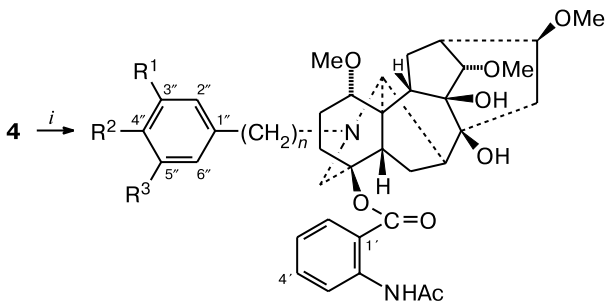
N(20)-Methyl-*N*(20)-deethyllappaconitine (**6**) was synthesized in virtually quantitative yield by the reaction of compound **4** with MeI in MeCN in the presence of K_2CO_3. Alkylation of amine **4** with allyl bromide in DMF in the presence of K_2CO_3 in an inert atmosphere afforded *N*(20)-allyl-*N*(20)-deethyllappaconitine (**7**) in 72% yield.

The introduction of a β-cyanoethyl substituent into the 3-azabicyclo[3.3.1]nonane fragment holds considerable promise. The reaction of *N*(20)-deethyllappaconitine **4** with an excess of acrylonitrile in EtOH in the presence of Et_3N for 48 h (*cf.* lit.[16]) gave rise to *N*(20)-β-cyanoethyl-*N*(20)-deethyllappaconitine (**8**) in 80% yield.

Many highly active diterpenoid alkaloids have dimeric structures.[17] We succeeded in synthesizing a compound containing two lappaconitine residues linked by a hydrocarbon bridge. For this purpose, we carried out the reaction of *N*(20)-deethyllappaconitine **4** with 1,3-dibromopropane in a molar ratio of 2 : 1 giving rise to dimeric product **9** in 31% yield (see Scheme 1).

Alkylation of compound **4** with benzyl and phenethyl halides afforded *N*(20)-benzyl and -aralkyl derivatives **11—14** (Scheme 2).

Scheme 2



11: $R^1 = R^2 = R^3 = H$; $n = 1$
12: $R^1 = R^3 = H$, $R^2 = OH$; $n = 2$
13: $R^1 = H$, $R^2 = OH$, $R^3 = Bu^t$; $n = 2$
14: $R^1 = R^3 = Bu^t$, $R^2 = OH$; $n = 2$

Reagents and conditions: *i*. BnBr, K_2CO_3, MeCN, Ar, 80—90 °C, 2 h (for **11**); $Br(CH_2)_2C_6H_4OH$, K_2CO_3, DMF, 70 °C, 24 h (for **12**); 4-$Cl(CH_2)_2$-2-$Bu^tC_6H_3OH$, K_2CO_3, DMF, 70—80 °C, 24 h (for **13**); $Cl(CH_2)_2$Ph-*o,o*-Bu^t-*p*-OH, K_2CO_3, DMF, 70—80 °C, 24 h (for **14**).

The structures of new compounds were established based on spectroscopic data. Compounds **1***, **4—9**, and **11—14** were obtained by chemical transformations of lappaconitine **1**, and full assignment of the signals in the ^1H and ^{13}C NMR spectra of these compounds required that the precise assignment of the signals in the NMR spectra of the starting compound be carried out. The assignments of the signals in the ^{13}C NMR spectra of lappaconitine published earlier[4,11,13,18—20] are somewhat incorrect because no direct experiments on the determination of the sequence of linkage of the skeleton carbon atoms were carried out. We refined the assignment of the signals for the carbon atoms in the ^{13}C NMR spectra of lappaconitine **1** and related lappaconine[6] (**10**) using the direct experiment, *viz.*, the $^{13}C—^{13}C$ 2D INADEQUATE method.[21,22] We also made full assignments of the signals for the protons in the ^1H NMR spectra of compounds **1**, **4**, **7**, **8**, and **11—13**. The chemical shifts for the carbon atoms in compounds **1***, **4—14** are given in Tables 1 and 2.

A comparison of the ^{13}C NMR spectrum of secondary amine **4** with the spectrum of hydroxylamine **3**[5] shows that the absence of the oxygen atom at the N(20) atom leads to upfield shifts of the signals for the C(19) and C(17) atoms as well as for the C(5) and C(2) atoms and a downfield shift of the signal for the C(7) atom.

Unlike the earlier study[13] in which the doublet at δ 44.0 in the ^{13}C NMR spectrum of *N*(20)-deethyllappaconitine **4** was assigned to the C(7) atom, we assigned this signal to the C(5) atom based on the fact that the 2D $^1H—^1H$ (COSY) spectrum has a signal due to coupling between the H(5) and H(19a) protons. This coupling is impossible for the H(7) proton. In addition, based on the couplings of the H(5) proton with the $H_a(6)$ and $H_b(6)$ protons in the 2D $^1H—^1H$ (COSY) spectrum, we assigned the triplet at δ 23.5 in the $^{13}C—^1H$ (COSY) NMR spectrum to the C(6) atom rather than to C(12) as reported earlier.[13]

The ^1H NMR spectrum of *N*(20)-methyl-*N*(20)-deethyllappaconitine **6** has a singlet at δ 2.23 corresponding to the NMe group, which is manifested in the ^{13}C NMR spectrum as a quartet at δ 41.9.

The formation of compound **7** is confirmed by the fact that the ^1H NMR spectrum shows new signals, *viz.*, two doublets (δ 5.08 and 5.25) and a multiplet (δ 5.83), in the region of olefinic protons. The presence of the allylic fragment bound to the N(20) atom leads to downfield shifts of the signals for the C(19) and C(17) atoms as well as for the C(5) and C(2) atoms compared to the corresponding signals in the spectrum of compound **4**.

The ^{13}C NMR spectrum of compound **8** has a characteristic signal at δ 118.7 for the carbon atom of the cyano group. The IR spectrum has a band at 2247 cm^{-1} characteristic of C≡N stretching vibrations.

Since compound **9** is symmetrical with respect to the central methylene group of the propane fragment, the ^1H NMR spectrum of this compound is virtually identical with that of lappaconitine **1**. Thorough analysis of the ^{13}C NMR spectrum shows that the integral intensity of the signal corresponding to the central C(22) atom (δ 25.14) of compound **9** is approximately half as great as those of other "duplicate" carbon atoms. The elemental analysis data for compound **9** correspond to the molecular formula $C_{63}H_{84}N_4O_{16}$.

A characteristic feature of the ^{13}C NMR spectra of lappaconitine derivatives, particularly, of compounds con-

Table 1. ^{13}C NMR spectra of bases **1**, **1***, **4**—**6**, and **10** and hydrobromides **1** · HBr and **4** · HBr

Atom	δ							
	1[a]	**1** · HBr[b]	**1*** [c]	**4**[a]	**4** · HBr[d]	**5**[e]	**6**[e]	**10**[f]
C(1)	84.0	91.6	84.0	82.3	82.9	83.1	83.7	84.6
C(2)	26.6	35.8	26.6	24.3	23.4	26.7	26.3	26.5
C(3)	31.7	37.4	31.7	29.8	29.9	31.0	31.3	36.8
C(4)	84.4	83.1	84.5	83.3	81.7	84.9	84.1	70.3
C(5)	48.4	56.4	48.4	44.0	42.7	48.5	47.4	50.0
C(6)	24.0	30.8	24.0	23.5	22.5	24.1	23.7	23.1
C(7)	47.5	50.8	47.6	52.3	51.1	47.7	46.4	47.2
C(8)	75.5	86.0	75.4	75.5	75.4	75.2	75.0	75.0
C(9)	78.4	89.6	78.4	77.0	77.8	78.5	78.2	78.2
C(10)	49.7	58.4	49.7	49.2	48.9	49.8	49.7	49.4
C(11)	50.8	59.7	50.8	52.7	51.0	50.7	50.7	50.3
C(12)	26.0	32.0	26.1	26.1	27.1	26.1	25.7	26.0
C(13)	36.1	45.2	36.2	36.8	36.3	36.2	35.8	35.6
C(14)	90.0	98.1	90.0	89.9	89.7	90.0	89.7	89.6
C(15)	44.7	51.4	44.6	43.7	42.4	44.7	44.2	43.9
C(16)	82.7	89.2	82.8	82.3	80.6	82.5	82.5	82.5
C(17)	61.4	70.7	61.2	56.8	58.7	65.0	62.9	61.1
C(19)	55.4	65.5	55.3	50.8	48.8	57.8	57.4	57.3
C(21)	48.9	58.5	48.8	—	—	168.6	41.9	48.5
C(22)	13.4	19.6	13.4	—	—	—	—	13.0
1-OCH_3	56.4	65.0	56.3	55.8	56.5	56.3	56.4	55.9
14-OCH_3	57.8	66.7	57.7	57.5	58.7	57.9	57.4	57.3
16-OCH_3	56.0	65.1	55.9	55.6	56.4	56.0	55.7	55.5
O=C$\underline{C}H_3$	25.4	33.8	25.3	25.2	24.2	25.5	25.1	—
O$\underline{C}$=O	167.3	175.1	167.3	167.0	167.6	167.1	166.9	—
NH$\underline{C}$=O	168.9	177.9	168.9	168.2	173.4	168.8	168.5	—
NO$\underline{C}$OCH$_3$	—	—	—	—	—	168.6	—	—
NOCO$\underline{C}$H$_3$	—	—	—	—	—	19.7	—	—
C(1′)	115.6	129.3	115.7	115.2	122.6	115.0	115.3	—
C(2′)	141.5	148.3	141.5	141.6	137.9	142.0	141.3	—
C(3′)	120.1	131.4	120.1	119.9	124.8	120.3	119.8	—
C(4′)	134.2	143.1	134.1	134.1	135.1	134.6	133.9	—
C(5′)	122.2	132.9	122.1	121.9	126.4	122.2	121.9	—
C(6′)	130.9	140.0	130.9	130.6	131.8	130.9	130.6	—

[a] 125.76 MHz, a 20% solution in $CDCl_3$.
[b] 100.61 Hz, a 10% solution in DMSO-d_6.
[c] 50.32 MHz, a 10% solution in $CDCl_3$.
[d] 50.32 MHz, a 5% solution in D_2O.
[e] 100.61 Hz, a 15% solution in $CDCl_3$.
[f] 125.76 MHz, a 25% solution in $CDCl_3$.

taining bulky substituents at the N(20) atom, is broadening of the high-field signals for the C atoms of ring A, which is apparently associated with deceleration of the inversion of ring A. An analogous effect has been observed earlier for cyclic compounds.[23]

The ^{13}C NMR spectra of compounds **11**—**14** have low-field signals for the carbon atoms of the substituent introduced, *viz.*, the second aromatic ring. In the spectrum of compound **11**, a new singlet appears at δ 138.3, which is unambiguously assigned to the C(1″) atom. Coinciding doublets at δ 127.8—128.7 correspond to the symmetrical C(2″), C(6″) and C(3″), C(5″) atoms and, consequently, the doublet at δ 126.6 belongs to the C(4″) atom. In the spectrum of *p*-hydroxyphenethyl derivative **12**, two doublets at δ 115.0 and 115.6 are assigned to the C(3″) and C(5″) atoms, respectively, and two doublets at δ 129.7 and 129.8 belong to the C(2″) and C(6″) atoms, respectively. The singlet at δ 154.1 corresponds to the C(4″) atom. The assignments of the signals for the aromatic protons in the spectra of compounds **13** and **14** were made from comparison with the spectra of compounds **11** and **12**.

Table 2. ^{13}C NMR spectra of compounds **7—9** and **11—14**[a]

Atom	δ						
	7[b]	**8**[b]	**9**[b]	**11**[b]	**12**[b]	**13**[c]	**14**[b]
C(1)	83.7	82.5	83.5	82.8	83.9	84.0	84.2
C(2)	26.7	26.6	26.4	26.7	26.5	26.4	26.5
C(3)	31.5	31.3	31.4	31.3	31.6	31.6	31.5
C(4)	84.2	83.7	84.2	84.1	84.5	84.4	84.5
C(5)	48.2	47.9	48.1	48.0	48.4	49.5	48.4
C(6)	23.8	24.1	23.8	23.8	24.1	24.0	23.9
C(7)	46.9	48.6	47.0	46.3	47.7	47.8	47.9
C(8)	75.5	75.2	75.1	75.3	75.5	75.5	75.4
C(9)	78.4	78.2	78.2	78.3	78.5	78.5	78.4
C(10)	49.8	49.6	49.6	49.7	49.7	50.3	49.7
C(11)	50.8	50.7	50.6	50.7	50.9	50.9	50.9
C(12)	26.0	25.5	25.7	25.6	26.1	26.1	26.2
C(13)	36.5	36.0	35.8	36.7	36.1	36.0	36.2
C(14)	89.9	89.9	89.7	89.8	89.9	89.8	89.9
C(15)	44.3	44.8	44.3	44.2	44.7	44.5	44.7
C(16)	82.4	82.4	82.6	82.0	82.8	82.6	82.7
C(17)	60.0	57.7	59.3	58.9	61.9	62.2	62.1
C(19)	56.1	55.2	56.0	56.3	55.8	55.6	55.8
C(21)	57.5	50.6	50.4	58.5	57.1	57.5	57.5
C(22)	136.5	17.2	25.1	—	33.4	33.8	34.1
C(23)	116.4	118.7	—	—	—	—	—
1-OCH_3	56.2	55.9	55.7	55.7	56.0	56.3	56.4
14-OCH_3	57.7	57.7	57.4	57.4	57.8	57.8	57.7
16-OCH_3	55.9	55.8	55.7	55.7	56.2	56.0	56.0
O=C$\underline{C}H_3$	25.3	25.3	25.0	25.2	25.4	25.3	25.4
O$\underline{C}$=O	167.1	167.3	166.9	167.0	167.3	167.2	167.3
NHC=O	168.7	168.8	168.3	168.6	169.1	169.3	168.8
C(1′)	115.5	115.2	115.3	115.4	115.7	115.7	115.7
C(2′)	141.4	141.5	141.2	141.3	141.5	141.3	141.5
C(3′)	120.0	120.1	119.7	119.9	120.2	120.2	120.1
C(4′)	134.1	134.4	133.9	134.0	134.3	134.3	134.2
C(5′)	122.1	122.1	121.9	122.0	122.3	122.4	122.2
C(6′)	130.8	130.8	130.7	130.7	131.0	130.9	130.9
C(1″)	—	—	—	138.3	132.1	129.0	130.8
C(2″)	—	—	—	127.8	129.8*	126.7*	125.1
C(3″)	—	—	—	128.6*	115.0**	135.7	135.7
C(4″)	—	—	—	126.7	154.1	153.0	151.6
C(5″)	—	—	—	128.7*	115.6**	116.2	135.7
C(6″)	—	—	—	127.8	129.7*	127.2*	125.1
$(CH_3)_3\underline{C}$	—	—	—	—	—	34.4	34.5
$(\underline{C}H_3)_3C$	—	—	—	—	—	29.4	30.2

[a] In the spectra of compounds **11—13**, an alternative assignment is possible for the signals marked with the same superscripts.
[b] 125.76 MHz, a 15% solution in $CDCl_3$.
[c] 100.61 MHz, a 15% solution in $CDCl_3$.

Experimental

Freshly distilled solvents, "chemically pure" and "analytical grade" reagents, and haloethyl(*tert*-butyl)phenols* with 98% purity were used. Labeled lappaconitine was synthesized using 1,1-dideuteriobromoethane (Federal State Unitary Enterprise "Isotope", Russia; the content of the major compound was 99%). Analytical TLC was carried out on Silufol UV 254 plates (Kavalier, Czechoslovakia) using $CHCl_3$—MeOH—Et_3N (4 : 0.5 : 0.03, v/v) (*A*) and $CHCl_3$—Me_2CO—Et_3N (5 : 4 : 0.3, v/v) (*B*) solvent systems. Preparative TLC was carried out on Al_2O_3 (50—250 μm) activated at 250 °C for 6 h and then deactivated to the Brockmann activity II by adding 3% of water. This

* Samples of haloethyl(*tert*-butyl)phenols were kindly provided by A. P. Krysin (N. N. Vorozhtsov Novosibirsk Institute of Organic Chemistry of the Siberian Branch of the Russian Academy of Sciences).

sorbent was mixed with luminophore K-35 (1 wt.%) to enhance the sensitivity of visual control over the process of separation in the UV light. Plates (30×30 cm) with thickness of a sorbent layer of 2 mm and the $Pr^iOH—Et_2O$ solvent system (1 : 9, v/v) were used.

The IR spectra were recorded on a Vector 22 spectrometer. The UV spectra were measured on a Specord UV-VIS spectrophotometer. The molecular weights and elemental compositions were determined on a Finnigan MAT 8200 high-resolution mass spectrometer (EI, 70 eV).

The melting points were measured on a Kofler hot-stage apparatus.

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

The ^1H and ^{13}C NMR spectra were recorded on Bruker AC-200 (200.13 MHz for ^1H and 50.32 MHz for ^{13}C), Bruker AC-400 (400.13 MHz for ^1H and 100.61 MHz for ^{13}C), and Bruker DRX-500 (500.13 MHz for ^1H and 125.76 MHz for ^{13}C) instruments at 25 °C with resonance stabilization based on the deuterium signal of the solvent ($CDCl_3$, DMSO-d_6, or D_2O). The chemical shifts (δ) were measured with respect to the signals of $CHCl_3$ (δ_H 7.24 and δ_C 76.90), DMSO (δ_H 2.50 and δ_C 39.50), or dioxane (δ_H 3.53 and δ_C 66.60) as the internal standards. The multiplicities of signals in the ^{13}C NMR spectra were determined according to standard procedures using *J* modulation (*J*MOD) and off-resonance irradiation of protons.[23] The assignments of the signals in the NMR spectra were made using various types of proton-proton and carbon-proton correlations. The $^{13}C—^{13}C$ 2D INADEQUATE, 2D $^1H—^1H$ (COSY), and $^{13}C—^1H$ (COSY 125 Hz, COLOC 7—10 Hz) spectra were measured on a Bruker DRX 500 instrument using the standard Bruker software. The ^{13}C NMR spectroscopic data are presented in Tables 1 and 2.

Lappaconitine, 4β-(2-acetylaminobenzoyloxy)-20-ethyl-1α,14α,16β-trimethoxyaconitane-8,9-diol (1), was isolated from air-dried roots of northern wolfsbane *Aconitum septentrionale* Koelle.[5] ^1H NMR (20% solution in $CDCl_3$, 500.13 MHz), δ: 1.10 (t, 3 H, C(22)Me, *J* = 7.2 Hz); 1.57 (dd, 1 H, H_b(6), *J* = 15.2 Hz, *J* = 8.3 Hz); 1.78 (br.t, 1 H, H_b(3), *J* = 13.5 Hz); 1.95 (m, 1 H, H_b(12)); 1.99 (m, 1 H, H_b(15)); 2.08 (dd, 1 H, H(10), *J* = 12.6 Hz, *J* = 4.4 Hz); 2.13 (m, 1 H, H(7)); 2.14 (m, 1 H, H_b(2)); 2.20 (s, 3 H, NHCOC$\underline{H}_3$); 2.26 (m, 1 H, H_a(2)); 2.35 (m, 1 H, H(13)); 2.37 (m, 1 H, H(5)); 2.38 (m, 1 H, H_a(15)); 2.46 (dd, 1 H, H_a(12), *J* = 14.5 Hz, *J* = 4.7 Hz); 2.48 (m, 1 H, H_b(21)); 2.52 (m, 1 H, H_b(19)); 2.53 (m, 1 H, H_a(21)); 2.63 (m, 1 H, H_a(3)); 2.67 (dd, 1 H, H_a(6), *J* = 15.2 Hz, *J* = 7.3 Hz); 3.00 (s, 1 H, H(17)); 3.16 (dd, 1 H, H(1), *J* = 10.4 Hz, *J* = 6.7 Hz); 3.27 (m, 1 H, H(16)); 3.27, 3.28, and 3.38 (all s, 3 H each, 1-, 16-, and 14-OMe, respectively); 3.40 (d, 1 H, H(14), *J* = 5.1 Hz); 3.56 (d, 1 H, H_a(19), *J* = 11.4 Hz); 7.00 (ddd, 1 H, H(5′), *J* = 8.0 Hz, *J* = 7.4 Hz, *J* = 1.1 Hz); 7.47 (ddd, 1 H, H(4′), *J* = 8.8 Hz, *J* = 7.4 Hz, *J* = 1.5 Hz); 7.89 (dd, 1 H, H(6′), *J* = 8.0 Hz, *J* = 1.5 Hz); 8.64 (br.d, 1 H, H(3′), *J* = 8.8 Hz); 11.02 (s, 1 H, N$\underline{H}$COMe).

N*(20)-Deethyllappaconitine, 4β-(2-acetylaminobenzoyloxy)-1α,14α,16β-trimethoxyaconitane-8,9-diol (4).** ***A. A mixture of lappaconitine **1** (0.584 g, 1 mmol), *N*-bromosuccinimide (0.328 g, 2 mmol), and water (6 mL) was heated with stirring at 50 °C for 1 h, cooled to 20 °C, and filtered. A 25% aqueous NH_3 solution was added to the filtrate to pH 8 and the mixture was extracted with $CHCl_3$ (3×5 mL). The extract was concentrated *in vacuo* to 2 mL and subjected to preparative TLC on Al_2O_3. A UV-absorbing zone of the sorbent with R_f 0.38 was collected. The target product was eluted with MeOH. After removal of the solvent from the eluate, the residue was extracted with $CHCl_3$. The chloroform was distilled off *in vacuo*, the residue was triturated with anhydrous Et_2O, and the solid product was filtered off and dried at 50 °C (3 Torr). The yield of compound **4** was 0.320 g (58%), amorphous powder, $[\alpha]_{578}^{20}$ +42.6 (*c* 3.90, $CHCl_3$).

B. Activated Zn dust (3.10 g, 47.40 mmol) was added portionwise with stirring to a solution of hydroxylamine **3**[5] (4.26 g, 7.43 mmol) in glacial AcOH (22.90 mL, 400 mmol). The reaction mixture was stirred at ~20 °C for 5 h until the starting compound was consumed (TLC, system *B*). Then a solution of NaOH was added to the reaction mixture to pH ≈ 9 and the mixture was extracted with $CHCl_3$ (3×30 mL). The organic layer was dried with $MgSO_4$, the solvent was removed, and the residue was dried *in vacuo*. After reprecipitation from chloroform with hexane, the yield of amine **4** was 3.11 g (75%), m.p. 124—126 °C; $[\alpha]_{578}^{27}$ +39.0 (*c* 3.00, $CHCl_3$). MS, *m*/*z* (I_{rel} (%)): 556 $[M]^+$ (0.3), 527 (5.4), 526 (15.4), 525 (5.3), 511 (2.5), 495 (2.6), 405 (2.3), 394 (2.3), 379 (4.3), 378 (25.2), 377 (100), 362 (14.1), 348 (14.7), 347 (36.5), 346 (21.7), 317 (16.9), 162 (17.8), 137 (13.7), 120 (17.0), 119 (22.4). High-resolution mass spectrum. Found: *m*/*z* 556.2792 $[M]^+$. $C_{30}H_{40}N_2O_8$. Calculated: M = 556.2774. ^1H NMR (20% solution in $CDCl_3$, 500.13 MHz), δ: 1.56 (ddd, 1 H, H_b(12), *J* = 13.5 Hz, *J* = 11.1 Hz, *J* = 11.1 Hz); 1.67 (m, 1 H, H_b(6)); 1.82 (m, 1 H, H_b(2)); 1.88 (m, 1 H, H_a(12)); 1.89 (m, 1 H, H(7)); 1.90 (m, 1 H, H(10)); 1.94 (m, 1 H, H_b(15)); 1.95 (m, 1 H, H_a(2)); 1.98 (m, 1 H, H_b(3)); 2.10 (s, 3 H, NHCOC$\underline{H}_3$); 2.15 (m, 1 H, H_a(3)); 2.24 (m, 1 H, H(13)); 2.35 (m, 1 H, H_a(15)); 2.46 (d, 1 H, H(5), *J* = 8.0 Hz); 2.60 (m, 1 H, H_a(6)); 2.81 (br.s, 1 H, H(17)); 2.98 and 3.12 (both d, AB system, 1 H each, H_2C(19), *J* = 12.0 Hz); 3.16, 3.18, and 3.27 (all s, 3 H each, 1-, 16-, and 14-OMe, respectively); 3.19 (m, 1 H, H(16)); 3.22 (dd, 1 H, H(1), *J* = 4.6 Hz, *J* = 4.3 Hz); 3.28 (m, 1 H, H(14)); 6.86 (ddd, 1 H, H(5′), *J* = 8.0 Hz, *J* = 7.5 Hz, *J* < 1.0 Hz); 7.35 (ddd, 1 H, H(4′), *J* = 8.0 Hz, *J* = 8.0 Hz, *J* = 2.0 Hz); 7.78 (dd, 1 H, H(6′), *J* = 7.5 Hz, *J* = 1.5 Hz); 8.54 (dd, 1 H, H(3′), *J* = 8.0 Hz, *J* < 1.0 Hz); 10.92 (s, 1 H, N$\underline{H}$COMe). IR (KBr), ν/cm^{-1}: 757, 847, 1086, 1269, 1297, 1317, 1369, 1448, 1526, 1589, 1605, 1680, 1700, 2823, 2887, 2938, 3265, 3313, 3400, 3454. UV (MeOH), λ_{max}/nm (log ε): 223 (4.30), 252 (4.05), 309 (3.59).

N(20)-Deethyllappaconitine **4** was also characterized as hydrobromide. A solution of 46% HBr (0.059 g) in EtOH (0.5 mL) was added dropwise with stirring to a solution of base **4** (0.17 g, 0.31 mmol) in CH_2Cl_2 (0.5 mL; equimolar amounts of **4** and HBr). The solvent was removed *in vacuo* and the residue was triturated with anhydrous Et_2O, filtered off, and dried. Hydrobromide of base **4** was prepared in a yield of 0.15 g (76%) as an amorphous powder, $[\alpha]_{578}^{20}$ +27.5 (*c* 4.00, H_2O). Found (%): Br, 12.88. $C_{30}H_{40}N_2O_8 \cdot HBr$ ($C_{30}H_{41}BrN_2O_8$). Calculated (%): Br, 12.53. ^1H NMR (5% solution in D_2O, 200.13 MHz), δ: 2.24 (s, 3 H, NHCOCH_3); 3.39, 3.40, and 3.44 (all s, 3 H each, 1-, 16-, and 14-OMe, respectively); 7.35 (t, 1 H, H(5′), *J* = 8.0 Hz); 7.66—7.74 (m, 2 H, H(4′), H(6′)); 7.93 (d, 1 H, H(3′), *J* = 8.0 Hz). IR (KBr), ν/cm^{-1}: 761, 964, 1002, 1086, 1128,

1267, 1299, 1372, 1449, 1529, 1588, 1606, 1685 (NHC=O), 1695 (OC=O), 2829, 2933, 3410. UV (EtOH), λ_{max}/nm (log ε): 223 (4.29), 253 (4.00), 313 (3.57).

"Synthetic" lappaconitine (1). A mixture of *N*(20)-deethyllappaconitine **4** (0.043 g, 0.08 mmol) and EtBr (0.073 g, 0.67 mmol) was sealed and kept at 20 °C for 4 days. An excess of EtBr was removed *in vacuo*. A 25% aqueous NH_3 (0.15 mL) was added to a suspension of the residue in $CHCl_3$ (5 mL). The mixture was vigorously stirred for 5 min and then the organic layer was separated. According to the data from analytical TLC ($Pr^iOH—Et_2O$, 1 : 9, v/v), the resulting mixture contained lappaconitine **1** (R_f 0.85) and the starting compound **4** (R_f 0.38). The mixture was subjected to preparative TLC on Al_2O_3. A UV-absorbing zone of the sorbent with R_f 0.85 was collected. The target product was eluted with MeOH, the solvent was removed, and the residue was extracted with $CHCl_3$. Then $CHCl_3$ was distilled off *in vacuo* and the residue was triturated with anhydrous Et_2O, filtered off, and dried. The yield of lappaconitine **1** was 0.032 g (70%). Analogously, "synthetic" lappaconitine was synthesized with the use of iodoethane in 76% yield. The products were identified by comparing with the starting lappaconitine isolated from the natural source.

Lappaconitine **1** was also characterized as hydrobromide. A solution of 46% HBr (0.035 g) in EtOH (0.6 mL) was added dropwise with stirring to a solution of base **1** (0.117 g, 0.20 mmol) in CH_2Cl_2 (0.3 mL; equimolar amounts of **1** and HBr). The solvent was distilled off *in vacuo* until crystallization started. The reaction mixture was kept at 0 °C for 16 h. The crystals that formed were filtered off and dried, the yield was 0.123 g (92.5%); m.p. 223—226 °C (with decomp.); $[\alpha]_{578}^{20}$ +22.4 (*c* 10.0, DMSO). Found (%): Br, 12.21; H_2O (according to Fischer), 0.04±0.02. $C_{32}H_{44}N_2O_8 \cdot HBr$ ($C_{32}H_{45}BrN_2O_8$). Calculated (%): Br, 12.00 (*cf.* lit.[6]: the air-dried product has the composition $C_{32}H_{44}N_2O_8 \cdot HBr \cdot 0.5H_2O$, m.p. 225.5 °C). ^{1}H NMR (10% solution in DMSO-d_6, 400.13 MHz), δ: 1.25 (t, 3 H, $NCH_2C\underline{H}_3$, *J* = 7.0 Hz); 2.14 (s, 3 H, $NHCOC\underline{H}_3$); 3.23, 3.28, and 3.29 (all s, 3 H each, 1-, 16-, and 14-OMe, respectively); 7.20 (t, 1 H, H(4′), *J* = 8 Hz); 7.58 (t, 1 H, H(5′), *J* = 8 Hz); 7.82 (dd, 1 H, H(6′), *J* = 8 Hz, *J* = 1 Hz); 7.98 (d, 1 H, H(3′), *J* = 8 Hz); 10.35 (s, 1 H, NH). IR (KBr), ν/cm^{-1}: 765, 1024, 1042, 1083, 1131, 1225, 1240, 1271, 1294, 1318, 1376, 1449, 1526, 1586, 1683 (NHC=O), 1699 (OC=O), 2934, 2978, 3215, 3293. UV (EtOH), λ_{max}/nm (log ε): 223 (4.42), 252 (4.06), 308 (3.70).

[21,21-$^2H_2$]-Lappaconitine, 4β-(2-acetylaminobenzoyloxy)-20-(1,1-dideuterioethyl)-1α,14α,16β-trimethoxyaconitane-8,9-diol (1*), was synthesized as described above using 1,1-dideuteriobromoethane. The yield was 70%, m.p. 220—222 °C (Et_2O). High-resolution mass spectrum. Found: *m/z* 586 $[M]^+$. $C_{32}H_{42}D_2N_2O_8$. Calculated: M = 586. For the most intense fragmentation ion, found: *m/z* 407.2637. $C_{32}H_{42}D_2N_2O_8 - C_9H_9NO_3 = C_{23}H_{33}D_2NO_5$. Calculated: M = 407.2641. ^{1}H NMR (10% solution in $CDCl_3$, 200.13 MHz), δ: 1.06 (s, 3 H, $NCD_2C\underline{H}_3$); 2.18 (s, 3 H, $NHCOC\underline{H}_3$); 3.25, 3.27, and 3.36 (all s, 3 H each, 1-, 16-, and 14-OMe, respectively); 6.97 (t, 1 H, H(5′), *J* = 8 Hz); 7.44 (t, 1 H, H(4′), *J* = 8 Hz); 7.90 (d, 1 H, H(6′), *J* = 8 Hz); 8.64 (d, 1 H, H(3′), *J* = 8 Hz); 11.00 (s, 1 H, N<u>H</u>). IR (KBr), ν/cm^{-1}: 758, 1087, 1114, 1146, 1202, 1237, 1269, 1296, 1317, 1368, 1448, 1525, 1589, 1608, 1684 (NHC=O), 1704 (OC=O), 2928, 3326, 3449. UV (MeOH), λ_{max}/nm (log ε): 224 (4.41), 253 (4.17), 310 (3.55).

***N*(20)-Acetoxy-*N*(20)-deethyllappaconitine, 20-acetoxy-4β-(2-acetylaminobenzoyloxy)-1α,14α,16β-trimethoxyaconitane-8,9-diol (5).** Potassium carbonate (124 mg, 0.90 mmol) was added to a solution of hydroxylamine **3** (270 mg, 0.47 mmol) in $CHCl_3$ (2.00 mL) and Ac_2O (2.50 mL, 26.50 mmol). The reaction mixture was stirred at ~20 °C for 24 h and then kept without stirring for 24 h (TLC, system *A*). Then the mixture was cooled with ice and a 25% aqueous NH_3 was added to pH ≈ 11. The reaction mixture was extracted with $CHCl_3$ (3×5 mL) and the combined extracts were dried with $MgSO_4$. After removal of the solvent, the residue was dried *in vacuo* to yield 255 mg (87%) of product **5**, m.p. 226—227.5 °C (needles, from ethyl acetate), $[\alpha]_{578}^{23}$ +36.6 (*c* 1.53, $CHCl_3$). Found (%): C, 61.85; H, 6.89; N, 4.46. $C_{32}H_{42}N_2O_{10}$. Calculated (%): C, 62.53; H, 6.89; N, 4.56. MS, *m/z* (I_{rel} (%)): 554 $[M - AcOH]^+$ (6.0), 394 (7.5), 393 (36.1), 377 (10.9), 375 (19.5), 362 (7.4), 345 (15.4), 333 (11.4), 179 (11.9), 163 (14.0), 162 (100), 161 (15). High-resolution mass spectrum. Found: *m/z* 554.2628 $[M - AcOH]^+$. $C_{30}H_{38}N_2O_8$. Calculated: M – AcOH = 554.2318. ^{1}H NMR (15% solution in $CDCl_3$, 400.13 MHz), δ: 2.07 (s, 3 H, AcON); 2.20 (s, 3 H, Ac); 3.26, 3.29, and 3.39 (all s, 3 H each, 1-, 16-, and 14-OMe, respectively); 4.16 and 3.48 (both d, AB system, 1 H each, $H_2C(19)$, *J* = 11 Hz); 6.99 (ddd, 1 H, H(5′), *J* = 8.0 Hz, *J* = 7.5 Hz, *J* < 1.0 Hz); 7.48 (ddd, 1 H, H(4′), *J* = 8.0 Hz, *J* = 8.0 Hz, *J* = 1.5 Hz); 7.87 (dd, 1 H, H(6′), *J* = 7.5 Hz, *J* = 1.5 Hz); 8.66 (dd, 1 H, H(3′), *J* = 8.0 Hz, *J* < 1.0 Hz); 10.98 (s, 1 H, N<u>H</u>COMe). IR (KBr), ν/cm^{-1}: 762, 1083, 1205, 1232, 1263, 1372, 1443, 1468, 1510, 1585, 1605, 1694, 1745, 2819, 2886, 2932, 3260, 3420. UV (MeOH), λ_{max}/nm (log ε): 223 (4.30), 252 (4.05), 309 (3.56).

***N*(20)-Methyl-*N*(20)-deethyllappaconitine, 4β-(2-acetylaminobenzoyloxy)-1α,14α,16β-trimethoxy-20-methylaconitane-8,9-diol (6).** Potassium carbonate (180 mg, 1.26 mmol) and MeI (134 μL, 305.30 mg, 2.15 mmol) were added to a solution of compound **4** (348 mg, 0.63 mmol) in MeCN (5.50 mL). The reaction mixture was stirred for 24 h and then kept without stirring at 40—45 °C under a stream of argon for 24 h (TLC, system *B*). After completion of the reaction, a cooled saturated NaCl solution (15 mL) was added. The reaction mixture was extracted with $CHCl_3$ (7×15 mL). The combined extracts were washed with a saturated NaCl solution and dried with $MgSO_4$. After removal of the solvent, the residue was dried *in vacuo* to prepare product **6** in a yield of 341 mg (95%), m.p. 94—98 °C, $[\alpha]_{578}^{30}$ +20.4 (*c* 1.57, $CHCl_3$). MS, *m/z* (I_{rel} (%)): 570 $[M]^+$ (0.9), 539 (7.4), 392 (27.8), 391 (100), 378 (9.0), 377 (1.41), 376 (48.5), 362 (18.0), 361 (53.2), 360 (50.9), 346 (12.9), 344 (8.3), 332 (18.9), 331 (53.3), 330 (14.3), 314 (10.5), 301 (10.4), 262(17.4), 249 (11.7), 164 (29.3), 162 (22.2), 120 (22.6), 119 (13.0). High-resolution mass spectrum. Found: *m/z* 570.2945 $[M]^+$. $C_{31}H_{42}N_2O_8$. Calculated: M = 570.2941. ^{1}H NMR (15% solution in $CDCl_3$, 400.13 MHz), δ: 2.09 (s, 3 H, MeCO); 2.23 (s, 3 H, NMe); 3.16, 3.17, and 3.27 (all s, 3 H each, 1-, 16-, and 14-OMe, respectively); 6.89 (dd, 1 H, H(5′), *J* = 8.0 Hz, *J* = 7.5 Hz); 7.36 (dd, 1 H, H(4′), *J* = 8.0 Hz, *J* = 8.0 Hz); 7.76 (d, 1 H, H(6′), *J* = 7.5 Hz); 8.55 (d, 1 H, H(3′), *J* = 8.0 Hz); 10.92 (s, 1 H, N<u>H</u>Ac). IR (KBr), ν/cm^{-1}: 757, 1035, 1088, 1270, 1296, 1317, 1368, 1448, 1526, 1589, 1605, 1683, 1705, 2820, 2927, 3312, 3462. UV (MeOH), λ_{max}/nm (log ε): 222 (4.32), 252 (4.05), 308 (3.61).

***N*(20)-Allyl-*N*(20)-deethyllappaconitine, 4β-(2-acetylaminobenzoyloxy)-1α,14α,16β-trimethoxy-20-(propen-3-yl)aconitane-**

8,9-diol (7). Potassium carbonate (53.8 mg, 0.39 mmol) was added to a solution of compound **4** (200 mg, 0.36 mmol) in DMF (3.00 mL) and then AllBr (65.9 μL, 94.2 mg, 0.78 mmol) was added dropwise with stirring. The reaction mixture was stirred at 90—95 °C under a stream of argon for 4 h (TLC, system *B*) and then worked up as described above. After removal of the solvent, the residue was dried *in vacuo* to prepare product **7** in a yield of 155 mg (72%), m.p. 97—100 °C, $[\alpha]_{578}^{24}$ +58.4 (*c* 1.37, $CHCl_3$). MS, *m/z* (I_{rel} (%)): 596.3 $[M]^+$ (0.9), 566 (2.3), 565 (8.4), 547 (2.3), 418 (29.5.0), 417 (100), 403 (13.1), 402 (49.8), 387 (26.3), 386 (38.9), 372 (11.1), 358 (18.6), 357 (43.4), 288 (16.0), 190 (21.4), 162 (18.4), 120 (31.3). High-resolution mass spectrum. Found: *m/z* 596.3094 $[M]^+$. $C_{33}H_{44}N_2O_8$. Calculated: M = 596.3098. ^{1}H NMR (15% solution in $CDCl_3$, 500.13 MHz), δ: 1.54 (dd, 1 H, H_b(6), *J* = 15.0 Hz, *J* = 7.0 Hz); 1.76 (m, 1 H, H_b(3)); 1.90 (m, 1 H, H(10)); 1.92 (dd, 1 H, H_b(15), *J* = 14.5 Hz, *J* = 7.5 Hz); 2.04 (dd, 1 H, H_b(12), *J* = 12.0 Hz, *J* = 4.5 Hz); 2.10 (dd, 1 H, H(7), *J* = 8.0 Hz, *J* ≈ 2.0 Hz); 2.13 (m, 1 H, H_b(2)); 2.16 (s, 3 H, MeCO); 2.26 (m, 1 H, H_a(2)); 2.28 (m, 1 H, H(13)); 2.30 (m, 1 H, H_a(15)); 2.33 (m, 1 H, H(5)); 2.45 (dd, 1 H, H_a(12), *J* = 14.5 Hz, *J* ≈ 4.5 Hz); 2.57 (d, 1 H, H_b(19), *J* = 11.0 Hz); 2.58 (m, 1 H, H_a(3)); 2.66 (dd, 1 H, H_a(6), *J* = 15.0 Hz, *J* = 8.5 Hz); 2.99 (s, 1 H, H(17)); 3.09 (m, 2 H, H_2C(21)); 3.21 (m, 1 H, H(16)); 3.22, 3.24, and 3.35 (all s, 3 H each, 16-, 1-, and 14-OMe, respectively); 3.25 (m, 1 H, H(1)); 3.36 (d, 1 H, H(14), *J* = 5.0 Hz); 3.46 (d, 1 H, H_a(19), *J* = 11.0 Hz); 5.08 (d, 1 H, H_b(23), J_{cis} = 10.0 Hz); 5.25 (d, 1 H, H_a(23), J_{trans} = 17.0 Hz); 5.83 (ddt, 1 H, H(22), *J* = 17.0 Hz, *J* = 10.0 Hz, *J* = 6.5 Hz); 6.96 (ddd, 1 H, H(5′), *J* = 8.0 Hz, *J* = 7.5 Hz, *J* < 1.0 Hz); 7.43 (ddd, 1 H, H(4′), *J* = 8.0 Hz, *J* = 8.0 Hz, *J* = 1.5 Hz); 7.86 (dd, 1 H, H(6′), *J* = 7.5 Hz, *J* = 1.5 Hz); 8.61 (dd, 1 H, H(3′), *J* = 8.0 Hz, *J* < 1.0 Hz); 10.99 (s, 1 H, NHAc). IR (KBr), ν/cm^{-1}: 758, 1040, 1088, 1242, 1316, 1368, 1447, 1526, 1589, 1605, 1683, 1700, 2820, 2827, 3316, 3455. UV (MeOH), λ_{max}/nm (log ε): 223 (4.34), 252 (4.08), 308 (3.63).

***N*(20)-β-Cyanoethyl-*N*(20)-deethyllappaconitine, 4β-[2-(acetylamino)benzoyloxy]-22-cyanoethyl-1α,14α,16β-trimethoxyaconitane-8,9-diol (8).** Triethylamine (0.58 mL, 4.40 mmol) and acrylonitrile (4×53.0 μL, 4×0.8 mmol) were added to a solution of compound **4** (500 mg, 0.89 mmol) in EtOH (3.00 mL). The reaction mixture was stirred at 70—80 °C under a stream of argon for 48 h and then kept at ~20 °C for ~16 h (TLC, system *B*). After standard work-up, a crude product was obtained in a yield of 548 mg. After twofold precipitation from diethyl ether, the yield of product **8** was 80%, m.p. 242—244 °C, $[\alpha]_{578}^{24}$ +30.2 (*c* 2.19, $CHCl_3$). MS, *m/z* (I_{rel} (%)): 608 $[M - 1]^+$ (2.3), 578 (4.1), 569 (100), 566 (1.5), 560 (2.0), 534 (2.3), 526 (2.0). High-resolution mass spectrum. Found: *m/z* 430.24530 $[M - C_9H_9NO_3]^+$. $C_{24}H_{34}N_2O_5$. Calculated: $M - C_9H_9NO_3$ = 430.24675. ^{1}H NMR (15% solution in $CDCl_3$, 500.13 MHz), δ: 1.58 (dd, 1 H, H_b(6), *J* = 15.5 Hz, *J* = 8.3 Hz); 1.72 (dddd, 1 H, H_b(3), *J* = 13.0 Hz, *J* = 13.0 Hz, *J* = 7.0 Hz, *J* = 2.0 Hz); 1.98 (ddd, 1 H, H_b(12), *J* = 15.0 Hz, *J* = 12.0 Hz, *J* = 7.5 Hz); 2.02 (d, 1 H, H(7), *J* = 7.3 Hz); 2.03 (dd, 1 H, H_b(15), *J* = 15.0 Hz, *J* = 8.5 Hz); 2.08 (dd, 1 H, H(10), *J* = 12.0 Hz, *J* = 5.0 Hz); 2.18 (m, 1 H, H_b(2)); 2.19 (s, 3 H, AcO); 2.21 (m, 1 H, H_a(2)); 2.32 (d, 1 H, H_a(15), *J* = 8.5 Hz); 2.35 (d, 1 H, H(5), *J* = 8.3 Hz); 2.36 (m, 1 H, H(13)); 2.48 (dd, 1 H, H_a(12), *J* = 15.0 Hz, *J* = 5.0 Hz); 2.50 (t, 2 H, H_2C(22), *J* = 7.0 Hz, *J* = 7.0 Hz); 2.64 (m, 1 H, H_a(3)); 2.70 (d, 1 H, H_b(19), *J* = 11.0 Hz); 2.71 (m, 1 H, H_b(21)); 2.74 (dd, 1 H, H_a(6), *J* = 15.5 Hz, *J* = 7.3 Hz); 2.87 (dt, 1 H, H_a(21), *J* = 7.0 Hz, *J* = 13.0 Hz); 2.92 (s, 1 H, H(17)); 3.16 (dd, 1 H, H(1), *J* = 8.0 Hz, *J* = 2.0 Hz); 3.25, 3.29, and 3.37 (all s, 3 H each, 1-, 16-, and 14-OMe, respectively); 3.27 (m, 1 H, H(16)); 3.41 (dd, 1 H, H(14), *J* = 5.0 Hz, *J* ≈ 1.0 Hz); 3.60 (d, 1 H, H_a(19), *J* = 11.0 Hz); 6.99 (ddd, 1 H, H(5′), *J* = 8.0 Hz, *J* = 7.5 Hz, *J* < 1.0 Hz); 7.47 (ddd, 1 H, H(4′), *J* = 8.0 Hz, *J* = 8.0 Hz, *J* = 1.5 Hz); 7.87 (dd, 1 H, H(6′), *J* = 7.5 Hz, *J* = 1.5 Hz); 8.63 (dd, 1 H, H(3′), *J* = 8.0 Hz, *J* < 1.0 Hz); 10.97 (s, 1 H, NHAc). IR (KBr), ν/cm^{-1}: 758, 1044, 1088, 1117, 1142, 1160, 1198, 1232, 1268, 1296, 1316, 1368, 1447, 1469, 1526, 1589, 1605, 1682, 1702, 2823, 2928, 3319, 3453. UV (MeOH), λ_{max}/nm (log ε): 228 (4.49), 307 (3.69).

1,3-Bis[*N*(20)-deethyllappaconitin-20-yl]propane, 1,3-bis[4β-(2-acetylaminobenzoyloxy)-8,9-dihydroxy-1α,14α,16β-trimethoxyaconitan-20-yl]propane (9). Potassium carbonate (125 mg, 0.91 mmol) and 1,3-dibromopropane (42.0 μL, 83.0 mg, 0.41 mmol) were added to a solution of compound **4** (500 mg, 0.91 mmol) in DMF (7.50 mL). The mixture was stirred at 70 °C under a stream of argon for 4.5 h (TLC, system *B*). After completion of the reaction, cold brine was added to the reaction mixture. Then the mixture was extracted with $CHCl_3$ (6×15 mL). The combined extracts were washed with brine and dried with $MgSO_4$. The mixture was concentrated and product **9** was isolated in a yield of 161 mg (31%) from the residue (457 mg) by preparative TLC in system *B*, $[\alpha]_{578}^{22}$ +20.2 (*c* 1.19, $CHCl_3$), m.p. 154—155 °C. Found (%): C, 62.98; H, 7.12; N, 4.53. $C_{63}H_{84}N_4O_{16}\cdot 1/2CHCl_3$. Calculated (%): C, 62.87; H, 7.02; N, 4.62. According to the elemental analysis data, this compound contained no bromine. MS (EI, 70 eV), *m/z* (I_{rel} (%)): 843 $[M - 309]^+$ (18), 827 (19), 797 (26), 754 (9), 596 (23), 583 (28), 566 (29), 553 (13), 526 (50), 507 (72), 478 (58), 463 (100), 390 (19). ^{1}H NMR (15% solution in $CDCl_3$, 500.13 MHz), δ: 1.11 (t, 2 H, H_2C(22)); 2.10 (s, 3 H, AcO); 3.19, 3.22, and 3.28 (all s, 3 H each, 1-, 16-, and 14-OMe, respectively); 6.90 (ddd, 1 H, H(5′), *J* = 8.0 Hz, *J* = 7.5 Hz, *J* < 1.0 Hz); 7.34 (ddd, 1 H, H(4′), *J* = 8.0 Hz, *J* = 8.0 Hz, *J* = 1.5 Hz); 7.81 (dd, 1 H, H(6′), *J* = 7.5 Hz, *J* = 1.5 Hz); 8.54 (dd, 1 H, H(3′), *J* = 8.0 Hz, *J* < 1.0 Hz); 10.96 (s, 1 H, NHAc). IR (KBr), ν/cm^{-1}: 758, 1019, 1040, 1213, 1239, 1368, 1447, 1525, 1589, 1605, 1683, 1700, 2821, 2926, 3329, 3465. UV (MeOH), λ_{max}/nm (log ε): 223 (4.69), 252 (4.44), 308 (3.98).

***N*(20)-Benzyl-*N*(20)-deethyllappaconitine, 4β-(2-acetylaminobenzoyloxy)-20-benzyl-1α,14α,16β-trimethoxyaconitane-8,9-diol (11).** Potassium carbonate (64.9 mg, 0.47 mmol) and BnBr (56.0 μL, 80.4 mg, 0.47 mmol) were added to a solution of compound **4** (261 mg, 0.47 mmol) in MeCN (5.00 mL). The reaction mixture was heated at 80—90 °C with stirring under a stream of argon for 2 h (TLC, system *B*) and then worked up as described in the synthesis of compound **9**. The yield of product **11** was 258 mg (85%), m.p. 120—123 °C, $[\alpha]_{578}^{20}$ +20.9 (*c* 2.14, $CHCl_3$). MS, *m/z* (I_{rel} (%)): 615 $[M - OMe]^+$ (2.8), 468 (17.1), 467 (43.1), 454 (12.9), 452 (26 6), 438 (9.0), 437 (17.1), 436 (21.8), 408 (11.2), 407 (27.1), 240 (9.8), 162 (11.7), 120 (18.6), 92 (12.8), 91 (100). High-resolution mass spectrum. Found: *m/z* 615.30256 $[M - OMe]^+$. $C_{36}H_{43}N_2O_7$. Calculated: M − OMe = 615.30700. ^{1}H NMR (15% solution in $CDCl_3$, 500.13 MHz), δ: 1.59 (dd, 1 H, H_b(6) *J* = 15.0 Hz, *J* = 8.0 Hz); 1.77 (m, 1 H, H_b(12)); 1.78 (m, 1 H, H_b(3)); 1.80 (m, 1 H,

H_b(15)); 1.98 (dd, 1 H, H_a(15), J = 14.5 Hz, J = 8.0 Hz); 1.99 (dd, 1 H, H(10), J = 12.0 Hz, J = 4.0 Hz); 2.10 (dd, 1 H, H(13), J = 7.5 Hz, J = 5.0 Hz); 2.12 (m, 1 H, H(7)); 2.14 (s, 3 H, AcO); 2.20 (m, 1 H, H_b(2)); 2.25 (m, 1 H, H_a(12)); 2.34 (m, 1 H, H_a(2)); 2.36 (br.d, 1 H, H(5), J = 7.0 Hz); 2.45 (br.t, 1 H, H(16), J = 8.0 Hz, J = 8.0 Hz); 2.61 (m, 1 H, H_a(3)); 2.67 (dd, 1 H, H_a(6), J = 15.0 Hz, J = 8.0 Hz); 2.70 (d, 1 H, H_b(19), J = 12.0 Hz); 2.83 (s, 1 H, H(17)); 2.97, 3.25, and 3.28 (all s, 3 H each, 16-, 1-, and 14-OMe, respectively); 3.12 (dd, 1 H, H(1), J = 10.0 Hz, J = 7.0 Hz); 3.29 (d, 1 H, H(14), J = 4.5 Hz); 3.50 and 3.55 (both d, AB system, 1 H each, H_2C(21), J = 10.0 Hz); 3.53 (d, 1 H, H_a(9) J = 12.0 Hz); 6.96 (ddd, 1 H, H(5′), J = 7.5 Hz, J = 7.5 Hz, J = 1.0 Hz); 7.17 (ddd, 1 H, H(4′), J = 7.0 Hz, J = 7.0 Hz, J < 1.0 Hz); 7.25 (t, 2 H, H(3″), H(5″), J = 7.5 Hz, J = 7.5 Hz); 7.38 (br.d, 2 H, H(2″), H(6″), J = 7.5 Hz); 7.42 (dt, 1 H, H(4″), J = 7.5 Hz, J = 2.0 Hz), 7.87 (d, 1 H, H(6′), J = 7.5 Hz, J = 1.0 Hz); 8.61 (dd, 1 H, H(3′), J = 8.0 Hz, J < 1.0 Hz); 10.98 (s, 1 H, NHAc). IR (KBr), ν/cm^{-1}: 670, 757, 1088, 1115, 1146, 1238, 1269, 1296, 1316, 1367, 1448, 1495, 1526, 1589, 1605, 1682, 1701, 2819, 2927, 3325, 3454. UV (MeOH), λ_{max}/nm (log ε): 228 (3.79), 253 (3.78), 311 (3.39).

***N*(20)-*p*-Hydroxyphenethyl-*N*(20)-deethyllappaconitine, 4β-(2-acetylaminobenzoyloxy)-20-(4-hydroxyphenethyl)-1α,14α,16β-trimethoxyaconitane-8,9-diol (12).** Potassium carbonate (125 mg, 0.91 mmol) was added to a solution of compound **4** (500 mg, 0.91 mmol) in DMF (7.50 mL) and then 4-(2-bromoethyl)phenol (201 mg, 1 mmol) was added portionwise with stirring. The reaction mixture was stirred until the starting compound was consumed (24 h, 70 °C, TLC, system *B*). Standard work-up afforded the reaction mixture (512 mg), from which compound **12** was isolated in a yield of 418 mg (69%) by repeated precipitation from pentane, m.p. 118—121 °C, $[\alpha]_{578}^{21}$ +32.9 (*c* 3.0, $CHCl_3$), $[\alpha]_{578}^{28}$ +31.1 (*c* 3.0, MeOH). MS, *m*/*z* (I_{rel} (%)): 675 $[M - H]^+$ (2.2), 631 (2.8), 605 (2.6), 585 (4.6), 569 (78.5), 551 (20.0), 505 (6.2), 497 (92.3), 431 (30.8), 408 (100), 372 (38.5). High-resolution mass spectrum. Found: *m*/*z* 569.28590 $[M - C_7H_7O]^+$. $C_{31}H_{41}N_2O_8$. Calculated: $M - C_7H_7O$ = 569.28627. ^{1}H NMR (15% solution in $CDCl_3$, 500.13 MHz), δ: 1.59 (dd, 1 H, H_b(6), J = 15.0 Hz, J = 8.2 Hz); 1.77 (br.td, 1 H, H_b(3), J = 13.6 Hz, J = 4.8 Hz); 1.97 (m, 1 H, H_b(12)); 2.01 (m, 1 H, H_b(15)); 2.09 (dd, 1 H, H(10), J = 5.0 Hz, J = 13.0 Hz); 2.14 (m, 1 H, H_b(2)); 2.15 (m, 1 H, H(7)); 2.19 (m, 1 H, H_a(2)); 2.21 (s, 3 H, AcO); 2.35 (m, 1 H, H_a(15)); 2.36 (m, 1 H, H(13)); 2.37 (m, 1 H, H(5)); 2.46 (dd, 1 H, H_a(12), J = 15.2 Hz, J = 4.3 Hz); 2.60 (m, 1 H, H_b(21)); 2.62 (m, 2 H, H_a(3), H_b(19)); 2.66 (m, 1 H, H_b(22)); 2.68 (m, 1 H, H_a(6)); 2.74 (m, 1 H, H_a(21)); 2.76 (m, 1 H, H_a(22)); 3.01 (s, 1 H, H(17)); 3.18 (dd, 1 H, H(1), J = 10.3 Hz, J = 7.3 Hz); 3.28 (m, 1 H, H(16)); 3.27, 3.28, and 3.38 (all s, 3 H each, 1-, 16-, and 14-OMe, respectively); 3.42 (d, 1 H, H(14), J = 4.6 Hz); 3.59 (d, 1 H, H_a(19), J = 13.0 Hz); 6.74 (d, 2 H, H(3″), H(5″), J = 8.0 Hz); 7.01 (ddd, 1 H, H(5′), J = 8.0 Hz, J = 7.5 Hz, J = 1.0 Hz); 7.07 (d, 2 H, H(2″), H(6″), J = 8.0 Hz); 7.47 (ddd, 1 H, H(4′), J = 7.5 Hz, J = 7.5 Hz, J < 1.0 Hz); 7.90 (dd, 1 H, H(6′), J = 7.5 Hz, J = 1.5 Hz); 8.64 (dd, 1 H, H(3′), J = 8.0 Hz, J < 1.0 Hz); 11.06, (s, 1 H, NHAc). IR (KBr), ν/cm^{-1}: 757, 1041, 1088, 1162, 1238, 1298, 1315, 1368, 1448, 1516, 1589, 1607, 1681, 2821, 2927, 3329, 3410. UV (MeOH), λ_{max}/nm (log ε): 224 (4.27), 252 (4.05), 287 (3.49), 308 (3.61).

***N*(20)-(3-*tert*-Butyl-4-hydroxyphenethyl)-*N*(20)-deethyllappaconitine, 4β-(2-acetylaminobenzoyloxy)-20-(3-*tert*-butyl-4-hydroxyphenethyl)-1α,14α,16β-trimethoxyaconitane-8,9-diol (13).** Potassium carbonate (74.5 mg, 0.54 mmol) was added to a solution of amine **4** (300 mg, 0.54 mmol) in DMF (5.00 mL) and then 2-*tert*-butyl-4-(2-chloroethyl)phenol[24] (121 mg, 0.54 mmol) was added portionwise with stirring. The reaction mixture was stirred at 70—80 °C for 16 h until the starting compound was consumed (TLC, system *B*) and then kept at ~20 °C for ~16 h. Standard work-up gave rise to a mixture (486 mg) from which compound **13** was isolated. After twofold precipitation from $CHCl_3$ with hexane, the yield of **13** was 241 mg (61%), m.p. 91—94 °C, $[\alpha]_{578}^{25}$ +14.7 (*c* 3.0, MeOH). MS, *m*/*z* (I_{rel} (%)): 569 $[M - C_{11}H_{15}O]^+$ (53.6), 553 (19.8), 436 (23.2), 428 (31.6), 427 (22.3), 426 (100), 409 (19.3), 408 (96.5),406 (12.5), 392 (48.4), 390 (15.3), 220 (13.7), 177 (39.3), 176 (17.9), 161 (31.2), 137 (17.5), 133 (12.1), 118 (3.35). High-resolution mass spectrum. Found: *m*/*z* 569.28703 $[M - C_{11}H_{15}O]^+$. $C_{31}H_{41}N_2O_8$. Calculated: $M - C_{11}H_{15}O$ = 569.28627. ^{1}H NMR (15% solution in $CDCl_3$, 500.13 MHz), δ: 1.38 (s, 9 H, C(7)Me_3); 1.62 (m, 1 H, H_b(6)); 1.80 (m, 1 H, H_b(3)); 1.99 (m, 1 H, H_b(12)); 2.03 (m, 1 H, H_b(15)); 2.10 (m, 1 H, H_a(12)); 2.19 (m, 1 H, H(7)); 2.21 (s, 3 H, Ac); 2.21—2.26 (AB system, 2 H, H_aH_bC(2)); 2.36 (m, 1 H, H(5)); 2.37 (m, 1 H, H(13)); 2.39 (m, 1 H, H_a(15)); 2.59 (m, 1 H, H_b(22)); 2.62 (m, 1 H, H_a(3)); 2.64 (m, 1 H, H_b(19)); 2.65 (m, 1 H, H_b(21)); 2.66 (m, 1 H, H_a(22)); 2.69 (m, 1 H, H_a(21)); 2.72 (m, 1 H, H_a(6)); 3.03 (s, 1 H, H(17)); 3.19 (m, 1 H, H(1)); 3.26, 3.28, and 3.38 (all s, 3 H each, 1-, 16-, and 14-OMe, respectively); 3.30 (m, 1 H, H(16)); 3.43 (m, 1 H, H(10)); 3.43 (m, 1 H, H(14)); 3.64 (m, 1 H, H_a(19)); 6.67 (d, 1 H, H(2″), J = 8.0 Hz); 6.84 (dd, 1 H, H(3″), J = 8.0 Hz, J = 1.5 Hz); 7.01 (t, 1 H, H(5′), J = 7.5 Hz, J = 7.5 Hz); 7.03 (br.s, 1 H, H(6″)); 7.47 (br.t, 1 H, H(4′), J = 7.5 Hz, J = 7.5 Hz); 7.91 (br.d, 1 H, H(6′), J = 8.0 Hz); 8.64 (br.d, 1 H, H(3′), J = 8.0 Hz); 11.08 (s, 1 H, NHAc). IR (KBr), ν/cm^{-1}: 758, 818, 1088, 1115, 1145, 1205, 1269, 1299, 1367, 1423, 1448, 1515, 1589, 1607, 1684, 2823, 2875, 2951, 3320, 3399. UV (MeOH), λ_{max}/nm (log ε): 224 (4.47), 252 (4.02), 280 (3.66), 285 (3.67), 308 (3.55).

***N*(20)-(3,5-Di-*tert*-butyl-4-hydroxyphenethyl)-*N*(20)-deethyllappaconitine, 4β-(2-acetylaminobenzoyloxy)-20-(3,5-di-*tert*-butyl-4-hydroxyphenethyl)-1α,14α,16β-trimethoxyaconitane-8,9-diol (14).** Potassium carbonate (74.5 mg, 0.54 mmol) was added to a solution of amine **4** (249 mg, 0.45 mmol) in DMF (5.00 mL) and then 2,6-di-*tert*-butyl-4-(2-chloroethyl)phenol[24] (121 mg, 0.45 mmol) was added portionwise with stirring. The reaction mixture was stirred at 70—80 °C for 16 h until the starting compound was consumed (TLC, system *B*) and then kept at ~20 °C for ~16 h. Standard work-up gave rise to a mixture (300.30 mg) from which compound **14** was isolated by repeated precipitation from chloroform with hexane, the yield of **14** was 224 mg (63%), m.p. 99—102 °C, $[\alpha]_{578}^{18}$ +22.06 (*c* 3.0, $CHCl_3$). MS, *m*/*z* (I_{rel} (%)): 788 $[M - 1]^+$ (1.0), 757 (0.3), 671 (0.2), 627 (1.0), 609 (6.8), 605 (1.0), 569 (100), 551 (7.1), 436 (6.2), 431 (15.4), 408 (78.6), 393 (42.7), 376 (3.8), 276 (2.2). ^{1}H NMR (15% solution in $CDCl_3$, 400.13 MHz), δ: 1.43 (s, 18 H, 2 Bu^t); 2.21 (s, 3 H, Ac); 3.27, 3.28, and 3.38 (all s, 3 H each, 1-, 16-, and 14-OMe, respectively); 5.06 (s, 1 H, HOC(4″)); 7.00 (s, 2 H, H(2″), H(6″)); 7.01 (t, 1 H, H(5′), J = 8.0 Hz, J = 7.5 Hz, J < 1.0 Hz); 7.47 (ddd, 1 H, H(4′), J = 8.0 Hz, J = 8.0 Hz, J = 1.5 Hz); 7.92 (dd, 1 H, H(6′), J = 7.5 Hz, J = 1.5 Hz); 8.66 (dd, 1 H, H(3′), J = 8.0 Hz, J < 1.0 Hz); 11.05 (s, 1 H, NHAc). IR (KBr), ν/cm^{-1}: 758, 1089,

1117, 1236, 1269, 1297, 1316, 1365, 1448, 1526, 1589, 1606, 1640, 1682, 1740, 2825, 2879, 2925, 2956, 3444. UV (MeOH), λ_{max}/nm (log ε): 252 (417), 285 (3.30), 310 (3.60).

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