STRUCTURAL AND CONFORMATIONAL ANALYSIS OF NATURALLY OCCURRING CULARINE *N*-OXIDE ALKALOIDS†

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Abstract- (+)-*cis*- and (+)-*trans*-Cularidine *N*-oxides were isolated from *Ceratocapnos heterocarpa*. Their structures and conformations were derived from ^{1}H, ^{13}C, one dimensional nOe nmr data and their chemical behaviour. The *trans* isomer possesses the usual conformation of cularine alkaloids and readily undergoes Cope elimination. The *cis* isomer exhibits a different conformation at the dihydroxepine ring.

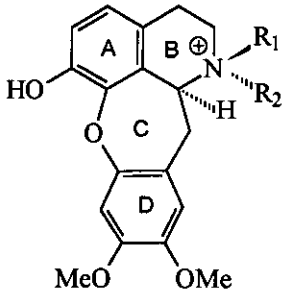
The dihydro-dibenzoxepine skeleton is the basic structural feature of cularine alkaloids.[1] Cularines and isocularines[2] (which differ in the position of substituents at ring-D) are found in some genera of Papaveraceae, usually as monomers or bonded to a morphinan unit (cancentrine alkaloids).[3,4] Like the closely related aporphines, cularine alkaloids occur naturally in several oxidation states, namely 4-hydroxycularines,[5] oxocularines,[6] 4,5-dioxocularines and aristocularines.[7]

In addition to lactam C-seco derivatives,[8] B-secocularines have frequently been found.[9] 1,2-Seco derivatives probably arise from β-elimination of an *N*-quaternized cularine and may account for the scarcity of naturally occurring cularine-*N*-oxides. Sarcocapnidine *N*-oxide isolated from *Sarcocapnos baetica* is the sole member which has been partially characterized so far.[10] On the other hand, *m*CPBA oxidation of cularines is known to give unresolved mixtures of cularine-*N*-oxides which have been used as synthetic intermediates in the preparation of norsecocularines.[11]

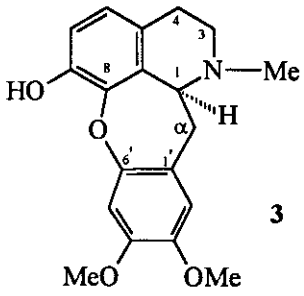
This paper reports the structure and conformation of two isomeric cularidine-*N*-oxides ((+)-**1**) and ((+)-**2**) isolated from *Ceratocapnos heterocarpa* (Papaveraceae) species endemic in the mediterranean region. The

† Dedicated to the memory of Professor Fèlix Serratosa

plant proved to be unique in its alkaloid composition in two respects, *viz* a high ratio of crassifoline/reticuline derived alkaloids and the co-occurrence of 1,2-berbines[12] and cularines[13] (hence its value for biosynthetic purposes).



	R_1	R_2
1	$O^{\ominus}$	Me
2	Me	$O^{\ominus}$
4	Me	Me



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By chromatography of the polar fraction of the alkaloid extract of *C. heterocarpa*, compounds (**1**) and (**2**) were isolated as amorphous powder. Alkaloid (**1**) exhibited a molecular ion at *m/z* 344 (MH^+) in the FAB mass spectrum and analysed for $C_{19}H_{21}NO_5$. The bathochromic shift observed in the 286 nm band of the uv spectrum on addition of a base suggested a phenolic alkaloid. The ^{13}C nmr spectrum reveled five quaternary aromatic carbons bonded to oxygen, a feature of the cularine structure. From the aromatic pattern of the ^1H nmr spectrum, with four protons: two singlets and two *ortho* coupled, the 3',4'-oxygenation pattern for ring D was obvious.[14] 2D-COSY and NOESY experiments correlated the two aromatic singlets with the methoxy groups, so the hydroxyl group must be at position 7 of the isoquinoline nucleus. From these data, the cularidine (**3**) basic structure with an extra oxygen atom was inferred. The aliphatic part of the ^1H nmr spectrum with the ABX system of C-1 and C-α protons and the four coupled protons at C-3 and C-4 excluded the possibility of **1** being a hydroxycularine.[5]

Compared with that for cularidine (**3**) (Table 1), the ^{13}C nmr spectrum for **1** exhibited a significant downfield shift in the carbons bonded to nitrogen (Δδ +12.2, +11.0 and +13.2 for C-1, C-3 and NMe, respectively), as well as an upfield shift in C-α and C-4 (Δδ -4.0 and -0.2). The β-induced substituent effect and the γ-effect suggested nitrogen quaternization, consistent with the finding for synthetic cularidine methiodide (**4**).[15] Thus, an *N*-oxide structure was assumed for alkaloid (**1**).

Table 1. Relevant ^{13}C nmr Data for Cularidine (**3**), its Methiodide (**4**) and the *N*-Oxides (**1**) and (**2**)

	3	**1**	**2**	**4**
C-1	57.7	69.9	73.8	65.8
C-3	48.4	59.4	66.0	55.8
NMe	42.1	55.3	49.1	51.1, 50.9
C-α	36.3	32.3	28.8	31 1
C-4	26.1	25.9	26.5	22.8

The ^1H *nmr spectrum exhibited the culanne characteristic* ABX *system of protons at C-1 and C-α. The* high field resonance for H-αβ and the coupling constants $J_{1,\alpha\alpha}$ and $J_{1,\alpha\beta}$ suggested a dihydroxepine ring in a twist-boat conformation; moreover, the deshielding of H-1 can be partly attributed to the nearness of the oxygen bridge. In fact, the same conformation has been found in the solid state for culanne methiodide[16] and assumed for simple culanines[17] and 4-hydroxycularines.[5] Regarding ring B, a half-chair conformation is to be expected from such a large diaxial coupling constant, $J_{3\beta,4\alpha}$=12.8 Hz and a near-zero diequatorial $J_{3\alpha,4\beta}$ value (Table 2).

Table 2. Aliphatic ^1H nmr Signals for Cularidine, its Methiodide and the *N*-Oxides

	cularidine (**3**)[a]		*trans-N*-oxide (**1**)[a]		cularidine methiodide (**4**)[b]		*cis-N*-oxide (**2**)[a]	
	δ	**J(Hz)**	**δ**	**J(Hz)**	**δ**	**J(Hz)**	**δ**	**J(Hz)**
H-1	4.25	$J_{1,\alpha\alpha}$=3.3 $J_{1,\alpha\beta}$=11.8	4.94	$J_{1,\alpha\alpha}$=2 8 $J_{1,\alpha\beta}$=12 7	5.03	$J_{1,\alpha\alpha}$=3.7 $J_{1,\alpha\beta}$=12.4	4.46	$J_{1,\alpha\alpha} \approx 0$ $J_{1,\alpha\beta}$=12.0
H-αα	3.20	$J_{\alpha\alpha,\alpha\beta}$=15.7	4.40	$J_{\alpha\alpha,\alpha\beta}$=15.3	3.50	$J_{\alpha\alpha,\alpha\beta}$=14.7	4.20	$J_{\alpha\alpha,\alpha\beta}$=12.0
H-αβ	3 06		2.99		3.01		3.36	
H-3β	3.07		3.69	$J_{3\beta,3\alpha}$=12 8 $J_{3\beta,4\beta}$= 5 4 $J_{3\beta,4\alpha}$=12.8	: : :		3.76	$J_{3\beta,3\alpha}$=12.7 $J_{3\beta,4\beta}$= 7.1 $J_{3\beta,4\alpha}$=3.1
H-3α	: :		3.53	$J_{3\alpha,4\alpha}$= 6.5 $J_{3\alpha,4\beta}$= 0	2 8-3.1 ·		3 66	$J_{3\alpha,4\alpha}$= 6.5 $J_{3\alpha,4\beta}$=12.7
H-4α	2 7-2.9		3.15	$J_{4\alpha,4\beta}$=17.6	·		3.25	$J_{4\alpha,4\beta}$=17.4
H-4β	:		3.09		·		3.07	
N-Me	2.57		3.34		3.21, 3.16		3.08	

a) 500 MHz, b) 200 MHz

The stereochemistry at the quaternized nitrogen atom was derived from nOe experiments (Table 3). The strong effect observed between the N-Me group and H-1 clearly demonstrates the *trans* relationship of this proton to the *N*-oxide oxygen. In addition, irradiation of the methyl group revealed a nOe effect on H-4α that required an axial arrangement from both. One result of the axial position of this methyl group is the lack of spatial interaction with H-αα. Thus, the structure of **1** was finally established as the *trans*-cularidine-*N*-oxide.

Table 3. Selected nOe Observed in *N*-Oxides (**1**) and (**2**).

irradiated proton	observed nOe (%)	
	1	**2**
H-1	H-αα (3.7), *N*-Me (5.2)	H-3α (4 9), H-αα (1)
H-αα	H-1 (8.4), H-αβ (25.1), H-2' (8.4)	*N*-Me (2), H-αβ (24), H-2' (6.8)
N-Me	H-1 (8.0), H-3α (2.9), H-4α (1.4)	H-αβ (1), H-3β (1.5)
H-αβ	H-3β (8.6), H-2' (3.7), H-αα (26)	*N*-Me (1), H-αα (18.2)

Compound (**2**) proved to be an isomer of **1** on the basis of FABms (*m/z* 344, MH^+). The closely related proton and carbon nmr spectra sufficed to assume the structure of the *cis*-cularidine-*N*-oxide for **2**. The *syn* arrangement of the *N*-oxide oxygen and H-1 was expected to shift this proton further downfield in the nmr spectrum (as observed in *N*-oxides of related systems such as 1-benzyl isoquinolines,[18] aporphines,[19] protoberberines[20] and indoloquinolizidines[21]); however, the opposite effect (almost -0.5 ppm) was actually observed. Also worth of notice is the deshielding undergone by H-αβ, which was quite different from that observed for **1**, cularidine or its methiodide (Table 2). All these facts, the decrease in $J_{1,\alpha\alpha}$ to near zero and the large γ-effect observed for C-α can be ascribed to a conformational change at the dihydroxepine ring.

From molecular models and molecular mechanics calculations of the benzoxepine-isoquinoline system present in the cularine alkaloids, three main conformations (**I-III**) can be visualized (Figure 1).

Conformation (**I**) has the dihydroxepine ring in a twist-boat conformation, the oxygen atom being the bow, so H-1 is near it. Ring B adopts a half-chair or a distorted half-chair conformation that can ready be interconverted simply by rotation about $N\text{-}C_3\text{-}C_4$ bonds. Conformation (**II**) is the result of rotation about $C_1\text{-}C_\alpha\text{-}C_{1'}$, which brings H-αα near the oxepine oxygen, as the B ring changes to a rather rigid half-boat conformation. The last possibility, conformation (**III**), can readily be arrived at from conformation (**I**) by inversion at the oxygen bridge (or rotation about $C_8\text{-}O\text{-}C_{6'}$ bonds). In this conformation, the heterocyclic

oxygen atom moves away from H-1 while coming close to H-αβ. Ring B is forced to adopt a half-chair conformation that is appreciably distorted towards a sofa form.[22]

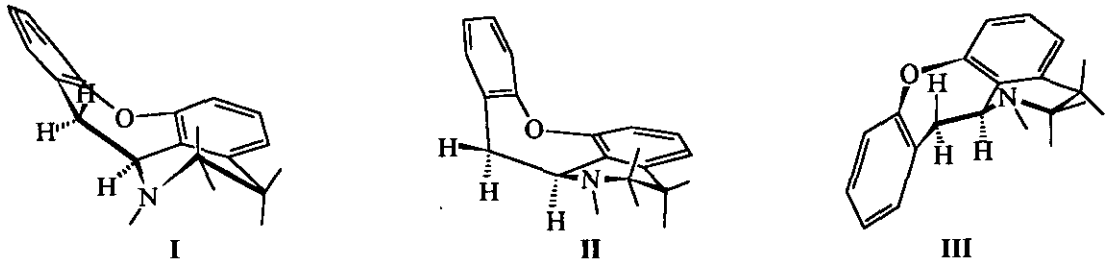


Figure 1. Proposed conformations for rings B and C of cularine alkaloids

Both dissolved (^{1}H and ^{13}C nmr data) and solid (X-ray structure determination) cularine alkaloids have been shown to exist in the preferred conformation (**I**),[17, 23, 16] which is the one assigned to the *trans-N*-oxide (**1**) from the observed coupling constant between H-1 and H-αβ and the strong nOe between H-αβ and H-3β (this requires a half-chair conformation in ring B). In conformation (**II**), H-1 bisects the tetrahedral angle between the geminal protons at C-α, with dihedral angles close to 60° as to anticipate similarly small vicinal coupling constants. The experimental $J_{1,\alpha\beta}$=12.0 and $J_{1,\alpha\alpha}\approx$0 exclude this conformation for the *cis-N*-oxide (**2**). Thus, the H-1 and H-αβ chemical shifts, the vicinal coupling constant and the absence of a nOe effect between the *N*-methyl group and H-1 substantiate an *anti* arrangement in a preferred conformation (**III**) for the *N*-oxide (**2**). Significant enough was the H-1 to H-3α observed nOe, consistent with the axial *N*-methyl group required for this conformation.

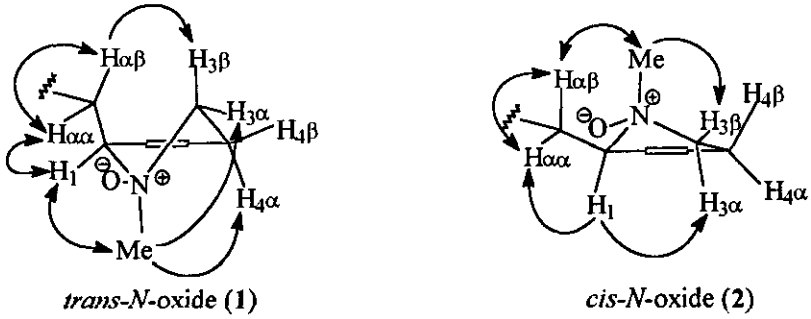
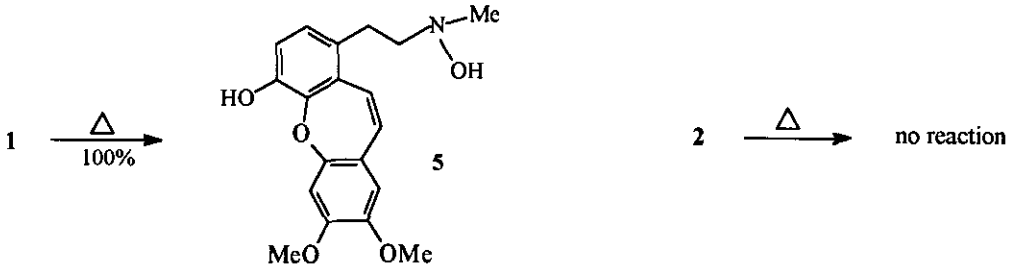


Figure 2. Qualitative nOe effects (measured value are given in Table 3)

With this spatial arrangement, the pseudo-axial H-4β and the *N*-Me group should exhibit a nOe effect; however, overlap of the corresponding signals prevented the predicted observation. The smaller values measured in the nOe experiments of **2** relative to **1** suggests a more flexible conformation for the latter *N*-oxide.

Further confirmation of these stereochemical assignments was obtained from a study of the Cope reaction on both *N*-oxides. It is well established that the hydrogen transfer in the ring-opening Cope elimination of heterocyclic amine oxides takes place *via* a bent cyclic transition state, simultaneously with the formation of a *cis* cycloalkene (for eight-membered and smaller rings).[24] With this stereo requirements in mind, and assuming the *S* configuration for H-1, the H-αβ proton is the one to be taken by the oxygen and to allow simultaneous orbital overlap in order to give a *cis* double bond. Consequently, we predicted higher stereoselectivity than that observed for 1-benzyl isoquinoline *N*-oxides,[18] so only the *trans*-*N*-oxide (**1**) would be able to acquire the appropriate spatial arrangement for a Cope elimination.

Heating a toluene-d_8 solution of **1** (containing 50 μl of CD_3OD) at 83°C for 2 h decreased the signals for the *N*-oxide as two extra aromatic doublets with a large coupling constant (11.5 Hz) appeared and the cyclic aliphatic protons collapsed to two triplets Raising the temperature to 100°C and heating for a further 1 h led to complete conversion of **1** to the *N*-hydroxy-*nor*-secocularidine (**5**) in quantitative yield. Under identical conditions, the *N*-oxide (**2**) remained unchanged, even after 14 h at 100°C. The only process observed after standing in solution for one month at room temperature was a slow loss of oxygen to give cularidine.

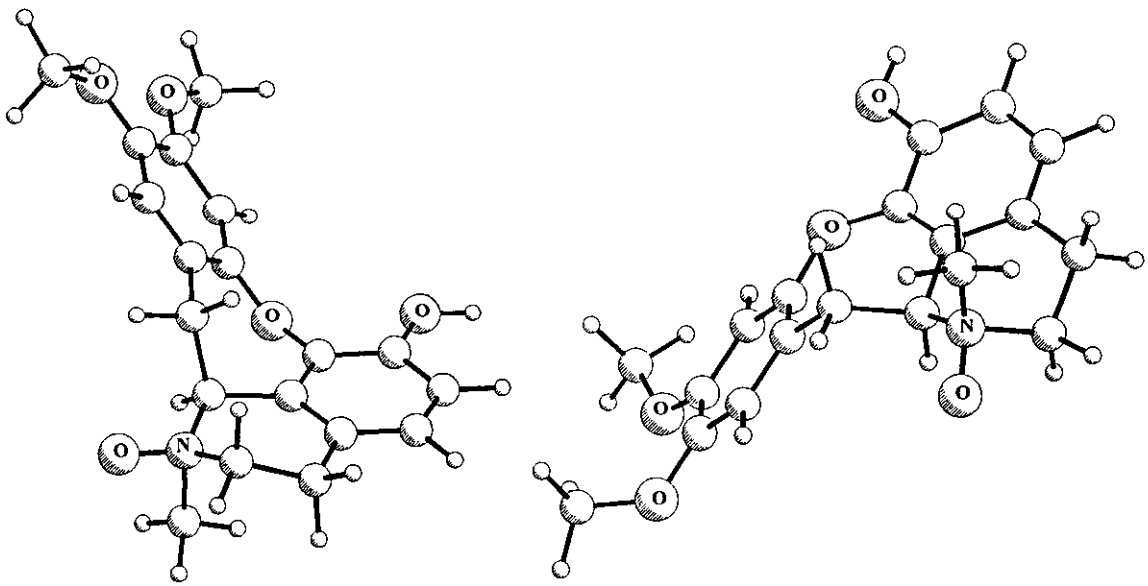


These results help us interpret the differences observed in the electron impact mass spectra (DIP) for **1** and **2**. When a heating rate of 50°C/min was applied to the probe, the ms (70 eV) of **2** exhibited the expected peaks for the *N*-oxide, *viz.* a very small molecular ion (M^+ 2%), loss of oxygen to the ion at *m/z* 327 (28%) and elimination of a methyl group to the base peak at *m/z* 312. However, under identical conditions, the

spectrum for the *N*-oxide (**1**) exhibited a more intense molecular ion (10%), a much reduced intensity for the 327 and 312 peak, and the base peak at *m/z* 284, together with an intense peak at *m/z* 60; the ms was thus almost identical with that recorded for **5**.

Finally, oxidation of (+)-cularidine with *m*CPBA afforded a mixture of (+)-**1** and (+)-**2** in a 3:1 ratio, which confirmed the proposed 1*S* configuration for both *N*-oxides. Since the chromatographic separation and purification of the minor component (**2**) proved rather difficult, the Cope reaction of the synthetic *N*-oxides mixture carried out in DMSO (70°C, 15 min) converted **1** to **5** quantitatively and afforded pure *N*-oxide (**2**).

MMX calculations[25] revealed that the most populated conformations (energy minima) for the *N*-oxides (**1**) and (**2**) are almost identical with those derived from spectroscopic data (Figures 2 and 3). These results substantiate the axial position of the methyl group in both *N*-oxides and the conformational change undergone by the dihydroxepine ring of **2**, the first example of a cularine alkaloid with an inverted oxygen bridge.



(1*S*)-**1** (1*S*)-**2**

Figure 3. PLUTO representations for the calculated conformations of cularidine-*N*-oxides (**1**) and (**2**)

They also suggest the possibility for oxepines such as oxocularines, 3,4-dioxocularines and aristocularines to exist in stable enantiomeric forms. This is currently being theoretically and experimentally considered by our group despite the absence of optical rotation observed in these naturally occurring alkaloids.

EXPERIMENTAL

General. All mp values are uncorrected. Optical rotations were measured at 20-22°C with a Perkin-Elmer mod. 241 polarimeter. EIms were measured at 70 eV on a HP-5988A instrument. FABms (2-hydroxyethyl disulfide as matrix) and HRms were recorded on a Kratos-50 instrument. Silica gel 60 (70-230 mesh) and silica gel 60 F_{254} were used for open column chromatography and thin layer chromatography (tlc). Routine ^{1}H and ^{13}C nmr spectra were recorded on a Bruker WP-200 SY spectrometer High field ^{1}H nmr spectra were obtained on a Bruker AMX-500 instrument. Proton chemical shifts are referred to residual chloroform (δ 7.24) and carbon chemical shifts to the solvent ($^{13}CDCl_3$ = 77 ppm). ^{1}H- and ^{13}C nmr signals were assigned from 2D COSY, NOESY and DEPT experiments.

Isolation procedure. The source of the plant material and part of the isolation procedure were reported elsewhere.[13] The mixture of *N*-oxides was isolated by open column chromatography using 1:4 EtOAc-MeOH as eluent. Separation was carried out by prep. tlc (1:5 EtOAc-MeOH). After five elutions **1** and **2** were extracted with methanol from the upper and lower bands respectively. Further purification was achieved by crystallization of the *N*-oxides from 1:3 MeOH-CH_2Cl_2 solutions.

Confirmation that **1** and **2** were genuine natural products and not artifacts, was provided by the demostration that cularidine (**3**) was not converted into *N*-oxides when subjected to the same extraction procedure, or when a methanolic solution was treated with O_2 (12 h).

***(+)-Trans*-cularidine-*N*-oxide (1)** : 18 mg. Amorphous solid, mp 200-202°C; $[\alpha]_D$= + 201° (c 0.06, MeOH). Uv λ_{max} nm (log ε) MeOH· 228 (4.06), 286 (3.75); MeOH + NaOH: 240 (3.88), 292 (3.70). ^{1}H Nmr (500 MHz, $CDCl_3$) δ: 6.94 (d, 1H, J= 8.4 Hz, H-5), 6.91 (d, 1H, J= 8.4 Hz, H-6), 6.73 (s, 1H, H-5'), 6.61 (s, 1H, H-2'), 4.94 (dd, 1H, J= 12.7 and 2.8 Hz, H-1), 4 40 (dd, 1H, J= 15.3 and 2.8 Hz, H-αα), 3.88 (s, 3H, OMe on C-4'), 3.79 (s, 3H, OMe on C-3'), 3.69 (td, 1H, J = 12.8, 12.8 and 5.4, H-3β), 3.53 (dd,

1H, J = 12.8 and 6.5 Hz, H-3α), 3.34 (s, 3H, NMe), 3 15 (ddd, 1H, J = 17.6, 12 8, 6.5 Hz, H-4α), 3.09 (dd, 1H, J= 17 6 and 5.4 Hz, H-4β) and 2.99 (dd, 1H, J = 15.3 and 12.7 Hz, H-αβ). ^{13}C Nmr ($CDCl_3$+CD_3OD) δ: 148.1, 147.8 , 147.2, 145.7, 142.7 (C-7, C-8, C-3', C-4', C-6'), 127.8, 118.4, 115.4 (C-4a, C-8a, C-1'), 125.4 (C-5), 117.2 (C-2'), 113.8 (C-6), 105.3 (C-5'), 69.6 (C-1), 59.4 (C-3), 56.1 (2xOMe), 55.3 (NMe), 32.3 (C-α), 25.9 (C-4). FABms *m/z* (%): 344 (MH^+, 100), 328 (9), 327 (7). EIms *m/z* (%): 343 (M^+, 10), 327 (M^+-16, 11), 325 (M^+-18, 12), 312 (M^+-16-15, 7), 284 (M^+-59, 100), 60 (90). HRms: found 343.1428 [calcd for $C_{19}H_{21}NO_5(M^+)$ 343.1420]. Anal. Calcd for $C_{19}H_{21}NO_5$: C, 66.44; H, 6 17; N, 4.08. Found· C, 66.08; H, 6.20; N, 3.91.

***(+)-Cis*-cularidine-*N*-oxide (2)**: 44 mg. Amorphous solid, mp 258-260°C. $[\alpha]_D$= + 240° (c 0.075, MeOH) Uv λ_{max} nm (log ε) MeOH: 230 (4.03), 288 (3.80); +NaOH: 242 (3.94), 292 (3.76). ^{1}H Nmr (500 MHz, $CDCl_3$) δ: 6.95 (d, 1H, J= 8.2 Hz, H-6), 6.90 (s, 1H, H-2'), 6.80 (d, 1H, J= 8.2 Hz, H-5), 6.79 (s, 1H, H-5'), 4.46 (br d, 1H, J= 12.0 Hz, H-1), 4.20 (br d, 1H, J= 12.0 Hz, H-αα), 3.86 (s, 3H, OMe), 3.85 (s, 3H, OMe), 3.76 (ddd, 1H, J= 12.7, 7.1 and 3.1 Hz, H-3β), 3.66 (td, 1H, J= 12.7, 12.7 and 6.5 Hz, H-3α), 3.36 (t, 1H, J= 12.0 Hz, H-αβ), 3.25 (ddd, 1H, J= 17.4, 6.5 and 3.1 Hz, H-4α), 3.07 (ddd, 1H, J= 17.4, 12.7 and 7.1 Hz, H-4β) and 3.08 (s, 3H, NMe). ^{13}C Nmr ($CDCl_3$+CD_3OD) δ: 149.9, 148.7, 147.1, 146.7, 143.0 (C-7, C-8, C-3', C-4', C-6'), 124.0 (C-5), 122.2, 122.0, 119.7 (C-4a, C-8a, C-1'), 116.3 (C-2'), 112 6 (C-6), 104.7 (C-5'), 73.8 (C-1), 66.0 (C-3), 56.3, 56.2 (2xOMe), 49.1 (NMe), 28.8 (C-α), 26.5 (C-4) FABms *m/z* (%): 344 (MH^+, 100), 328 (25), 327 (11). EIms *m/z* (%): 343 (M^+, 2), 327 (M^+-16, 28), 325 (M^+-18, 12), 312 (M^+-16-15, 100), 284 (M^+-59, 22). HRms: found 343.1421 [calcd for $C_{19}H_{21}NO_5(M^+)$ 343.1420]. Anal. Calcd for $C_{19}H_{21}NO_5$: C, 66 44; H, 6.17; N, 4.08. Found: C, 66.20; H, 5.99, N, 4 01

Oxidation of (+)-cularidine. *m*CPBA (90 mg, 0.5 mmol) was added to a stirred $CHCl_3$ (3 ml) solution of (+)-cularidine (60 mg, 0.18 mmol). After 1 h at 22°C and addition of a few drops of aqueous 5% $NaHCO_3$ a white precipitate was formed that was filtered and showed to be a mixture of (+)-**1** and (+)-**2** (33 mg, 51%, 3:1 ratio) that were separated as above.

Cope reaction of the mixture of 1 and 2. A synthetic mixture of *N*-oxides (35 mg) was dissolved in 0.8 ml of DMSO-d_6 and placed in a nmr tube. The sample was heated at 70°C until the ^{1}H nmr signals corresponding to **1** completely disappeared while those of **2** persisted. Removal of the solvent at room temperature in high vacuum, followed by prep. tlc (silica gel; 9:1 CH_2Cl_2-MeOH) afforded a lower band (7 mg) identified as **2** (tlc, ^{1}H nmr, EIms) and an upper band (20 mg) characterized as the *N*-hydroxy-*nor*-secocularidine (**5**): amorphous powder. ^{1}H Nmr (200 MHz, $CDCl_3$) δ: 6.89 (d, 1H, J= 8.2 Hz, H-6), 6.84 (d, 1H, J= 8.2 Hz, H-5), 6.83 and 6.73 (two d, 1H each, J= 11.6 Hz, H-1 and H-α), 6.66 and 6.63 (two s, 1H each, H-2' and H-5'), 3.86 and 3.83 (two s, 3H each, 2xOMe), 3.10-2.90 (m, 4H, 2xCH_2), 2.83 (s, 3H, NMe). EIms *m/z* (%): 343 (M^+, 11), 284 (M^+-C_2H_5NO, 100), 60 (CH_2=N^+(OH)Me, 32).

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