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Norditerpene and diterpene alkaloids from *Aconitum variegatum*

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Abstract

Aerial parts of *Aconitum variegatum* L. from the Pyrenees furnished four norditerpene alkaloids, 16β-hydroxycardiopetaline, 8-ethoxysachaconitine, 14-acetylgenicunine B, *N*-deethyl-*N*-19-didehydrosachaconitine, five diterpene alkaloids 15-veratroyldictizine, 15-veratroyl-17-acetyldictizine, 15-veratroyl-17-acetyl-19-oxodictizine, *N*-ethyl-1α-hydroxy-17-veratroyldictizine, variegatine and the known alkaloids sachaconitine, 14-*O*-acetylsachaconitine, karakoline, talatizamine, 10-hydroxytalatizamine, 14-acetyltalatizamine, 14-acetyl-10-hydroxytalatizamine, *N*-methylarmepavine, pengshenin B, delsoline, dihydrodelsoline, delcosine and genicunin B. Structures of the alkaloids were established by MS, 1D- and 2D-NMR techniques.

Keywords: *Aconitum variegatum*; Ranunculaceae; Diterpene alkaloids; Norditerpene alkaloids

1. Introduction

Aconitum variegatum L. is a species found in the alpine regions of Western and Central Europe. Previous studies on *A. variegatum* from the Carpathians led to the isolation of the norditerpene alkaloids talatizamine and commaconine (Khaimova et al., 1967, 1971; Mody et al., 1980), while the major alkaloids isolated from the tubers of *A. variegatum* collected in Switzerland and Austria were talatizamine and 14-*O*-acetyltalatizamine (Katz et al., 1987). In the Atlantic Pyrenees and the Sierra de Aralar of the Basque region the species is found at the bottom of limestone ledges at an altitude of 1200–1800 m. We have now studied a collection of *A. variegatum* from near Ibon-Estanes in the French Pyrenees and report the isolation and structure determination of 11 natural products (**1**–**11**), including four new norditerpene alkaloids 16β-hydroxycardiopetaline (**1**), 8-ethoxysachaconitine (**3**), 14-acetylgenicunine B (**4b**) and *N*-deethyl-*N*-19-didehydrosachaconitine (**6**) and five new diterpene alkaloids 15-veratroyldictizine (**7**), 15-veratroyl-17-acetyldictizine (**8**), 15-veratroyl-17-acetyl-19-oxodictizine (**9**) *N*-ethyl-1α-hydroxy-17-veratroyldictizine (**10**) and variegatine (**11**) from the aerial parts. Thirteen previously known norditerpene alkaloids also found in this collection were sachaconitine and talatizamine (Pelletier et al., 1985), 14-*O*-acetylsachaconitine (Aiyar et al., 1986), karakoline (Konno et al., 1982; Liu and Katz, 1996), 10-hydroxytalatizamine and 14-acetyl-10-hydroxytalatizamine (Takayama et al., 1992), 14-acetyl-talatizamine (Pelletier et al., 1985), *N*-methylarmeparvine (Wu et al., 1980), pengshenine B (Xie et al., 2003), delsoline and dihydrodelsoline (de la Fuente and Ruiz-Mesía, 1994), delcosine (Sakai et al., 1979) and genicunin B (Wang et al., 2000). All known alkaloids were identified by MS, ^{1}H and ^{13}C NMR spectrometry and comparison with data in the literature.

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2. Results and discussion

We discuss first the structures of the four new norditerpene alkaloids. 16β-Hydroxycardiopetaline (**1**), an amorphous solid whose mass spectrum exhibited significant peaks at *m/z* 363 (M^+), 344 $(M - CH_3)^+$, 346 $(M - OH)^+$ and 345 $(M - H_2O)^+$, had spectral properties characteristic of an aconitine type norditerpene alkaloid with signals of an angular methyl at δ_H 0.87 (3H, s) and δ_C 27.5 (q) and those of an ethyl group at δ 2.53 and 2.47 (each 1H, *dq*, $J = 13.7$, 7.2 Hz), and δ 1.10 (3H, *t*, $J = 7.2$ Hz), δ_C 48.3 (*t*) and 13.0 (q), but without the methoxy group typical of this alkaloid type (Table 1). Three carbon singlets at δ 32.9, 48.7 and 74.5 (Table 2) could be assigned to C-4, C-11 and C-8, the chemical shift of the last indicating that it bore a tertiary hydroxyl group (Pelletier et al., 1984; Konno et al., 1982). Three doublets at δ 72.4, 72.5 and 76.1 which in the HSQC spectrum correlated with protons at δ 3.70 (*t*, $J = 3$ Hz), 3.83 (*dd*, $J = 9.3$, 4.3 Hz) and 4.30 (*t*, $J = 5$ Hz) indicated the presence of three hydroxyl groups. The total of 21 carbon signals, together with evidence for the presence of four oxygen atoms and the high resolution mass spectrum, then led to molecular formula $C_{21}H_{33}NO_4$ for the new alkaloid.

The three secondary hydroxyl groups were provisionally placed at C-1, C-14 and C-16 to conform with the customary functionalization pattern of norditerpene alkaloids (Pelletier et al., 1984). This was confirmed as follows. The base peak in the mass spectrum at *m/z* 346 $(M - OH)^+$ was in accord with the presence of a C-1 hydroxyl group (Takayama et al., 1989, 1992) while

Table 1
^{1}H NMR spectroscopic data of compounds **1**, **3**, **4a,b**, **5** and **6** ($CDCl_3$)[a]

H	**1**[b]	**3**[c]	**4a**[b]	**4b**[b]	**5**[b]	**6**[c]
1	3.70 *t* (3)	3.07 *dd* (10.7, 6.6)	3.76 *dd* (10.5, 6.9)	3.74 *dd* (10.3, 6.9)	3.90 *dd* (10.6, 7)	3.18 *dd* (10.2, 7)
2[a]	1.58 *m*	2.28 *dddd* (14.5, 13, 10.5, 3)	2.32 *ddd* (14.5, 13, 10.5)	2.35 *m*	2.33 *m*	1.99 *m*
2b	1.58 *m*	1.91 *m*	1.95 *m*	1.98 *m*	2.00 *m*	1.33 *dddd* (14, 12.5, 10, 5)
3[a]	1.72 *dtd* (14.5, 12.6, 6.3)	1.57 *m*	1.57 *m*	1.60 *m*	1.60 *m*	1.57 *ddd* (13.5, 5, 3)
3b	1.49 *m*	1.21 *m*	1.19 *dddd* (14.5, 13.5, 4.5, 2.5)	1.22 *dddd* (14.5, 13.5, 4.5, 2.5)	1.21 *dddd* (14.5, 13.5, 4.5, 2.5)	1.22 *ddd* (13.5, 13.5, 4.3)
5	1.61 *d* (7.8)	1.41 *d* (7.3)	1.59 *d* (7.4)	1.63 *d* (6.5)	1.64 *d* (7.2)	1.50 *dd* (7.9,1)
6a	1.88 *dd* (14.8, 7.8)	1.91 *dd* (14.8, 7.3)	1.95 *dd* (15.1, 7.4)	1.89 *dd* (15.6, 6.5)	2.33 *m*	2.03 *dd* (15, 7.9)
6b	1.58 *m*	1.33 *dd* (14.8, 8)	1.51 *dd* (15.1, 7.8)	1.56 *dd* (15.6, 8)	1.54 *dd* (14.8, 7.8)	1.45 *dd* (15, 7.5)
7	2.04 *brd* (8)	2.35 *brd* (8)	2.09 *d* (8)	2.08 *d* (8)	2.21 *d* (7.5)	2.12 *d* (7.5)
9	2.20 *brt* (∼6)	2.21 *brt* (∼6)	2.14 *brd* (4.8)	2.18 *d* (5)	2.24 *brs*	2.21 *t* (5)
10	1.82 *ddd* (11.6, 6.2,6)	1.76 *ddd* (11.6, 6.3,6)				1.70 *m*
12a	1.98 *m*	2.06 *dd* (14.8, 6.3)	2.46 *m*	2.71 *d* (16)	2.58 *brd* (15.6)	1.84 *ddd* (16, 10.5, 7)
12b	1.63 *m*	1.84 *ddd* (14.8, 11.6, 8)	2.07 *dd* (15.7, 12.7)	1.74 *dd* (16, 8)	1.92 *dd* (15.6, 8)	1.76 *dd* (16, 7)
13	2.25 *m*	2.32 *brt* (5.5)	2.41 *s*	2.78 *brdd* (8, 5)	2.74 *brt* (6.4)	2.40 *brt* (7)
14	4.30 *t* (5)	4.01 *brq* (5.3)	4.72 *t* (5.2)	5.32 *t* (5)		4.15 *t* (s)
15a	2.54 *m*	2.18 *dd* (15.7, 4.8)	2.48 *m*	2.41 *dd* (16.5, 9.5)	2.50 *dd* (16.9, 6)	2.62 *dd* (17.5, 8.5)
15b	2.00 *m*	3.33 *brd* (15.7, 9)	1.70 *dd* (16.2, 8.4)	1.91 *dd* (16.5, 4.5)	1.81 *d* (16.9)	2.01 *d* (17.5)
16	3.83 *dd* (9.2, 4.3)	2.91 *brs*	3.40 *brd* (9)	3.17 *dd* (9.5, 4.5)	3.88 *t* (6)	3.50 *dd* (8.5, 3)
17	2.79 *brs*	0.77 *brs*	3.00 *brs*	2.85 *brs*	3.46 *brs*	4.19 *brs*
18[d]	0.87 *s*	2.46 *d* (11.6)	0.78 *s*	0.80 *s*	0.80 *s*	1.09 *s*
19[a]	2.28 *d* (11.1)	2.00 *dd* (11.6, 1.7)	2.50 *d* (11.6)	2.50 *d* (11.1)	2.50 *d* (11)	7.1 *brs*
19b	2.06 *brd* (11.1)	2.50 *m*	2.07 *d* (11.6)	2.04 *brd* (11)	2.10 *brd* (11)	
20[a]	2.53 *m*	2.39 *m*	2.48 *m*	2.48*m*	2.52 *m*	
20b	2.47 *m*	1.11 *t* (7)	2.38 *m*	2.41 *m*	2.41 *m*	
21[d]	1.10 *t* (7.2)	3.25 *s*	1.05 *t* (7.1)	1.06 *t* (7.1)	1.09 *t* (7)	
OCH_3[d]		3.36 *s*	3.26 *s*	3.28 *s*	3.31 *s*	3.22 *s*
OCH_3[d]			3.33 *s*	3.22 *s*	3.34 *s*	3.36 *s*
OAc[d]				2.05 *s*		
8′a		3.38 *m*				
8′b		3.37 *m*				
8″[d]		1.12 *t* (7)				
–OH		3.60 *d* (6.5)				

[a] Chemical shifts in ppm relative to TMS; coupling constants (in parentheses) are in Hz.
[b] 400 MHz.
[c] 500 MHz.
[d] Intensity three protons.

Table 2
^{13}C NMR spectra of compounds **1**, **2**, **3**, **4a,b**, **5** and **6** ($COHCl_3$, 125 MHz)[a]

C	1	2	3	4a	4b	5	6
1	72.4 *d*	86.6 *d*	86.2 *d*	78.7 *d*	78.8 *d*	78.3 *d*	85.2 *d*
2	29.7 *t*	26.3 *t*	26.7 *t*	26.2 *t*	26.4 *t*	25.7 *t*	26.3 *t*
3	31.3 *t*	37.9 *t*	37.9 *t*	37.6 *t*	37.4 *t*	37.4 *t*	32.9 *t*
4	32.9 *s*	34.6 *s*	34.5 *s*	34.6 *s*	34.3 *s*	34.5 *s*	46.3 *s*
5	46.6 *d*	50.9 *d*	51.0 *d*	46.7 *d*	46.5 *d*	46.6 *d*	47.0 *d*
6	25.0 *t*	25.2 *t*	24.3 *t*	25.8 *t*	25.8 *t*	25.7 *t*	26.5 *t*
7	45.5 *d*	45.8 *d*	40.6 *d*	45.2 *d*	45.5 *d*	45.0 *d*	52.5 *d*
8	74.5 *s*	72.9 *s*	78.2 *s*	72.2 *s*	72.8 *s*	81.5 *s*	72.3 *s*
9	46.4 *d*	47.0 *d*	45.9 *d*	56.0 *d*	55.0 *d*	64.5 *d*	46.4 *d*
10	43.8 *d*	45.8 *d*	45.5 *d*	81.2 *d*	80.7 *d*	77.2 *d*	46.6 *d*
11	48.7 *s*	48.9 *s*	49.0 *s*	54.2 *s*	54.3 *s*	54.0 *s*	47.5 *s*
12	28.1 *t*	27.7 *t*	28.9 *t*	39.6 *t*	39.4 *t*	36.1 *t*	27.1 *t*
13	44.0 *d*	37.6 *d*	38.8 *d*	37.8 *d*	35.4 *d*	45.8 *d*	37.3 *d*
14	76.1 *d*	75.6 *d*	75.2 *d*	74.1 *d*	76.2 *d*	215.8 *d*	75.5 *d*
15	45.4 *t*	38.5 *t*	35.0 *t*	37.6 *t*	42.0 *t*	36.6 *t*	37.4 *t*
16	72.5 *d*	82.3 *d*	82.6 *d*	81.7 *d*	81.2 *d*	85.0 *d*	82.1 *d*
17	63.2 *d*	62.5 *d*	62.2 *d*	63.5 *d*	62.6 *d*	64.2 *d*	62.0 *d*
18	27.6 *q*	26.3 *q*	26.4 *q*	26.3 *q*	26.4 *q*	26.1 *q*	22.5 *q*
19	60.3 *t*	56.9 *t*	56.8 *t*	56.6 *t*	56.7 *t*	56.5 *t*	168.9 *t*
20	48.3 *t*	49.4 *t*	49.3 *t*	49.4 *t*	49.3 *t*	49.4 *t*	
21	13.0 *q*	13.6 *q*	13.6 *q*	13.6 *q*	13.5 *q*	13.6 *q*	
8′			55.9 *t*				
8″			16.1 *q*				
OCH_{3C-1}		56.3 *q*	56.2 *q*	56.0 *q*	55.9 *q*	55.9 *q*	55.9 *q*
OCH_{3C-16}		56.5 *q*	56.3 *q*	56.4 *q*	56.1 *q*	56.1 *q*	56.5 *q*
OAc_{C-14}					170.7 *s*		
					21.5 *q*		

[a] Assignments were made with the aid of HSQC and HMBC experiments.

the triplet at δ 3.70 was typical of hydrogen under an α-orientated hydroxyl group on C-1. As a result ring A adopts a boat conformation, thus forming a hydrogen bond between the hydroxyl and the unshared electron pair on nitrogen (Pelletier et al., 1976, 1977). The triplet at δ 4.30 (J = 5 Hz) and the *dd* at δ 3.83 (J = 9.2, 4.3 Hz) were assigned to protons under the hydroxyls at C-14 resp. C-16 (Takayama et al., 1992; Liu and Katz, 1996) with the coupling constants involving H-14, H-9 and H-13 indicating that the hydroxyl group on C-14 was α-oriented. β-Configuration of the C-16 hydroxyl was inferred from the coupling constants (9.2 and 4.3 Hz) between H-16 and the two protons on C-15 in agreement with all naturally occurring C-16 hydroxylated norditerpene alkaloids encountered previously. Strong interactions between H-14β and H-9β as well as H-10β on the one hand and between H-16α and H-17α on the other demonstrated by ROESY corroborated this stereochemistry. The stereochemistry assigned to **1** is also borne out by comparison with literature data for cardiopetaline and related alkaloids (González et al., 1980; de la Fuente et al., 1993).

In the mass spectrum of a second new constituent **3** the molecular ion at *m/z* 419 was in accord with molecular formula $C_{23}H_{41}NO_4$ while its ^1H and ^{13}C NMR spectra (Tables 1 and 2) resembled those of sachaconitine (**2**) (Pelletier et al., 1977) but exhibited the signals of an additional CH_3CH_2O-group which because the C-8 signal had experienced a shift of 5.3 ppm to lower field was placed on C-8 as in **3**. To exclude the possibility (Pelletier et al., 1977) that **3** was an artifact resulting from displacement of an –OH or acyl group by ethyl alcohol during the isolation procedure a sample of **2** was exposed to boiling ethanol for 5 days and recovered without change.

The ^1H NMR spectrum (Table 1) of a third alkaloid **4a**, $C_{23}H_{37}NO_5$ from HRMS, and a base peak at *m/z* 376 $[M - OCH_3]^+$ suggesting the presence of a methoxy group on C-1 (Takayama et al., 1992), indicated a close relationship to **2** although the latter contained one less oxygen atom. Signals at δ 3.76 (1H, *dd*, J = 10.6, 6.9 Hz) and δ 4.72 (1H, *t*, J = 5.2 Hz) for protons on carbon carrying oxygen could thus be assigned to H-1β and H-14β, while the extra oxygen atom, the absence of an additional low field signal for hydrogen under oxygen and the presence of a new carbon singlet at δ 81.2 (Table 2) indicated that this hydroxyl was tertiary and at C-10 in view of the changes in the signals of C-10 ($\Delta\delta_c$ = 35.4 ppm), C-9 ($\Delta\delta_c$ = 9 ppm), C-11 ($\Delta\delta_c$ = 5.3 pm) and C-12 ($\Delta\delta_c$ = 11.9 ppm). This was confirmed by HMBC (Table 3) which showed three-bond connectivities between C-10 at δ 81.2 on the one hand and three

Table 3
^{1}H NMR spectroscopic data of compounds **7**–**11** ($CDCl_3$, 500 MHz)[a]

H	7	8	9	10	11
1a	1.89 *dd* (13, 4.7)	1.89 *dd* (13.4, 4.5)	2.01 *m*	3.86 *dd* (10.5, 7)	2.61 *dd* (15.1, 2.0)
1b	1.32 *m*	1.40 *m*	1.42 *m*		2.28 *d* (15.0)
2[a]	2.23 *m*	2.22 *m*	2.21 *m*	2.50 *m*	
2b	1.44 *brdd* (13.5, 4.7)	1.45 *m*	1.42 *m*	2.18 *m*	
3[a]	1.56 *brd* (13)	1.56 *brd* (13.1)	1.82 *brd* (13.1)	1.62 *m*	2.24 *m*
3b	1.18 *dddd* (12,12,4,2)	1.17 *m*	1.18 *m*	1.35 *m*	2.13 *dd* (14.5, 2.1)
5	1.15 *brd* (7.3)	1.16 *brd* (7)	1.35 *brd* (8.6)	1.53 *m*	2.00 *s*
6a	2.37 *dd* (13.8, 7.9)	2.29 *dd* (13.4, 7.5)	2.58 *dd* (13.9, 7.9)	3.23 *dd* (13.7, 7.9)	
6b	1.30 *m*	1.26 *m*	1.32 *m*	1.30 *m*	
7a	2.12 *brd* (5.5)	2.12 *brd* (4.8)	2.10 *brd* (5)	2.34 *m*	2.57 *d* (19.0)
7b					2.17 *d* (19.0)
9	1.80 *t* (10, 10)	1.85 *dd* (11.5, 9.5)	1.93 *t* (10.5)	2.04 *t* (10) m	1.85 *brd* (10.7)
11a	1.71 *m*	1.64 *m*	1.67 *m*	2.27 *t* (12)	1.82 *dd* (14.0, 2.5)
11b	1.31 *t* (13.1)	1.30 *m*	1.40 *m*	1.84 *m*	1.67 *ddt* (14, 11, 2)
12	1.90 *brs*	1.81 *m*	1.86 *brs*	1.82 *brs*	2.20 *m*
13a	2.07 *m*	2.13 *m*	1.56 *m*	2.06 *m*	1.97 *tt* (12.3, 2.2)
13b	1.38 *m*	1.35 *m*	0.81 *m*	1.5 *m*	1.39 *dd* (12.3, 3.7)
14a	2.12 *m*	2.02 *m*	2.01 *m*	2.05 *m*	1.97 *brs*
14b	1.38 *m*	1.36 *m*	1.50 *m*	1.31 *m*	
15a	5.08 *s*	5.17 *s*	5.19 *s*	4.11 *s*	2.34 *dt* (18.0, 2.3)
15b					2.25 *m*
17a	3.69 *d* (11.5)	4.30 *d* (11.6)	4.29 *d* (11.6)	4.68 *d* (12.3)	4.70 *dd* (4.0, 2.3)
17b	3.62 *d* (11.5)	4.23 *d* (11.6)	4.22 *d* (11.6)	4.56 *d* (12.3)	4.53 *dd* (3.7, 2.0)
18[b]	0.66 *s*	0.65 *s*	1.02 *s*	0.86 *s*	1.45 *s*
19a	2.40 *brd* (11.2)	2.45 *brd* (11.6)		3.18 *m*	2.46 *d* (12.3)
19b	2.23 *dd* (11.2, 2)	2.20 *dd* (11.6, 1.8)		2.49 *m*	1.78 *d* (12.3)
20	3.38 *brs*	3.40 *brs*	3.72 *brs*	4.37 *brs*	1.93 *s*
21	2.24 *brs*	2.24 *brs*[b]	2.89 *brs*[b]	3.23 *m*	2.20 *s*[b]
21				2.92 *m*[b]	
22				1.55 *t* (7)[b]	
3′	7.52 *d* (2)	7.50 *d* (2)	7.49 *d* (2)	7.51 *d* (2)	
6′	6.91 *d* (8.5)	6.9 *d* (8.5)	6.91 *d* (8.5)	6.89 *d* (8.5)	
7′	7.65 *dd* (8.5, 2)	7.64 *dd* (8.5, 2)	7.62 *dd* (8.5, 2)	7.64 *dd* (8.5, 2)	
4′-OCH_3[b]	3.90 *s*	3.89 *s*	3.90 *s*	3.93 *s*	
5′-OCH_3[b]	3.93 *s*	3.92 *s*	3.94 *s*	3.95 *s*	
OAc[b]		1.77 *s*	1.76 *s*		

[a] Chemical shift in ppm relative to TMS; coupling constants in parentheses are in Hz.
[b] Intensity three protons.

signals at δ 3.76 (1H, *dd*, J = 10.6, 5.9 Hz, H-1), δ 1.59 (1H, d, J = 7.4 Hz, H-5) and δ 4.72 (1H, t, J = 5.2 Hz, H-14) on the other. The paramagnetic displacement of these signals relative to those in sachaconitine (**2**) can be attributed to the deshielding effect of the new β-orientated C-10 hydroxyl group which is 1,3-diaxial to H-1β, H-5β and H-14β. Acetylation of **4a** furnished a monoacetate **4b** whose ^{1}H NMR spectrum (Table 1) exhibited the expected downfield shift of the H-14 resonance and smaller shifts in the signals of H-12a, b, H-13 and H-15. Acetate **4b** was also isolated from *A. variegatum* itself as a new naturally occurring norditerpene alkaloid.

To confirm the location of the secondary hydroxyl group chromic acid oxidation of **4a** yielded a ketone **5**. Disappearance in the ^{1}H NMR spectrum (Table 1) of the signal of H-14 at δ 4.72 was accompanied by appearance in the ^{13}C NMR spectrum (Table 2) of a carbonyl frequency at δ 215.8 and of deshielding effects on C-9 ($\Delta\delta_c$ = 8.2 ppm) and C-13 ($\Delta\delta_c$ = 9.0 ppm). After completion of our study we became aware of a report that **4a**, named genicunin B, had recently been isolated from *A. geniculatum* (Wang et al., 2000) although details of the work are not easily available. Naturally occurring alkaloid **4b** and the synthetic dehydro derivative **5** are therefore 14-acetylgenicunin B and dehydrogenicunin B, respectively.

The infrared spectrum of the remaining new norditerpene alkaloid **6** from our collection exhibited absorptions at 3418 and 1094 cm^{-1} (–OH) and 1667 cm^{-1}, the latter characteristic of a C=N double bond, while the mass spectrum indicated the composition $C_{21}H_{31}NO_4$ with characteristic peaks at *m*/*z* 346 (16.2) $[M - CH_3]^+$ and 330 (90.8) $[M - OCH_3]^+$ indicative of a norditerpene alkaloid with a methoxy group on C-1. These deductions could be expanded by analysis of the ^{1}H and ^{13}C NMR spectra (Tables 1 and 2) which exhib-

ited signals of an angular methyl group at δ 1.09 (δ_c 22.5 *q*) and two methoxy groups at δ 3.22 and 3.66 (δ_c 55.99 and 56.59). Signals at δ 3.18 (1H, *dd*, J = 10.2, 7 Hz), δ 4.15 (1H, *t*, J = 5 Hz),δ 4.55 (1H, *t*, J = 5 Hz) δ 3.50 (1H, dd, J = 8.5, 3 Hz) corresponding to carbon doublets at δ 85.2, 75.5 and 82.1 could be assigned to protons under hydroxyl groups at C-1, C-14 and C-16, respectively. Notable also was the absence of signals corresponding to the N-ethyl group of alkaloids **1**–**5**, the presence at low field of a singlet at δ 7.19 characteristic of –N=CH– and the displacement of the H-17 signal to lower field at δ 4.13, all characteristic of the presence of a –C=N double bond. Correlations from the HMBC spectrum (Table 3) between the angular methyl group (H-18) and the imino carbon (C-19) at δ 168.9 ppm and between the latter and H-17 corroborated these deductions while the remaining assignments for the protons and carbons in Table 3 were deduced from HSQC and HMBC measurements.

We now proceed to a discussion of the five new diterpene alkaloids. The first of these, 15-veratroyldictizine (**7**), an amorphous solid, had significant IR absorptions at 3350 and 1713 cm^{-1} characteristic of a hydroxyl and an ester function while the mass spectrum exhibited the molecular ion at *m*/*z* 511 (100%) corresponding to a molecular formula $C_{30}H_{41}NO_6$ verified by HRMS, and significant fragments at *m*/*z* 510 $[M - H]^+$ (63%), 496 $[M - CH_3]^+$ (9%), 469 $[M - C_3 - H_6]^+$ (6%), 468 $[M - C_3 - H_7]^+$ (20%) and 346 $[M - C_6H_9O_3]^+$ (30%). The ^1H NMR spectrum (Table 3) contained signals of an angular methyl group at δ 2.23, two methoxyls at δ 3.40 and 3.93 and aromatic protons at δ 7.52, (1H, *d*, J = 2 Hz), 6.91 (1H, *d*, J = 2 Hz) and 7.65 (1H, *d*, J = 2 Hz) indicative of a 1,3,4-trisubstituted aromatic ring, obviously an ester as verified by the ^{13}C NMR spectrum (Table 4) which contained nine signals characteristic of a veratroyl group. Of the remaining 21 carbon signals, chemical shifts of five at δ 23.4, 42.5, 45.5, 28.5

Table 4
^{13}C NMR spectra of compounds **7–11** ($CDCl_3$)[a]

C	**7**[b]	**8**[c]	**9**[b]	**10**[b]	**11**[c]
1	26.3 *t*	26.2 *t*	26.1 *t*	68.3 *d*	49.1 *t*
2	20.6 *t*	24.4 *t*	20.8 *t*	29.2 *t*	209.3 *s*
3	39.9 *t*	39.8 *t*	37.2 *t*	37.3 *t*	55.8 *t*
4	34.1 *s*	34.1 *s*	45.8 *s*	34.6 *s*	41.1 *s*
5	53.0 *d*	52.7 *d*	52.1 *d*	50.4 *d*	58.9 *d*
6	23.4 *t*	23.1 *t*	26.5 *t*	23.7 *t*	204.8 *s*
7	42.5 *d*	42.4 *d*	47.2 *d*	42.9 *d*	52.6 *t*
8	41.5 *s*	41.4 *s*	41.6 *s*	41.2 *s*	40.2 *s*
9	43.0 *d*	42.5 *d*	42.7 *d*	42.9 *d*	49.4 *d*
10	45.5 *s*	45.5 *s*	44.8 *s*	52.9 *s*	47.5 *s*
11	23.1 *t*	22.9 *t*	22.7 *t*	23.2 *t*	27.7 *t*
12	34.2 d	35.7 *d*	35.7 *d*	35.8 *d*	34.0 *d*
13	21.3 *t*	21.1 *t*	20.3 *t*	20.4 *t*	36.1 *t*
14	28.5 *t*	28.0 *t*	27.1 *t*	27.7 *t*	45.5 *d*
15	88.7 *d*	87.3 *d*	86.0 *d*	84.0 *d*	35.6 *t*
16	79.6 *s*	78.3 *s*	78.1 *s*	79.9 *s*	150.9 *s*
17	66.0 *t*	68.6 *t*	68.4 *t*	69.8 *t*	103.6 *t*
18	26.5 *q*	26.4 *q*	22.1 *q*	25.7 *q*	29.6 *q*
19	59.4 *t*	59.1 *t*	174.2 *s*	55.6 *t*	62.0 *t*
20	73.0 *d*	72.8 *d*	72.7 *d*	69.0 *d*	80.9 *d*
21	43.9 *q*	43.8 *q*	34.4 *q*	54.6 *t*	43.2 *q*
22				10.3 *q*	
1′	168.2 *s*	167.3 *s*	167.3 *s*	167.1 *s*	
2′	121.8 *s*	122.0 *s*	121.8 *s*	122.0 *s*	
3′	111.8 *d*	111.8 *d*	111.9 *d*	112.1 *d*	
4′	148.8 *s*	148.7 *s*	148.9 *s*	148.9 *s*	
5′	153.5 *s*	153.3 *s*	153.6 *s*	153.5 *s*	
6′	110.5 *d*	110.5 *d*	110.6 *d*	110.4 *d*	
7′	123.8 *d*	123.8 *d*	123.8 *d*	123.7 *d*	
4′-OCH_3	55.7 *q*	55.7 *q*	56.1 *q*	56.1 *q*	
5′-OCH_3	55.9 *q*	55.9 *q*	55.9 *q*	56.1 *q*	
17′-OAc		170.8 *s*	170.8 *s*		
		20.5 *q*	20.5 *q*		

[a] Assignments were made with the aid of HSQC and HMBC experiments.
[b] 100 MHz.
[c] 125 MHz.

and 73.0 were characteristic of C-6, C-7, C-10, C-14 and C-20 of a denudatine type alkaloid (Feng and Liu, 1997; Martin and Ruiz-Mesía, 1997), a conclusion supported by HMBC correlations between the signal of H-20 at δ 3.80 with C-6 and C-9 at δ 23.4 and δ 43.0. The most obvious property of the new substance was the absence of the C-16, C-17 exocyclic double bound characteristic of such alkaloids; instead the NMR spectrum contained two mutually coupled doublets at δ 3.69 and δ 3.62 (J = 11.5 Hz) on a methylene carbon at δ 66.0 indicative of a CH_2OH group on C-17 which in turn was attached to C-16 at δ 79.6 functionalized by a tertiary hydroxyl group as shown by two-bond HMBC correlations. Further correlations were noted between C-16, C-17 and a doublet at δ 5.08 (H-15) attached to a carbon atom at δ 88.7. The downfield shift of H-15 and a three-bond correlation between H-15 and the carbonyl group of the veratroyl ester at δ 168.2 confirmed the location of the ester on C-15. The stereochemistries deduced for the substituents on C-15 and C-16 were confirmed by ROESY. Thus, one of the diastereotopic protons, H-17a, exhibited clear NOEs with H-9β and H-11β in accordance with β-orientation of the hydroxymethylene group on C-16, while the correlation between H-15α and H-14β showed that the ester on C-15 was β-orientated.

^{1}H and ^{13}C NMR spectra (Tables 3 and 4) of the second new diterpene alkaloid **8**, an amorphous solid, differed from those of **7** essentially only in downfield shifts of the two H-17 protons and the presence of signals associated with an acetate, obviously due to esterification of the hydroxyl on C-17 as also indicated by its molecular formular $C_{32}H_{43}NO_7$. The obvious conclusion that the veratroyl ester had remained on C-15 and that the acetate was located on C-17 was confirmed by connectivities from HMBC between the acetate carbonyl at δ 170.8 and H-17a,b, on the one hand, and the veratroyl carbonyl at 167.8 and H-15 on the other. Hence the new substance was 15-veratroyl-17-acetyldictizine (**8**).

^{1}H and ^{13}C NMR spectroscopic data (Tables 3 and 4) of the third new diterpene alkaloid **9** differed significantly from those of **8** in only two respects, namely the replacement of a methylene by a carbonyl group, as shown by the presence of a singlet at δ 174.2 which replaced a triplet, that of C-19, usually found near δ 59, and a shift in the resonance of the angular methyl group from δ 0.65 to δ 1.20. The obvious conclusion that the substance was the C-19 lactone **9** was supported by the presence of an IR band at 1628 cm^{-1} characteristic of lactones, by HMBC correlations between C-19 and H-12 on the one hand, between C-19 and H-20 on the other and by the HRMS which was in accord with formula $C_{32}H_{41}NO_3$. That the substituents on C-15 and C-17 had not been interchanged was further demonstrated by HMBC and ROESY. Hence the substance was 15-veratroyl-17-acetyl-19-oxodictizine (**9**).

Mass spectral fragmentation of a fourth alkaloid **10**, $C_{31}H_{43}NO_7$, isolated only in very small amount (1.6 mg), to give peaks at 540 $[M - H]^+$ (8%), 524 $[M - OH]^+$ (4%), and 523 $[M - H_2O]^+$ (4%) was characteristic of an atisane type diterpene alkaloid carrying a hydroxyl or ether function on C-15 (Martin and Ruiz-Mesía, 1997). The ^{1}H and ^{13}C NMR spectra (Tables 3 and 4) were similar to those of **7** in demonstrating the presence of an angular methyl group at δ_H 0.865 and δ_C 25.89, and the three protons, two methoxyls and one carbonyl as well as the six aromatic carbons of a veratroyl ester, but differed in also including signals of an *N*-ethyl group with δ_H 1.55 (3H, *t*, J = 7 Hz), HSQ δ_C 10.399, δ_H 3.23 and 3.92 (each 1H, *m*), HSQ δ_C 54.6, and one signal at δ 3.86 (1H, *dd*, J = 10.5, 7 Hz) attributable to an α-oriented hydroxyl group whose multiplicity and coupling constants agreed with those of an 1α-hydroxyl in an alkaloid of the denudatine type (Takayama et al., 1989; Zhang et al., 1990). The signals of C-2 at δ 29.2 t and C-10 at 52.9s were shifted by 8.6, resp. 7.4 pm to lower field compared with C-2 and C-10 of **7** which again suggested presence of an α-orientated hydroxyl group on C-1 as did the downfield shift of the H-11α signal to δ 3.23 due to the deshielding effect of the hydroxyl function. The chemical shifts of H-17a and H-17b (δ_H 4.68 and 4.56, HSQC δ_C 69.8) as well as HMBC indicated that the veratroyl ester was attached to C-17 whereas the hydroxyl group on C-15 (δ_H 4.11s, δ_C 84.0d) was now not esterified, opposite to the situation prevailing in alkaloids **7**–**9**. Hence we were dealing with a new alkaloid *N*-ethyl-12-hydroxy-17-veratroyldictizine (**10**).

The ^{1}H NMR spectrum of the remaining new alkaloid, an amorphous substance of formula $C_{21}H_{27}NO_2$ whose IR spectrum exhibited absorptions at 1697 and 873 cm^{-1} indicative of carbonyl groups and double bonds, indicated the presence of an exocyclic methylene double bond (two *dd*s, J = 4.0, 2 Hz and 3.7, 2 Hz at δ 4.70, resp. δ 4.53), a tertiary methyl at δ 1.45 (3H, s) and an *N*-methyl group (methyl singlet at δ 2.20) while the ^{13}C NMR spectrum with 21 signals (Table 4) confirmed the presence of the two methyl groups, the exocyclic methylene double bond (singlet at 150.9, triplet at 103.6) two carbonyl groups at δ 204.8 and 209.3, seven saturated methylenes, five methine carbons and three quaternary carbons and suggested the presence of a hexacyclic atisane type alkaloid. The chemical shift of C-16 at δ 150.9 indicated that C-15 was not functionalized, a conclusion further supported by the fact that the protons of the exocyclic methylene group were allytically coupled to two signals at δ 2.34 and δ 2.25 (H-15a,b). Location of one of the two carbonyl groups on C-2 was supported by the chemical shifts of C-1 and C-3 at δ 49.1 resp. δ 55.8 while the second carbonyl group could be placed on C-6 because of the chemical shifts of C-5 and C-7 at δ 58.9 resp. δ 52.6, a conclusion

further supported by the chemical shift (δ 1.45, δ_C 29.6) of the angular methyl group (Mericli et al., 1999). Finally correlations from HMBC between C-19 and the protons of the angular methyl group, between H-19 and C-20 and between H-20 and C-13 led to formulation of the new alkaloid as the hetidine-type (Ulubelen et al., 1995) alkaloid **11** which we have named variegatine.

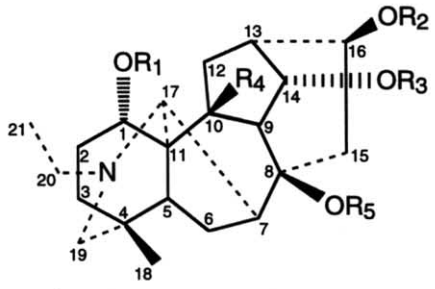
3. Experimental

3.1. General experimental procedures

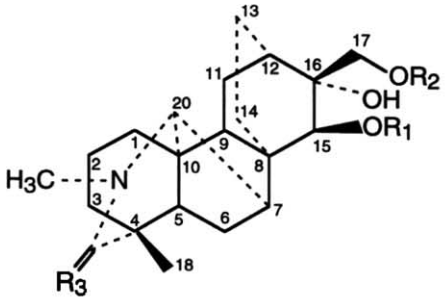
Mps are uncorrected and were taken on a Reichert Thermovar apparatus. IR spectra were run on a Bruker-TFS-55 spectrometer. Optical rotations were determined using a Perkin–Elmer-2H polarimeter with a 1-dm cell. EIMS and exact mass measurements were determined on a Micromass Autospec mass spectrometer at 70 eV. ^{1}H and ^{13}NMR spectra were determined on a Bruker-AMX-400 or AMX-500 spectrometer. Merck Al_2O_3 (neutral, 200–300 mesh) and Schleicher and Schuell 394 732 and Sephadex LH-20 were used for column chromatography (CC) and TLC, respectively. Spots on chromatograms were detected with Dragendorff's reagent.

3.2. Plant material

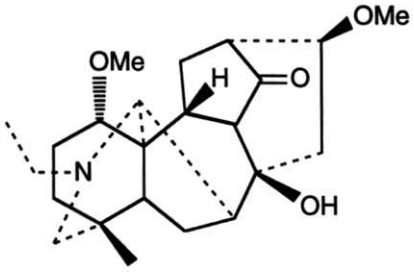
A. variegatum L. was collected on October 3, 1996 in Espelenguere near Ibon-Estanes, French Pyrenees, by



1 $R_1,R_2,R_3,R_4,R_5 = H$
2 $R_1,R_2 = Me$, $R_3,R_4,R_5 = H$
3 $R_1,R_2 = Me$, $R_3,R_4 = H$, $R_5 = Et$
4a $R_1,R_2 = Me$, $R_3,R_5 = H$, $R_4 = OH$
4b $R_1,R_2 = Me$, $R_3 = Ac$, $R_4 = OH$, $R_5 = H$



7 $R_1 = Ver$, $R_2 = H$, $R_3 = H_2$
8 $R_1 = Ver$, $R_2 = Ac$, $R_3 = H_2$
9 $R_1 = Ver$, $R_2 = Ac$, $R_3 = O$



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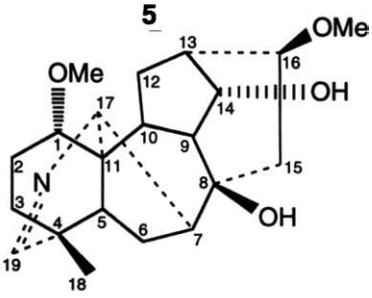

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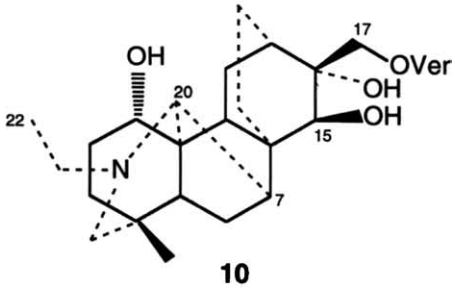

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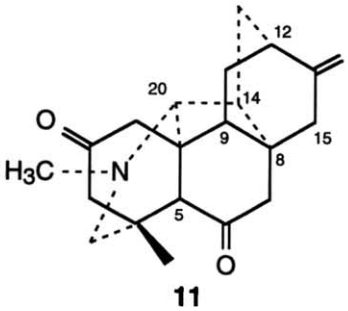

11

Dr. Julian Molero Briones, Department of Botany, Faculty of Pharmacy, University of Barcelona. A voucher specimen (BCF/S/N) is on deposit in the herbarium of that department.

3.3. Extraction and isolation

Air-dried and powdered aerial parts (1.85 kg) were extracted with 90% EtOH at room temperature for 8 days. After removal of solvent at reduced pressure the residue was treated with 0.4 M H_2SO_4 and filtered. The acidic filtrate was extracted with CH_2Cl_2 to give crude material (extract A, 1.78 g). The acidic aqueous phase was neutralized to pH 7 and extracted with CH_2Cl_2 to give extract B (1.62 g) after evaporation in vacuo. The neutral aqueous phase was basified with 20% NaOH to pH 12 and extracted with CH_2Cl_2 to give extract C (1.43) g after evaporation in vacuo.

Extract A (1.78 g) was applied to a Sephadex LH-20 column (hexane–CH_2Cl_2–MeOH, 1:1:2), with 70 fractions of 250 ml each being collected. Fractions 1, 2 and 6–10 did not contain alkaloids and were discarded. Fraction 3 on rechromatography over Sephadex LH-20 (hexane–CH_2Cl_2–MeOH, 6:4:1) afforded **8** (6.3 mg). Rechromatography of Fraction 4 over Sephadex LH-20 (hexane–CH_2Cl_2–MeOH, 6:3:1) followed by rechromatography over alumina (hexane–EtOAc, 3:2) furnished **9** (3.0 mg). Fraction 5 furnished **10** (1.6 mg) after rechromatography over Sephadex LH-20 (hexane–CH_2Cl_2–MeOH, 2:2:1).

Extract B (1.62 g) on chromatography over Sephadex LH-20 (hexane–CH_2Cl_2–MeOH, 4:3:3) gave 8 fractions. Fractions 1 and 2 (257 mg) and fractions 6–8 (230 mg) did not contain alkaloids and were discarded. Rechromatography of fraction 3 (806.2 mg) over Sephadex LH-20 (hexane–CH_2Cl_2–MeOH, 6:3:1) and subsequent column chromatography over Al_2O_3 using hexane–EtOAc mixtures in different proportions as eluent led to isolation of 14-acetylsachaconitine (9.5 mg) (Li et al., 2000), 14-acetyltalatizamine (25 mg) (Pelletier et al., 1985), **3** (1.8 mg), sachaconitine (12.2 mg) (Pelletier et al., 1977), talatizamine (550 mg) (Pelletier et al., 1985), **6** (4 mg) , pengshenine B (25.5 mg) (Xie et al., 2003) and genicunine B (36 mg) (Wang et al., 2000). Fraction 4 (175.0 mg) on chromatography over Sephadex LH-20 (hexane–CH_2Cl_2–MeOH, 6:3:1) furnished an additional talatizamine (15.5 mg), **7** (9.8 mg), karakoline (60.7 mg) (Liu and Katz, 1996), delsoline (4.3 mg) (Sakai et al., 1979), delcosine (10.6 mg) (de la Fuente and Ruiz-Mesía, 1994) and *N*-methylarmepavine (5.6 mg) (Wu et al., 1980). Fraction 5 (140.5 mg) on rechromatography over Sephadex LH-20 (hexane–CH_2Cl_2–MeOH, 6:3:1) gave more talatizamine (15.5 mg), karakoline (5 mg) and variegatine (**11**) (8.3 mg).

Extract C (1.43) on chromatography over Sephadex LH-20 (hexane–CH_2Cl_2–MeOH, 2:3:3) gave two fractions containing alkaloids. Fraction 1 (102.1 mg) on chromatography over SiO_2 (EtOAc–MeOH, 4:1) gave dehydrodelsoline (8.1 mg) (de la Fuente and Ruiz-Mesía, 1994), delsoline (6 mg) and 10-hydroxytalatizamine (20 mg) (Takayama et al., 1992). Fraction 2 (967 mg) on rechromatography over alumina using EtOAc–MeOH mixtures of increasing polarity furnished four subfractions containing alkaloids which on rechromatography over Sephadex LH-20 yielded talatizamine (480 mg), **5** (11 mg), 14-acetyl-10-hydroxytalatizamine (5 mg) (Sakai et al., 1979), **4a** (21.6 mg), an additional 10-hydrosytalatizamine (60 mg) and **1** (3.1 mg).

3.4. 16-β-Hydroxycardiopetaline (*1*)

Amorphous solid; $[\alpha]_D^{20}$ −11.3° (c = 0.15, $CHCl_3$), IR ν_{max}^{NaCl} 3373, 2926, 1579, 1459, 1376, 1092, 1046, 753 cm^{-1}. For ^1H NMR and ^{13}C NMR spectra, see Tables 1 and 2; HREIMS *m/z* 363.2432 (calcd for $C_{21}H_{33}NO_4$, 363.2409); EIMS *m/z* 363 $[M]^+$ (12), 348 $[M - CH_3]^+$ (22), 346 $[M - OH]^+$ (100), 345 $[M - H_2O]^+$ (13), 344 (5), 331 $[M - OH - CH_3]^+$ (4), 330 $[M - H_2O - CH_3]^+$ (20), 329 $[M - 204]^+$ (4), 328 $[M - OH - H_2O]^+$ (16), 327 $[M - 2H_2O]^+$ (17), 312 $[M - 2H_2O - CH_3]^+$ (9), 310 $[M - OH - 2H_2O]^+$ (6.7), 309 (1.4), 212 (29), 207 (16), 26 (42).

3.5. Ethoxysachaconitine (*3*)

Amorphous solid; $[\alpha]_D^{25}$ −17.6° (c = 0.08, $CHCl_3$), IR ν_{max}^{NaCl} 3403, 2921, 2360, 1643, 1459, 1377, 1093 cm^{-1}. For ^1H NMR and ^{13}C NMR spectra, see Tables 1 and 2; HREIMS *m/z* 419.3022 (calcd for $C_{23}H_{41}NO_4$, 419.3035); EIMS *m/z* 419 $[M]^+$ (2), 418 $[M - H]^+$ (2), 404 $[M - CH_3]^+$ (3.5), 403 (6), 402 (12.3) 390 (5.5), 389 $[M + H - OCH_3]^+$ (28.3), 388 $[M - OCH_3]^+$ (100), 387 $[M - CH_3OH]^+$ (2.2), 386 $[M - H_2O - CH_3]^+$ (6.6), 375 (5.8), 374 (22.4), 361 (9.2), 360 (38.8), 358 (5.7), 356 $[M - OCH_3 - CH_3OH]^+$ (3.2), 312 (12.7).

3.6. Genicunin B (*4a*)

Although this substance has been reported previously (Wang et al., 2000), its properties are not readily available from the literature; amorphous solid; $[\alpha]_D^{20}$ +3.4° (c = 0.52, $CHCl_3$), IR ν_{max}^{NaCl} 3406, 2925, 2817, 1588, 1450, 1371, 1294, 1213, 1152, 1092, 753 cm^{-1}. For ^1H NMR and ^{13}C NMR spectra, see Tables 1 and 2; HREIMS *m/z* 407.2616 (calcd for $C_{23}H_{37}NO_5$, 407.2671); EIMS *m/z* 407 $[M^+]$ (4.6), 406 (13.4), 392 $[M - CH_3]^+$ (1.6), 390 $[M - OH]^+$ (2.5), 389, $[M - H_2O]^+$ (1.5), 377 (24.3, 376) $[M - OCH_3]^+$ (100), 359 $[M - H_2O - CH_3OH]^+$ (12.4), 357 $[M - H_2O - CH_3]^+$ (3), 326 (5).

3.7. 14-Acetyl genicunin B (**4b**)

Amorphous solid; $[\alpha]_D^{20}$ +24.2° (*c* = 0.55, $CHCl_3$), IR ν_{max}^{NaCl} 3466, 2965, 2926, 2817, 1737, 1453, 1368, 1290, 1244, 1168, 1153, 1093, 1056, 755 cm^{-1}. For ^1H NMR and ^{13}C NMR spectra, see Table 1 and 2; HREIMS *m/z* 449.2651 (calcd for $C_{25}H_{39}NO_6$, 449.2777); EIMS *m/z* 449 $[M^+]$ (2), 434 $[M - CH_3]^+$ (1.3), 432 $[M - OH]^+$ (1.0), 431, $[M - H_2O]^+$ (1.7), 419 $[M - CH_2]^+$ (27), 418 $[M - OCH_3]^+$ (100), 417 $[M - CH_3 - OH]^+$ (1.0), 416(5) $[M - H_2O - CH_3]^+$ (2), 403 $[M - CH_3O - CH_3]^+$ (0.9), 402 $[M - CH_3 - CH_3]^+$ (3.7), 400 $[M - H_2O - CH_3]^+$ (9.5), 399 $[M - H_2O - CH_3OH]^+$ (1.4), 268 (11.3).

This substance was also obtained in 11 mg yield by acetylation of **4a** (15 mg) in the usual manner (Ac_2O–pyridine) and purification by chromatography over alumina using hexane–ethyl acetate (3:7).

3.8. 14-Dehydrogenicunin B (**5**)

Amorphous solid; $[\alpha]_D^{25}$ +10.7° (*c* = 0.14, $CHCl_3$), IR ν_{max}^{NaCl} 34,226, 2962, 2926, 2854, 2823, 1746, 1644, 1455, 1372, 1212, 1165, 1095, 930, 755 cm^{-1}. For ^1H NMR and ^{13}C NMR spectra, see Tables 1 and 2; HREIMS *m/z* 405.2496 (calcd for $C_{23}H_{35}NO_5$, 405.2515); EIMS *m/z* 405 $[M^+]$ (2), 404 $[M - H]^+$ (1.5), 390 $[M - CH_3]^+$ (2), 374 $[M - OCH_3]^+$ (100), 373 $[M - CH_3OH]^+$ (1.0), 372 $[M - H_2O - CH_3]^+$ (1.5), 362 $[M - CO - CH_3]^+$ (0.9), 360 (1.9), 359 $[M - CH_3 - OCH_3]^+$ (0.9), 358 $[M - CH_3 - CH_3OH]^+$ (3.9), 357 $[M - OH - OCH_3]^+$ (0.9), 356 $[M - H_2O - CH_3]^+$ (3.5), 399 $[M - H_2O - CH_3OH]^+$ (1.4), 268 (11.3).

This substance was prepared by oxidation of **4a** as follows. To **4** (10 mg (0.025 mol)) dissolved in 2 ml of HOAc-H_2O (9:1) was added dropwise a solution of CrO_3 (100 mg) in 2 ml of acetic acid–H_2O (9:1). The mixture was stirred at room temperatuer for 6 h, diluted with H_2O (20 ml) and extracted with CH_2Cl_2. The extract was dried over Na_2SO_4, evaporated at reduced pressure and chromatographed (EtOAc–MeOH, 3:2) to give of **5** (3 mg (29.6%)).

3.9. N-Deethyl-N-19-didehydrosachaconitine (**6**)

Amorphous solid; $[\alpha]_D^{25}$ +181.8° (*c* = 0.11, $CHCl_3$), IR ν_{max}^{NaCl} 3418, 2964, 2853, 1731, 1667, 1462, 1380, 1260, 1094, 755 cm^{-1}. For ^1H NMR and ^{13}C NMR spectra, see Tables 1 and 2; HREIMS *m/z* 361.2277 (calcd for $C_{21}H_{31}NO_4$, 361.2253); EIMS *m/z* 361 $[M^+]$ (70), 346 $[M - CH_3]^+$ (16.2), 332 (39.9), 331 (76), 330 $[M - OCH_3]^+$ (100), 329 $[M - CH_3 - OH]^+$ (70.5), 316(18), 314 $[M - CH_3 - CH_3OH]^+$ (18), 313 $[M - OCH_3OH]^+$ (19), 312 (29.4), 311 $[M - H_2O - CH_3OH]^+$ (60.2).

3.10. 15-Veratroyldictizine (**7**)

Amorphous solid; $[\alpha]_D^{20}$ +79.6° (*c* = 0.72, $CHCl_3$), IR ν_{max}^{NaCl} 3395, 3008, 2932, 2870, 1713, 1600, 1516, 1455, 1417, 1292, 1271, 1221, 1176, 1133, 1105, 1025, 758, 661 cm^{-1}. For ^1H NMR and ^{13}C NMR spectra, see Tables 3 and 4; HREIMS *m/z* 511.2932 (calcd for $C_{30}H_{41}NO_6$, 511.2933); EIMS *m/z* 511 $[M^+]$ (100), 510 $[M - H]^+$ (63), 496 $[M - CH_3]^+$ (9), 496, $[M - CH_3]^+$ (9), 494 $[M - OH]^+$ (6), 480 $[M - OCH_3]^+$ (6), 469 $[M - CH_3 - H_6]^+$ (6), 468 $[M - C_3H_7]^+$ (20), 346 $[M - C_9H_9O_3]^+$ (30), 330 (19), 329 (12), 328 (11), 312 (20), 300 (23), 298 (10).

3.11. 15-Veratroyl-17-acetyldictizine (**8**)

Amorphous solid; $[\alpha]_D^{25}$ +69.1° (*c* = 0.81, $CHCl_3$), IR ν_{max}^{NaCl} 3443, 3008, 2932, 2870, 1714, 1651, 1600, 1515, 1462, 1417, 1271, 1221, 1176, 1025, 7511 cm^{-1}. For ^1H NMR and ^{13}C NMR spectra, see Tables 3 and 4; HREIMS *m/z* 553.3030 (calcd for $C_{32}H_{43}NO_7$, 553.3039); EIMS *m/z* 553 $[M]^+$ (100), 552 $[M - H]^+$ (16), 537 $[M - CH_2]^+$ (4), 510 (19), 389 (10), 388 $[M - C_9H_9O_3]^+$ (38), 312 (7), 256 (17), 172 (27.5), 165 (67).

3.12. 15-Veratroyl-17-acety-19-oxodictizine (**9**)

Amorphous solid; $[\alpha]_D^{25}$ +49.3° (*c* = 0.15, $CHCl_3$), IR ν_{max}^{NaCl} 3402, 2920, 2849, 1717, 1628, 1598, 1515, 1459, 1416, 1372, 1271, 1220, 1100, 1042, 759 cm^{-1}. For ^1H NMR and ^{13}C NMR spectra, see Tables 3 and 4; HREIMS *m/z* 567.2910 (calcd for $C_{32}H_{41}NO_8$, 567.2832); EIMS *m/z* 567 $[M]^+$ (6), 507 (7), 385 (2), 342 $[M - C_9H_{10}O_4\text{-Ac}]^+$ (3), 325 $[M - C_9H_{10}O_4\text{-OH-Ac}]^+$ (15), 314 (6), 297 $[M - C_9H_{10}O_4\text{-CO-OH-Ac}]^+$ (5), 182 (18), 165 (100).

3.13. N-Ethyl-1α-hydroxy-17-veratroyldictizine (**10**)

Amorphous solid $[\alpha]_D^{25}$ +30.0° (*c* = 0.11, $CHCl_3$), IR ν_{max}^{NaCl} 3382, 2920, 2850, 1700, 1600, 1514, 1462, 1418, 1293, 1270, 1223, 1177, 1134, 1105, 1021, 762 cm^{-1}. For ^1H NMR and ^{13}C NMR spectra, see Tables 3 and 4; HREIMS *m/z* 541.3087 (calcd for $C_{31}H_{43}NO_7$, 541.3039); EIMS *m/z* 541 $[M]^+$ (25), 540 $[M - H]^+$ (8), 526 $[M - CH_3]^+$ (2), 524 $[M - OH]^+$ (4), 523 $[M - H_2O]^+$ (4) 512 $[M - C_2H_5]^+$ (7), 482 $[M - C_3H_7O]^+$ (9), 359 $[M - C_9H_{10}O_4]^+$ (20), 342 $[M - C_9H_{11}O_5]^+$ (25), 330 $[M - C_{10}H_{11}O_5]^+$ (72), 328 (17), 314 (21), 182 $[M - C_{22}H_{33}NO_3]^+$ (100), 186 (41).

3.14. Variegatine (**11**)

Amorphous solid; $[\alpha]_D^{20}$ +20.5° (*c* = 0.41, $CHCl_3$), IR ν_{max}^{NaCl} 2923, 2789, 1697, 1457, 1304, 1252, 1108 and 873 cm^{-1}. For ^1H NMR and ^{13}C NMR spectra, see

Tables 3 and 4; HREIMS *m/z* 325.2047 (calcd for $C_{21}H_{27}NO_2$, 325.2041); EIMS *m/z* 325 $[M]^+$ (100), 324 (22), 311 $[M - CH_2]^+$ (7), 310 $[M - CH_3]^+$ (32), 309 (2) 308 (9), 297 $[M - CO]^+$ (14), 296 (5), 283 $[M - CO - H_2O]^+$(2.2), 282 $[M - CH_3\text{-}CO]^+$ (9.5), 768 (20.4).

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