



## (±)-HETEROCARPINE, A HYDROXYMETHYLATED ISOQUINOLINE ALKALOID FROM *CERATOCAPNOS HETEROCARPA*

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**Key Word Index**—*Ceratocapnos heterocarpa*; Fumariaceae; heterocarpine; structure; synthesis; isoquinoline alkaloids.

**Abstract**—Heterocarpine, a novel alkaloid from *Ceratocapnos heterocarpa*, has been characterised as (±)-1-hydroxymethyl-2-(3-hydroxy-4-methoxybenzyl)-7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline. The alkaloid was synthesized from the corresponding 3,4-dihydro isoquinolinium salt. A key step in the process is the acid resin catalysed methanolysis of the 1-carbamoyl isoquinoline. The structural correlation of the hydroxymethylated alkaloids heterocarpine and malacitanine with their unsubstituted counterparts capnosine and caseamine, also present in the plant, might be of biosynthetic significance. © 1998 Elsevier Science Ltd. All rights reserved

### INTRODUCTION

The biosynthesis of most types of isoquinoline alkaloids depends on the oxygenation pattern of the 1-benzylisoquinoline precursor. Thus, reticuline, oxygenated at positions 6,7 of the heterocyclic ring, is a precursor for morphinans, aporphinoids and 2,3-berbines [1,2]. On the other hand, crassifoline [3], oxygenated at positions 7,8, is associated with the biosynthesis of cularines, quettamines and 1,2-berbines. In previous papers [4–11], we reported that *Ceratocapnos heterocarpa* is a particularly interesting species by virtue of its ability to express both metabolic pathways. It produces (either in the plant or in *in vitro* cultures) a wide variety of types of isoquinoline alkaloids including isoquinolones, *N*-benzylisoquinolines, cularines, berbines, protopines, aporphines, benzophenanthridines and ribasines [12].

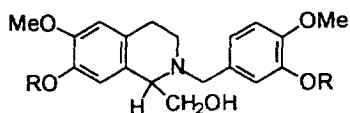
In this paper, we report on the isolation of a new alkaloid named heterocarpine (**1**), a phenolic *N*-benzylisoquinoline bearing a hydroxymethyl group at position 1, from *C. heterocarpa*. The structure of **1** was established spectroscopically and confirmed by total synthesis of heterocarpine and its O,O-dimethyl derivative **2**.

### RESULTS AND DISCUSSION

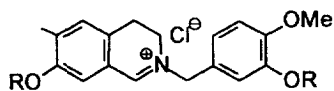
Optically inactive heterocarpine (**1**) was isolated as an amorphous powder and analysed for  $C_{19}H_{23}NO_5$ . The UV spectrum of **1** was consistent with an unconjugated tetrahydroisoquinoline ( $\lambda_{max}$  284 nm) with phenolic substituents ( $\lambda_{max}$  + NaOH: 290 nm). The mass spectrum in the CI mode produced the expected  $[M + H]^+$  ion at  $m/z$  346. The EI-mass spectrum revealed two important features: the absence of  $[M]^+$ , a strong peak at  $[M-CH_3O]^+$  ( $m/z$  314.1387,  $C_{18}H_{20}NO_4$ ) was obtained instead, and the splitting of the  $m/z$  314 ion into two fragments at  $m/z$  178 (11%) and 137 (100%). These peaks were assigned to tetrahydroisoquinolinium and a benzyl ion respectively, both substituted with one methoxy and one hydroxy group [13]. Heterocarpine (**1**) reacted with diazomethane to give O,O-dimethyl heterocarpine (**2**), which also exhibited in the mass spectrum the ion  $[M-31]^+$  and others at  $m/z$  192 and 151.

The  $^{13}C$  NMR spectrum of **1** revealed the presence of four aliphatic methylene groups. In addition to the expected C-3 and C-4 signals of the tetrahydroisoquinoline nucleus ( $\delta$  41.9 and 22.5), a signal at  $\delta$  56.7 was assigned to a benzyl carbon, while a low field one ( $\delta$  63.5) suggested the presence of a hydroxymethyl substituent that was tentatively located at C-1 in accordance with a methine carbon

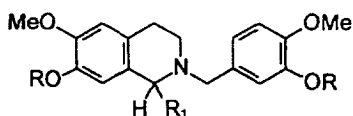
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- 1, R = H  
2, R = Me



- 3a, R = CH<sub>2</sub>Ph  
3b, R = Me

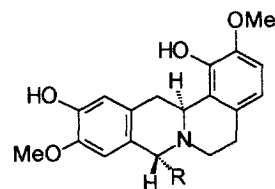


- 4a, R = CH<sub>2</sub>Ph; R<sub>1</sub> = CN  
4b, R = Me; R<sub>1</sub> = CN  
5a, R = H; R<sub>1</sub> = CONH<sub>2</sub>  
5b, R = Me; R<sub>1</sub> = CONH<sub>2</sub>  
6a, R = H; R<sub>1</sub> = CO<sub>2</sub>Me  
6b, R = Me; R<sub>1</sub> = CO<sub>2</sub>Me  
7, R = H; R<sub>1</sub> = H

signal at  $\delta$  61.1; thus, the benzyl substituent must be linked to the nitrogen atom. From the aromatic part of the  $^1\text{H}$  NMR spectrum of **1**, the OMe and the OH groups on the isoquinoline nucleus were assigned to positions 6 and 7 (two singlets for H-5 and H-8), also three protons in an ABX pattern indicated 1,3,4-substitution of the benzyl unit. The position of the substituents on the aromatic rings was inferred from the 2D-COSY spectrum. The correlation between the proton at  $\delta$  6.67 (H-5) and the high-field multiplet assigned to H-4 and a methoxy group, indicated that **1** must be methoxylated at C-6 and hydroxylated at C-7. In addition, an *ortho* coupled proton (H-5') was found to be correlated with the methoxy group at C-4'. On biosynthetic grounds the hydroxy group was assigned to the neighbouring carbon (C-3'). Consequently, heterocarpine (**1**) was tentatively characterized as ( $\pm$ )-1-hydroxymethyl-2-(3'-hydroxy-4'-methoxybenzyl)-7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline. In order to confirm this structure, a synthesis for **1** and **2** was developed. Most of the syntheses for 1,2,3,4-tetrahydroisoquinolines bearing a substituent at position 1 introduce the substituent before the heterocycle is formed, *via* the Pictet–Spengler or the Bischler–Napieralski reaction. In the latter case, however, the introduction of a hydroxymethyl group meets with some difficulties that have been partially resolved [14]. The most direct approach, based on the photoaddition of methanol to isoquinolinium salts *via* single electron transfer, has been

used to synthesize solidaline, an 8-hydroxymethylberberine alkaloid [15]. However, this methodology was discounted since the irradiation of *N*-benzyl-3,4-dihydro-isoquinolinium salts in methanol/HCl does not stop at the addition stage because dehydration is followed by photoreduction of the iminium ion [16]. One other, particularly interesting, approach to inserting a hydroxymethyl group uses the electrophilicity of C-1 in isoquinolines or 3,4-dihydroisoquinolines and the addition of hydroxymethyl anion equivalents or the cyanide ion [17], which requires further manipulation of the functionality. We chose this last strategy because of our interest in the synthetic and cyclization potentials of 1-carbamoyl isoquinolines.

Conventional Bischler–Napieralski reactions were used to prepare the starting 3,4-dihydroisoquinolines, which were alkylated with the corresponding benzyl chlorides to afford the isoquinolinium chlorides **3a** and **3b**. The cyanides **4a,b** were obtained in high yield when the reactions were conducted in aqueous solutions [18]. Hydrolysis to the amide in related systems has been reported [17] to proceed with good yield by reaction in benzene/ethanol/HCl. Under these conditions, however, we only observed elimination of hydrogen cyanide. Concentrated hydrochloric acid at a temperature below 5° produced the carboxyamides **5a** and **5b**. As expected, the concomitant removal of the protecting groups during the reaction of **4a** was also observed. Hydrolysis of the amide **5a** to the carboxylic acid under acid or basic conditions [19,20] gave very low yields that were attributed to solubility problems. The alternative step going from the amide to the ester was found to be very convenient. The reaction was carried out by using the acid resin Amberlite® IR-120 in methanol [21]. Extraction of **6b** from the resin was readily achieved with methanol–pyridine (3:1), by contrast the extraction of **6a** required more basic conditions, i.e. methanol–triethylamine (3:1). LiAlH<sub>4</sub> reduction of **6a** and **6b** afforded ( $\pm$ )-heterocarpine (**1**) and O,O-dimethyl heterocarpine (**2**) which were shown to be identical to the natural compounds (TLC, IR,  $^1\text{H}$  and  $^{13}\text{C}$  NMR, MS). The hydroxymethyl group at position 1 of the heterocyclic nucleus is a common structural feature of isoquinoline alkaloids. Examples [22] include simple isoquinolines (e.g. calycotomine),



- 8 R = CH<sub>2</sub>OH  
9 R = H

protoberberines (e.g. malacitanine, solidaline), benzophenanthridines (e.g. bocconoline), and the more complex quinocarins [23] and ecteinascidins [24]. It is assumed that the additional carbon atom is introduced at the heterocycle forming step, pyruvate or glyoxylate being two potential precursors [25].

It is interesting to note that heterocarpine (**1**) and the C-1 unsubstituted *N*-benzylisoquinoline capnosine (**7**) occur concomitantly in *Ceratocarpus heterocarpus* [8]. Moreover, the 1,2,10,11-substituted berberine alkaloids (–)-malacitanine (**8**) [6] and (–)-caseamine (**9**) [4] have also been isolated from this source. Structurally, **8** can be considered the hydroxymethyl derivative of **9**. This suggests that introduction of this substituent at position 1 of the isoquinoline nucleus might occur after the heterocycle has been formed.

## EXPERIMENTAL

### General

Mps: uncorr.; EIMS: direct inlet, 70 eV; CC: Silica gel 60 (70–230 mesh); TLC: silica GF<sub>254</sub>; <sup>1</sup>H and <sup>13</sup>C NMR: 200 and 50 MHz, respectively. Proton chemical shifts are referred to the residual CHCl<sub>3</sub> (δ 7.24) signal, and carbon chemical shifts to the solvent (<sup>13</sup>CDCl<sub>3</sub> δ 77). <sup>1</sup>H and <sup>13</sup>C NMR signals were assigned from 2D COSY and DEPT expts.

(±)-Heterocarpine (**1**). Acid-base fractionation of the methanolic extract of *Ceratocarpus heterocarpus* (3 kg of air dried plant) afforded an alkaloid fraction soluble in CHCl<sub>3</sub>–MeOH that was separated CC [5]. The fraction eluted with EtOAc was further purified by prep. TLC (CHCl<sub>3</sub>–MeOH) to give heterocarpine (70 mg). Yellowish amorphous solid, mp 105–106°, [α]<sub>D</sub> 0°. UV λ<sub>max</sub> nm (log ε) MeOH: 226 (4.08), 284 (3.79); +NaOH: 240 (4.01), 290 (3.86); IR ν<sub>max</sub> cm<sup>–1</sup> (KBr): 3386 (OH); <sup>1</sup>H NMR (acetone-*d*<sub>6</sub>): δ 6.90 (1 H, *d*, *J* = 2.0 Hz, H-2'), 6.87 (1 H, *d*, *J* = 8.2 Hz, H-5'), 6.78 (1 H, *dd*, *J* = 2.0, 8.2 Hz, H-6'), 6.67 (1 H, *s*, H-5), 6.60 (1 H, *s*, H-8), 3.82, 3.80 (3 H each, two *s*, 2 × OMe), 3.70 (2 H, *s*, CH<sub>2</sub>Ph), 3.68–3.50 (3 H, *m*, H-1, CH<sub>2</sub>OH), 3.30–2.35 (4 H, *m*, H-3, H-4); <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 146.1, 145.7, 145.6, 144.1 (C-6, C-7, C-3', C-4'), 131.1, 126.0, 125.5, (C-1', C-4a, C-8a), 120.6 (C-6'), 115.3, 113.3, 110.9, 110.6 (C-5, C-8, C-2', C-5'), 63.5 (CH<sub>2</sub>OH), 61.1 (C-1), 56.7 (CH<sub>2</sub>Ph), 55.9, 55.8 (2 × OMe), 41.9 (C-3), 22.5 (C-4); CIMS (CH<sub>4</sub>, probe) *m/z*: 346 [M + H]<sup>+</sup>; EIMS *m/z* (rel. int.): 314 [M-31]<sup>+</sup> (40), 178 (11), 137 (100); HRMS:[M-CH<sub>3</sub>O]<sup>+</sup> (found: 314.1387; C<sub>18</sub>H<sub>20</sub>NO<sub>4</sub> requires: 314.1392). Found: C, 63.19; H, 6.59; N, 3.85. C<sub>19</sub>H<sub>23</sub>NO<sub>5</sub>·H<sub>2</sub>O requires: C, 62.80; H, 6.93; N, 3.85%.

*O,O*-Dimethyl heterocarpine (**2**). To a soln of **1** (25 mg) in Et<sub>2</sub>O (10 ml containing a few drops of MeOH) a large excess of an ethereal soln of CH<sub>2</sub>N<sub>2</sub> was added. The mixture was allowed to stand at room temp. for 24 hr and the solvent removed under a N<sub>2</sub> stream to give **2** as a white powder, mp 95–97°. IR ν<sub>max</sub> cm<sup>–1</sup> (KBr): 3417 (OH); <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 6.88 (1 H, *s*, H-2'), 6.80 (2 H, *s*, H-6', H-5'), 6.59 (1 H, *s*, H-5), 6.50 (1 H, *s*, H-8), 4.70 (1 H, *br s*, OH), 3.85 (6 H, *s*, 2 × OMe), 3.83, 3.81 (3 H each, two *s*, 2 × OMe), 3.80–3.65 (3 H, *m*, 2 H, CH<sub>2</sub>Ph), 3.70–3.60 (1 H, *m*, H-1), 3.65–3.45 (2 H, *m*, CH<sub>2</sub>OH), 3.30–2.30 (4 H, *m*, H-3, H-4); <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 149.0, 148.3, 147.8, 147.6 (C-6, C-7, C-3', C-4'), 130.9 (C-1'), 126.3, 125.4 (C-4a, C-8a), 121.1 (C-6'), 111.9, 111.6, 110.9, 110.3 (C-5, C-8, C-2', C-5'), 63.6 (CH<sub>2</sub>OH), 60.9 (C-1), 56.9 (CH<sub>2</sub>Ph), 55.9, 55.8, 55.7 (4 × OMe), 42.0 (C-3), 22.4 (C-4); EIMS *m/z* (rel. int.): 342 [M-31]<sup>+</sup> (30), 192 (10), 151 (100). Found: C, 63.80; H, 7.61; N, 3.46. C<sub>21</sub>H<sub>27</sub>NO<sub>5</sub>·H<sub>2</sub>O requires C, 64.43; H, 7.47; N, 3.58%.

### Preparation of 1-cyano-1,2,3,4-tetrahydroisoquinoline derivatives **4a,b**.

The isoquinolinium salt **3a** was prepared by reaction of 7-benzyloxy-6-methoxy-3,4-dihydroisoquinoline [8] and 3-benzyloxy-4-methoxybenzyl chloride in MeCN at reflux temp for 4 hr, followed by removal of the solvent. Similar conditions were used to prepare **3b** from 6,7-dimethoxy-3,4-dihydroisoquinoline [8] and 3,4-dimethoxybenzyl chloride.

To a soln of the corresponding 3,4-dihydroisoquinolinium salts (**3a,b**, 1 mmol) in H<sub>2</sub>O (10–12 ml), KCN–H<sub>2</sub>O (3 mmol) was added. The mixture was stirred at room temp. for 30 min, extracted with CHCl<sub>3</sub> (4 × 20 ml), dried over MgSO<sub>4</sub> and the solvent evaporated.

1-Cyano-2-(3-benzyloxy-4-methoxybenzyl)-7-benzyloxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline (**4a**). Yield 88%, pale yellow powder, mp 60–65°. IR ν<sub>max</sub> cm<sup>–1</sup> (CHCl<sub>3</sub>): 2256 (CN); <sup>1</sup>H NMR (CHCl<sub>3</sub>): δ 7.5–7.2 (10H, *m*, 2 × Ph), 6.96 (1 H, *d*, *J* = 1.8 Hz, H-2'), 6.93 (1 H, *dd*, *J* = 8.0, 1.8 Hz, H-6'), 6.84 (1 H, *d*, *J* = 8.0 Hz, H-5'), 6.62 (1 H, *s*, H-5), 6.59 (1 H, *s*, H-8), 5.1, 5.05 (2 H each, two *s*, 2 × OCH<sub>2</sub>Ph), 4.42 (1 H, *s*, H-1), 3.87, 3.84 (3 H each, two *s*, 2 × OMe), 3.78 (1 H, *d*, *J* = 13.0 Hz, H-α), 3.64 (1 H, *d*, *J* = 13.0 Hz, H-α'), 3.05–2.55 (4 H, *m*, H-3, H-4); EIMS *m/z* (rel. int.): 494 [M-26]<sup>+</sup> (1), 268 (11), 227 (32), 91 (100).

1-Cyano-2-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**4b**). Yield 91%, yellowish oil, pure based on TLC (Lit.: mp 98° [20]). IR ν<sub>max</sub> cm<sup>–1</sup> (CHCl<sub>3</sub>): 2260 (CN); <sup>1</sup>H NMR (CHCl<sub>3</sub>): δ 6.92 (2 H, *m*, H-2', H-6'), 6.81 (1 H, *d*, *J* = 8.6 Hz, H-5'), 6.59 (1 H, *s*, H-5), 6.55 (1 H, *s*, H-8), 4.53 (1 H, *s*, H-1), 3.85, 3.84, 3.82, 3.79 (3 H

each, four s, 4 × OMe), 3.85 (1 H, d,  $J$  = 12.8 Hz, H- $\alpha$ ), 3.69 (1 H, d,  $J$  = 12.8 Hz, H- $\alpha'$ ), 3.10–2.60 (4 H, m, H-3, H-4);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  149.1, 149.0, 148.5, 147.7 (C-6, C-7, C-3', C-4'), 128.9, 126.7 (C-1', C-4a), 121.4 (C-6'), 121.2, 116.7 (C-8a, CN), 111.9, 111.4, 110.9, 109.5 (C-5, C-8, C-2', C-5'), 59.6 ( $\text{CH}_2\text{Ph}$ ), 55.9, 55.8 (4 × OMe), 53.8 (C-1), 46.6 (C-3), 28.1 (C-4); EIMS  $m/z$  (rel. int.): 368  $[\text{M}]^+$  (1), 151 (100).

#### Preparation of 1-carbamoyl derivatives **5a,b**

A cooled (0°) mixture of the corresponding 1-cyano derivative (**4a,b** 1 mmol) and conc. HCl (4 ml) was stirred to complete dissolution and the soln allowed to stand at 4° for 36–48 hr. The mixture was made alkaline (pH 8–9) with conc. ammonia, extracted with  $\text{CHCl}_3$  (3 × 20 ml) and dried ( $\text{MgSO}_4$ ). The extracts were concentrated to afford a solid residue that was purified by recrystallization.

*1-Carbamoyl-2-(3-hydroxy-4-methoxybenzyl)-7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline (5a)*. Yield 76%, white solid, mp 218–220° ( $\text{Me}_2\text{CO}$ ). IR  $\nu_{\text{max}}$   $\text{cm}^{-1}$  (KBr): 3430, 3300–3200 (OH, NH), 1684 (Amide I);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.09 (1 H, s, H-8), 6.90 (1 H, d,  $J$  = 1.4 Hz, H-2'), 6.79 (1 H, d,  $J$  = 8.5 Hz, H-5'), 6.78 (1 H, dd,  $J$  = 8.5, 1.4 Hz, H-6'), 6.52 (1 H, s, H-5), 4.04 (1 H, s, H-1), 3.86, 3.81 (3 H each, two s, 2 × OMe), 3.79 (1 H, d,  $J$  = 13.3 Hz, H- $\alpha$ ), 3.36 (1 H, d,  $J$  = 13.3 Hz, H- $\alpha'$ ), 3.03 (1 H, ddd,  $J_{3\text{eq},4\text{ax}}$  = 4.3,  $J_{3\text{eq},4\text{eq}}$  = 3.5 Hz, H-3<sub>eq</sub>), 2.79 (1 H, ddd,  $J_{4\text{ax},4\text{eq}}$  = 16.0,  $J_{4\text{ax},3\text{ax}}$  = 11.0,  $J_{4\text{ax},3\text{eq}}$  = 4.3 Hz, H-4<sub>ax</sub>), 2.57 (1 H, dt,  $J_{4\text{eq},4\text{ax}}$  = 16.0,  $J_{4\text{eq},3\text{ax}}$  =  $J_{4\text{eq},3\text{eq}}$  = 3.5 Hz, H-4<sub>eq</sub>), 2.39 (1 H, dt,  $J_{3\text{ax},3\text{eq}}$  =  $J_{3\text{ax},4\text{ax}}$  = 11.0,  $J_{3\text{ax},4\text{eq}}$  = 3.5 Hz, H-3<sub>ax</sub>);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  176.6 (CO), 146.3, 146.0, 145.7, 144.2 (C-6, C-7, C-3', C-4'), 130.7, 125.5, 124.2, (C-1', C-4a, C-8a), 120.4 (C-6'), 115.0, 113.2, 110.7, 110.5 (C-5, C-8, C-2', C-5'), 67.5 (C-1), 59.5 ( $\text{CH}_2\text{Ph}$ ), 55.9, 55.8 (2 × OMe), 46.4 (C-3), 28.1 (C-4); EIMS  $m/z$  (rel. int.): 314  $[\text{M}-44]^+$  (67), 178 (11), 137 (100); CIMS ( $\text{CH}_4$ , probe)  $m/z$ : 358  $[\text{M} + \text{H}]^+$ . Found: C, 60.49; H, 6.57; N, 7.41.  $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_5 \cdot \text{H}_2\text{O}$  requires: C, 60.63; H, 6.43; N, 7.44%.

*1-Carbamoyl-2-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (5b)*. Yield 65%, white solid, mp 156–9° ( $\text{Me}_2\text{CO}$ ) (Lit.: 189–192° [19]). IR  $\nu_{\text{max}}$   $\text{cm}^{-1}$  (KBr): 3437, 3319 (NH), 1659 (Amide I);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.0 (2 H, s, H-2', H-8), 6.84 (1 H, d,  $J$  = 8.0 Hz, H-6'), 6.82 (1 H, d,  $J$  = 8.0 Hz, H-5'), 6.54 (1 H, s, H-5), 5.50 (2 H, br s,  $\text{NH}_2$ ), 4.09 (1 H, s, H-1), 3.85 (6 H, s, 2 × OMe), 3.84 (1 H, d,  $J$  = 13.5 Hz, H- $\alpha$ ), 3.81 (6 H, s, 2 × OMe), 3.44 (1 H, d,  $J$  = 13.5 Hz, H- $\alpha'$ ), 3.07 (1 H, ddd,  $J_{3\text{eq},3\text{ax}}$  = 11.0,  $J_{3\text{eq},4\text{ax}}$  = 4.5,  $J_{3\text{eq},4\text{eq}}$  = 3.6 Hz, H-3<sub>eq</sub>), 2.82 (1 H, ddd,  $J_{4\text{ax},4\text{eq}}$  = 16.0,  $J_{4\text{ax},3\text{ax}}$  = 11.0,  $J_{4\text{ax},3\text{eq}}$  = 4.5 Hz, H-4<sub>ax</sub>), 2.61 (1 H, dt,  $J_{4\text{eq},4\text{ax}}$  = 16.0,

$J_{4\text{eq},3\text{ax}}$  =  $J_{4\text{eq},3\text{eq}}$  = 3.6 Hz, H-4<sub>eq</sub>), 2.43 (1 H, dt,  $J_{3\text{ax},3\text{eq}}$  =  $J_{3\text{ax},4\text{ax}}$  = 11.0,  $J_{3\text{ax},4\text{eq}}$  = 3.6 Hz, H-3<sub>ax</sub>);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  176.1 (CO), 148.9, 148.4, 148.1, 147.4 (C-6, C-7, C-3', C-4'), 129.9, 126.1, 123.7, 121.1 (C-1', C-6', C-4a, C-8a), 112.1, 111.1, 110.9, 109.8 (C-5, C-8, C-2', C-5'), 67.5 (C-1), 59.6 ( $\text{CH}_2\text{Ph}$ ), 55.9, 55.8 (4 × OMe), 46.5 (C-3), 28.1 (C-4); EIMS  $m/z$  (rel. int.): 342  $[\text{M}-44]^+$  (27), 151 (100); CIMS ( $\text{CH}_4$ , probe)  $m/z$ : 387  $[\text{M} + \text{H}]^+$ .

#### Synthesis of heterocarpine (1)

A mixture of the 1-carboxamide derivative **5a**, (210 mg, 0.75 mmol) in MeOH (10 ml) and Amberlite<sup>®</sup> IR-120 resin (2.5 g, thoroughly rinsed with MeOH) was gently stirred in a tightly capped flask at 65° for 14 hr. The mixture was cooled and the resin filtered and washed once with MeOH. The Amberlite was suspended in a mixture of MeOH– $\text{Et}_3\text{N}$  (3:1) and shaken at room temp. for 48 hr. Solvent evaporation gave a yellowish syrup that solidified on standing. The solid was ground with  $\text{Et}_2\text{O}$  to obtain a white solid that was characterized as the 1-methoxycarbonyl derivative **6a** and used without further purification (190 mg, 68%); mp 108–110°. IR  $\nu_{\text{max}}$   $\text{cm}^{-1}$  (KBr): 3440 (OH), 1732 (CO);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  6.93 (1 H, d,  $J$  = 1.4 Hz, H-2'), 6.82 (1 H, dd,  $J$  = 8.1, 1.4 Hz, H-6'), 6.76 (1 H, d,  $J$  = 8.1 Hz, H-5'), 6.76 (1 H, s, H-8), 6.57 (1 H, s, H-5), 4.39 (1 H, s, H-1), 3.70–3.60 (2 H, m,  $\text{CH}_2\text{Ph}$ ), 3.86, 3.83 (3 H each, two s, 2 × OMe), 3.70 (3 H, s,  $\text{CO}_2\text{Me}$ ), 3.40–2.10 (4 H, m, H-3, H-4);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  173.0 (CO), 145.9, 145.7, 145.5, 143.7 (C-6, C-7, C-3', C-4'), 131.5, 126.7, 124.5, (C-1', C-4a, C-8a), 120.4 (C-6'), 115.1, 112.6, 110.9, 110.3 (C-5, C-8, C-2', C-5'), 63.9 (C-1), 58.7 ( $\text{CH}_2\text{Ph}$ ), 55.9, 55.8 (2 × OMe), 51.7 ( $\text{CO}_2\text{Me}$ ), 44.7 (C-3), 28.1 (C-4); EIMS  $m/z$  (rel. int.): 314  $[\text{M}-59]^+$  (70), 178 (6), 137 (100).

To a stirred soln of **6a** (90 mg, 0.24 mmol) in dry THF (10 ml) a soln of  $\text{LiAlH}_4$  (40 mg, 1 mmol) in THF (8 ml) was added under a  $\text{N}_2$  atmosphere. After stirring for 1 hr, excess hydride was destroyed with  $\text{H}_2\text{O}$  (0.15 ml) and 1%  $\text{H}_2\text{SO}_4$  was added to make the pH slightly acidic. The ppt. was removed by filtration, the residue washed with  $\text{CHCl}_3$  and MeOH, and the combined filtrate concentrated to dryness. The residues was taken up in  $\text{CHCl}_3$ , washed with diluted aq.  $\text{NaHCO}_3$  and dried ( $\text{MgSO}_4$ ). After solvent removal, the crude product was purified by prep. TLC to afford heterocarpine (**1**) as a yellowish foam that was identical in all respects with the alkaloid isolated from the plant.

#### Synthesis of *O,O*-dimethyl-heterocarpine (2)

The reaction of the carboxyamide **5b** with amberlite in MeOH was carried out as above. The ester **6b** was extracted from the resin with MeOH–pyridine (3:1). **6b** (96% yield) was characterized and used without further purification in the reduction

step. IR  $\nu_{\max}$   $\text{cm}^{-1}$  (film): 1732 (CO);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  6.92 (1 H, *d*,  $J = 1.4$  Hz, H-2'), 6.83 (1 H, *dd*,  $J = 8.2, 1.4$  Hz, H-6'), 6.77 (1 H, *d*,  $J = 8.2$  Hz, H-5'), 6.68 (1 H, *s*, H-8), 6.58 (1 H, *s*, H-5), 4.40 (1 H, *s*, H-1), 3.95–3.75 (2 H, *m*,  $\text{CH}_2\text{Ph}$ ), 3.83 (6 H, *s*,  $2 \times \text{OMe}$ ), 3.80, 3.77 (3 H each, two, *s*,  $2 \times \text{OMe}$ ), 3.69 (3 H, *s*,  $\text{CO}_2\text{Me}$ ), 3.50–2.60 (4 H, *m*, H-3, H-4);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  172.7 (CO), 148.8, 148.3, 148.2, 147.2 (C-6, C-7, C-3', C-4'), 130.0, 127.0, 123.0, (C-1', C-4a, C-8a), 121.0 (C-6'), 111.9, 111.4, 110.6, 109.8 (C-5, C-8, C-2', C-5'), 63.5 (C-1), 58.7 ( $\text{CH}_2\text{Ph}$ ), 55.8, 55.7, 55.6 ( $4 \times \text{OMe}$ ), 51.6 ( $\text{CO}_2\text{Me}$ ), 44.6 (C-3), 27.6 (C-4); EIMS  $m/z$  (rel. int.): 342 [ $\text{M}-59$ ] $^+$  (45), 151 (100).

The reduction of **6b** with  $\text{LiAlH}_4$  was carried out as above. Although the work up of the reaction was conducted at alkaline pH. The 1-hydroxymethyl derivative **2** was purified by prep. TLC ( $\text{CHCl}_3$ –MeOH, 20:1). The product was identical to the above described O,O-dimethyl heterocarpine.

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