Supporting Information

Nature-Inspired Stereospecific Total Synthesis of *P*-(+)-Dispegatrine as well as the Total Synthesis of Four Other Monomeric *Sarpagine* Indole Alkaloids

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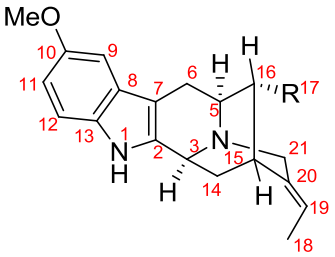
Table of Contents

General Experimental Considerations:

All reactions were carried out under an argon atmosphere with dry solvents using anhydrous conditions unless otherwise stated. Tetrahydrofuran (THF) and diethyl ether were freshly distilled from Na/benzophenone ketyl prior to use. Dichloromethane was distilled from calcium hydride prior to use. Methanol was distilled over magnesium sulfate. Benzene and toluene were distilled over Na. Acetonitrile was distilled over CaH_2 prior to use. Reagents were purchased at the highest commercial quality and used without further purification unless otherwise stated. Thin layer chromatography (TLC) was performed using Dynamic Adsorbents Inc. UV active silica gel, 200 µm, plastic backed; Dynamic Adsorbents Inc. UV active alumina N, 200 µm, F-254 plastic backed. Flash and gravity chromatography were performed using silica gel P60A, 40-63 µm purchased from Silicycle. Basic alumina (Act I, 50-200 µm) for chromatography was purchased from Dynamic Adsorbents. Neutral alumina (Brockman I, ~150 mesh) for chromatography was purchased from Sigma-Aldrich. TLC plates were visualized by exposure to short wavelength UV light (254 nm). Indoles were visualized with a saturated solution of ceric ammonium sulfate in 50% sulfuric acid.[1] Elemental analyses were performed on a Carlo Erba model EA-1110 carbon, hydrogen, and nitrogen analyzer. All samples submitted for CHN analyses were first dried under high vacuum for a minimum of six hours using a drying pistol with isopropyl alcohol or benzene as the solvent with potassium hydroxide pellets in the drying bulb. Proton (^{1}H NMR) and carbon high resolution nuclear magnetic resonance spectra (^{13}C NMR) were obtained on a Bruker 300-MHz/GE 500-MHz/Bruker 600-MHz NMR spectrometer. ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, dd = doublet of doublet, dt = doublet of triplet, ddd = doublet of doublet of doublets, td = triplet of doublets, qd = quartet of doublets, m = multiplet), integration, and coupling constants (Hz). ^{13}C NMR data are reported in parts per million

(ppm) on the δ scale. The low resolution mass spectra (LRMS) were obtained as electron impact (EI, 70 eV), which were recorded on a Hewlett-Packard 5985B gas chromatography-mass spectrometer, while high resolution mass spectra (HRMS) were recorded on a VG Autospec (Manchester, England) mass spectrometer. HRMS recorded by fast atom bombardment (FAB) were performed at University of Kansas Mass Spectrometry Laboratory on a VG Analytical ZAB. HRMS recorded by electrospray ionization (ESI) and Matrix-assisted laser desorption (MALDI) methods were performed at the Laboratory for Biological Mass Spectrometry at Texas A&M University on a API QStar Pulsar model, manufactured by MDS Sciex and Voyager-DE STR, manufactured by Applied Biosystems, respectively. Optical rotations were measured on a JASCO Model DIP-370 digital polarimeter. Infra-red spectra were recorded on a Thermo Nicolet Nexus 870 FT-IR or a Perkin Elmer 1600 series FT-IR spectrometer.

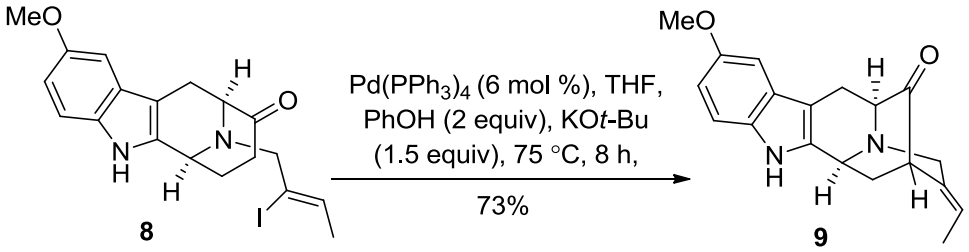
Biogenetic Numbering[2] of *Sarpagine* Indole Alkaloids:



4 R = CHO, (+)-10-methoxyvellosimine

5 R = CH_2OH, (+)-lochnerine

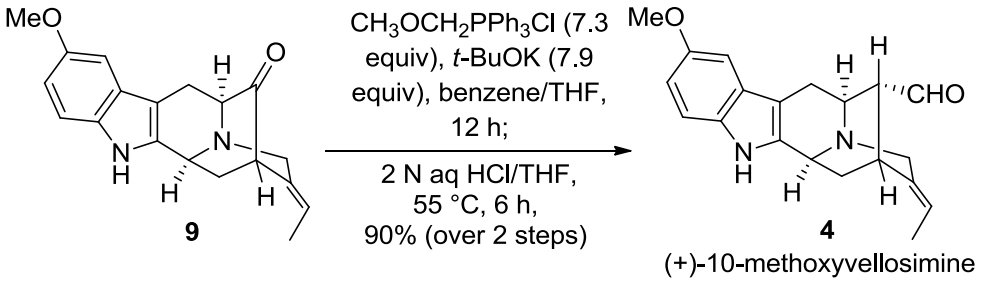
Experimental Procedures and Analytical Data:



(6*S*,11a*S*,*E*)-9-ethylidene-2-methoxy-6,8,9,10,11a,12-hexahydro-6,10-methanoindolo-[3,2-*b*]quinolizin-11(5*H*)-one (9)

A solution of the N_a-H vinyl iodo tetracyclic ketone **8** (1.47 g, 3.36 mmol) and $Pd(PPh_3)_4$ (233 mg, 0.202 mmol) in freshly distilled THF (70 mL) under an inert atmosphere was degassed under reduced pressure at rt and back filled with argon (3 times) and then allowed to stir at rt. To a second flask which contained a stirred solution of PhOH (634 mg, 6.72 mmol) in freshly distilled THF (48 mL) at rt was added *t*-BuOK (567 mg, 5.04 mmol). The mixture which resulted was stirred for 10 min and then was introduced into the first reaction mixture by a double ended needle transfer and the system was again degassed under reduced pressure at rt and back filled with argon (4 times). The mixture was then heated to 70 - 75 °C (oil bath temperature) under argon for 8 h, cooled to rt and quenched with ice-water. The THF volume was reduced to half under reduced pressure and the mixture was diluted with EtOAc (70 mL). The aq layer was extracted with EtOAc (2 x 15 mL) and the combined organic layers were washed with brine (2 x 30 mL) and dried (Na_2SO_4). The EtOAc was then removed under reduced pressure and the residue was flash chromatographed with CH_2Cl_2 on basic alumina to provide the cross-coupled pentacyclic ketone **9** as a light brown colored solid (73%, 750 mg). Recrystallization with CH_2Cl_2/hexanes provided buff colored crystals for X-ray analysis: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.15 (d, 1H, *J* = 8.7 Hz), 6.95 (d, 1H, *J* = 2.4 Hz), 6.81 (dd, 1H, *J* = 8.7, 2.5 Hz), 5.53 (q, 1H, *J* = 6.9 Hz), 4.22 (dd, 1H, *J* = 9.4, 2.0 Hz), 3.86 (s, 3H), 3.83 – 3.81 (m, 2H), 3.61 (d, 1H, *J* = 5.7 Hz), 3.40 (dd, 1H, *J* = 3.9,

1.8 Hz), 3.27 (dd, 1H, *J* = 15.5, 1.4 Hz), 2.96 (dd, 1H, *J* = 15.4, 6.3 Hz), 2.46 (ddd, 1H, *J* = 12.4, 7.7, 1.9 Hz), 2.20 (ddd, 1H, *J* = 12.7, 3.8, 2.5 Hz), 1.67 (dt, 3H, *J* = 6.9, 1.8 Hz); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 217.1 (C), 154.1 (C), 136.9 (C), 132.2 (C), 131.3 (C), 127.3 (C), 120.9 (CH), 111.7 (CH), 111.4 (CH), 105.5 (C), 100.6 (CH), 64.1 (CH), 55.8 (CH_3), 55.2 (CH_2), 50.8 (CH), 44.6 (CH), 36.5 (CH_2), 22.4 (CH_2), 12.6 (CH_3); **EIMS** (*m/e*, relative intensity) 308 ($M^{+\bullet}$, 20), 280 (100), 279 (100), 265 (24), 199 (80), 198 (27), 184 (22), 156 (13); **HRMS** (EI) calcd for $C_{19}H_{20}N_2O_2$ 308.1525, found 308.1526.

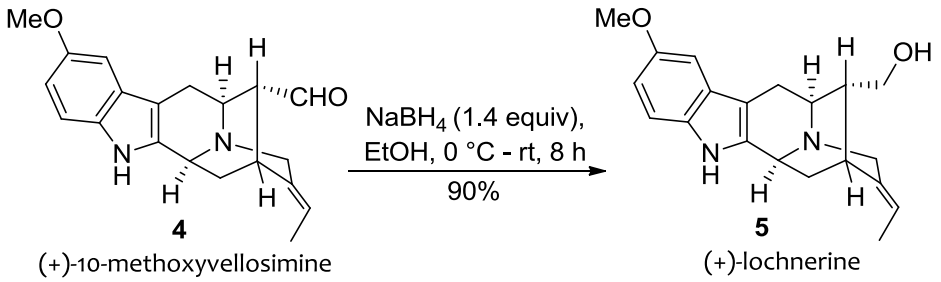


(+)-10-Methoxyvellosimine (4)

To a solution of methoxymethyltriphenylphosphonium chloride (6.1 g, 17.77 mmol) in dry benzene (100 mL) under an inert atmosphere was added anhydrous potassium *tert*-butoxide (2.15 g, 19.23 mmol) and the mixture which resulted was allowed to stir at rt for 1 h. A solution of the pentacyclic ketone **9** (750 mg, 2.43 mmol) in THF (40 mL) was then added to the above red colored solution dropwise at 0 °C. The mixture which resulted was stirred at rt for 12 h. After 12 h at rt, analysis of the mixture by TLC (silica gel, CH_2Cl_2 : MeOH, 4.7 : 0.3) indicated the absence of starting material **9**. The reaction mixture was diluted with EtOAc (100 mL) and quenched with water (50 mL). The aqueous layer was extracted with EtOAc (2 x 15 mL), and the combined organic layers were washed with brine (2 x 30 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford the enol ethers as a reddish brown oil. The baseline materials (silica gel, TLC) were removed by percolation through a wash column. The solvent was removed under reduced pressure and the residue was dissolved (without further purification) in a solution of 2 N aqueous HCl in

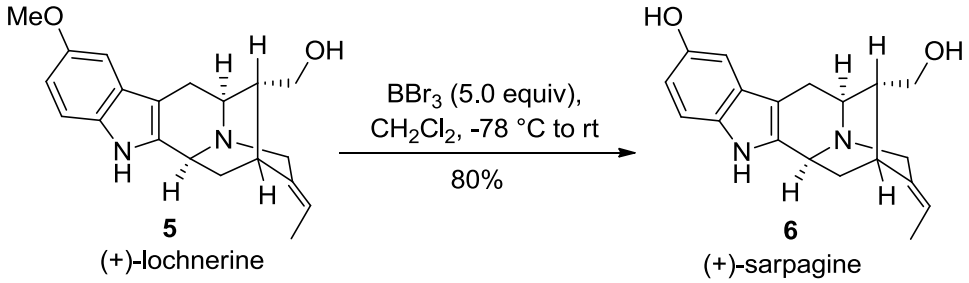
H_2O/THF (1:1, 400 mL). The solution which resulted was stirred at 55 °C (oil bath temperature) under an atmosphere of argon for 6 h. The reaction mixture was then cooled to 0 ^oC, extracted with ethyl ether (5 × 100 mL) to remove phosphorous based byproducts, after which the aqueous layer was brought to pH = 8 with an ice-cold solution of 14% aqueous NH_4OH. The aqueous layer was extracted with EtOAc (3 x 15 mL) and the combined organic layers were washed with brine (2 x 15 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford an oil which was flash chromatographed on basic alumina to provide 10-methoxyvellosimine **4** (720 mg, 90% yield). **^{1}H NMR** (300 MHz, DMSO-d_6) δ 10.66 (s, 1H), 9.57 (s, 1H), 7.17 (d, 1H, *J* = 8.7 Hz), 6.87 (d, 1H, *J* = 2.4 Hz), 6.66 (dd, 1H, *J* = 8.7, 2.4 Hz), 5.24 (q, 1H, *J* = 6.6 Hz), 4.10 (d, 1H, *J* = 8.3 Hz), 3.73 (s, 3H), 3.53 – 3.40 (m, 3H), 3.20 (t, 1H, *J* = 2.0 Hz), 2.88 (dd, 1H, *J* = 15.1, 5.0 Hz), 2.45 (d, 1H, *J* = 5.5 Hz), 2.41 (br, s, 1H), 1.97 (ddd, 1H, *J* = 22.3, 11.0, 1.3 Hz), 1.69 (dt, 1H, *J* = 12.4, 2.9 Hz), 1.56 (d, 3H, *J* = 6.7 Hz); **^{13}C NMR** (75 MHz, DMSO-d_6) δ 204.0, 153.4, 140.3, 136.4, 131.5, 127.8, 115.6, 112.0, 110.5, 102.5, 100.2, 55.7, 55.6 , 54.8, 50.2, 50.0, 33.2, 27.3, 26.7, 12.7; **EIMS** (*m/e*, relative intensity) 322 ($M^{+\bullet}$, 86), 321 (40), 293 (100), 279 (24), 199 (42), 198 (34), 85 (17), 83 (26); **HRMS** (ESI) *m/z* calcd for $C_{20}H_{23}N_2O_2$ $(M + H)^+$ 323.1760, found 323.1758. The spectral data for **4** were in good agreement with those of the natural product.[3]

Anal. Calcd. for $C_{20}H_{22}N_2O_2$ • 0.1032 CH_2Cl_2: C, 72.91; H, 6.76; N, 8.46. Found: C, 72.92; H, 7.05; N, 8.24.



(+)-Lochnerine (5)

To a stirred solution of (+)-10-methoxyvellosimine **4** (1 g, 3.10 mmol) in EtOH (20 mL) cooled to 0 °C in an ice bath, was added $NaBH_4$ (0.167g, 4.4 mmol) in one portion. The mixture which resulted was stirred at rt for 8 h. At this point analysis by TLC (silica gel) indicated the disappearance of the aldehyde **4**. The reaction was quenched with H_2O (0.2 mL) and the ethanol was evaporated under reduced pressure after which the residue was partitioned between CH_2Cl_2 (80 mL) and H_2O (5 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford a sticky solid which was flash chromatographed on silica gel, CH_2Cl_2/MeOH (9 : 1) to provide (+)-lochnerine **5** (900 mg, 90%) as a buff colored solid. **^{1}H NMR** (300 MHz, DMSO-d_6) δ 10.7 (s, 1H), 7.18 (d, 1H, *J* = 8.7 Hz), 6.88 (d, 1H, *J* = 2.3 Hz), 6.67 (dd, 1H, *J* = 8.7, 2.4 Hz), 5.37 (q, 1H, *J* = 6.6 Hz), 4.43 (t, 1H, *J* = 4.5 Hz), 4.20 (d, 1H, *J* = 7.1 Hz), 3.75 (s, 3H), 3.55 (dd, 2H, *J* = 38.5, 17.4 Hz), 3.32 – 3.29 (m, 2H), 2.85 (dd, 1H, *J* = 15.1, 4.6 Hz), 2.78 (br, s, 2H), 2.58 (d, 1H, *J* = 15.1 Hz), 2.03 – 1.97 (m, 1H), 1.73 – 1.64 (m, 2H), 1.58 (d, 3H, *J* = 6.6 Hz); **^{13}C NMR** (75 MHz, DMSO-d_6) δ 153.5 (C), 139.2 (C), 135.4 (C), 131.6 (C), 127.7 (C), 116.5 (CH), 112.1 (CH), 110.6 (CH), 103.0 (C), 100.2 (CH), 63.5 (CH_2), 55.7 (CH_3), 55.3 (CH_2), 55.2 (CH), 50.4 (CH), 44.2 (CH), 33.4 (CH_2), 27.4 (CH), 26.9 (CH_2), 13.0 (CH_3); **EIMS** (*m/e*, relative intensity) 324 ($M^{+\bullet}$, 100), 323 (88), 293 (31), 199 (44), 198 (42), 85 (21), 83 (32); **HRMS** (ESI) *m/z* calcd for $C_{20}H_{25}N_2O_2$ $(M + H)^+$ 325.1916, found 325.1912. The spectral data for **5** were identical to those reported in the literature.[4, 5]

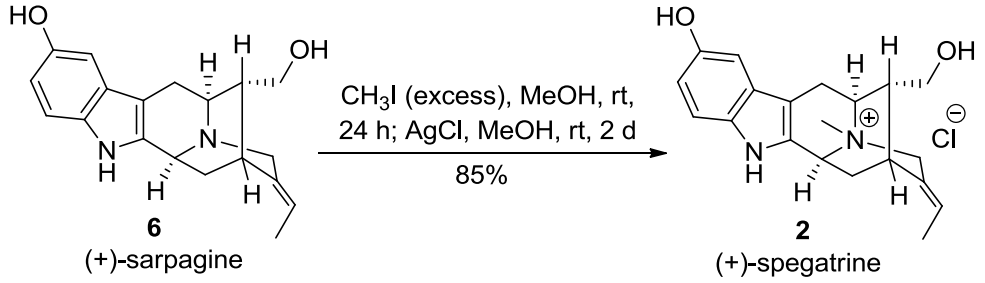


5
(+)-lochnerine

6
(+)-sarpagine

(+)-Sarpagine (6)

To a degassed solution of lochnerine **5** (45 mg, 0.138 mmol) in CH_2Cl_2 at -78 ^oC was added BBr_3 (0.76 mL, 1.0 M solution in CH_2Cl_2, 0.76 mmol) dropwise under an inert atmosphere. The solution was stirred at the same temperature for 2 h and then allowed to warm to rt and stirred for an additional 4 hours. The solvent was removed *in vacuo*. Then CH_2Cl_2 (10 mL) and solid $KHCO_3$ (0.14 g, 1.0 mmol) were added, and the mixture was cooled to 0 ^oC and MeOH (5 mL) was added dropwise. After stirring for 0.5 h at 0 ^oC the mixture was allowed to warm to rt and stirred for 1 h. The solvent was removed under reduced pressure to afford the crude product which was chromatographed [silica gel, $CHCl_3$/MeOH (v/v, 9 : 1)] to provide (+)-sarpagine **6** (34.4 mg, 80% yield). **^{1}H NMR** (300 MHz, CD_3OD) δ 7.24 (d, 1H, *J* = 8.7 Hz), 6.88 (d, 1H, *J* = 1.8 Hz), 6.75 (dd, 1H, *J* = 8.7, 2.4 Hz), 5.67 (q, 1H, *J* = 6.9 Hz), 5.02 (d, 1H, *J* = 9.9 Hz), 4.14 (dd, 2H, *J* = 21.5, 15.6 Hz), 3.66 – 3.50 (m, 3H), 3.27 (dd, 1H, J_2 = 5.1 Hz, part of the peak is embedded in the CD_3OD peak), 3.04 (br, s, 1H), 2.95 (d, 1H, *J* = 16.5 Hz), 2.43 (t, 1H, *J* = 11.7 Hz), 2.10 (dd, 1H, *J* = 14.7, 7.2 Hz), 2.00 (d, 1H, *J* = 14.1 Hz), 1.70 (d, 3H, *J* = 6.6 Hz); **^{13}C NMR** (75 MHz, CD_3OD) δ 150.5 (C), 132.4 (C), 131.8 (C), 126.9 (C), 126.1 (C), 121.8 (CH), 112 (CH), 111.6 (CH), 102.1 (CH), 101.3 (C), 62.4, 57.2, 53.8, 51.7, 42.5, 31.2, 26.1, 24.9, 11.9; **HRMS** (ESI) *m/z* calcd for $C_{19}H_{23}N_2O_2$ $(M + H)^+$ 311.1754, found 311.1743. The spectral data for **6** were identical to those reported in the literature.[6]

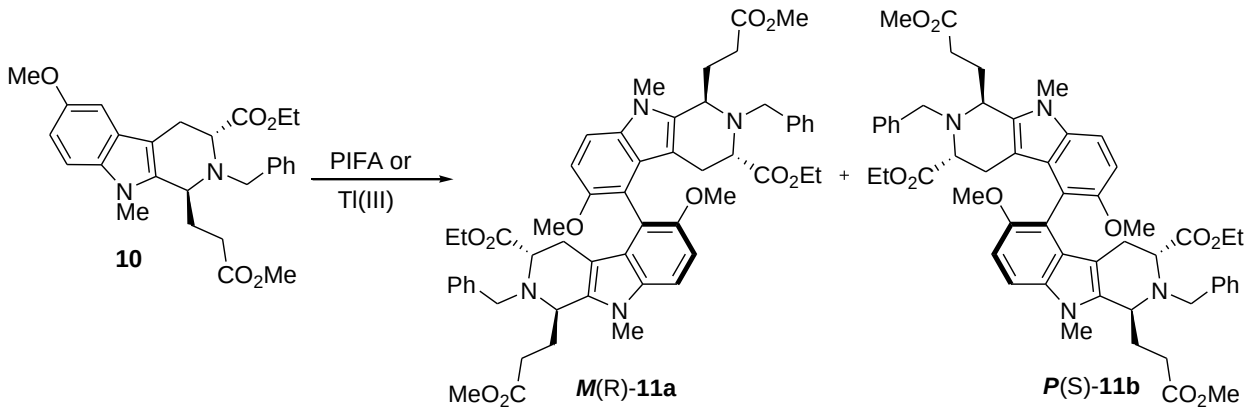


(+)-Spegatrine (2)

To a stirred solution of (+)-sarpagine **6** (40 mg, 0.13 mmol) in freshly distilled MeOH (1 mL) was added MeI (1 mL) and the reaction was allowed to stir at rt in the dark (48 h) until disappearance of the starting material **6** (TLC, silica gel). The solvent and excess MeI were removed under reduced pressure to provide the N_b-methiodide salt. The N_b-methiodide salt was then dissolved in freshly distilled MeOH (1 mL) and AgCl (100 mg) was added to it and the reaction mixture was then allowed to stir at rt in the dark for 2 days. The mixture was then filtered through Celite and the solvent was removed under reduced pressure to give a light brown colored oil. Column chromatography was carried out on neutral alumina with $CHCl_3$/MeOH (16 : 1) to provide (+)-spegatrine **2** (40 mg, 85% yield). **^{1}H NMR** (300 MHz, CD_3OD) δ 7.24 (d, 1H, *J* = 8.7 Hz), 6.89 (d, 1H, *J* = 2.3 Hz), 6.76 (dd, 1H, *J* = 8.7, 2.3 Hz), 5.66 (q, 1H, *J* = 6.6 Hz), 4.90 (1H, part of the peak is embedded in CD_3OD peak), 4.45 (dt, 1H, *J* = 15.6, 2.3 Hz), 4.23 (d, 1H, *J* = 15.6 Hz), 3.61 – 3.53 (m, 3H), 3.28 (dd, 1H, *J* = 17.2, 4.9 Hz), 3.16 – 3.01 (m, 5H), 2.53 (t, 1H, *J* = 11.2 Hz), 2.21 – 2.12 (m, 2H), 1.72 (d, 3H, *J* = 6.8 Hz); **^{13}C NMR** (75 MHz, CD_3OD) δ 150.8, 132.0, 131.6, 127.6 (2 x C), 126.7, 120.6, 112.2, 111.6, 102.0, 99.7, 65.3, 64.3, 62.3, 60.9, 46.6, 43.5, 31.9, 25.9, 23.8, 11.5; **HRMS** (ESI) *m/z* calcd for $C_{20}H_{25}N_2O_2$ $(M)^+$ 325.1916, found 325.1920.

^{1}H NMR (300 MHz, D_2O) δ 7.32 (d, 1H, *J* = 8.7 Hz), 6.95 (d, 1H, *J* = 1.9 Hz), 6.79 (dd, 1H, *J* = 8.4, 2.4 Hz), 5.58 (q, 1H, *J* = 6.7 Hz), 4.76 (d, 1H, *J* = 10.7 Hz, part of the peak is embedded in D_2O peak), 4.28 (d, 1H, *J* = 14.6 Hz), 4.08 (d, 1H, *J* = 15.6 Hz), 3.49 (d, 2H, *J* = 7.2 Hz), 3.38 (t, 1H, *J* = 6.3 Hz), 3.15 (dd, 1H, *J* = 17.4, 4.2 Hz), 3.01 – 2.88 (m, 5H), 2.42 (t, 1H, *J* = 11.5 Hz), 2.04 - 1.96 (m, 2H), 1.58 (d, 3H, *J* = 6.6 Hz); **^{13}C NMR** (75 MHz, D_2O) δ 149.1, 132.6, 131.9, 126.3 (2 x C), 121.6, 112.8, 112.3, 102.7, 100.3, 64.6, 64.6, 62.0, 60.7, 47.1, 43.1, 31.3, 25.5, 23.4, 12.0. The spectral data for **2** were identical to those reported in the literature.[7, 8]

Non-phenolic oxidative coupling of the β-carboline 10



PIFA-mediated oxidative coupling: To a stirred solution of the β-carboline **10** (55 mg, 0.118 mmol) in dry CH_2Cl_2 (1.0 mL) under an inert atmosphere at -40 °C was added a solution of PIFA (40 mg, 0.094 mmol) and boron trifluoride diethyl etherate [50.41 mg, 0.355 mmol in CH_2Cl_2 (2.0 mL), precooled to -40 °C] via a double ended needle transfer. The reaction mixture which resulted was stirred at -40 °C for 0.5 h. Analysis of the reaction mixture by TLC [silica gel, $CHCl_3$: MeOH (v/v, 9 : 1)] indicated complete conversion of the starting material **10**. The reaction mixture was diluted CH_2Cl_2 (25 mL) and cooled to 0 ^oC, after which it was brought to pH = 8 with a cold aqueous solution of saturated $NaHCO_3$. The aqueous layer which resulted was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic layers were washed with a saturated aqueous solution of $NaHSO_3$ (2 x 15 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford a dark oil. The crude diastereomeric mixture was purified by flash chromatography on silica gel (hexanes/ethyl acetate) to provide a combined yield of **11a** + **11b**: 33 mg (30%) with a diastereomeric ratio of 4 : 1 in favor of **11a** by integration of the ^1H NMR spectrum.

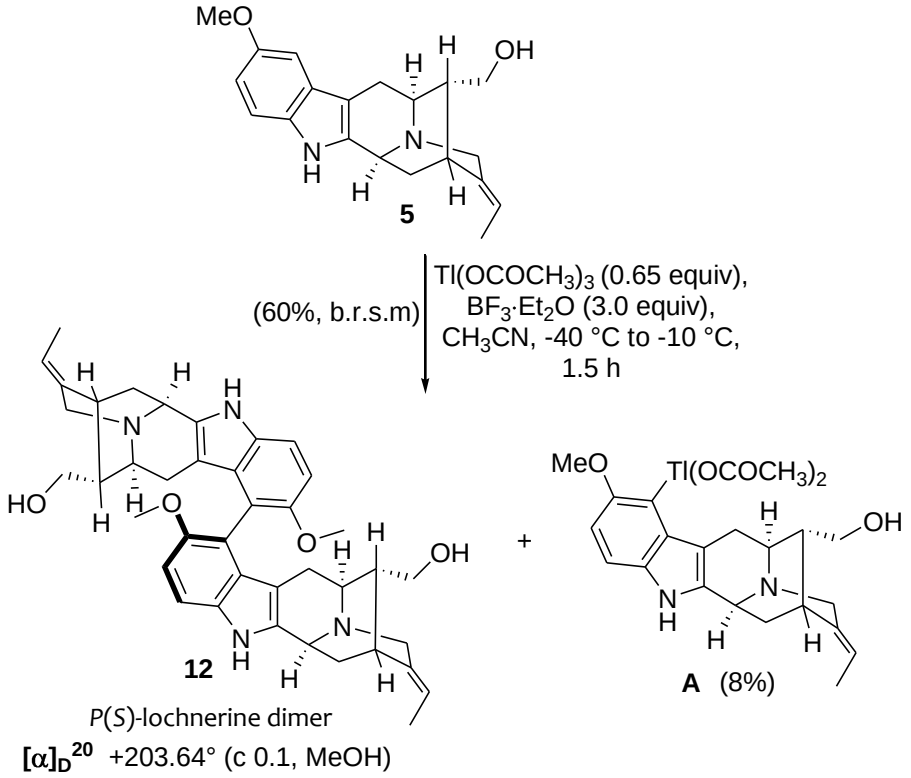
Thallium-mediated oxidative coupling:

To a stirred solution of the β-carboline **10** (200 mg, 0.430 mmol) in dry acetonitrile (10 mL) under an inert atmosphere at -40 °C was added a solution of thallium(III) acetate (115.0 mg, 0.301 mmol) and boron trifluoride diethyl etherate [183.0 mg, 1.29 mmol in MeCN (10 mL) precooled to -40 °C]via a double ended needle transfer. The reaction mixture which resulted

was stirred at -40 °C for 1.25 h. Analysis of the reaction mixture by TLC [silica gel, $CHCl_3$/MeOH (v/v, 9 : 1)] indicated formation of the two atropdiastereomers (**11a** and **11b**) accompanied by some unreacted starting material **10**. The cold reaction mixture was diluted with CH_2Cl_2 (25 mL) and the solvent was removed under reduced pressure to give a brown residue. The residue was dissolved in fresh CH_2Cl_2 (25 mL) and cooled to 0 °C after which it was brought to pH = 8 with a cold aqueous solution of saturated $NaHCO_3$. The aqueous layer which resulted was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic layers were washed with brine (2 x 15 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford a dark brown oil. The crude diastereomeric mixture was purified by flash chromatography on silica gel (hexanes/ethyl acetate) to provide a combined yield of **11a** + **11b**: 227 mg (67%) with a diastereomeric ratio of 3 : 7 in favor of **11b**; recovered starting material **10** (28 mg, 14%). Recrystallization of **11b** from ethanol gave light brown crystals. X-ray analysis of **11b** established the axial chirality as ***P***(S). **Note: Thallium compounds are toxic. Do not breath, ingest or get on skin: Use Caution.**

***M*(R)-(11a)**: $\mathbf{[\alpha]_D^{20}}$ -90 (c 0.9, MeOH); $\mathbf{R_f}$ 0.35 (silica gel, EtOAc/hexanes, 2 : 3); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.34 – 7.23 (m, 12H), 7.06 (d, 2H, *J* = 8.8 Hz), 4.11 – 4.01 (m, 4H), 3.83 – 3.80 (m, 8H), 3.73 (d, 2H, *J* = 13.1 Hz), 3.68 – 3.64 (m, 8H), 3.50 (s, 6H), 3.41 (d, 2H, *J* = 13.3 Hz), 2.53 (dt, 2H, *J* = 17.3, 7.0 Hz), 2.41 – 2.26 (m, 4H), 2.10 – 1.99 (m, 2H), 1.91 – 1.84 (m, 2H), 1.77 (dd, 2H, *J* = 16.6, 4.9 Hz), 1.20 (t, 6H, *J* = 7.1 Hz); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 174.1 (2 x C), 172.7 (2 x C), 151.7 (2 x C), 139.6 (2 x C), 136.2 (2 x C), 133.1 (2 x C), 129.2 (4 x CH), 128.0 (4 x CH), 127.1 (2 x C), 126.8 (2 x CH), 117.1 (2 x C), 108.7 (2 x CH), 108.2 (2 x CH), 106.9 (2 x C), 60.2 (2 x CH_2), 57.8 (2 x CH_3), 56.2 (2 x CH), 53.4 (2 x CH), 52.7 (2 x CH_2), 51.2 (2 x CH_3), 30.0 (2 x CH_3), 29.3 (2 x CH_2), 28.0 (2 x CH_2), 20.7 (2 x CH_2), 14.1 (2 x CH_3); **HRMS** (ESI) *m/z* calcd for $C_{54}H_{63}N_4O_{10}$ $(M + H)^+$ 927.4539, found 927.4580.

***P*(S)-(11b)**: $[\alpha]_D^{20}$ -61.06 (c 0.8, MeOH); $\mathbf{R}_f$ 0.27 (silica gel, EtOAc/hexanes, 2 : 3); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.27 (d, 2H, *J* = 11.5 Hz), 7.21 – 7.14 (m, 10H), 7.05 (d, 2H, *J* = 11 Hz), 4.13 (q, 4H, *J* = 9 Hz), 3.80 – 3.77 (m, 8H), 3.66 – 3.58 (m, 10H), 3.47 (s, 6H), 3.24 (d, 2H, *J* = 16 Hz), 2.58 – 2.51 (m, 2H), 2.37 (dt, 2H, *J* = 22, 6.5 Hz), 2.20 (dd, 2H, *J* = 20.5, 14.5 Hz), 2.02 (dd, 2H, *J* = 21, 6.0 Hz), 1.97 – 1.88 (m, 2H), 1.83 – 1.74 (m, 2H), 1.22 (t, 6H, *J* = 9.0 Hz); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.9 (2 x C), 172.6 (2 x C), 151.5 (2 x C), 139.1 (2 x C), 135.9 (2 x C), 133.2 (2 x C), 129.0 (4 x CH), 127.9 (4 x CH), 127.5 (2 x C), 126.7 (2 x CH), 117.2 (2 x C), 108.5 (2 x CH), 108.0 (2 x CH), 106.3 (2 x C), 60.2 (2 x CH_2), 58.0 (2 x CH_3), 55.7 (2 x CH), 52.9 (2 x CH), 52.5 (2 x CH_2), 51.2 (2 x CH_3), 29.6 (2 x CH_3 + 2 x CH_2), 27.8 (2 x CH_2), 20.2 (2 x CH_2), 14.1 (2 x CH_3); **EIMS** (*m/e*, relative intensity) 927 ($M^{+\bullet}$, 14), 840 (16), 838 (100), 661 (14); **HRMS** (ESI) *m/z* calcd for $C_{54}H_{63}N_4O_{10}$ $(M + H)^+$ 927.4539, found 927.4584.



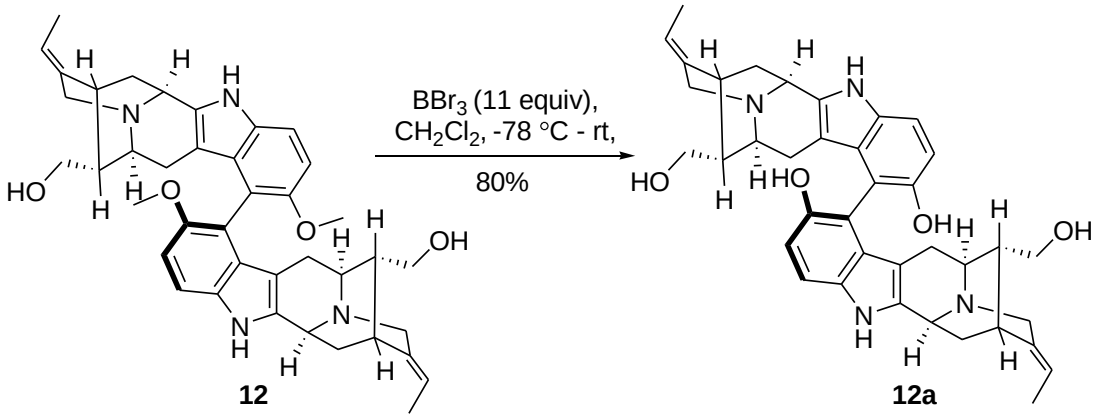
C(9)-C(9′) lochnerine dimer (12)

To a stirred solution of thallium(III) acetate (47 mg, 0.123 mmol) in acetonitrile (2.5 mL) cooled to -40 °C was added boron trifluoride diethyl etherate (80.0 mg, 72.0 μL, 0.567 mmol) and the reaction mixture allowed to stir at -40 °C for 15 min. To this solution was added solid lochnerine **5** (61.4 mg, 0.189 mmol) in one portion followed by additional acetonitrile (2 mL). The dark red-colored reaction mixture was stirred at -40 °C for 15 min after which the temperature was allowed to rise to -10 °C. At this time the color of the reaction mixture had turned brownish. Analysis of the reaction mixture by TLC [silica gel, $CHCl_3$/MeOH (v/v, 4 : 1)] indicated the presence of unreacted starting material **5**, followed by the arylthallium compound **A** and the dimer **12** with a little baseline impurity. The reaction mixture was diluted with dichloromethane (10 mL) and neutralized with a cold aqueous solution of saturated $NaHCO_3$. The organic layer was separated, the aqueous layer was then extracted with dichloromethane (3 x 20 mL) and the combined organic extracts were dried ($MgSO_4$), after which the solvent was evaporated under reduced pressure to provide a light brown residue. This solid was subjected to flash silica gel column chromatography (gradient elution from chloroform to 40% methanol in chloroform with 5% methanolic ammonia solution). Evaporation of the eluant under reduced pressure followed by crystallization of the residual solid thus obtained from methanol gave the dimer **12** (64.6 mg, 60% yield, b.r.s.m), recovered starting material **5** (7.36 mg, 12%). Recrystallization of the dimer **12** from methanol gave light brown crystals. X-ray analysis of **12** established the axial chirality as ***P***(S). The arylthallium byproduct **A** was confirmed by mass spectroscopy and isolated in 8% (9 mg) yield.

12: $\mathbf{[\alpha]_D^{25}}$ + 203.64 (c 0.1, MeOH), $\mathbf{R_f}$ 0.44 (silica gel, CH_2Cl_2/MeOH, 4.4 : 0.6); **^{1}H NMR** (600 MHz, CD_3OD) δ 7.29 (d, 2H, *J* = 9.0 Hz), 6.94 (d, 2H, *J* = 8.4 Hz), 5.40 (q, 2H, *J* = 6.0 Hz), 4.12 (d, 2H, *J* = 9.6 Hz), 3.70 (s, 6H), 3.52 (d, 2H, *J* = 16.8 Hz), 3.28 (dd, 4H, J_2 = 9.6 Hz, part of the peak is embedded in CD_3OD peak), 3.24 (dd, 2H, *J* = 10.2, 5.4 Hz), 2.88 (br, s,

2H), 2.23 (t, 2H, *J* = 5.4 Hz), 2.09 (t, 2H, *J* = 11.4 Hz), 2.03 (dd, 2H, *J* = 15.9, 4.8 Hz), 1.82 – 1.77 (m, 6H), 1.62 (d, 6H, *J* = 7.2 Hz); **^{13}C NMR** (150 MHz, CD_3OD) δ 150.9 (2 x C), 138.8 (2 x C), 134.5 (2 x C), 132.5 (2 x C), 128.1 (2 x C), 117.0 (2 x C), 116.9 (2 x CH), 109.9 (2 x CH), 108.1 (2 x CH), 103.9 (2 x C), 63.2 (2 x CH_2), 56.8 (2 x CH_3), 55.0 (2 x CH_2), 54.2 (2 x CH), 50.4 (2 x CH), 43.8 (2 x CH), 32.9 (2 x CH_2), 27.0 (2 x CH), 26.7 (2 x CH_2), 11.6 (2 x CH_3); **HRMS** (MALDI) *m/z* calcd for $C_{40}H_{47}N_4O_4$ $(M + H)^+$ 647.3597, found 647.3561; **HRMS** (ESI) *m/z* calcd for $[C_{40}H_{48}N_4O_4]^{2+}$ $(M + 2H)^{2+}$ 324.1837, found 324.1837.

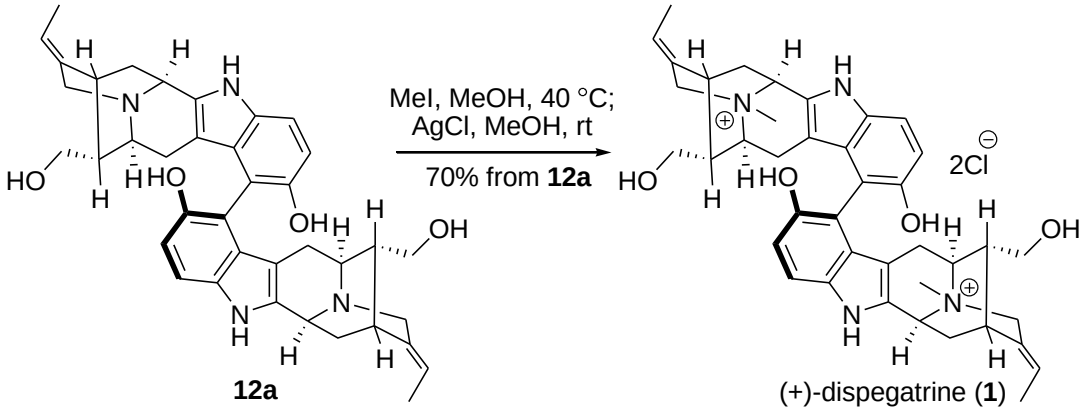
A: $\mathbf{R_f}$ 0.60 (silica gel, DCM/MeOH, 4.4 : 0.6); **HRMS** (MALDI) *m/z* ($M^{+\bullet}$) calcd for $C_{24}H_{29}N_2O_6Tl$, 646.1770, found 646.1765.



C(9)-C(9′) sarpagine dimer (12a)

To a degassed solution of **12** (18 mg, 0.0278 mmol) in CH_2Cl_2 (1 mL) at -78 °C was added a solution of BBr_3 (0.306 mL of a 1.0 M solution of BBr_3 in dry CH_2Cl_2, 0.306 mmol) dropwise under an inert atmosphere of Ar. The mixture was stirred at -78 °C for 2 h and slowly allowed to warm to rt. After an additional 2 h of stirring at rt, the reaction solution was cooled in an ice bath and treated with a saturated aqueous solution of $NaHCO_3$ to bring the pH to 8. The aqueous layer was extracted with DCM/MeOH (v/v, 9: 1; 5 x 15 mL), and the combined organic extracts were dried ($MgSO_4$) and the solvent evaporated under reduced pressure to provide an off-white residue of **12a** (13.77 mg, 80% yield). No further purification was attempted on the material and it was used directly in the next step. $\mathbf{R_f}$ 0.38

(silica gel, DCM : MeOH, 4.4 : 0.6); **^{1}H NMR** (300 MHz, CD_3OD) δ 7.27 (d, 2H, *J* = 8.6 Hz), 6.88 (d, 2H, *J* = 8.6 Hz), 5.53 (q, 2H, *J* = 6.9 Hz), 4.61 (d, 2H, *J* = 9.4 Hz), 3.92 (d, 2H, *J* = 15.9 Hz), 3.72 (d, 2H, *J* = 16.0 Hz), 3.28 (dd, 2H, *J* = 10.5, 8.7 Hz), 3.17 (dd, 2H, *J* = 10.7, 5.9 Hz), 2.93 (br, s, 2H), 2.68 (t, 2H, *J* = 5.6 Hz), 2.28 (t, 2H, *J* = 11.2 Hz), 2.08 (dd, 2H, *J* = 16.4, 4.9 Hz), 1.94 – 1.87 (m, 2H), 1.74 (q, 2H, *J* = 6.6 Hz), 1.63 (d, 8H, *J* = 6.2 Hz); **^{13}C NMR** (75 MHz, CD_3OD) δ 147.3 (2 x C), 134.9 (2 x C), 131.9 (2 x C), 129.6 (2 x C), 128.0 (2 x C), 119.6 (2 x CH), 113.3 (2 x C), 111.5 (2 x CH), 110.9 (2 x CH), 103.2 (2 x C), 62.5 (2 x CH_2), 55.6 (2 x CH), 54.4 (2 x CH_2), 51.1 (2 x CH), 42.7 (2 x CH), 31.9 (2 x CH_2), 26.3 (2 x CH), 25.9 (2 x CH_2), 11.6 (2 x CH_3); **HRMS** (MALDI) *m/z* calcd for $C_{38}H_{43}N_4O_4$ $(M + H)^+$ 619.3284, found 619.3299.



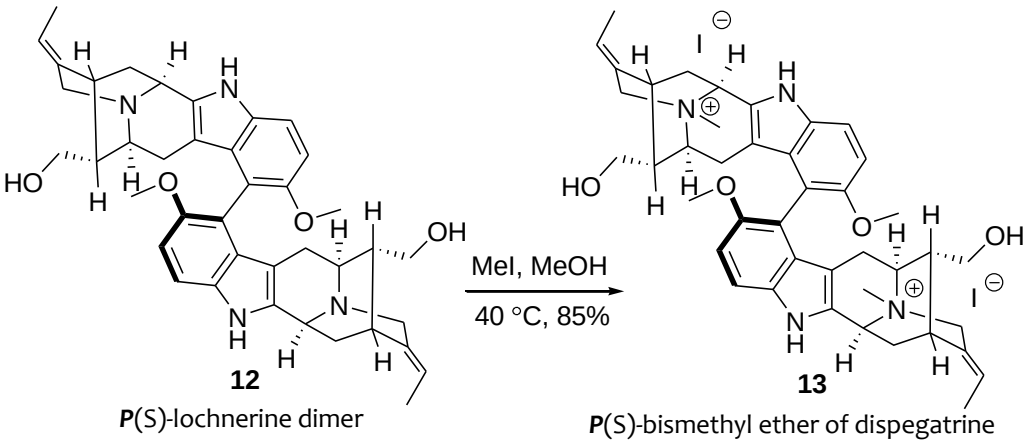
(+)-Dispegatrine (**1**)

To a stirred solution of bisphenol **12a** (10 mg, 0.016 mmol) in freshly distilled MeOH (1 mL) was added MeI (2 mL) and the reaction was allowed to stir in a sealed tube at 40 °C in the dark until disappearance of the starting material **12a** by TLC. The solvent and excess MeI was removed under reduced pressure to provide the N_b-methiodide salt. A sample for LRMS indicated formation of this salt.

HRMS (FAB) *m/z* calcd for $C_{40}H_{48}IN_4O_4$ (M^+) 775.2720, found 775.2752.

The N_b-methiodide salt was then dissolved in freshly distilled MeOH (1 mL) and AgCl (2.0 mg) was added to it and the reaction mixture was allowed to stir at rt in the dark for 2 days.

The mixture was then filtered through Celite, and the solvent was removed under reduced pressure to afford (+)-dispegatrine **1** (8.1 mg, 70%). The ^{1}H NMR of **1** is in good agreement with the values reported in the literature (Tables 4).[5] The ambiguity with the reported C-5 protons in the reported ^{1}H NMR was resolved by carrying out correlation experiments on compound **12**, **13** and comparing the chemical shifts of the dimeric intermediates **12, 13** and **12a**. $\mathbf{R_f}$ 0.25 (silica gel, EtOAc : acetone : methanol : H_2O : conc HCl; 3 : 1 : 1 : 0.5 : 2 drops); **^{1}H NMR** (500 MHz, CD_3OD) δ 7.30 (d, 2H, *J* = 9.0 Hz), 6.92 (d, 2H, *J* = 8.5 Hz), 5.59 (q, 2H, *J* = 6.5 Hz), 4.99 (d, 2H, *J* = 10 Hz, part of the peak is embedded in the CD_3OD peak), 4.45 (d, 2H, *J* = 15.5 Hz), 4.13 (d, 2H, *J* = 15.5 Hz), 3.40 – 3.29 (4H's are embedded in the CD_3OD peak), 3.18 – 3.15 (m, 2H), 3.11 (br, s, 2H), 2.99 (s, 6H), 2.52 (t, 2H, *J* = 11.0 Hz), 2.30 - 2.26 (m, 4H), 2.12 – 2.06 (m, 4H), 1.68 (d, 6H, *J* = 6.0 Hz); **^{1}H NMR** (500 MHz, D_2O) δ 7.37 (d, 2H, *J* = 8.5 Hz), 6.87 (d, 2H, *J* = 8.5 Hz), 5.48 (q, 2H, *J* = 6.4 Hz), 4.79 (2H's are embedded in the D_2O peak), 4.19 (d, 2H, *J* = 15.0 Hz), 3.93 (d, 2H, *J* = 15.0 Hz), 3.33 (d, 4H, *J* = 8.0 Hz), 2.96 (br, s, 4H), 2.77 (s, 6H), 2.40 (t, 2H, *J* = 11.0 Hz), 2.14 (dd, 2H, *J* = 18.8, 6.5 Hz), 2.04 – 2.00 (m, 4H), 1.93 (q, 2H, *J* = 7.5 Hz), 1.51 (d, 6H, *J* = 7.5 Hz); **HRMS** (ESI) *m/z* calcd for $[C_{40}H_{48}N_4O_4]^{2+}$ $[(M)^{2+}]$ 324.1838, found 324.1845.



12
P(S)-lochnerine dimer

13
P(S)-bismethyl ether of dispegatrine

Bismethyl ether of dispegatrine (**13**)

To a stirred solution of **12** (20 mg, 0.0309 mmol) in freshly distilled MeOH (2 mL) was added MeI (3 mL) and the reaction was allowed to stir at 40 °C in a sealed tube in the dark until disappearance of the starting material **12** was observed by TLC (12 h). The solvent and excess MeI was removed under reduced pressure to provide a reddish brown oil. Column chromatography was carried out on neutral alumina with $CHCl_3$/MeOH (16 : 1) to provide the N_b-methiodide salt **13** as a buff colored solid (17.79 mg, 85%). **^{1}H NMR** (600 MHz, CD_3OD) δ 7.44 (d, 2H, *J* = 8.4 Hz), 7.11 (d, 2H, *J* = 9.0 Hz), 5.60 (q, 2H, *J* = 6.6 Hz), 4.94 (2H, Protons embedded in CD_3OD peak), 4.39 (d, 2H, *J* = 15.6 Hz), 4.08 (d, 2H, *J* = 15.6 Hz), 3.74 (s, 6H), 3.43 (t, 2H, *J* = 9.6 Hz), 3.33 (2H, Protons embedded in CD_3OD peak), 3.13 – 3.11 (m, 4H), 2.92 (s, 6H), 2.53 (t, 2H, *J* = 11.4 Hz), 2.22 (s, 4H), 2.16 (d, 2H, *J* = 9.6 Hz), 2.07 (q, 2H, *J* = 7.2 Hz), 1.69 (d, 6H, *J* = 6.0 Hz); **^{13}C NMR** (150 MHz, CD_3OD) δ 151.6 (2 x C), 132.9 (2 x C), 132.6 (2 x C), 127.5 (2 x C), 126.6 (2 x C), 120.7 (2 x C), 116.4 (2 x C), 111.2 (2 x CH), 109.8 (2 x CH), 100.6 (2 x C), 64.9 (2 x CH), 64.2 (2 x CH_2), 62.1 (2 x CH_2), 60.8 (2 x CH), 56.7 (2 x CH_3), 46.5 (2 x CH_3), 43.3 (2 x CH), 31.9 (2 x CH_2), 25.8 (2 x CH), 24.2 (2 x CH_2), 11.6 (2 x CH_3); **LRMS** (FAB) *m/z* calcd for $C_{42}H_{52}IN_4O_4$ (M^+) 803.3033, found 803.3057; **HRMS** (ESI) *m/z* calcd for $[C_{42}H_{52}N_4O_4]^{2+}$ $(M)^{2+}$, 338.1994, found 338.1982.

Table 1. Comparison of the ^{1}H NMR Data for Natural and Synthetic (+)-10-Methoxy-vellosimine (**4**)[3, 5]

Protons[a]	**^{1}H NMR Natural**[a,b,c,d]	**^{1}H NMR Synthetic (300 MHz, DMSO-d_6)**[b]
	nr	10.66 (s, 1H)
H-17	9.0 (s, 1H)	9.57 (s, 1H)
	nr	7.17 (d, 1H, *J* = 8.7 Hz)
	nr	6.87 (d, 1H, *J* = 2.4 Hz)
	nr	6.66 (dd, 1H, *J* = 8.7, 2.4 Hz)
H-19	5.00 (q, *J* = 7.0 Hz)	5.24 (q, 1H, *J* = 6.6 Hz)
	nr	4.10 (d, 1H, *J* = 8.3 Hz)
Ar-OMe	3.58 (s)	3.73 (s, 3H)
	nr	3.53 – 3.40 (m, 3H)
	nr	3.20 (t, 1H, *J* = 2.0 Hz)
	nr	2.88 (dd, 1H, *J* = 15.1, 5.0 Hz)
	nr	2.45 (d, 1H, *J* = 5.5 Hz)
	nr	2.41 (br, s, 1H)
	nr	1.97 (ddd, 1H, *J* = 22.3, 11.0, 1.3 Hz)
	nr	1.69 (dt, 1H, *J* = 12.4, 2.9 Hz)
3(H-18)	1.50 (d, *J* = 7.0 Hz)	1.56 (d, 3H, *J* = 6.7 Hz)

[a]The numbering and the assignment of the protons follows from the literature.[3, 5] [b]Values are in ppm (δ). [c]nr = not reported. [d]NMR solvent and frequency (MHz) not reported.

Table 2. Comparison of the ^{1}H NMR Data for Natural and Synthetic (+)-Lochnerine (**5**)[4, 5]

Protons[a]	**^{1}H NMR Natural ($CDCl_3$: CD_3OD, 1 : 1)**[a,b,c]	**^{1}H NMR Synthetic (300 MHz, DMSO-d_6)**[b]
NH	9.30 (br, s)	10.7 (s, 1H)
H-12, 11, 9	7.30 – 6.70 {	7.18 (d, 1H, *J* = 8.7 Hz) 6.88 (d, 1H, *J* = 2.3 Hz) 6.67 (dd, 1H, *J* = 8.7, 2.4 Hz)
H-19	5.35 (q)	5.37 (q, 1H, *J* = 6.6 Hz)
	nr	4.43 (t, 1H, *J* = 4.5 Hz)
	nr	4.20 (d, 1H, *J* = 7.1 Hz)
Ar-OMe	3.85 (s)	3.75 (s, 3H)
	nr	3.55 (dd, 2H, *J* = 38.5, 17.4 Hz)
	nr	3.32 – 3.29 (m, 2H)
	nr	2.85 (dd, 1H, *J* = 15.1, 4.6 Hz)
	nr	2.78 (br, s, 2H)
	nr	2.58 (d, 1H, *J* = 15.1 Hz)
	nr	2.03 – 1.97 (m, 1H)
	nr	1.73 – 1.64 (m, 2H)
3(H-18)	1.60 (d)	1.58 (d, 3H, *J* = 6.6 Hz)

[a]The numbering and the assignment of the protons follows from the literature.[4, 5] [b]Values are in ppm (δ). [c]nr = not reported.

Table 3. Comparison of the ^{13}C NMR Data for Natural and Synthetic (+)-Lochnerine (**5**)[4a, 5]

Carbons[a]	^{13}C NMR Natural (22.63/15.08 MHz, DMSO-d_6)[a,b]	^{13}C NMR Synthetic (75 MHz, DMSO-d_6)[b]
2	137.3 (C)	135.4 (C)
3	49.8 (CH)	50.4 (CH)
5	54.4 (CH)	55.2 (CH)
6	27.4 (CH_2)	26.9 (CH_2)
7	102.9 (C)	103.0 (C)
8	127.6 (C)	127.7 (C)
9	99.8 (CH)	100.2 (CH)
10	153.0 (C)	153.5 (C)
11	109.8 (CH)	110.6 (CH)
12	111.5 (CH)	112.1 (CH)
13	131.2 (C)	131.6 (C)
14	33.5 (CH_2)	33.4 (CH_2)
15	27.4 (CH)	27.4 (CH)
16	44.4 (CH)	44.2 (CH)
17	63.4 (CH_2)	63.5 (CH_2)
18	12.5 (CH_3)	13.0 (CH_3)
19	114.9 (CH)	116.5 (CH)
20	140.4 (C)	139.2 (C)
21	55.5 (CH_2)	55.3 (CH_2)
MeO	55.5 (CH_3)	55.7 (CH_3)

[a]The numbering and the assignment of the carbon atoms follows from the literature.[4a, 5] [b]Values are in ppm (δ).

Table 4. Comparison of the ^{1}H NMR Data for Natural and Synthetic (+)-Sarpagine (**6**)[6]

Protons[a]	**^{1}H NMR Natural (200 MHz, $CDCl_3$: DMSO-d_6 1 : 1)**[a,b,c]	**^{1}H NMR Synthetic (300 MHz, CD_3OD)**[b]
NH	10.08 (s)	-
H-12, 11, 9	6.96 – 6.48 {	7.24 (d, 1H, *J* = 8.7 Hz) 6.88 (d, 1H, *J* = 1.8 Hz) 6.75 (dd, 1H, *J* = 8.7, 2.4 Hz),
H-19	5.27 (q, *J* = 7.0 Hz)	5.67 (q, 1H, *J* = 6.9 Hz)
	nr	5.02 (d, 1H, *J* = 9.9 Hz)
H-17	3.96 (br, d, 1H)	4.14 (dd, 2H, *J* = 21.5, 15.6 Hz)
	nr	3.66 – 3.50 (m, 3H)
	nr	3.27 (dd, 1H, J_2 = 5.1 Hz, part of the peak is embedded in the CD_3OD peak)
	nr	3.04 (br, s, 1H)
	nr	2.95 (d, 1H, *J* = 16.5 Hz)
	nr	2.43 (t, 1H, *J* = 11.7 Hz)
	nr	2.10 (dd, 1H, *J* = 14.7, 7.2 Hz)
	nr	2.00 (d, 1H, *J* = 14.1 Hz)
3(H-18)	1.55 (d, *J* = 7.0 Hz)	1.70 (d, 3H, *J* = 6.6 Hz)

[a]The numbering and the assignment of the protons follows that from the literature.[6] [b]Values are in ppm (δ)

[c]nr = not reported.

Table 5. Comparison of the ^{13}C NMR Data for Natural and Synthetic (+)-Sarpagine (**6**)[6]

Carbons[a]	**^{13}C NMR Natural (50 MHz, $CDCl_3$: DMSO-d_6 1 : 1)**[a,b]	**^{13}C NMR Synthetic (75 MHz, CD_3OD)**[b]
2	136.6 (C)	131.8 (C)
3	50.2 (CH)	51.7
5	54.5 (CH)	53.8
6	26.9 (CH_2)	24.9
7	102.3 (C)	102.1 (C)
8	128.0 (C)	126.1 (C)
9	102.0 (CH)	101.3 (CH)
10	150.1 (C)	150.5 (C)
11	110.0 (CH)	111.6 (CH)
12	111.0 (CH)	112.0 (CH)
13	130.7 (C)	126.9 (C)
14	33.6 (CH_2)	31.2
15	27.4 (CH)	26.1
16	44.3 (CH)	42.5
17	63.6 (CH_2)	62.4
18	12.6 (CH_3)	11.9
19	115.2 (CH)	121.8 (CH)
20	139.9 (C)	132.4 (C)
21	55.8 (CH_2)	57.2

[a]The numbering and the assignment of the carbon atoms follows that from the literature.[6] [b]Values are in ppm (δ).

Table 6. Comparison of the ^{1}H NMR Data for Natural and Synthetic (+)-Spegatrine (**1**)[7]

Protons[a]	**^{1}H NMR Natural (400 MHz, D_2O)**[a,b]	**^{1}H NMR Synthetic (300 MHz, D_2O)**[b]
H-12	7.35 (d, *J* = 8.0 Hz)	7.32 (d, 1H, *J* = 8.7 Hz)
H-9	6.97 (d, *J* = 2.0 Hz)	6.95 (d, 1H, *J* = 1.9 Hz)
H-11	6.82 (dd, *J* = 8.0, 2.0 Hz)	6.79 (dd, 1H, *J* = 8.4, 2.4 Hz)
H-19	5.59 (q, *J* = 6.0 Hz)	5.58 (q, 1H, *J* = 6.7 Hz)
H-3	4.75 (dd, *J* = 8.0, 4.0 Hz)	4.76 (d, 1H, *J* = 10.7 Hz, part of the peak is embedded in D_2O peak)
H-21α	4.27 (d, *J* = 16.0 Hz)	4.28 (d, 1H, *J* = 14.6 Hz)
H-21β	4.06 (d, *J* = 16.0 Hz)	4.08 (d, 1H, *J* = 15.6 Hz)
2(H-17)	3.48 (m)	3.49 (d, 2H, *J* = 7.2 Hz)
H-5	3.30 (t, *J* = 6.0 Hz)	3.38 (t, 1H, *J* = 6.3 Hz)
H-6α	3.10 (dd, *J* = 17.0 Hz)	3.15 (dd, 1H, *J* = 17.4, 4.2 Hz)
N_b^+-Me	2.86 (s, 3H)	} 3.01 – 2.88 (m, 5H)
H-6β, 16	2.86 (t)	
H-15	2.37 (t)	2.42 (t, 1H, *J* = 11.5 Hz)
H-14α	1.92 (dd, *J* = 14.0, 8.0 Hz)	} 2.04 - 1.96 (m, 2H)
H-14β	1.83 (dd, *J* = 14.0, 4.0 Hz)	
3(H-18)	1.59 (d, *J* = 6.0 Hz)	1.58 (d, 3H, *J* = 6.6 Hz)

[a]The numbering and the assignment of the protons follows that from the literature.[7] [b]Values are in ppm (δ).

Table 7. Comparison of the ^{13}C NMR Data for Natural and Synthetic (+)-Spegatrine (**1**)[8]

Carbons[a]	**^{13}C NMR Natural (90 MHz, CF_3COOD)**[a,b]	**^{13}C NMR Synthetic (75 MHz, D_2O)**[b]
2	126.8 (C)	126.3 (C)
3	63.4 (CH)	60.7
5	67.7 (CH)	64.6
6	25.3 (CH_2)	23.4
7	102.3 (C)	100.3 (C)
8	126.1 (C)	126.3 (C)
9	102.0 (CH)	102.7 (CH)
10	149.5 (C)	149.1 (C)
11	125.8 (CH)	121.6 (CH)
12	125.0 (CH)	112.8 (CH)
13	128.1 (C)	131.9 (C)
14	33.4 (CH_2)	31.3
15	27.6 (CH)	25.5
16	42.1 (CH)	43.1
17	69.0 (CH_2)	64.6
18	13.0 (CH_3)	12.0
19	114.4 (CH)	112.3 (CH)
20	132.7 (C)	132.6 (C)
21	67.2 (CH_2)	62.0
N_b-Me	49.2	47.1

[a]The numbering and the assignment of the carbon atoms follows that from the literature.[8] [b]Values are in ppm (δ).

Table 8. Comparison of the ^{1}H NMR Data for Natural and Synthetic Dispegatrine (**1**)[8] and the Bismethyl Ether of Dispegatrine (**13**).

Proton's[a,b]	**^{1}H NMR Natural 1 (200 MHz, D_2O)**[a,b]	**^{1}H NMR Synthetic 1 (500 MHz, D_2O)**[b,c]	**^{1}H NMR of 13 600 MHz (CD_3OD)**[b]
H-12,12′	7.48 (d, *J* = 8.0 Hz)	7.37 (d, 2H, *J* = 8.5 Hz)	7.44 (d, 2H, *J* = 8.4 Hz)
H-11,11′	6.98 (d, *J* = 8.0 Hz)	6.87 (d, 2H, *J* = 8.5 Hz)	7.11 (d, 2H, *J* = 9.0 Hz)
H-19,19′	5.48 (d, *J* = 6.0 Hz)	5.48 (q, 2H, *J* = 6.4 Hz)	5.60 (q, 2H, *J* = 6.6 Hz)
H-3,3′	Overlap with D_2O peak (4.79)	4.79 (2H) (Protons are embedded in the D_2O peak)	4.94 (2H) Protons embedded in CD_3OD peak
H-5,5′	Overlap with D_2O peak	2.96 (br, s, 2H)	3.13 – 3.11 (m, 2H)
H-21a,21a′ & H-21b,21b′	4.32 (d, *J* = 16.0 Hz) & 4.02 (d, *J* = 16.0 Hz)	4.19 (d, 2H, *J* = 15.0 Hz) & 3.93 (d, 2H, *J* = 15.0 Hz)	4.39 (d, 2H, *J* = 15.6 Hz) & 4.08 (d, 2H, *J* = 15.6 Hz)
H-17a,17a′, 17b,17b′	3.41 (m)	3.33 (d, 4H, *J* = 8.0 Hz)	3.43 (t, 2H, *J* = 9.6 Hz), 3.33 (2H embedded in CD_3OD peak)
H-6a,6a′, 6b,6b′	3.07	2.14 (dd, 2H, *J* = 18.8, 6.5 Hz), 2.04 – 2.00 (m, 4H)	2.22 (s, 4H)
2(N_b-Me)	2.84 (s)	2.77 (s, 6H)	2.92 (s, 6H)
H-15,15′	2.50 (t, *J* = 12.0 Hz)	2.96 (br, s, 2H)	3.13 – 3.11 (m, 2H)
H-14a,14a′, 14b,14b′,	2.21 – 2.05 (m)	2.40 (t, 2H, *J* = 11.0 Hz) & 2.04 – 2.00 (m, 4H)	2.53 (t, 2H, *J* = 11.4 Hz), 2.16 (d, 2H, *J* = 9.6 Hz)
H-16,16′	2.21 – 2.05 (m)	1.93 (q, 2H, *J* = 7.5 Hz),	2.07 (q, 2H, *J* = 7.2 Hz)
3(H-18,18)	1.61 (d, *J* = 6.0 Hz)	1.51 (d, 6H, *J* = 7.5 Hz)	1.69 (d, 6H, *J* = 6.0 Hz)

[a]The numbering and the assignment of the protons follows from the literature.[8] [b]Values are in ppm (δ).

[c]The assignment of the protons and its ppm values of the synthetic dispegatrine is based on 2D NMR correlation experiments on **12** and **13**.

Structural Analysis of Dimers 12, 13 and 1

Synthetic (+)-dispeagtrine (**1**) exhibited ^{1}H NMR spectrum, that compared favorably with the reported values.[8] The coupling constants and the splitting pattern were in good agreement with the literature. However, a minor difference was observed in the ppm values for protons H-15,15′, 2(H-6a,6b) protons, and a significant difference was observed for the H-5,5′ protons (≥ 2.0 ppm). In order to clear this ambiguity, the structures of the dimers **12** and **13** were first established by 2D NMR correlation experiments. The relative assignments of protons for synthetic dispegatrine (**1**) were then based on the comparison of its proton spectrum with **12**, **13** and **12a**.

A comparison of the proton spectra of the dimers **12** and **13** showed that upon quaternization of the N_b-nitrogen in **12** (to form **13**): (a) the H-3,3′ protons had shifted downfield by 0.81 ppm, (b) the four [2(H-21,21′)] protons had shifted downfield by 0.84 ppm and (c) the H-5,5′ protons shifted downfield by 0.9 ppm (see Figure 1 & Table 9). A similar but minor downfield shifts (due to hydrogen bonding between the phenolic-OH group and the N_b-nitrogen atom) were observed for the above mentioned set of protons, first when **12** was demethylated to form the bisphenol **12a** and a further downfield shift resulted upon N_b-quaternization of **12a** to form **1** (see Figure 1 & Table 9). The trend of downfield shifts of the H-3, H-5 and H-21 protons is a common occurrence upon N_b-quaternization as reported for the quaternary sarpagine salts such as spegatrine, lochneram etc.[5] and a difference of ~ 1.0 ppm is expected.

Based on these observations and our correlation data, the H-5,5′ protons have been assigned at 2.96 ppm (D_2O). It is difficult to accept the reported value of 4.93 ppm[8] and it is our opinion that they are misassigned in the natural product.[8] Such a large difference would also be difficult to accept if the natural dispegatrine (**1**) had *M*(R) axial chirality.

Figure 1: Comparison of ^{1}H NMR signals

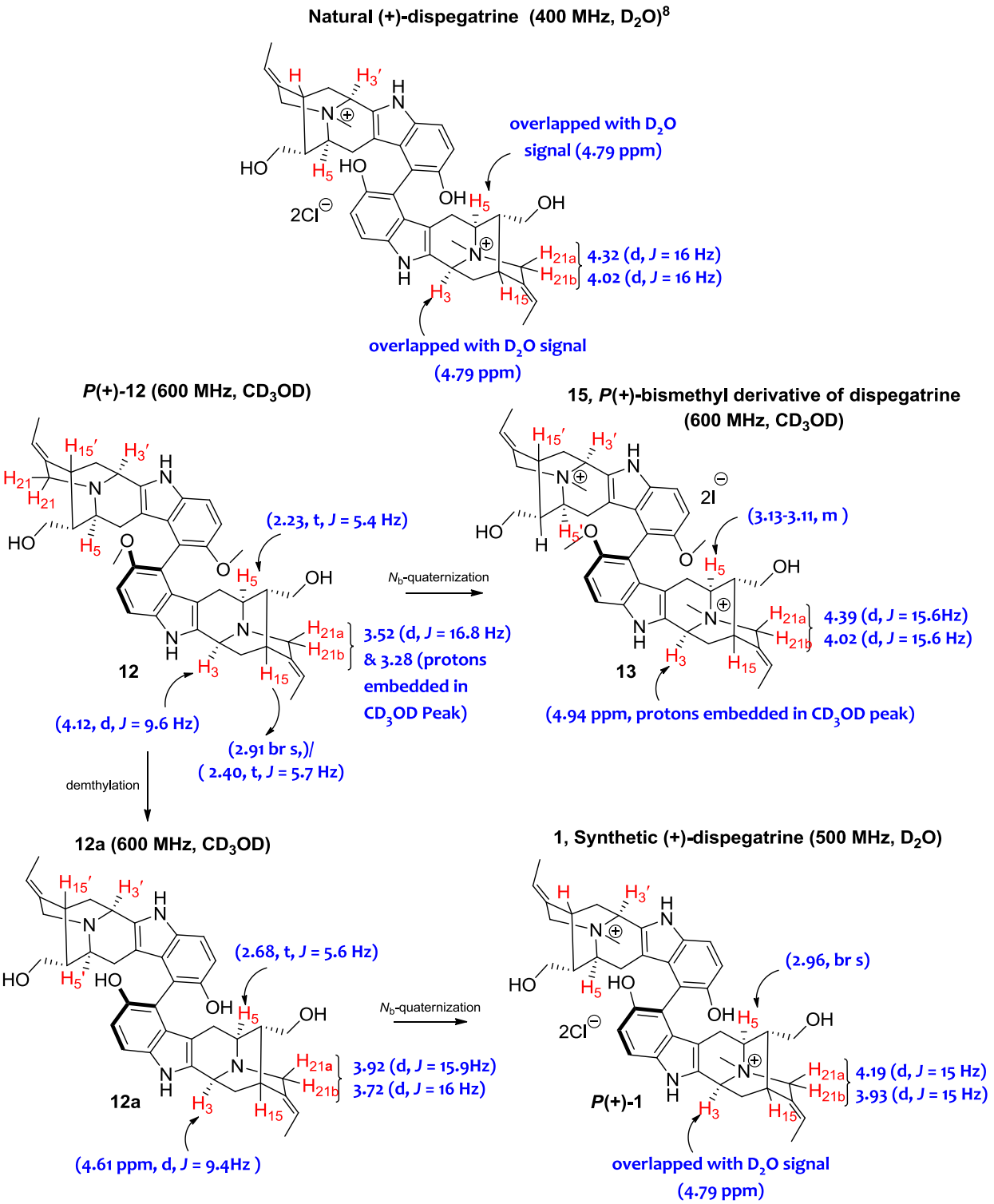


Table 9. Comparison of the ^{1}H NMR data for the dimers **12**, **13** and **12a**.

Protons	**^{1}H NMR of Lochneram Dimer (13) 600 MHz (CD_3OD)**	**^{1}H NMR of Lochnerine Dimer (12) 600 MHz (CD_3OD)**	**^{1}H NMR of Sarpagine Dimer (12a) 300 MHz (CD_3OD)**
H-3,3′	Protons embedded in CD_3OD peak (4.94)	4.12 (d, *J* = 9.6 Hz)	4.61 (d, *J* = 9.4 Hz)
H-5,5′	3.13 – 3.11 (m)	2.23 (t, *J* = 5.4 Hz)	2.68 (t, *J* = 5.6 Hz)
H-6α,6α′ &	2.22 (s)	2.03 (dd, *J* = 15.9, 4.8 Hz)	2.08 (dd, *J* = 16.4, 4.9 Hz)
H-6β,6β′	2.22 (s)	& 1.82 – 1.77 (m)	& 1.63 (Peak embedded in H-18 protons)
H-12,12′	7.44 (d, *J* = 8.4 Hz)	7.29 (d, *J* = 9.0 Hz)	7.27 (d, *J* = 8.6 Hz)
or	or	or	or
H-11,11′	7.11 (d, *J* = 9.0 Hz)	6.94 (d, *J* = 8.4 Hz)	6.88 (d, *J* = 8.6 Hz)
H-14α,14α′	2.53 (t, *J* = 11.4 Hz)	2.09 (t, *J* = 11.4 Hz)	2.28 (t, *J* = 11.2 Hz)
H-14β,14β′	2.16 (d, *J* = 9.6 Hz)	1.82 – 1.77 (m)	1.94 – 1.87 (m)
H-15,15′	3.13 – 3.11 (m)	2.88 (br, s)	2.93 (br, s)
H-16,16′	2.07 (q, *J* = 7.2 Hz)	1.82 – 1.77 (m)	1.74 (q, *J* = 6.6 Hz)
H-17a,17a′ & 17b,17b′	3.43 (t, *J* = 9.6 Hz) & 3.33 (Protons embedded in CD_3OD peak)	3.28 (Protons embedded in CD_3OD peak) & 3.24 (dd, *J* = 10.2, 5.4 Hz)	3.28 (dd, *J* = 10.5, 8.7 Hz) & 3.17 (dd, *J* = 10.7, 5.9 Hz)
3(H-18,18′)	1.69 (d, *J* = 6.0 Hz)	1.62 (d, *J* = 7.2 Hz);	1.63 (d, *J* = 6.2 Hz)
H-19,19′	5.60 (q, *J* = 6.6 Hz)	5.40 (q, *J* = 6.0 Hz)	5.53 (q, *J* = 6.9 Hz)
H-21a,21a′, & 21b,21b′	4.39 (d, *J* = 15.6 Hz) & 4.08 (d, *J* = 15.6 Hz)	3.52 (d, *J* = 16.8 Hz) & 3.28 (Protons embedded in CD_3OD peak)	3.92 (d, *J* = 15.9 Hz) & 3.72 (d, *J* = 16.0 Hz)
2(MeO)	3.74 (s)	3.70 (s)	—
2(N_b-Me)	2.92 (s)	—	—

[c]The assignment of the protons and its ppm values of the synthetic sarpagine (**12a**) are based on comparison of its proton spectra with the proton spectrums of **12** and **13**, which in turn were assigned by 2D NMR correlation experiments.

Table 10. Comparison of the ^{13}C NMR data for the dimers **12**, **13** and **12a**.

Carbons[a]	**^{13}C NMR of Lochneram Dimer (13) 150 MHz (CD_3OD)**[a,c]	**^{13}C NMR of Lochnerine Dimer (12) 150 MHz (CD_3OD)**[a,c]	**^{13}C NMR of Sarpagine Dimer (12a) 75 MHz (CD_3OD)**[a,b,c]
C-3,3′	60.8	50.4	51.1
C-5,5′	64.9	54.2	55.6
2(C-6,6′)	24.2	26.7	25.9
2(C-12,12′)	111.2	109.9	111.5
or	or	or	or
2(C-11,11′)	100.6	108.1	110.9
2(C-14,14′)	31.9	32.9	31.9
C-15,15′	25.8	27.0	26.3
C-16,16′	43.3	43.8	42.7
2(C-17,17′)	62.1	63.2	62.5
3(C-18,18′)	11.6	11.6	11.6
2(C-19,19′)	120.7	116.9	119.6
2(C-21,21′)	64.2	55.0	54.4
2(MeO)	56.7	56.8	—
2(N_b-Me)	46.5	—	—

[a]Values are in ppm (δ). [b]The assignment of the carbons and its ppm values of the sarpagine dimer (**12a**) are based on comparison of its carbon spectra with the carbon spectrums of **12** and **13**, which in turn were assigned by 2D NMR correlation experiments. [c]Quaternary carbons are not shown.

References:

[1] J. J. Li, C. Limberakis, D. A. Pflum, *Modern Organic Synthesis in the Laboratory*, Oxford University Press, New York, NY, **2007**, Chapter 1, pp 17-20.

[2] J. LeMen, J, W. I. Taylor, *Experientia* **1965**, *21*, 508.

[3] M. Plat, R. Lemay, J. Le Men, M.-M. Janot, C. Djerassi, H. Budzikiewicz, *Bull. Soc. Chim. Fr*. **1965**, 2497.

[4] a) J. Abaul, E. Philogene, P. Bourgeois, G. Merault, C. Poupat, A. Ahond, P. Potier, *J. Nat. Prod*. **1986**, *49*, 829; b) J. A. Martínez, R. Valero, M. E. Sosa, M. Manchúa, *Rev. Cubana Quim*. **1992**, *6*, 48.

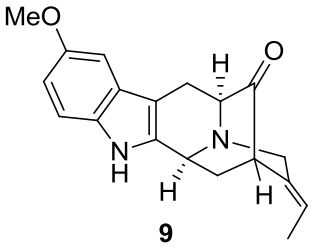
[5] M. Lounasmaa, P. Hanhinen, M. Westersund in *The Alkaloids*, *Vol. 52* (Ed.: G. Cordell), Academic Press, San Diego, CA, **1999**, pp 103-195.

[6] A. K. Kiang, A. S. C. Wan, *J. Chem. Soc.* **1960**, 1394.

[7] a) O. O. Orazi, R. A. Corral, M. E. Stoichevich, *Can. J. Chem.* **1966**, *44*, 1524; b) M. Lin, D. Yu, X. Liu, F. Fu, Q. Zheng, C. He, G. Bao, C. Yu, *Yaoxue Xuebao* **1985**, *20*, 198.

[8] M. Lin, B. Yang, D.-Q. Yu, *Acta. Pharm. Sinica* **1986**, *21*, 114.

Copies of ^{1}H and ^{13}C NMR Spectra:



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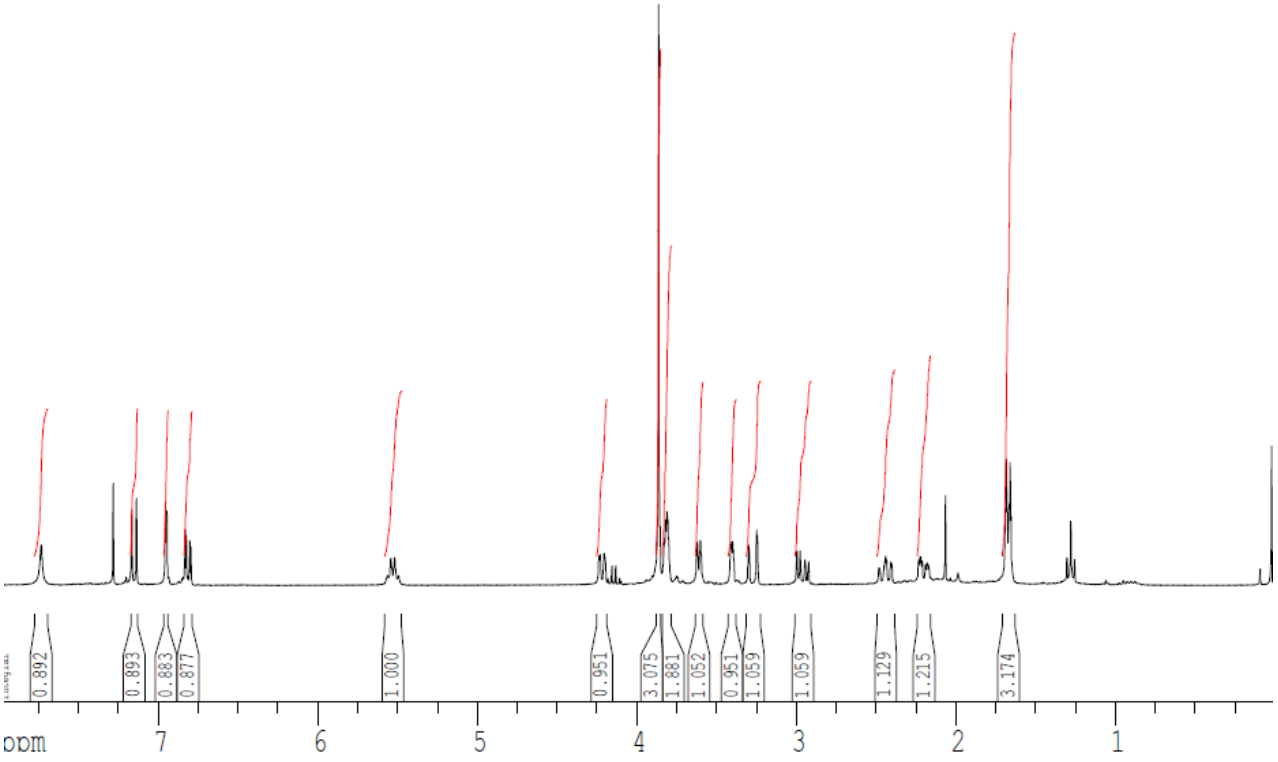

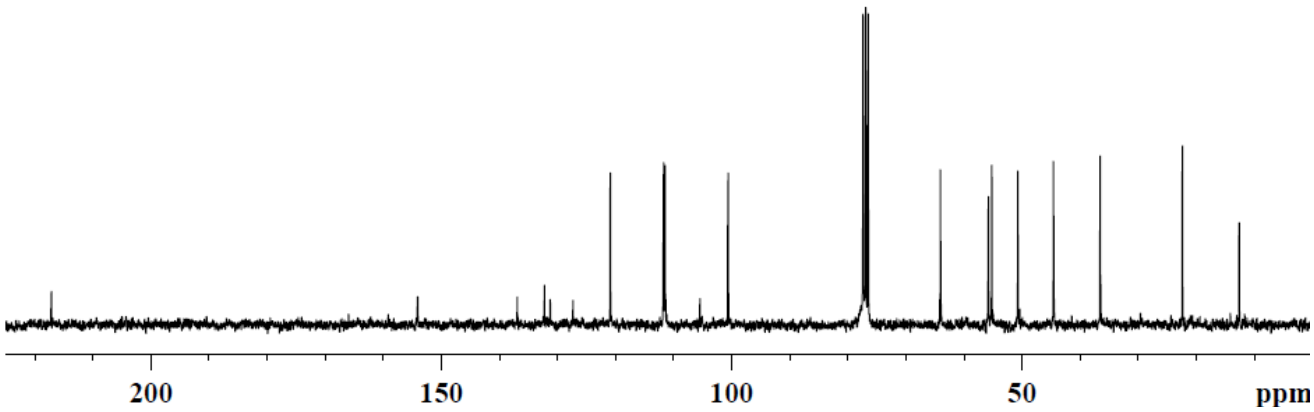

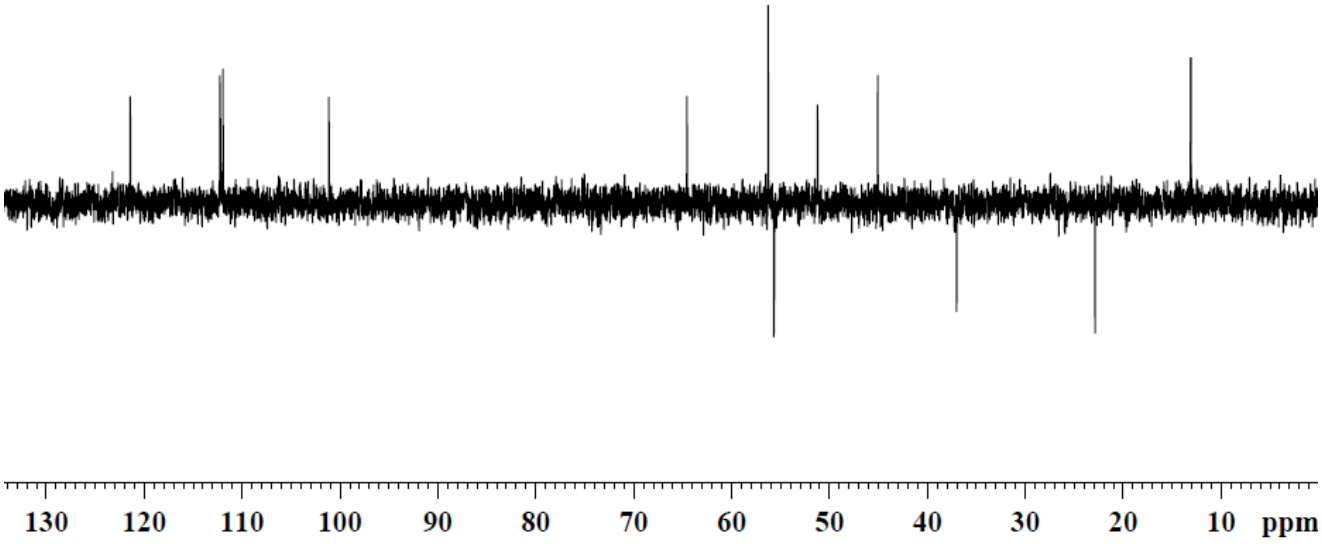
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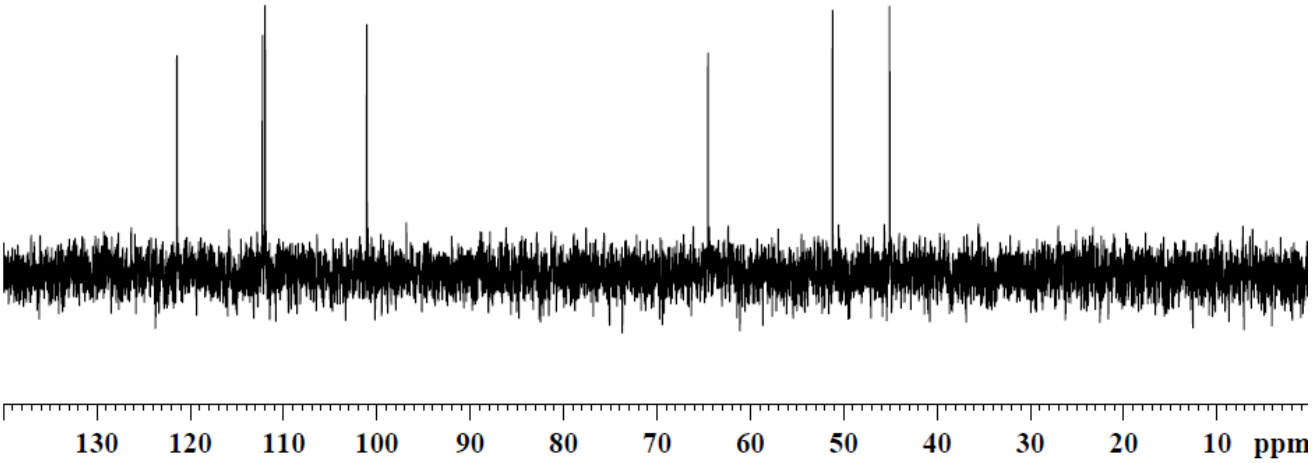
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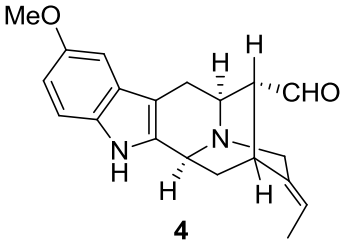

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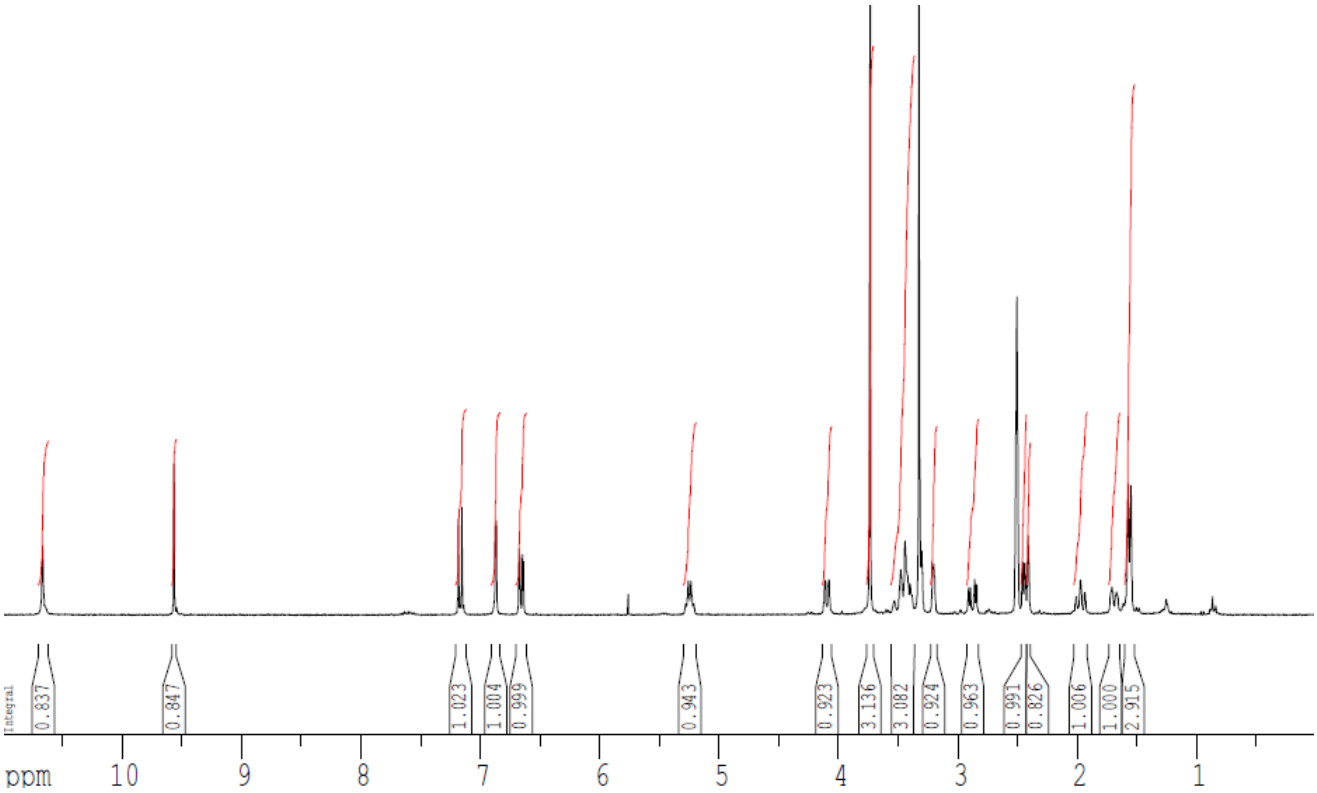

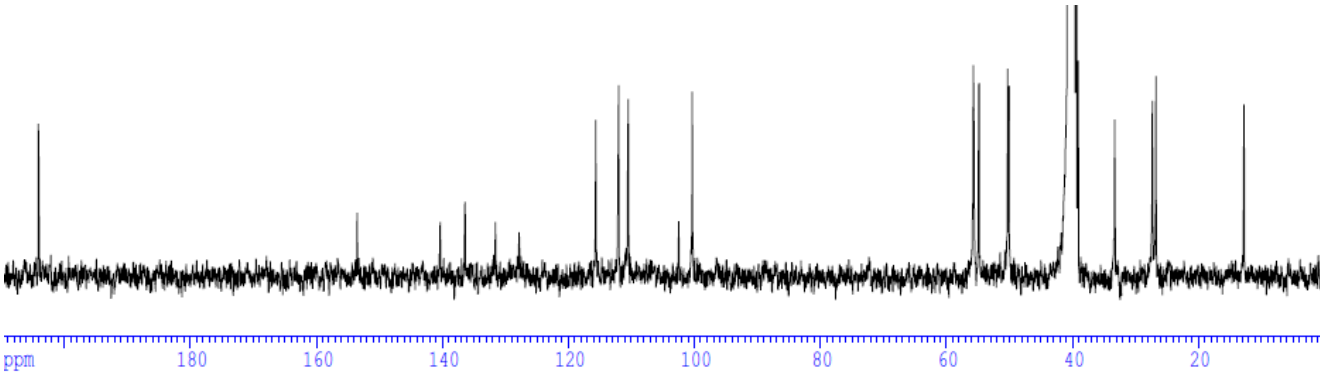

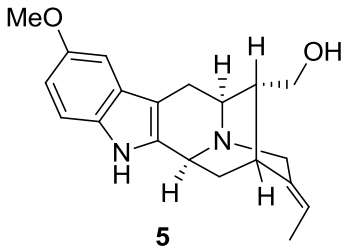

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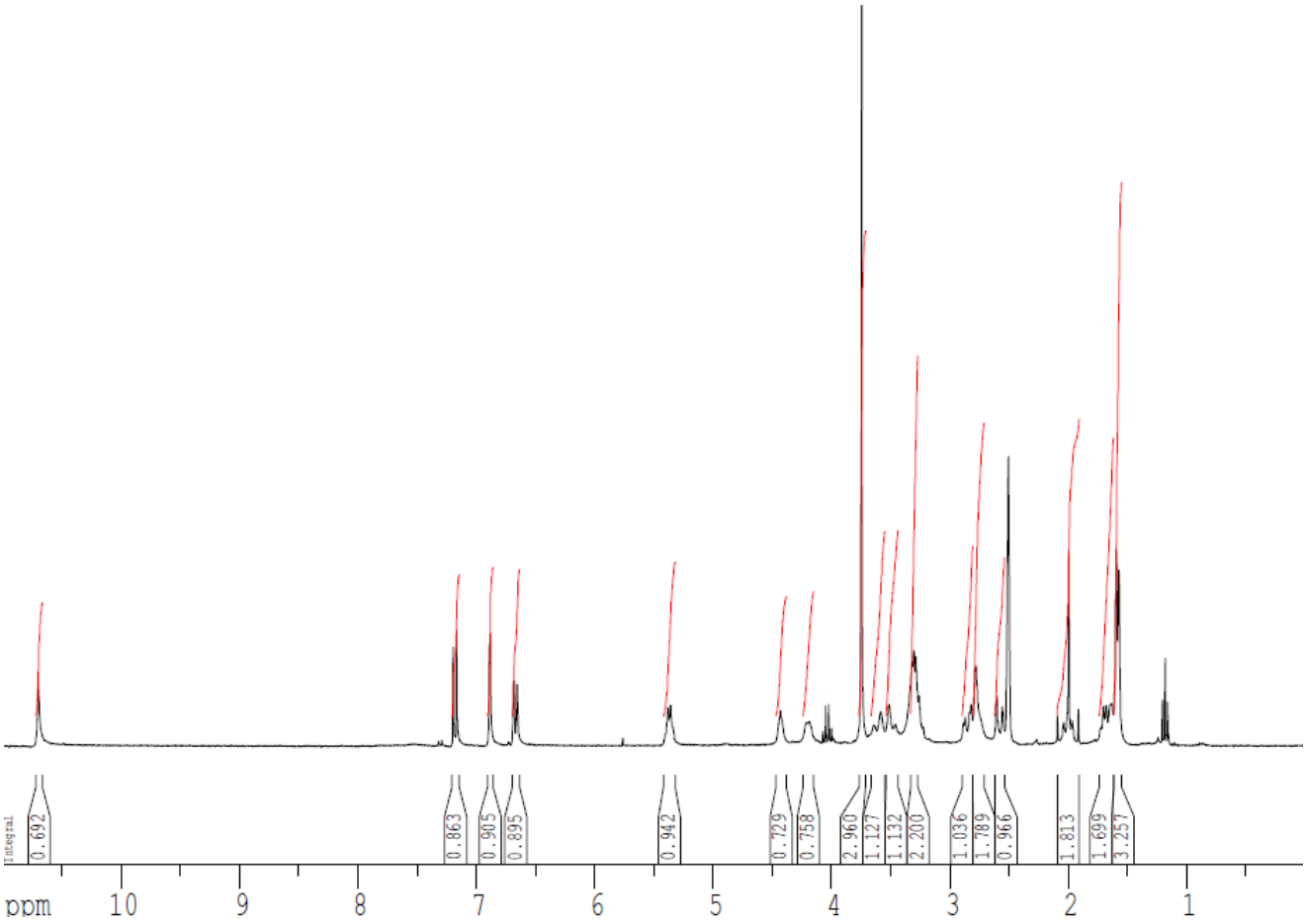
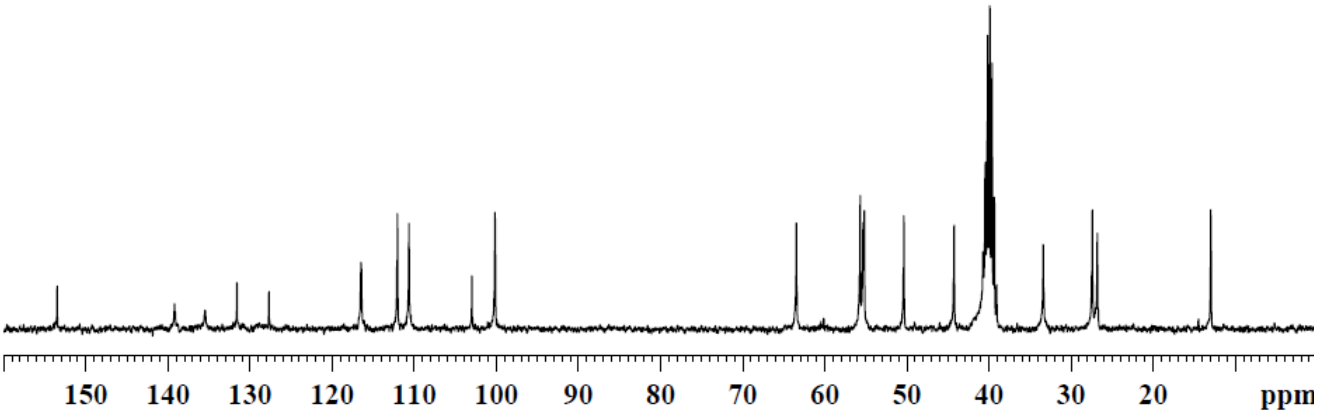
(+)-Iochnerine

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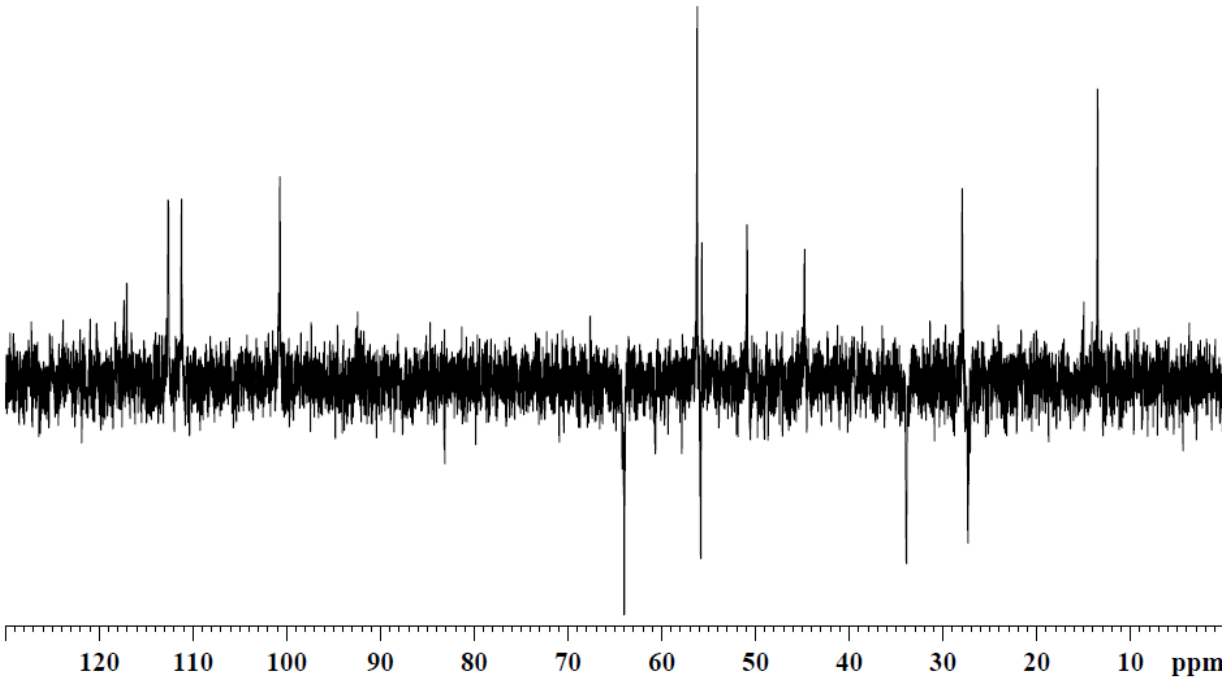
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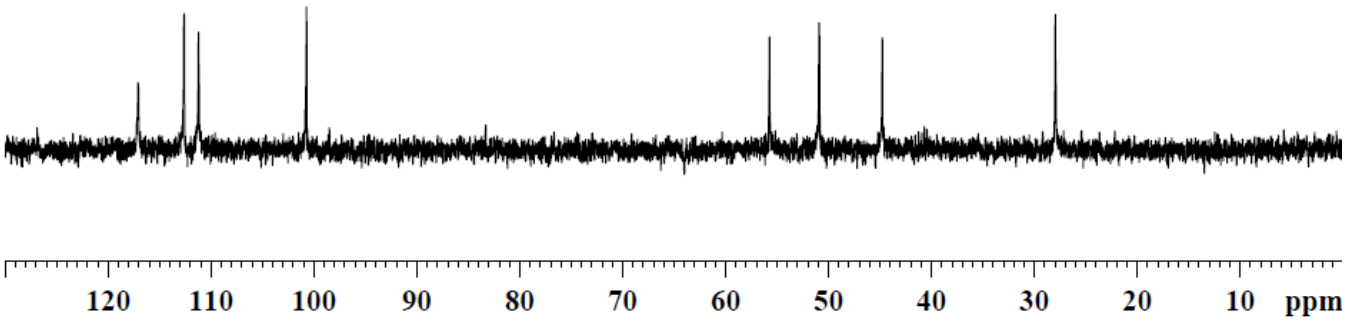
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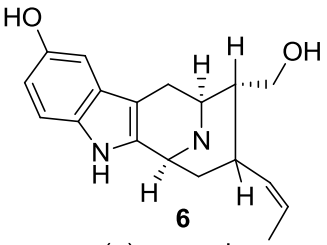
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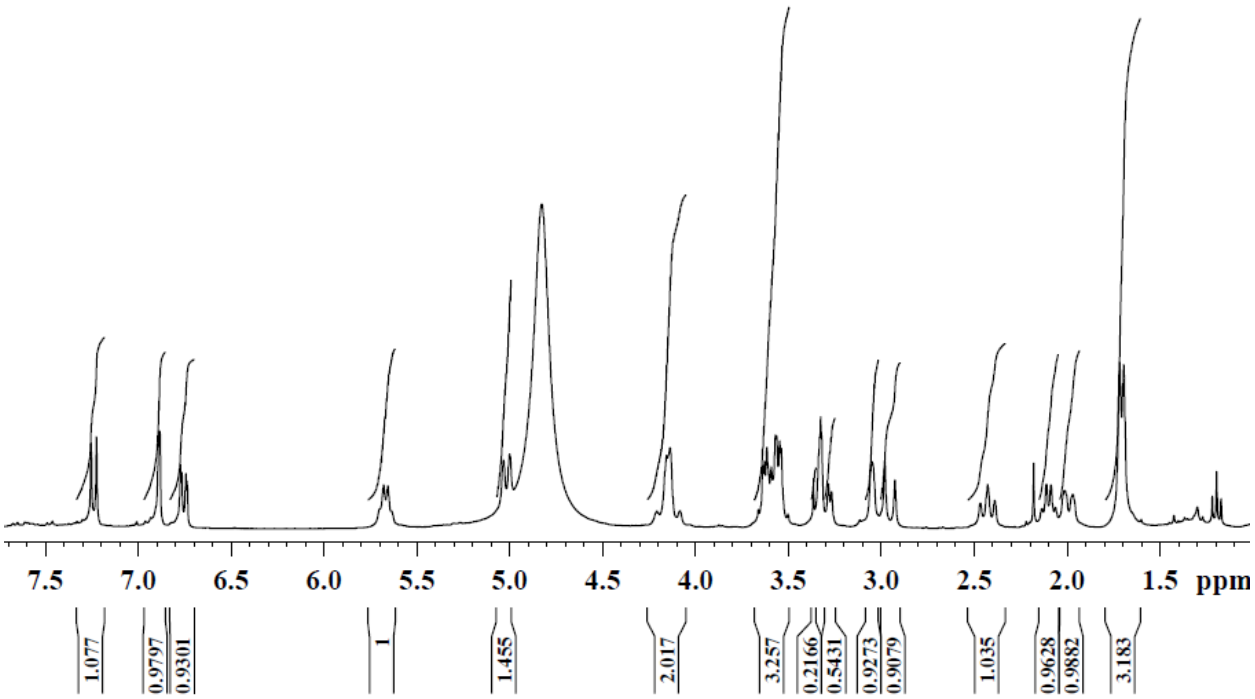
OH
H
N
N
H
H
H

6

(+)-sarpagine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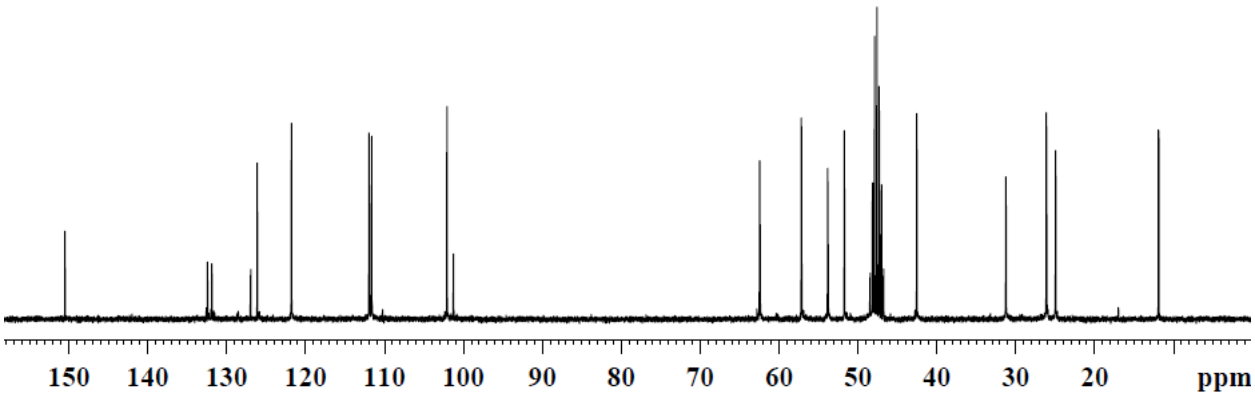
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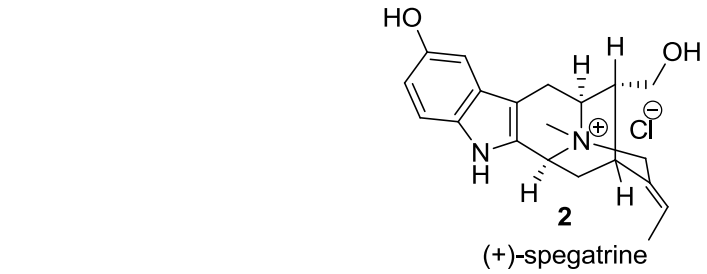

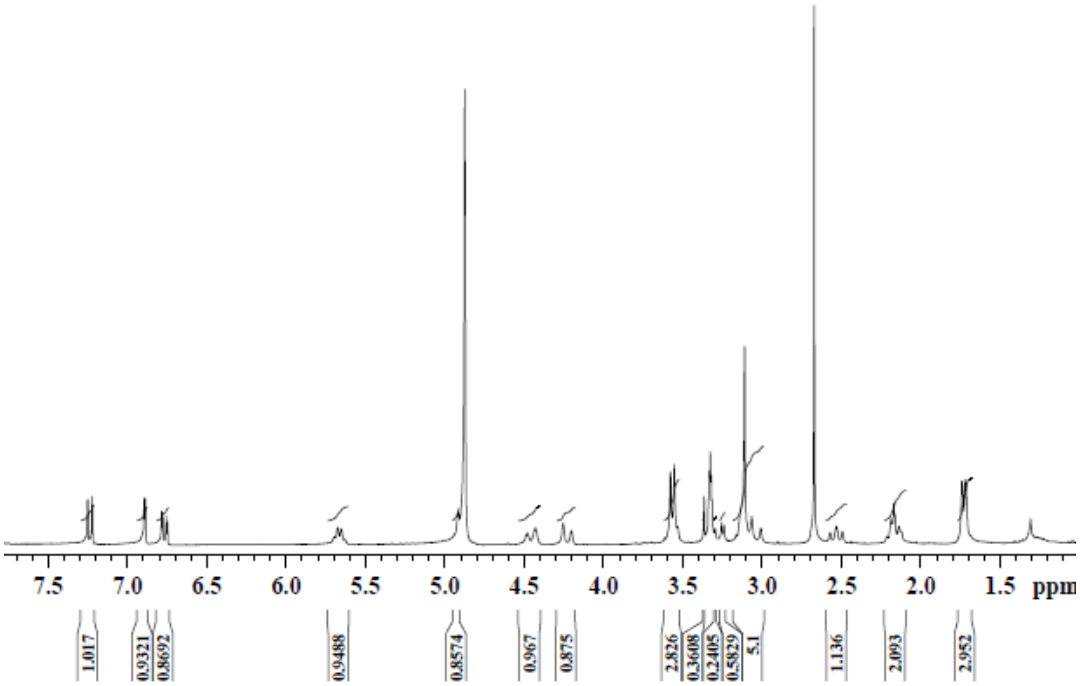

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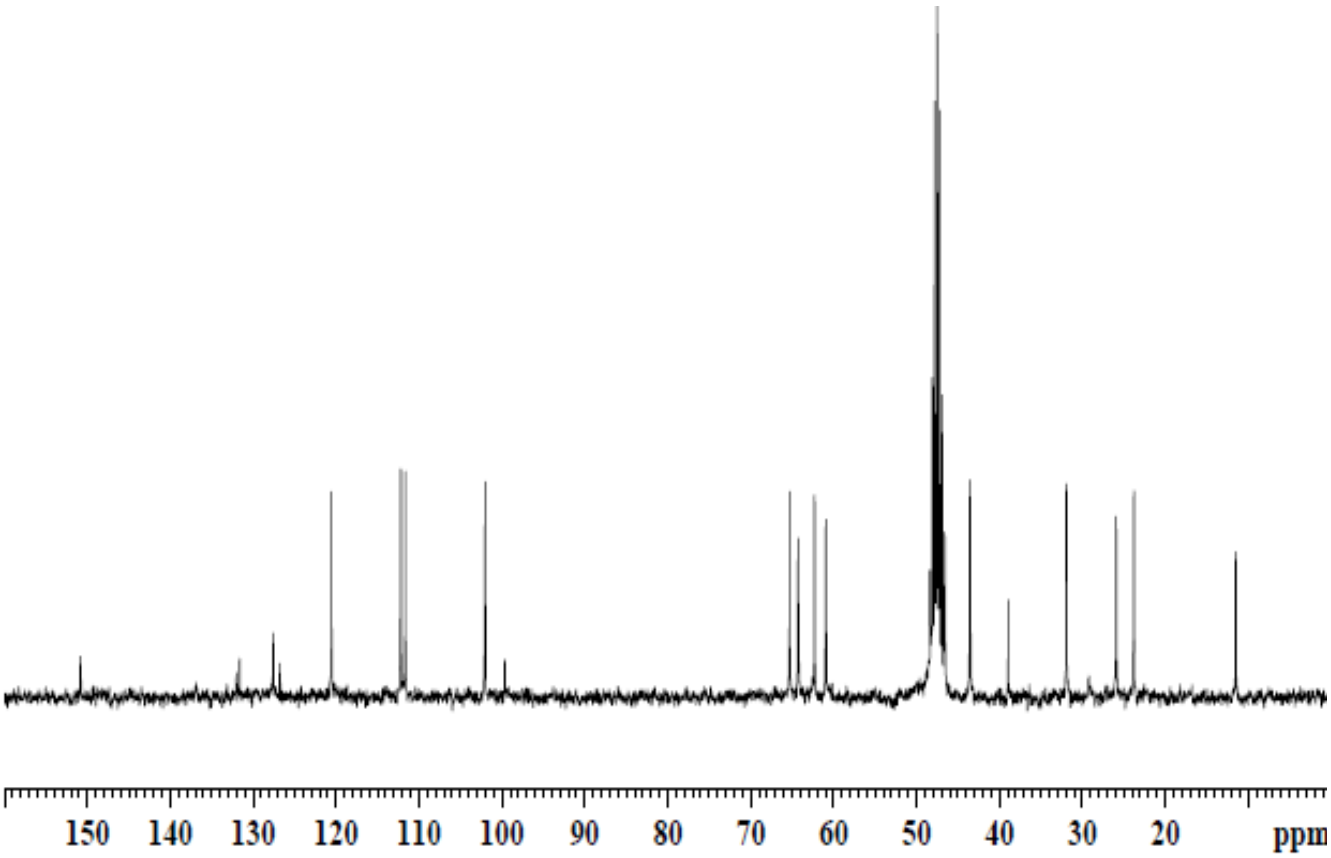
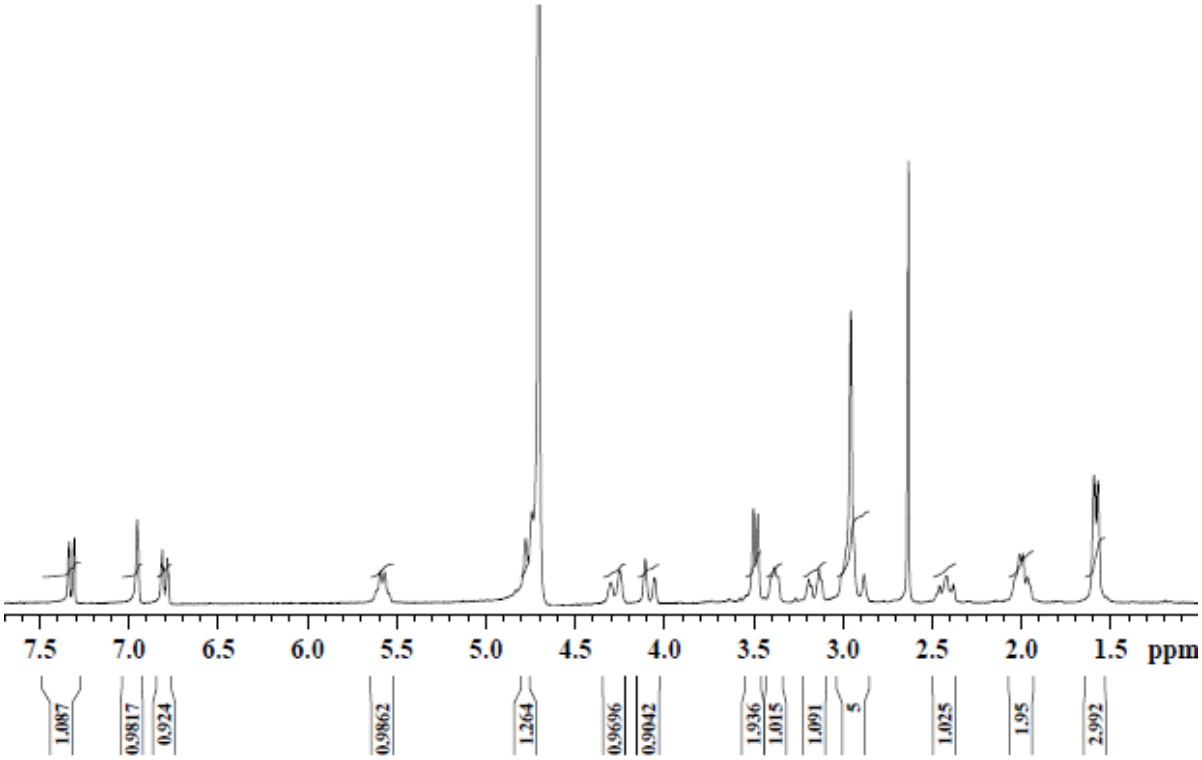
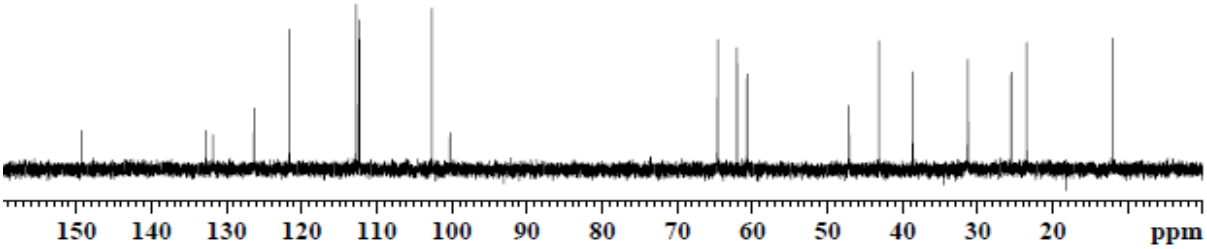


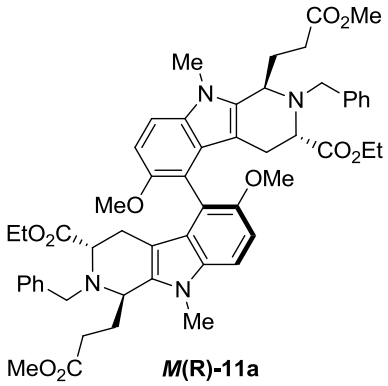
The peak at 38.931 is a DMSO peak.



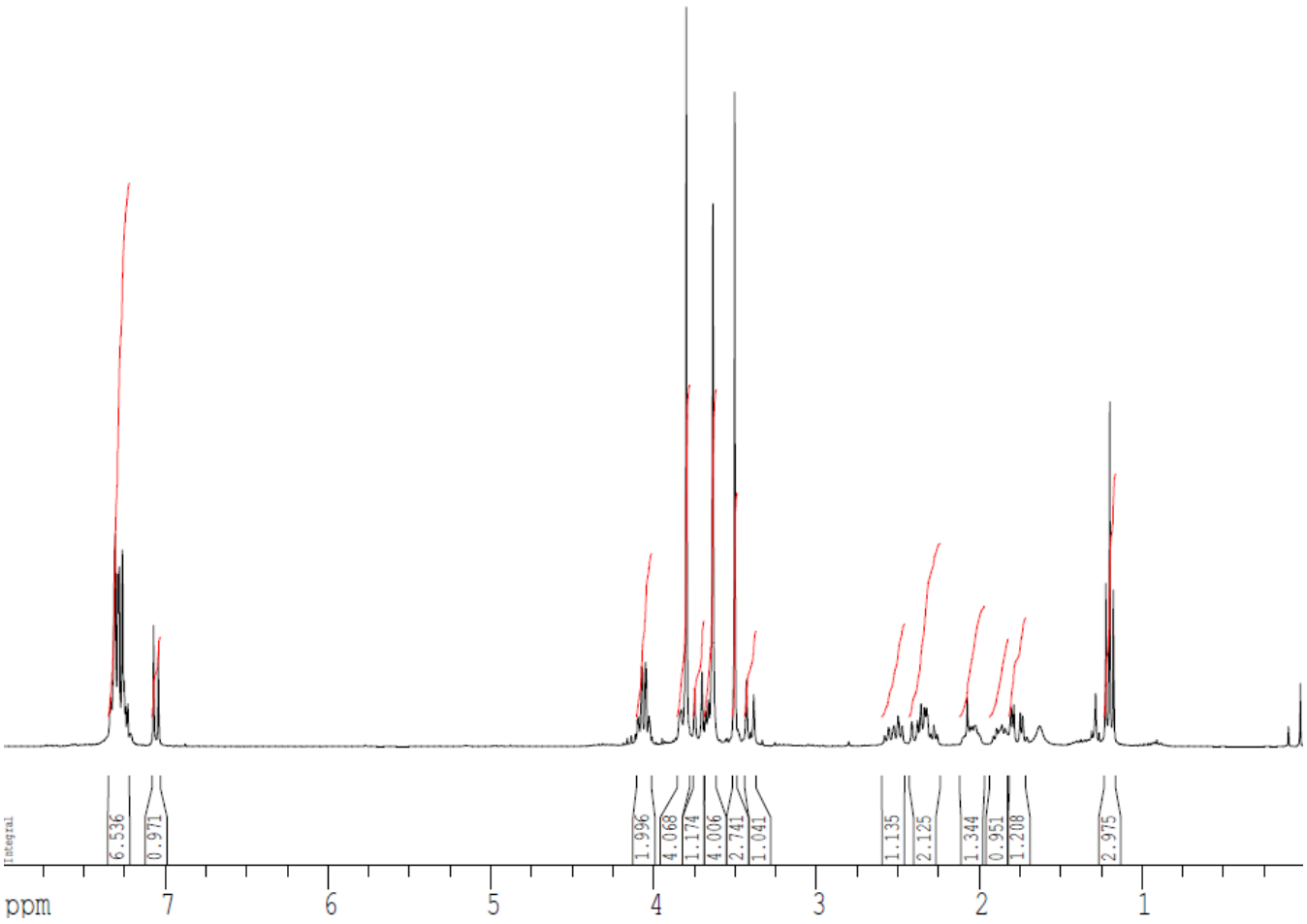
The peak at 2.63 ppm is a DMSO peak.

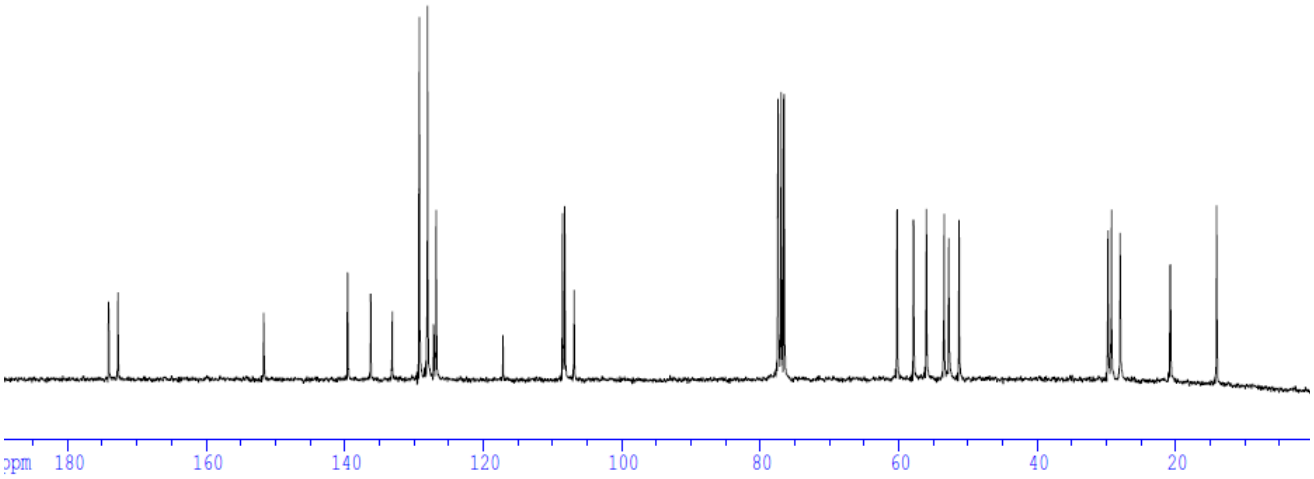


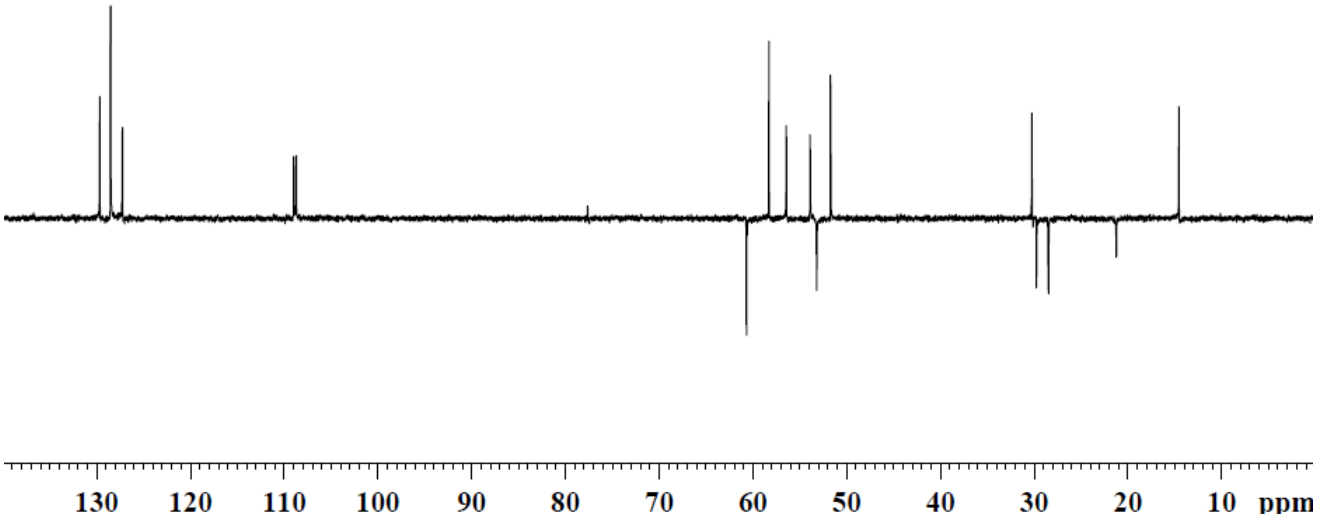
The peak at 38.596 is a DMSO peak.

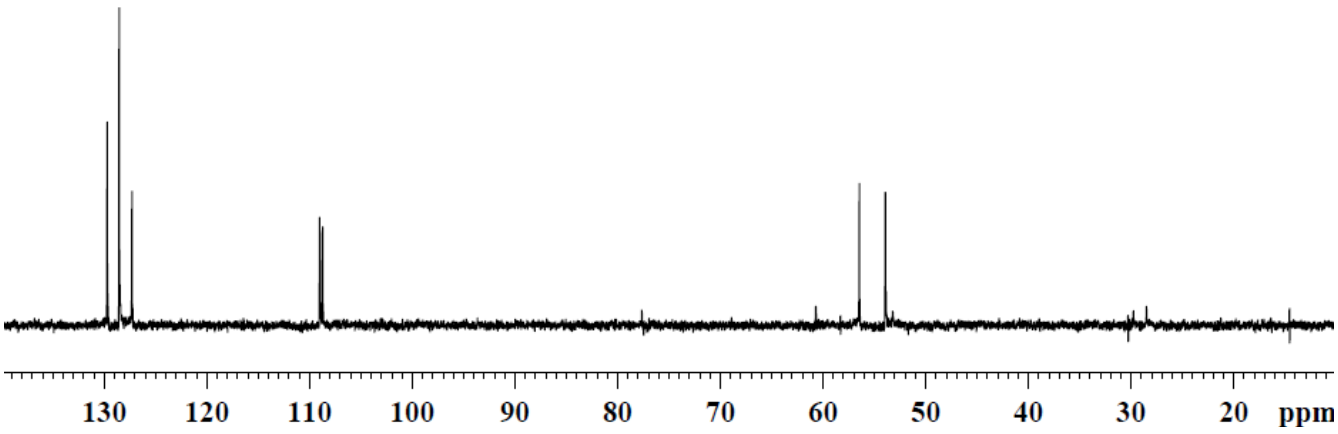

CO2Me
Me
N
N
Ph
CO2Et
OMe
MeO
EtO2C
Ph
N
N
Me
MeO2C

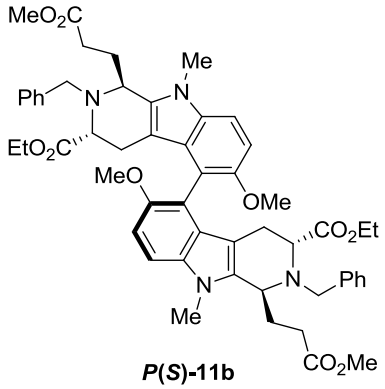
***M*(R)-11a**


Integral
6.536
0.971
1.996
4.068
1.174
4.006
2.741
1.041
1.135
2.125
1.344
0.951
1.208
2.975
ppm
7
6
5
4
3
2
1

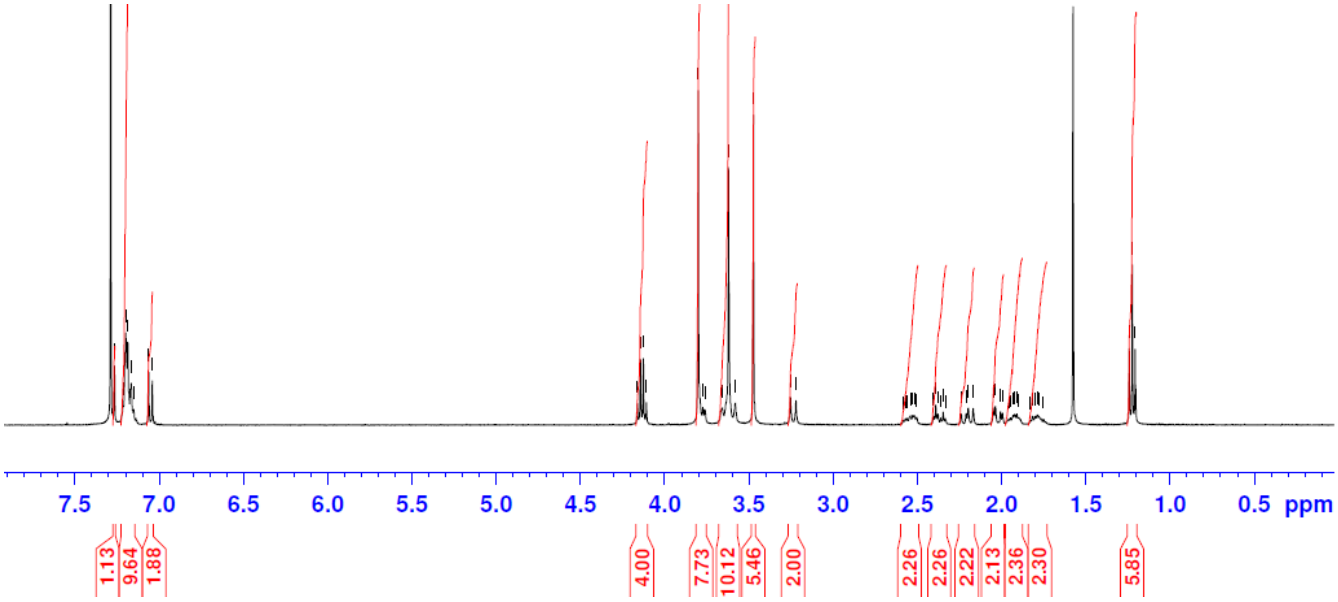

ppm 180
160
140
120
100
80
60
40
20

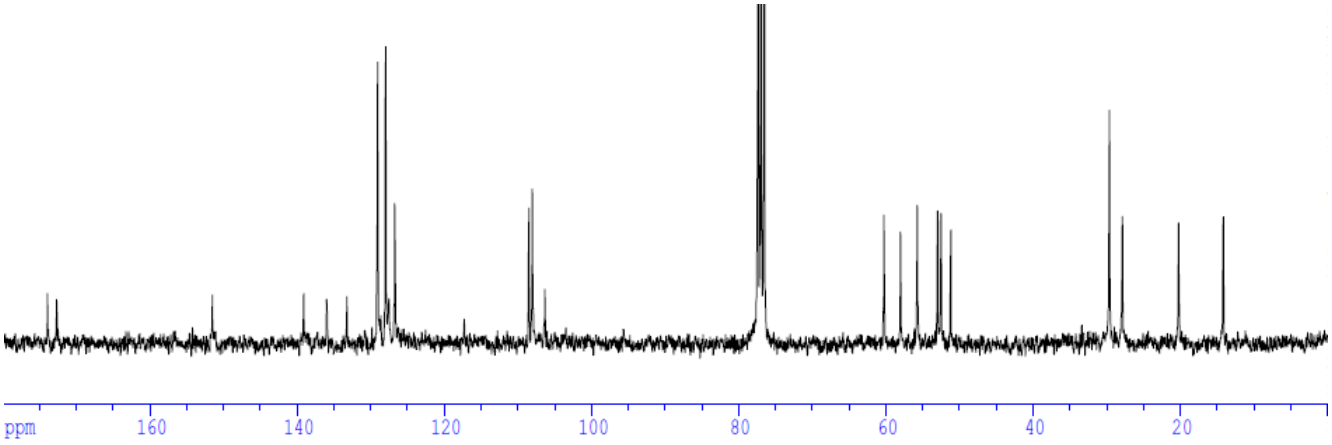

130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

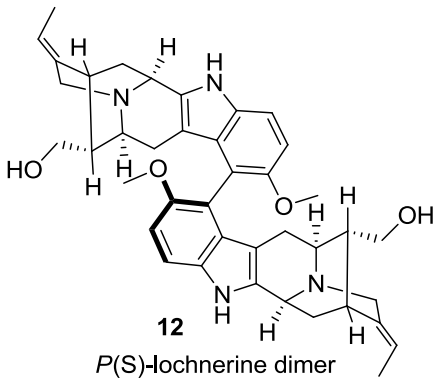

130
120
110
100
90
80
70
60
50
40
30
20
ppm


MeO2C
Me
Ph
N
N
EtO2C
MeO
OMe
CO2Et
N
N
Ph
Me
CO2Me

***P*(*S*)-11b**

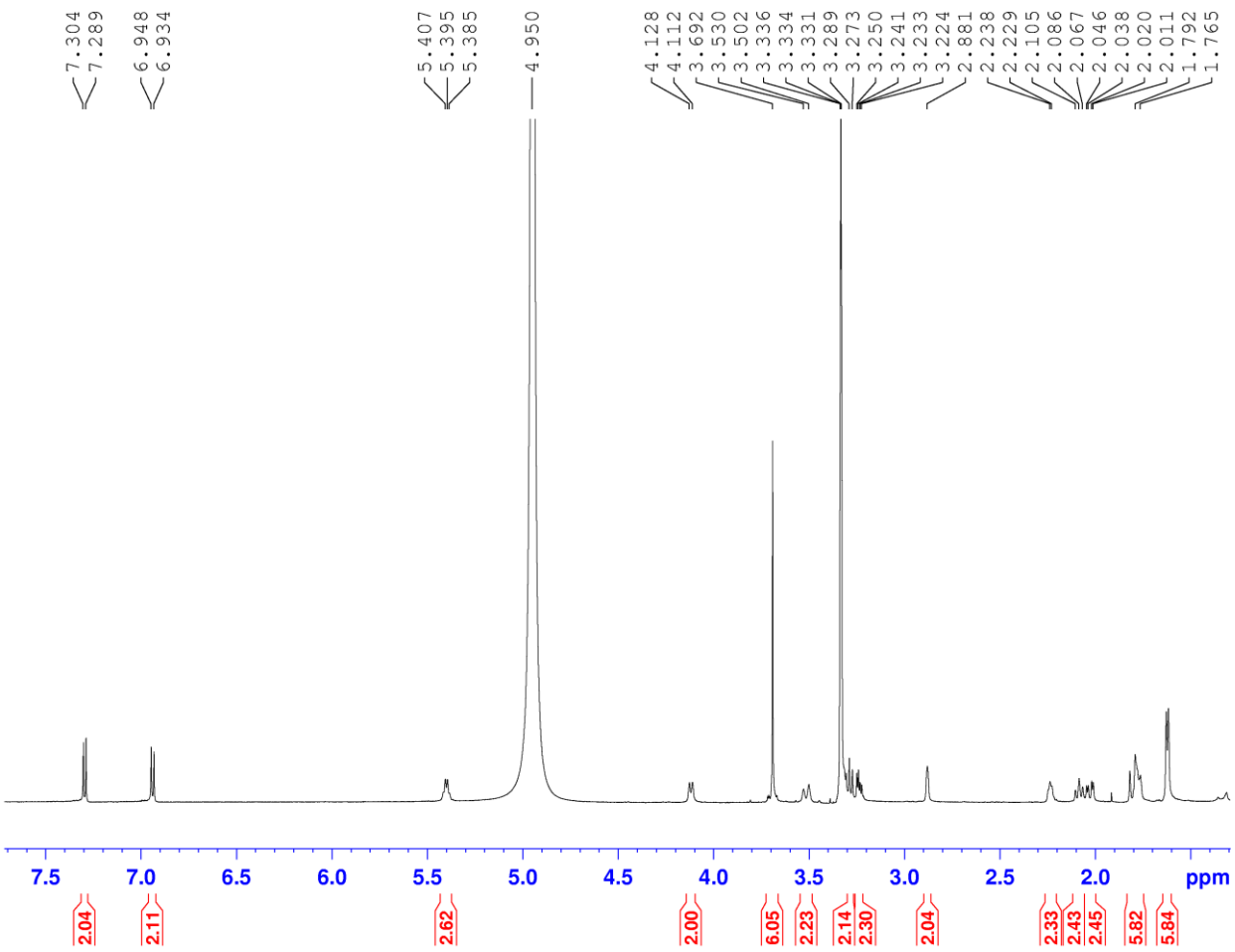

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.13
9.64
1.88
4.00
7.73
10.12
5.46
2.00
2.26
2.26
2.22
2.13
2.36
2.30
5.85

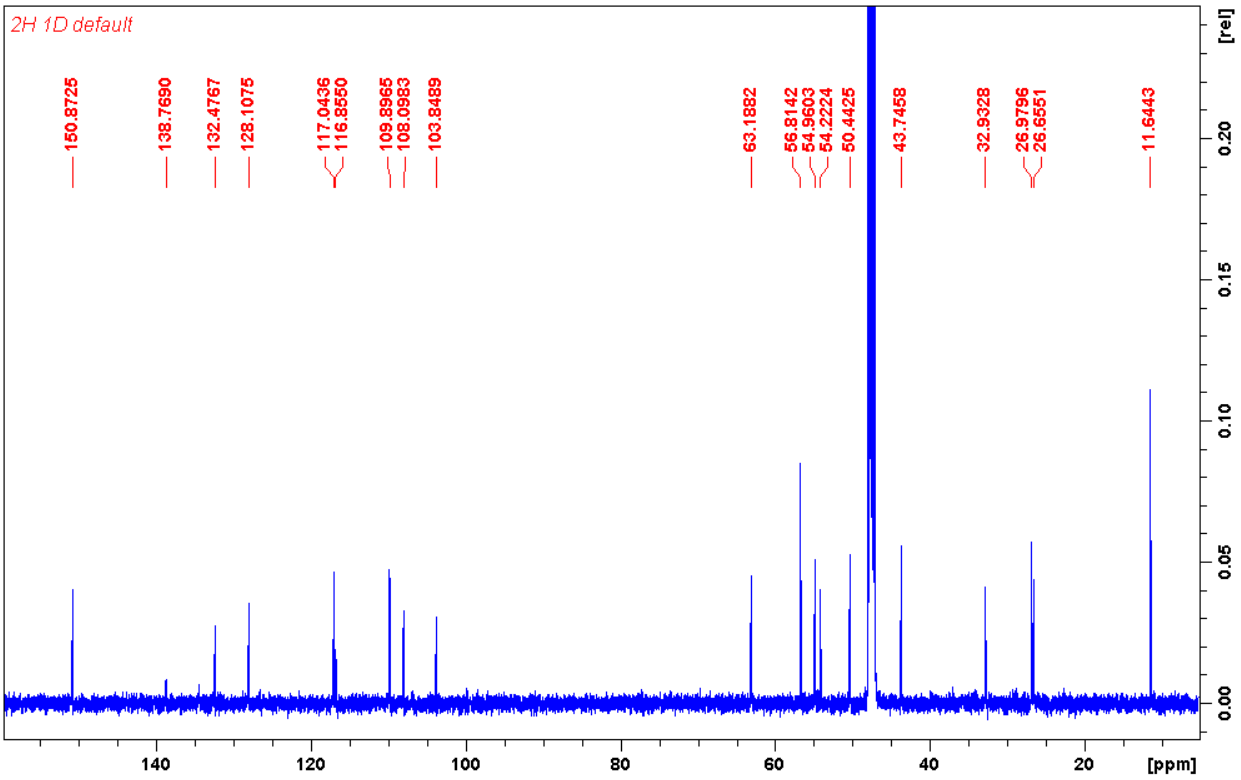

ppm
160
140
120
100
80
60
40
20

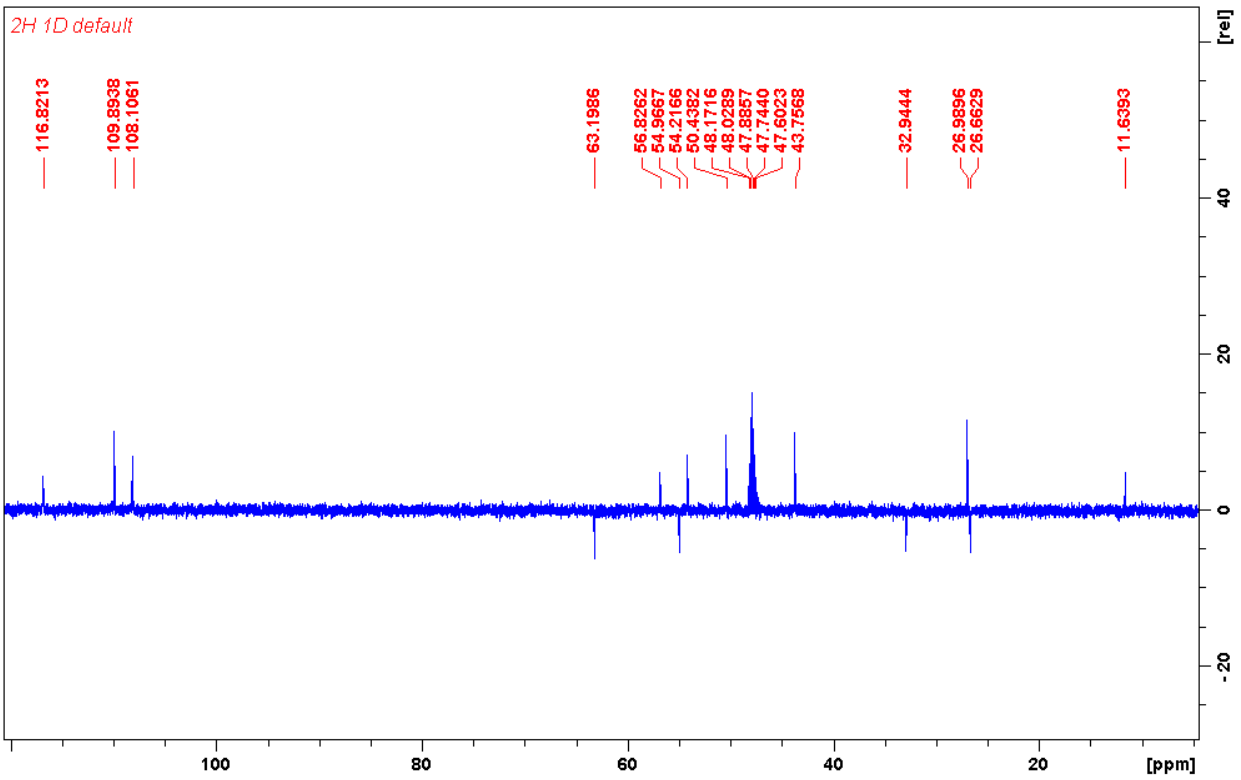


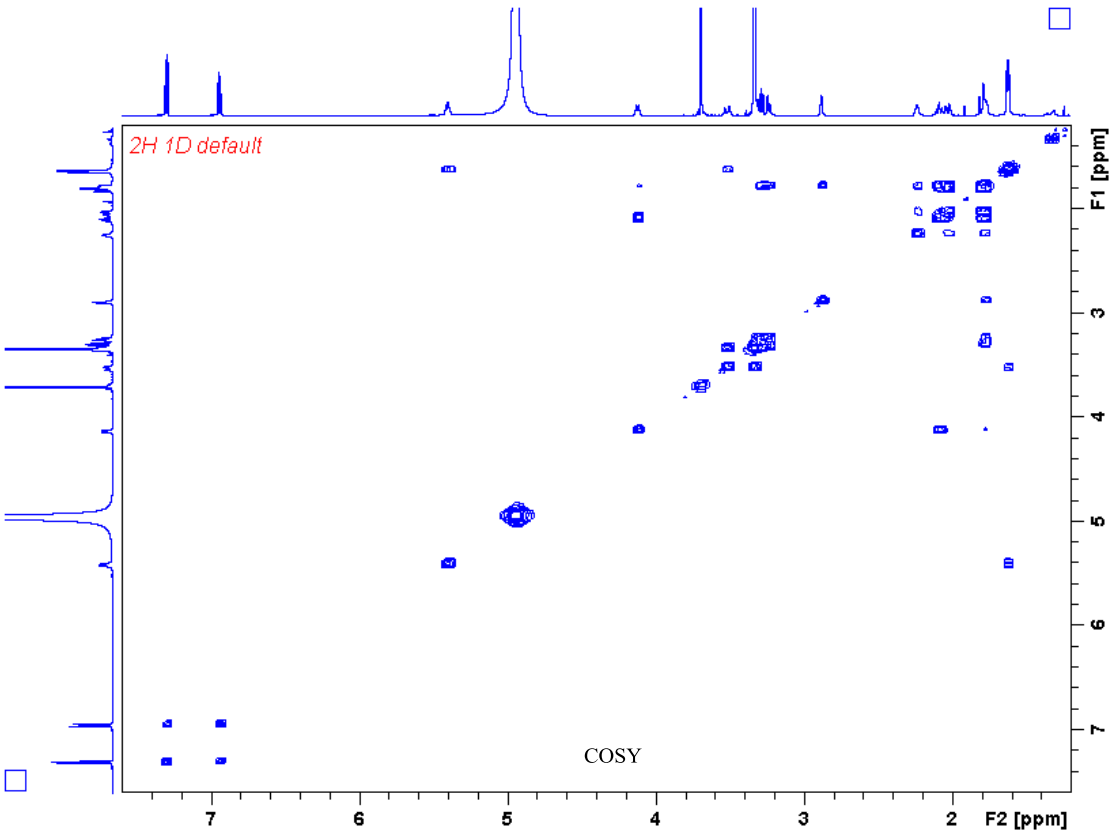
12

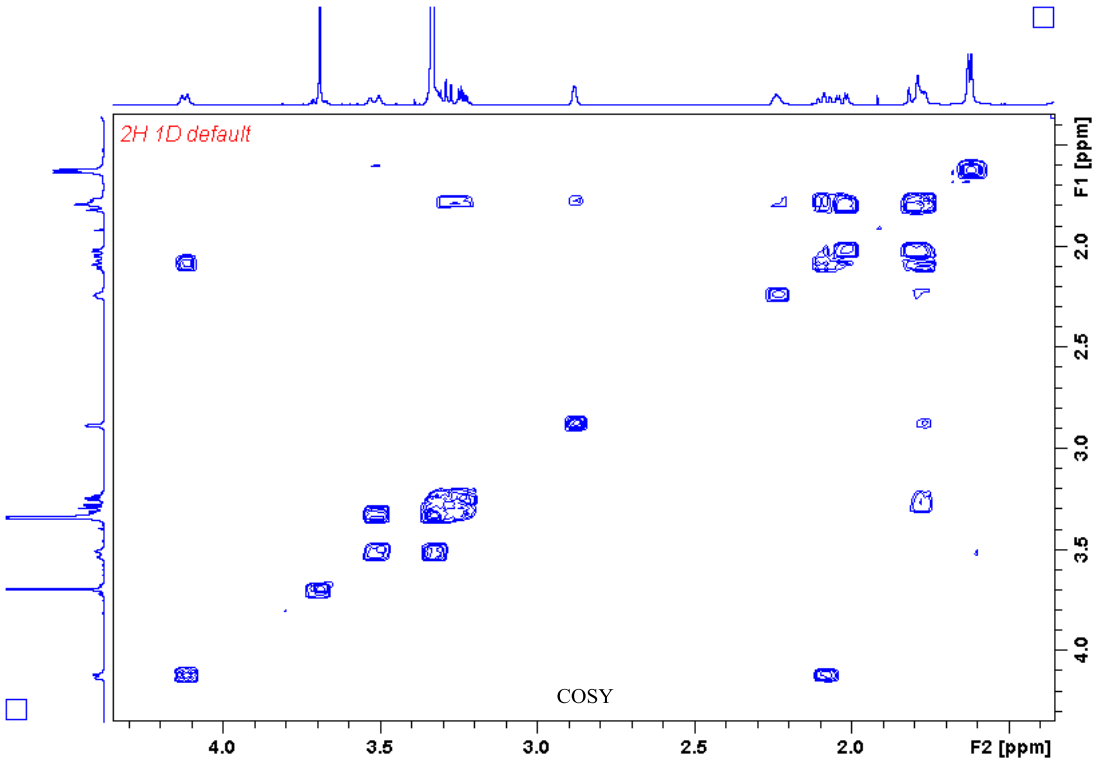
P(S)-Iochnerine dimer

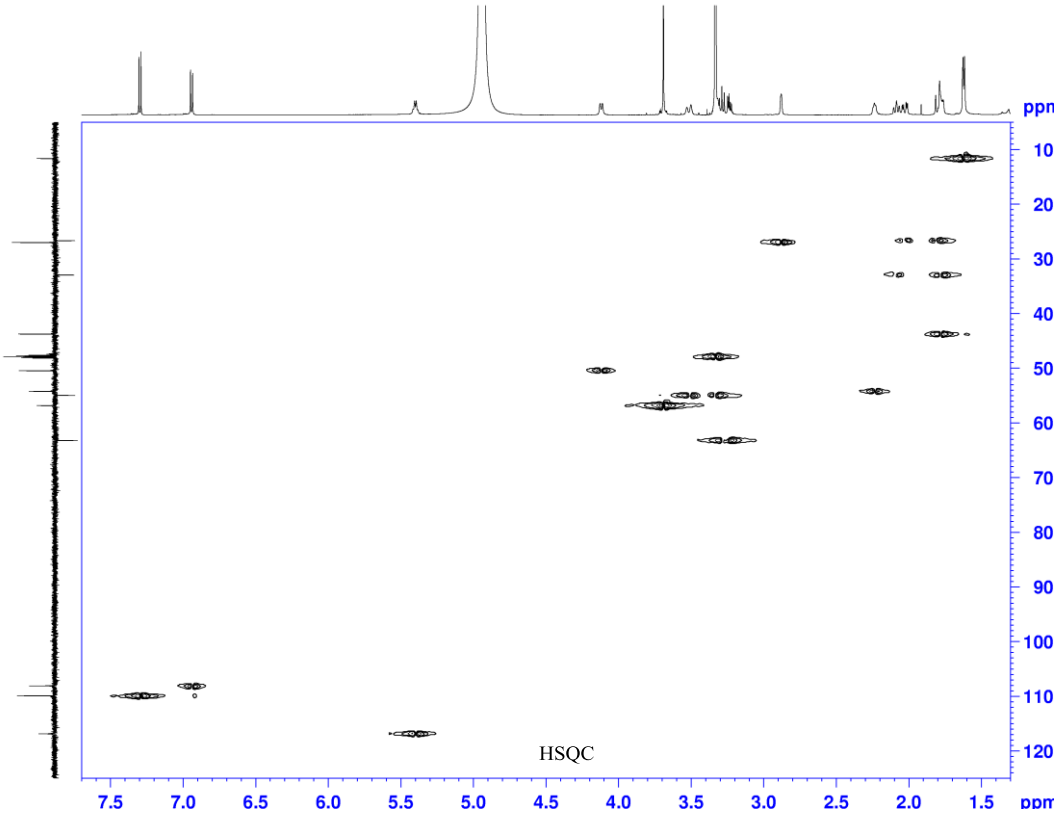


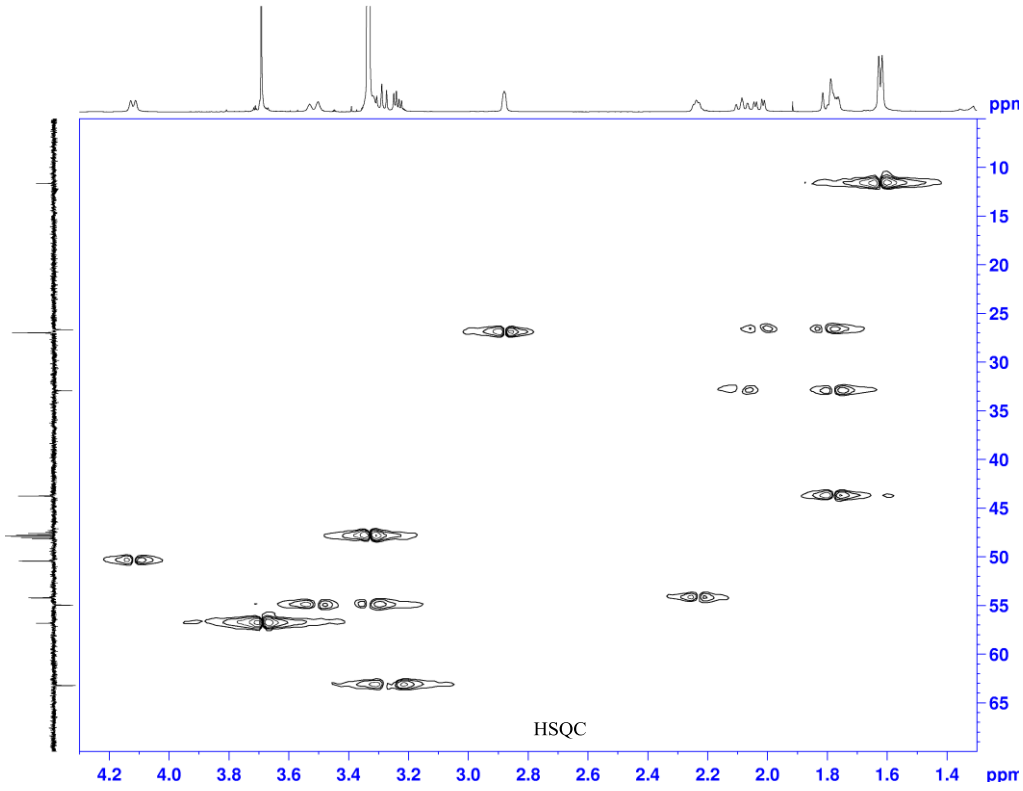

2H 1D default
150.8725
138.7690
132.4767
128.1075
117.0436
116.8550
109.8965
108.0983
103.8489
63.1882
56.8142
54.9603
54.2224
50.4425
43.7458
32.9328
26.9796
26.6551
11.6443
[rel]
0.20
0.15
0.10
0.05
0.00
140
120
100
80
60
40
20
[ppm]

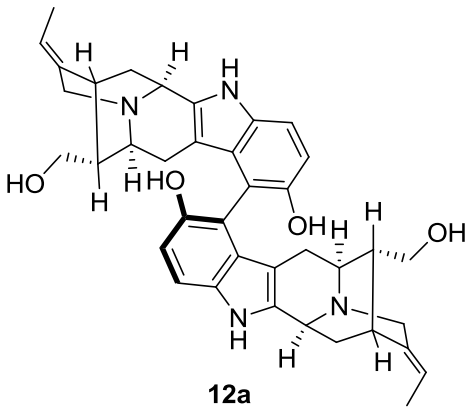

2H 1D default
116.8213
109.8938
108.1061
63.1986
56.8262
54.9667
54.2166
50.4382
48.1716
48.0289
47.8857
47.7440
47.6023
43.7568
32.9444
26.9896
26.6629
11.6393
[rel]
40
20
0
-20
100
80
60
40
20
[ppm]


2H 1D default
COSY
F1 [ppm]
F2 [ppm]
7
6
5
4
3
2

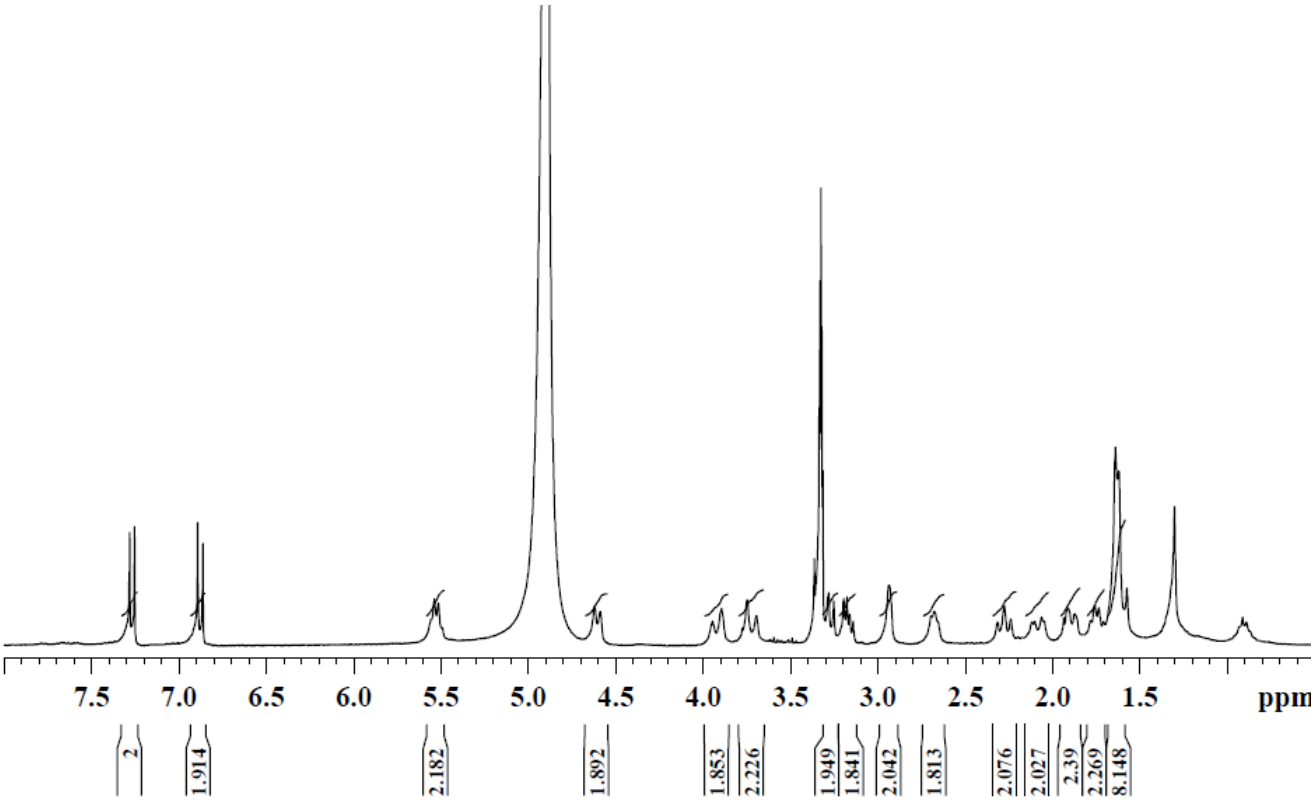

2H 1D default
COSY
F1 [ppm]
F2 [ppm]
4.0
3.5
3.0
2.5
2.0

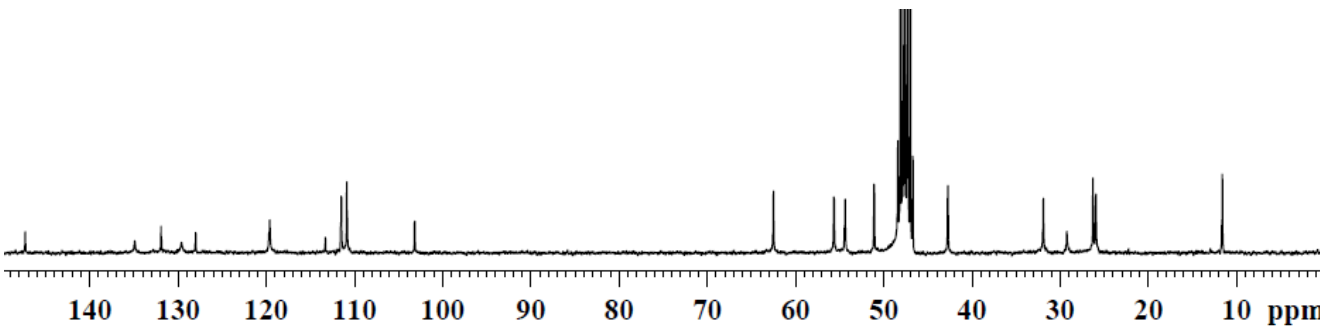

ppm
10
20
30
40
50
60
70
80
90
100
110
120
HSQC
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

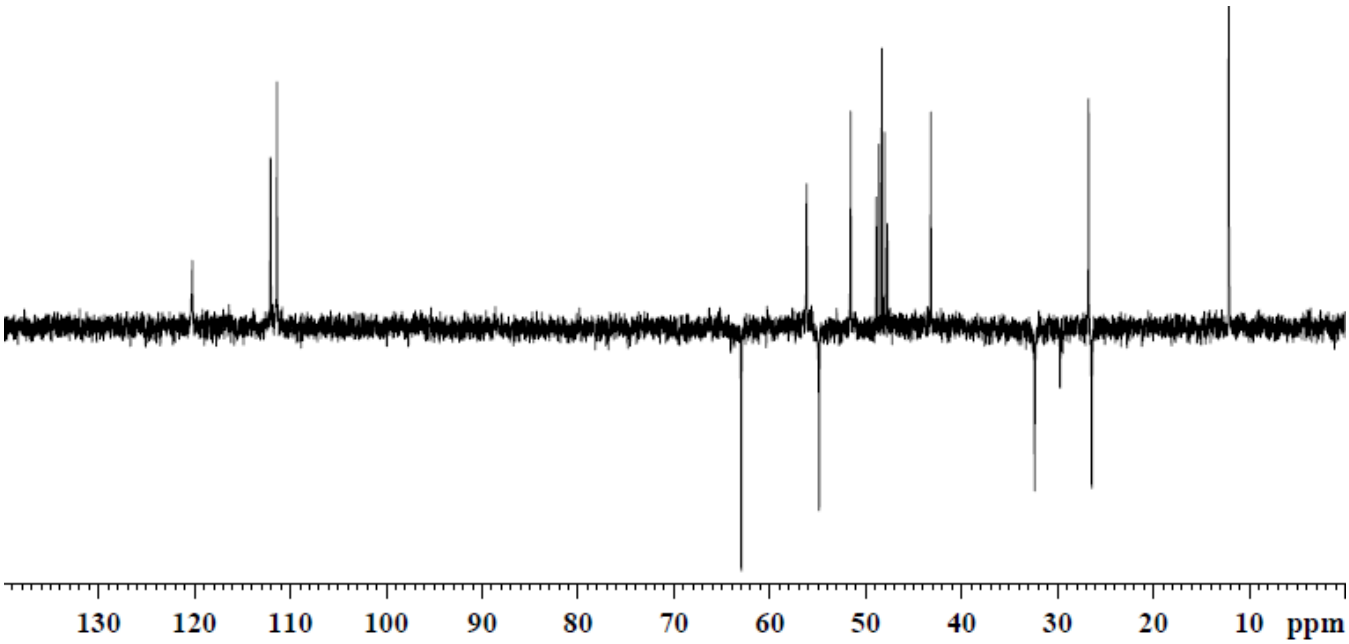

ppm
10
15
20
25
30
35
40
45
50
55
60
65
HSQC
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
ppm

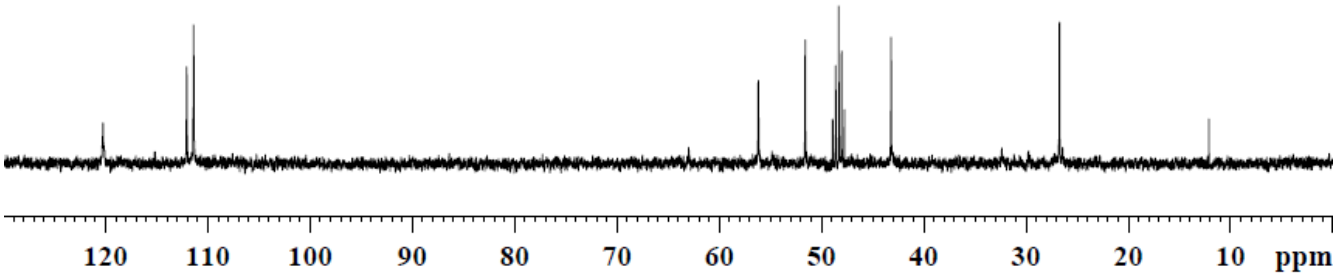

H
H
H
N
HO
H
H
HO
OH
H
H
OH
N
N
H
H
H

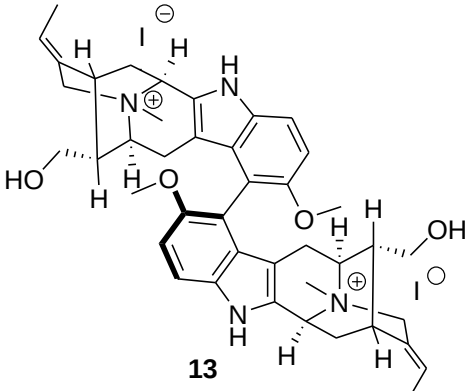
12a


7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
2
1.914
2.182
1.892
1.853
2.226
1.949
1.841
2.042
1.813
2.076
2.027
2.39
2.269
8.148


140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

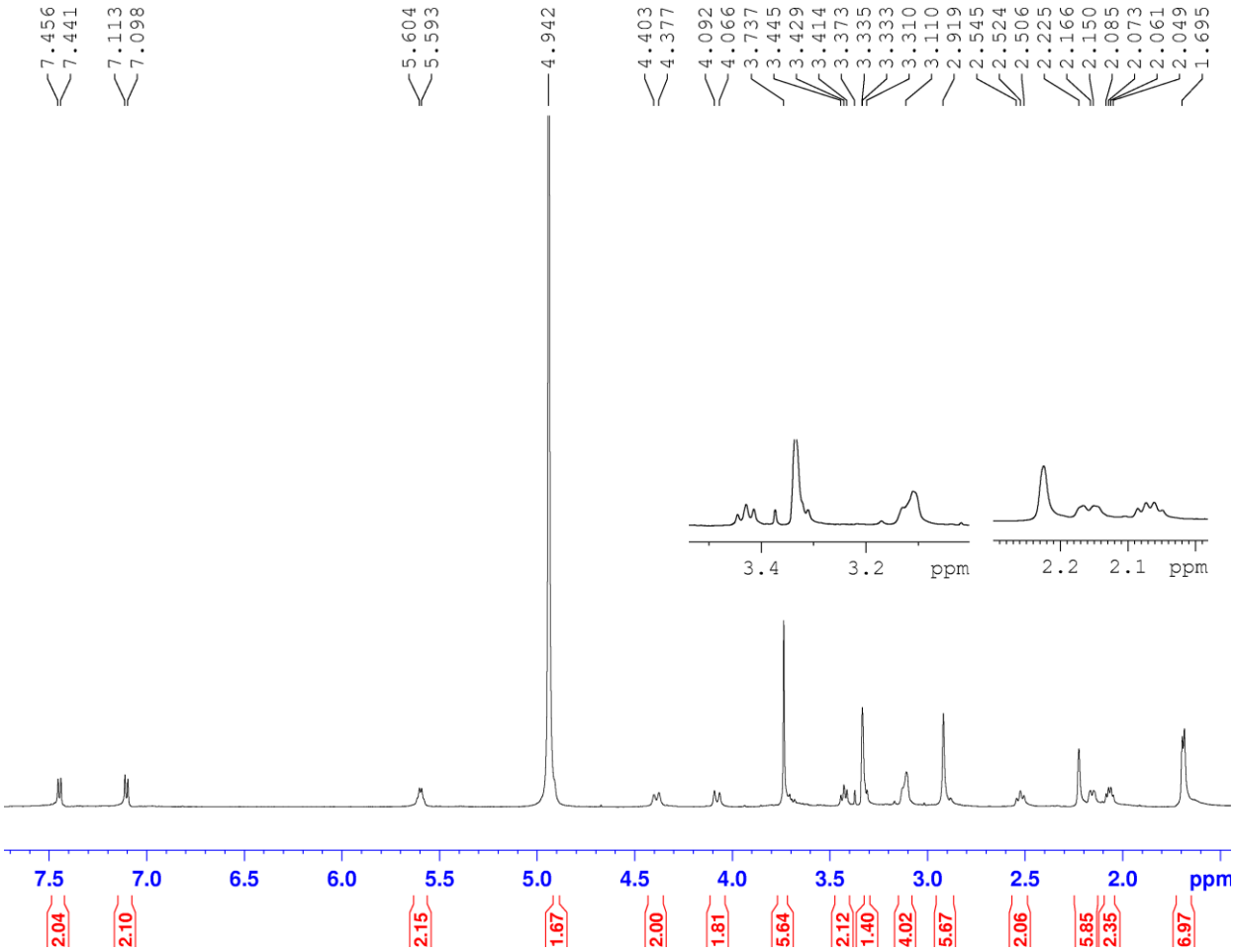

130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

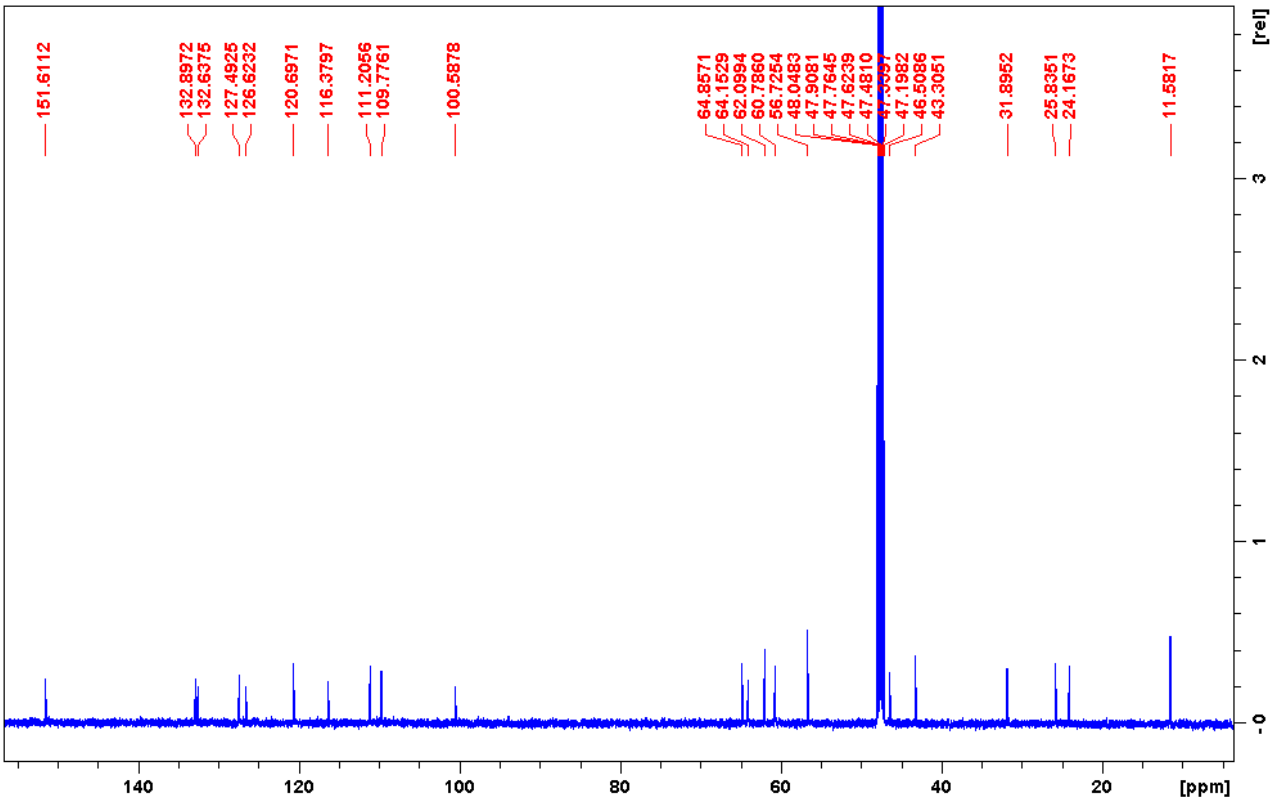

120
110
100
90
80
70
60
50
40
30
20
10
ppm

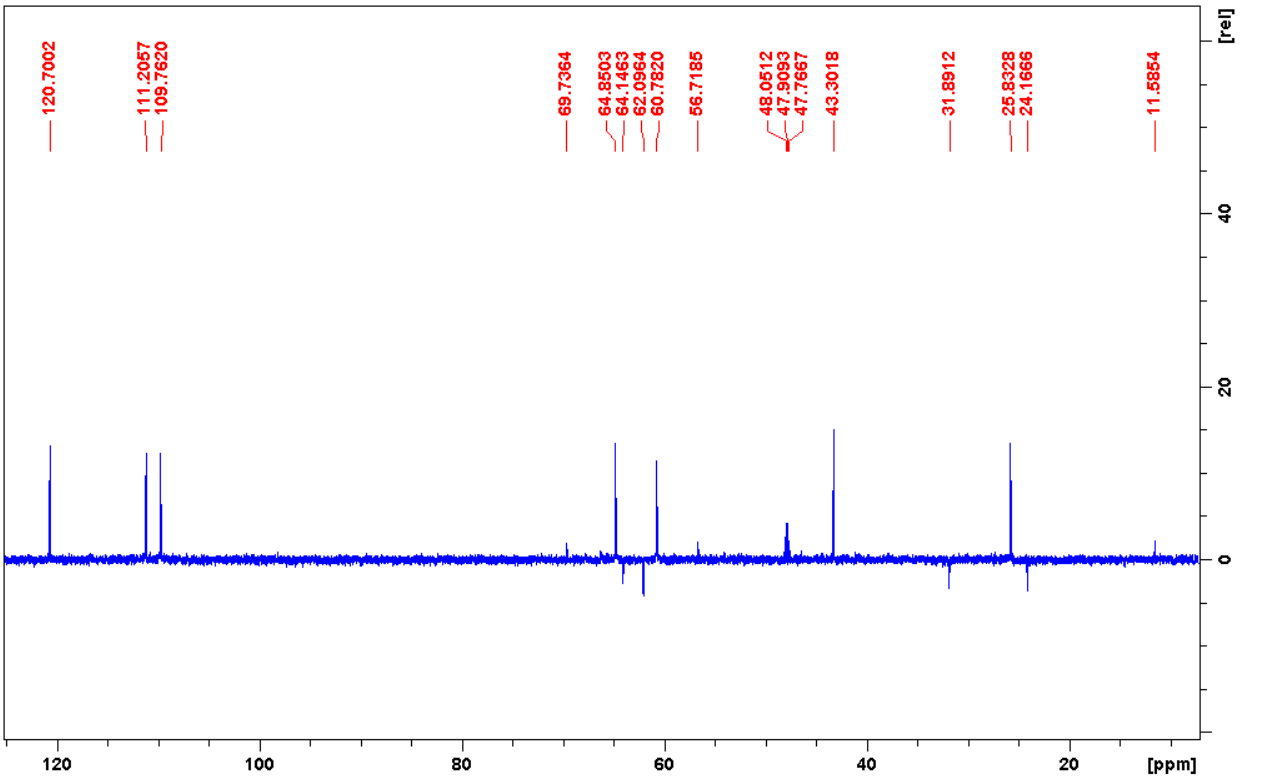


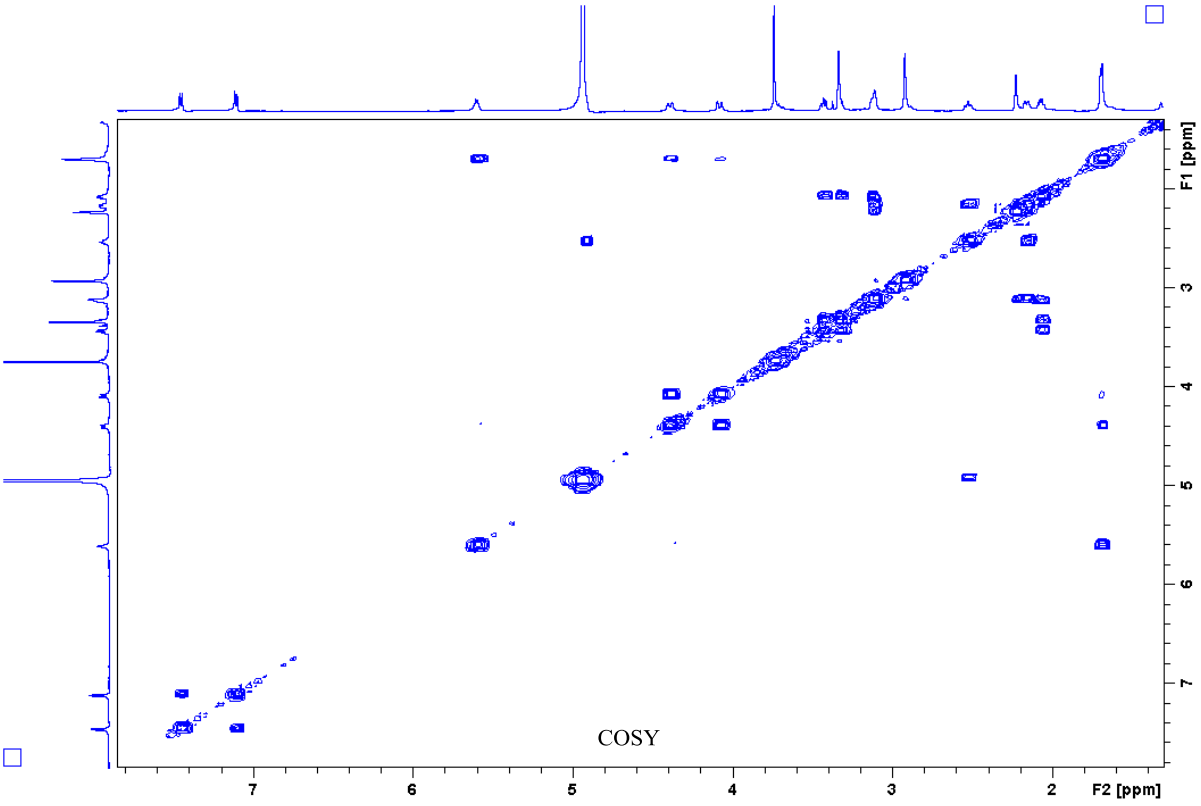
13

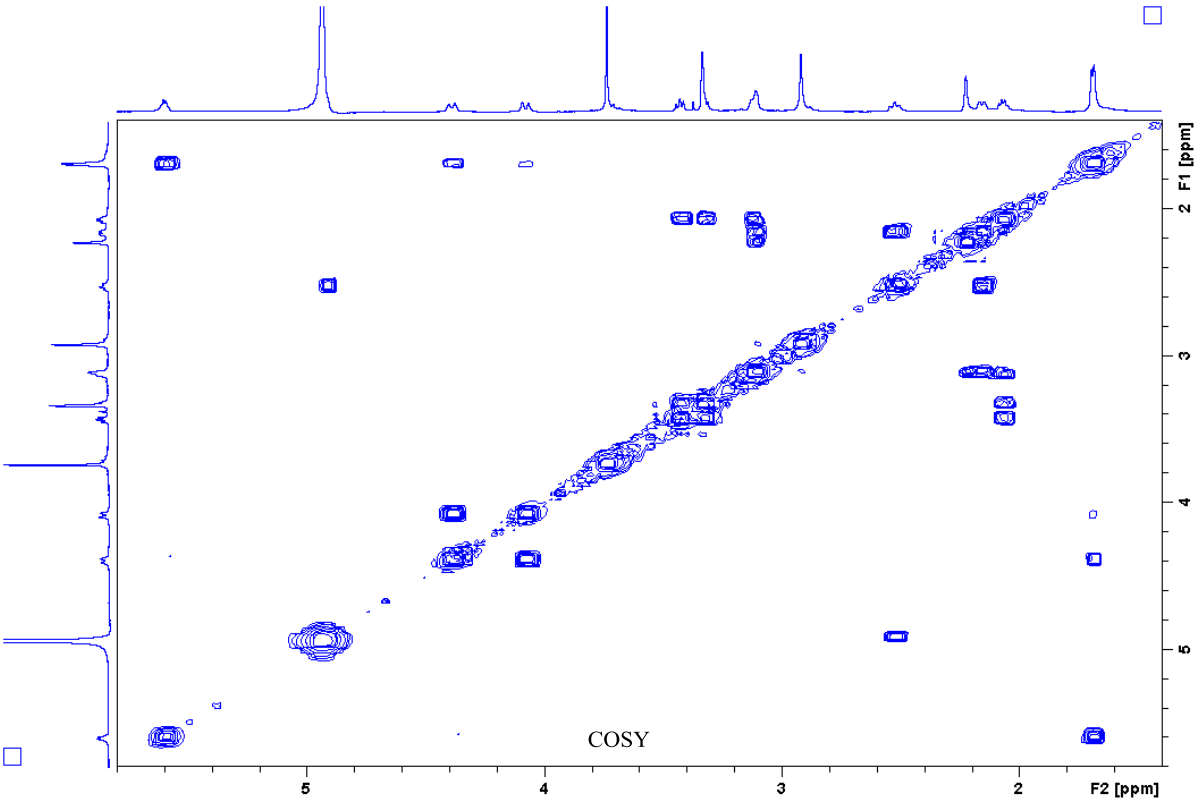
P(*S*)-bismethyl ether of dispegatrine

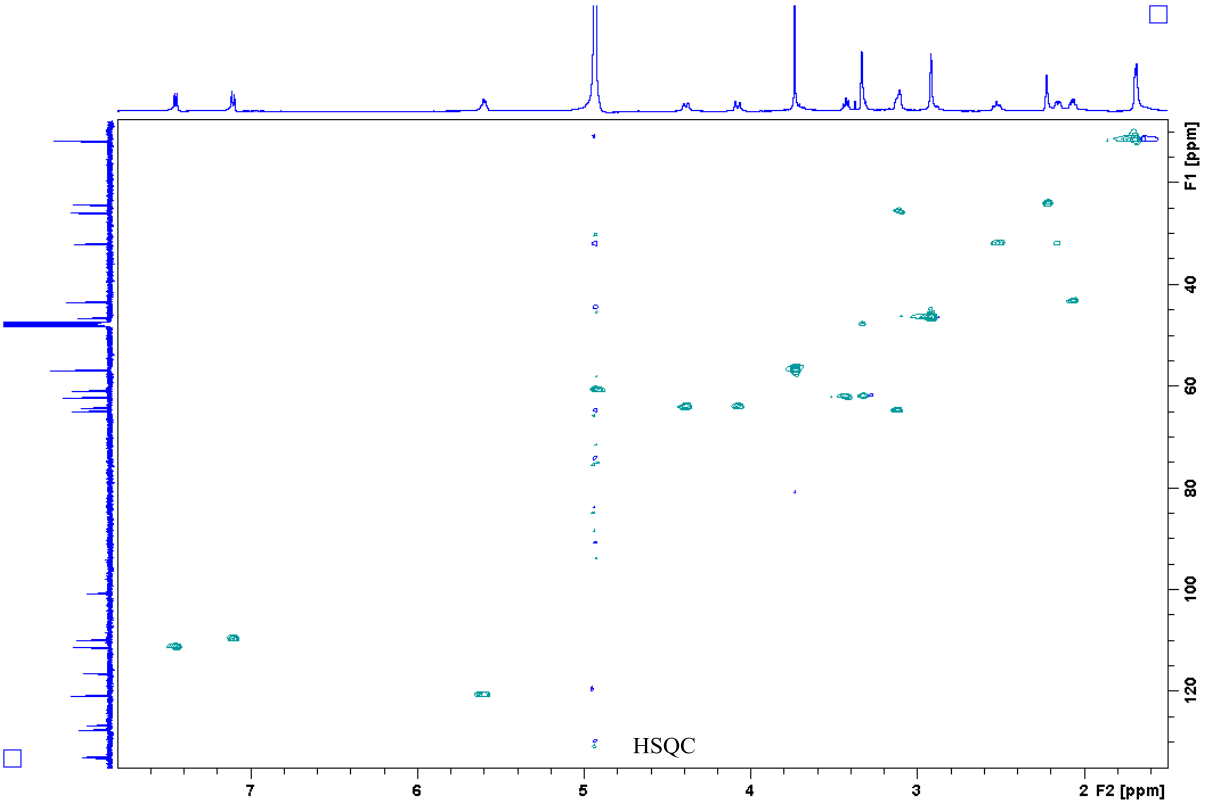


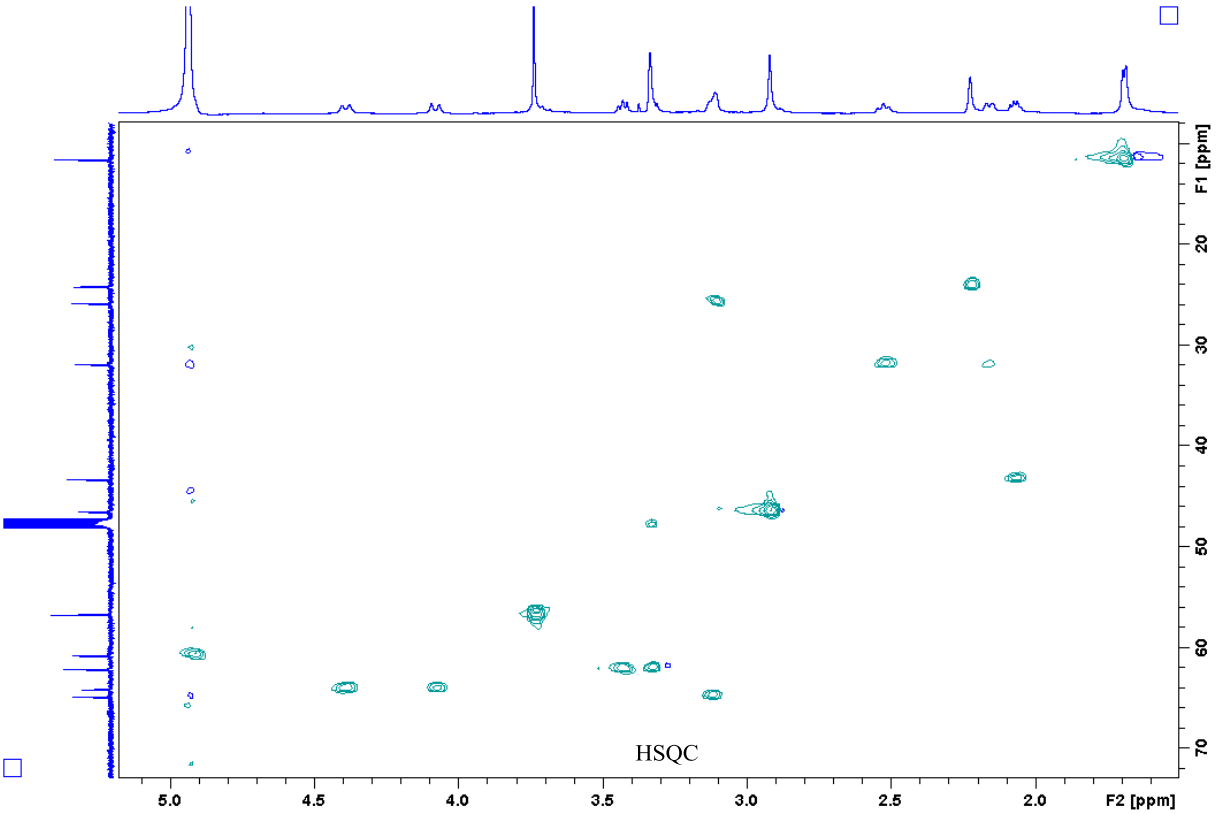

151.6112
132.8972
132.6375
127.4925
126.6232
120.6971
116.3797
111.2056
109.7761
100.5878
64.8571
64.1529
62.0994
60.7860
56.7254
48.0483
47.9081
47.7645
47.6239
47.4810
47.1982
46.5086
43.3051
31.8952
25.8351
24.1673
11.5817
[rel]
[ppm]

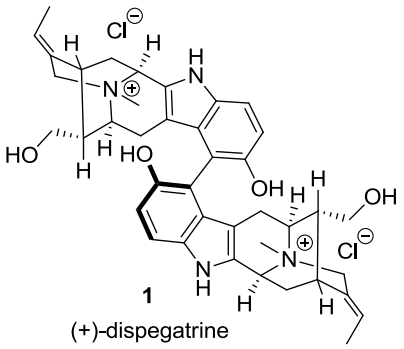

120.7002
111.2057
109.7620
69.7364
64.8503
64.1463
62.0964
60.7820
56.7185
48.0512
47.9093
47.7667
43.3018
31.8912
25.8328
24.1666
11.5854
[rel]
[ppm]


F1 [ppm]
F2 [ppm]
COSY


F1 [ppm]
F2 [ppm]
COSY


F1 [ppm]
40
60
80
100
120
HSQC
7
6
5
4
3
2 F2 [ppm]

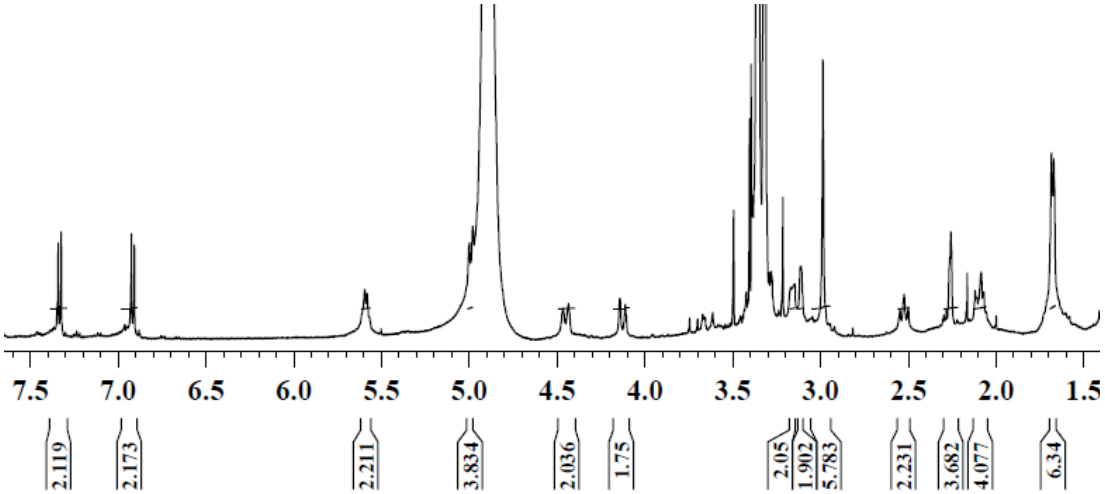

F1 [ppm]
20
30
40
50
60
70
HSQC
5.0
4.5
4.0
3.5
3.0
2.5
2.0
F2 [ppm]



1

(+)-dispegatrine

Solvent: CD_3OD



4 hydrogen atoms are embedded under the CD_3OD multiplet at 3.3 ppm

Solvent: D_2O