Supporting information

Efficient Access to the Iboga Skeleton: Optimized Procedure to Obtain Voacangine from *Voacanga africana* Root Bark

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Electronic Supplementary Information

1. General Considerations

All solvents were distilled prior to use; chemicals and reagents were purchased from Sigma-Aldrich and used as received. Mass spectra (MS) were recorded on a HPLC MS/MS Shimadzu LCMS 8040, with LC-20AD HPLC pump, DAD SPD-M20A detector, CTO-20A oven and SIL-20A injector; the software used to process data was LabSolutions LCMS. NMR spectra were obtained in $CDCl_3$ on a Bruker Avance DPX-400 instrument. Proton chemical shifts (δ) are reported in ppm downfield from TMS as an internal reference, and carbon chemical shifts are reported in ppm relative to the center line of the $CDCl_3$ triplet (77.0 ppm). Analytical TLC was performed on silica gel 60F-254 plates and visualized with UV light (254 nm) and/or *p*-anisaldehyde in acidic ethanolic solution. Flash column chromatography was performed using silica gel (Kieselgel 60, EM reagent, 230–400 mesh). Centrifugation was performed in a Thermo Sorvall RC6 plus Centrifuge, using the conditions specified in the protocol. The extraction of 0.5 Kg was carried out in a 10 L Reactor GR-10 Greatwall equipped with a high temperature circulator Greatwall SY series. Microwave reactions were made in a CEM Discovery reactor. The voacamine/voacamidine cleavage of 1g was carried out in a Synthware round bottom pressure vessel with PTFE bushing (150 mL, O.D. × L 60 mm × 139 mm, bushing #15). Sonication was applied using a Jeio Tech ultrasonic bath (Labcompanion).

2. Extraction protocols

2.1 Acid-base extraction.

To an Erlenmeyer flask (1000 mL) containing 50 grams of dry *Voacanga africana* root bark powder was added 250 mL of 1 % HCl. The suspension was mechanically stirred for 30 min and then filtered through cellulose based NWF (Nonwoven fabric), the plant residue was recovered and another 250 mL of fresh 1 % HCl were added; this procedure was repeated 6 times. The combined acidic extracts were treated with concentrated NH_4OH under constant stirring until pH 10-11 was reached. The alkaloids precipitated forming an opaque suspension which was centrifuged at 5000 rpm during 15 min at 10 °C. The supernatant was discarded while the solid residue was dried at 60 °C overnight (12-14h). The dried brown amorphous solid was dissolved in acetone and filtered through paper to afford a clear solution. Silica gel was added and the organic solvent was removed *in vacuo*; the resulting solid was used to load a preparative chromatography column (mobile phase gradient: (9:1)→(8:2)→(6:4)→(1:1)→(3:7) (Hex:EtOAc) + 1 % NH_4OH). As a result 429 mg (0.85 %) of voacangine (**2**), 191 mg (0.38 %) of voacristina (**5**) and 1203 mg (2.41 %) of a mixture voacamine (**3**) : voacamidine (**4**) : unidentified dimer (3.5 : 1 : 0.3) were obtained. (See figure.S1)

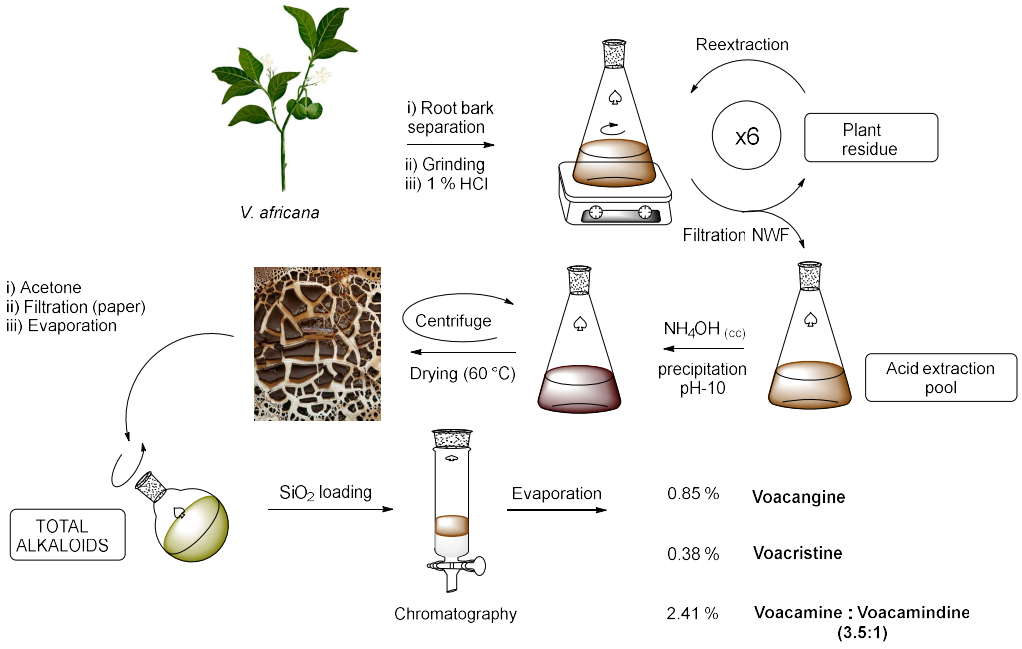
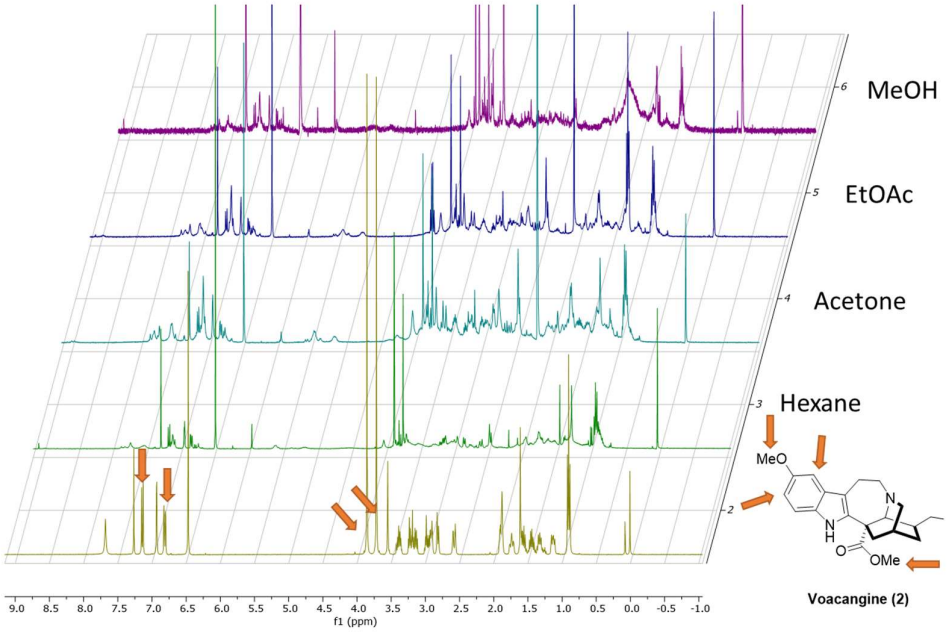


Figure S1. Process of extraction with aqueous acidic conditions.

2.2 Organic solvent screening

To a 5 mL vial containing 0.3 g of dry *Voacanga africana* root bark powder was added 30 mg (10 % w/w) of solid $NaHCO_3$ and 4 mL of the chosen solvent. The resulting suspension was stirred one hour at room temperature and then filtered through Whatman® filter paper. The process was repeated four times with the same plant material. The combined organic extracts were evaporated *in vacuo* to afford a crude extract that was dissolved in $CDCl_3$ (0.7 mL) with 5 µL of trichloroethylene (TCE) as an internal standard. The extracts were analyzed by ^{1}H-RMN; the comparison with ^{1}H spectrum of the pure compounds (voacangine (**2**) and voacamine (**3**)) allowed for the selection of characteristic and well resolved signals to quantify the alkaloids in the sample, using TCE as internal standard. Selected signals: (3.71 ppm, s), (3.84 ppm, s), (6.93 ppm, d, J = 2.3 Hz), (6.80 ppm, dd, J = 8.7, 2.4 Hz). Ethyl acetate and acetone show the best results (see Figure.S2 and Table.S1)



Selected signals: 3.84 (s, 3H), 3.70 (s, 3H), 6.93 (d, J = 2.3 Hz, 1H), 6.80 (dd, J = 8.7, 2.4 Hz, 1H)

Figure S2. Stacked ^{1}H-RMN spectrums used for the quantification of voacangine and voacamine in the full extracts. Trichloroethylene (TCE) was used as internal standard. Orange arrows indicates de selected signals for quantification, full assignment ^{1}H-RMN of voacangine (2) is shown in Figure S5.

SOLVENT	TOTAL EXTRACT	ESTIMATED VOACAMINE (3)	ESTIMATED VOACANGINE (2)	%TA
EtOAc	30 mg	18.9 mg	4.7 mg	79
Acetone	43 mg	28.6 mg	7.7 mg	84
Hexanes	14 mg	5.3 mg	3.8 mg	65
MeOH	76 mg	14.0 mg	4.5 mg	24

Table S1. Results of organic solvent screening for the extraction of *V. africana*. **% TA** (total alkaloids percentage) was calculated as the sum of estimated amounts of **2** and **3** over the weight of dry extract.

2.3 Acetone based extraction (100 g scale)

To an Erlenmeyer flask (1000 mL) containing 100 g of dry *Voacanga africana* root bark powder was added 10 g of $NaHCO_3$ and 800 mL of acetone. The suspension was sonicated at room temperature for 30 minutes and filtered through Whatman paper. The plant residue was recovered and the same procedure was repeated until no alkaloids were detected in the supernatant by TLC analysis [SiO_2, (8:2 Hex: EtOAc) + 1 % NH_4OH]. The combined organic extracts were concentrated *in vacuo* to afford a dark brown solid which accounts for 9-10 % of the initial mass of plant material. The extract was loaded on silica gel to run a preparative chromatography column. (mobile phase gradient: (95:5)→(9:1)→(8:2)→(6:4)→(1:1)→(3:7) (Hex:EtOAc) + 1 % NH_4OH). As a result, after three independent replicates of this procedure, 1.06 ± 0.17 % of voacangine **(2),** 0.46 ± 0.02 % of voacristine **(5)** and 2.92 ± 0.21 % of a mixture of dimers voacamine **(3) :** voacamidine **(4) :** unidentified dimer (1,9 : 1 : 0.5) were obtained.

2.4 Acetone based extraction (0.5 kg scale)

0.5 kg of dry *Voacanga africana* root bark powder was charged into a 10 L reactor followed by 50 g of $NaHCO_3$ and 4 L of acetone. (See Figure S4) The resulting suspension was stirred and heated at 200 rpm and 40 °C, respectively. After 45 minutes the mechanical agitation was stopped, the suspension decanted, and the supernatant was filtered through Whatman paper. The plant residue was recovered and the same procedure was repeated 5 times. The combined organic extracts were concentrated *in vacuo* to afford a dark brown solid which accounts for 9-10 % of the initial mass of plant material. The extract was loaded on silica gel to run a preparative chromatography column (mobil phase gradient: (95:5)→(9:1)→(8:2)→(6:4)→(1:1)→(3:7)→(0:1) (Hex:EtOAc) + 1 % NH_4OH). After several

chromatographic separations (See Figure S3) we obtained 0.82 % of voacangine **(2),** 0.45 % of voacristine **(5)** and 3.70 % of a mixture voacamine **(3):** voacamidine **(4) :** unidentified dimer (1.7 : 1 : 0.4). (See Figure S3)

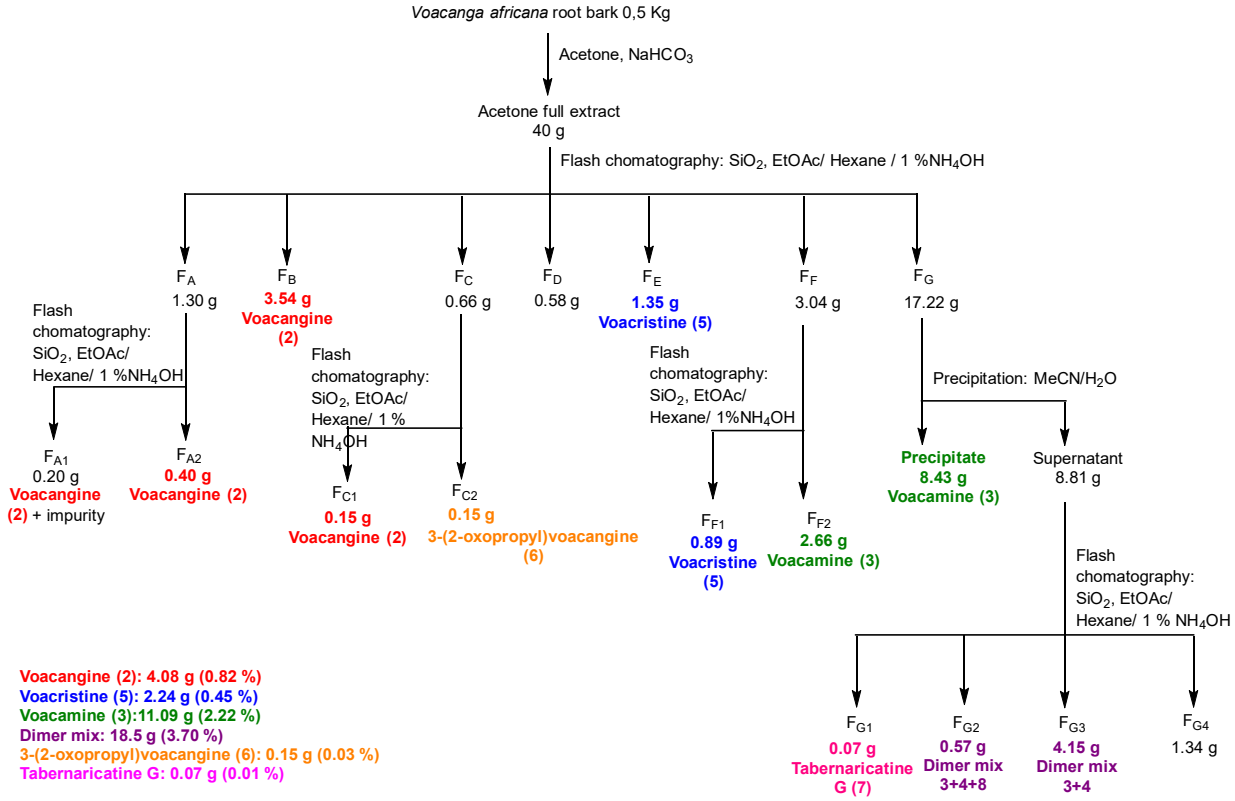


Figure S3. Isolation of alkaloids from *Voacanga africana* root bark crude.

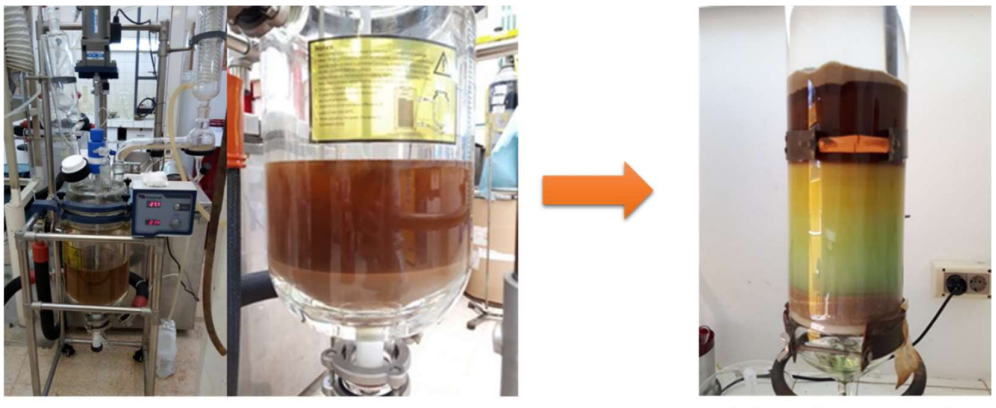


Figure S4. Acetone based extraction (0.5 kg scale). Graphical record of the process. Pictures were taken by the authors.

3 Voacamine and voacamidine cleavage protocols

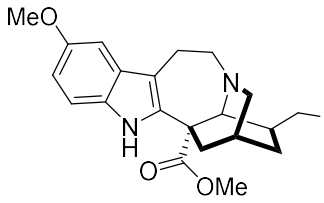
3.1 Cleavage of voacamine using microwave assisted heating (30–100 mg) (optimization of reaction conditions)

General procedure: Voacamine (**3**) (35 mg, 0.049 mmol) and 1mL HCl 3 M (or the appropriate solvent) were added to a CEM Discovery reactor's tube (6 mL). The heating program was set on the equipment [100°C, 100W, 9 min] (or the appropriate conditions); and the tube was sealed and kept with constant stirring. After the irradiation was completed, the system was allowed to reach room temperature, the solution was neutralized by addition of solid $NaHCO_3$, extracted with EtOAc (3x), and the combined organic phases dried over Na_2SO_4. The solvent was removed *in vacuo* and the resulting crude was purified by column chromatography. (mobile phase gradient: 8:2)→(6:4)→(1:1)→(3:7) (Hex:EtOAc) + 1 % NH_4OH).

3.2 Cleavage of voacamine using conventional heating (0.5 – 1.0 g)

To a 150 mL round-bottom pressure flask containing voacamine (**3**) (0.5 g, 0.709 mmol) was added triisopropylsilane (0.43 mL, 2.12 mmol) and an aqueous solution of HCl (3M, 50 mL). The suspension was heated at 110 °C for the indicated time under constant stirring. Then, the mixture was cooled to room temperature and basified by adding solid $NaHCO_3$. The resulting suspension was extracted exhaustively with EtOAc. The combined organic layers were dried using Na_2SO_4, and the solvent distilled *in vacuo* to obtain a crude reaction mixture, which was purified using column chromatography (SiO_2, Hex: EtOAc, 9:1/1 % NH_4OH) to obtain voacangine (**2**) as a pure solid in 51 % molar yield. The same protocol was used to cleave 1.0 g of voacamine (**3**) (voacangine molar yield: 49 %) and 34 mg of a voacamidine(**4**)/voacamine(**3**) (4:1) mixture (voacangine molar yield: 47 %).

4 Iboga alkaloids characterization



Voacangine (2)

Voacangine (2):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (bs, 1H), 7.13 (d, *J* = 8.7 Hz, 1H), 6.93 (d, *J* = 2.3 Hz, 1H), 6.80 (dd, *J* = 8.7, 2.4 Hz, 1H), 3.84 (s, 3H), 3.70 (s, 3H), 3.55 (s, 1H), 3.39 (ddd, *J* = 12.2, 7.2, 3.7 Hz, 1H), 3.26 – 3.08 (m, 2H), 3.03 – 2.86 (m, 2H), 2.81 (d, *J* = 8.5 Hz, 1H), 2.58 (d, *J* = 14.0 Hz, 1H), 1.93 – 1.83 (m, 2H), 1.73 (t, *J* = 11.1 Hz, 1H), 1.57 (dt, *J* = 13.2, 3.8 Hz, 1H), 1.49-1.39 (m, 1H), 1.31 (dt, *J* = 14.4, 7.3 Hz, 1H), 1.16 – 1.08 (m, 1H), 0.90 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 154.0, 137.5, 130.5, 129.2, 116.6, 111.8, 111.1, 110.1, 100.7, 57.5, 56.0, 55.1, 53.1, 52.6, 51.5, 39.1, 36.6, 32.0, 27.3, 26.8, 22.2, 11.7.

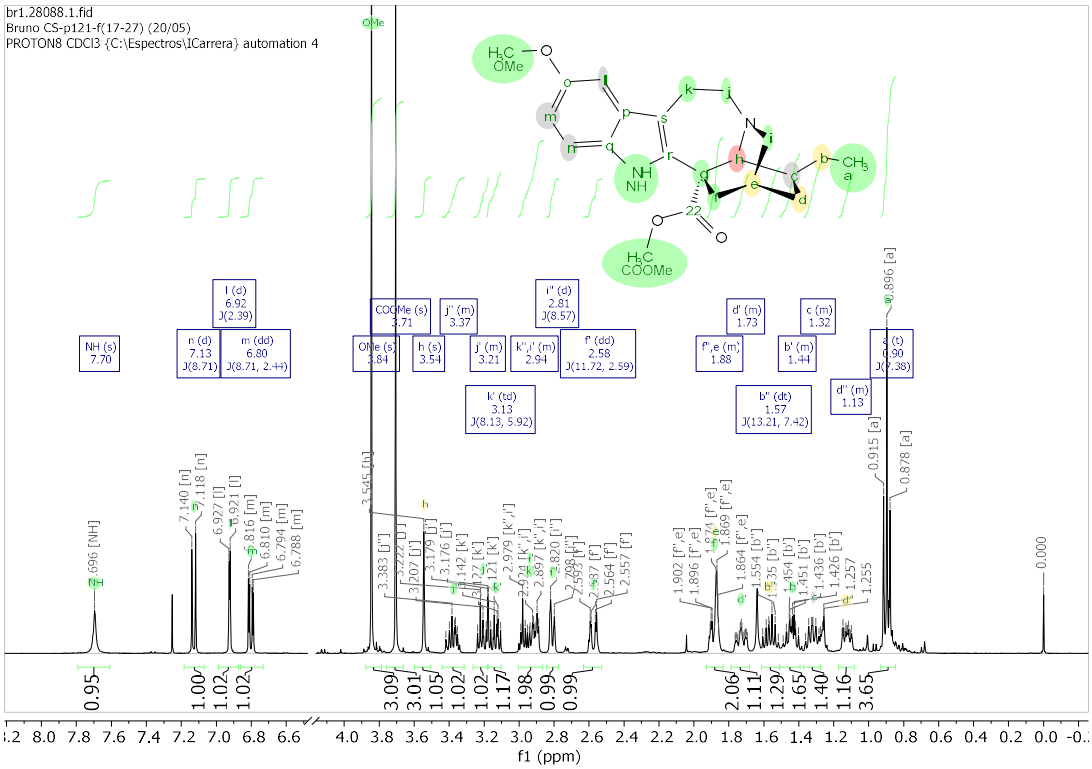


Figure S5. ^{1}H NMR of Voacangine (2) in $CDCl_3$

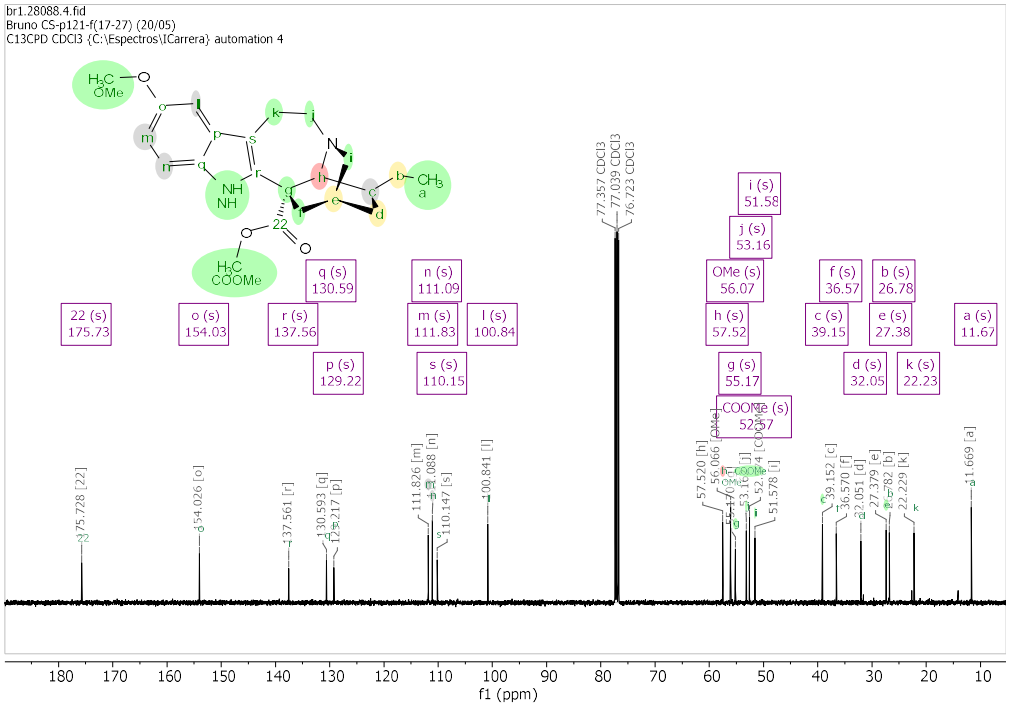


Figure S6. ^{13}C NMR of Voacangine (2) in $CDCl_3$

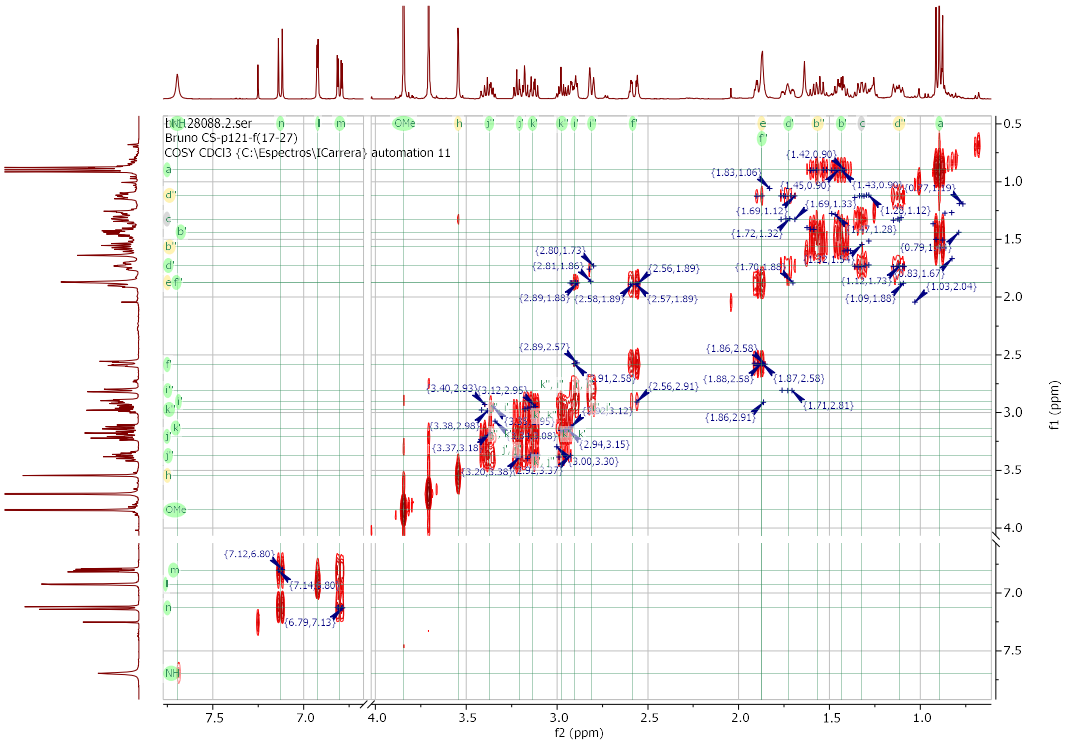


Figure S7. COSY of Voacangine (2) in $CDCl_3$

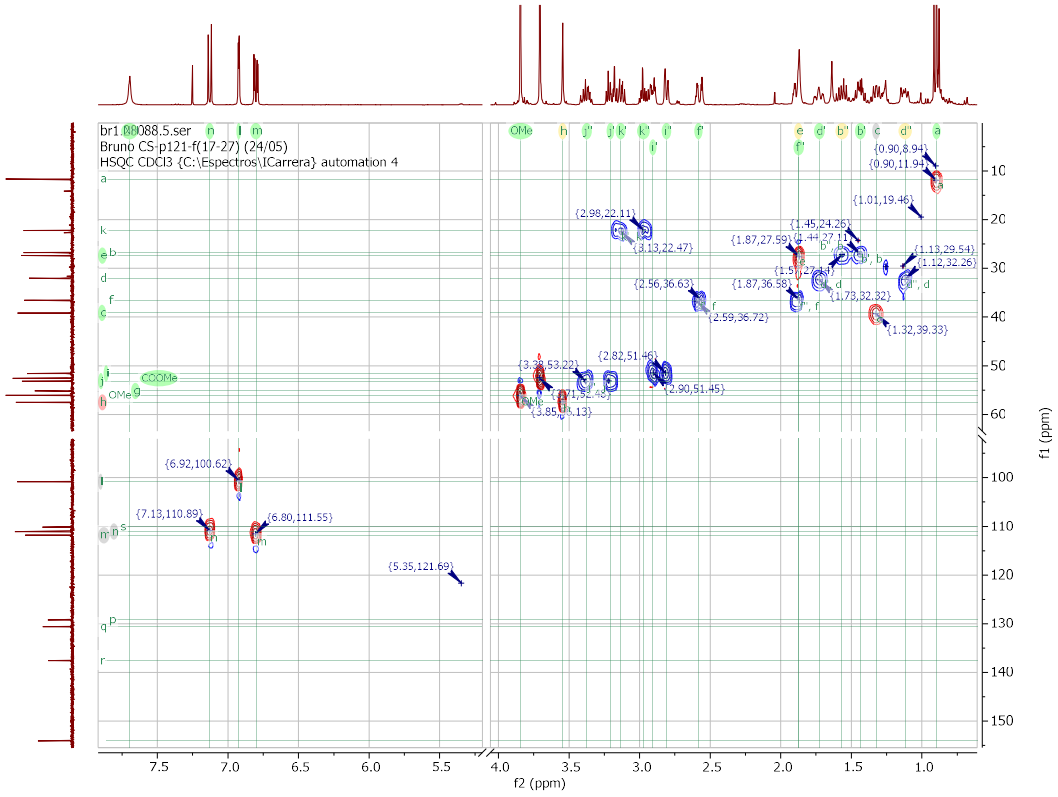
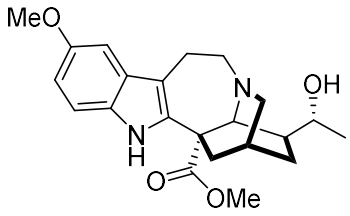


Figure S8. HSQC of Voacangine (2) in $CDCl_3$



Voacristine (5)

Voacristine (5):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (bs, 1H), 7.15 (d, *J* = 8.7 Hz, 1H), 6.91 (d, *J* = 2.4 Hz, 1H), 6.83 (dd, *J* = 8.7, 2.4 Hz, 1H), 4.16 (q, *J* = 6.2 Hz, 1H), 3.85 (s, 4H), 3.73 (s, 3H), 3.49 – 3.40 (m, 1H), 3.19 – 3.08 (m, 2H), 3.08 – 3.02 (m, 1H), 2.99 (dt, *J* = 9.0, 3.1 Hz, 1H), 2.81 (d, *J* = 9.1 Hz, 1H), 2.60 (dt, *J* = 13.3, 1.8 Hz, 1H), 2.05 (s, 1H), 2.02 (bs, 1H), 1.97 (dt, *J* = 13.5, 3.4 Hz, 1H), 1.92 – 1.86 (m, 1H), 1.55 (tdd, *J* = 12.5, 3.8, 1.7 Hz, 1H), 1.49 – 1.41 (m, 1H), 1.10 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 154.1, 136.6, 130.6, 128.9, 112.2, 111.3, 109.6, 100.6, 71.4, 59.9, 56.0, 54.1, 53.0, 52.2, 51.1, 39.5, 37.0, 26.7, 22.9, 21.6, 20.4.

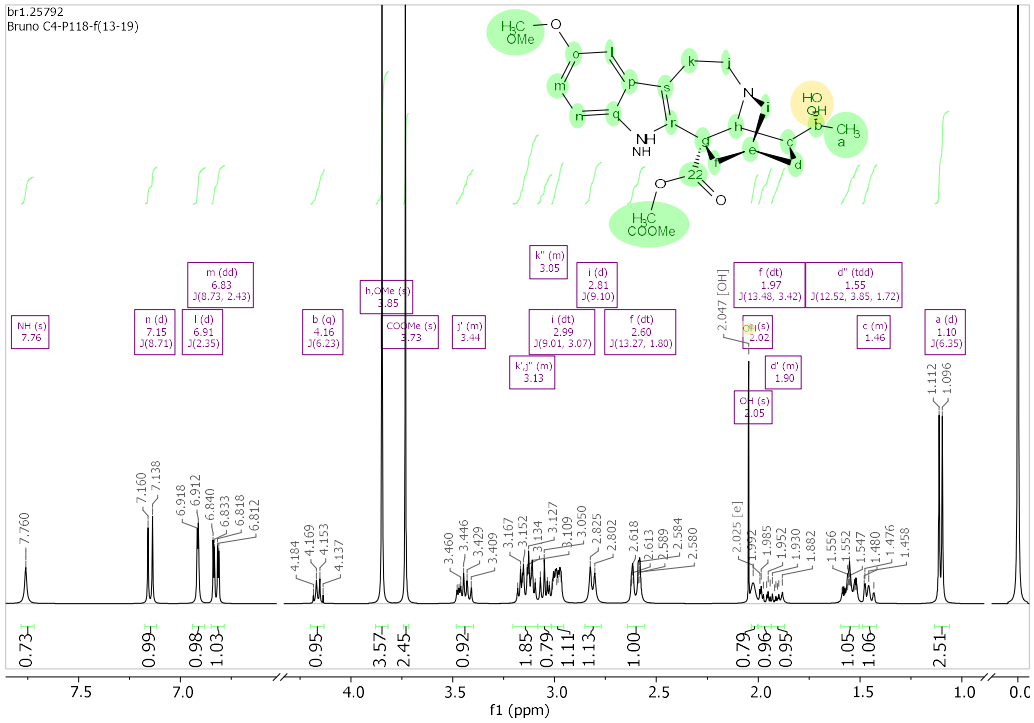


Figure S9. ^{1}H NMR of Voacristine (5) in $CDCl_3$

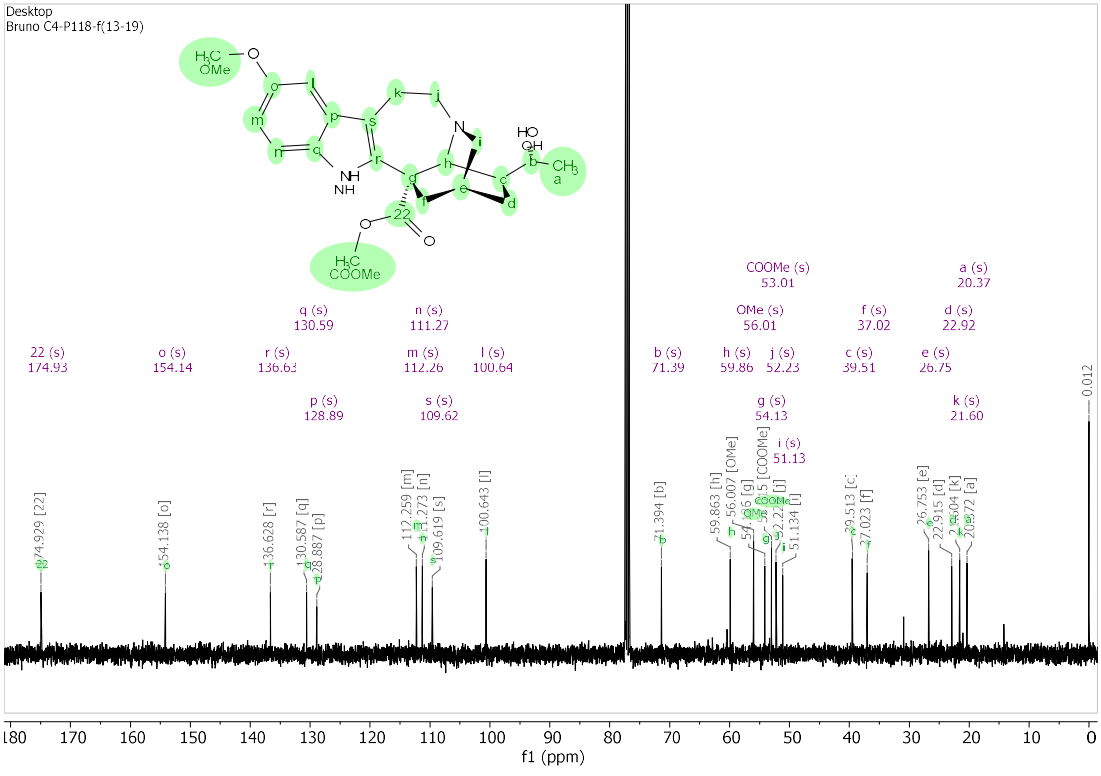


Figure S10. ^{13}C NMR of Voacristine (5) in $CDCl_3$

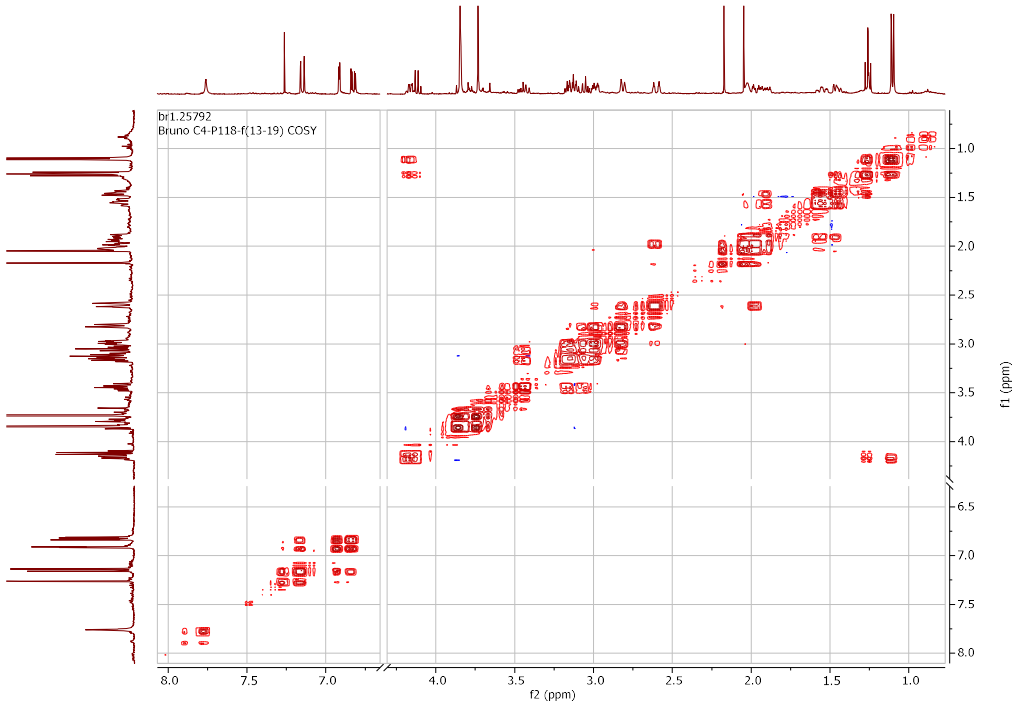


Figure S11. COSY of Voacristine (5) in $CDCl_3$

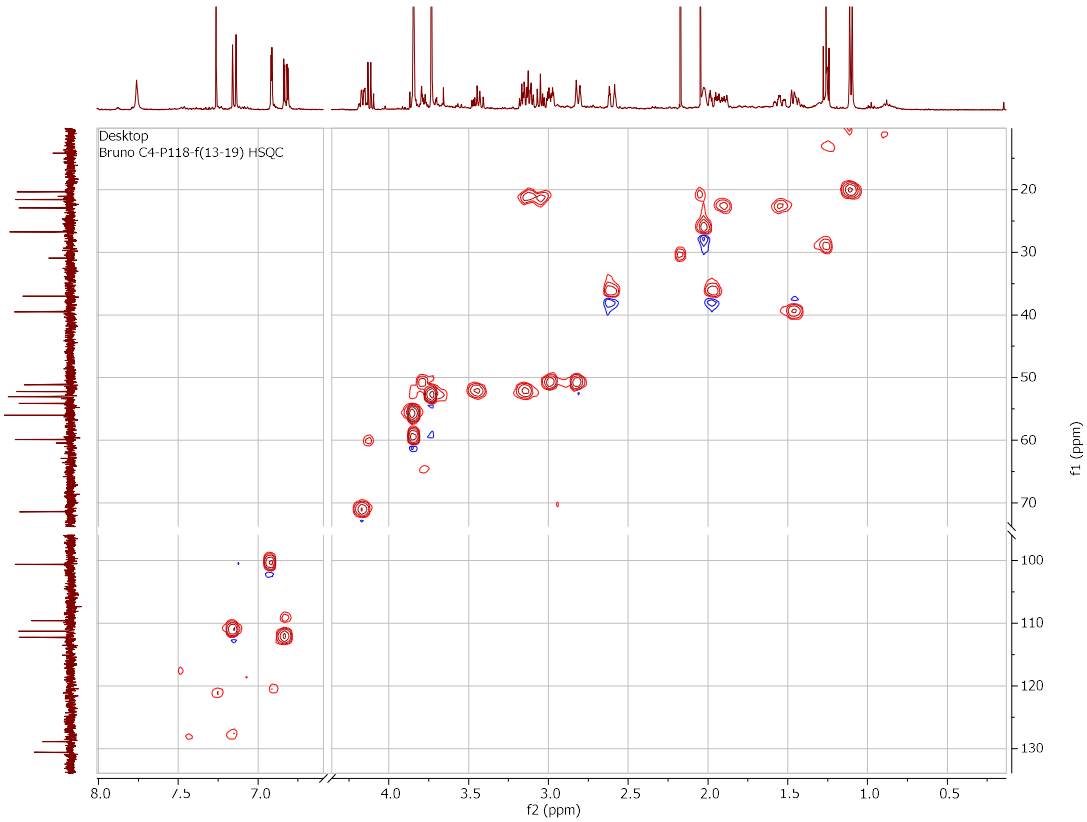
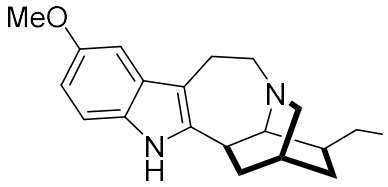


Figure S12. HSQC of Voacristine (5) in $CDCl_3$



ibogaine (1)

Hydrolysis and decarboxylation of voacangine (2). In a two-neck round bottom flask, voacangine (**2**) (0.547 g, 1.486 mmol) followed by (EtOH:H_2O) (3:2) (37 mL, 0.04 M) and KOH (0.832 g, 14.86 mmol, 10 eq) were added. The solution was bubbled with argon for 15 minutes at room temperature and then heated at reflux temperature over 12-15 h. Consumption of starting material was verified by TLC (8:2 , Hex:EtOAc + 1% NH_4OH). The solution was allowed to cool down to room temperature, and the ethanol was removed *in vacuo*. Then 5 N HCl (11.3 mL, 56.47 mmol, 37 eq) was added, and the solution was refluxed for 15 minutes. The solution was allowed to cool down to room temperature and was neutralized by adding solid $NaHCO_3$. The aqueous phase was extracted with EtOAc (4x), and the combined organic layers were dried over Na_2SO_4, then the solvent was removed *in vacuo* and the resulting crude purified by column chromatography (8:2, Hex:EtOAc + 1% NH_4OH)**.** Ibogaine free base (**1**) was obtained as a withe solid (414 mg, 90% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (bs, 1H), 7.14 (d, *J* = 8.7 Hz, 1H), 6.93 (d, *J* = 2.5 Hz, 1H), 6.76 (dd, *J* = 8.7, 2.5 Hz, 1H), 3.85 (s, 3H), 3.42 – 3.27 (m, 2H), 3.15 (d, *J* = 13.5 Hz, 1H), 3.07 (dt, *J* = 9.2, 2.4 Hz, 1H), 2.97 (d, *J* = 9.4 Hz, 1H), 2.90 (dd, *J* = 11.6, 3.7 Hz, 1H), 2.85 (s, 1H), 2.60 (d, *J* = 17.1 Hz, 1H), 2.10 – 1.98 (m, 1H), 1.84 (s, 1H), 1.79 (d, *J* = 11.2 Hz, 1H), 1.65 (ddd, *J* = 13.3, 6.7, 3.3 Hz, 1H), 1.55 – 1.41 (m, 3H), 1.22 – 1.16 (m, 1H), 0.89 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 142.8, 130.1, 129.7, 110.8, 110.7, 109.1, 100.4, 57.5, 56.0, 54.2, 50.0, 41.9, 41.6, 34.2, 32.1, 27.8, 26.5, 20.7, 11.9.

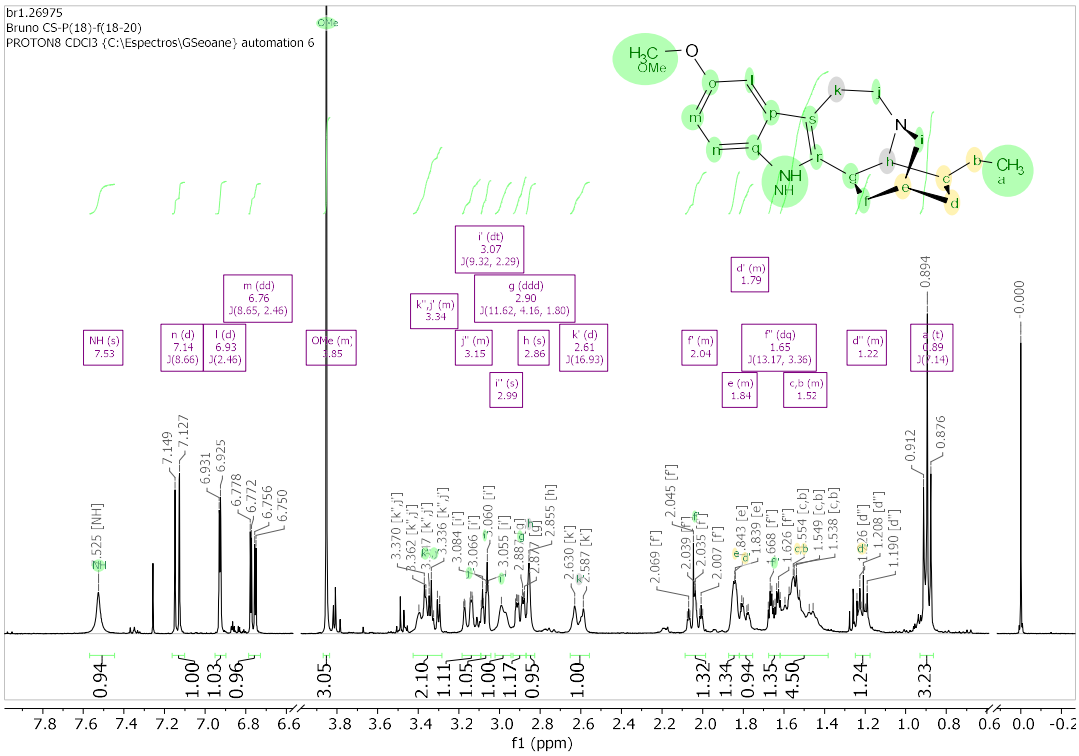


Figure S13. ^{1}H NMR of Ibogaine (1) in $CDCl_3$

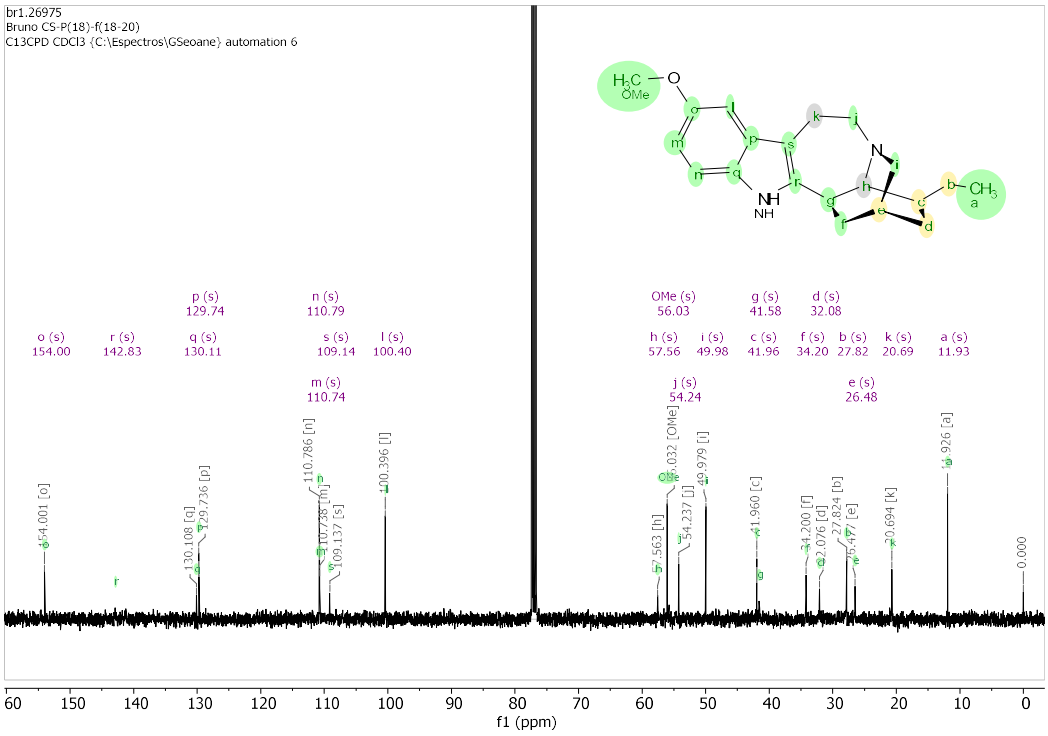


Figure S14. ^{13}C NMR of Ibogaine (1) in $CDCl_3$

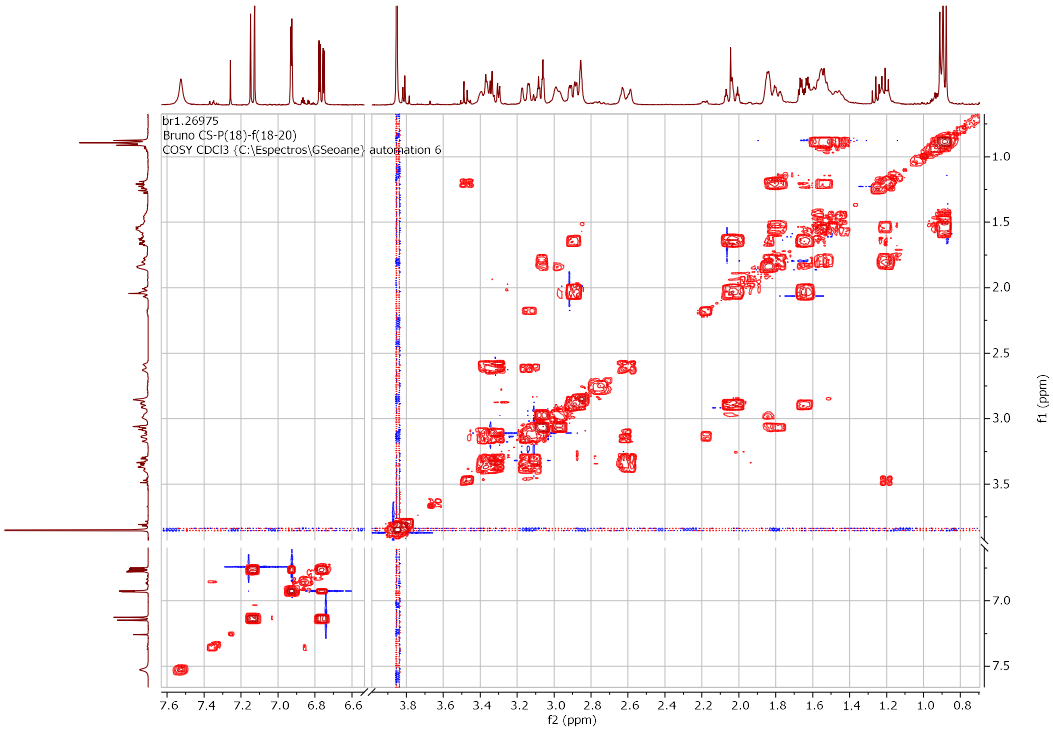


Figure S15. COSY of Ibogaine (1) in $CDCl_3$

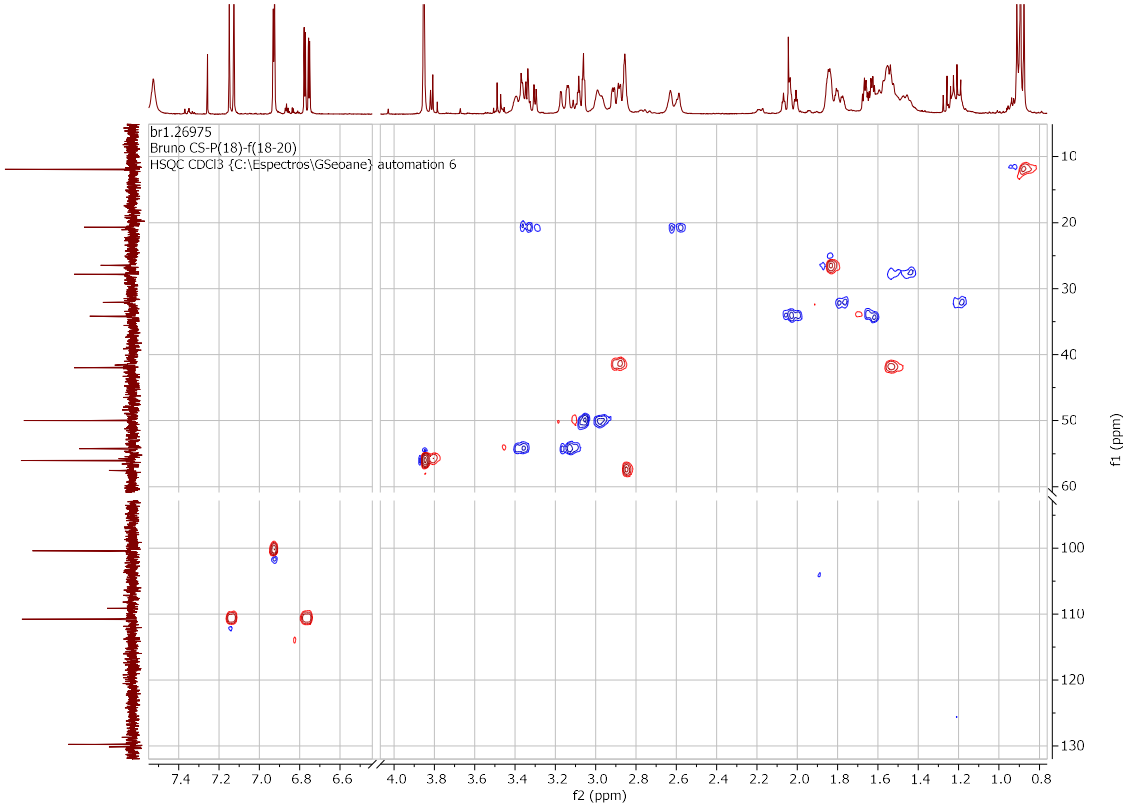
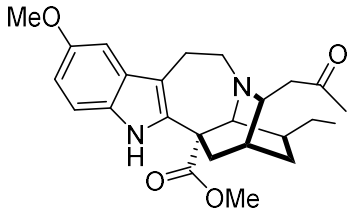


Figure S16. HSQC of Ibogaine (1) in $CDCl_3$



3-(2-oxopropyl)voacangine (6)

3-(2-oxopropyl)voacangine (6):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.13 (d, *J* = 8.7 Hz, 1H), 6.91 (d, *J* = 2.5 Hz, 1H), 6.80 (dd, *J* = 8.7, 2.4 Hz, 1H), 3.84 (s, 3H), 3.69 (s, 3H), 3.57 (s, 1H), 3.34 (dd, *J* = 8.6, 4.4 Hz, 1H), 3.31 – 3.17 (m, 2H), 3.17 – 3.10 (m, 1H), 2.98 – 2.91 (m, 1H), 2.70 (dd, *J* = 16.4, 3.7 Hz, 1H), 2.65 (dd, *J* = 13.6, 1.8 Hz, 1H), 2.51 (dd, *J* = 16.2, 8.5 Hz, 1H), 2.11 (s, 3H), 1.96 (ddd, *J* = 13.5, 4.0, 2.2 Hz, 1H), 1.69 (bs, 1H), 1.65 – 1.51 (m, 1H), 1.49 – 1.37 (m, 1H), 1.35 – 1.19 (m, 2H), 0.89 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 208.8, 175.6, 154.0, 137.5, 130.7, 129.1, 111.9, 111.2, 109.9, 100.8, 58.3, 56.0, 55.2, 54.9, 52.7, 51.5, 46.7, 38.5, 37.7, 31.0, 30.8, 27.0, 26.8, 22.2, 11.7.

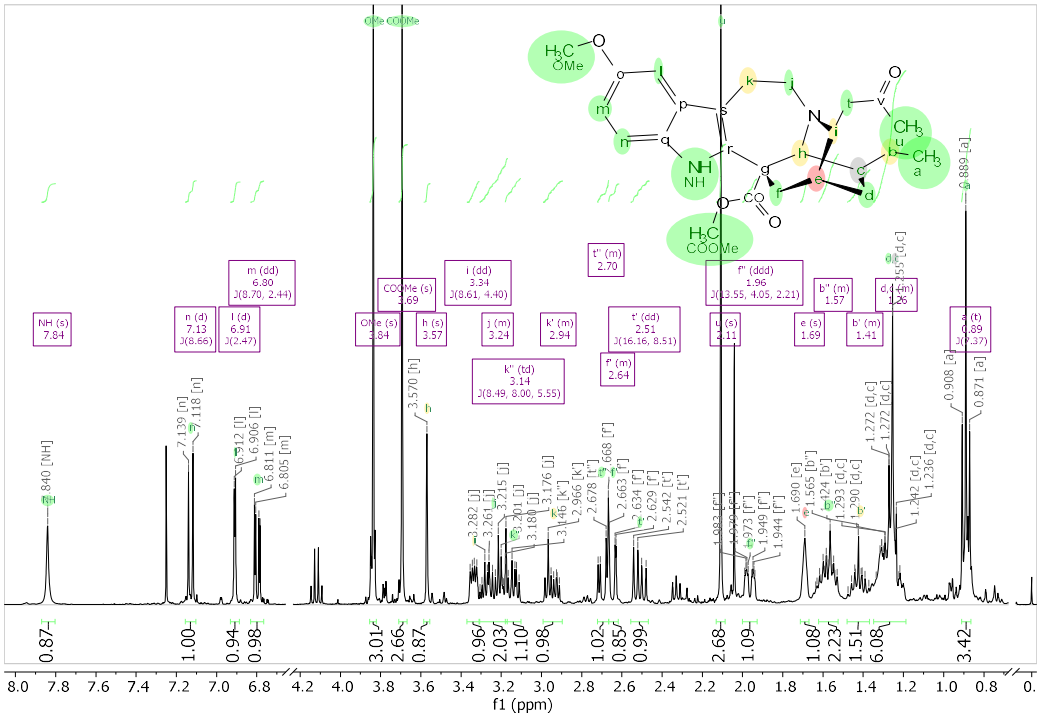


Figure S17. ^{1}H NMR of 3-(2-oxopropyl)voacangine (6) in $CDCl_3$

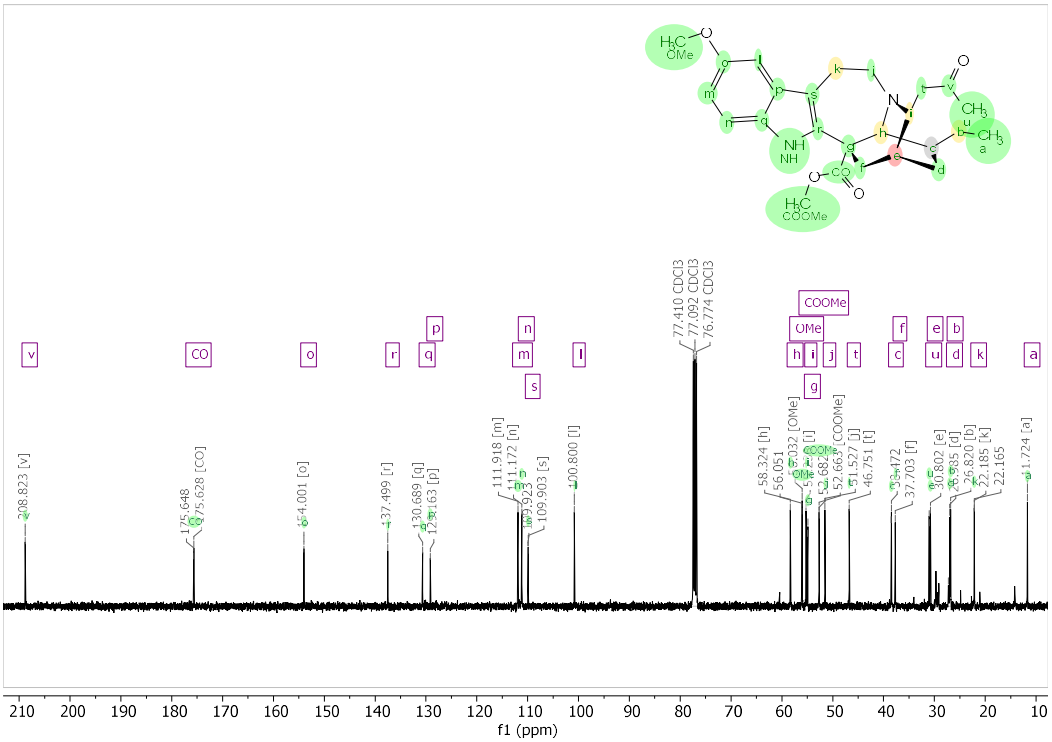


Figure S18. ^{13}C NMR of 3-(2-oxopropyl)voacangine (6) in $CDCl_3$

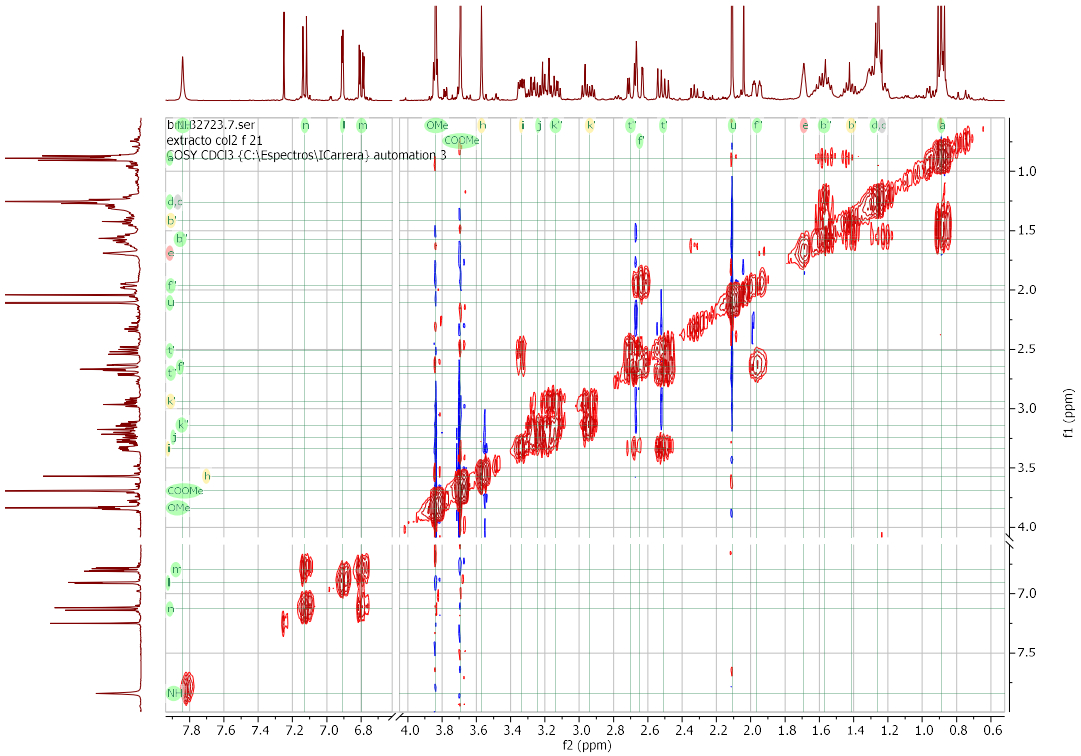


Figure S19. COSY of 3-(2-oxopropyl)voacangine (6) in $CDCl_3$

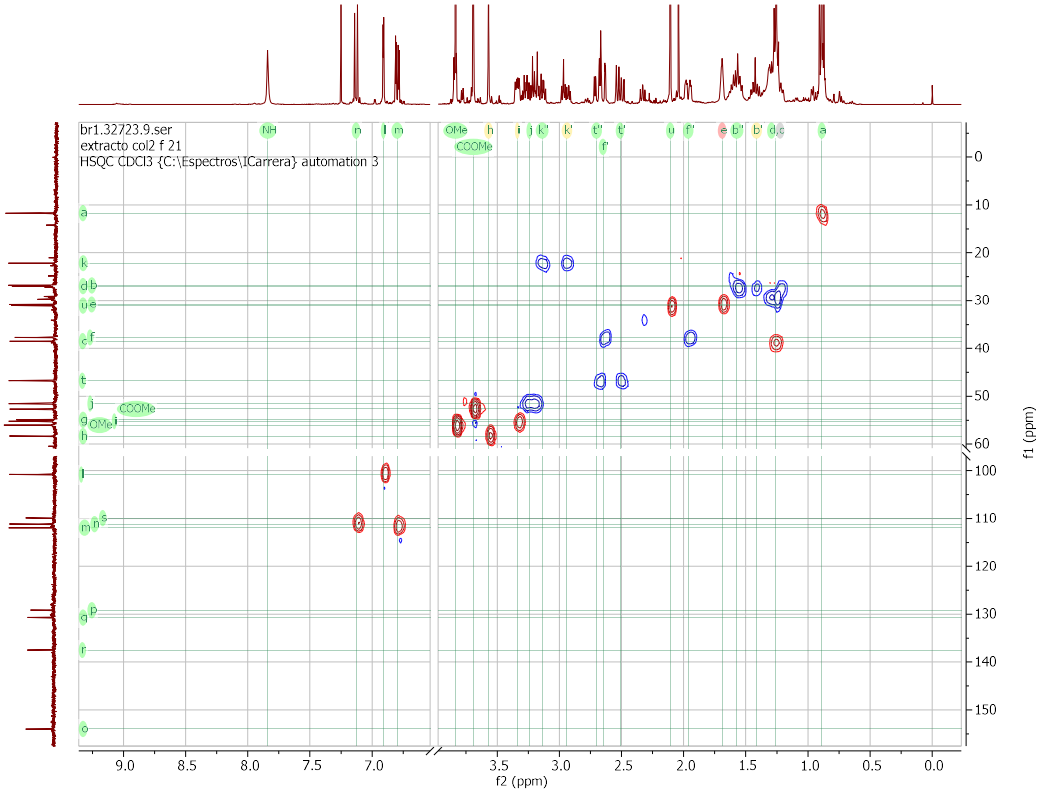
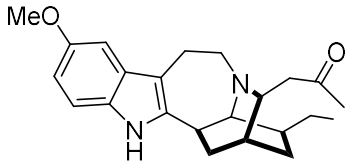


Figure S20. HSQC of 3-(2-oxopropyl)voacangine (6) in $CDCl_3$



Tabernaricatine G (7)

Tabernaricatine G (7):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.13 (d, *J* = 8.5 Hz, 1H), 6.91 (d, *J* = 2.4 Hz, 1H), 6.80 (dd, *J* = 8.5, 2.5 Hz, 1H), 3.85 (s, 3H), 3.63-3.57 (m, 1H), 3.43-3.30 (m, 2H), 3.06-2.97 (m, 1H), 2.93-2.87 (m, 1H), 2.86 (s, 1H), 2.73 (dd, *J* = 16.0, 4.9 Hz, 1H), 2.65-2.51 (m, 2H), 2.17 (s, 3H), 2.14-2.03 (m, 1H), 1.74-1.52 (m, 4H), 1.51-1.39 (m, 2H), 1.35-1.24 (m, 1H), 0.89 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 209.2, 154.0, 142.4, 130.1, 129.8, 110.8, 110.7, 108.8, 100.5, 58.7, 56.0, 53.6, 52.3, 47.6, 41.5, 41.3, 36.0, 31.1, 29.8, 27.4, 26.9, 20.8, 12.0.

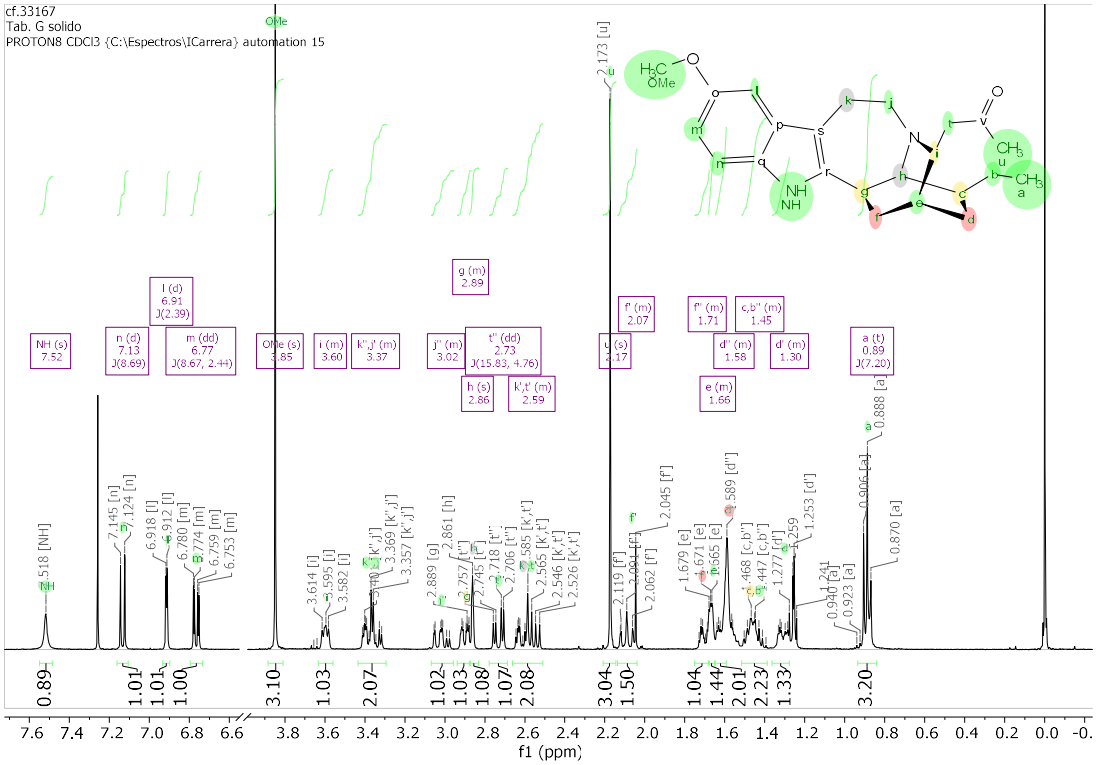


Figure S21. ^{1}H NMR of Tabernaricatine G (7) in $CDCl_3$

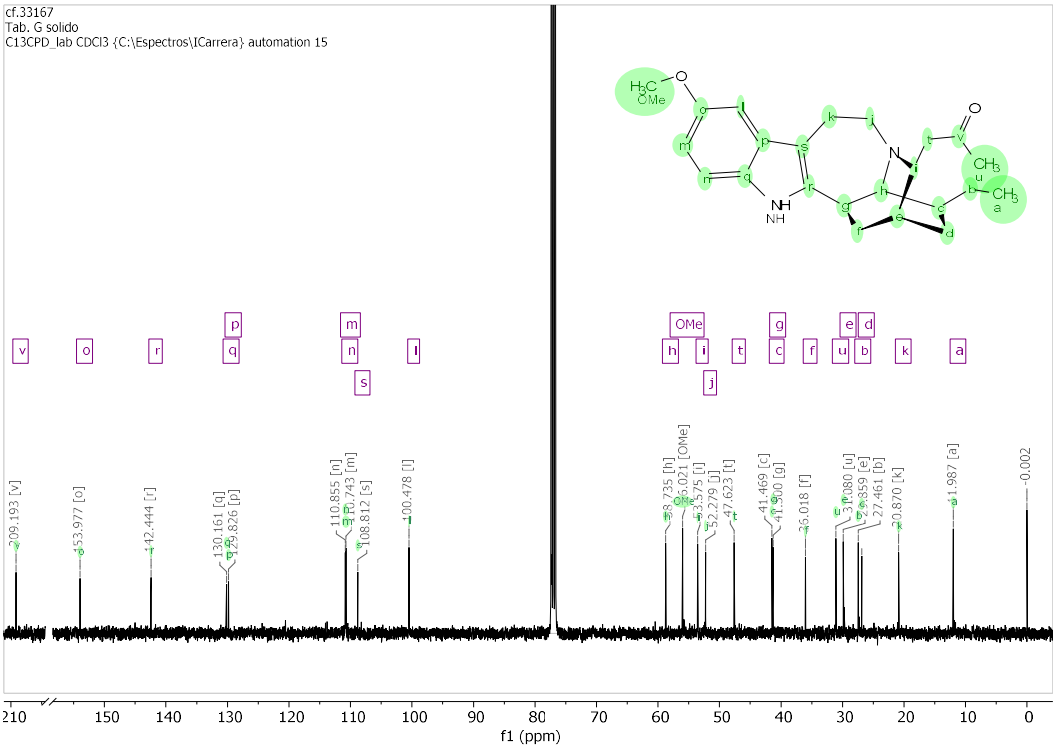


Figure S22. ^{13}C NMR of Tabernaricatine G (7) in $CDCl_3$

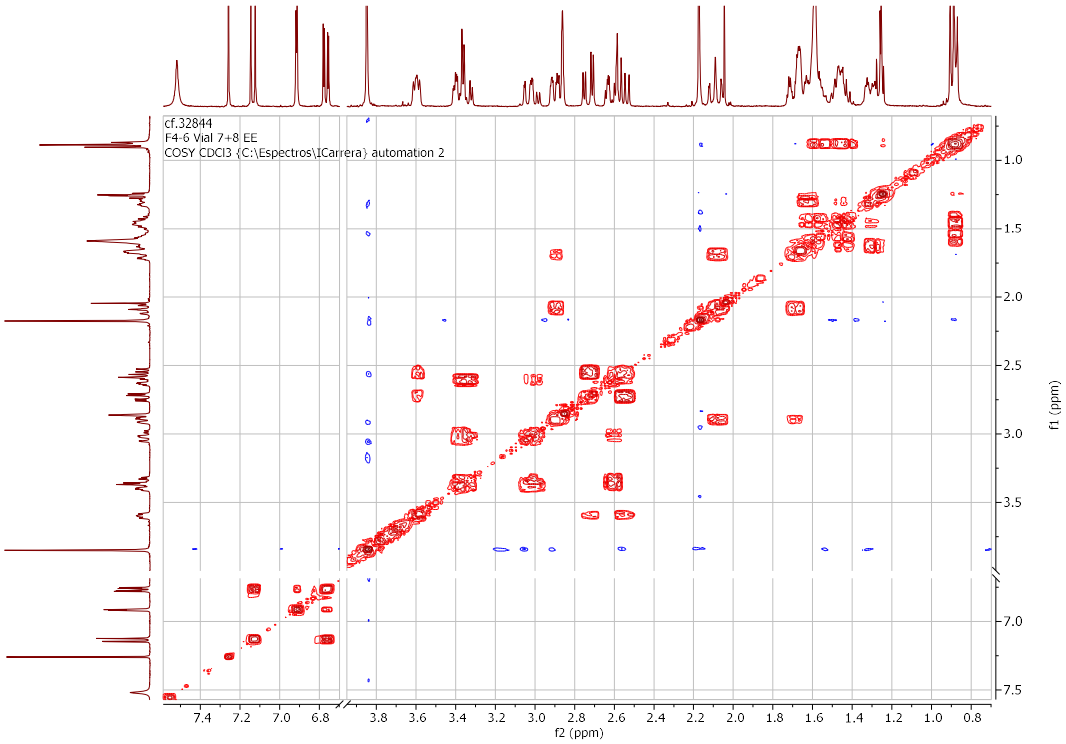


Figure S23. COSY of Tabernaricatine G (7) in $CDCl_3$

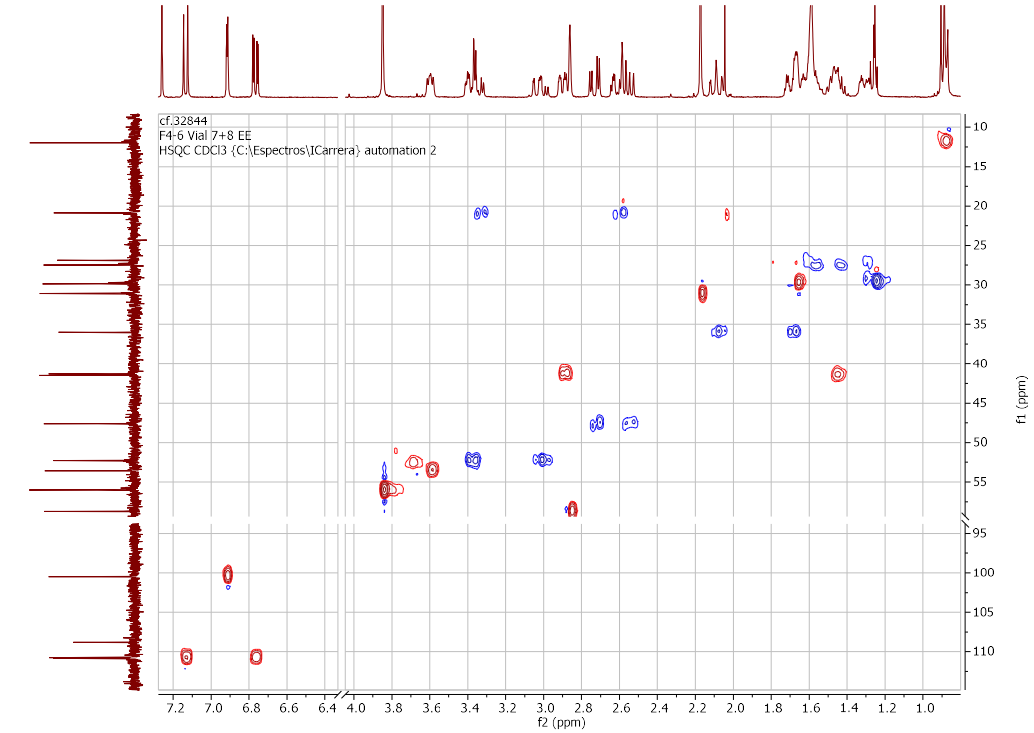


Figure S24. HSQC of Tabernaricatine G (7) in $CDCl_3$

5. Iboga-vobasinyl dimers separation and characterization

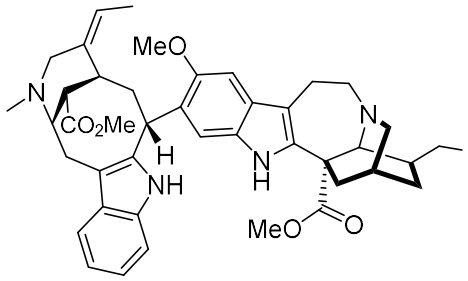
5.1 Purification protocols.

Voacamine crystallization: A solid mixture of Iboga-vobasinyl dimers (18.5 g) was dissolved completely in boiling acetonitrile (150 mL). Boiling water (175 mL) was added to the hot acetonitrile solution with constant stirring and then that solution was cooled with stirring to room temperature. The formed precipitate was filtered through paper and dried *in vacuo* at 50 °C. A white solid was obtained (8.43 g).

Voacamidine purification: The mother liquor of the above-mentioned crystallization procedure was evaporated *in vacuo* to obtain 10 g of a mixture of the 3 dimers, which was purified using column chromatography (SiO_2, Hex: EtOAc, 1:1 /1 % NH_4OH) to obtain 4.5 g of a voacamine: voacamidine (1:4) mixture.

Further purification trials for voacamidine (**4**) and the minor alkaloid using preparative HPLC and TLC methods were not successful. However, the separation of voacamine (**3**) and voacamidine (**4**) was achieved by analytical TLC using as mobile phase $CHCl_3$:EtOAc:MeOH, 1:4:0.5/ 0.5 % acetic acid.

5.2 Isolated compounds



Voacamine (3)

Voacamine (3):

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (bs, 1H), 7.56 – 7.51 (m, 1H), 7.46 (bs, 1H), 7.09 – 7.01 (m, 3H), 6.92 (s, 1H), 6.74 (bs, 1H), 5.31 (q, *J* = 6.6 Hz, 1H), 5.13 (bd, *J* = 9.7 Hz, 1H), 4.06 – 3.95 (m, 4H), 3.79 – 3.69 (m, 2H), 3.64 (bs, 3H), 3.50 (s, 1H), 3.46 (d, *J* = 11.5 Hz, 1H), 3.36 (ddd, *J* = 15.6, 8.6, 5.9 Hz, 1H), 3.22 (dd, *J* = 14.7, 8.1 Hz, 1H), 3.18 – 3.05 (m, 2H), 3.00 – 2.91 (m, 1H), 2.89 (d, *J* = 13.8 Hz, 1H), 2.89 – 2.83 (m, 1H), 2.73 – 2.68 (m, 2H), 2.58 (s, 3H), 2.58-2.53 (m, 1H), 2.50-2,44 (m, 1H), 2.46 (s, 3H), 1.98 (bd, *J* = 14.8 Hz, 1H), 1.83 (bs, 1H), 1.79 (bs, 1H), 1.73 (bd, *J* = 13.0 Hz, 1H), 1.66 (d, *J* = 6.4 Hz, 3H), 1.53 (dq, *J* = 14.7, 7.4 Hz, 1H), 1.41 (dp, *J* = 14.1, 7.2 Hz, 1H), 1.28 (p, *J* = 7.1 Hz, 1H), 1.07 (dd, *J* = 12.5, 7.2 Hz, 1H), 0.87 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 171.6, 150.8, 138.1, 137.9, 137.1, 135.8, 130.2, 129.9, 129.8, 127.3, 121.5, 118.9, 118.8, 118.5, 117.4, 110.4, 110.3, 109.9, 109.9, 109.8, 99.2, 77.3, 77.0, 76.7, 59.9, 57.1, 56.1, 54.9, 53.1, 52.5, 52.4, 51.8, 49.9, 47.0, 42.4, 39.0, 37.3, 36.4, 33.6, 32.0, 27.3, 26.7, 22.2, 19.4, 12.3, 11.6.

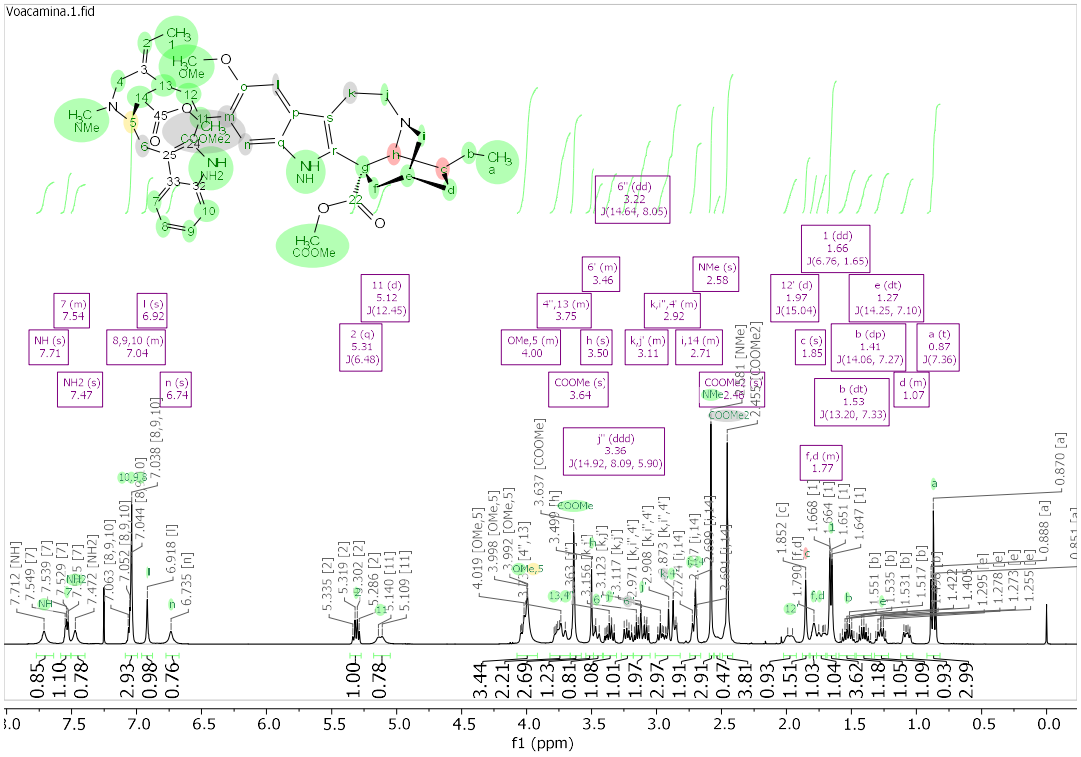


Figure S25. ^{1}H NMR of Voacamine (3) in $CDCl_3$

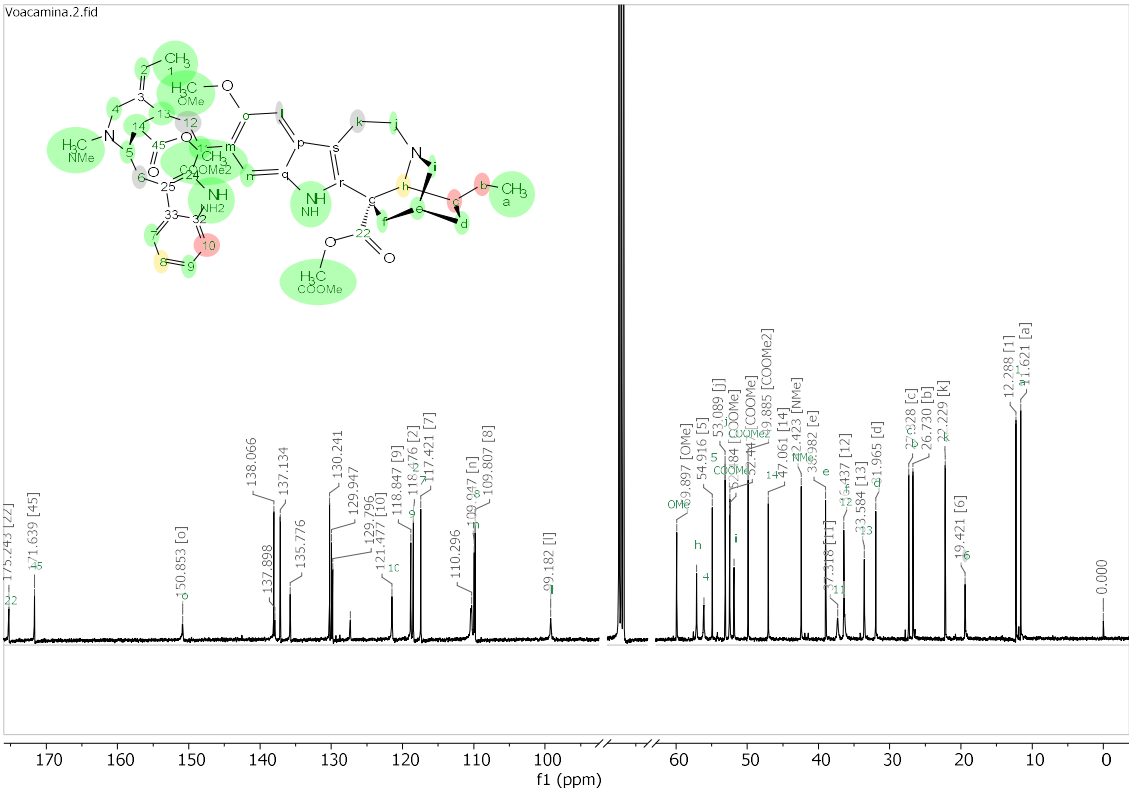


Figure S26. ^{13}C NMR of Voacamine (3) in $CDCl_3$

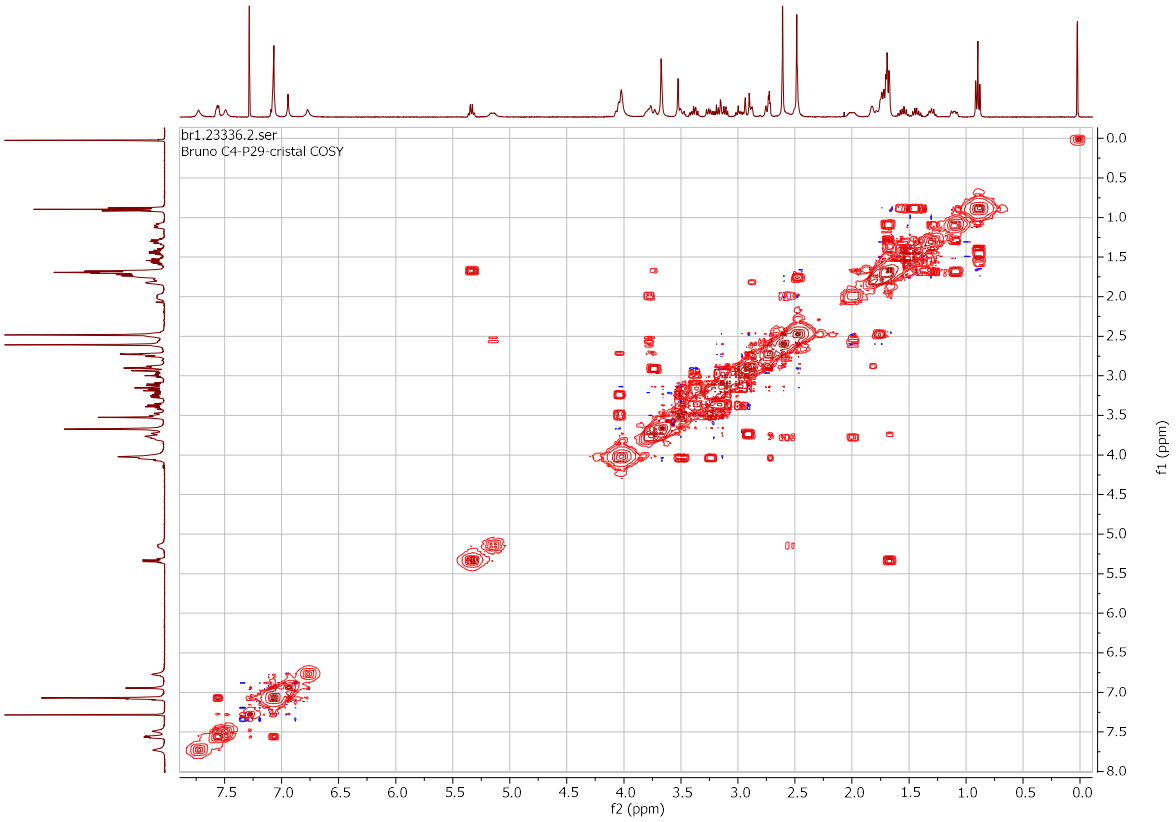


Figure S27. COSY of Voacamine (3) in $CDCl_3$

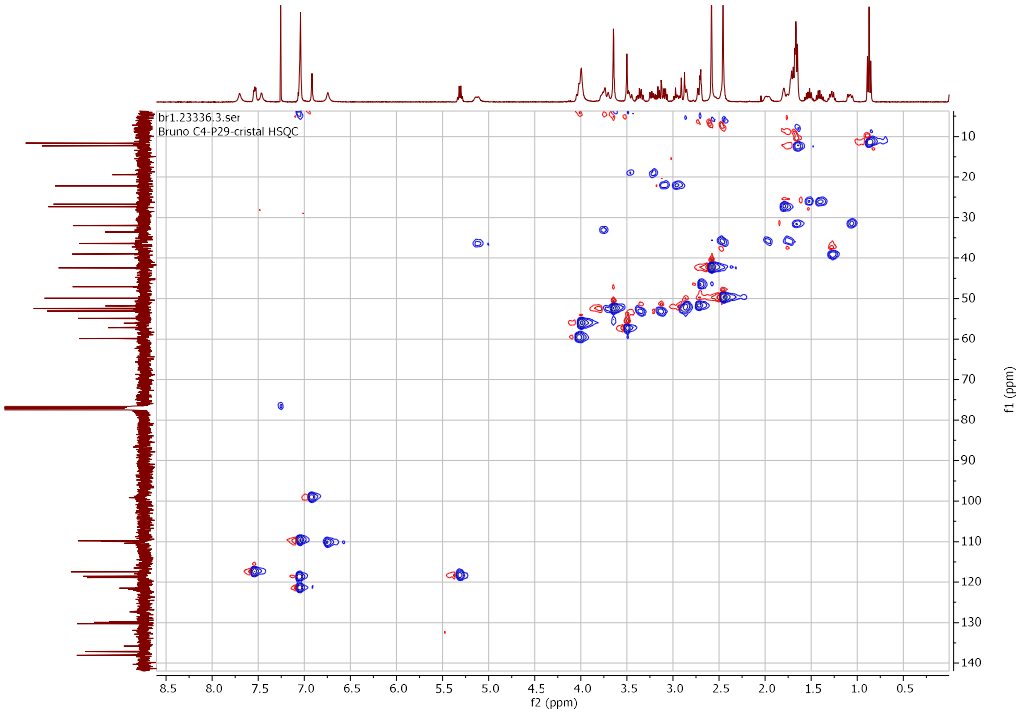
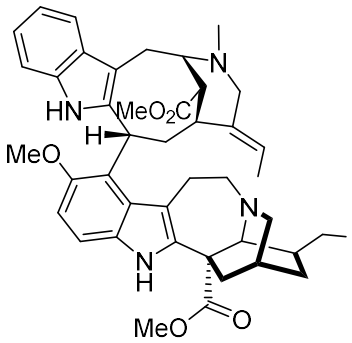


Figure S28. HSQC of Voacamine (3) in $CDCl_3$



Voacamidine (4)

Voacamidine (4):

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.77 (bs, 1H), 7.57 – 7.48 (m, 1H), 7.39 (bs, 1H), 7.09 – 6.95 (m, 4H), 6.75 (d, *J* = 8.7 Hz, 1H), 5.54 (dd, *J* = 12.7, 2.1 Hz, 1H), 5.31 (q, *J* = 6.4 Hz, 1H), 4.11 – 4.05 (m, 3H), 4.03 – 3.96 (m, 1H), 3.88 – 3.70 (m, 2H), 3.77 (s, 3H), 3.62 – 3.33 (m, 5H), 3.29 – 3.13 (m, 3H), 3.03-2.97 (m, 2H), 2.95-2.86 (m, 1H), 2.78 - 2.64 (m, 2H), 2.62 (s, 3H), 2.43 (s, 3H), 2.02 – 1.91 (m, 3H), 1.76 (dd, *J* = 17.6, 7.8 Hz, 1H), 1.71 – 1.56 (m, 4H), 1.50 – 1.41 (m, 1H), 1.34 (dd, *J* = 15.3, 8.3 Hz, 1H), 1.20 – 1.11 (m, 1H), 0.89 (t, *J* = 7.4 Hz,, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 175.9, 171.9, 152.7, 138.5, 138.1, 138.1, 135.1, 132.6, 131.9, 130.2, 126.8, 126.5, 120.7, 118.7, 118.2, 117.1, 112.8, 111.1, 109.6, 109.5, 59.9, 58.4, 58.0, 56.0, 54.0, 52.7, 52.0, 51.0, 49.9, 47.3, 42.4, 39.0, 37.2, 33.6, 32.9, 32.7, 31.9, 27.2, 26.8, 25.1, 21.0, 12.3, 11.7.

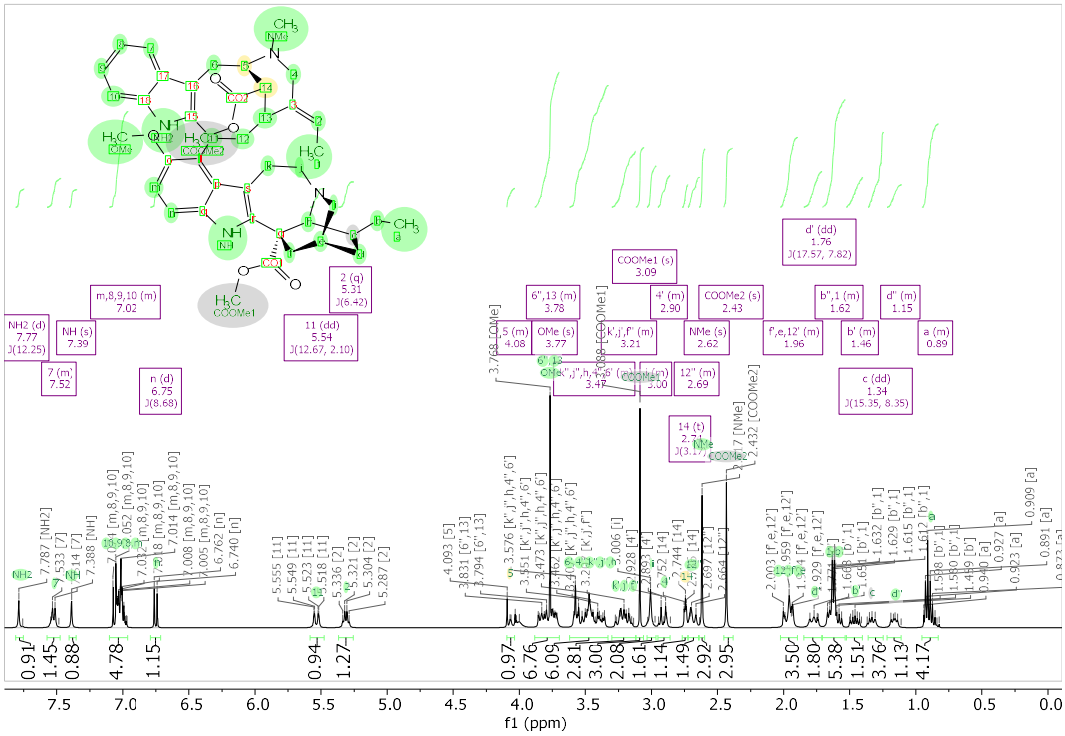


Figure S29. ^{1}H NMR of Voacamidine (4) in $CDCl_3$

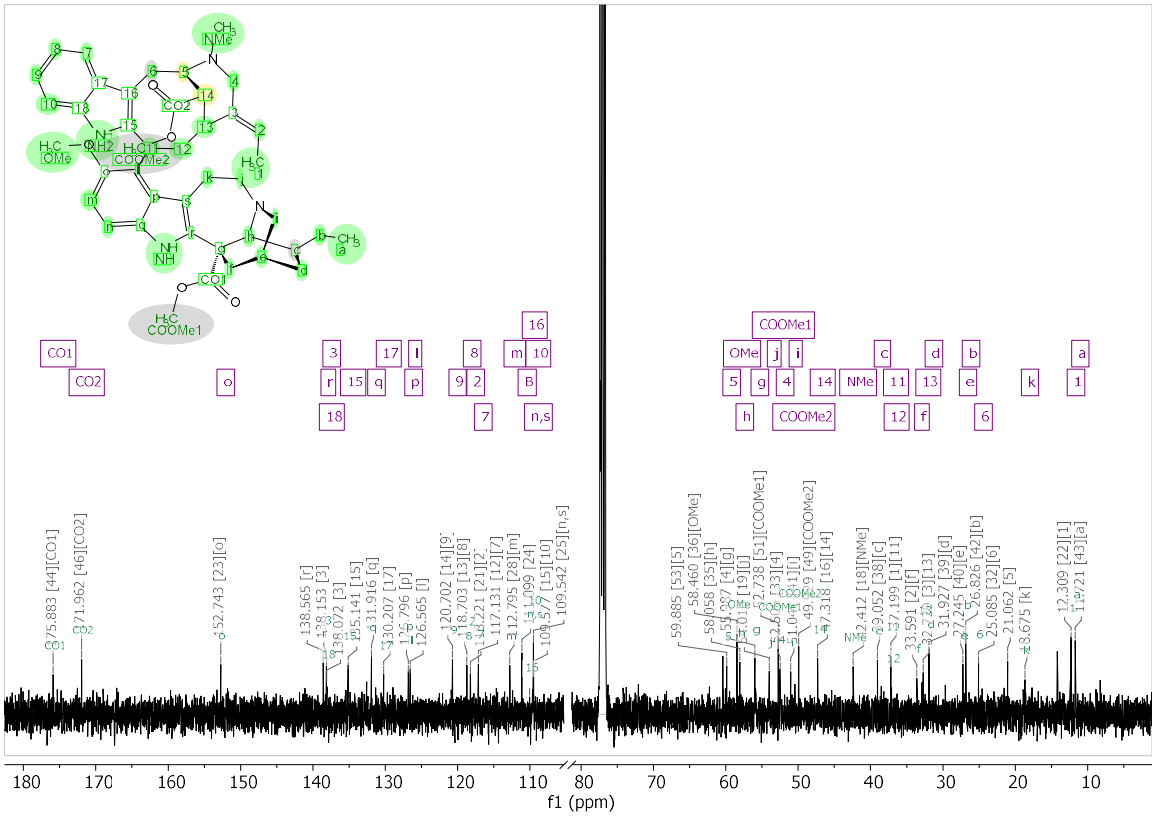


Figure S30. ^{13}C NMR of Voacamidine (4) in $CDCl_3$

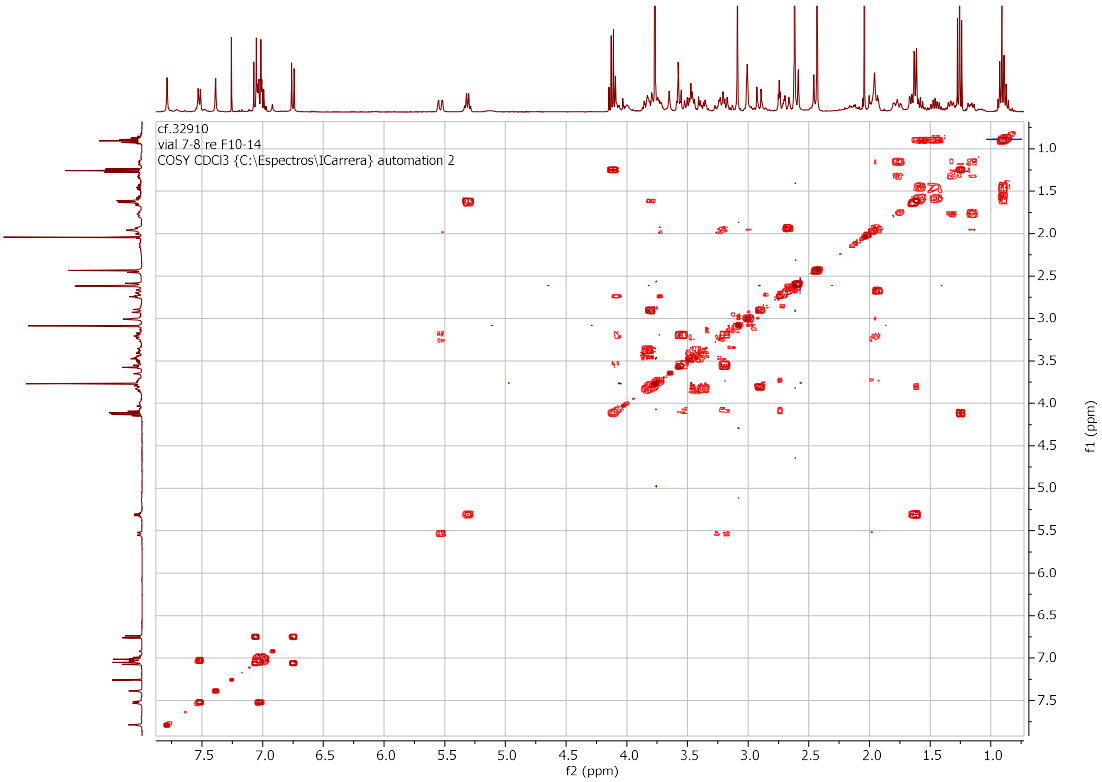


Figure S31. COSY NMR of Voacamidine (4) in $CDCl_3$

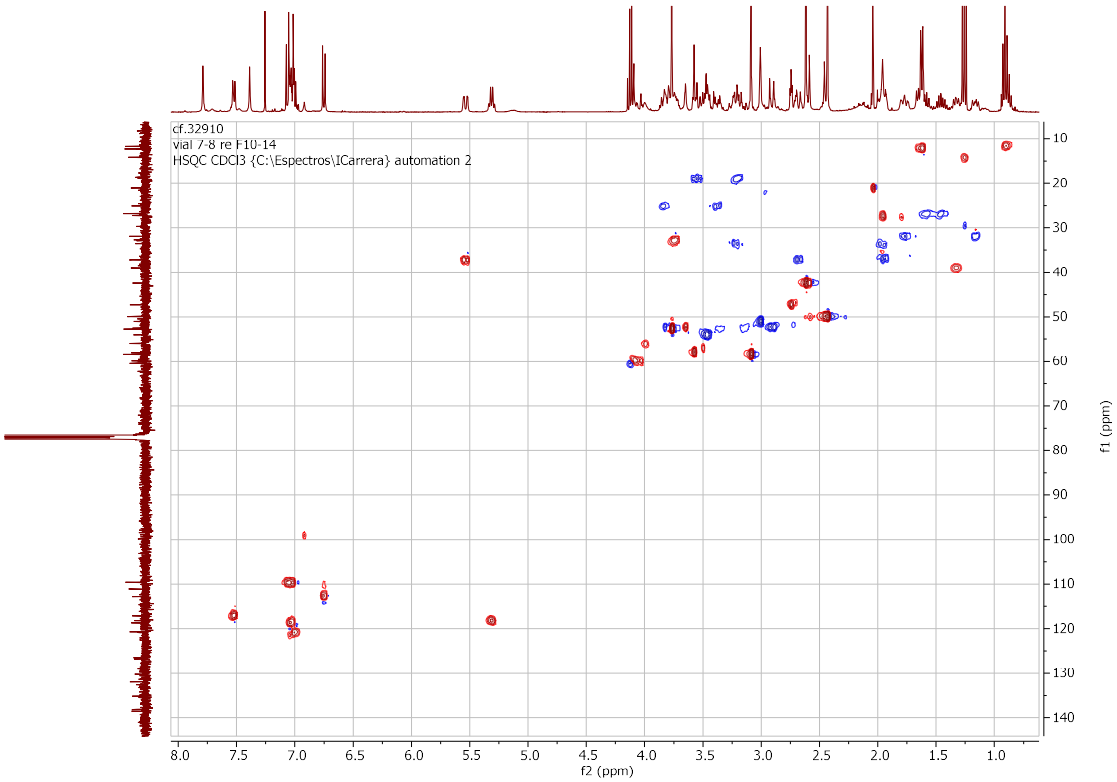


Figure S32. HSQC NMR of Voacamidine (4) in $CDCl_3$

5.2 Mixtures of bis-indole alkaloids

The ratio of the bis-indole alkaloids present in the mixtures obtained for each extraction protocol was established by ^{1}H-NMR spectroscopy. H_2 and H_{11} were selected as characteristic signals for each dimer (See Figure S33). Also, the mixture of bis-indole alkaloids obtained using the acid-base extraction protocol (Section 2.1) was analyzed by LC-MS where three major peaks were resolved, all of them showing the same ion (*m/z: 353*) corresponding to the $[M+2H]^{++}$. (See Figure S34) Unfortunately, we couldn't separate enough quantity of the minor compund for full structure characterization, although the molecular ion mass is the same as voacamidine and voacamine, what suggest it could share the iboga-vobasinyl structure resulting in another regioisomer of the same structural motives.

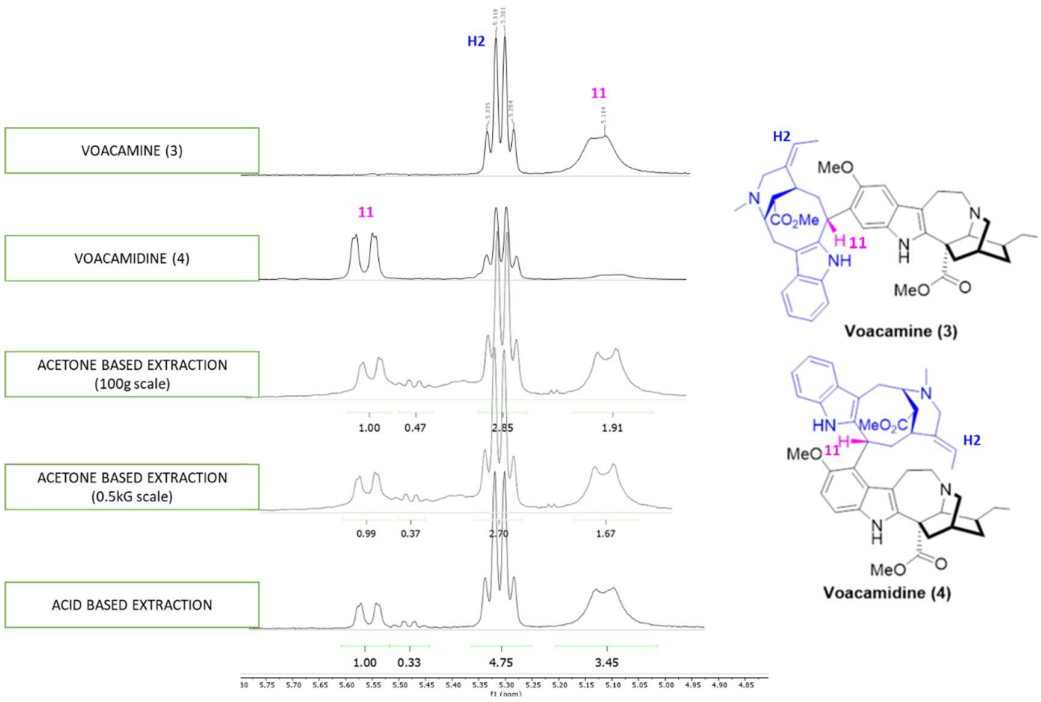
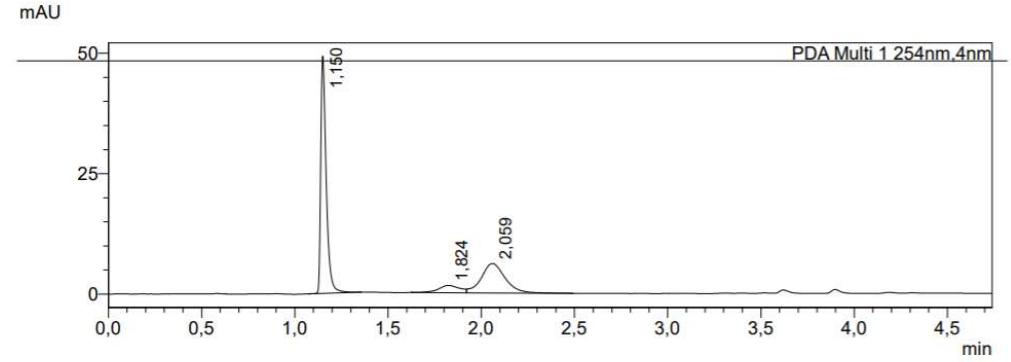


Figure S33. Determination of the dimeric compounds proportion in the mixture, composition comparing ^{1}H NMR of the mixtures obtained for each case.



Peak Table

PDA Ch1 254nm

Peak#	Ret. Time	Area	Area%	Conc.	Unit	Mark	Name
1	1,150	100631	60,371	0,000			
2	1,824	12057	7,234	0,000			
3	2,059	53999	32,395	0,000		V	
Total		166688	100,000				

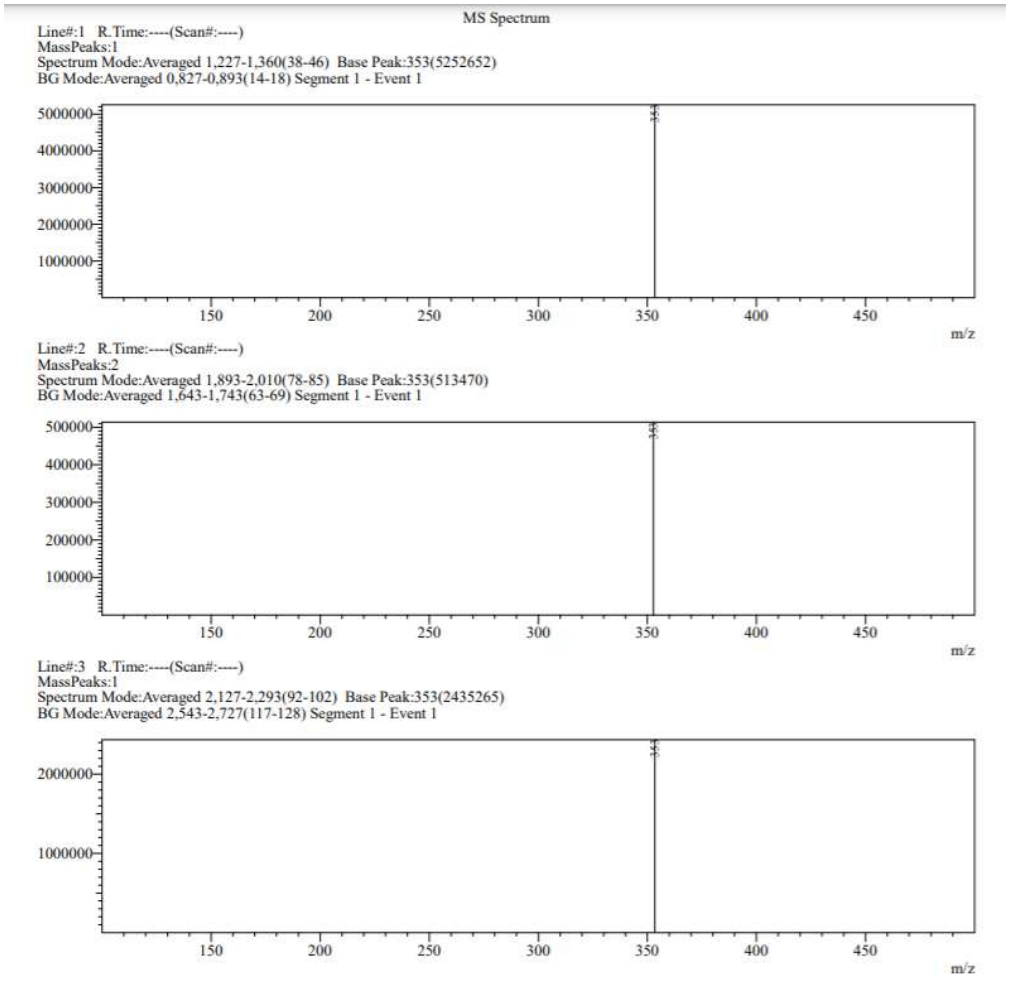


Figure S34. LC-MS analysis of the bis-indole alkaloid mixture, chromatogram and mass-spectrums for each compound. Chromatographic conditions: (Kinetex C18-EVO (150 x 4,6 mm) 5 µm), gradient: T_0 20%B, T_{5min} 50%B , T_{10min} 98 %B. A: 0.1% formic acid, B: MeCN.

6 X-ray diffraction

Voacamine (3):

Light-pink single crystals of voacamine hydrate suitable for X-ray diffraction were obtained by slow evaporation of a methanol-water dissolution. Two different batches of crystals were used for single-crystal data collection. A crystal from the first batch 0.04×0.071×0.16 mm of size was used to determine the unit cell (orthorhombic, a=21.933(3) Å, b=54.505(6) Å, c=10.1583(11) Å, α=β=γ=90°, V= 12177(2) Å^3) and collect a partial dataset at 250 K (- 23 °C) using a Bruker APEX-II CCD diffractometer with CuK_α (λ=1.5418 Å) radiation, with maximum resolution of 0.96 Å. The diffracted intensity from the crystal faded rapidly with diffraction angle making the effective resolution of the data of 1.1 Å. This dataset allowed to solve the crystal structure using the program SIR2004 [1] as shown in Figure S35. A crystal form the second batch 0.13×0.283×0.31 mm of size was used to determine the unit cell (orthorhombic, a=18.7939(10) Å, b=22.4746(12) Å, c=10.3719(5) Å, α=β=γ=90°, V= 4380.9(4) Å^3) and attempt to collect a full dataset (resolution of 0.833 Å) at room temperature (23 °C) using a Bruker D8 Venture diffractometer with Photon 100 detector also using CuK_α (λ=1.5418 Å) radiation. The diffracted intensity also faded rapidly at high 2θ values providing a dataset with effective resolution of 1.2 Å. The crystal structure was solved using SHELXT program [2], providing the structural model **3b** as shown in Figure S36. The structures were refined with the program SHELXL [2] running under shelXle graphical user interphase [3]. C, N and O atoms were located in the initial electron density map or in successive difference Fourier maps (ΔF) and refined free. Disordered atoms were refined using bond-distance, bond-angle and similar anisotropic displacement parameters restraints. The three independent molecules in 3a were subject to similarity restraints to compensate for the reduced number of observed reflections. Hydrogen atoms bonded to C and N were located at geometrically suitable positions and refined riding. H-atoms for water molecules in 3a were found in ΔF maps and refined with bond-distance and bond-angle restraints. H-atoms of water molecules for 3a were neither found nor included in the final model. The figures were obtained using Mercury 2020.3.0 [4]. Final details of the crystal structure analysis are provided in Table S2.

Crystals of **3a** seem to be a low-temperature form of **3b** since the unit cell of 3a is tripled in length in one axis [b(3a)=54.505 Å, a(3b)=18.7939 with the other two axes are only differing in the effect of the data collection temperature a(3a)=21.933 Å, b(3a)=22.4746 Å and c(3a)=10.1583 Å, c(3b)=10.3719 Å]. The unit cell volume is also tripled (V(3b)=12177≅ 3V(3a)=13143 Å^3) and the number of independent voacamine molecules in 3a is Z'(3a)=3 while only one in 3b [Z'(3b)=1]. The isostructural

phase transition that relates 3a and 3b is caused by the loss of 2-fold symmetry between voacamine.H_2O units that pack more efficiently at low temperatures and maybe reinforced by the loss of solvation water molecules during storage of the crystals (as extracted from the relatively large volume contraction observed from 23 to -23 °C). The phase transition probably occurs very close to room temperature, since a considerable amount of diffuse scattering between hkl and h+1,k,l reflections was observed in the room temperature diffraction frames during data collection.

CCDC 2049152 and 2049151 contain the supplementary crystallographic data for compounds **3a** and **3b** respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

Crystal	**3a**	**3b**
Empirical formula	$C_{43}H_{52}N_4O_5 \cdot H_2O$	$C_{43}H_{52}N_4O_5 \cdot 2.5H2O$
Formula weight	722.90	749.92
Temperature	250(2) K	298(2) K
Wavelength	1.5418 Å	1.5418 Å
Crystal system	Orthorhombic	Orthorhombic
Space group	$P2_12_12$	$P2_12_12$
Unit cell dimensions	a = 21.993(3) Å	a = 18.7939(10) Å
	b = 54.505(6) Å	b = 22.4746(12) Å
	c = 10.1583(11) Å	c = 10.3719(5) Å
Volume	12177(2) $Å^3$	4380.9(4) $Å^3$
Z, Z'	12, 3	4, 1
Density (calculated)	1.183 Mg/m^3	1.137 Mg/m^3
Absorption coefficient	0.632 mm^{-1}	0.628 mm^{-1}
F(000)	4656	1612
Crystal size	0.160 x 0.071 x 0.040 mm^3	0.310 x 0.283 x 0.130 mm^3
Theta range for data collection	2.166 to 53.536°.	3.065 to 68.927°.
Index ranges	-19<=h<=22, -55<=k<=54, -10<=l<=10	-22<=h<=22, -27<=k<=27, -12<=l<=11
Reflections collected	49964	169742
Independent reflections	14279 [R(int) = 0.2555]	8023 [R(int) = 0.0965]
Completeness to θ_{max} (θ_{max})	98.6 % (53.536°)	99.8 % (68.927°)
Absorption correction	Semi-empirical from equivalents	Semi-empirical from equivalents
Max. and min. transmission	0.7505 and 0.5736	0.7531 and 0.6735
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data / restraints / parameters	14279 / 2075 / 1454	8023 / 1572 / 874
Goodness-of-fit on F^2	0.988	1.071
Final R indices [I>2sigma(I)]	R1 = 0.0877, wR2 = 0.1811	R1 = 0.1276, wR2 = 0.3400
R indices (all data)	R1 = 0.1788, wR2 = 0.2249	R1 = 0.1552, wR2 = 0.3659
Absolute structure parameter	0.2(3)	0.01(13)
Extinction coefficient	n/a	n/a
Largest diff. peak and hole	0.367 and -0.266 $e.Å^{-3}$	0.540 and -0.292 $e.Å^{-3}$

Table S2: Crystal data, data collection and structure determination and refinement results for **3a** and **3b**.

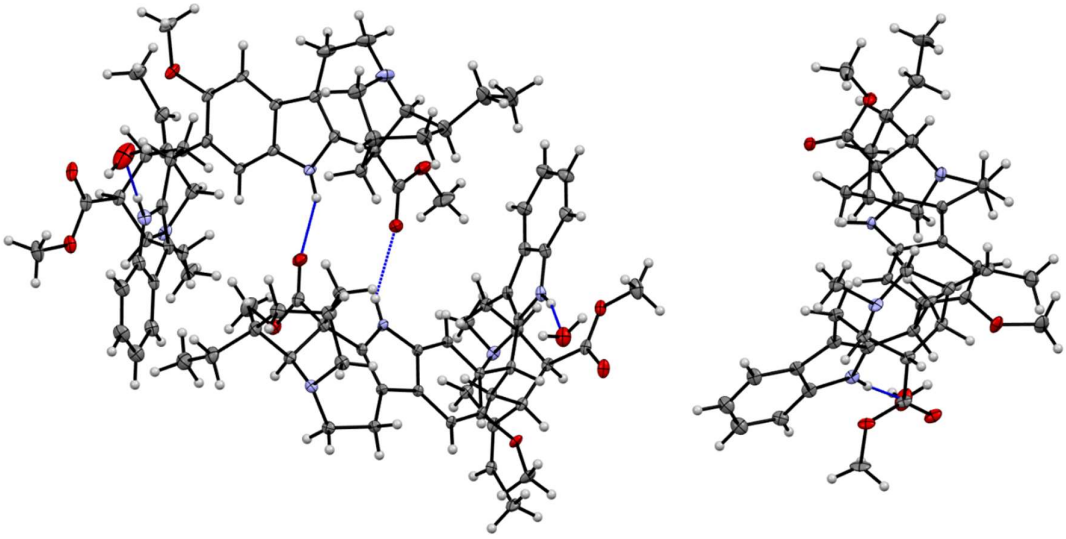


Figure S35: ORTEP view of the asymmetric unit of 3a showing three independent voacamine and water molecules connected through a N-H…OH_2 hydrogen bonds. H-bonds are represented as blue dashed lines. Ellipsoids are respresente with 30% probability.

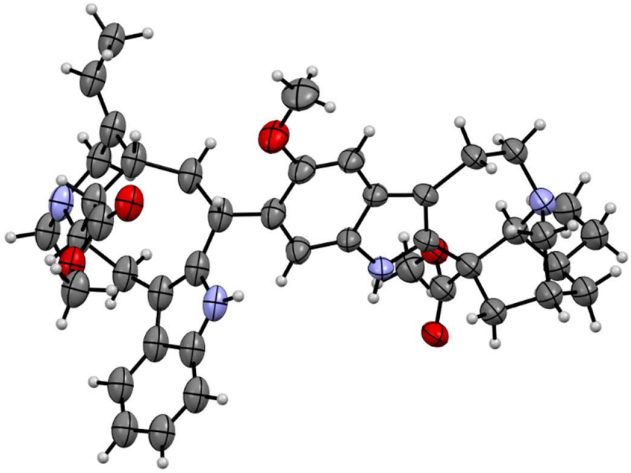


Figure S36: ORTEP view of the voacamine molecule in 3b. The ellipsoids are represented with 30% probability. Crystallization water molecules were excluded for clarity.

Ibogaine hydrochloride:

Colourless single crystals of ibogaine hydrochloride suitable for X-ray diffraction were obtained by slow evaporation of a metanolic solution of the salt at room temperature. Ibogaine hydrochloride was obtained treating a solution of ibogaine free base (1) in diethyl ether with a dry HCl 0.34M diethyl ether solution; the precipitate was filtered and washed several times with diethyl ether. A crystal with 0.26×0.201×0.158 mm of size was used to determine the unit cell (orthorhombic, a=9.3860(5) Å, b=10.6137(8) Å, c=18.3018(10) Å, α=β=γ=90°, V= 1823.2(2) $Å^3$) and collect a partial dataset at 100 K (- 173 °C) using a Bruker APEX-II CCD diffractometer with CuK_α (λ=1.5418 Å) radiation, with maximum resolution of 0.83 Å. The crystal structure was solved using SHELXT program [2], providing

the structural model **1** as shown in Figure S37. The structures were refined with the program OLEX2 [5] running under shelXle graphical user interphase [3]. C, N and O atoms were located in the initial electron density map or in successive difference Fourier maps (ΔF) and refined free. Disordered atoms were refined using bond-distance, bond-angle and similar anisotropic displacement parameters restraints. Hydrogen atoms bonded to C and N were located at geometrically suitable positions and refined riding. The figures were obtained using Mercury 2020.3.0 [4]. Final details of the crystal structure analysis are provided in Table S3.

Table S3: Crystal data, data collection and structure determination and refinement results for **1**.

Crystal	**1**
Empirical formula	$C_{20}H_{27}ClN_2O$
Formula weight	346.88
Temperature	100(2) K
Wavelength	1.5418 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 9.3860(5)Å
	b = 10.6137(8)Å
	c = 18.3018(10)Å
Volume	1823.2(2) Å^3
Z, Z'	4, 1
Density (calculated)	1.264 Mg/m^3
Absorption coefficient	1.910 mm^{-1}
F(000)	744.0
Crystal size	0.260 x 0.201 x 0.158 mm^3
Theta range for data collection	9.632 to 136.15°.
Index ranges	-11<=h<=11, -12<=k<=11, -21<=l<=21
Reflections collected	25396
Independent reflections	3318 [R(int) = 0.0707]
Completeness to θ_{max} (θ_{max})	99.8 % (68.075°)
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7530 and 0.5948
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3318 / 76 / 245
Goodness-of-fit on F^2	1.085
Final R indices [I>2sigma(I)]	R1 = 0.0604, wR2 = 0.1459

R indices (all data)	R1 = 0.0632, wR2 = 0.1482
Absolute structure parameter	0.014(11)
Extinction coefficient	n/a
Largest diff. peak and hole	0.372 and -0.366 e.Å^{-3}

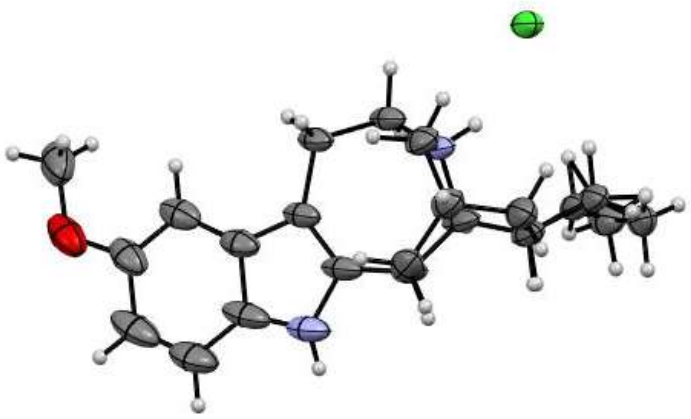


Figure S37: ORTEP view of the ibogaine chlorohydrate molecule in **1**. The ellipsoids are represented with 30% probability.

7 References

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