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# Psychollatine, a Glucosidic Monoterpene Indole Alkaloid from *Psychotria umbellata*

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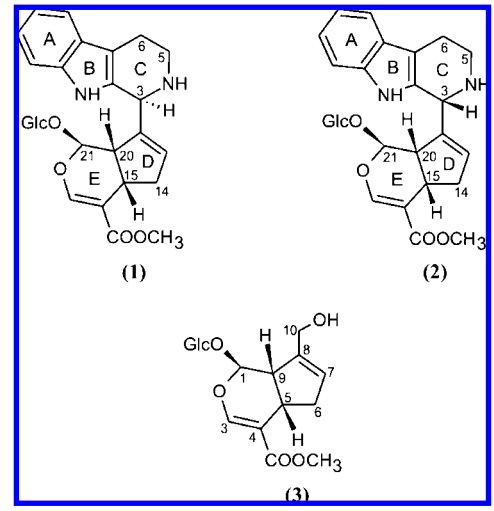
A monoterpene indole alkaloid, psychollatine (**1**), was isolated from *Psychotria umbellata* leaves. Its structure was characterized by interpretation of spectroscopic data and by comparison of its NMR data with those of croceaine A (**2**) from *Palicourea crocea*. The configuration of psychollatine (**1**) was established by NOE difference and circular dichroism (CD) techniques, while its conformation was evaluated through molecular modeling studies and NMR coupling constants.

*Psychotria* L. (Rubiaceae) is one of the largest genera of flowering plants, presenting between 1000 to 1650 species with a complex taxonomy. It is closely related to some species of the *Palicourea* genus, and molecular phylogenetic analysis suggested the fusion of *Palicourea* and *Psychotria* subg. *Heteropsychotria* in a proposed new genus.[1] This new classification profile is further supported by the presence of glucosidic monoterpene indole alkaloids in species belonging to the subgenus *Heteropsychotria* (*Psychotria dichroa* and *P. correae*) and in species of *Palicourea* (*Palicourea alpina*, *P. markgravii*, and *P. adusta*).[2,3]

The biogenetic and taxonomic importance of monoterpene indole alkaloids, as well as the several biological activities described for these compounds and for *Psychotria* species,[4] led us to initiate a phytochemical characterization of *Psychotria umbellata* Vell., also referred to as *Palicourea brachypoda* (Muell. Arg.) L. B. Smith & Downs[3] and as *Psychotria brachypoda* (Muell. Arg.) Britton.[5] *P. umbellata* is a shrub growing in the tropical and subtropical forests of Brazil, from the southeast (Minas Gerais) to the southernmost state (Rio Grande do Sul).[2,3] In a preliminary analysis, an ethanolic extract of *P. umbellata* leaves was active in a dose-dependent way and reversed by naloxone in the tail-flick test of analgesia, and this effect is associated with indole alkaloids.[6]

As part of our research on Rubiaceae alkaloids, we now report the isolation and the structural elucidation of a new glucosidic monoterpene indole alkaloid presenting a $\beta$-D-glucopyranosyl unit (**1**), isolated from *Psychotria umbellata* leaves, as well as a conformational analysis of **1** and croceaine A (**2**), a related compound from *Palicourea crocea*.[7]

Psychollatine (**1**), $[\alpha]^{20}_{D}$ −24 (*c* 0.6, MeOH), a glucosidic monoterpene indole alkaloid, was isolated from *P. umbellata* leaves as an amorphous, colorless powder. The UV spectrum exhibited maxima at 226 and 280 nm, indicating the presence of an indole chromophore. The molecular formula $C_{27}H_{32}O_9N_2$ was established from the molecular ion at *m/z* $[M + H]^+$ 529.2150 in the HRCIMS, in combination with the $^{13}C$ NMR data. The proton-bearing carbons were assigned from the HMQC spectrum. The $^{13}C$ and the $^1H$ NMR data of **1** presented similar features when compared to the data of croceaine A (**2**),[7] a related alkaloid from *Palicourea crocea*. The




NMR data of compounds **1** and **2** showed the absence of an exocyclic vinyl group, a characteristic of glucosidic monoterpene indole alkaloids containing a secologanin unit.[8] The $^{13}C$ NMR spectrum confirmed the presence of a tetrahydro-$\beta$-carboline system in **1**. The presence of a quaternary carbon ($\delta$ 140.0) and a methine $sp^2$ carbon ($\delta$ 138.5) suggest a modified monoterpenoid unit for **1**. The presence of a glucose moiety was indicated by the $^1H$ and $^{13}C$ NMR data, and the signal for the anomeric proton at $\delta$ 4.83 (d, $J$ = 7.9 Hz, H-1′) suggests a $\beta$-configuration for the glucose unit. Moreover, the presence of a $\beta$-D-glucose unit was confirmed by enzymatic hydrolysis.[9]

The 2D NMR spectra, $^1H-^1H$ COSY and HMQC, of psychollatine (**1**) and croceaine A (**2**) are in agreement with the presence of a tetrahydrocyclopenta[*c*]pyran ring attached at C-3 of the tetrahydro-$\beta$-carboline system. Comparison of the $^1H$ ($CD_3OD$, 300 MHz) and $^{13}C$ NMR ($CD_3OD$, 75 MHz) data of **1** and **2** with the data of geniposide (**3**) showed that the observed shifts for the iridoid moiety of **1** and **2** are closely related to those of geniposide iridoid (**3**) in $CD_3OD$ (500 and 125 MHz for $^1H$ and $^{13}C$ NMR, respectively),[10] indicating that the iridoid unit of **1** and **2** is probably a geniposide-like structure.

In spite of the apparent similarity, structural differences could be established between **1** and **2** based on NOESY and NOE data, suggesting that these compounds differ in relation to their stereochemistry. For compound **2**, the association of a cross-peak between H-21 and H-20 ($^3J_{20,21}$ = 9.0 Hz) in the NOESY spectrum indicates the presence of an iridoid derivative of the 1-*epi* series and hence the coplanarity of these hydrogens.[7] In contrast, compound **1** shows

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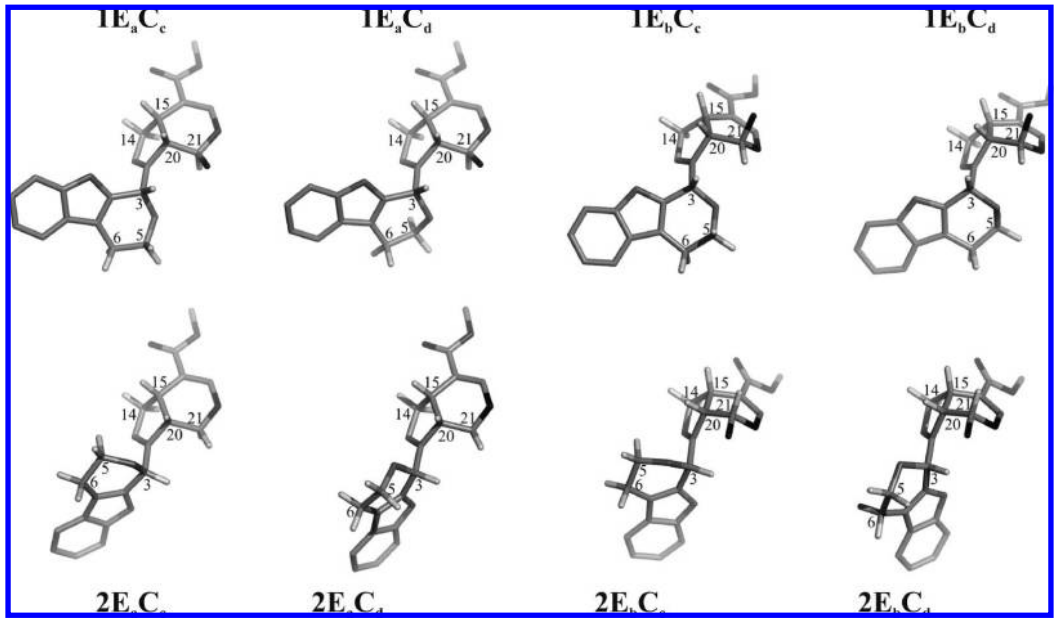


**Figure 1.** Structures of the conformations obtained by RM1 for psychollatine (**1**) and for croceaine A (**2**). [7] With the exception of the hydrogen atoms attached to C-3, C-5, C-6, C-14, C-15, C-20, and C-21 the nonpolar hydrogen atoms were omitted in order to clarify the image. The sugar moiety was also omitted in all conformers.

**Table 1.** Experimental and Theoretical $J_{H,H}$ Values for Alkaloids Psychollatine (**1**) and croceaine A (**2**)[7]

| | **1** | | | | **2** | | | |
|---|---|---|---|---|---|---|---|---|
| | | | theoretical $J_{H,H}$ (Hz)[a] | | | | theoretical $J_{H,H}$ (Hz)[a] | |
| position | $\delta_H$ (mult.) | $J_{H,H}$(Hz) | **1E$_a$C$_c$** | **1E$_a$C$_d$** | $\delta_H$ (mult.) | $J_{H,H}$(Hz) | **2E$_a$C$_c$** | **2E$_a$C$_d$** |
| 5α | 3.46 (dd) | 5.2, 8.3 | 5.5 | 4.6 | 3.08–3.14 (m) | | 6.5 | 4.5 |
| 5*β* | 3.63 (dd) | 5.5, 6.3 | 4.7 | 5.9 | 3.08–3.14 (m) | | 4.9 | 4.4 |
| 14α | 2.18 (bdd) | 16.9, 9.6 | 8.5 | 8.5 | 2.14 (ddd) | 15.9, 9.3, 1.0 | 9.1 | 9.3 |
| 14*β* | 2.97 (ddd) | 16.9, 8.5, 3.0 | 8.7 | 8.7 | 2.92 (ddd) | 15.9, 8.0, 2.7 | 8.3 | 8.2 |
| 20 | 2.90 (dd) | 9.0, 8.2 | 7.7, 8.0 | 7.6, 8.1 | 2.82 (m) | | 3.7, 7.6 | 3.4, 7.4 |
| 21 | 5.13 (d) | 9.0 | 7.7 | 7.6 | 5.16 (d) | 9.0 | 3.7 | 3.4 |

[a] Values for the H−C−C−H dihedral angle, in degrees, obtained from the RM1 minimized conformation.

no correlation between H-20 and H-21 in the NOE difference spectrum, suggesting a dihedral angle near 180°. Such data indicate that in psychollatine (**1**) the iridoid moiety retains the C-21 configuration of geniposide. Additionally, the different shifts observed for H-3 of compounds **1** and **2** in the $^1$H NMR spectrum suggest that these two alkaloids present distinct configurations at C-3. In an attempt to elucidate the configuration of C-3, circular dichroism (CD) measurements were carried out with psychollatine (**1**) and compared with data published for croceaine A (**2**).[7] The CD curve for **1** showed a positive Cotton effect between 270 and 300 nm, which suggests a tetrahydro-*β*-carboline alkaloid with *S*-configuration at C-3 (H-3α).[11,12] Unlike psychollatine (**1**), croceaine A (**2**) displayed a negative Cotton effect in the same wavelength range (270–300 nm), indicating its 3*R*-configuration.[7] Achenbach and Benirschke (1997)[11] suggested that Cotton effects in the 270–300 nm range could indicate the configuration at C-3. The experiments carried out by these authors indicated that glucosidic monoterpene indole alkaloids possessing an *S*-configuration at C-3 (H-3α) displayed positive Cotton effects in the 270–300 nm region.

In order to elucidate the results obtained by NMR and CD techniques, compounds **1** and **2** were subjected to conformational analysis using RM1 semiempirical methods and *ab initio* calculations based on previously described methodology.[13,14]

From the conformational analysis by RM1, four minimum energy conformations were evaluated for psychollatine (**1**) and four for croceaine A (**2**), i.e., two half-chairs due to the inversion of the dihydropyran ring (ring E) of the iridoid moiety (defined as conformers E$_a$ and E$_b$) and two half-chairs of ring C (defined as conformers C$_c$ and C$_d$). These conformations were obtained through analysis of the endocyclic dihedral angles, validated using vicinal proton coupling constants. Both endocyclic and exocyclic dihedral angles were allowed to freely search closest minimum energy conformations. Thus, four possible conformations for each alkaloid were identified: **1E$_a$C$_c$**, **1E$_a$C$_d$**, **1E$_b$C$_c$**, and **1E$_b$C$_d$** for psychollatine (**1**) and **2E$_a$C$_c$**, **2E$_a$C$_d$**, **2E$_b$C$_c$**, and **2E$_b$C$_d$** for croceaine A (**2**) (Figure 1). Additionally, the conformers obtained by RM1 were also submitted to *ab initio* calculations at the 6-31G** basis set.

In a subsequent step, the Haasnoot−Altona parametrization of the Karplus equation[15] was employed to calculate the theoretical $J_{H,H}$ values between vicinal protons for each of the obtained conformations, and these results were compared with the experimental data. The theoretical coupling constants calculated by RM1 for compounds **1** (conformers **1E$_a$C$_c$** and **1E$_a$C$_d$**) and **2** (conformers **2E$_a$C$_c$** and **2E$_a$C$_d$**) are presented in Table 1. No substantive difference was observed between the coupling constants calculated for the conformations obtained by RM1 or *ab initio* methods (data not shown), in agreement with previous results pointing to the potential of using newer semiempirical methods, such as PM5 and RM1, when compared to methods such as AM1 and even *ab initio* calculations.[13,14] The theoretical coupling constants calculated for the conformations **1E$_a$C$_c$** and **1E$_a$C$_d$** of psychollatine (**1**) showed good agreement with the experimental data (Table 1). However, for the conformers **1E$_b$C$_c$** and **1E$_b$C$_d$**, a significant difference between theoretical and experimental data was observed for $^3J_{20,21}$ (data not shown), suggesting that in the experimental conditions conformer **E$_a$** of the dihydropyran ring could be predominant. For the C ring, the theoretical $J_{H,H}$ values correlate with experimental

data for all conformers **1E$_a$C$_c$**, **1E$_a$C$_d$**, **2E$_a$C$_c$**, and **2E$_a$C$_d$** (Table 1) and **1E$_b$C$_c$**, **1E$_b$C$_d$**, **2E$_b$C$_c$**, and **2E$_b$C$_d$** (data not shown).

For croceaine A (**2**) the theoretical $^3J_{20,21}$ values showed an important difference when compared with the experimental value (Table 1). This difference was observed for all conformers **2E$_a$C$_c$**, **2E$_a$C$_d$**, **2E$_b$C$_c$**, and **2E$_b$C$_d$**. A detailed analysis of the 1D and 2D NMR data together with the conformational study suggests a dihedral angle near 180° between H-20 and H-21, indicating that the iridoid moiety of **2** retains the configuration of geniposide, as does psychollatine (**1**).

In an attempt to clarify the results obtained through comparison of coupling constants, we also evaluated the relevant distances between the interacting hydrogens and used these theoretical results as an auxiliary tool for interpretation of the NOE difference and NOESY data. In all conformers, the distances between hydrogen atoms (H-14α and H-15, H-14$\beta$ and H-15, H-15 and H-20, H-20 and H-21) were smaller than 4 Å, i.e., in agreement with the NOE difference and NOESY correlations observed for psychollatine (**1**) and croceaine A (**2**),[7] respectively.

The theoretical coupling constants and distances between interacting hydrogens calculated for **1** support an initial hypothesis that psychollatine (**1**) is a C-21$\beta$ glucosidic monoterpene indole alkaloid. Moreover, the conformational analysis together with the evaluation of theoretical coupling constants and the distances between interacting hydrogens reinforce the hypothesis of a dihedral angle near 180° between H-20 and H-21 in croceaine A (**2**). The combined results of spectroscopic and molecular modeling data suggest that both alkaloids **1** and **2** are formed by the combination of a geniposide derivative and tryptamine. In agreement with such an assumption, a recent paper noted the limitations in the use of 2D NMR techniques, such as NOE and NOESY, for the structural elucidation of some glucosidic iridoids.[16] This study suggests that this analysis could lead to mistakes in the configurational assignments for this class of compounds. In order to circumvent this limitation, the employment of other techniques, such as molecular modeling, X-ray crystallography, and/or CD spectroscopy, is recommended.[16]

In a subsequent pharmacological investigation, psychollatine (**1**) showed some important biological activities, including mild analgesic effects against a number of algogenic stimuli[17] and anxiolytic, antidepressive, and amnesic effects in mice models. These data indicate that this compound is able to modulate different neurotransmitter systems, including NMDA, opioid, and 5-HT$_{2A/C}$ receptors.[18] Further psychopharmacological studies investigated the role of NMDA and dopamine receptors in psychollatine's mode of action. These investigations supported the involvement of NMDA glutamate receptors in psychollatine's mode of action.[19]

The presence of psychollatine (**1**) in *P. umbellata* and the isolation of the alkaloids *N*,$\beta$-D-glucopyranosyl vincosamide from *Psychotria leiocarpa*,[20] brachycerine from *P. brachyceras*,[21,22] lyaloside, strictosamide, and naucletine from *P. suterella,*[23] and strictosidinic acid and myrianthosine from *P. myriantha*[9] together with a study by HPLC/PDA performed on 15 Brazilian *Psychotria* species, subgenus *Heteropsychotria*,[2] suggests that neotropical *Psychotria* are characterized by the presence of glucosidic indole monoterpene alkaloids. These metabolites are frequently found in Rubiaceae, particularly in neotropical species of the genus *Psychotria* and in *Palicourea*, which is an exclusively neotropical genus.[8,21]

The fact that *Palicourea crocea*, *Psychotria umbellata*, and *Psychotria brachyceras* accumulate the related alkaloids croceaine A,[7] (**2**), psychollatine (**1**), and brachycerine,[21] respectively, may be an indication of taxonomic affinity between American *Psychotria* and *Palicourea* species, in line with the evidence from both morphological and chemical analysis of *Palicourea* and *Psychotria* (subgenus *Heteropsychotria*) species.[1,2]

## Experimental Section

**General Experimental Procedures.** Optical rotations and UV spectra were obtained in MeOH, using a Perkin-Elmer 241 polarimeter and a Cintra 5 spectrophotometer, respectively. The CD spectrum was obtained on a JASCO J-720 spectropolarimeter with an RD-306 coupled unit. The $^1$H NMR and $^{13}$C NMR spectra were recorded in $CD_3OD$ on a Bruker AMX-300 spectrometer. $^1$H NMR spectra were obtained using residual MeOH as internal standard. 2D experiments (COSY, HMQC, and NOESY) and NOE difference were carried out using standard microprograms, with NOE difference experiments performed in both $CD_3OD$ and DMSO-$d_6$. Mass spectra were recorded using a Finnigan MAT TQS-70 double quadruple spectometer with an electrospray ionization interface. The purity of the compound was checked by Si gel 60 $F_{254}$ TLC eluted with $CHCl_3$−MeOH/$NH_3$ vapor (85:15; $R_f$ = 0.2) and by HPLC. Analyses by HPLC were carried out on a 2690 Waters Alliance analytical chromatograph with a Nova Pak C18 column (150 mm × 3.9 mm; Waters). The mobile phase consisted of a linear gradient (MeOH/$H_2O$, 50: 50, v/v), and the detector employed was a photo diode array (PDA, Waters).

**Plant Material.** Fresh leaves of *Psychotria umbellata* were collected from the native forest of Morretes (Parana State, Brazil) in February 1995. The species was identified by Gerdt Hatschbach from the Municipal Botanic Museum, Curitiba, Brazil. A voucher specimen is deposited at the herbarium of the same museum (MBM, No. 48571).

**Extraction and Isolation.** Dried leaves (100 g) were extracted three times with EtOH at room temperature during a week. The resulting extracts were combined and concentrated under vacuum at 40 °C to produce a dark green syrup. The ethanolic extract was dissolved in 2% HCl (0.5 L) and exhaustively extracted with $CH_2Cl_2$. The acidic solution was adjusted to pH 10 with 25% $NH_4OH$ and extracted with $CH_2Cl_2$ until the Mayer reaction for alkaloids was negative. During the $CH_2Cl_2$ extract concentration procedure, a colorless, amorphous alkaloid (954 mg) precipitated. Psychollatine (**1**) was obtained as an amorphous powder: $[\alpha]^{20}_D$ –24 (*c* 0.6, MeOH); UV $\lambda_{max}$ nm 226, 280; IR (KBr) cm$^{-1}$ 3325, 1705, 1635, 1450; $^1$H NMR ($CD_3OD$, 300 MHz) $\delta$ 7.58 (1H, d, $J$ = 1.0 Hz, H-17), 7.50 (1H, d, $J$ = 7.7 Hz, H-12), 7.32 (1H, d, $J$ = 8.0 Hz, H-9), 7.10 (1H, ddd, $J$ = 1.1, 7.1, 7.5 Hz, H-11), 7.01 (1H, ddd, $J$ = 1.0, 7.3, 7.9 Hz, H-10), 6.04 (1H, bs, H-18), 5.25 (1H, bs, H-3), 5.13 (1H, d, $J$ = 9.0 Hz, H-21), 4.83 (1H, d, $J$ = 7.9 Hz, H-1′), 3.84 (1H, dd, $J$ = 12.0, 2.3 Hz, H-6′$\beta$), 3.72 (3H, s, COOC*H*$_3$), 3.68 (1H, m, H-6′α), 3.63 (1H, dd, $J$ = 5.5, 6.3 Hz, H-5$\beta$), 3.46 (1H, dd $J$ = 5.2, 8.3 Hz, H-5α), 3.38 (1H, m, H-15), 3.37 (1H, m, H-3′), 3.34 (1H, m, H-5′), 3.18 (1H, m, H-4′), 3.17 (1H, m H-2′), 3.04 (1H, m, H-6$\beta$), 3.02 (1H, m, H-6α), 2.97 (1H, ddd, $J$ = 16.9, 8.5, 3.0 Hz, H-14$\beta$), 2.90 (1H, dd, $J$ = 9.0, 8.2 Hz, H-20), 2.18 (1H, ddd, $J$ = 16.9, 9.6 Hz, H-14$\beta$); $^{13}$C NMR ($CD_3OD$, 75 MHz) $\delta$ 169.1 (C, C-22), 153.4 (CH, C-17), 140.0 (C, C-19), 138.5 (CH, C-18), 138.1 (C, C-13), 131.1 (C, C-2), 127.6 (C, C-8), 123.6 (CH, C-11), 120.3 (CH, C-10), 119.0 (CH, C-9), 112.3 (CH, C-12), 112.2 (C, C-16), 107.9 (C, C-7), 101.5 (CH, C-1′), 99.4 (CH, C-21), 78.6 (CH, C-3′), 77.6 (CH, C-5′), 74.6 (CH, C-4′), 71.0 (CH, C-2′), 61.8 ($CH_2$, C-6′), 53.7 (C, C-3), 51.9 ($CH_3$, C-23), 49.0 (CH, C-20), 42.1 ($CH_2$, C-5), 40.5 ($CH_2$, C-14), 37.5 (CH, C-15), 20.5 ($CH_2$, C-6); CD (*c* 3.89 × 10$^{-4}$ M, MeOH) $\lambda_{max}$ nm ($\Delta\epsilon$) 239 (5.25), 266 (2.64), 283 (1.07), 291 (0.11), 296 (0.71); CI-MS *m*/*z* 529 [M + H]$^+$ 349, 247, 198, 180, HRCI-MS *m*/*z* 529.2150 [M + 1]$^+$.

**Enzymatic Hydrolysis.** Psychollatine (**1**) was treated with $\beta$-D-glucosidase from almonds (Sigma Chemical Co., St. Louis, MO) in 1 mL of NaOAC buffer (pH 5.0) for 3 days at 40 °C, as previously described.[9] The aglycone was extracted by partition with *n*-BuOH and submitted to HPLC/PDA analysis in order to confirm hydrolysis.

**Computational Details.** The semiempirical calculations were carried out using the RM1 Hamiltonian[23] of the MOPAC 7.0 program.[24] The MOLDEN program was employed as a graphic interface for construction and visualization of molecular structures.[25] The structures were minimized until the achievement of gradient norm values below 0.001. Hessian matrix analyses were employed to unequivocally characterize the obtained conformations as true minima on the potential energy surface. Additionally, the minimum energy conformations obtained by RM1 were further refined through *ab initio* calculations, using the GAMESS program,[26] at the HF/6-31G** level. Theoretical $J_{H,H}$ coupling constants were calculated employing the Karplus equation using the parametrization of Haasnoot and co-workers.[14]

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**Supporting Information Available:** Table S1 with theoretical $J_{H,H}$ values calculated for the iridoid moiety of psychollatine (**1**) and croceaine A (**2**) in all conformers evaluated by the present work. This table shows the data calculated for conformers obtained by semiempirical (RM1) and *ab initio* (6-31G**) calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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