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Hydroxymethylation of Protoberberine Alkaloids by Photoinduced SET. The Total Synthesis of (±)-Solidaline

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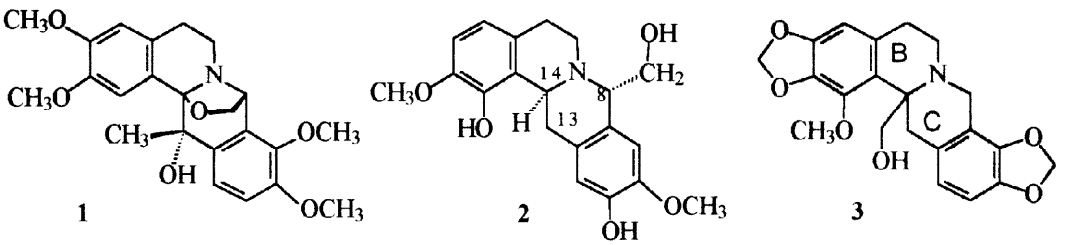
Abstract

The direct insertion of a hydroxymethyl group at position C-8 in a protoberberinium ion by photoaddition of methanol was approached *via* two mechanistic pathways: acetone-sensitized and single-electron transfer. The latter produces 8-hydroxymethylberbines in good yields after reduction. By combining this photochemical reaction with the oxidation of the photoproduct, syntheses of (±)-solidaline and its C-13 epimer from palmatine chloride were accomplished for the first time. On the other hand, insertion of a hydroxymethyl group at position 14 of the berberine skeleton in order to open a synthetic pathway for zijinlongine proved unsuccessful.

Keywords: Alkaloids; Isoquinolines; Iminium salts; Photochemistry.

The presence of a hydroxymethyl group as a substituent at position 1 of the isoquinoline nucleus is a common structural feature of isoquinoline alkaloids [1]. Typical examples isolated from higher plants include: i) simple tetrahydroisoquinolines such as the widespread calycotomine [2], and deglucopterocereine [3]; ii) benzophenanthridine alkaloids such as bocconoline [4], 8-hydroxymethyl-sanguinarine [5], 8-hydroxymethyldihydronitidine [6] and corynolamine [7]; iii) berbine (tetrahydroprotoberberine) alkaloids, and the more complex quinocarcins [8] of fungal origin and the marine alkaloids ecteinascidins [9]. Three berbine alkaloids share these structural characteristics, with the hydroxymethyl substituent at either C-8, as in (±)-solidaline (**1**) (isolated from *Corydalis solida*)



[10] and (+)-malacitanine (**2**) (isolated from *Ceratocapnos heterocarpa*) [11], or C-14, as in zijinlongine (**3**) (found in *Dactylocapnos torulosa)* [12].

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These berbines are minor alkaloids in their respective plants; the biosynthetic origin [13] of the additional substituent at C-8 is unknown, although the concurrence of the unsubstituted alkaloid suggest the *in vivo* addition of one carbon unit. The structure of **2** has been fully established and its total synthesis accomplished by condensation of *N*-norcrassifoline and glyoxylic acid to close the berberine bridge [11]; however, the structures of **1** and **3** have been proposed on spectroscopic grounds and thus require confirmation.

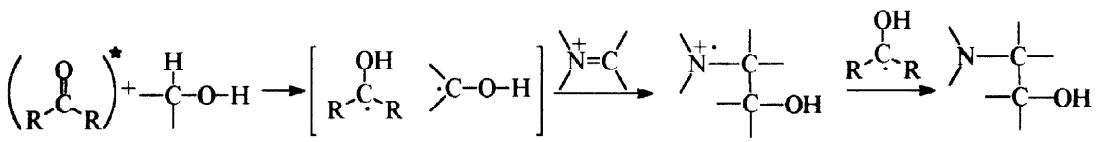
The fact that protoberberinium salts with different oxygenation patterns at rings A and D are readily available from natural sources [14] aroused our interest in exploring the insertion of a hydroxymethyl group at positions 8 and 14 of the berbine skeleton.

Alkyl derivatives can be incorporated at position 8 of a protoberberinium salt by addition of a carbon nucleophile such as a Grignard reagent or the anion of acetone [14, 15]. Similarly, these salts are expected to react with a suitable hydroxymethyl anion equivalent — prepared from *t*-butyl methyl ether [16], methyl 2,4,6-triisopropylbenzoate [17], (tributylstannyl) methanol [18], (chloromethyl)isopropoxydimethylsilane [19] or *N*-(chloromethylmethoxycarbonyl)-pyrrolidine [20]— to provide a route to 8-hydroxymethyl berbines. A more simple and expeditious synthetic alternative, however, is the photoaddition of methanol to the corresponding protoberberinium salt, a process that might provide an entry to either 8 or 14 hydroxymethyl substituted berbines.

This paper describes in detail the photochemical behaviour of protobeberinium alkaloids in the presence of methanol and reports the most suitable conditions for its hydroxymethylation at position 8. This synthetic approach enabled the first total synthesis of (±)-solidaline (**1**) and its C-13 epimer, as confirmed their physical and spectroscopic characterization [21].

Results and Discussion

The photochemistry of protoberberinium ions has scarcely been explored. Only the photooxidation to either berberine phenolbetaines or the products of the 13-14 bond cleavage, depending on the reaction conditions, has seemingly been investigated [14]. By contrast, the photoaddition of alcohols to imines and iminium salts has been widely studied [22]. With neutral imines, the reaction takes place *via* hydrogen atom abstraction to the alcohol by the n–π^* excited stated of the imine chromophore. Obviously, electronically excited iminium salts cannot react in direct hydrogen abstraction processes and two major mechanisms are operative in the alcohol photoaddition: chemical sensitization and single-electron transfer (SET). In the chemical sensitization mechanism (Scheme 1), the n–π^* triplet of a ketone (usually acetone or benzophenone) abstracts a hydrogen

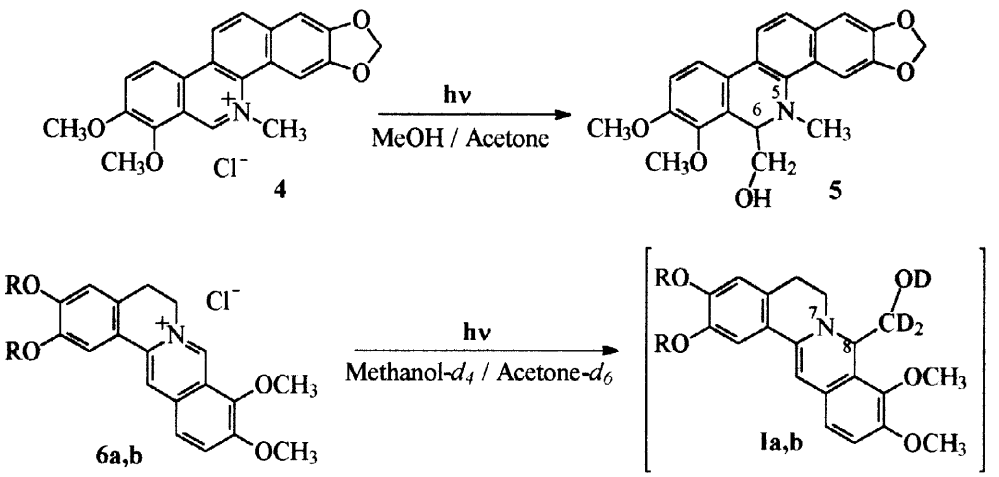


Scheme 1

atom from the alcohol to form α-hydroxymethyl radicals that add themselves to the iminium salts to produce an aminium radical that eventually yields the adduct.

This mechanism must be that responsible for the reported acetone-sensitized photoaddition of methanol to position 6 of chelerithrine chloride (**4**) to give bocconoline (**5**) [4] and is the sole reported example of photoaddition of a hydroxymethyl group to an isoquinolinium salt.

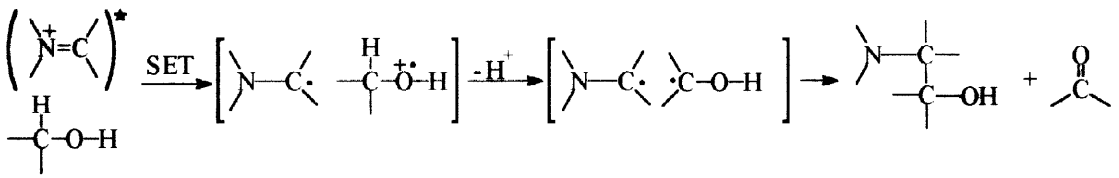
Deoxygenated solutions (1:1 CD_3COCD_3-CD_3OD) of berberine chloride (**6a, R+R = CH_2**) and palmatine chloride (**6b, R = R = CH_3**) were irradiated in NMR tubes. Reduction of ring C was inferred from the disappearance of the singlet signals for H-8 and H-13 ($\delta \approx 9.7$ and 8.6 ppm respectively) and the appearence of two new singlets at around δ 5.5 and 6.2 ppm (1 hydrogen each) that were attributed to those protons in the hydroxydeuteromethylated enamines (**Ia,b**). The reaction conducted on a preparative scale, however, yielded a complex mixture of compounds. In no instance could the hydroxymethylated enamines be isolated.



4 **5** **6a,b** **Ia,b**

We attributed the differential behaviour of the benzophenanthridinium and the protoberberium ions to the chemical stability of the photoaddition products. While 5,6-dihydrobenzophenanthridines are highly stable and commonly isolated from natural sources [23], 7,8-dihydroberbines behave as enamines and exhibit a high reactivity towards electrophiles. In fact, lambertine (7,8-dihydroberberine) is reportedly the sole naturally occurring alkaloid of this type [1].

The alternative mechanism operating in the alcohol photoaddition to iminium ions involves an initial single-electron transfer from the oxygen atom to the excited state of the carbon-nitrogen double bond to the radical-ion pair. Carbon deprotonation of the cation radical leads to the α-hydroxyalkyl radical, which can undergo various transformations including coupling with the α-amino radical to give the addition products (Scheme 2) and oxidation to the aldehyde.

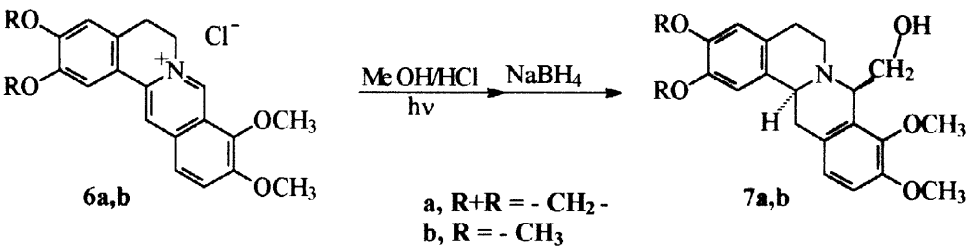


Scheme 2

Based on this mechanism, direct irradiation of a methanol solution of protoberberinium ions was expected to yield the corresponding hydroxymethyl enamine, which would be isolable in the absence of electrophiles. However, a deoxygenated solution of **6a,b** remained unchanged after extensive irradiation (more than one week) at either $\lambda = 254$ nm or $\lambda > 300$ nm.

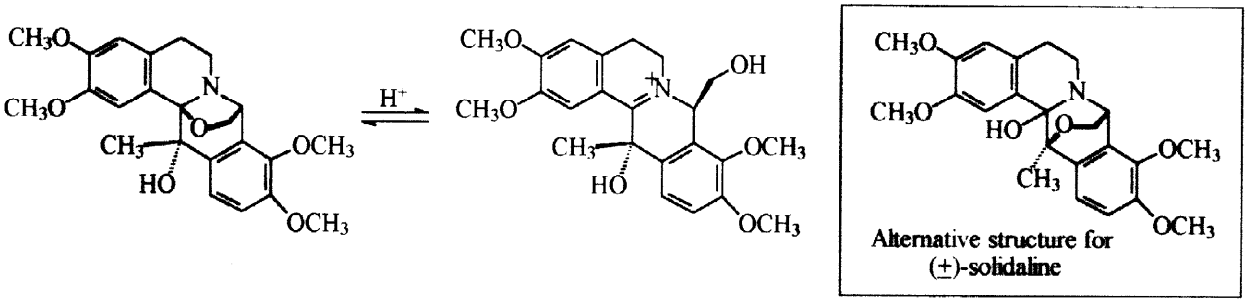
We thought that conducting the reaction in a strongly acidic medium might favour its development in several ways, *viz.* a) by facilitating the initial SET, b) by stabilising the C-8 radical intermediate through extended conjugation, and c) by preventing dark reactions of the photoadduct (**Ia,b**) while keeping the reactive enamine formed protonated.

A hydrogen chloride-saturated methanolic solution of **6a** (8.10^{-3} M) was irradiated at 254 nm. The reaction development was monitored *via* the disappearance of the H-8 iminium proton, and was allowed to proceed to approximately 90% conversion. The crude product was reacted with $NaBH_4$ to obtain 87% of (±)-8-hydroxymethylcanadine **7a,** the expected product for the reduction of the 8-hydroxymethyl-13-dihydroberberine photoadduct. A small proportion (less than 5%) of (±)-canadine (tetrahydroberberine) was also isolated as a result of the reduction of unreacted **6a.** Under identical conditions, the irradiation of palmatine chloride afforded (±)-8-hydroxymethyltetrahydropalmatine (**7b**) in a 57% yield.

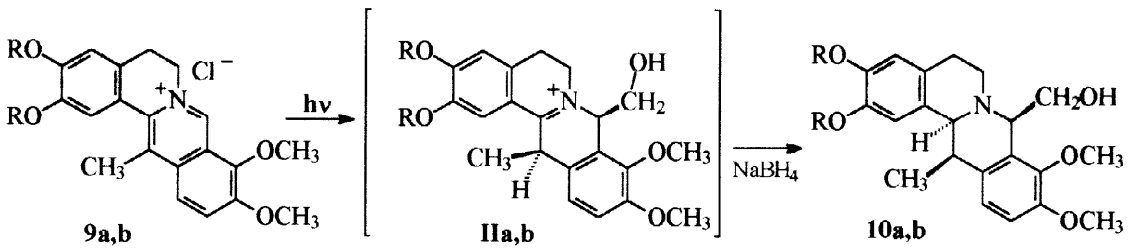


The stereochemistry of **7a,b** is the result of the attack of the hydride from the less-hindered side of the iminium ion. The B/C *trans*-quinolizidine conformation, and the *trans* arrangement between H-14 and the hydroxymethyl group at C-8, were both inferred from the downfield chemical shifts (cmr) for C-5, C-6, C-13 and C-14 (about 30, 49, 37 and 58 ppm); on the other hand, the H-14 appeared above (pmr) 4.0 ppm. In fact, when the substituent at C-8 and the H-14 are in *cis*, rings B and C are known to adopt a *cis*-quinolizidine conformation and the chemical shifts for C-6 and C-14 to move downfield through γ-gauche interactions [11].

The ready insertion of a substituent at C-8 prompted us to undertake the synthesis of (±)-solidaline (**1**), a racemic alkaloid isolated from *Corydalis solida* by Manske [10]. The proposed structure for this base, supported by spectroscopic data, includes a quaternary carbon at C-13 and a hydroxymethyl group at C-8 in a 7,14-dehydroberbine skeleton; under neutral conditions, the skeleton appears to cyclize to C-14. However, Shamma and Moniot [25] suggested that an alternative structure (**8**) with the oxygen bridge connected to C-13 could not be discarded. Both structures have the opposite relative configuration between the methyl and hydroxymethyl substituents. Consequently, the first step was to study the stereochemistry of the photoaddition on a 13-methyl-protoberberinium ion.



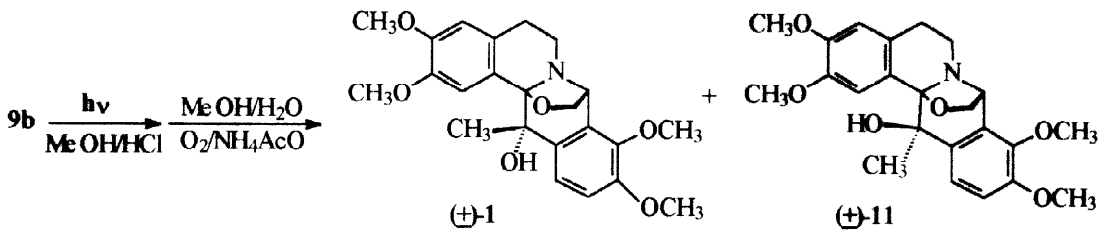
The preparation of **9a,b** involved the partial reduction of **6a,b** (dry pyridine/$NaBH_4$), followed by methylation of the enamine with formaldehyde in AcOH/NaAcO [26], isolation of the salt as iodide and anion-exchange to the chloride. A HCl-saturated methanol solution of dehydrocorydaline chloride (**9b**) was irradiated at 254 nm for 7 days until the deep yellow colour was almost extinct. Reduction of the reaction mixture, followed by preparative tlc separation, afforded a white solid (75%) that was characterised as **10b**. The chemical shifts for C-5 and C-6 (29.9 and 48.1 ppm, respectively) were consistent with a B/C *trans*-quinolizidine conformation; also, the *cis* arrangement between H-13 and H-14 was inferred from the measured vicinal coupling constant ($J_{13,14}$< 1 Hz). The nOe observed between H-8, H-14 and H-6_{ax} confirmed the quinolizidine conformation and the *cis* arrangement of both alkyl substituents.



Irradiation of 13-methylberberine chloride (**9a**) gave (±)-13-hydroxymethylthalictricavine (**10a**) in a 72% yield. In any case, we have not been able to isolate any other stereoisomer out of the reaction products. The high diastereoselectivity of this reaction, not in the reduction step but in the radical coupling process, is rather surprising. Probably, the C-8 methyl group in the radical intermediate adopts a pseudoequatorial position and the methoxy group at position-9 favours *syn* addition.

With this result in hand, the isolation of **IIb** was attempted. Precipitation as an iminium salt was unsuccessful and careful neutralisation of the reaction mixture only produced tarry material. Since this photoadduct is only one oxidation stage behind that proposed for the solidaline structure, its direct oxidation was undertaken. Molecular oxygen at an alkaline pH is a widely employed method for the hydroxylation of enamines at the β-carbon [24]. After several attempts at different pH values, we found that stirring the crude photoproduct under an oxygen

atmosphere at pH 6 for 48 h, afforded the isolation of two cyclized products. The major component was identified as (±)-solidaline (**1**) and the minor component as its C-13 epimer (**11**).

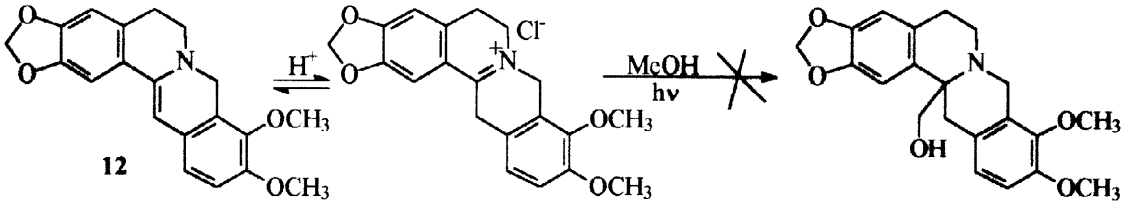


No sample of natural solidaline was available for direct comparison with the synthetic product. However, the m.p., UV, IR, EIMS, ^{1}H-NMR data for the synthetic compound were in good agreement with those reported for the alkaloid [10]. The ^{13}C-NMR exhibited some differences in the chemical shifts of C-13 and C-14, probably due to solvent effects and their influence in the concentration of the open form in the equilibrium. HMBC correlation among H-1 (7.22 ppm), C-14 (99.5 ppm) and H-16 (3.69 ppm) clearly indicated connection of the oxygen bridge to form an oxazolidine ring, thus excluding the proposed alternative structure with the oxygen bridge bonded to C-13. The reversible equilibrium observed from the UV-VIS spectra also supports this structural peculiarity. In acidic methanol, two bands were recorded at 312 and 366 nm that were ascribed to the immonium open form; in alkaline media, these bands collapse to a single one at 282 nm, the typical absorption band for a berbine (tetrahydroprotoberberine). NOESY experiments confirmed that the methyl group at C-13 (H-15) and the methylene of the bridge (H-16) were in a *cis* arrangement. For the natural alkaloid, a *cis* B/C ring junction was proposed based on the chemical shift for the methylene carbons at position 5 and 6. However, the NOESY experiment strongly suggested a B/C *trans* conformation for the quinolizidine heterocycle; in fact, H-8 appeared close to H-6_{eq}, whereas H-6_{ax} was near H-16.

In episolidaline (**11**), the *trans* arrangement between the methyl group and the bridge causes a downfield shift for the C-13, C-15 and C-16 resonances (78.6, 26.3 and 69.2 ppm, respectively); on the other hand the methyl protons are shifted upfield (1.21 ppm). The change in the C-13 configuration does not alter the conformation of the molecule, the UV-VIS behaviour of which is identical with that observed for solidaline.

Insertion of a hydroxymethyl group at C-14 in the protoberberine nucleus was then explored as a potential way of synthesising zijinlongine (**3**). Irradiation of 8,13-dihydroberberine (**12**) in hydrogen chloride-saturated methanol under a nitrogen atmosphere for one week did not give the expected photoadduct; rather slow oxidation to berberine was observed, followed by the photoaddition of methanol to position 8.

Tautomerization of the 8,13-dihydroberberinium ion (**12**) to the corresponding enamine does not allow one to use the addition of hydroxymethyl anion equivalents to incorporate this substituent at position 14. Synthetic alternatives to achieve this goal are currently being explored.



Experimental

General Methods

M.p.s. were determined on a Gallenkamp instrument and are given uncorrected. UV spectra were recorded on a Hewlett-Packard 8452A spectrophotometer and IR spectra on a Perkin-Elmer 883 spectrophotometer. Low- and high-resolution mass spectra were recorded on an HP-MS 5988A and a Kratos MS 50 spectrometer, respectively, both operating at 70 eV. NMR spectra were obtained on Bruker WP-200 SY or a Bruker WM-500 instruments, at 200 or 500 MHz for ^{1}H, and 50.3 or 125.8 MHz for ^{13}C. ^{1}H Chemical shifts (δ_H) are given relative to residual $CHCl_3$ (δ_H 7.24 ppm) in deuteriochloroform. *J* values are in Hz. ^{13}C Chemical shifts (δ_C) are given relative to $CDCl_3$ (δ_C 77.0 ppm) in deuteriochloroform. TLC analyses were performed on silica gel 60 F 256 plates, and column chromatography was carried out on silica gel 60 (70-230 mesh). Berberine chloride (**6a**) was supplied by Sigma Co. Palmatine chloride (**6b**, m.p 204 °C) was obtained by extraction of *Enantia chlorantha* powdered bark from Niger [27]. 13-Methyl berberine chloride (**9a**, m.p. 201-203 °C) [28] and dehydrocorydaline chloride (**9b**, m.p. 180-190 °C) [1] were prepared from **6a** and **6b** following the procedure described. 8,13-Dihydroberberine chloride (**12**) was obtained by partial reduction of **6a** and crystalized from MeOH/HCl.

Photohydroxymethylation-reduction of protoberberinium salt.

Protoberberinium salt (0.15 g, 0.4 mmol) was dissolved in MeOH/HCl (50 ml). The mixture was degassed with N_2 for 1 h and then irradiated in a cylindrical photochemical reactor (8x8 W, low presure mercury tube, Vycor tube) under N_2 to complete disappearance (6-8 d) of the starting material (nmr). The solution was reduced with excess $NaBH_4$ (0.34 g). The solvent was removed *in vacuo*, water added and the solution extracted with $CHCl_3$. The organic layer was washed with water, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by preparative tlc ($CHCl_3$/MeOH 100:4).

(8R,14S*)-(±)-8-Hydroxymethylcanadine* (**7a**)

Yield 87%; yellow pale solid; mp 157-158 °C (MeOH/H_2O); ν (KBr) cm^{-1} 3455, 1485, 1277, 1230, 1033; λ_{max} nm (log ε) MeOH: 226 (4.07), 288 (3.75); δ_H (C_6D_6) 6.70 (d, 1H, J = 8.3 Hz, H12), 6.64 (s, 1H, H1), 6.53 (d, 1H, J = 8.3 Hz, H11), 6.42 (s, 1H, H4), 5.38 (s, 2H, OCH_2O), 4.03 (s, 3H, H8, H16, H16'), 3.73 (s, 3H, C9-OMe), 3.49 (bd, 1H, J = 10.9 Hz, H14), 3.34 (s, 3H, C10-OMe), 3.10-2.60 (m, 5H, H5ax, H6eq, H13ax, H13eq, OH), 2.40-2.10 (m, 2H, H5eq, H6ax); δ_C ($CDCl_3$)

150.8, 146.1, 146.0, 145.6 (C2, C3, C9, C10), 130.9, 129.9, 129.6, 128.0 (C4a, C8a, C12a, C14a), 123.2, 111.3, 108.4, 105.6 (C1, C4, C11, C12), 100.8 (OCH_2O), 63.8 (C16), 61.9 (C8), 60.3 (C9-OMe), 58.3 (C14), 55.9 (C10-OMe), 49.0 (C6), 37.2 (C13), 30.6 (C5); *m/z* (%) 369 (M^+, 2), 368 (M^+-1, 7), 338 (M^+-31, 100), 322 (14); MS(FAB) *m/z*: 370 (MH^+). Anal. Calcd. for $C_{21}H_{23}NO_5$: C 68.28, H 6.28, N 3.79, found C 67.99, H 6.28, N 3.80.

(8R,14S*)-(±)-8-Hydroxymethyltetrahydropalmatine* **(7b)**

Yield 56%. Colourless oil; ν (KBr) cm^{-1} 3439, 1510, 1493, 1460, 1275, 1029; λ_{max} nm (log ε) MeOH: 212 (4.00), 224 sh (3.88), 282 (3.40); δ_H (C_6D_6) 6.78 (d, 1H, J = 8.3 Hz, H12), 6.70 (s, 1H, H1), 6.53 (d, 1H, J = 8.3 Hz, H11), 6.42 (s, 1H, H4), 4.13 (bs, 3H, H8, H16, H16'), 3.76 (s, 3H, C9-OMe), 3.71 (bd, 1H, J = 11.0 Hz, H14), 3.47, 3.43, 3.33 (3 s, 9H, 3 x OMe), 3.10 (m, 4H, H5ax, H6eq, H13eq, OH), 2.88 (dd, 1H, J = 14.9; 11.0 Hz, H13ax), 2.51 (dt, 1H, J = 11.1; 3.1 Hz, H6ax), 2.35 (bd, 1H, J = 15.3 Hz, H5eq); δ_C ($CDCl_3$) 150.8, 147.6, 147.3, 145.6 (C2, C3, C9, C10), 130.0, 129.8, 129.7, 127.0 (C4a, C8a, C12a, C14a), 123.2, 111.3, 108.7 (C1, C4, C11, C12), 63.8 (C16), 61.8 (C8), 60.3 (C9-OMe), 57.9 (C14), 56.1, 55.9, (3 x OMe), 49.1 (C6), 37.1 (C13), 30.2 (C5); *m/z* (%) 385 (M^+, 2), 354 (M^+-31, 100), 338 (16). Anal. Calcd. for $C_{22}H_{27}NO_5$: C 68.55, H 7.06, N 3.63, found C 68.85, H 7.25, N 3.39.

(8R,13R*,14S*)-(±)-8-Hydroxymethylthalictricavine* **(10a)**

Yield 72%. White crystals mp 120-121 °C ($MeOH/H_2O$); ν (KBr) cm^{-1} 3517, 1488, 1277, 1229, 1094, 1034; λ_{max} nm (log ε) MeOH: 220 (4.09), 286 (3.78); δ_H (500 MHz) (C_6D_6) 6.77 (d, 1H, J = 8.3 Hz, H12), 6.68 (s, 1H, H1), 6.64 (d, 1H, J = 8.3 Hz, H11), 6.48 (s, 1H, H4), 5.43 (d, 1H, J = 5.2 Hz, OCH_2O), 4.21 (dd,1H, J = 10.9; 2.5 Hz, H16), 4.15 (dd, 1H, J = 10.9; 2.5 Hz, H16'), 3.97 (t, 1H, J = 2.5 Hz, H8), 3.77 (s, 3H, C9-OMe), 3.74 (bs, 1H, H14), 3.41 (s, 3H, C10-OMe), 3.18 (ddd, 1H, J = 11.5; 5.0; 1.5 Hz, H6eq), 3.07 (dq, 1H, J = 7.0; 2.8 Hz, H13), 2.82 (ddd, 1H, J = 15.8; 11.5; 5.0 Hz, H5ax), 2.32 (dt, 1H, J = 11.5; 3.0 Hz, H6ax), 2.22 (bd, 1H, J = 15.8 Hz, H5eq), 1.19 (d, 3H, J = 7.0 Hz, C13-Me); δ_C ($CDCl_3$) 150.5, 146.3, 145.7 (C2, C3, C9, C10), 135.8, 129.7, 129.3, 129.1 (C4a, C8a, C12a, C14a), 123.4, 111.5, 108.2, 105.4 (C1, C4, C11, C12), 100.7 (OCH_2O), 63.7 (C16), 62.1 (C14), 61.3 (C9-OMe), 60.2 (C8), 55.9 (C10-OMe), 48.0 (C6), 38.6 (C13), 30.4 (C5), 16.8 (C15); *m/z* (%) 383 (M^+, 2), 382 (M^+-1, 7), 352 (M^+-31, 100), 336 (10); HRMS calcd. for $C_{22}H_{25}NO_5$: 383.1733; found: 383.1734; Anal. Calcd. for $C_{22}H_{25}NO_5$: C 68.92; H 6.57, N 3.65; found: C 68.60; H 6.45; N 3.64.

(8R,13R*,14S*)-(±)-8-Hydroxymethylcorydaline* **(10b)**

Yield 75%. White crystals mp 141-142 °C ($MeOH/H_2O$); ν (KBr) cm^{-1} 3590, 1492, 1280, 1251, 1100; λ_{max} nm (log ε) MeOH: 218 (4.21), 284 (3.69); δ_H (500 MHz) (C_6D_6) 6.85 (d, 1H, J = 8.3 Hz, H12), 6.73 (s, 1H, H1), 6.64 (d, 1H, J = 8.3 Hz, H11), 6.47 (s, 1H, H4), 4.27 (dd, 1H, J = 11.0; 3.1 Hz, H16), 4.26 (dd, 1H, J = 11.0; 3.1 Hz, H16'), 4.07 (t, 1H, J = 3.1 Hz, H8), 3.93 (bs, 1H, H14), 3.79, 3.53, 3.49, 3.41 (4 s, 12H, 4 x OMe), 3.34 (m, 2H, H6eq, H13), 3.00 (ddd, 1H, J = 15.6; 11.8; 2.5 Hz, H5ax), 2.46 (dt, 1H, J = 11.8; 2.9 Hz, H6ax), 2.39 (bd, 1H, J = 15.6 Hz, H5eq), 1.29 (d, 1H,

J = 7.0 Hz, C13-Me); δ_C ($CDCl_3$) 150.4, 147.4, 147.2, 145.7 (C2, C3, C9, C10), 135.8, 129.3, 128.5, 128.1 (C4a, C8a, C12a, C14a), 123.3, 111.4, 111.0, 108.5 (C1, C4, C11, C12), 63.6 (C16), 62.0 (C14), 60.8, 56.0, 55.8, 55.7 (4 x OMe), 60.1 (C8), 48.1 (C6), 38.4 (C13), 29.9 (C5), 16.8 (C15); *m/z* (%) 399 (M^+, 3), 398 (M^+-1, 10), 368 (M^+-31, 100), 352 (13); MSCI *m/z*: 400 $[M + H]^+$; Anal. Calcd. for $C_{23}H_{29}NO_5$: C 69.15; H 7.32; N 3.51; found: C 68.85; H 7.25; N 3.39.

Photohydroxymethylation and molecular oxidation of dehydrocorydaline **(9b).**

Dehydrocorydaline (0.32 g, 0.8 mmol) was dissolved in 100 ml MeOH/HCl. The reaction mixture was degassed with N_2 for 1 h and then irradiated in a cylindrical photochemical reactor (8x8 W low presure mercury tube, Vycor tube) under N_2 for 8 days to complete disappearance of the starting material. The solvent was removed to dryness *in vacuo* (0 °C, 1 mbar). The residue was dissolved in a solution of NH_4OAc (5 g) in 16 ml of MeOH and 4 ml of H_2O (pH=5-6). The resulting solution was stirred in an open flask at rt for 48 h. The mixture was concentrated and extracted with $CHCl_3$, washed with water, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The new residue gave two compounds after preparative tlc ($CHCl_3$/MeOH 100:4).

(±)-Solidaline **(1).**

Yield 12%; white solid; mp 192 °C ($CHCl_3/Et_2O$) [lit.: 196 °C ($CHCl_3/Et_2O$)] [10]. ν (KBr) cm^{-1} 3403 (OH), 2934, 1275 (C-O); λ_{max} nm (log ε) MeOH: 238 (3.74), 282 (3.64), 312 (3.54), 356 (3.42); +HCl: 238 (4.00), 316 (3.86), 366 (3.81); + NH_3 aq.: 236 (4.00), 280 (3.68); CH_2Cl_2: 236 (4.00), 282 (3.70), 306 (3.44); δ_H (500 MHz) ($CDCl_3$) 7.32 (d, 1H, J = 8.6 Hz, H12), 7.22 (s, 1H, H1), 6.88 (d, 1H, J = 8.6 Hz, H11), 6.63 (s, 1H, H4), 4.74 (d, 1H, J = 3.7 Hz, H8), 4.10 (dd, 1H, J = 6.9; 3.7 Hz, H16), 3.92, 3.87 (2 s, 6H, 2 x OMe), 3.86 (s, 6H, 2 x OMe), 3.69 (d, 1H, J = 6.9 Hz, H16'), 3.12 (ddd, 1H, J = 9.6; 3.7; 2.3 Hz, H6eq), 2.95 (ddd, 1H, J = 15.3; 11.9; 3.7 Hz, H5ax), 2.74 (ddd, 1H, J = 11.9; 9.6; 2.3 Hz, H6ax), 2.60 (ddd, 1H, J = 15.3; 2.3; 2.3 Hz, H5eq), 1.81 (s, 3H, C13-Me); δ_C (125.8 MHz) ($CDCl_3$) 150.8 (C9), 148.5 (C2), 146.8 (C3), 142.0 (C10), 134.1 (C12a), 132.7 (C8a), 130.0 (C14a), 125.2 (C4a), 123.8 (C12), 112.4 (C1), 111.5 (C11), 110.6 (C4), 99.5 (C14), 76.2 (C13), 68.6 (C16), 60.8 (C8), 60.7, 56.0, 55.8 (4 x OMe), 46.1 (C6), 30.5 (C5), 22.1 (C15); *m/z* (%) 413 (M^+, 6), 366 (10), 207 (100), 206 (59), 191 (43), 178 (37), 163 (10); MSCI ($C_{23}H_{28}NO_6$) *m/z*: 414 $[M + H]^+$; HRMS calcd. for $C_{23}H_{27}NO_6$: 413.1838; found: 413.1829.

(±)-Episolidaline **(11)**

Yield 10 mg, (4%); yellow oil; λ_{max} nm (log ε) MeOH: 240 (3.57), 280 (3.49), 326 (2.96); +HCl: 240 (3.59), 316 (3.57), 360 (3.56); +NH_3 aq.: 240 (3.57), 280 (3.46), 330 (2.93); δ_H (500 MHz) ($CDCl_3$) 7.67 (s, 1H, H1), 7.30 (d, 1H, J = 8.2 Hz, H12), 6.87 (d, 1H, J = 8.2 Hz, H11), 6.61 (s, 1H, H4), 4.73 (d, 1H, J = 4.0 Hz, H8), 4.20 (dd, 1H, J = 7.0; 4.0 Hz, H16), 3.90, 3.87, 3.86, 3.84 (4 s, 12H, 4 x OMe), 3.74 (d, 1H, J = 7.0 Hz, H16'), 3.11 (ddd, 1H, J = 10.2; 3.4; 2.3 Hz, H6eq), 3.04 (s, 1H, OH), 3.01 (ddd, 1H, J = 15.3; 12.5; 3.4 Hz, H5ax), 2.82 (ddd, 1H, J = 12.5; 10.2; 2.3 Hz, H6ax), 2.62 (ddd, 1H, J = 15.3; 2.3; 2.3 Hz, H5eq), 1.21 (s, 3H, C13-Me); δ_C ($CDCl_3$) 150.9, 148.5,

147.3, 140.5 (C2, C3, C9, C10), 135.2, 132.7, 128.3, 125.1 (C4a, C8a, C12a, C14a), 123.9, 111.8, 111.4, 110.4 (C1, C4, C11, C12), 99.8 (C14), 78.6 (C13), 69.2 (C16), 61.2 (C8), 60.9, 55.8, 55.7 (4 x OMe), 46.5 (C6), 29.5 (C5), 26.3 (C15); *m/z* (%) 413 (M^+, 13), 366 (12), 350 (12), 207 (100), 206 (86), 191 (58), 178 (25); MSCI *m/z*: 414 $[M + H]^+$; HRMS: calcd. for $C_{23}H_{27}NO_6$: 413.1838; found: 413.1832.

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