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PHYTOCHEMISTRY

Two novel dinitrogenous alkaloids from *Galanthus plicatus* subsp. *byzantinus* (Amaryllidaceae)

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Abstract

The minor alkaloids, (+)-plicamine and (−)-secoplicamine, from *Galanthus plicatus* subsp. *byzantinus* are the first examples of dinitrogenous alkaloids where the oxygen atom in position 7 of the basic tazettine molecule has been replaced by a nitrogen atom substituted by a pendant 4-hydroxyphenethyl moiety. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Galanthus plicatus subsp. *byzantinus*; Amaryllidaceae; Dinitrogenous alkaloids; (+)-Plicamine; (−)-Secoplicamine

1. Introduction

In the course of our ongoing phytochemical studies on Turkish *Galanthus* species (Amaryllidaceae), we had occasion to investigate *Galanthus plicatus* subsp. *byzantinus*, a plant native to northwestern Turkey (Brickell, 1984). The discovery of two novel optically active minor alkaloids, (+)-plicamine (**1**) and (−)-secoplicamine (**2**), in this plant marks the first occurrence of dinitrogenous bases in the Amaryllidaceae species. These new structures constitute a new subgroup of the Amaryllidaceae alkaloids, where the oxygen atom in position 7 of a tazettine molecule is replaced by a nitrogen atom substituted by a pendant 4-hydroxyphenethyl moiety. The structures and the stereochemistry of **1** and **2** are determined by detailed 1D and 2D NMR experiments and a possible biogenetic pathway is proposed.

2. Results and discussion

The initial evaluation of the signals in the ^{1}H NMR spectrum of our dextrorotatory compound, plicamine (**1**), revealed the presence of two *p*-oriented aromatic protons, a methylenedioxy and a methoxyl group as substituents and two olefinic hydrogens, which are commonly encountered features of various subgroups of the Amaryllidaceae alkaloids. A rather deshielded *N*-methyl signal was also noted. However, unusual signals were the two doublets in the aromatic region, integrating for two hydrogens each, and indicating the presence of a *p*-disubstituted benzene ring. In the aliphatic region, almost all signals displayed distinct couplings.

The multiplicities of the 26 carbons accounted for in the ^{13}C NMR spectrum were determined by DEPT experiments, while an HSQC experiment allowed the correlation of the protonated carbons with the corresponding hydrogens (Table 1). The most striking signals in the ^{13}C NMR spectrum were the two carbonyl resonances at δ 161.5 and 169.8, the presence of which were supported by strong absorptions in the carbonyl stretching frequency area of the IR spectrum. Also noteworthy in the ^{13}C NMR spectrum was the carbon singlet at δ 43.9, hinting at a spiro center as is the case in the tazettine subgroup, the presence of which had already been demonstrated by the isolation of (+)-tazettine (**3**) and (+)-3-epimacronine (**4**) from this plant (Akıneri, 1997). The 1D NMR information pointing to a tazettine-like molecule but with some unusual features prompted detailed 2D NMR experiments.

The construction of the main skeleton was initiated from ring A incorporating the methylenedioxy substituent. Using the $^2J_{CH}$ and $^3J_{CH}$ HMBC contours, H-9 (δ 7.60) was indisputably correlated to the resonance at δ 161.5, thus establishing the presence of a carbonyl group at C-8. The other aromatic singlet at δ 6.74 (H-12) had its most informative three-bond correlation outside ring A with the centrally located spiro carbon signal at δ 43.9 (C-12b), which also had further expected and instructive two- and three-bond correlations with ring C and D hydrogens.

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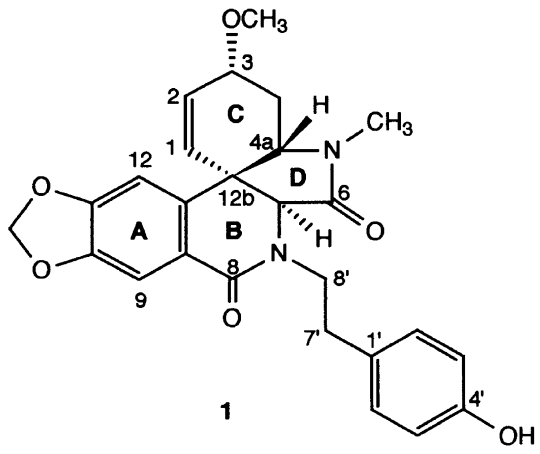

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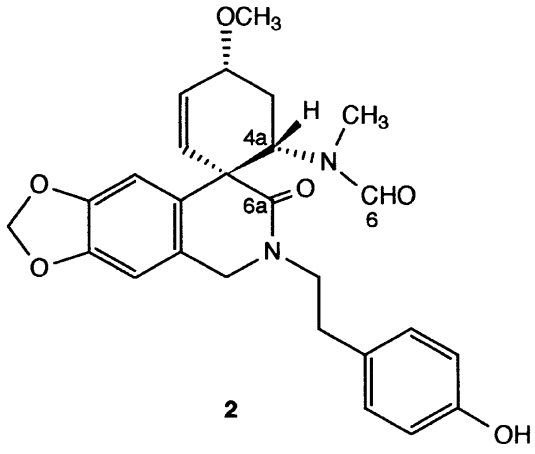

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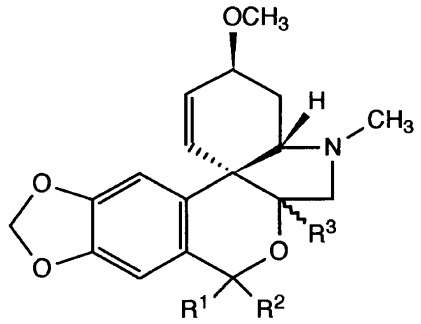


3 R^1= H, R^2= H, R^3= α-OH; (+)-tazettine

4 R^1+R^2= O, R^3= β-H; (+)-3-epimacronine

Table 1
HSQC, HMBC and NOESY data of plicamine (**1**), δ_c (ppm)

H	HSQC	HMBC	NOESY
1	133.3	C-3, C-4a, C-12b	H-2, H-6a
2	125.5	C-3, C-4, C-12b	H-1, H-3
3	70.8	OCH_3	H-2, H-4α, H-4β, OCH_3
4α	30.0		H-3, H-6a, NCH_3
4β	30.0		H-3, H-4a, NCH_3
4a	59.9	C-6, C-6a, C-12a, C-12b	H-4β, H-12, NCH_3
6a	63.9	C-1, C-6, C-8, C-12a, C-12b, C-8′	H-1, H-4α, H-7′, H-8′a, H-8′b
9	108.2	C-8, C-10, C-11, C-12a	
12	106.0	C-8a, C-10, C-11, C-12b	H-4a, OCH_3
7′	33.2	C-1′, C-2′(6′), C-8′	H-8′a, H-8′b, H-2′(6′)
8′a	49.5	C-6a, C-8, C-1′, C-7′	H-7′
8′b	49.5	C-6a, C-8, C-7′	H-6a, H-7′, H-8′a
2′,6′	130.1	C-4′, C-7′	H-3′(5′), H-7′, H-8′b
3′,5′	115.3	C-1′, C-4′	H-2′(6′)
OCH_3	56.7	C-3	H-2, H-4β
NCH_3	28.4	C-4a, C-6	H-4β, H-4a, H-6a
OCH_2O	101.8	C-10, C-11	

In the ^1H–^1H DQF-COSY spectrum, the olefinic doublet at δ 5.54 (H-1) coupled only with δ 6.00 (H-2), while the latter had a further coupling (J 5.2 Hz) with δ 3.91 (H-3). The rather high chemical shift of the latter suggested the presence of an oxygenated function on the same carbon (δ 70.8, C-3). The information gathered from the HMBC and NOESY experiments (Table 1) confirmed that the methoxyl group (δ 3.46) was indeed positioned at C-3. Meanwhile, H-3 (δ 3.91) coupled with the geminal protons, H-4 (δ 2.44 and 1.48). As complementary evidence, a TOCSY experiment interrelated all of the above mentioned protons (H-1, 2, 3 and 4) and also H-4a (δ 4.03), thus verifying their sequence on ring C of a probable tazettine structure.

HMBC data correlated the *N*-methyl protons (δ 2.80) to both δ 59.9 (C-4a) and also to δ 169.8 through $^3J_{CH}$ couplings, thus establishing the position of the second carbonyl group at C-6. The rather deshielded *N*-methyl resonance could, therefore, be justified by the 5-membered lactam nature of ring D.

Through relevant HMBC correlations, the position of the singlet at δ 3.87 was indisputably assigned to solitary methine proton, H-6a. Since this proton was strongly interlocked through NOESY correlations to H-1 and H-4a (δ 1.48), an α-orientation could easily be assigned to H-6a.

Some other prominent NOESY correlations were from H-12 to H-4a, which in turn had strong enhancements with the *N*-methyl protons as well as with δ 2.44 (H-4β), interrelating signals from all four rings and thus defining the conformational preference of the main skeleton.

With the so far accumulated data, a gross structure for a compound from the tazettine subgroup could be postulated. However, what still remained to be determined was the connection of this main structure to the *p*-disubstituted benzene ring and four aliphatic hydrogens which were evidenced by the ^1H and ^{13}C NMR spectra.

In the ^1H–^1H DQF-COSY experiment, the geminal protons resonating at δ 4.50 and 3.53, and the two lower frequency geminal protons with very close chemical shifts around δ 2.98–2.89, which, therefore, formed a higher order multiplet, were all members of an isolated four-spin system. All of these protons were connected by HMBC and NOESY correlations to the two-proton doublet (δ 7.10), therefore, constructing a 4′-substituted phenethyl moiety. This substitution at C-4′ was suggested to be a hydroxyl group, the presence of which was confirmed in the UV spectrum of **1** by the bathochromic shift produced upon the addition of alkali hydroxide.

The key information interlocking the main skeleton with the phenethyl group was furnished by the HMBC experiment, which documented $^2J_{CH}$ correlations from H-6a (δ 3.87) to δ 49.5 (C-8′) and from H-8′ methylene protons to δ 63.9 (C-6a) and to the carbonyl singlet at C-8 (δ 161.5). Strong NOESY correlations were also observed between H-6a and the protons of the four-spin system of the phenethyl group.

In the light of the above-mentioned data, the possible linkage of the main skeleton with the *p*-substituted phenethyl moiety could only be through a nitrogen atom positioned at C-7, where there is an oxygen atom in the case of a tazettine-type molecule.

The molecular formula for such a structure should then be $C_{26}H_{26}N_2O_6$. An ESI-MS furnished m/z 463 as $[M+H]^+$, which is in complete accordance with the calculated molecular weight of 462.

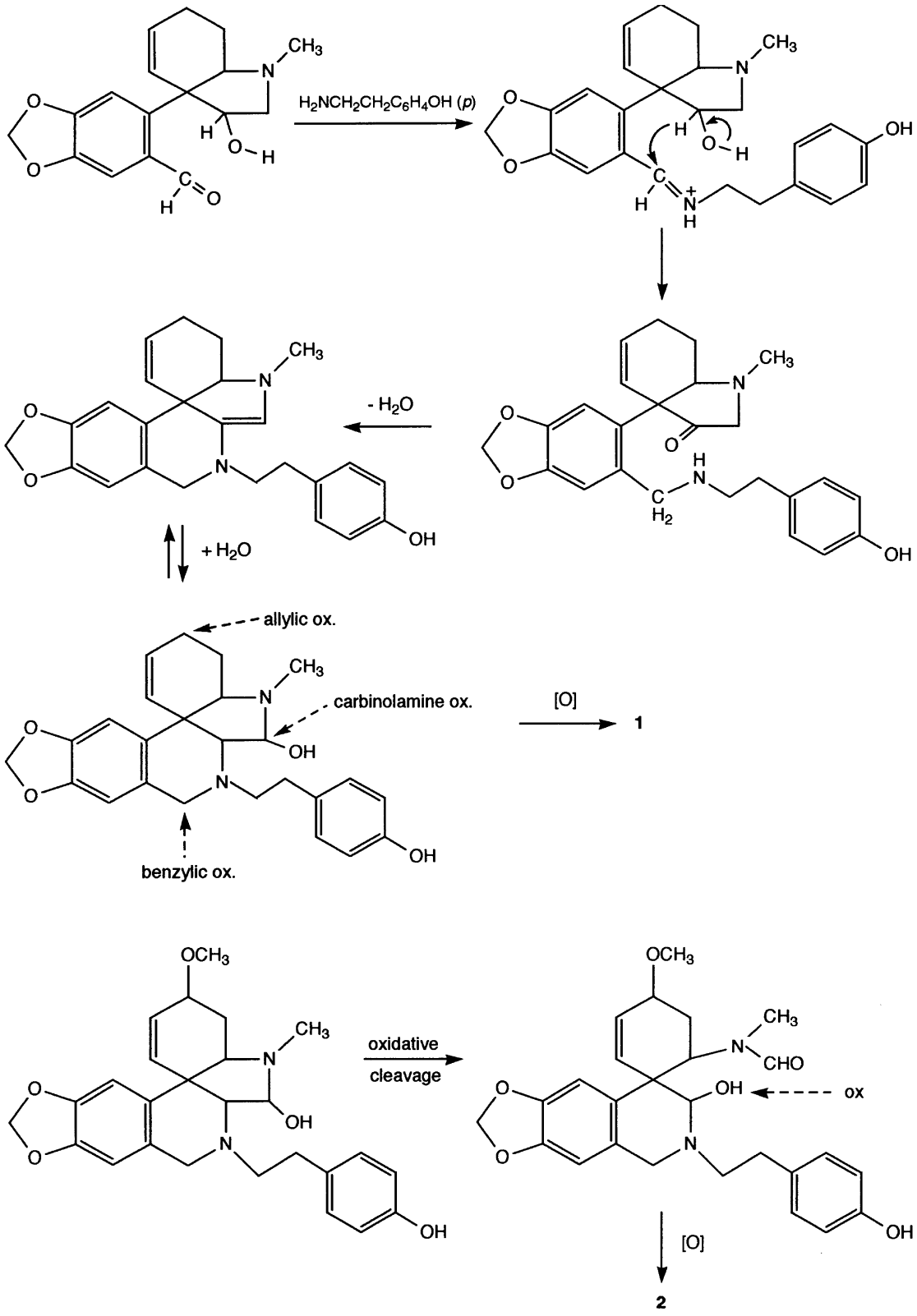
A biogenetic pathway probably proceeds via an aminoaldehyde, postulated to be a key intermediate interrelating the crinine and tazettine structures (Wildman & Bailey, 1969). A molecule of tyramine forms a Schiff base with this intermediate, which then undergoes an intramolecular rearrangement followed by ring closure. Subsequent hydration and facile oxidations of the allylic and benzylic sites as well as the carbinolamine may furnish (+)-plicamine (Scheme 1).

The ^1H NMR spectrum of the second optically active compound, for which the name secoplicamine (**2**) is suggested, closely resembled that of **1**, where conspicuous similarities in the aromatic region as compared to that of **1** were the two *p*-oriented aromatic protons, two doublets integrating for two hydrogens each and two olefinic protons. Again relevant signals for a rather deshielded *N*-methyl, a methylenedioxy group and a methoxyl substituent were readily observed, suggesting that compound **2** was analogous with compound **1** with respect to some of the structural features. A comparison of ^{13}C NMR data of **1** and **2** showed that a great majority of carbon chemical shifts and multiplicities were indeed very similar.

On the other hand, in the ^1H NMR spectrum of **2**, the presence of an additional deshielded proton resonating at δ 7.23 as well as of two high-frequency doublets at δ 4.30 and 4.12, reminiscent of an isolated methylene, were the readily noticeable differences. Additionally, one of the aromatic protons (δ 6.46), shielded by about 1.1 ppm as compared to the corresponding hydrogen in **1** (δ 7.60), remained to be accounted for the structural differences between **1** and **2**.

While the ^1H–^1H DQF-COSY and TOCSY experiments allowed the assignment of chemical shifts and couplings of protons, the ^{13}C NMR and DEPT spectra revealed the presence of 26 carbons as in compound **1**. Moreover, a thorough evaluation of the HSQC and HMBC experiments performed on **2** (Table 2) confirmed that rings A and C consisted exactly of the same structural features as those of **1**. Therefore, it now remained to be shown that the differences observed in the ^1H and ^{13}C NMR spectra of **1** and **2** originated from the structural diversities located in ring B.

A readily noticeable difference in the ^{13}C NMR spectrum of **2** as compared to that of **1** was the presence of a


H2NCH2CH2C6H4OH (p)
- H2O
+ H2O
allylic ox.
carbinolamine ox.
benzylic ox.
[O]
1
oxidative
cleavage
ox
[O]
2

Scheme 1.

Table 2
HSQC, HMBC and NOESY Data of secoplicamine (**2**), δ_c (ppm)

H	HSQC	HMBC	NOESY
1	133.3	C-3a, C-4a, C-12a, C-12b	H-1, H-12
2	128.4	C-1, C-3, C-4, C-6, C-12b	H-1, H-3, OCH_3
3	73.1	C-1, C-2, C-4a, OCH_3	H-2, H-4α, H-4β, OCH_3
4α	29.1	C-4a, C-12b	H-6, NCH_3
4β	29.1	C-2, C-3, C-4a, C-12b	H-3, H-4a, H-6, OCH_3, NCH_3
4a	61.8	C-3, C-4, C-6, C-6a, C-12a, C-12b, NCH_3	H-1, H-3, H-6, H-12, H-4β, H-8′a, NCH_3
6	163.2	C-4a, NCH_3	H-4α, H-4a, NCH_3
8α	50.7	C-6a, C-8a, C-9, C-12a, C-8′	H-9, H-2′(6′), H-7′, H-8′b
8β	50.7	C-6a, C-8a, C-9, C-12a	H-6, H-9, H-7′, H-8′b, NCH_3
9	104.8	C-8, C-10, C-11, C-12, C-12a	H-8α, H-8β
12	106.7	C-8a, C-9, C-10, C-11, C-12a, C-12b	H-1
7′	32.3	C-6′, C-8′	H-2′(6′), H-8′a
8′a	50.5	C-6a, C-8, C-1′, C-7′	H-2′(6′), H-7′, NCH_3
8′b	50.5	C-6a, C-8	H-8α, H-8β, H-2′(6′), H-7′
2′,6′	129.8	C-3′(5′), C-4′, C-7′	H-7′, H-8′a, H-8′b
3′,5′	115.5	C-1′, C-4′	H-1, H-4a
OCH_3	56.9	C-3	H-2, H-3, H-4β, H-4a
NCH_3	27.5	C-4a, C-6	H-4α, H-4β, H-4a, H-6, H-8β, H-8′a, H-8′b
OCH_2O	101.5	C-10, C-11	

secondary carbon (δ 50.7), which incorporated the isolated geminal hydrogens (δ 4.30 and 4.12). In the HMBC experiment, these protons showed $^2J_{CH}$ and $^3J_{CH}$ correlations with relevant carbons located in ring A. Among them, the most diagnostic three-bond correlation was with C-9 (δ 104.8). Thus, one of the structural differences between **1** and **2** was shown to be the presence of an isolated methylene at C-8 in **2**, whereas a lactam carbonyl was located at the same site in **1**.

Although the ^{13}C NMR of **2** also had two carbonyl signals as in **1**, in the HSQC clearly correlated one of these signals (δ 163.2) with the deshielded proton at δ 7.23. In the HMBC experiment, the aforementioned hydrogen showed strong three-bond correlations with δ 61.8 (C-4a) and δ 27.5 (NCH_3), while the *N*-methyl protons (δ 2.64) had prominent $^2J_{CH}$ correlations with δ 163.2 and also with C-4a (δ 61.8), therefore, establishing the presence of an *N*-methyl-*N*-formylamino moiety attached to C-4a. This structure probably resulted from an oxidative cleavage of the C(6)–C(6a) bond present in compound **1**. Consequently, compound **2** no longer possessed ring D of the tazettine-type structure, and encompassed one ring less than compound **1**.

A further task was to define the effect of the postulated oxidative bond rupture at C-6a, where ring D was originally fused to ring B in compound **1**. In consonance with an expected oxidation also at this site, the only ^{13}C NMR signal which remained to be assigned was the carbonyl singlet at δ 167.0. The important $^3J_{CH}$ correlations from H-8, H-8′ and H-4a to this carbon not only confirmed its position at C-6a, but also interlocked the main skeleton with the 4-hydroxyphenethyl portion substituted on N-7.

The structure designed by the information deduced from the 1D and 2D NMR experiments accounted for a molecular formula of $C_{26}H_{28}N_2O_6$. The molecular weight calculated for this formula, 464, was verified by an ESI-mass spectrum.

To ascertain the stereochemistry of **2**, the evaluation of the NOESY spectrum Table 2 was initiated from the assumed configuration at C-12b. Although ring C was quite flexible, the NOESY correlations of the ring C protons as well as of the methoxyl positioned at C-3 all pointed to a twisted chair conformation of ring C. The α-orientation of the methoxyl group at C-3 was established by the magnitude of the $J_{2,3}$ (Haugwitz, Jeffs, & Wenkert, 1965). A β-orientation was assigned to H-4a (δ 3.88) according to its strong NOESY correlation with H-12 (δ 6.72). In turn, mutual cross signals between H-4a and H-4 at δ 1.94 reflected their identical orientations. Cross signals were also observed between H-4a and H-6 (δ 7.23) and also the *N*-methyl protons. Furthermore, the NOESY data furnished information also for the orientations of the geminal protons located at C-8. The α-oriented hydrogen of this geminal pair (δ 4.12) displayed correlations with the ethylene hydrogens pendant on N-7, pointing to their spatial proximity.

Although the CD curves of compounds **1** and **2** in methanol resembled remarkably those of the tazettine-type bases **3** and **4** of established stereochemistry (Wild-

man & Bailey, 1969; Kobayashi, Kihara, Shingu, & Shingu, 1980; Akıneri, 1997), we are unable to predict the absolute configurations of these two new compounds.

In the biogenetic sequence, a diversion at the final oxidative stage seems to produce **2** instead of **1** (Scheme 1).

Despite their close resemblance to the tazettine-type Amaryllidaceae alkaloids, the novel compounds, plicamine (**1**) and secoplicamine (**2**), are characterized by a unique structural diversity, where a nitrogen atom is incorporated in position 7 of the basic tazettine nucleus instead of an oxygen atom. The isolation of these dinitrogenous compounds marks the introduction of a new subgroup, the plicamines, to the Amaryllidaceae alkaloids, which have so far been classified into eight subgroups (Martin, 1987).

3. Experimental

3.1. General

Optical rotations: Perkin-Elmer 241 Polarimeter; UV: Perkin-Elmer 555 Spectrometer; IR: Perkin-Elmer 297 Infrared Spectrometer; ^{1}H NMR, ^{13}C NMR, DEPT, gs-HSQC, gs-HMBC, TOCSY (mixing time: 100 ms), DQF-COSY, NOESY (mixing time: 400 ms): Bruker AMX-600 Spectrometer at 300 K calibration: ^{1}H $\delta_{CDCl_3} = 7.27$ ppm, ^{13}C $\delta_{CDCl_3} = 77$ ppm; ESI-MS: Finnigan MAT TSQ 700; CD: Jasco J-715 Spectropolarimeter.

3.2. Plant material

G. plicatus Bieb. subsp. *byzantinus* (Baker) D.A. Webb was collected from the vicinity of forest houses around Lake Abant, Bolu, on April 6, 1995. A voucher specimen, No. 1194, is deposited in the Herbarium of the Department of Pharmacognosy, Faculty of Pharmacy, Ege University.

3.3. Extraction and isolation

Dried and powdered total plant material of *G. plicatus* subsp. *byzantinus* (3.7 kg) was extracted with EtOH at room temp to furnish the crude alcoholic extract (425 g) which was then dissolved in 2% aq. HCl and filtered. This acidic solution basified with 10% aq. NH_4OH and extracted with $CHCl_3$, the evaporation of which furnished the crude basic extract (10.28 g). During the preliminary separation through a silicagel column (Merck, 70–230 mesh) using $CHCl_3$ gradually enriched with MeOH, a fr eluted with 1% MeOH in $CHCl_3$ afforded 0.434 g of a mixture, which was subjected to prep CC on silica gel H (Merck, Type 60) using C_6H_6–EtOAc–EtOH (80:15:5). Among the 20 ml frs collected, fr 10–13 was further purified by prep TLC on silica gel coated ready-made plates (Merck, 0.5 mm thickness) using the same solvent system to yield to yield **1** (3 *mg*) *and* **2** (6 *mg*).

3.4. (+)-Plicamine (*1*)

Amorphous solid. $[\alpha]_D$ +74.4 (MeOH; *c* 0.117). UV λ_{max} (MeOH) nm ($\log\varepsilon$) 226 (4.41), 265 sh (3.71), 299 (3.49). CD (MeOH) nm ($\log\varepsilon$) 325 (0), 307 (−0.48), 291 (0), 262 (+1.91), 259 (+1.56), 250 sh (+1.43), 229 (+19.85), 209 (+9.69), negative tail beyond 209 nm. IR ν_{max} ($CHCl_3$) cm^{-1} 3300, 3000, 2950, 2920, 2860, 1700, 1660, 1645, 1610, 1505, 1465, 1440, 1430, 1405, 1390, 1370, 1350, 1330, 1265, 1215, 1160, 1140, 1100, 1085, 1035, 930. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.60 (1H, s, H-9), 7.10 (2H, d, J=8.4 Hz, H-2′ and H-6′), 6.74 (2H, d, J=8.4 Hz, H-3′ and H-5′), 6.74 (1H, s, H-12), 6.02 and 6.01 (2H, 2d, J=1.3 Hz, OCH_2O), 6.00 (1H, dd, J=9.8, 5.2 Hz, H-2), 5.54 (1H, d, J=9.8 Hz, H-1), 4.50 (1H, ddd, J=14.0, 8.4, 5.4 Hz, H-8′a), 4.03 (1H, dd, J=11.9, 4.5 Hz, H-4a), 3.91 (1H, dt, J=5.1, 3.2, H-3), 3.87 (1H, s, H-6a), 3.53 (1H, m, H-8′b), 3.46 (3H, s, OMe), 2.98–2.89 (2H, m, H-7′), 2.80 (3H, s, NMe), 2.44 (1H, m, H-4β), 1.48 (1H, m, H-4a). ^{13}C NMR (150 MHz, $CDCl_3$) δ 28.4 (NMe), 30.0 (C-4), 33.2 (C-7′), 43.9 (C-12b), 49.5 (C-8′), 56.7 (OMe), 59.9 (C-4a), 63.9 (C-6a), 70.8 (C-3), 101.8 (OCH_2O), 106.0 (C-12), 108.2 (C-9), 115.3 (C-3′ and C-5′), 123.4 (C-8a), 125.5 (C-2), 130.1 (C-2′ and C-6′), 131.0 (C-1′), 133.3 (C-1), 135.1 (C-12a), 147.8 (C-10), 151.3 (C-11), 154.2 (C-4′), 161.5 (C-8), 169.8 (C-6). ESI-MS m/z 463 [M + H$^+$].

3.5. (−)-Secoplicamine (*2*)

Amorphous solid. $[\alpha]_D$ −16.9 (MeOH; *c* 0.142). UV λ_{max} (MeOH) nm ($\log\varepsilon$) 221 sh (4.41), 243 sh (4.02), 287 (3.67). CD (MeOH) nm ($\log\varepsilon$) 325 (0), 313 (−0.22), 308 (0), 289 (+2.11), 262 (+0.72), 245 sh (+2.35), 239 (+3.38), 228 (0), 225 (−0.88), 220 (0), 207 (+18.58), negative tail beyond 208 nm. IR ν_{max} ($CHCl_3$) cm^{-1} 3300, 3000, 2920, 1665, 1645, 1615, 1505, 1480, 1445, 1425, 1410, 1370, 1360, 1335, 1325, 1265, 1215, 1120, 1090, 1085, 1075, 1040, 935, 925. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.23 (1H, s, H-6), 7.03 (2H, d, J=8.4 Hz, H-2′ and H-6′), 6.75 (2H, d, J=8.4 Hz, H-3′ and H-5′), 6.72 (1H, s, H-12), 6.46 (1H, s, H-9), 6.33 (1H, dd, J=9.9, 4.9 Hz, H-2), 6.00 and 5.96 (2H, 2d, J=1.3 Hz, OCH_2O), 5.73 (1H, d, J=9.9 Hz, H-1), 4.30 (1H, d, J=16.2 Hz, H-8β), 4.12 (1H, d, J=16.2 Hz, H-8α), 4.09 (1H, m, H-3), 3.96 (1H, m, H-8′a), 3.88 (1H, dd, J=13.1, 2.8 Hz, H-4a), 3.44 (3H, s, OMe), 3.17 (1H, m, H-8′b), 2.83–2.77 (3H, m, H-4a and H-7′), 2.64 (3H, s, NMe), 1.94 (1H, bd, J=13.2 Hz, H-4b). ^{13}C NMR (150 MHz, $CDCl_3$) δ 27.5 (NMe), 29.1 (C-4), 32.3 (C-7′), 50.5 (C-8′), 50.7 (C-8), 52.7 (C-12b), 56.9 (OMe), 61.8 (C-4a), 73.1 (C-3), 101.5 (OCH_2O), 104.8 (C-9), 106.7 (C-12), 115.5 (C-3′ and C-

5′), 124.4 (C-8a), 128.4 (C-2), 129.3 (C-12a), 129.8 (C-2′ and C-6′), 130.1 (C-1′), 133.3 (C-1), 147.6 (C-10), 148.1 (C-11), 154.8 (C-4′), 163.2 (C-6), 167.0 (C-6a). ESI-MS m/z 487 [$M+Na^+$], 465 [$M+H^+$].

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