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Alkaloids from *Hippeastrum Equestre* Herb. -5. Circular Dichroism Studies[1]

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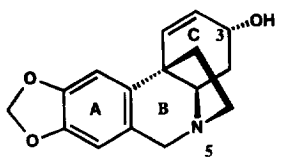
Abstract: A survey of the CD spectra of eight Amaryllidaceae alkaloids (**3**, **5**, **7**, **8**, **11**, **12**, **13**, **14**) isolated from *Hippeastrum equestre* Herb. and six Amaryllidaceae alkaloids (**1**, **2**, **4**, **6**, **9**, **10**) of related structure indicates that this technique can provide useful structural information regarding the basic heterocyclic ring system and the stereochemistry of the dominant ring junction, respectively.

INTRODUCTION

When linearly polarized light passes through an absorbing optically active substance, the left and the right circularly polarized rays travel at different speeds leading to $\lambda_L \neq \lambda_R$ and a rotation of the plane of the linearly polarized light (optical rotation). In an absorbing region these two rays are also absorbed to a different extent, i.e. their molar absorption coefficients (ε) are different. The difference $\Delta\varepsilon = \varepsilon_L - \varepsilon_R$ is called circular dichroism. The electric vector of the light follows an elliptical path, i.e. the originally plane-polarized light has become elliptically polarized. The shape of this ellipse is mathematically determined by the angle θ, the so-called ellipticity, which is proportional to the circular dichroism. CD spectra are therefore given in terms of $\Delta\varepsilon$ or the molar ellipticity $[\Theta]$.

Circular dichroism (CD) spectroscopy is widely used as a powerful tool in stereochemical analysis including configurational and conformational aspects of optically active compounds.[2-5] Applications cover low molecular weight substances as well as biopolymers and lyotropic liquid crystals.[6,7] CD spectra differ in shape,amplitude and sign. Configurational information is usually related to the sign of CD bands, e.g. spectra of enantiomers are mirror images. In general, reference compounds of known stereochemistry are necessary.



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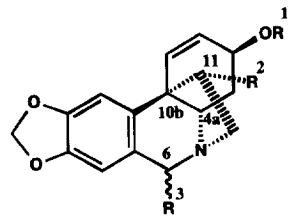
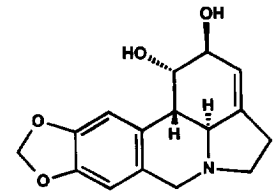


2 $R^1 = R^2 = R^3 = H$
3 $R^1 = R^3 = H$, $R^2 = OH$
4 $R^1 = Me$, $R^2 = R^3 = OH$



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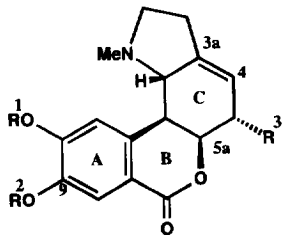
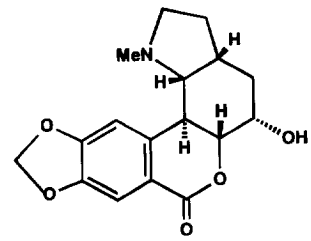


6 $R^1 = R^2 = Me$, $R^3 = H$
7 $R^1 = Me$, $R^2 = R^3 = H$
8 R^1-$R^2 = -CH_2-$, $R^3 = OH$



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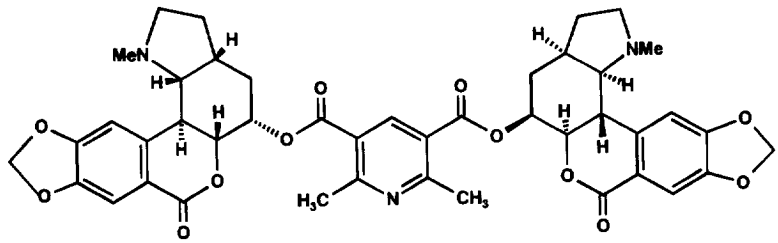

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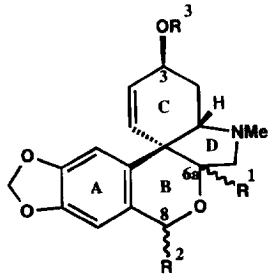

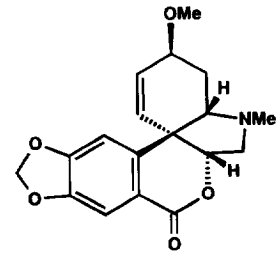

11 R^1 = ····· OH, $R^2 = H$, $R^3 = Me$
12 R^1 = ····· OH, $R^2 = R^3 = H$
13 R^1 = ▬ H, R^2 = OH, R^3 = Me

14

Fig. 1. Structures of Amaryllidaceae alkaloids used in this study.

The signs of the CD bands can often be obtained by sector rules, like the octant rule for the $n \rightarrow \pi^*$ transition in carbonyl compounds[8] or simple geometric considerations in the case of coupled oscillators (exciton chirality method)[9].

However, in the field of Amaryllidaceae alkaloids, relatively little use has been made of CD spectral results for structural purposes.[10-13] DeAngelis and Wildman introduced in 1969 a quadrant rule for the optically active aromatic chromophore in rigid polycyclic systems, which also covers many Amaryllidaceae alkaloids.[14] The CD spectra differ in shape and amplitude, which is related to the basic ring system (shape, sign) and conformational effects, rigidness and epimeric substituents (amplitude), respectively. However, the CD spectra obtained are, in general, rather complex and the proposed quadrant rule is difficult to handle.

In the present paper, we have measured a series of fourteen Amaryllidaceae alkaloids with known stereochemistry (Fig.1). Most have been isolated from *Hippeastrum equestre* Herb.. They belong to three different basic ring systems, the phenanthridine ring system (**1-5**), the [2]benzopyrano[3,4-g]indole ring system (**6-10**) and the [2]benzopyrano[3,4-c]indole ring system (**11-14**). Relevant UV transitions are caused by the methylenedioxyphenyl chromophore and/or the arylconjugated lactone ring. The main objective of our investigation was the use of the CD technique in the field of Amaryllidaceae alkaloids for inter- and intrasystem identifications within a given structural type, i.e. to what extent conclusions can be inferred regarding the heterocyclic ring system and the type of ring fusion.

RESULTS AND DISCUSSION

As mentioned above, DeAngelis et al. found that the shape of the CD spectra of Amaryllidaceae alkaloids depends on the stereochemistry of the optically active benzylic carbon atom in rigid polycyclic systems, such as carbon 10b in vittatine (**2**), cf. Fig.1. The configuration of that bridgehead carbon is caused by the type of ring fusion, e.g. *trans* B:C ring junction in vittatine (**2**). A general treatment of types of B:C ring fusion is given in Fig.2. In order to distinguish between all these possible *trans* and *cis* configurations of respective B:C (B:D) ring fusions in the alkaloid structures used for this study, we have simplified all the stereochemical configurations into the model of two fused cyclohexane rings (chair conformation) to name the various stereoconfigurations of the bridgehead carbons. Fig.2 shows that we obtain two *trans* (diaxial hydrogen bonds) configurations (one enantiomeric pair) and four *cis* (axial and equatorial hydrogen bonds) configurations (two enantiomeric pairs), respectively. If one considers the polycyclic nature of alkaloid structures as well as the presence of heterocyclic rings, all *cis* and *trans* configurations are stereochemically distinguishable. However, the alkaloids used in this study represent both *trans* configurations, but only the *cis-3* type (B:C or B:D) ring fusion (cf. Fig. 1).

Tab.1 summarizes CD spectral data of compound **1-14**. Appropriate CD spectra are given in Fig.3-6. In order to discuss the CD of amaryllidaceae alkaloids, they need to be classified in terms of the basic heterocyclic ring system and /or the dominant chromophore (cf. Tab.1).

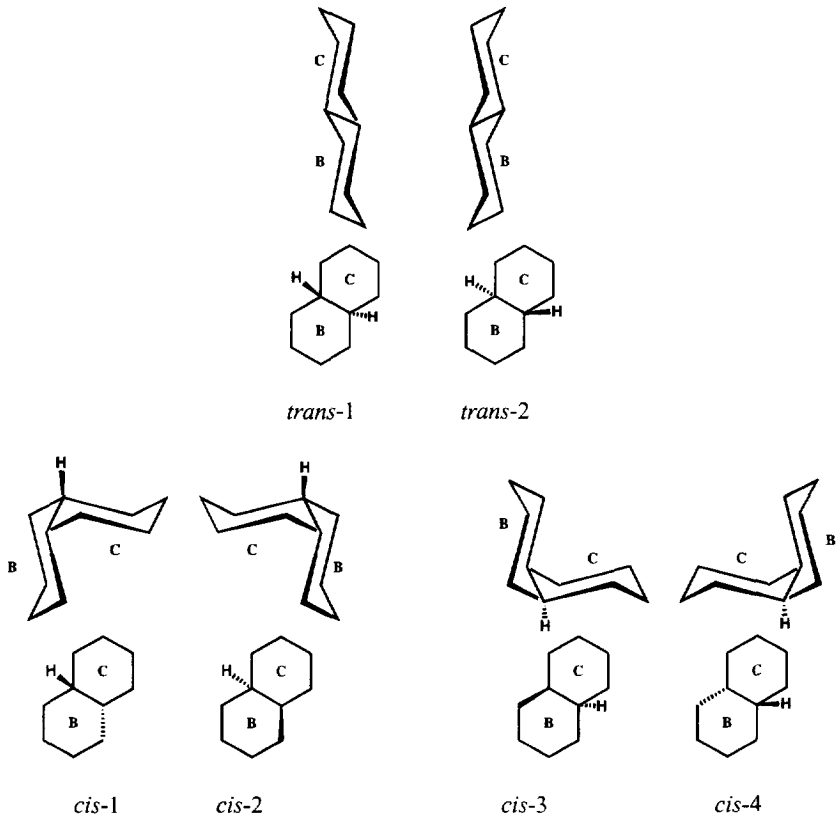

Fig.2. General types of B:C ring fusion illustrated by the model of two fused cyclohexane rings (chair conformation; ━, ····· refer to axial bonds).

Fig.3 shows the CD spectra of a series of phenanthridine alkaloids, which UV and CD transitions are dominated by the methylenedioxyphenyl chromophore. The spectra are characterized by two antipodal CD bands at ca. 294 nm and ca. 245 nm, both of which correspond to the maxima observed in the UV. As crinidine (**1**) and vittatine (**2**) are enantiomers, their CD spectra are mirror images exhibiting a -/+ (294 nm /245 nm) sequence of the sign of corresponding Cotton effects for crinidine. All alkaloids **1-5** possess a B:C trans-diaxial configuration, which corresponds to crinidine (*trans*-1 in .Fig.2) or vittatine (*trans*-2 in Fig.2). In the same way, their CD corresponds to crinidine type or vittatine type, respectively. Therefore, the general shape of the CD spectra of alkaloids **1-5** is caused by the stereochemistry of the B:C ring junction. Substituents on the C-ring are not likely have any substantial influence on the general shape of the CD (cf. crinidine/ lycorine in Fig.3). The 5,10b-ethylene bridge seems to enhance the rigidness of the polycyclic ring system, which causes an increase in magnitude of the CD.

Tab.1. Circular Dichroism Spectral Data on Amaryllidaceae Alkaloids of the Phenanthridine and Benzopyranoindole Series

alkaloid	heterocyclic ring system[a)]	type of ring fusion[b)]	dominant chromophore[c)]	CD maxima, λ (nm) [θ]
crinidine (**1**)	A	B:C trans-1	MDP	293.2 244.4 -10480 +13140
vittatine (**2**)	A	B:C trans-2	MDP	294.2 244.2 +9440 -11790
11-hydroxy-vittatine (**3**)	A	B:C trans-2	MDP	294.4 244.4 +13540 -13810
haemanthidine (**4**)	A	B:C trans-2	MDP	293.2 245.4 +11650 -12020
lycorine (**5**)	A	B:C trans-1	MDP	293.0 245.2 -6995 +5080
homolycorine (**6**)	B	B:C cis-3	lactone	305.4 273.6 252.0 233.0 -2730 -23500 +17830 -42170
9-O-demethyl-homolycorine (**7**)	B	B:C cis-3	lactone	316.2 272.8 252.0 232.6 -1030 -13260 +8920 -25400
hippeastrine (**8**)	B	B:C cis-3	lactone	304.0 275.4 255.6 234.2 +692 -9760 +3510 -26405
clivonine (**9**)	B	B:C trans-2	lactone	314.0 269.2 251.6 233.2 -8730 +2980 -4810 +55810
clivimine (**10**)	B	B:C trans-2	lactone	.313.2 268.6 250.6 233.2 -29030 +8830 -16080 +180800
tazettine (**11**)	C	B:D cis-3[*)]	MDP	289.2 240.4 -3090 +32600
3-O-demethyl-tazettine (**12**)	C	B:D cis-3[*)]	MDP	295.0 240.0 -1760 +15860
pretazettine (**13**)	C	B:D trans-2	MDP	291.0 249.6 +13130 -9830
3-epimacronine (**14**)		B:D trans-2	lactone	308.2 276.8 251.4 229.0 +2980 +15240 -9270 +97820

a) A - phenanthridine ring system
B - [2]benzopyrano[3,4-g]indole ring system
C - [2]benzopyrano[3,4-c]indole ring system

b) cf. Fig. 2; *) strongly deformed *cis* configuration caused by the five-membered D-ring

c) MDP - methylenedioxyphenyl

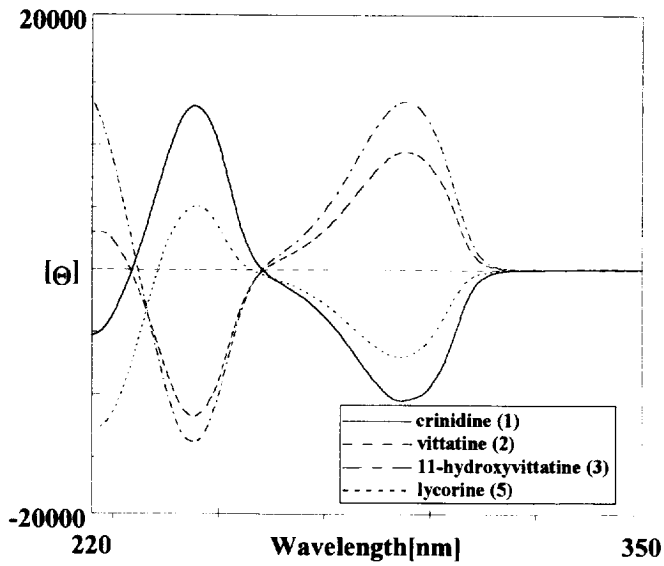

Fig.3. CD spectra of crinidine (**1**), vittatine (**2**), 11-hydroxyvittatine (**3**) and lycorine (**5**) in methanol.

But it is known that a decrease in magnitude appears to be a general phenomenon for alkaloids related to the 5,10b-ethanophenanthridine system when the configuration of the substituent at C_3 position is changed from pseudo axial to pseudo equatorial.[14] One example for intra-system identification is given by alkaloids **2** (vittatine) and **3** (11-hydroxyvittatine). The CD clearly proves that they belong to the same enantiomeric series.

The CD spectra of some lactone alkaloids (**6-10**) related to the [2]benzopyrano[3,4-g]indole system are given in Fig.4 and 5, respectively. The UV and CD transitions are dominated by the arylconjugated lactone chromophore, i.e. they possess significant CD bands at ca. 270nm, 252nm and 233 nm. The absence of electron-transfer bands involving the nitrogen was ascertained from the observation that the CD spectra of the free bases and the hydrochlorides were identical.[10] For alkaloids **6-8**, which are stereochemically homogeneous (*cis*-3 B:C ring junction), the shape of the CD is very close and a +/-/+ sequence of the sign of Cotton effects was obtained (Fig.4). For alkaloid **7** (the isolation and structural designation as 9-O-demethylhomolycorine by means of EI-MS, IR, ^{1}H NMR and ^{13}C NMR data are described in part 3 of this series[15]) the CD technique provides us with an additional proof of the absolute stereochemistry. Moreover, one can clearly distinguish between lactone bases containing a 3a,4-unsaturation and *cis* B:C ring junction and the 5a epimeric 3a,4-dihydrobases (clivonine, clivimine), which have a *trans*-2 B:C ring junction (cf. Fig.2). The latter possess antipodal Cotton effects in the 280nm-220nm λ-region (+/-/+ sequence of corresponding CD bands, cf. Tab.1).

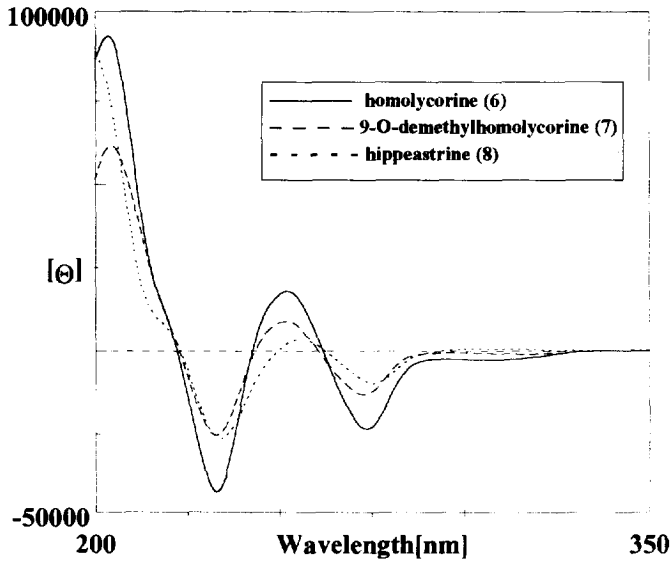

Fig.4. CD spectra of homolycorine (**6**), 9-O-demethylhomolycorine (**7**) and hippeastrine (**8**) in methanol.

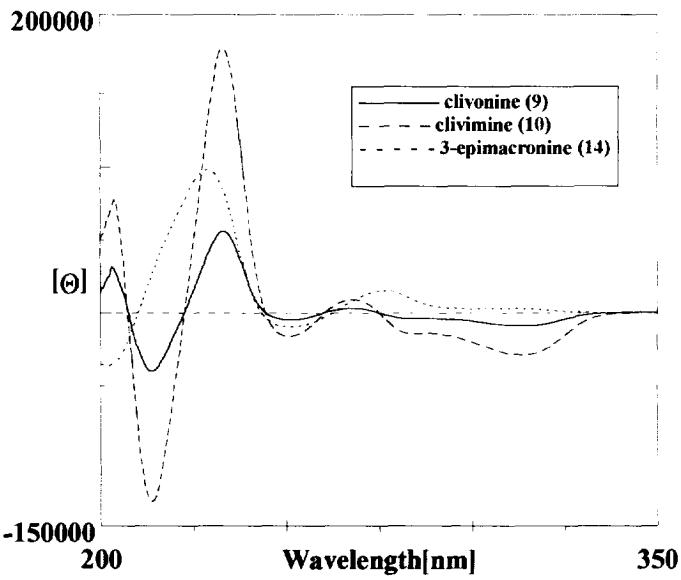

Fig.5. CD spectra of clivonine (**9**), clivimine (**10**) and 3-epimacronine (**14**) in methanol.

In addition, Fig.5 proves that both clivonine and clivimine possess the same *trans* B:C ring fusion, which has been widely discussed in the literature.[19] Remarkable however, is the positive exciton centered at ca. 223 nm.

CD spectra of representatives of the [2]benzopyrano[3,4-c]indole ring system are given in Fig.6. UV and CD transitions of alkaloids **11-13** seem to be related to the methylenedioxyphenyl chromophore. Comparable to Fig.3, two significant CD bands are obtained, which are centered at approx. 290nm and 240nm, respectively. Alkaloid **12** is a quite new compound isolated from *Hippeastrum equestre* Herb., and the structural designation as 3-O-demethyltazettine was established by means of EI-MS, IR, ^{1}H NMR and ^{13}C NMR spectral data.[1] As it was already mentioned above for alkaloids **3** and **7**, the CD spectral analysis provides us with additional proof of the stereochemistry. Alkaloid **12** and tazettine (**11**) belong to the same enantiomeric series possessing a *cis*-3 B:D ring junction (cf. Fig.2). It should be mentioned that the five-membered D-ring causes a strongly deformed *cis* configuration in that particular case. Their CD is virtually the same, exhibiting a -/+ order (ca. 290nm/ ca. 240nm) of corresponding Cotton effects related to the methylenedioxyphenyl chromophore. However, 3-O-demethyltazettine (**12**) possesses a significantly lower magnitude of [Θ]. Lastly, Fig.6 shows the CD of the 6a epimeric pretazettine (**13**), which has a *trans*-2 B:D ring junction.

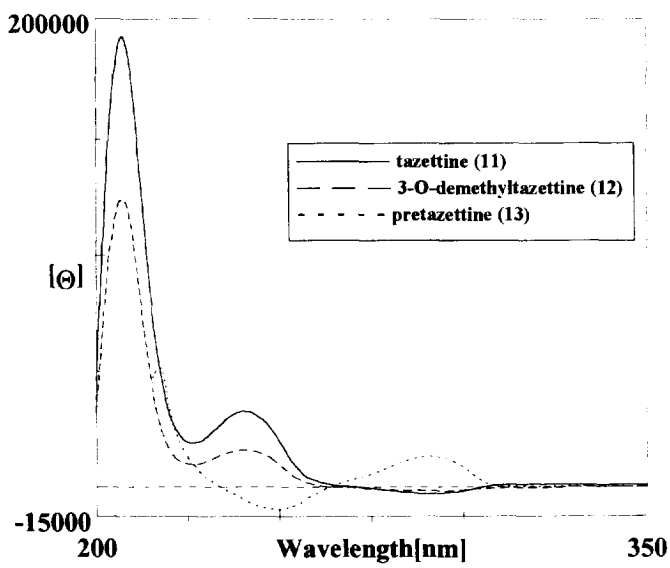

Fig.6. CD spectra of tazettine (**11**), 3-O-demethyltazettine (12) and pretazettine (**13**) in methanol.

Pretazettine shows an antipodal relationship for corresponding CD bands related to the methylenedioxyphenyl chromophore [+/-(291nm/ 250nm); see Tab.1]. Apparently, the CD of alkaloids **11-13** are determined by the

stereochemistry of the B:D ring fusion. Once more, the CD technique may be used as a rapid and reliable method for the stereochemical identification of a new alkaloid.

The UV and CD transitions of 3-epimacronine (**14**), whose structure is also related to the [2]benzopyrano[3,4-c]indole ring system, are caused by the arylconjugated lactone chromophore. Therefore, the shape of the CD is different to what was obtained for alkaloids **11-13** and rather comparable to those spectra of clivonine and clivimine (Fig.5). Remarkable is the almost antipodal relationship of CD bands between 3-epimacronine (*trans*-2 B:D ring junction) and alkaloids **6-8** (Fig.4), which possess a *cis*-3 B:C ring fusion (cf. Tab.1).

The CD spectral analysis of Amaryllidaceae alkaloids of the phenanthridine and benzopyranoindole series clearly indicates that the shape of the CD spectrum is determined by the stereochemistry of the appropriate heterocyclic ring system, in conjunction with the type of dominant chromophores. Within given structural types and chromophores, therefore, the CD technique may be used as a rapid and reliable method for stereochemical analysis of alkaloids, such as the stereochemistry of dominant ring junction. Both, intra-system identification and inter-system identification, is possible. In addition to NMR and MS spectral techniques, CD spectroscopy is a powerful tool for the structural identification of new alkaloids.

EXPERIMENTAL

Isolation and identification of the alkaloids from *Hippeastrum equestre* Herb. (**3**, **5**, **7**, **8**, **11-14**) were described elsewhere.[1,15,17] Crinidine (**1**), vittatine (**2**), haemanthidine (**4**), homolycorine (**6**), clivonine (**9**), and clivimine (**10**) were authentic samples obtained from other plant sources.[16,18,19]

UV and circular dichroism (CD) spectra were recorded at room temperature at a concentration of usually 1 mg/ml on a Philips UV/VIS scanning spectrophotometer PU 8730 (Philips Analytical, Cambridge, UK) and a JASCO J-710 spectropolarimeter (Jasco, Japan). Optical rotation $[\alpha]_D$ was determined using a JASCO DIP-370 digital polarimeter. HPLC grade methanol (Ferak, Berlin, Germany) was used as the solvent.

11-Hydroxyvittatine (**3**): UV[MeOH, λ (nm) / ε (m^2/ mol]: 202.7/ 5180, sh 240/ 421, 295.2/ 675; CD (MeOH, $[\theta]_\lambda$): $[\theta]_{205.8}$ +93900, $[\theta]_{230.0}$ 0, $[\theta]_{244.4}$ -13810, $[\theta]_{260.2}$ 0, $[\theta]_{294.4}$ +13540; $[\alpha]_D^{25}$ +35° (c 0.1, MeOH; lit.[19] $[\alpha]_D^{20}$ +25°, c 0.5, MeOH).

Lycorine (**5**): UV[MeOH, λ (nm) / ε (m^2/ mol]: 208.6/ 1689, sh 238/ 448, 292.8/ 583; CD (MeOH, $[\theta]_\lambda$): $[\theta]_{207.7}$ 0, $[\theta]_{221.2}$ -12640, $[\theta]_{235.7}$ 0, $[\theta]_{245.2}$ +5080, $[\theta]_{257.7}$ 0, $[\theta]_{293.0}$ -6995; $[\alpha]_D^{23}$ - 71.2° (c 0.125, MeOH; lit.[17] $[\alpha]_D^{22}$ -108°, c 1.0, MeOH).

9-O-Demethylhomolycorine (**7**): UV[MeOH, λ (nm) / ε (m^2/ mol]: 227.7/ 1490, 266.6/ 504, 307.2/ 313; CD (MeOH, $[\theta]_\lambda$): $[\theta]_{204.6}$ +61700, $[\theta]_{222.9}$ 0, $[\theta]_{232.6}$ -25400, $[\theta]_{243.3}$ 0, $[\theta]_{252.0}$ +8920, $[\theta]_{260.5}$ 0, $[\theta]_{272.8}$ -13260, $[\theta]_{316.2}$ -1030; $[\alpha]_D^{25}$ + 58° (c 0.1, MeOH; lit.[20] $[\alpha]_D^{25}$ + 71.6°, c 0.2, EtOH).

Hippeastrine (**8**): CD (MeOH, $[\theta]_\lambda$): $[\theta]_{223.2}$ 0, $[\theta]_{234.2}$ -26405, $[\theta]_{249.6}$ 0, $[\theta]_{255.6}$ +3510, $[\theta]_{262.2}$ 0, $[\theta]_{275.4}$ -9760, $[\theta]_{294.0}$ 0, $[\theta]_{304.0}$ +692; $[\alpha]_D^{20}$ + 144° (c 0.1, $CHCl_3$; lit.[19] $[\alpha]_D$ + 160°, c 0.3, $CHCl_3$).

Clivonine (**9**): UV[MeOH, λ (nm) / ε (m^2/ mol]: 205.3/ 1881, 225.9/ 1443, 271.5/ 457, 308.3/ 335; CD (MeOH, $[\theta]_\lambda$): $[\theta]_{207.6}$ 0, $[\theta]_{213.6}$ -40180, $[\theta]_{222.6}$ 0, $[\theta]_{233.2}$ +55810, $[\theta]_{244.6}$ 0, $[\theta]_{251.6}$ -4810, $[\theta]_{260.1}$ 0, $[\theta]_{269.2}$ +2980, $[\theta]_{275.2}$ 0, $[\theta]_{314.0}$ -8730; $[\alpha]_D^{25}$ -140° (c 0.03, MeOH; lit.[21] $[\alpha]_D^{23}$ +41.24°, c 1.11, $CHCl_3$).

Clivimine (**10**): UV[MeOH, λ (nm) / ε (m^2/ mol]: 206.9/ 5309, 225.9/ 4323, 271.2/ 1364, 308.8/ 1003; CD (MeOH, $[\theta]_\lambda$):$[\theta]_{203.6}$ +77600, $[\theta]_{207.3}$ 0, $[\theta]_{214.0}$ -129200, $[\theta]_{222.7}$ 0, $[\theta]_{233.2}$ +180800, $[\theta]_{244.6}$ 0, $[\theta]_{250.6}$ -16080, $[\theta]_{260.6}$ 0, $[\theta]_{268.6}$ +8830, $[\theta]_{275.2}$ 0, $[\theta]_{313.2}$ -29030; $[\alpha]_D^{25}$ -310° (c 0.01, MeOH; lit.[21] $[\alpha]_D^{25}$ +32°, c 0.25, $CHCl_3$).

Tazettine (**11**): UV[MeOH, λ (nm) / ε (m^2/ mol]: 205.9/ 3428, 240.0/ 490, 293.1/ 447; CD (MeOH, $[\theta]_\lambda$):$[\theta]_{207.2}$ +194500, $[\theta]_{240.4}$ +32600, $[\theta]_{271.0}$ 0, $[\theta]_{289.2}$ -3090; $[\alpha]_D^{24}$ + 170.4° (c 0.125, MeOH; lit.[17] $[\alpha]_D^{22}$ +145°, c 1.0, $CHCl_3$).

3-O-Demethyltazettine (**12**): UV[MeOH, λ (nm) / ε (m^2/ mol]: 205.1/ 2367, 239.2/ 486, 292.0/ 360; CD (MeOH, $[\theta]_\lambda$): $[\theta]_{207.2}$ +124180, $[\theta]_{226.4}$ +9530 (minimum), $[\theta]_{240.0}$ +15860, $[\theta]_{262.6}$ 0, $[\theta]_{295.0}$ -1760; $[\alpha]_D^{25}$ +85.5° (c 0.055, MeOH).

Pretazettine (**13**): UV[MeOH, λ (nm) / ε (m^2/ mol]: 209.1/ 1722, 244.3/ 344, 291.8/ 407; CD (MeOH, $[\theta]_\lambda$): $[\theta]_{217.6}$ +51600, $[\theta]_{233.7}$ 0, $[\theta]_{249.6}$ -9830, $[\theta]_{263.6}$ 0, $[\theta]_{291.0}$ +13130; $[\alpha]_D^{25}$ +5.7° (c 0.105, MeOH; lit.[21] $[\alpha]_D^{24}$ +180°, c 0.2, $CHCl_3$).

3-Epimacronine (**14**): UV[MeOH, λ (nm) / ε (m^2/ mol]: 229.7/ 2278, 268.9/ 498, 308.8/ 515; CD (MeOH, $[\theta]_\lambda$): $[\theta]_{201.8}$ -36460, $[\theta]_{210.4}$ 0, $[\theta]_{229.0}$ +97820, $[\theta]_{243.5}$ 0, $[\theta]_{251.4}$ -9270, $[\theta]_{262.6}$ 0, $[\theta]_{276.8}$ +15240, $[\theta]_{308.2}$ 2980; $[\alpha]_D^{25}$ +212° (c 0.06, MeOH; lit.[22] $[\alpha]_D^{28}$ +225.6°, c 0.15, $CHCl_3$).

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