Pyrrolizidine Alkaloids from *Echium setosum* and *Echium vulgare*

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The major pyrrolizidine alkaloids (PAs) of *Echium setosum* and *Echium vulgare* were isolated and characterized as echimidine and a tigloyl isomer of echimidine. 3′-Acetylechimidine was identified in *E. vulgare* as a major new PA on the basis of MS and ^{1}H and ^{13}C NMR. Sixteen further alkaloids were recorded by GLC−MS in the reduced alkaloid extracts.

The genus *Echium*, a member of the family Boraginaceae, is especially rich in pyrrolizidine alkaloids (PA).[1,2] This class of alkaloids received considerable attention during the past decades not only because of their hepatotoxic, mutagenic, and carcinogenic activities, but also for their antimitotic, antitumor, antispasmodic, and mydriatic properties.[3] *Echium setosum* Vahl. is a small annual herb that grows naturally in Egypt,[4] whereas *Echium vulgare* L. is common throughout most of Europe. Pyrrolizidine alkaloids have not been previously documented in *E. setosum*. We report here the results of our investigation of *E. setosum*, as well as a re-examination of *E. vulgare* L. The latter species should contain heliosupine,[5] asperumine,[6] and on the basis of TLC and MS−echinatine and acetylheliosupine (or their isomers).[7] Our samples of *E. vulgare* and *E. setosum* showed echimidine as a major component as well as 3′-acetylechimidine (a new PA). In addition, we have recorded 7-angeloylretronecine, 9-angeloylretronecine, 7-tigloylretronecine, and 9-tigloylretronecine, which have not been reported before for these species.

Results and Discussion

Preparative TLC of the total alkaloidal extracts of *E. setosum* and *E. vulgare*, which had been reduced with Zn dust (to convert the alkaloid *N*-oxides into free bases) prior to isolation, afforded compound **1** as the main alkaloid. The structure was established by MS and ^{1}H- and ^{13}C-NMR spectroscopy. Alkaloid **1** was obtained as an oil $[\alpha]_D = 8°$ (EtOH; *c* 0.1); its molecular ion was established as *m/z* 397 by GLC−EIMS, corresponding to $C_{20}H_{31}NO_7$. In ^{1}H NMR, the chemical shifts of the necine proton signals are in close agreement with the values reported for other acyclic diester alkaloids with the retronecine skeleton.[8,9] ^{13}C NMR exhibited signals at δ 132.89 and 128.59, indicating a double bond between C-1 and C-2. The signals at δ 75.98 (C-8), 73.66 (C-7), and 34.51 (C-6) signify the presence of a retronecine diester.[10,11] The physical and spectral data of this alkaloid are consistent with those reported for echimidine.[11]

A new alkaloid, **2,** was obtained as an oil and its molecular ion determined as *m/z* 439 (corresponding to $C_{22}H_{33}NO_8$) by EIMS. Alkaloid **2** seems to be a derivative of **1**, and the difference in molecular ions can be explained by $CH_3C{=}O$. ^{1}H NMR of **2** showed similar signals as echimidine (**1**) except for the appearance of a singlet at δ 1.95 for an acetyl group. The presence of this acetyl group was confirmed by the downfield shift of the H-3′ to δ 5.44 and H-4′ to δ 1.37. ^{13}C NMR also corroborated this assumption: extra signals appear at δ 166.75 (for C=O) and δ 20.96 (for the methyl group of the acetyl moiety). Thus, **2** was identified as 3′-acetylechimidine, which has not been described before.

The combination of capillary GLC and MS is the method of choice for the separation and identification of complex pyrrolizidine alkaloid mixtures. Retention index RI data, molecular weight [M^+], and group-specific MS fragmentations provide sufficient information for an unequivocal identification of most PAs, which are present as trace components, or of geometrical isomers.[12−18] Thirteen PAs were detected in the reduced alkaloidal extract of *E. setosum* and 18 in *E. vulgare* (Tables 1 and 2). The major alkaloid in both extracts was identified as echimidine (**1**) (see above), while retronecine (**3**), 7-angeloylretronecine (**4**), 9-angeloylretronecine (**5**), 7-tigloylretronecine (**6**), 9-senecioylretronecine (**7**), 9-tigloylretronecine (**8**), and echihumiline (**9**) were unambiguously identified by their specific **RI**s and MS. Alkaloids **10**−**19** were only tentatively identified, inasmuch as amounts were too limited for a thorough spectroscopic analysis.

Alkaloids **10** and **11** showed a molecular ion at *m/z* 239 corresponding to $C_{13}H_{21}NO_3$. The MS of **10** exhibited significant ions at *m/z* 137, 124, 111, 106, and 80 (base peak); these fragments are characteristic for 1,2-unsaturated necines with a monoester at C-7.[18, 20,21] The fragment ion at *m/z* 137 is probably due to loss of the acid attached at C-7 ($M - C_5H_{10}O_2$). The fragments *m/z* 85 and 57 indicated that this acid is saturated and has two mass units more than angelic acid (or its isomers tiglic or senecic acid). In analogy to the patterns observed in other alkaloids we assume that it

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Table 1. GLC-MS Data of Pyrrolizidine Alkaloids of *E. setosum* and *E. vulgare*

alkaloid	RI	formula	M^+	characteristic ions (relative abundance, %)	ref
1, echimidine	2560	$C_{20}H_{31}NO_7$	397 (0.1)	382 (0.1), 352 (0.1), 297 (2), 221 (21), 220 (100), 219 (5), 138 (5), 137 (6), 136 (48), 121 (26), 120 (75), 119 (30), 106 (5), 94 (30), 93 (61), 83 (39), 80 (10), 59 (10), 55 (25), 43 (18)	19
2, 3′-acetylechimidine[a]	2640	$C_{22}H_{33}NO_8$	439 (0.1)	424 (0.1), 322 (1.3), 238 (1.6), 221 (25.3),220 (100), 219 (3.3), 138 (4.5),137 (5.8), 136 (48.5), 121 (8), 120 (61), 119 (28), 106 (6.4), 94 (23.6), 93 (45.9), 83 (13.8), 59 (10.6), 55 (12.5)	
3, retronecine[a]	1432	$C_8H_{13}NO_2$	155 (26)	138 (2), 137 (2), 111 (60), 106 (4), 94 (20), 93 (8), 82 (6), 81 (12), 80 (100), 68 (15), 53 (8), 41 (10)	12, 21
4, 7-angeloylretronecine[a]	1787	$C_{13}H_{19}NO_3$	237 (2)	219 (3), 204 (0.5), 191 (1), 154 (2), 138 (5), 137 (23), 136 (18), 124 (23), 111 (38), 106 (40), 94 (20), 93 (6), 83 (11), 80 (100), 55 (22)	12, 18
5, 9-angeloylretronecine[a]	1797	$C_{13}H_{19}NO_3$	237 (1)	219 (0.5), 193 (3), 154 (16), 138 (32), 137 (25), 136 (10), 126 (7) , 120 (2), 108 (2), 94 (25), 93 (100), 83 (8), 80 (10), 55 (13)	12, 18
6, 7-tigloylretronecine[a]	1816	$C_{13}H_{19}NO_3$	237 (3)	219 (0.5), 154 (2), 138 (3), 137 (29) 136 (15), 124 (25), 120 (5), 111 (44), 106 (50), 94 (20), 93 (6), 83 (15), 80 (100), 55 (22)	12, 13
7, 9-senecionylretronecine[a]	1835	$C_{13}H_{19}NO_3$	237 (0)	138 (19), 137 (30), 136 (15), 93 (100), 83 (30), 80 (10), 67 (18), 55 (35)	
8, 9-tigloylretronecine[a]	1843	$C_{13}H_{19}NO_3$	237 (0)	193 (5), 154 (15), 138 (20), 137 (26), 136 (13), 126 (7), 119 (5), 109 (4), 94 (23), 93 (100), 83 (10), 80 (12), 55 (18)	12, 13
9, echihumiline[a]	2578	$C_{20}H_{31}NO_7$	397 (0)	297 (1), 221 (20), 220 (100), 219 (3), 138 (10), 137 (10), 136 (58), 121 (20), 120 (46), 119 (22), 106 (5), 94 (25), 93 (41), 83 (50), 55 (8)	
10, 7-(2-methylbutyryl)-retronecine (or its isomer)[a,b]	1760	$C_{13}H_{21}NO_3$	239 (20)	222 (2), 154 (20), 138 (12), 137 (12), 136 (28), 124 (37), 120 (20), 111 (28), 108 (15), 106 (28), 94 (30), 93 (20), 80 (100), 68 (10), 57 (19)	
11, 9-(2-methylbutyryl)-retronecine (or its isomer)[a,b]	1795	$C_{13}H_{21}NO_3$	239(2)	195 (5), 154 (3), 138 (98), 137 (8), 136 (5), 120 (6), 108 (5), 94 (60), 93 (100), 80 (27), 67 (15), 57 (30)	
12, 7-angeloyl-9-(2-methyl-butyryl)retronecine[a,b,c]	2155	$C_{18}H_{27}NO_4$	321 (0)	221 (35), 220 (100), 195 (5), 141 (25), 138 (3), 137 (9), 136 (90), 121 (6), 120 (53), 119 (20), 106 (8), 94 (50), 93 (70), 83 (35), 80 (15), 57 (20), 55 (35)	
13, 7-tigloyl-9-(2-methylbutyryl)-retronecine[a,b,c]	2170	$C_{18}H_{27}NO_4$	321 (0)	221 (36), 220 (100), 195 (5), 141 (32), 138 (2), 137 (10), 136 (82), 121 (6), 120 (53), 119 (25), 106 (10), 94 (53), 93 (80), 83 (40), 80 (15), 57 (20), 55 (33)	
14, 7-angeloyl-9-(2,3-dimetyl-butyryl)retronecine[a,b]	2195	$C_{19}H_{29}NO_4$	335 (0)	235 (14), 221 (15), 220 (100), 151 (3), 141 (19), 138 (2), 137 (14), 136 (78), 121 (7), 120 (53), 119 (18), 106 (13), 94 (30), 93 (53), 83 (25), 80 (12), 71 (15), 67 (7), 55 (20)	
15, uplandicine or its Isomer[b]	2302	$C_{17}H_{27}NO_7$	357 (0)	297 (0.5), 221 (0.5), 198 (3), 181 (21), 180 (100), 136 (16), 121 (14), 120 (50), 119 (15), 106 (5), 101 (11), 94 (21), 93 (44), 80 (9), 59 (6), 43 (30)	
16, 7-angeloyl-9-(2,3-dihydroxy-butyryl)retronecine[a,b]	2315	$C_{17}H25NO_6$	339 (1)	239 (5), 238 (5), 237 (5), 221 (25), 220 (99), 219 (15), 141 (20), 138 (10), 137 (11), 136 (100), 121 (15), 120 (83), 119 (34), 106 (10), 94 (55), 93 (95), 83 (41), 80 (20), 75 (2), 57 (10), 55 (40), 45 (10)	
17, isomer of (**16**), tigloyl?[a,b]	2325	$C_{17}H_{25}NO_6$	339 (1)	239 (5), 238 (5), 237 (8), 221 (22), 220 (90), 219 (20), 141 (20), 138 (10), 137 (11), 136 (100), 121 (15), 120 (80), 119 (35), 106 (10), 94 (58), 93 (90), 83 (46), 80 (20), 75 (2), 57 (9), 55 (40), 45 (10)	
18, isomer of (**16**) or (**17**)[a,b]	2348	$C_{17}H_{25}NO_6$	339 (1)	239 (5), 238 (5), 237 (8), 221 (21), 220 (95), 219 (5), 141 (25), 138 (9), 137 (10), 136 (79), 121 (15), 120 (79), 119 (40), 106 (11), 94 (55), 93 (100), 83 (48), 80 (20), 75 (2), 57 (9), 55 (35), 45 (10)	
19, isomer of **1**, Tigloyl?[a,b]	2580	$C_{20}H_{31}NO_7$	397 (0)	382 (0.1), 297 (2), 238 (3), 221 (21), 220 (100), 219 (3), 138 (5), 137 (6), 136 (48), 121 (28), 120 (62), 119 (23), 106 (5), 94 (28), 93 (46), 83 (30) , 80 (10), 59 (10), 55 (20), 43 (18)	

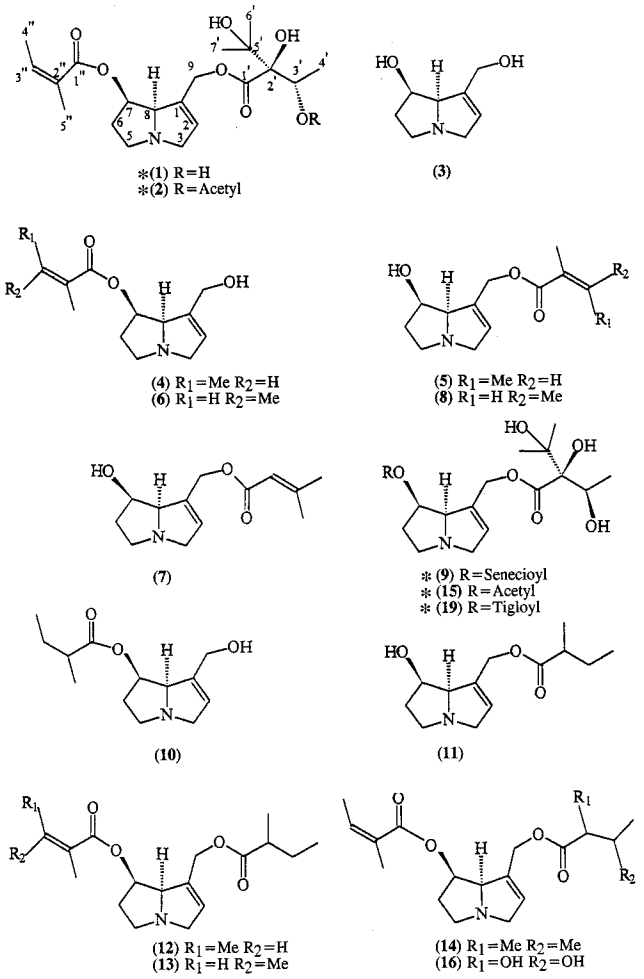
[a] This represents a new PA for genus *Echium*. [b] This is tentatively identified. [c] Later experiments revealed that **12** and **13** are formed by decomposition of 3′-acetylechimidine and echimidine.

is 2-methylbutanoic acid, which has been previously observed in the Boraginaceae.[22] The MS of compound **11** displayed significant ions at *m/z* 138, 94, 93 (base peak), and 80, which are characteristic for 1,2-unsaturated necines with a monoester at C-9.[18, 20,21] Based upon the mass fragmentation and biogenic considerations, alkaloids **10** and **11** were tentatively identified as 7-(2-methylbutyryl)retronecine and 9-(2-methylbutyryl)retronecine, respectively.

Compound **12** showed a series of ions at *m/z* 136, 120, 119, 93, and 80, which are characteristic of 1,2- unsaturated pyrrolizidine diesters.[20,21] The base peak at *m/z* 220 is due to the cleavage of the weak allylic ester bond, and the ion at *m/z* 221 is due to the loss of the acid attached at C-7. Although the molecular ion was not detected in the mass spectrum, the fragment ion at *m/z* 57 indicated an α side chain (C_4H_9) in the C-9 position. Based upon mass fragmentation and biogenic considerations, compound **12** was tentatively identified as 7-angeloyl-9-(2-methylbutyryl)retronecine. The same fragmentation pattern as in compound **12** was observed in the mass spectrum of compound **13**, only small

Table 2. Alkaloid Composition of *E. setosum* and *E. vulgare* (Total Alkaloid 100%)

alkaloid	t_R in GLC−MS (min)	RI	area (%) *E. setosum*	area (%) *E. vulgare*
1, echimidine	16.36	2560	62.53	49.82
2, 3′-acetylechimidine	17.21	2640		10.20
3, retronecine	0.46	1432		trace
4, 7-angeloylretronecine	4.26	1787	1.60	3.25
5, 9-angeloylretronecine	4.48	1797	0.91	6.13
6, 7-tigloylretronecine	4.50	1815	trace	2.17
7, 9-senecioylretronecine	5.06	1835		trace
8, 9-tigloylretronecine	5.16	1843	trace	2.53
9, echihumiline	16.48	2578		trace
10,7-(2-methylbutyryl) retronecine (or its isomer)	4.21	1760		trace
11, 9-(2-methylbutyryl) retronecine (or its isomer)	4.47	1795		trace
12, 7-angeloyl −9-(2-methylbutyryl)retronecine (or its isomer)	10.10	2155	2.51	3.97
13, 7-tigloyl-9-(2-methylbutyryl)retronecine (or its isomer)	10.28	2170	1.37	2.89
14, 7-angeloyl-9-(2,3-dimethylbutyryl)retronecine (or its isomer)	10.57	2195	trace	
15, uplandicine (or its isomer)	12.39	2302	1.83	8.30
16, 7-angeloyl-9-(2,3-dihydroxybutyryl)-retronecine	12.48	2315	1.14	trace
17, isomer of **16** (tigloyl ?)	13.03	2325	3.89	trace
18, isomer of **16** or **17**	13.17	2328	1.14	trace
19, echimidine isomer (tigloyl ?)	16.54	2580	22.88	20.94



*Stereochemistry at position 3′ of echimidinic acid not established.

differences occurred in the relative intensities of some fragment ions, indicating that **13** is a stereoisomer of **12**. Because compound **13** displayed a delayed retention time in GLC−MS, it was assumed to be 7-tigloyl-9-(2-methylbutyryl)retronecine.

The MS of compound **14** showed the characteristic fragmention pattern of 1,2 unsaturated PA diesters. The fragment ion at *m/z* 235 is due to the loss of the angelic acid attached to C-7, and the base peak *m/z* 220, to the cleavage of the weak allylic ester bond at C-9. The fragment ion at *m/z* 71 indicates an α ester side chain (C_5H_{11}) attached to C-9 . This compound was tentatively identified as 7-angeloyl-9-(2,3-dimethylbutyryl)-retronecine.

Compound **15** exhibited a base peak at *m/z* 180, which is typical for 7-acetyl esters; the ion peak at *m/z* 297 is due to the loss of acetic acid attached to C-7 ($M^+ - 60$), and the fragment ion at *m/z* 59 is probably due to C_3H_7O from the echimidinyl moiety. The presence of *m/z* 43 and absence of *m/z* 83 and 55 provide good evidence for the presence of acetate at C-7 and absence of angelic acid or its isomers. Thus, compound **15** was tentatively identified as 7-acetyl-9-echimidinylretronecine (uplandicine).

Compounds **16, 17**, and **18** represent an isomer series with M^+ 339 with the typical fragmentation pattern of 1,2-unsaturated PA diesters. The ion at *m/z* 239 is due to the loss of the acid attached to C-7. The strong peak at *m/z* 220 is due to the cleavage of the weak allylic ester bond at C-9, and the fragment at *m/z* 57 (C_3H_5O) is proposed to be derived from *m/z* 75 ($C_3H_7O_2$) through the loss of one molecule of H_2O. These isomers showed similar fragmentation patterns but differed in GLC retention times and in the relative intensities of some fragment ions, for example, 93 and 136. Compound **16** was tentatively identified as 7-angeloyl-9-(2,3 dihydroxybutyryl)retronecine; compounds **17** and **18** were assumed to be isomers of compound **16**.

Compound **19** is an isomeric form of echimidine, because it exhibited a fragmentation pattern similar to that of **1** and showed only small differences in relative intensities of the fragment ions *m/z* 119, 120, 93, and 83. Because angeloyl esters (such as **1**) elute earlier in capillary GLC than tigloyl esters [23] (compare retention times of **4** and **6** or **5** and **8**), we tentatively suggest that **19** is the tigloyl isomer of echimidine. Alkaloid **19** does not arise by isomerization in the GC, inasmuch as such a change has not not been encountered in our numerous alkaloid analyses.

The current literature of the phytochemistry of *Echium* species reports various retronecine base derivatives.[2−4] The alkaloid composition of *E. vulgare* as described in this paper differs significantly from data obtained from plants grown in Russia, in which heliosupine, asperumine, echinatine, and acetylheliosupine were identified.[5−7] These PAs are of the heliotridine type, whereas we found only PAs of the retronecine type in *E. vulgare* (Tables 1 and 2). The presence of PAs of the retronecine type is in agreement with the frequent occurrence of retronecine rather than heliotridine bases in the genus *Echium*. This difference in the alkaloid pattern of *E. vulgare* (Russia versus Germany) could be due to the presence of ecotypes in *E. vulgare*, environ-

mental conditions or (less likely) a wrong identification of the Russian plant. Because heliosupine and 3′-acetylheliosupine are stereoisomers of echimidine and 3′-acetylechimidine, a wrong assignment of stereochemistry in the former publications[5−7] appears more likely.

Experimental Section

General Experimental Procedures. A Carlo Erba Mega 5160 gas chromatograph equipped with a fused silica column (DB1, J&W Scientific) was employed for PA analysis. The capillary column was directly coupled to a quadrupole mass spectrometer (Finnigan MAT 4515). EIMS were recorded at 40 eV. Condition: injector 250 °C; temperature program 150−300 °C, 6 °C/min; split ratio 1:20; carrier gas He 0.5 bar. A Carlo Erba ICU 600 gas chromatograph equipped with FID and spectra physics integrator was used. DB1−30W (J & W Scientific) fused silica capillary column 30 m × 0.317-mm film thickness; carrier gas He; detector temp. 300 °C; injector temperature 250 °C; oven temperature program; initial temperature 170 °C, 5 min isothermal, 170−300 °C, 10 °C/min, 300 °C, 15 min isothermal.

Kovats indices[24] were calculated with respect to a set of co-injected even-numbered hydrocarbons (C_{14}−C_{28}). Each RI was subjected to a library search by comparison with the reference RI stored in an extensive data base of the Institute.

Plant Material. Aerial parts of *E. setosum* were collected in El-Agamy, Alexandria, Egypt, in October 1992. The identity was verified by Dr. A. El-Hadidi, Faculty of Science, Cairo University. *E. vulgare* was collected from an area located around Mannheim, Germany, in July 1994, and identified unambiguously by one of the authors (M.W.). Voucher specimens are deposited at the Institut für Pharmazeutische Biologie, Heidelberg.

Extraction. Air-dried plant material (700 g of *Echium setosum*) and fresh plants of *Echium vulgare* (1000 g) were extracted twice in 0.5 N HCl by homogenization with an Ultra-turrax and left to stand for one hour each. The extract was brought to 2 N HCl and reduced with Zn dust while being stirred overnight. Excess Zn was removed by filtration. The aqueous solution was rendered alkaline with NH_4OH, extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4 and evaporated to give the total alkaloidal fractions of 140 mg (for *E. setosum*) and 1940 mg (for *E. vulgare*); total alkaloid contents were 0.021% dry wt. for *E. setosum* and 0.194% fresh wt. for *E.vulgare*. PTLC [Si gel F_{254}, CH_2Cl_2−MeOH−NH_4OH (25%), 85:15:2] of the alkaloid extract from *E. setosum* yielded alkaloid **1** with R_f 0.43; from *E. vulgare* compound **2** (R_f 0.51) and compound **1** (R_f 0.43) were isolated. The isolated alkaloids were identified by MS and ^{1}H and ^{13}C NMR.

Alkaloid 1: ^{1}H NMR ($CDCl_3$, 300 MHZ) δ 6.06 (1H, qq, J = 1.5, 7.3 Hz, H-3″), 5.82 (1H, m, H-2), 5.41 (1H, m, H-7), 4.88 (1H, dm, J = 13 Hz, H-9d), 4.62 (1H, dm, J = 13 Hz, H-9u),4.39 (1H, m, H-8), 4.14 (1H, q, J = 6.3 Hz, H-3′), 3.94 (1H, dm, J = 15.6 Hz, H-3d), 3.36 (1H, m, H-3u), 3.33 (1H, m, H-5d), 2.65 (1H, m, H-5u), 2.08 (2H, m, H-6), 1.93 (3H, quin, J = 1.5 Hz, H-4″), 1.77 (3H, dq, J = 1.5, 7.3 Hz, H-5″), 1.26 (3H, s, H-7′), 1.22 (3H, d, J = 6.3 HZ, H-4′), 1.19 (3H, s, H-7′); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.23 (s, C-1′), 166.92 (s, C-1″), 139.27 (d, C-3″), 132.89 (s, C-1), 128.59 (d, C-2), 127.42 (s, C-2″), 83.06 (s, C-2′), 75.98 (d, C-8), 73.66 (d, C-7), 73.61 (s, C-5′), 69.74 (d, C-3′), 62.69 (t, C-3), 62.48 (t, C-9), 53.73 (t, C-5), 34.51 (t, C-6), 25.96 (q, C-6′), 24.86 (q, C-7′), 18.51 (q, C-4′), 15.74 (q, C-4″).

Alkaloid 2: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.10 (1H, qq, J = 1.5, 7.3 HZ, H-3″), 5.84 (1H, m, H-2), 5.45 (1H, m, H-7), 5.44 (1H, q, J = 6.3 Hz, H-3′), 4.76 (1H, dm, J = 13.3 Hz, H-9d), 4.62 (1H, dm, J = 13.3 Hz, H-9u), 4.42 (1H, m, H-8), 4.00 (1H, dm, J = 15.5, H-3d), 3.41 (1H, m, H-3u), 3.41 (1H, m, H-5d), 2.71 (1H, m, H-5u), 2.15 (2H, m, H-6), 1.96 (3H, dq, J = 1.5, 7.3 Hz, H-5″), 1.95 (3H, s, H-3′-OAc), 1.80 (3H, quin, J = 1.5 Hz, H-4″), 1.39 (3H, s, H-7′), 1.37 (3H, d, J = 6.3, H-4′), 1.17 (3H, s, H-6′); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.37 (s, C-1′), 169.47 (s, C-1″), 166.75 (s, 3′-OAc:C═O), 139.57 (d, C-3″), 132.76 (s, C-1), 128.67 (d, C-2), 127.32 (s, C-2″), 82.87 (s, C-2′), 75.83 (d, C-8), 73.46 (d, C-7), 73.09 (s, C-5′), 72.56 (d, C-3′), 62.57 (t, C-2), 62.48 (t, C-9), 53.81 (t, C-5), 34.46 (t, C-6), 26.59 (q, C-6′), 24.61 (q, C-7′), 20.96 (q, 3′-OAc: Me), 15.82 (q, C-4″), 15.42 (q, C-4′).

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