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Ipecac alkaloids from *Cephaelis acuminata*

Atsuko Itoh, Yuki Ikuta, Yoshikazu Baba, Takao Tanahashi*, Naotaka Nagakura

Kobe Pharmaceutical University, Higashinada-ku, Kobe 658-8558, Japan

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Abstract

From the dried roots of *Cephaelis acuminata*, five ipecac alkaloids, neocephaeline, 7′-*O*-demethylcephaeline, 10-*O*-demethylcephaeline, 2′-*N*-(1″-deoxy-1″-β-D-fructopyranosyl)cephaeline and 2′-*N*-(1″-deoxy-1″-β-D-fructopyranosyl)neocephaeline, were isolated, along with emetine, cephaeline, psychotrine, protoemetine, 9-demethylprotoemetinol and isocephaeline. Structures were determined by spectroscopic and chemical means. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: *Cephaelis acuminata*; Rubiaceae; Structure elucidation; Ipecac alkaloids; Emetine; Cephaeline; Neocephaeline; Demethylcephaelines; Amadori rearrangement compounds

1. Introduction

The crude drug 'Ipecac' is defined as the dried roots of either *Cephaelis ipecacuanha* A. Richard, or *Cephaelis acuminata* Karsten belonging to the family Rubiaceae. It has been used in therapy since the beginning of the 17th century as an emetic and expectorant, and was further used against dysentery in the 18th century (Janot, 1953). Because of the emetic activity of its main alkaloids, emetine (**1**) and cephaeline (**2**), ipecac syrup is still used as an emetic for emergencies resulting from drug overdose, and in some cases, poisoning. Of two kinds of ipecac, Carthagena ipecac, supplied by *C. acuminata* is the ipecac of commerce in the world now, because Rio ipecac (*C. ipecacuanha*) is difficult to obtain commercially (Yoshimatsu & Shimomura, 1993). Previous phytochemical studies resulted in the isolation from *C. ipecacuanha* of six ipecac alkaloids, emetine (**1**), cephaeline (**2**), psychotrine (**3**), protoemetine (**4**), *O*-methylpsychotrine and emetamine (Shamma, 1972). Alkaloids **1–3** were also detected in *C. acuminata* (Janot, 1953). Recently, we have investigated the glucosidal fractions of *C. acuminata*[1] and isolated 11 tetrahydroisoquinoline-monoterpene glucosides which were closely related to the ipecac alkaloids (Itoh, Tanahashi & Nagakura, 1989, 1991; Nagakura, Itoh & Tanahashi, 1993; Itoh, Tanahashi, Nagakura & Nayeshiro, 1994). In a continuation of our chemical studies on ipecac, we re-examined the alkaloidal constituents of the same plant material, and report here the isolation and characterization of five new ipecac alkaloids.

2. Results and discussion

The roots of *C. acuminata* were extracted with hot MeOH and the MeOH extract was successively partitioned between H_2O/$CHCl_3$ and H_2O/*n*-BuOH. Since alkaloids were detected in the H_2O layer with Dragendorff's reagent, the H_2O layer was basified and extracted with Et_2O and then with $C_2H_4Cl_2$. The organic layers were separated by a combination of chromatographic procedures, affording 11 ipecac alkaloids (**1–11**). Alkaloids **1–6** were identified as emetine (**1**) (Wiegrebe, Kramer & Shamma, 1984), cephaeline (**2**) (Wiegrebe et al., 1984), psychotrine (**3**) (Wiegrebe et al., 1984), protoemetine (**4**) (Wiegrebe et al., 1984), 9-

* Corresponding author. Fax: +81-78-441-7546.
E-mail address: tanahash@kobepharma-u.ac.jp (T. Tanahashi).

[1] In previous papers, we reported that the ipecac used for our studies was *C. ipecacuanha*. We correct here the plant material to be *C. acuminata* according to the kind suggestion and identification of the voucher (KPFY-831) by Dr. M. Satake, National Institute of Health Sciences, Tokyo, Japan.

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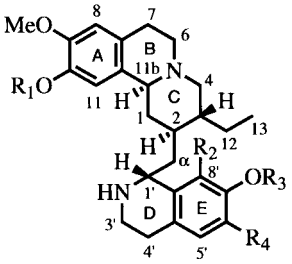

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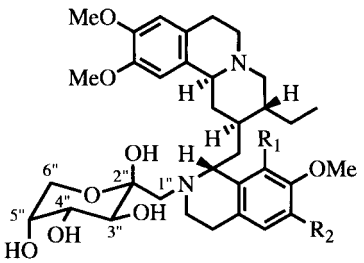
8: R_1=Me, R_2=R_3=H, R_4=OH
9: R_1=R_2=H, R_3=Me, R_4=OH
13: R_1=Me, R_2=OH, R_3=R_4=H



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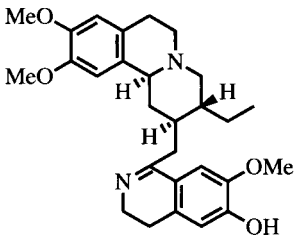
11: R_1=OH, R_2=H
14: R_1=H, R_2=OMe



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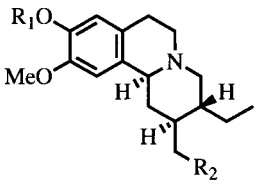
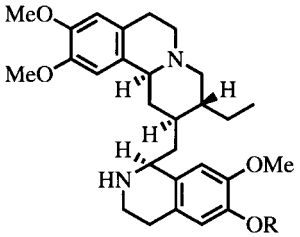


4: R_1=Me, R_2=CHO
5: R_1=H, R_2=CH_2OH



6: R=H
12: R=Me

demethylprotoemetinol (**5**) (Fujii, Ohba, Suzuki, Pakrashi & Ali, 1982) and isocephaeline (**6**) (Achari, Ali, Ghosh Dastidar, Sinha & Pakrashi, 1980), from their spectroscopic data. The last three alkaloids were isolated for the first time from *C. acuminata*. The structures of the new alkaloids **7**–**11** were characterized as follows.

Alkaloid **7**, which we have named neocephaeline, was isolated as an amorphous powder, and was an isomer of cephaeline (**2**), $C_{28}H_{38}N_2O_4$, from its HR-MS. It showed UV maxima at 207, 230sh and 282 nm, IR bands at 3496, 2833, 2754, 1611 and 1512 cm^{-1}, and EIMS fragment ions at *m/z* 288, 272, 246, 205, 192, 191 and 178. Its ^1H NMR spectrum exhibited signals for three methoxyl groups at δ 3.84 (3H, s) and 3.85 (6H, s), signals for an ethyl group at δ 0.90 (3H, t, J = 7.0 Hz), 1.14 (1H, d of quint, J = 14.0, 7.0 Hz) and 1.66 (1H, dqd, J = 14.0, 7.0, 3.0 Hz) and two singlets at δ 6.58 and 6.80. Its ^{13}C NMR spectrum showed eight quaternary carbons, eight methines, eight methylenes and four methyl groups. These spectral features were closely similar to those of **2**, but there were remarkable differences in ^1H NMR spectra, with two aromatic protons of **7** appearing as a pair of *ortho* coupled doublets (J = 8.0 Hz) at δ 6.60 and 6.70, instead of two singlets at δ 6.50 and 6.63 as in **2**. There were further significant differences between **2** and **7** in the chemical shifts of the carbon signals due to the lower tetrahydroisoquinoline nucleus (Table 1). All these findings demonstrated that **7** differs from **2** in its substitution pattern of the lower aromatic moiety, which could be determined from the 2D NMR spectra. The signal at δ 6.60 (d, J = 8.0 Hz) was assigned to H-5′ in the lower aromatic ring by the HMBC correlation between H-5′ and C-4′ (δ 28.8) which was established by the HMBC correlations between H-1′ and C-3′ and between H-4′ and C-3′, and the HMQC cross-peak between H-4′ and C-4′. The signal at δ 6.70 (d, J = 8.0 Hz) coupled with H-5′ was assigned to H-6′. The NOESY correlation between H-6′ and OMe indicated the placement of a methoxyl group at C-7′ and, therefore, a hydroxyl group at C-8′. The B/C *trans* junction was demonstrated by the Bohlmann bands in the IR spectrum and the absolute configurations at C-2, C-3 and C-11b were deduced to be the same as in **1** and **2** by the similarity of the ^1H and ^{13}C NMR spectral data for rings A, B, C in **7** with those in **1** and **2** (Table 1), together with biogenetic considerations. The remaining configuration of C-1′ was suggested to be *R* by almost the same coupling constant between H-1′ and H-α as in **1** and **2** in the ^1H NMR spectrum, along with the chemical shifts of C-1 and C-2 in ^{13}C NMR spectrum (Fujii & Ohba, 1985). Finally, this assumption was supported by a comparative study of the CD spectra of **1**, **2**, isocephaeline (**6**), a C-1′ epimer of cephaeline, and isoemetine (**12**), derived from **6** by methylation. Thus, the structure of neocephaeline was determined to be **7**.

The second new alkaloid **8**, $C_{27}H_{36}N_2O_4$, was unstable and its solution turned dark easily, implying that it possessed a catecholic moiety in the molecule. The spectral features of **8** were analogous to those of **1**

Table 1
^{13}C NMR spectral data for compounds **1**, **2**, **6–12** and **14**

C	**1**[a]	**2**[a]	**6**[a]	**7**[a]	**8**[b]	**9**[b]	**10**[a]	**11**[a]	**12**[a]	**14**[a]
1	36.9	36.9	39.3	36.3	37.2	36.5	36.5	36.1	39.4	36.3
2	36.7	36.7	38.5	37.3	38.0	37.5	37.5	37.9	38.8	37.4
3	41.7	41.7	42.8	41.5	42.7	42.6	41.4	41.4	42.8	40.6
4	61.3	61.3	61.5	61.6	62.2	62.1	61.2	61.4	61.5	61.1
6	52.3	52.3	52.6	52.4	53.3	53.6	52.1	52.2	52.5	52.1
7	29.1[c]	29.2	29.1	29.2	29.5	29.4	29.1	29.1	29.1[p]	29.7
7a	126.1[d]	126.8	126.5	126.7	127.9	126.1	127.0	126.9[n]	126.5[q]	126.9
8	111.8	111.5	111.4	111.5	113.2	112.7	111.7	111.6	111.4[r]	109.4
9	147.4[e]	147.2[f]	147.2[h]	147.4[i]	148.9[j]	145.9	147.3[k]	147.7[o]	147.1	147.3[s]
10	147.6[e]	147.5[f]	147.4[h]	147.2[i]	149.4[j]	147.9	147.8[k]	147.3[o]	147.1	148.0
11	108.7	108.6	108.2	108.7	110.5	113.2	109.4	109.3	108.2	111.7
11a	130.0	130.1	129.9	130.4	130.9	130.8	129.9	130.1	129.9[q]	130.3
11b	62.4	62.4	62.8	62.7	63.8	63.5	62.4	62.6	62.8	61.5
12	23.6	23.6	24.0	23.6	24.5	24.4	23.5	23.5	24.0	23.4
13	11.2	11.2	11.3	11.2	11.6	11.5	11.1	11.2	11.3	11.0
α	40.7	40.9	40.4	35.8	40.8	40.3	40.9[l]	40.5	40.7	40.6
1′	51.9	51.9	55.3	47.7	53.4	53.3	62.4	62.6	55.3	62.4
3′	40.1	40.1	41.4	37.9	41.4	41.1	40.8[l]	40.5	41.1	41.0
4′	29.2[c]	29.0	29.3	28.8	28.5	27.9	20.9	20.5	29.4[p]	21.2
4′a	126.7[d]	127.6	127.7	127.9	126.1	127.0	126.2	126.8[n]	127.0	126.3
5′	111.5	114.7	114.8	119.7	116.4	116.4	114.7	119.8	111.8[r]	111.7
6′	147.2[e]	143.9[g]	144.0	108.7	145.0	148.0	144.2[m]	109.1	147.4	147.4[s,t]
7′	147.4[e]	145.0[g]	144.9	144.1	145.4	146.8	145.0[m]	143.9	147.4	147.7[t]
8′	109.2	108.4	108.6	141.6	114.0	110.7	109.2	141.8	109.5	109.9
8′a	131.6	131.1	131.0	126.8	129.2	128.6	127.0	125.1	131.8	125.5
OMe	55.9	55.8	55.8	55.9	56.4	56.4	55.9	55.9	55.8	55.9
OMe	56.0	56.0	56.0	56.1	56.9	56.6	56.0	56.0	55.8	55.9
OMe	56.3	56.3	56.0	56.2	–	–	56.7	56.1	56.0	56.0
OMe	56.9	–	–	–	–	–	–	–	56.0	56.8
1″	–	–	–	–	–	–	57.5	57.4	–	57.5
2″	–	–	–	–	–	–	97.2	97.2	–	97.2
3″	–	–	–	–	–	–	70.9	71.1	–	71.0
4″	–	–	–	–	–	–	71.8	72.0	–	71.9
5″	–	–	–	–	–	–	69.2	69.1	–	69.2
6″	–	–	–	–	–	–	62.7	62.6	–	62.7

[a] Measured in $CDCl_3$.
[b] Measured in CD_3OD.
[c–t] Values with the same superscript are interchangeable.

and **2**, except that its ^1H and ^{13}C NMR spectra showed only two methoxyl signals. EIMS fragment ion peaks at *m*/*z* 288, 272 and 164 showed that two methoxyl groups were located at C-9 and C-10 (Budzikiewicz, Pakrashi & Vorbrueggen, 1964). The NOESY correlations between H-8 and an OMe and between H-11 and an OMe provided additional support for these assignments. The absolute stereochemistry of **8** was established by its methylation to **1**. Accordingly, **8** was designated as 7′-*O*-demethylcephaeline.

The next alkaloid, **9**, was recognized as an isomer of **8** from its HR-MS. Compound **9** was methylated with CH_2N_2–Et_2O to give emetine (**1**), suggesting **9** to be a demethyl derivative of **1**. The positions of the two methoxyl groups in **9** were determined to be C-9 and C-7′ by EIMS fragment ion peaks at *m*/*z* 274, 258 and 178 (Budzikiewicz et al., 1964) and the cross-peaks between H-8 and OMe and between H-8′ and OMe in the NOESY spectrum of **9**. Thus, alkaloid **9** was determined as 10-*O*-demethylcephaeline. Pakrashi and Achari (1970) had previously reported the isolation of a demethylcephaeline from *Alangium lamarckii*. The synthesis of the two possible alternatives, 9- and 10-demethylcephaelines, has been established, but the natural product from *A. lamarckii* still remains to be identified (Fujii & Ohba, 1985). Although **9** might be identical to demethylcephaeline from *A. lamarckii*, this is the first report of the isolation and definite characterization of 10-*O*-demethylcephaeline as a natural product.

Alkaloid **10** was obtained as an amorphous powder and its ^1H and ^{13}C NMR spectral features were closely similar to those of cephaeline (**2**), indicating the presence of the cephaeline moiety in the molecule. Its molecular formula of $C_{34}H_{48}N_2O_9$, obtained from the HR-SIMS, comprises $C_6H_{10}O_5$ more than **2**. The ^1H

and ^{13}C NMR spectra showed, besides the signals due to a cephaeline moiety, signals for an isolated methylene group at δ 2.75 (br d, $J = 13.5$ Hz) and 3.03 (d, $J = 13.5$ Hz), signals for a pyranose moiety at δ 3.44 (br d, $J = 9.5$ Hz), 3.81 (dd, $J = 9.5$, 3.1 Hz), 3.95 (dt, $J = 3.1$, 1.5 Hz), 3.70 (dd, $J = 13.0$, 1.5 Hz) and 4.00 (dd, $J = 13.0$, 1.5 Hz) and six carbon signals at δ_C 57.5–97.2. In its HMBC spectrum, the quaternary carbon signal at δ 97.2 was correlated with the signals for the isolated methylene group at δ 2.75 and 3.03, a methine proton at δ 3.44, and a methylene group at δ 3.70 and 4.00. These results clearly demonstrated that **10** possessed a fructopyranose moiety (Tjan & Quweland, 1974). The β-configuration of the fructopyranosyl unit was shown by the correlation between H-3″ (δ 3.44) and H-1″ (δ 2.75) in the NOESY spectrum. HMBC correlations from H-1″ (δ 2.75 and 3.03) to C-1′ (δ 62.4), from H-1″ to C-3′ and from H-1′ to C-1″, along with the NOESY correlation between H-1″ and H-3′, revealed the linkage between C-1″ of the fructopyranose unit and N-2′ of cephaeline moiety. *N*-(1-Deoxy-1-β-D-fructopyranosyl) derivatives are known as the products of Amadori rearrangement on the condensation of D-glucose and amino acids (Hodge & Fisher, 1963). Cephaeline (**2**) was heated with D-glucose in acetic acid and triethylamine to afford **10** in 24% yield. Thus, **10** was assigned the structure 2′-*N*-(1″-deoxy-1″-β-D-fructopyranosyl)cephaeline.

Alkaloid **11** was isomeric with **10** from its HR-SIMS. Its spectral features closely resembled those of **10**, except for the signals arising from the aromatic region in its NMR spectra which were analogous to those of **7**. Furthermore, 2D NMR experiments allowed the characterization of the structure of **11** as 2′-*N*-(1″-deoxy-1″-β-D-fructopyranosyl)neocephaeline. Final structure confirmation was given by the preparation of **11** from neocephaeline (**7**) and D-glucose in a similar way to that used for **10**.

The occurrence of the alkaloids **7**, **8**, **10** and **11** is of great interest from the viewpoint of the biogenesis of ipecac alkaloids. Protoemetine (**4**) has already been postulated as a precursor of several ipecac alkaloids including cephaeline (**2**) and emetine (**1**) (Nagakura, Höfle, Coggiola & Zenk, 1978), but their detailed biosynthetic sequence remains obscure. Alkaloid **8**, which could be formed by condensation of **4** with dopamine, is recognized as an intermediate between protoemetine (**4**) and cephaeline (**2**). Alkaloid **7** is the first example of an unusually-substituted ipecac alkaloid. Protoemetine (**4**) was assumed to be condensed with dopamine in an unusual manner such as seen for neoipecoside (Itoh et al., 1991), to form 7′-*O*-demethylneocephaeline (**13**), which could be further transformed to neocephaeline (**7**) by *O*-methylation. The alkaloids **10** and **11** possess quite unique structures with a *N*-(1-deoxy-1-β-D-fructopyranosyl) moiety. The possibility of the artificial formation, during extraction, of **10** from **2** and D-glucose, and of **11** from **7** and D-glucose, was excluded because of the absence in the extracts of ipecac of 2′-*N*-(1″-deoxy-1″-β-D-fructopyranosyl)emetine (**14**), which was easily obtained from a major alkaloid, emetine (**1**), and D-glucose under similar reaction conditions. This is the first instance of the isolation from a natural source of Amadori rearrangement compounds derived from alkaloids.

3. Experimental

3.1. General

UV spectra were recorded on a Shimadzu UV-240 spectrophotometer and IR spectra on a Shimadzu FTIR-8200 spectrophotometer. Optical rotations were measured on a Jasco DIP-370 digital polarimeter and CD spectra on a Shimadzu-AVIV 62 A DS circular dichroism spectrometer. ^1H (500 MHz) and ^{13}C (125 MHz) NMR spectra were recorded on a Varian VXR-500 spectrometer with TMS as an internal standard. MS and HR-MS were obtained with a Hitachi M-4100 mass spectrometer. For SIMS, glycerol and 3-nitrobenzyl alcohol were used as the matrix. HPLC was performed using a Waters system (600E multisolvent delivery system, 486 tunable absorbance detector). MPLC was carried out with Wakogel FC-40. TLC was performed on precoated Kieselgel $60F_{254}$ plates (Merck).

3.2. Plant material

The crude drug 'Ipecac' (roots of *Cephaelis acuminata*) was purchased from Nippon Funmatsu Yakuhin Co., Osaka, Japan and identified by Dr. M. Satake, National Institute of Health Sciences, Tokyo, Japan. A voucher specimen (KPFY-863) is deposited in our laboratory.

3.3. Extraction and isolation

Dried roots of *C. acuminata* (5.0 kg) were extracted with hot MeOH. After concn, the extract (857 g) was suspended in H_2O and extracted successively with $CHCl_3$ and *n*-BuOH. A part (104 g) of the residue (593 g) from the H_2O layer was redissolved in H_2O, basified with Na_2CO_3 and extracted with Et_2O and $C_2H_4Cl_2$, successively. A part (7.2 g) of the residue (8.2 g) from the Et_2O layer was subjected to MPLC. Elution with $CHCl_3$/MeOH mixtures of the indicated MeOH content gave 9 fractions, I (5%, 45.7 mg), II (5%, 838 mg), III (5%, 2.53 g), IV (5%, 2.06 g), V

(8%, 334 mg), VI (10%, 388 mg), VII (15%, 73.3 mg), VIII (15%, 119 mg), IX (20%, 120 mg). Fraction I was purified by prep. TLC ($CHCl_3$–MeOH–NH_4OH, 95:4.5:0.5 and C_6H_6–EtOAc–Et_2NH, 7:2:1), affording **1** (3.4 mg) and **4** (2.4 mg). Fraction II was submitted to MPLC ($CHCl_3$–MeOH–NH_4OH, 97:3:0.3 and 99:1:0.1) to afford **1** (552 mg). Fraction III was purified by MPLC ($CHCl_3$–MeOH, 98:2–95:5 and $CHCl_3$–MeOH–NH_4OH, 97:3:0.3), prep. TLC ($CHCl_3$–MeOH–NH_4OH, 97:3:0.3–90:9:1 and C_6H_6–EtOAc–Et_2NH, 7:2:1) and prep. HPLC (Cosmosil 5C18-AR, 0.2M $NaClO_4$ containing 0.01% $HClO_4$–MeCN, 7:3) to afford **1** (330 mg), **2** (1011 mg) and **7** (53.7 mg). In the same way, the following fractions were purified by a combination of MPLC with $CHCl_3$–MeOH (98:2–8:2) or $CHCl_3$–MeOH–NH_4OH (99:1:0.1–85:15:1.5), prep. TLC with $CHCl_3$–MeOH–NH_4OH (95:4.5:0.5–85:15:1.5) or C_6H_6–EtOAc–Et_2NH (7:2:1) and prep. HPLC with 0.2M $NaClO_4$ containing 0.01% $HClO_4$–MeCN (7:3). Fraction IV yielded **2** (1421 mg), **7** (0.4 mg); fraction V: **3** (2.0 mg), **2** (211 mg), **5** (7.0 mg), **10** (35.8 mg), **11** (4.7 mg); fraction VI: **2** (70.3 mg), fraction VII: **2** (56.7 mg), **10** (7.5 mg); fraction VIII: **3** (16.4 mg), **2** (14.2 mg), **8** (7.1 mg), **9** (13.9 mg), **6** (18.8 mg); fraction IX: **2** (3.9 mg), **4** (3.0 mg), **8** (24.6 mg), **9** (7.3 mg). The $C_2H_4Cl_2$ layer (3.9 g) was also purified in a similar manner as for Et_2O layer to give **1** (348 mg), **2** (1537 mg), **3** (288 mg), **4** (22.6 mg), **7** (7.0 mg), **8** (16.4 mg), **9** (14.5 mg) and **10** (133 mg).

Below fully assigned high-resolution ^1H NMR spectra are given even for some of the known compounds as earlier reported data now seem incomplete.

3.4. Emetine (*1*)

CD λ_{max}^{MeOH} nm ($\Delta\varepsilon$): 207 (−26.5), 228 (−2.3), 238 (+1.5). ^1H NMR ($CDCl_3$): δ 0.91 (3H, t, $J = 7.5$ Hz, H_3-13), 1.14 (1H, d of quint, $J = 14.0$, 7.5 Hz, H-12), 1.26 (1H, br q, $J = 13.0$ Hz, H-1), 1.40–1.49 (1H, m, H-3), 1.44 (1H, ddd, $J = 14.0$, 11.0, 2.5 Hz, H-α), 1.61–1.70 (1H, m, H-2), 1.65 (1H, dqd, $J = 14.0$, 7.5, 3.0 Hz, H-12), 2.10 (1H, ddd, $J = 14.0$, 11.0, 2.5 Hz, H-α), 2.13 (1H, br t, $J = 11.0$ Hz, H-4), 2.53 (1H, td, $J = 11.5$, 4.0 Hz, H-6), 2.62 (1H, dt, $J = 13.0$, 3.0 Hz, H-1), 2.65 (1H, br d, $J = 15.0$ Hz, H-7), 2.73 (2H, t, $J = 6.0$ Hz, H_2-4′), 3.02 (1H, ddd, $J = 11.5$, 6.0, 3.0 Hz, H-6), 3.04 (1H, dt, $J = 13.0$, 6.0 Hz, H-3′), 3.10 (1H, dd, $J = 11.0$, 4.0 Hz, H-4), 3.14 (1H, ddd, $J = 15.0$, 11.5, 6.0 Hz, H-7), 3.20 (1H, br d, $J = 11.0$ Hz, H-11b), 3.24 (1H, dt, $J = 13.0$, 6.0 Hz, H-3′), 3.81 (3H, s, OMe), 3.847 (6H, s, 2 × OMe), 3.851 (3H, s, OMe), 4.13 (1H, br d, $J = 11.0$ Hz, H-1′), 6.52 (1H, s, H-8′), 6.57 (1H, s, H-5′), 6.60 (1H, s, H-8), 6.77 (1H, s, H-11). ^{13}C NMR: see Table 1.

3.5. Cephaeline (*2*)

CD λ_{max}^{MeOH} nm ($\Delta\varepsilon$): 206 (−24.7), 227 (−1.6), 238 (+1.0). ^1H NMR ($CDCl_3$): δ 0.91 (3H, t, $J = 7.5$ Hz, H_3-13), 1.15 (1H, d of quint, $J = 14.0$, 7.5 Hz, H-12), 1.25 (1H, br q, $J = 13.0$ Hz, H-1), 1.39–1.47 (1H, m, H-3), 1.42 (1H, ddd, $J = 15.0$, 11.0, 3.5 Hz, H-α), 1.62–1.71 (1H, m, H-2), 1.66 (1H, dqd, $J = 14.0$, 7.5, 3.0 Hz, H-12), 2.10 (1H, ddd, $J = 15.0$, 11.0, 2.5 Hz, H-α), 2.11 (1H, br t, $J = 11.5$ Hz, H-4), 2.52 (1H, td, $J = 11.0$, 4.0 Hz, H-6), 2.63 (1H, dt, $J = 13.0$, 3.0 Hz, H-1), 2.63–2.70 (1H, m, H-7), 2.69 (2H, t, $J = 6.0$ Hz, H_2-4′), 3.00 (1H, m, H-6), 3.01 (1H, dt, $J = 13.0$, 6.0 Hz, H-3′), 3.07–3.20 (1H, m, H-7), 3.10 (1H, dd, $J = 11.5$, 4.0 Hz, H-4), 3.18 (1H, br d, $J = 11.0$ Hz, H-11b), 3.20 (1H, dt, $J = 13.0$, 6.0 Hz, H-3′), 3.81, 3.84, 3.85 (9H, each s, 3 × OMe), 4.11 (1H, br d, $J = 11.0$ Hz, H-1′), 6.50 (1H, s, H-8′), 6.59 (1H, s, H-8), 6.63 (1H, s, H-5′), 6.77 (1H, s, H-11). ^{13}C NMR: see Table 1.

3.6. Isocephaeline (*6*)

CD λ_{max}^{MeOH} nm ($\Delta\varepsilon$): 206 (−12.3), 216 (+3.9), 238 (+2.1). ^1H NMR ($CDCl_3$): δ 0.95 (3H, t, $J = 7.5$ Hz, H_3-13), 1.14–1.22 (2H, m, H-1, H-12), 1.52 (1H, m, H-3), 1.59–1.68 (2H, m, H-2, H-α), 1.77 (1H, dqd, $J = 15.0$, 7.5, 2.5 Hz, H-12), 2.05 (1H, br t, $J = 11.5$ Hz, H-4), 2.15 (1H, m, H-α), 2.34 (1H, dt, $J = 13.0$, 3.0 Hz, H-1), 2.47 (1H, td, $J = 11.5$, 4.0 Hz, H-6), 2.61 (1H, dd, $J = 15.5$, 4.0 Hz, H-7), 2.64 (1H, dt, $J = 16.0$, 5.5 Hz, H-4′), 2.77 (1H, ddd, $J = 16.0$, 7.5, 5.5 Hz, H-4′), 2.98 (1H, dd, $J = 11.5$, 6.5 Hz, H-6), 3.00 (1H, ddd, $J = 12.5$, 7.5, 5.5 Hz, H-3′), 3.05 (1H, br d, $J = 11.0$ Hz, H-11b), 3.08 (1H, dd, $J = 11.5$, 4.0 Hz, H-4), 3.11 (1H, ddd, $J = 15.5$, 11.5, 6.5 Hz, H-7), 3.27 (1H, dt, $J = 12.5$, 5.5 Hz, H-3′), 3.79, 3.82, 3.83 (9H, each s, 3 × OMe), 4.09 (1H, br t, $J = 5.5$ Hz, H-1′), 6.52 (1H, s, H-11), 6.55 (1H, s, H-8), 6.61 (1H, s, H-5′), 6.63 (1H, s, H-8′). ^{13}C NMR: see Table 1.

3.7. Neocephaeline (*7*)

Amorphous powder. $[\alpha]_D^{25}$ −87° (*c* 1.0, $CHCl_3$). UV λ_{max}^{MeOH} nm (log ε): 207 (4.76), 230sh (4.12), 282 (3.71). IR ν_{max}^{KBr} cm^{-1}: 3496, 2833, 2754, 1611, 1512. CD λ_{max}^{MeOH} nm ($\Delta\varepsilon$): 208 (−38.0), 237 (+2.6). EIMS *m*/*z* (rel. int.): 466 $[M]^+$ (100), 288 (64), 272 (73), 246 (29), 205 (24), 192 (64), 191 (26), 178 (89). HR-EIMS Found 466.2842 $[M]^+$; $C_{28}H_{38}N_2O_4$ requires 466.2833. ^1H NMR ($CDCl_3$): δ 0.90 (3H, t, $J = 7.0$ Hz, H_3-13), 1.14 (1H, d of quint, $J = 14.0$, 7.0 Hz, H-12), 1.36 (1H, br q, $J = 12.0$ Hz, H-1), 1.39–1.48 (1H, m, H-3), 1.57–1.70 (2H, m, H-2, H-α), 1.66 (1H, dqd, $J = 14.0$, 7.0,

3.0 Hz, H-12), 2.04 (1H, br t, $J = 11.0$ Hz, H-4), 2.11 (1H, br t, $J = 11.0$ Hz, H-α), 2.51 (1H, td, $J = 11.5$, 4.5 Hz, H-6), 2.61–2.71 (2H, m, H-7, H-4′), 2.68 (1H, dt, $J = 12.0$, 4.0 Hz, H-1), 2.79 (1H, ddd, $J = 16.5$, 10.0, 6.0 Hz, H-4′), 3.00 (1H, ddd, $J = 11.5$, 6.0, 2.5 Hz, H-6), 3.04 (1H, ddd, $J = 13.0$, 6.0, 3.0 Hz, H-3′), 3.03–3.10 (1H, m, H-7), 3.08 (1H, dd, $J = 11.0$, 4.0 Hz, H-4), 3.09–3.20 (1H, m, H-3′), 3.15 (1H, dd, $J = 11.0$, 4.0 Hz, H-11b), 3.84 (3H, s, OMe), 3.85 (6H, s, 2 × OMe), 4.42 (1H, br d, $J = 11.0$ Hz, H-1′), 6.58 (1H, s, H-8), 6.60 (1H, d, $J = 8.0$ Hz, H-5′), 6.70 (1H, d, $J = 8.0$ Hz, H-6′), 6.80 (1H, s, H-11). ^{13}C NMR: see Table 1. NOESY: OMe (δ 3.84)/H-8; H-8/H-7 (δ 2.61–2.71); OMe (δ 3.83)/H-11; H-11/H-11b; OMe (δ 3.85)/H-6′. HMBC: H-8 to C-7; H-11 to C-11b; H-1′ to C-3′; H-4′ (δ 2.79) to C-3; H-5′ to C-4′.

3.8. 7′-O-Demethylcephaeline (*8*)

Amorphous powder. $[\alpha]_D^{25}$ −3.4° (*c* 0.56, MeOH). UV λ_{max}^{MeOH} nm (log ε): 208 (4.54), 229sh (4.08), 286 (3.81). IR ν_{max}^{KBr} cm^{-1}: 3410, 2844, 2760, 1612, 1514. EIMS *m/z* (rel. int.): 452 $[M]^+$ (38), 288 (30), 272 (79), 246 (38), 205 (37), 192 (63), 191 (69), 178 (100), 164 (63). HR-EIMS Found 452.2655 $[M]^+$; $C_{27}H_{36}N_2O_4$ requires 452.2677. ^{1}H NMR (CD_3OD): δ 0.95 (3H, t, $J = 7.5$ Hz, H_3-13), 1.12–1.22 (1H, m, H-12), 1.17 (1H, br q, $J = 13.0$ Hz, H-1), 1.42 (1H, br q, $J = 10.0$ Hz, H-3), 1.51–1.63 (2H, m, H-2, H-α), 1.73 (1H, dqd, $J = 14.0$, 7.5, 3.0 Hz, H-12), 2.10 (1H, br t, $J = 11.0$ Hz, H-α), 2.16 (1H, br t, $J = 12.0$ Hz, H-4), 2.54 (1H, td, $J = 11.0$, 6.0 Hz, H-6), 2.62 (1H, dt, $J = 13.0$, 3.5 Hz, H-1), 2.68–2.77 (2H, m, H-7, H-4′), 2.81 (1H, ddd, $J = 16.0$, 7.0, 6.0 Hz, H-4′), 2.83 (1H, dt, $J = 15.5$, 7.0 Hz, H-4′), 3.00–3.08 (2H, m, H-6, H-3′), 3.08–3.15 (1H, m, H-7), 3.11 (1H, dd, $J = 12.0$, 4.0 Hz, H-4), 3.21 (1H, br d, $J = 11.0$ Hz, H-11b), 3.28 (1H, dt, $J = 13.0$, 7.0 Hz, H-3′), 3.78, 3.79 (6H, each s, 2 × OMe), 4.20 (1H, br d, $J = 11.0$ Hz, H-1′), 6.53 (1H, s, H-5′), 6.57 (1H, s, H-8′), 6.69 (1H, s, H-8), 6.84 (1H, s, H-11). ^{13}C NMR: see Table 1. NOESY: OMe (δ 3.78)/H-8; H-8/H-7 (δ 2.68–2.76); OMe (δ 3.79)/H-11; H-11/H-1 (δ 2.62); H-11/H-11b; H-8′/H-1′; H-5′/H-4′ (δ 2.81).

3.9. 10-O-Demethylcephaeline (*9*)

Amorphous powder. $[\alpha]_D^{25}$ −9.9° (*c* 1.0, MeOH). UV λ_{max}^{MeOH} nm (log ε): 209 (4.50), 225sh (4.11), 286 (3.83). IR ν_{max}^{KBr} cm^{-1}: 3389, 2862, 2780, 1614, 1516. EIMS *m/z* (rel. int.): 452 $[M]^+$ (73), 274 (35), 258 (47), 230 (25), 192 (64), 191 (29), 178 (100). HR-EIMS Found 452.2655 $[M]^+$; $C_{27}H_{36}N_2O_4$ requires 452.2677. ^{1}H NMR (CD_3OD): δ 0.94 (3H, t, $J = 7.5$ Hz, H_3-13), 1.10–1.25 (2H, m, H-1, H-12), 1.39–1.48 (1H, m, H-3), 1.51–1.60 (2H, m, H-2, H-α), 1.71 (1H, dqd, $J = 14.0$, 7.5, 3.0 Hz, H-12), 2.07–2.20 (1H, m, H-α), 2.11 (1H, t, $J = 11.5$ Hz, H-4), 2.48–2.55 (1H, m, H-6), 2.64 (1H, dt, $J = 13.0$, 3.0 Hz, H-1), 2.67–2.73 (1H, m, H-7), 2.76–2.84 (1H, m, H-4′), 2.84–2.92 (1H, m, H-4′), 3.03–3.13 (5H, m, H-4, H-6, H-7, H-11b, H-3′), 3.10–3.20 (1H, m, H-3′), 3.80, 3.82 (6H, each s, 2 × OMe), 4.38 (1H, br d, $J = 10.5$ Hz, H-1′), 6.59 (1H, s, H-5′), 6.66 (1H, s, H-8), 6.70 (1H, s, H-8′), 6.88 (1H, s, H-11). ^{13}C NMR: see Table 1. NOESY: OMe (δ 3.80)/H-8; H-8/H-7 (δ 2.67–2.73); OMe (δ 3.82)/H-8′; H-8′/H-1′; H-11/H-11b; H-5′/H-4′ (δ 2.84–2.92).

3.10. 2′-N-(1″-Deoxy-1″-β-D-fructopyranosyl)cephaeline (*10*)

Amorphous powder. $[\alpha]_D^{26}$ −58° (*c* 0.46, $CHCl_3$). UV λ_{max}^{MeOH} nm (log ε): 209 (4.50), 223sh (4.11), 285 (3.78). IR ν_{max}^{KBr} cm^{-1}: 3418, 2858, 2758, 1612, 1514. SIMS *m/z* (rel. int.): 629 $[M + H]^+$ (88), 465 (23), 340 (100), 272 (97), 244 (29), 192 (59). HR-SIMS Found 629.3422 $[M + H]^+$; $C_{34}H_{49}N_2O_9$ requires 629.3440. ^{1}H NMR ($CDCl_3$): δ 0.90 (3H, t, $J = 7.5$ Hz, H_3-13), 1.13 (1H, d of quint, $J = 14.0$, 7.5 Hz, H-12), 1.23 (1H, br q, $J = 14.0$ Hz, H-1), 1.23 (1H, ddd, $J = 15.0$, 10.0, 3.5 Hz, H-α), 1.43 (1H, br q, $J = 10.0$ Hz, H-3), 1.60 (1H, br q, $J = 11.0$ Hz, H-2), 1.62 (1H, dqd, $J = 14.0$, 7.5, 3.0 Hz, H-12), 2.13 (1H, br t, $J = 11.5$ Hz, H-4), 2.23 (1H, ddd, $J = 15.0$, 11.0, 2.5 Hz, H-α), 2.36 (1H, dd, $J = 16.0$, 5.0 Hz, H-4′), 2.53 (1H, td, $J = 12.0$, 4.0 Hz, H-6), 2.66 (1H, dt, $J = 14.0$, 3.0 Hz, H-1), 2.75 (1H, br d, $J = 14.0$ Hz, H-7), 2.75 (1H, br d, $J = 13.5$ Hz, H-1″), 3.02 (1H, ddd, $J = 12.0$, 6.0, 4.0 Hz, H-6), 3.03 (1H, d, $J = 13.5$ Hz, H-1″), 3.07–3.16 (1H, m, H-4′), 3.10 (1H, dd, $J = 11.5$, 4.0 Hz, H-4), 3.11–3.20 (1H, m, H-7), 3.12 (1H, dt, $J = 10.5$, 4.5 Hz, H-3′), 3.18 (1H, br d, $J = 12.0$ Hz, H-11b), 3.20–3.26 (1H, m, H-3′), 3.44 (1H, br d, $J = 9.5$ Hz, H-3″), 3.62 (1H, br d, $J = 11.0$ Hz, H-1′), 3.70 (1H, dd, $J = 13.0$, 1.5 Hz, H-6″), 3.81 (1H, dd, $J = 9.5$, 3.1 Hz, H-4″), 3.82, 3.85, 3.87 (9H, each s, 3 × OMe), 3.95 (1H, dt, $J = 3.1$, 1.5 Hz, H-5″), 4.00 (1H, dd, $J = 13.0$, 1.5 Hz, H-6″), 6.40 (1H, s, H-8′), 6.59 (1H, s, H-8), 6.63 (1H, s, H-5′), 6.80 (1H, s, H-11). ^{13}C NMR: see Table 1. COSY: H-3″/H-4″; H-4″/H-5″; H-5″/H_2-6″. NOESY: OMe (δ 3.85)/H-8; H-8/H-7 (δ 2.75); OMe (δ 3.87)/H-11; H-11/H-11b; OMe (δ 3.82)/H-8′; H-8′/H-1′; H-5′/H-4′ (δ 2.36); H-6″ (δ 4.00)/H-4″ (δ 3.81). HMBC: H-4″ to C-3″; H_2-6″ to C-2″; H_2-1″ to C-2″; H_2-1″ to C-1′; H-1″ (δ 3.03) to C-3′; H-1′ to C-1″; H-3″ to C-1″.

3.11. 2′-N-(1″-Deoxy-1″-β-D-fructopyranosyl)neocephaeline (*11*)

Amorphous powder. $[\alpha]_D^{26}$ −50° (*c* 0.18, $CHCl_3$). UV λ_{max}^{MeOH} nm (log ε): 207 (4.62), 224sh (4.05), 283 (3.55). IR ν_{max}^{KBr} cm^{-1}: 3410, 2863, 2791, 1620, 1541, 1516.

SIMS m/z (rel. int.): 629 $[M + H]^+$ (100), 467 (9), 340 (38), 272 (19), 246 (18), 178 (15). HR-SIMS Found 629.3427 $[M + H]^+$; $C_{34}H_{49}N_2O_9$ requires 629.3440. ^1H NMR ($CDCl_3$): δ 0.90 (3H, t, $J = 7.5$ Hz, H_3-13), 1.12 (1H, d of quint, $J = 14.0$, 7.5 Hz, H-12), 1.23–1.30 (2H, m, H-1, H-α), 1.45 (1H, br q, $J = 11.0$ Hz, H-3), 1.60 (1H, br q, $J = 11.0$ Hz, H-2), 1.63 (1H, dqd, $J = 14.0$, 7.5, 3.0 Hz, H-12), 2.14 (1H, br t, $J = 12.0$ Hz, H-4), 2.25 (1H, m, H-α), 2.42 (1H, dd, $J = 16.0$, 5.5 Hz, H-4′), 2.54 (1H, td, $J = 11.5$, 4.5 Hz, H-6), 2.61 (1H, dt, $J = 13.0$, 3.5 Hz, H-1), 2.74 (1H, br d, $J = 14.0$ Hz, H-7), 2.76 (1H, br d, $J = 13.5$ Hz, H-1″), 2.99–3.09 (1H, m, H-6), 3.02 (1H, dd, $J = 12.0$, 4.5 Hz, H-4), 3.03 (1H, d, $J = 13.5$ Hz, H-1″), 3.07–3.14 (1H, m, H-7), 3.10 (1H, dt, $J = 11.0$, 4.0 Hz, H-3′), 3.13–3.22 (1H, m, H-4′), 3.17 (1H, br d, $J = 10.0$ Hz, H-11b), 3.18–3.22 (1H, m, H-3′), 3.43 (1H, br d, $J = 9.0$ Hz, H-3″), 3.64–3.68 (1H, m, H-1′), 3.73 (1H, dd, $J = 12.0$, 1.5 Hz, H-6″), 3.83 (1H, dd, $J = 9.0$, 3.5 Hz, H-4″), 3.84, 3.85, 3.88 (9H, each s, 3 × OMe), 3.98 (1H, dt, $J = 3.5$, 1.5 Hz, H-5″), 4.02 (1H, dd, $J = 12.0$, 1.5 Hz, H-6″), 6.59 (1H, s, H-8), 6.62 (1H, d, $J = 8.0$ Hz, H-5′), 6.71 (1H, d, $J = 8.0$ Hz, H-6′), 6.81 (1H, s, H-11). ^{13}C NMR: see Table 1. COSY: H-5′/H-6′; H-3″/H-4″; H-4″/H-5″; H-5″/H_2-6″. NOESY: OMe (δ 3.85)/H-8; H-8/H-7 (δ 2.74); OMe (δ 3.88)/H-11; H-11/H-11b; OMe (δ 3.84)/H-6′; H-5′/H-4′ (δ 2.42); H-6″ (δ 4.02)/H-4″; H-3″/H_2-1″; H-1″ (δ 2.76)/H-3′ (δ 3.10). HMBC: H_2-1″ to C-1′; H-1″ (δ 3.03) to C-3′; H-3″ to C-1″; H-4″ to C-3″; H-6″ (δ 3.73) to C-5″; H-6″ (δ 4.02) to C-2″.

3.12. Preparation of isoemetine (*12*) from *6*

A methanolic solution (2 ml) of **6** (14.8 mg) was treated with CH_2N_2 and further purified by prep. TLC ($CHCl_3$–MeOH–NH_4OH, 90:10:1) to afford isoemetine (**12**) (5.3 mg) as an amorphous powder. $[\alpha]_D^{21}$ −41° (*c* 0.37, $CHCl_3$). UV λ_{max}^{MeOH} nm (log ε): 208 (4.54), 225 (4.19), 255 (3.64), 282 (3.79). IR ν_{max}^{KBr} cm^{-1}: 3318, 2835, 2750, 1610, 1516. CD λ_{max}^{MeOH} nm (Δε): 208 (−4.6), 217 (+2.1), 237 (−0.7). EIMS m/z (rel. int.): 480 $[M]^+$ (86), 288 (28), 272 (61), 246 (26), 244 (41), 205 (27), 192 (100), 191 (21). HR-EIMS Found 480.2968 $[M]^+$; $C_{29}H_{40}N_2O_4$ requires 480.2990. ^1H NMR ($CDCl_3$): δ 0.96 (3H, t, $J = 7.5$ Hz, H_3-13), 1.20 (1H, d of quint, $J = 15.0$, 7.5 Hz, H-12), 1.20–1.27 (1H, m, H-1), 1.52 (1H, br q, $J = 11.0$ Hz, H-3), 1.57–1.66 (2H, m, H-2, H-α), 1.79 (1H, dqd, $J = 15.0$, 7.5, 3.0 Hz, H-12), 2.05 (1H, br t, $J = 11.5$ Hz, H-4), 2.30 (1H, dd, $J = 13.5$, 8.0 Hz, H-α), 2.39 (1H, dt, $J = 12.5$, 3.5 Hz, H-1), 2.48 (1H, td, $J = 11.5$, 4.0 Hz, H-6), 2.62 (1H, br d, $J = 15.0$ Hz, H-7), 2.78 (2H, br t, $J = 6.0$ Hz, H_2-4′), 2.98 (1H, ddd, $J = 11.5$, 6.0, 2.0 Hz, H-6), 3.02 (1H, dt, $J = 12.0$, 6.0 Hz, H-3′), 3.09 (1H, dd, $J = 11.5$, 3.5 Hz, H-4), 3.10 (1H, m, H-11b), 3.14 (1H, m, H-7), 3.28 (1H, dt, $J = 12.0$, 6.0 Hz, H-3′), 3.81 (3H, s, OMe), 3.83 (6H, s, 2 × OMe), 3.84 (3H, s, OMe), 4.08 (1H, br t, $J = 6.0$ Hz, H-1′), 6.557 (1H, s, H-8), 6.563 (1H, s, H-11), 6.57 (1H, s, H-5′), 6.66 (1H, s, H-8′). ^{13}C NMR: see Table 1.

3.13. Methylation of *8* and *9*

A methanolic solution (2 ml) of **8** (13.4 mg) was methylated with CH_2N_2 and purified by prep. TLC ($CHCl_3$–MeOH–NH_4OH, 85:15:1.5) to afford amorphous powder (5.6 mg). The product was identified as authentic emetine (UV, IR, ^1H NMR, EIMS, $[\alpha]_D^{24}$ −45° (*c* 0.32, $CHCl_3$)). In a similar manner, **9** (9.6 mg) was methylated and purified to afford amorphous powder (4.2 mg), which was identified as authentic emetine (UV, IR, ^1H NMR, EIMS, $[\alpha]_D^{25}$ −46° (*c* 0.42, $CHCl_3$)).

3.14. Preparation of *10* from cephaeline (*2*) and D-glucose

The mixture of cephaeline (**2**) (10.2 mg), D-glucose (4.3 mg), AcOH (0.75 ml) and Et_3N (1.3 ml) was stirred at 95°–100° for 15 min. The cooled reaction mixture was basified and extracted with $CHCl_3$ and the extract was washed, dried over $MgSO_4$ and concentrated. The same reaction was repeated three times and the combined $CHCl_3$ extract (31.1 mg) was purified by prep. TLC ($CHCl_3$–MeOH–NH_4OH, 85:15:1.5) to give **10** (13.6 mg, 24%), along with **2** (14.9 mg). Its UV, IR, ^1H NMR, SIMS and optical rotation ($[\alpha]_D^{25}$ −57° (*c* 1.2, $CHCl_3$)) were identical with those of the natural product.

3.15. Preparation of *11* from neocephaeline (*7*) and D-glucose

The mixture of neocephaeline (**7**) (11.2 mg), D-glucose (4.2 mg), AcOH (0.75 ml) and Et_3N (1.3 ml) was stirred at 70°–73° for 20 min. The reaction mixture was worked-up in the same way as described for **10** to yield **11** (8.5 mg, 56%). Its UV, IR, ^1H NMR, SIMS and optical rotation ($[\alpha]_D^{26}$ −56° (*c* 0.85, $CHCl_3$)) were identical with those of the natural product.

3.16. Preparation of *14* from emetine (*1*) and D-glucose

The mixture of emetine (**1**) (10.2 mg), D-glucose (4.2 mg), AcOH (0.75 ml) and Et_3N (1.3 ml) was stirred at 95°–100° for 15 min. The reaction mixture was worked-up in the same way as described for **10** to yield **14** (8.1 mg, 59%) as an amorphous powder: $[\alpha]_D^{24}$ −50° (*c* 0.79, $CHCl_3$). UV λ_{max}^{MeOH} nm (log ε): 209 (4.49), 223sh (4.14), 282 (3.79), 285 (3.80). IR ν_{max}^{KBr} cm^{-1}: 3410, 2935, 2837, 2752, 1611, 1514. SIMS m/z (rel.

int.): 643 $[M + H]^+$ (100), 481 (9), 354 (68), 272 (69), 244 (15), 205 (12), 192 (28), 191 (15). HR-SIMS Found 643.3601 $[M + H]^+$; $C_{35}H_{51}N_2O_9$ requires 643.3597. ^1H NMR ($CDCl_3$): δ 0.91 (3H, t, $J = 7.5$ Hz, H_3-13), 1.14 (1H, d of quint, $J = 14.0$, 7.5 Hz, H-12), 1.23–1.30 (2H, m, H-1, H-α), 1.45 (1H, br q, $J =$ 11.0 Hz, H-3), 1.58–1.68 (1H, m, H-2), 1.64 (1H, dqd, $J = 14.0$, 7.5, 3.0 Hz, H-12), 2.17 (1H, br t, $J = 12.0$ Hz, H-4), 2.23 (1H, ddd, $J = 14.0$, 12.0, 2.5 Hz, H-α), 2.41 (1H, dd, $J = 16.0$, 5.5 Hz, H-4′), 2.54 (1H, td, $J = 11.5$, 4.5 Hz, H-6), 2.61 (1H, dt, $J = 13.0$, 3.5 Hz, H-1), 2.70 (1H, br d, $J = 14.0$ Hz, H-7), 2.76 (1H, br d, $J = 13.5$ Hz, H-1″), 2.99–3.09 (1H, m, H-6), 3.02 (1H, dd, $J = 12.0$, 4.5 Hz, H-4), 3.05 (1H, d, $J = 13.5$ Hz, H-1″), 3.07–3.14 (1H, m, H-7), 3.10 (1H, dt, $J = 11.0$, 4.0 Hz, H-3′), 3.10–3.20 (1H, m, H-4′), 3.17 (1H, br d, $J = 10.0$ Hz, H-11b), 3.18–3.22 (1H, m, H-3′), 3.44 (1H, br d, $J = 9.0$ Hz, H-3″), 3.64 (1H, dd, $J = 11.0$, 3.5 Hz, H-1′), 3.73 (1H, dd, $J = 12.0$, 1.5 Hz, H-6″), 3.81, 3.845, 3.848, 3.87 (12H, each s, 4 × OMe), 3.83 (1H, dd, $J = 9.0$, 3.5 Hz, H-4″), 3.98 (1H, dt, $J = 3.5$, 1.5 Hz, H-5″), 4.01 (1H, dd, $J = 12.0$, 1.5 Hz, H-6″), 6.42 (1H, s, H-8′), 6.57 (1H, s, H-5′), 6.60 (1H, s, H-8), 6.80 (1H, s, H-11). ^{13}C NMR: see Table 1. COSY: H-3″/H-4″; H-4″/H-5″; H-5″/H_2-6″. NOESY: H-1″ (δ 2.76)/H-3′ (δ 3.10); H-1″ (δ 3.05)/H-3″; H-4″/H-6″ (δ 4.01). HMBC: H_2-1″ to C-1′; H-1″ (δ 3.05) to C-3′; H-3″ to C-1″; H-1″ (δ 3.05) to C-2″; H-3″ to C-2″; H-4″ to C-3″; H-6″ (δ 3.73) to C-5″; H-6″ (δ 4.01) to C-2″; H-1′ (δ 3.64) to C-1″; H-3′ (δ 3.10) to C-1″.

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