Supporting Information

Regiospecific, Enantiospecific Total Synthesis of C-19 Methyl Substituted Sarpagine Alkaloids Dihydroperaksine-17-al and Dihydroperaksine

Rahul V. Edwankar,[†] Chitra R. Edwankar,[†] Jeffrey Deschamps[‡] and James M. Cook[*,†]

[†] Department of Chemistry and Biochemistry, University of Wisconsin-Milwaukee, Milwaukee, WI-53201, USA

[‡] Centre for Bimolecular Science and Engineering, Naval Research Laboratory, Code 6930, Washington, D.C. 20375, USA

To whom correspondence should be addressed. Tel: 414-229-5856; Fax: 414-229-5530; E-mail: capncook@uwm.edu

Table of Contents

1) General Experimental Considerations…….S-3

2) Biogenetic Numbering for Compounds **1** and **2**……..S-4

3) Experimental Procedures and Analytical Data…….....S-5

4) NMR (^{1}H and ^{13}C) Comparison Tables 1 & 2 for 19(*S*),20(*R*)-Dihydroperaksine-17-al (**1**)…….S-26

5) NMR (^{1}H and ^{13}C) Comparison Tables 3 & 4 for 19(*S*),20(*R*)-Dihydroperaksine (**2**)…….S-28

6) X-ray Structural Analysis and Methods for **14**……..S-30

7) References……..S-31

8) Copies of ^{1}H and ^{13}C NMR Spectra…….....S-32

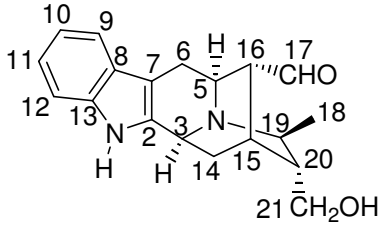
9) Copies of Correlation Experiments for Compound **2**…….....S-53

General Experimental Considerations:

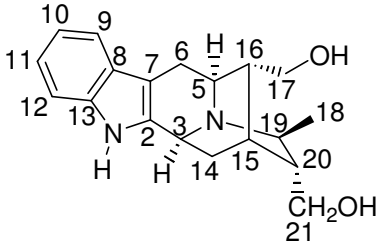
All reactions were carried out under an argon atmosphere with dry solvents using anhydrous conditions unless otherwise stated. Tetrahydrofuran (THF) and diethyl ether were freshly distilled from Na/benzophenone ketyl prior to use. Dichloromethane was distilled from calcium hydride prior to use. Methanol was distilled over magnesium sulfate prior to use. Benzene and toluene were distilled over Na prior to use. 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 was 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] Alkynes were visualized by immersing the TLC plate in a permanganate solution[1] followed by gentle heating with a heat gun; these compounds appeared as either yellow or light brown spots on a light purple or pink background. 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. Melting points were taken on a Stuart melting point apparatus

SMP3 manufactured by Barloworld Scientific US Ltd. Proton (^{1}H NMR) and carbon high resolution nuclear magnetic resonance spectra (^{13}C NMR) were obtained on a Bruker 300-MHz or a GE 500-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 doublets, dt = doublet of triplet, ddd = doublet of doublet of doublet, 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, 70eV), 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 electrospray ionization (ESI) methods were performed at the Laboratory for Biological Mass Spectrometery at Texas A&M University on a API QStar Pulsar model, manufactured by MDS Sciex. 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] for Compounds 1 and 2:

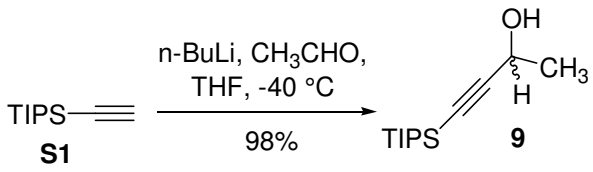


1, 19(*S*),20(*R*)-dihydroperaksine-17-al



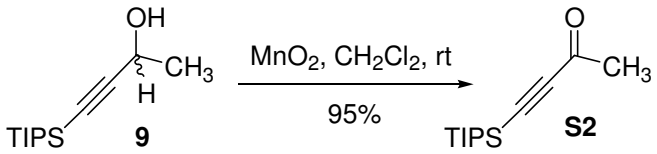
2, 19(*S*),20(*R*)-dihydroperaksine

Experimental Procedures and Analytical Data:



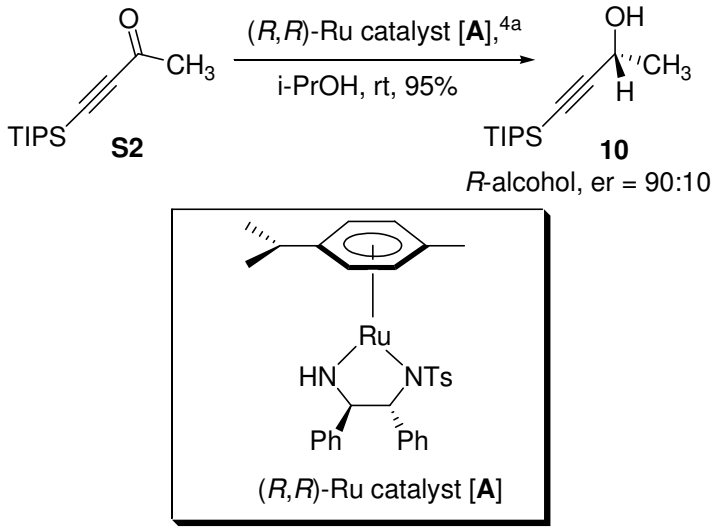
4-Triisopropylsilyl-3-butyn-2-ol (9)[3]

A 3 L round bottom flask, which had been flame dried, was equipped with two addition funnels and a stir bar under argon and was charged with triisopropylacetylene (**S1**, 125 g, 685 mmol) and dry THF (1.2 L). The reaction mixture which resulted was cooled to -40 ^{o}C (dry ice-ethyl acetate bath), and *n*-BuLi (343 mL, 857 mmol, 2.5 M solution in hexane) was added dropwise. The bright yellow mixture, which resulted was stirred at -40 °C for 30 min, after which dry acetaldehyde (47.3 mL, 788 mmol) was added dropwise. The reaction mixture which resulted was stirred for an additional 30 min at -40 °C before the mixture was poured at -40 °C into a saturated aq solution of NH_4Cl (2.5 L). After 15 min, the two phases were separated, and the aq layer was extracted with diethyl ether. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by passing through a short pad of silica gel and the solvent concentrated under reduced pressure to yield the racemic alcohol **9** as a pale yellow oil (152 g, 98% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.60 – 4.52 (m, 1H), 1.81 (d, 1H, *J* = 5.2 Hz), 1.49 (d, 3H, *J* = 6.6 Hz), 1.09 (s, 21H). The proton NMR for this compound was identical in all respects with that reported in the literature.[4a]



4-Triisopropyl-3-butyn-2-one (S2)[4a]

An oven dried three neck 3 L round bottom flask equipped with an overhead stirrer, was cooled under argon and charged with CH_2Cl_2 (1.5 L) and racemic alcohol **9** (82 g, 362 mmol). Activated MnO_2 (455 g, 4708 mmol, technical, activated, ≥90% Fluka works much better than 85%, activated, Aldrich grade) was then added in one portion. The reaction mixture which resulted was stirred for 12 h at rt or until anlysis by TLC (silica gel, EtOAc/hexanes, 0.4 mL : 3.6 mL) indicated the disappearance of the starting material **9** (After running the TLC, the plate was dipped into $KMnO_4$ solution and dried with a heat gun). Once analysis by TLC indicated the disappearance of starting material **9**, the reaction mixture was passed through a short pad of celite and concentrated under reduced pressure to yield the ketone as a pale yellow oil (77.2 g, 95% yield). $\mathbf{R}_f$ 0.20 (ethyl acetate/hexanes, 1 : 7); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 2.38 (s, 3H), 1.13 (s, 21H). The proton NMR data for this compound was identical in all respects with that reported in the literature.[4a]



(*R*)-4-Triisopropylsilyl-3-butyn-2-ol (10)

(a) RuCl[(*R*,*R*)-NTsCH(C_6H_5)CH(C_6H_5)NH_2](η^6-cymene) (A)[4a]

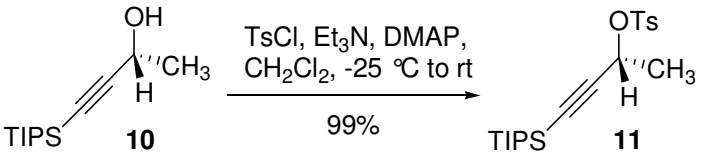
A flame dried 100 mL round bottom flask equipped with a magnetic stir bar was charged with freshly distilled CH_2Cl_2 (32 mL), (1*R*,2*R*)-(+)-N-p-tosyl-1,2-diphenylethylene-diamine (582 mg, 1.59 mmol), dichloro(p-cymene)ruthenium (II) dimmer (486 mg, 0.79 mmol, Aldrich), and powdered KOH (655 mg, 11.67 mmol). The orange mixture which resulted was stirred for 10 min, after which H_2O (32 mL) was added in one portion. The biphasic mixture which resulted was stirred vigorously for 15 min, during which time the organic phase took on a dark purple color. The mixture was transferred to a separatory funnel and diluted with water, and the layers were separated. The aq phase was then extracted with CH_2Cl_2. The combined organic extracts were dried over CaH_2, vacuum filtered, and concentrated to furnish the catalyst **A** (845 mg, 90% yield) as a dark purple solid which was used immediately in the subsequent reduction.

(b) Noyori Reduction[4a]

A flame dried 2 L round bottom flask equipped with a magnetic stir bar was charged with dry *i*-PrOH (1.36 L) and ketone **S2** (25 g, 98 mmol). The (*R*,*R*)-catalyst **A** (845 mg) was taken up in a minimal amount of CH_2Cl_2 (25 ml) and added to the reaction mixture in one portion. The reaction mixture was stirred for 1.5 h. Analysis by TLC (silca gel, EtOAc/hexanes, 0.4 mL/3.6 mL), by observation of the disappearance of a UV active spot for the ketone indicated the absence of starting material **S2**. The reaction mass was concentrated under reduced pressure to give a brown oil which was further purified by distillation (1 mmHg; 101 °C) to yield the (*R*)-alcohol **10** as a clear oil (21.2 g, 95%). $\mathbf{R_f}$ 0.59 (ethyl acetate/hexanes, 1 : 7); $\mathbf{[\alpha]^{20}_D}$ + 22.9 (c 1.63 $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.59 – 4.54 (m, 1H), 2.06 (br s), 1.49 (d, 3H, *J* = 6.4 Hz), 1.09 (s, 21H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 109.8, 84.4, 58.8, 24.6, 18.6, 11.1. The proton and carbon NMR data for this compound was identical in all respects with that reported in the literature.[4b]

(c) Determination of er. The enantiomeric ratio for the optically active (*R*)-alcohol **10** was determined by protecting the secondary alcoholic group in **10** as an acetate. The acetate was synthesized by dissolving the (*R*)-alcohol **10** (60 mg, 0.26 mmol) in CH_2Cl_2 (1.5 mL) followed by the addition of triethylamine (40 mg, 0.40 mmol) and DMAP (3 mg, 10 mol%). The reaction mixture was cooled to 0 °C and acetic anhydride (28 μL, 0.29 mmol) was added dropwise. The resulting solution was stirred at rt for 1 h, after which the solvent was evaporated under reduced pressure. The residue was redissolved in CH_2Cl_2 and washed with a sat aq solution of $NaHCO_3$, brine and dried ($MgSO_4$) to give the optically active (*R*)-acetate **S3**. The optical purity of the sample (er = 90:10) was determined by analysis of the ^{1}H NMR spectrum of the acetate **S3** by adding the chiral

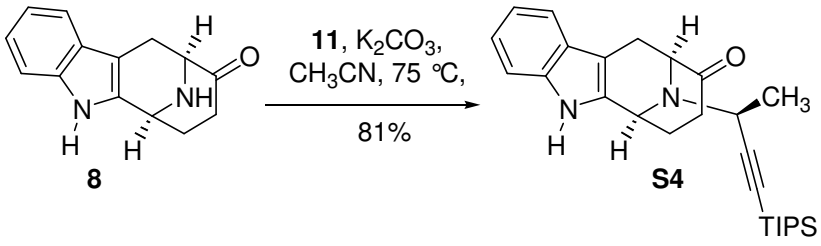
shift reagent $Eu(hfc)_3$, according to the procedure of Burgess et al.[5] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.49 (q, 1H, *J* = 9.6 Hz), 2.10 (s, 3H), 1.51 (d, 3H, *J* = 10.2 Hz), 1.09 (s, 21H). The acetate **S3** was not subjected to any further characterization.



(*R*)-4-Triisopropylsilyl-3-butyn-2-yl Tosylate (11)

A 3 L round bottom flask equipped with a large magnetic stir bar was flame dried under a continuous flow of argon and was then allowed to cool. The flask was then charged with freshly distilled CH_2Cl_2 (284 mL) and (*R*)-alcohol **10** (15 g, 66.3 mmol), after which the mixture was cooled to -25 °C (outside bath temperature). Triethylamine (26.8 g, 265 mmol) and a catalytic amount of DMAP (0.81 g, 6.6 mmol) were added, and after a few minutes of stirring, tosyl chloride (27.8 g, 146 mmol, Alfa Aesar-98%) was added in one portion. The reaction mixture was allowed to stir at -25 °C for 45 min and the solution was allowed to slowly warm to rt. After stirring the reaction mixture for 3 h at rt, analysis by TLC was carried out after which the reaction mixture was quenched with a large excess of water (1200 mL) and the mixture was allowed to stir vigorously for 45 min. After 45 min, the two layers were separated (aq layer was not extracted with CH_2Cl_2). The CH_2Cl_2 layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to furnish **11** (25 g, 99%) as a light brown colored oil, which was used without further purification. $\mathbf{R}_f$ 0.41 (ethyl acetate/hexanes, 1 : 7); $\mathbf{[\alpha]^{20}_D}$ + 94.45 (c 1.73 $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.84 (d, 2H, *J* = 8.3 Hz), 7.32 (d, 2H, *J* = 8.1 Hz), 5.22 (q, 1H, *J* = 6.7 Hz), 2.44 (s, 3H), 1.63 (d, 3H, *J* = 6.6 Hz), 0.98 (s, 21H); **^{13}C NMR** (75

MHz, $CDCl_3$) δ 144.1, 134.1, 129.6, 127.8, 103.0, 89.1, 68.4, 23.2, 18.3, 10.8; **HRMS (ESI)** *m/z* $(M + Li)^+$ calcd for $C_{20}H_{32}O_3SSiLi$, 387.2001, found 387.1992.



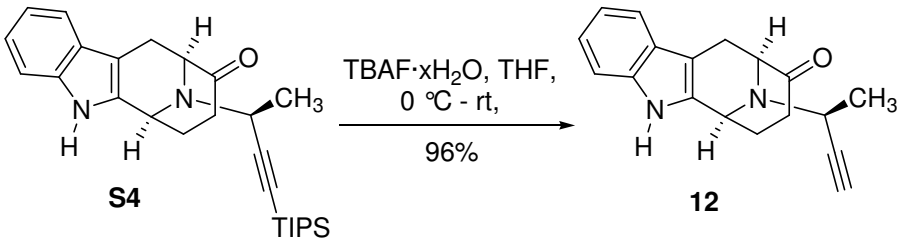
Alkylation of 8 to provide (6*S*,10*S*)-12-((*S*)-4-(triisopropylsilyl)but-3-yn-2-yl)-7,8,-10,11-terahydro-5*H*-6,10-epiminocycloocta[*b*]indol-9(6*H*)-one (S4)

An oven dried 1 L flask, cooled under argon, was charged with optically active N_a-H, N_b-H tetracyclic ketone **8**[6] (5.0 g, 22.1 mmol). The solid **8** was dissolved in freshly distilled acetonitrile (150 mL) after which a solution of (*R*)-4-triisopropylsilyl-3-butyn-2-ol tosylate **11** (13.5 g, 35.4 mmol) in dry acetonitrile (50 mL) was added. Anhydrous potassium carbonate (6.1 g, 44.2 mmol) was added and the mixture which resulted was allowed to heat and stirred at 75 °C (outside oil bath temperature) for 12 h under argon. Analysis by TLC (silica gel, $CHCl_3$/EtOH, 9:1) indicated the absence of tetracyclic ketone **8** after 12 h. The reaction mixture was cooled to rt and the K_2CO_3 was filtered off by passing the solution through a bed of Celite using EtOAc as eluent. After removal of the solvent under reduced pressure, the crude product was purified by flash chromatography (silca gel, EtOAc/hexanes) to provide the C(12)-*S*-N_a-H, TIPS acetylenic tetracyclic ketone **S4** as a light yellow colored solid (7.8 g) in 81% yield.

A small amount of the C(12)-*R*-N_a-H, TIPS acetylenic tetracyclic ketone (Not Shown) as a buff colored solid (0.8 g) was obtained because of the (90:10) enantiomeric ratio of tosylate **11**.

[C(12)-*S*] diastereomer (**S4**): **mp** 129-131 °C; **$[\alpha]^{20}_{D}$** −183.58 (c 0.95 $CHCl_3$); **IR** (KBr) 3316, 2169, 1701cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.47 (d, 1H, *J* = 7.6 Hz), 7.35 (d, 1H, *J* = 7.8 Hz), 7.19 (td, 1H, *J* = 7.1, 1.2 Hz), 7.12 (td, 1H, *J* = 7.6, 1.2 Hz), 4.74 (d, 1H, *J* = 3.0 Hz), 3.97 (d, 1H, *J* = 6.2 Hz), 3.70 (q, 1H, *J* = 6.7 Hz), 3.16 (dd, 1H, *J* = 16.6, 6.4 Hz), 2.72 (dd, 1H, *J* = 16.6, 0.9 Hz), 2.63 – 2.45 (m, 2H), 2.18 – 2.03 (m, 2H), 1.48 (d, 3H, *J* = 6.7 Hz), 1.03 (s, 21H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 210.4 (C), 135.8 (C), 132.5 (C), 126.8 (C), 121.9 (CH), 119.6 (CH), 118.1 (CH), 110.8 (CH), 108.8 (C), 107.5 (C), 84.6 (C), 62.1 (CH), 50.0 (CH), 47.9 (CH), 34.6 (CH_2), 29.6 (CH_2), 21.4 (CH_2), 20.8 (CH_3), 18.5 (6 x CH_3), 11.1 (3 x CH); **EIMS** (*m/e*, relative intensity) 434 ($M^{+\bullet}$, 69), 406 (33), 391 (10), 377 (88), 363 (9), 324 (15), 225 (25), 183 (54), 169 (100), 157 (32).

Anal. Calcd. for $C_{27}H_{38}N_2OSi$: C, 74.60; H, 8.81; N, 6.44. Found: C, 74.11; H, 9.13; N, 6.25.



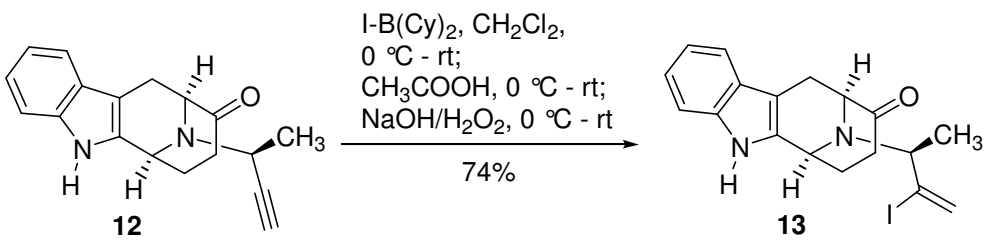
S4 **12**

(6*S*,10*S*)-12-((*S*)-but-3-yn-2-yl)-7,8,10,11-terahydro-5*H*-6,10-epiminocycloocta[*b*]-indol-9(6*H*)-one (12)

TBAF·xH_2O (104 mL, 103.7 mmol, 1.0 M solution in THF) was added to a solution of the N_a-H, TIPS protected acetylenic tetracyclic ketone (**S4**, 30 g, 69.1 mmol) in THF (477 mL) at 0 °C. The solution which resulted was allowed to stir at 0 °C for 0.5 h, after which the ice bath was removed and the mixture was stirred at rt for 3 h until analysis by TLC

indicated the disappearance of the starting material **S4**. The reaction solution was then quenched with H_2O (150 mL) at rt, followed by dilution with EtOAc (500 mL). The two layers were separated. The organic layer was washed with water, brine and dried (Na_2SO_4). The EtOAc was removed under reduced pressure and the residue was passed through a small pad of silica gel to give the N_a-H acetylenic tetracyclic ketone **12** as an offwhite colored solid (18.5 g, 96% yield). **mp**: 125-127 °C; **$[\alpha]^{20}_D$** −192.58 (c 0.97 $CHCl_3$); **IR** (KBr) 3382, 3238, 2944, 2111, 1706, 742 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.48 (d, 1H, *J* = 7.7 Hz), 7.36 (d, 1H, *J* = 7.9 Hz), 7.20 (td, 1H, *J* = 7.1, 1.3 Hz), 7.13 (td, 1H, *J* = 7.6, 1.2 Hz), 4.68 (d, 1H, *J* = 3.2 Hz), 3.97 (d, 1H, *J* = 6.4 Hz), 3.66 (qd, 1H, *J* = 6.7, 2.2 Hz), 3.14 (dd, 1H, *J* = 16.7, 6.5 Hz), 2.72 (dd, 1H, *J* = 16.7, 0.9 Hz), 2.67 - 2.45 (m, 2H), 2.27 (d, 1H, *J* = 2.2 Hz), 2.19 - 2.05 (m, 2H), 1.48 (d, 3H, *J* = 6.7 Hz); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 210.3 (C), 135.8 (C), 132.4 (C), 126.7 (C), 122.0 (CH), 119.7 (CH), 118.1 (CH), 110.8 (CH), 107.4 (C), 84.8 (C), 72.3 (CH), 61.5 (CH), 50.4 (CH), 47.1 (CH), 34.5 (CH_2), 29.6 (CH_2), 21.5 (CH_2), 20.4 (CH_3); **EIMS** (*m/e*, relative intensity) 278 ($M^{+\bullet}$, 34), 249 (7), 221 (100), 206 (7), 182 (14), 169 (60), 154 (8), 140 (8), 115 (18), 77 (7), 53 (24).

Anal. Calcd. for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.06. Found: C, 77.38; H, 6.67; N, 9.93.



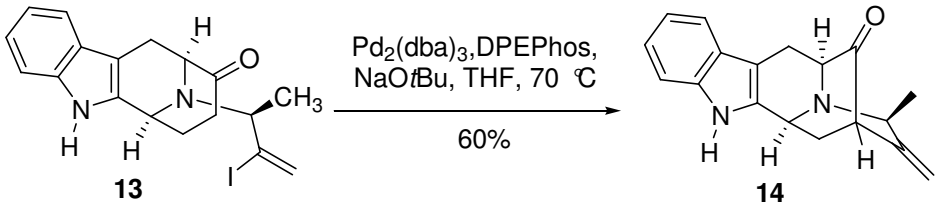
Haloboration reaction on 12 to give (6*S*,10*S*)-12-((*S*)-3-iodobut-3-en-2-yl)-7,8,10,11-tetrahydro-5*H*-6,10-epiminocycloocta[*b*]indol-9(6*H*)-one (13)

An oven dried flask fitted with an addition funnel was cooled under argon and charged with N_a-H acetylenic tetracyclic ketone **12** (2.10 g, 7.55 mmol) dissolved in freshly distilled CH_2Cl_2 (52.5 mL) and hexanes (7.0 mL). The flask was cooled to 0 °C with ice and I-B(Cy)$_2$ (30.2 mL, 15.1 mmol, 0.5 M solution in hexanes) was added dropwise every 0.5 h in three portions, over a total period of 1.5 h. After the last addition the reaction mixture was allowed to stir at 0 °C for another 0.5 h, after which the ice bath was removed and the mixture was stirred at rt for 2.0 h. After stirring at rt for 2.0 h, another 0.5 eq of I-B(Cy)$_2$ (7.6 mL, 3.78 mmol) was added dropwise at rt and the mixture was allowed to stir for another 2.0 h. After this 2.0 h, the mixture was treated with glacial acetic acid (4.8 mL, 83.1 mmol) at 0 °C and stirred at rt for 1.15 h. At this point, the flask was again cooled to 0 °C and a solution of cold aq 3M NaOH (40.3 mL, 121 mmol) and 30% H_2O_2 (2.6 mL, 23 mmol) were added and the stirring was maintained for 1.0 h at rt. The biphasic solution which resulted was transferred to a bigger flask, diluted with CH_2Cl_2 (400 mL) and water (50 mL) after which the two layers were separated. The original reaction flask still had some residual solid attached to the bottom of the flask. The solid was dissolved in acetone (50 mL). The acetone was evaporated under reduced pressure to ¾ th the volume and the mixture was diluted with CH_2Cl_2 (50 mL). Again the two layers were separated and the combined CH_2Cl_2 layers were treated with solutions of 5% KF in methanol (160 mL) and 5% aq sodium bisulfite (160 mL) under vigorous stirring for 5 min. The aq layer was separated, extracted with CH_2Cl_2 (2 x 80 mL) after which the combined organic layers were washed with brine, dried (Na_2SO_4), filtered and

concentrated under reduced pressure. Purification by chromatography on silica gel (ethyl acetate/hexanes, 2 : 8) afforded vinyl iodide **13** as a white solid (74%, 2.3 g).

mp 192 - 194 °C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.50 (d, 1H, *J* = 7.6 Hz), 7.43 (d, 1H, *J* = 7.9 Hz), 7.22 (td, 1H, *J* = 6.8, 0.9 Hz), 7.16 (t, 1H, *J* = 6.7 Hz), 6.26 (d, 1H, *J* = 0.5 Hz), 5.86 (d, 1H, *J* = 0.9 Hz), 4.20 (d, 1H, *J* = 2.7 Hz), 4.01 (d, 1H, *J* = 6.2 Hz), 3.12 (dd, 1H, *J* = 16.8, 6.4 Hz), 2.78 (d, 1H, *J* = 16.8 Hz), 2.67 (q, 1H, *J* = 6.3 Hz), 2.60 – 2.49 (m, 2H), 2.20 – 2.01 (m, 2H), 1.20 (d, 3H, *J* = 6.2 Hz); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 210.4 (C), 135.8 (C), 131.8 (C), 126.8 (C), 125.8 (CH_2), 122.3 (C), 122.0 (CH), 119.7 (CH), 118.1 (CH), 110.9 (CH), 107.6 (C), 62.2 (CH), 60.8 (CH), 48.8 (CH), 34.5 (CH_2), 30.2 (CH_2), 21.1 (CH_2), 19.7 (CH_3); **EIMS** (*m/e*, relative intensity) 406 ($M^{+\bullet}$, 61), 349 (100), 279 (41), 251 (59), 221 (20), 197 (17), 182 (24), 169 (95), 154 (20), 140 (18), 115 (24).

Anal. Calcd. for $C_{18}H_{19}IN_2O$: C, 53.22; H, 4.71; N, 6.90. Found: C, 52.77; H, 4.86; N, 6.48.

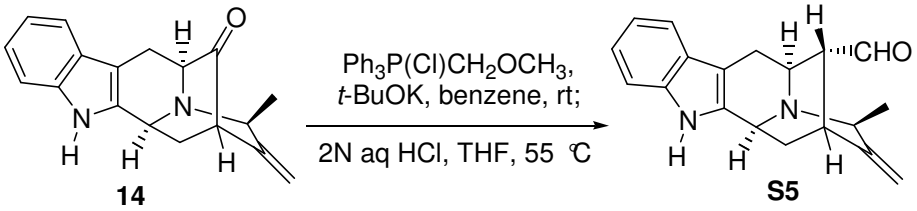


13 **14**

Enolate-mediated palladium catalyzed cyclization of vinyl iodide 13 to provide (6*S*,8*S*,11a*S*)-8-methyl-9-methylene-6,8,9,10,11a,12-hexahydro-6,10-methanoindolo-[3,2-*b*]quinolizin-11(5*H*)-one (14)

A mixture of N_a-H vinyl iodo tetracyclic ketone **13** (1.0 g, 2.46 mmol), DPEPhos (99 mg, 0.18 mmol) and *t*-BuONa (473 mg, 4.93 mmol) in a solution of freshly distilled THF (48

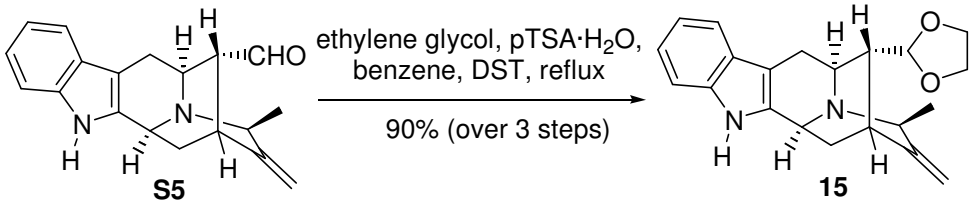
mL) was degassed under reduced pressure at rt and back filled with argon (3 times). The catalyst $Pd_2(dba)_3$ (113 mg, 0.12 mmol) along with dry THF (3 mL) was introduced into the reaction mixture and the system was again degassed under reduced pressure at rt and back filled with argon (4 times). The mixture was then heated to 70 - 75 °C (oil bath temperature) under argon for 3.5 h. The mixture was then 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 **14** as a light brown colored solid (60%, 410 mg). Part of the solid was crystallized by using EtOAc to give **14** as white crystals for x-ray analysis. $\mathbf{R}_f$ 0.38 (EtOAc/MeOH, 4.8 : 0.2); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.50 (d, 1H, *J* = 7.4 Hz), 7.28 (d, 1H, *J* = 7.7 Hz), 7.16 (td, 1H, *J* = 7.0, 1.1 Hz), 7.11 (td, 1H, *J* = 7.5, 1.6 Hz), 5.12 (d, 1H, *J* = 2.7 Hz), 5.01 (d, 1H, *J* = 2.4 Hz), 4.33 (d, 1H, *J* = 9.3 Hz), 3.89 – 3.83 (m, 1H), 3.74 (d, 1H, *J* = 5.3 Hz), 3.34 (dd, 1H, *J* = 15.6, 1.4 Hz), 3.07 (q, 1H, *J* = 1.6 Hz), 2.92 (dd, 1H, *J* = 15.6, 6.1 Hz), 2.55 (t, 1H, *J* = 11.8 Hz), 2.13 – 2.16 (m, 1H), 1.50 (d, 3H, *J* = 6.8 Hz); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 217.5 (C), 148.2 (C), 136.3 (C), 135.7 (C), 126.9 (C), 121.9 (CH), 119.6 (CH), 118.5 (CH), 111.3 (CH_2), 110.7 (CH), 106.2 (C), 58.6 (CH), 57.6 (CH), 52.2 (CH), 52.0 (CH), 36.2 (CH_2), 22.3 (CH_2), 17.3 (CH_3); **EIMS** (*m/e*, relative intensity) 278 ($M^{+\bullet}$, 47), 250 (98), 235 (36), 169 (100), 140 (10), 115 (27), 81 (11).



Conversion of the pentacyclic ketone 14 into (6*S*,8*S*,11*R*,11a*S*)-8-methyl-9-methylene-5,6,8,9,10,11,11a,12-octahydro-6,10-methanoindolo[3,2-*b*]quinolizine-11-carbaldehyde (S5) via the Wittig reaction followed by acid-mediated hydrolysis and epimerization

A mixture of anhydrous potassium *tert*-butoxide (1.82 g, 16.2 mmol) and methoxy-methyltriphenylphosphonium chloride (5.13 g, 15.0 mmol) in dry benzene (82.1 mL) was allowed to stir at rt for 1 h. The pentacyclic ketone **14** (570 mg, 2.05 mmol) in THF (23 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, R_f 0.58) indicated the absence of starting material **14**. The mixture was then diluted with EtOAc (100 mL) and the reaction solution was quenched with water (50 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 solvent was removed under reduced pressure to afford a mixture of two enol ethers as an 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 THF/H_2O (1:1, 28 mL). To the above solution, a solution of aq 12 N conc HCl was added and the mixture which resulted was stirred at 55 °C (oil bath temperature) for 6 h. The reaction mixture was then cooled to 0 °C and extracted with ethyl ether (4 x 15 mL) to remove the phosphorous

byproducts, after which the aq layer was then brought to pH 8 with an ice-cold solution of 14% aq NH_4OH. The aq 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 the α-aldehyde **S5** as an oil, which was directly subjected to the next step without any further purification.

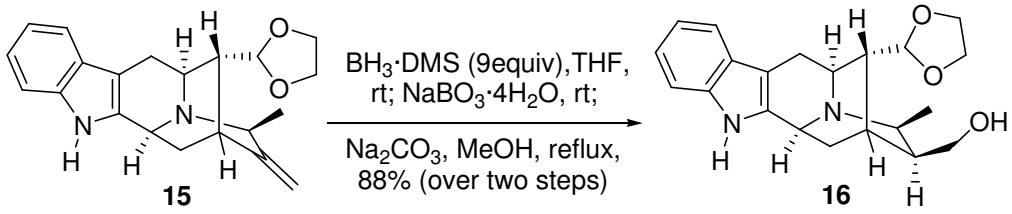


Protection of α-aldehyde S5 as an acetal to provide (6*S*,8*S*,11*R*,11a*S*)-11-(1,3-dioxolan-2-yl)-8-methyl-9-methylene-5,6,8,9,10,11,11a,12-octahydro-6,10-methano-indolo[3,2-*b*]quinolizine (15)

The crude alkenic aldehyde **S5** (2.0 g, 6.84 mmol) was dissolved in dry benzene (233 mL) and this was followed by the addition of dry ethylene glycol (4.67 g, 75 mmol) and p-toluenensulfonic acid monohydrate(1.43 g, 7.52 mmol). The mixture which resulted was heated to reflux for 6 h followed by removal of water via a DST. Analysis of the mixture by TLC (silica gel, CH_2Cl_2 : MeOH) indicated the absence of starting material **S5**. The mixture was allowed to cool to rt, diluted with EtOAc and at 0 °C was brought to pH 8-9 with 14% aq NH_4OH. The aq layer was separated and then extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (2 x 20 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and chromatographed [silica gel, CH_2Cl_2/MeOH, (10 : 0.3) to provide the ethylene acetal **15** (620 mg, 90% yield over 3 steps from **14**). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.51 (d, 1H, *J* = 7.4 Hz), 7.32 (d, 1H, *J* = 7.3 Hz), 7.15 (td, 1H, *J* = 7.1, 1.3 Hz), 7.10 (td, 1H, *J* = 7.2, 1.1 Hz),

4.98 (d, 1H, *J* = 2.4 Hz), 4.91 (d, 1H, *J* = 1.5 Hz), 4.82, (d, 1H, *J* = 8.0 Hz), 4.21 (d, 1H, *J* = 8.9 Hz), 3.97 – 3.80 (m, 4H), 3.64 – 3.57 (m, 1H), 3.36 (t, 1H, *J* = 6.0 Hz), 3.02 (dd, 1H, *J* = 15.6, 5.1 Hz), 2.85 (dd, 1H, *J* = 14.7, 1.1 Hz), 2.54 (t, 1H, *J* = 1.8 Hz), 2.10 (ddd, 1H, *J* = 12.3, 10.2, 2.0 Hz), 1.77 – 1.66 (m, 2H), 1.44 (d, 3H, *J* = 6.8 Hz); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 151.8 (C), 137.7 (C), 136.3 (C), 127.8 (C), 121.3 (CH), 119.2 (CH), 118.2 (CH), 110.7 (CH), 107.7 (CH_2), 106.1 (CH), 105.2 (C), 64.7 (CH_2), 64.4 (CH_2), 57.9 (CH), 51.8 (CH), 47.0 (CH), 45.6 (CH), 35.6 (CH), 33.5 (CH_2), 27.0 (CH_2), 16.8 (CH_3); **EIMS** (*m/e*, relative intensity) 336.5 ($M^{+\bullet}$, 100), 293.5 (14), 263.5 (98), 207.4 (12), 169.4 (71), 115.3 (18), 91.3 (12); **HRMS** (EI) calcd for $C_{21}H_{24}N_2O_2$ 336.1838, found 336.1831.

Anal. Calcd. for $C_{21}H_{24}N_2O_2$ •1/8 $CHCl_3$: C, 72.19; H, 6.91; N, 7.97. Found: C, 72.19; H, 7.15; N, 7.83.

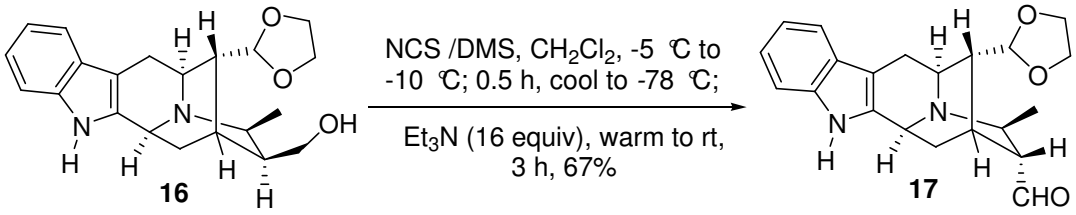


Hydroboration of terminal olefin 15 to provide the ((6*S*,8*S*,9*S*,11*R*,11a*S*)-11-(1,3-dioxolan-2-yl)-8-methyl-5,6,8,9,10,11,11a,12-octahydro-6,10-methanoindolo[3,2-*b*]-quinolizin-9-yl) methanol (16)

To a solution of the alkenic acetal **15** (251 mg, 0.64 mmol) in dry THF (9.3 mL) was added BH_3·DMS (2.0 M solution in THF, 2.88 mL, 5.75 mmol) at rt. The mixture which resulted was stirred at rt for 2 h. The reaction mixture was then quenched by careful addition of ice cold water (8.5 mL) at 0 °C (initial addition of water results in a large

amount of effervescence). At this point $NaBO_3 \cdot 4H_2O$ (2.26 g, 14.7 mmol) was added to the mixture in one portion at 0 °C. The mixture which resulted was allowed to stir at rt for 2 h after which EtOAc (200 mL) and H_2O (25 mL) were added. The organic layer was separated, washed with water (2 x 20 mL), brine (2 x 20 mL) and dried (Na_2SO_4). The EtOAc was then removed under reduced pressure to provide the N_b-BH_3 complex as a mixture of isomers at [C(20)], the major of which was the primary alcohol. This material was used in the next step without any further purification. The above mixture of isomers was dissolved in freshly distilled MeOH (20 mL) and Na_2CO_3 (614 mg, 3.20 mmol) was added. The mixture was then warmed to 60 °C (oil bath) for 5 h under vigorous stirring. The reaction mixture which resulted was cooled to rt followed by filtration through a bed of celite to remove the solids. The filtrate was concentrated under reduced pressure to provide a turbid oil which was redissolved in CH_2Cl_2. The CH_2Cl_2 layer was washed with H_2O (1 x 10 mL), brine (4 x 10 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford a crude solid, which was purified by flash chromatography [silica gel, EtOAc/EtOH/Et_3N (10:0.3:0.1)] to provide the primary alcohol **16** (192 mg) in 73% yield after which the tertiary alcohol (9 mg, Not Shown) was obtained. **16**: $\mathbf{R}_f$ 0.42 (CH_2Cl_2/MeOH/aq NH_4OH, 9:1:0.1); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.51 (d, 1H, *J* = 7.3 Hz), 7.34 (d, 1H, *J* = 7.1 Hz), 7.15 (td, 1H, *J* = 7.1, 1.3 Hz), 7.10 (td, 1H, *J* = 7.1, 1.1 Hz), 5.01 (d, 1H, *J* = 7.6 Hz), 4.19 (d, 1H, *J* = 9.4 Hz), 3.99 – 3.83 (m, 4H), 3.80 – 3.67 (m, 2H), 3.42 (t, 1H, *J* = 6.4 Hz), 3.31 (dt, 1H, *J* = 17.3, 9.0 Hz), 2.98 (dd, 1H, *J* = 10.0, 5.5 Hz), 2.90 (dd, 1H, *J* = 14.6, 7.0 Hz), 2.32 (s, 1H), 1.99 – 1.88 (m, 2H), 1.76 (t, 1H, *J* = 7.9 Hz), 1.68 (dt, 1H, *J* = 12.3, 3.2 Hz), 1.29 (d, 3H, *J* = 3.7 Hz); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 137.3 (C), 136.3 (C), 127.7 (C), 121.3 (CH), 119.2 (CH),

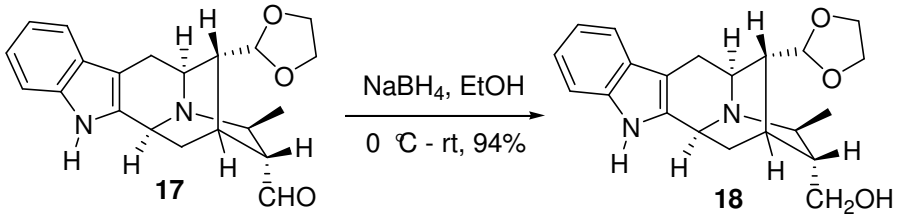
118.2 (CH), 110.8 (CH), 106.9 (CH), 105.0 (C), 65.0 (CH_2), 64.2 (CH_2), 62.5 (CH_2), 53.8 (CH), 52.3 (CH), 47.9 (CH), 43.1 (CH), 39.3 (CH), 36.3 (CH_2), 26.7 (CH_2), 25.6 (CH), 12.9 (CH_3); **EIMS** (*m/e*, relative intensity) 354.6 ($M^{+\bullet}$, 100), 323.6 (45), 281.5 (66), 267.5 (21), 251.5 (26), 209.4 (43), 196.4 (33), 182.4 (24), 169.4 (59), 129.3 (14), 115.3 (14), 73.2 (46); **HRMS** (EI) calcd for $C_{21}H_{26}N_2O_3$ 354.1943, found 354.1940.



Corey-Kim oxidation of primary alcohol 16 to provide (6*S*,8*S*,9*R*,11*R*,11a*S*)-11-(1,3-dioxolan-2-yl)-8-methyl-5,6,8,9,10,11,11a,12-octahydro-6,10-methanoindolo[3,2-*b*]quinolizine-9-carboxaldehyde (17)

To a stirred solution of N-chlorosuccinimide (33 mg, 0.25 mmol) in dry CH_2Cl_2 (1.5 mL) was added dimethyl sulfide (0.036 mL, 0.49 mmol) at -5 to -15 °C (outside bath temperature) under argon. A white precipitate appeared immediately after addition of the sulfide, which was stirred for an additional 0.5 h at the above mentioned temperature range. After 0.5 h, the temperature of the reaction mixture was lowered to -78 °C (EtOAc-dry ice bath). The alcohol **16** (25 mg, 0.07 mmol) in dry CH_2Cl_2 (1.0 mL) also at -78 °C was then added via canula to the white complex, and the stirring was continued for 2 h at -78 °C. A solution of distilled triethylamine (0.17 mL, 1.20 mmol) was then added to the above mixture dropwise (neat) and the stirring was continued for an additional 1 h at -78 °C. The cooling bath was then removed and the reaction mixture was left standing at rt for 3 h. The reaction mixture was partioned between CH_2Cl_2 and H_2O.

The organic layer was separated, washed with brine and dried (Na_2SO_4). The solvent was removed under reduced pressure to provide the mixture of crude aldehydes. Addition of EtOAc from the sides of the flask resulted in the formation of a white insoluble precipitate. The precipitate was filtered and the EtOAc layer was concentrated under reduced pressure. The same process was repeated 4 to 5 times until one no longer sees any precipitate formation after addition of EtOAc to the residue to remove the sulfur impurities. The residue was then further dissolved in MeOH (3 mL) and triethylamine (0.17 mL) was then added and the mixture was stirred overnight at rt for epimerization of the β-aldehyde to the α-aldehyde. The methanol was then removed under reduced pressure to give an oil, which was further purified by flash column chromatography (basic alumina, EtOAc : EtOH, 9 : 0.1) to give the α-aldehyde **17** as a colorless oil (67%, 16.5 mg). $\mathbf{R}_f$ 0.54 (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.1); **IR** (AgCl) 1717 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.83 (s, 1H), 7.84 (s, 1H), 7.50 (d, 1H, *J* = 7.3 Hz), 7.31 (d, 1H, *J* = 7.7 Hz), 7.17 – 7.07 (m, 2H), 4.97 (d, 1H, *J* = 5.3 Hz), 4.10 (d, 1H, *J* = 9.1 Hz), 4.05 – 3.83 (m, 4H), 3.52 (t, 1H, *J* = 5.7 Hz), 3.37 (quin., 1H, *J* = 6.9 Hz), 3.00 (dd, 1H, *J* = 15.6, 4.9 Hz), 2.87 (d, 1H, *J* = 15.3 Hz), 2.62 (d, 1H, *J* = 8.4 Hz), 2.48 (d, 1H, *J* = 1.6 Hz), 1.85 – 1.79 (m, 2H), 1.48 – 1.42 (m, 1H), 1.36 (d, 3H, *J* = 6.7 Hz); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 203.5 (CH), 137.3 (C), 136.3 (C), 127.7 (C), 121.7 (CH), 119.2 (CH), 118.2 (CH), 110.7 (CH), 105.4 (CH), 65.1 (CH_2), 64.4 (CH_2), 51.8 (CH), 51.6 (CH), 51.2 (CH), 46.0 (CH), 42.8 (CH), 29.9 (CH_2), 27.2 (CH_2), 26.1 (CH), 19.1 (CH_3) (One quaternary carbon atom is embedded in the carbons in the aromatic region); **HRMS** (ESI) *m/z* $(M + H)^+$ calcd for $C_{21}H_{25}N_2O_3$, 353.1865, found 353.1868.

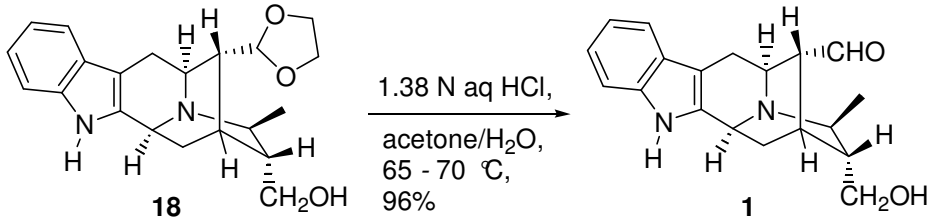


Sodium borohydride mediated reduction of aldehyde 17 to provide ((6*S*,8*S*,9*R*,11*R*,11a*S*)-11-(1,3-dioxolan-2-yl)-8-methyl-5,6,8,9,10,11,11a,12-octahydro-6,10-methanoindolo[3,2-*b*] quinolizin-9-yl)methanol (18)

The acetal aldehyde **17** (16 mg, 0.05 mmol) was dissolved in EtOH (3 mL). The $NaBH_4$ (3 mg, 0.08 mmol) was then added to the above solution in one portion at 0 °C. The mixture which resulted was stirred at rt for 3 h. At this point analysis by TLC indicated the disappearance of the aldehyde **17**. 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 aq 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 evaporated with distilled EtOAc (2 x 3 mL) to give acetal alcohol **18** (15 mg, 94%) as a white colored solid. $\mathbf{R}_f$ 0.37 (CH_2Cl_2/MeOH/aq NH_4OH, 9:1:0.1); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.51 (d, 1H, *J* = 7.3 Hz), 7.32 (d, 1H, *J* = 7.9 Hz), 7.18 – 7.08 (m, 2H), 4.98 (d, 1H, *J* = 6.6 Hz), 4.01 – 3.79 (m, 5H), 3.72 – 3.61 (m, 2H), 3.48 (t, 1H, *J* = 5.8 Hz), 2.98 (dd, 1H, *J* = 15.5 Hz), 2.88 (d, 1H, *J* = 15.3 Hz), 2.49 (quin., 1H, *J* = 7.2 Hz), 2.05 – 2.00 (m, 2H), 1.82 – 1.68 (m, 2H), 1.35 (d, 4H, *J* = 6.7 Hz); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 137.8 (C), 136.3 (C), 127.9 (C), 121.1 (CH), 119.1 (CH), 118.2 (CH), 110.7 (CH), 105.5 (C), 105.3 (CH), 64.9 (CH_2), 64.3 (CH_2), 63.5 (CH_2), 56.2 (CH), 52.2 (CH), 46.2 (CH), 43.9 (CH), 39.5 (CH), 28.6 (CH_2), 27.2 (CH_2),

26.4 (CH), 18.8 (CH_3); **EIMS** (*m/e*, relative intensity) 354 ($M^{+\bullet}$, 97), 323 (19), 281 (100), 209 (37), 197 (11), 182 (12), 169 (51), 156 (10), 73 (37), 57 (15), 45 (25); **HRMS** (ESI) *m/z* $(M + H)^+$ calcd for $C_{21}H_{27}N_2O_3$, 355.2022, found 355.2020. This material was employed directly in the next step.

Note: On small scales such as the above, all extraction and chromatography solvents were distilled.

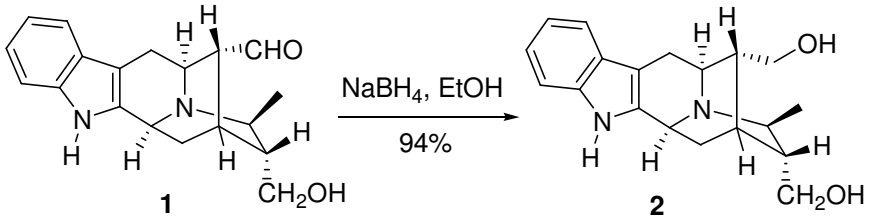


18 1

19(*S*),20(*R*)-dihydroperaksine-17-al (1)

To a solution of monol **18** (30 mg, 0.08 mmol) in distilled acetone (9 mL) was added a 1.38 N aq solution of HCl (0.6 mL of 12 N HCl dissolved in 5.2 mL of H_2O) at 0 °C. The solution which resulted was allowed to stir at 65 - 70 °C (oil bath) for 10 h. After stirring for 10 h at 65 - 70 °C, the acetone was removed under reduced pressure after which, the residue was diluted with H_2O (8 mL). The reaction mixture was then cooled to 0 °C and extracted with diethyl ether (2 x 10 mL) to remove grease. The aq layer was diluted with distilled CH_2Cl_2 (20 mL) and the mixture was brought to pH 8 – 9 at 0 °C with a solution of 14% aq NH_4OH under ice cold conditions. The aq layer was extracted with distilled CH_2Cl_2 (2 x 10 mL), and the combined organic layers were washed with brine (1 x 10 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford a sticky solid that was flash evaporated with distilled EtOAc (2 x 3 mL) to give 19(*S*),20(*R*)-dihydroperaksine-17-al **1** (25 mg, 96%) as a buff colored solid. $\mathbf{R}_f$ 0.39 (CH_2Cl_2/MeOH/aq NH_4OH, 4.3 : 0.7 : 0.05); **^{1}H NMR** (300 MHz, pyridine-d_5, 99%) δ

11.81 (br s, 1H), 9.83 (s, 1H), 7.67 (m, 1H), 7.57 (dd, 1H, J_2 = 1.7 Hz, The other doublet is embedded in the solvent peak), 7.29 (ddd, 1H, *J* = 7.1, 7.1, 1.3 Hz), 7.24 (ddd, 1H, *J* = 7.1, 7.1, 1.1 Hz), 6.18 (br s, 1H), 4.27 (d, 1H, *J* = 8.7 Hz), 4.16 (dd, 1H, *J* = 7.3, 4.5 Hz), 3.81 – 3.70 (m, 2H), 3.22 (dd, 1H, *J* = 15.1, 5.0 Hz), 2.76 – 2.71 (m, 1H,), 2.71 (br s, 1H), 2.55 – 2.45 (m, 1H), 2.31 (d, 1H, *J* = 7.8 Hz), 2.22 (ddd, 1H, *J* = 12.3, 9.5, 1.3 Hz), 1.57 (dd, 1H, *J* = 14.2, 8.2 Hz), 1.47 (dd, 1H, *J* = 13.0, 2.4 Hz), 1.31 (d, 3H, *J* = 6.7 Hz); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 205.6 (CH), 141.2 (C), 138.9 (C), 129.8 (C), 122.4 (CH), 120.5 (CH), 119.6 (CH), 112.9 (CH), 105.6 (C), 63.5 (CH_2), 57.0 (CH), 55.9 (CH), 54.1 (CH), 45.6 (CH), 43.1 (CH), 29.6 (CH_2), 29.2 (CH_2), 27.7 (CH), 19.9 (CH_3); **EIMS** (*m/e*, relative intensity) 310 ($M^{+\bullet}$, 97), 309 (66), 281 (100), 279 (31), 251 (13), 237 (23), 209 (52), 169 (46), 168 (41); **HRMS** (MALDI) *m/z* $(M + H)^+$ calcd for $C_{19}H_{23}N_2O_2$, 311.1754, found 311.1739. The R_f of **1** was identical to an authentic sample[2] including an admixed TLC.



19(*S*),20(R)-dihydroperaksine (2)

The 19(*S*),20(*R*)-dihydroperaksine-17-al **1** (16 mg, 0.05 mmol) was dissolved in EtOH (3 mL). The $NaBH_4$ (3 mg, 0.08 mmol) was then added to the above solution in one portion at 0 °C. The mixture which resulted was stirred at rt for 3 h. At this point analysis by TLC indicated the disappearance of the aldehyde **1**. The reaction was quenched with H_2O (0.2 mL), after which the ethanol was evaporated under reduced pressure and the residue

was partitioned between CH_2Cl_2 (80 mL) and H_2O (5 mL). The aq layer was extracted with CH_2Cl_2 in methanol (9 : 1, 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 that was flash evaporated with distilled EtOAc (2 x 3 mL) to give pure 19(*S*),20(*R*)-dihydroperaksine **2** (15 mg, 94%) as a white colored solid. **R_f** 0.26 (CH_2Cl_2/MeOH/aq NH_4OH, 4.3 : 0.7 : 0.05); **^{1}H NMR** (300 MHz, pyridine-d_5, 99.5%) δ 11.8 (br s, 1H), 7.68 (dd, 1H, *J* = 7.8, 1.8), 7.57 (dd, 1H, J_2 = 1.7 Hz, The other doublet was embedded in the solvent peak), 7.29 – 7.23 (m, 2H), 6.10 (br s, 2H), 4.26 (d, 1H, *J* = 8.9 Hz), 4.07 – 4.01 (m, 2H), 3.92 – 3.79 (m, 2H), 3.34 (dd, 1H, *J* = 7.7, 4.9 Hz), 3.23 (dd, 1H, *J* = 14.8, 4.9 Hz), 3.04 (d, 1H, *J* = 15.0 Hz), 2.64 – 2.55 (m, 1H), 2.49 (br s, 1H), 2.22 (ddd, 1H, *J* = 12.4, 10.4, 1.3), 1.97 (dd, 1H, *J* = 14.4, 7.8 Hz), 1.45 (m, 1H), 1.39 (d, 3H, *J* = 6.7 Hz); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 142.2 (C), 138.8 (C), 130.0 (C), 122.1 (CH), 120.3 (CH), 119.6 (CH), 112.9 (CH), 106.4 (C), 64.3 (2 x CH_2), 58.0 (CH), 54.5 (CH), 50.3 (CH), 45.4 (CH), 41.4 (CH), 31.3 (CH_2), 29.2 (CH_2), 28.8 (CH), 20.4 (CH_3); **EIMS** (*m/e*, relative intensity) 312 ($M^{+\bullet}$, 85), 311 (100), 281 (41), 239 (41), 209 (18), 169 (32), 168 (24); **HRMS** (MALDI) *m/z* $(M + H)^+$ calcd for $C_{19}H_{25}N_2O_2$, 313.1910, found 313.1925. The R_f of **2** was identical to an authentic sample[2] including an admixed TLC.

Table 1. Comparison of the ^{1}H NMR Spectral Data for Natural[2] and Synthetic 19(*S*),20(*R*)-Dihydroperaksine-17-al **1** in Pyridine-d_5[a]

Proton [a]	**^{1}H Natural (600 MHz)**[a, b]	**^{1}H Synthetic (300 MHz)**[b]
3	4.28 (d, *J* = 9.4)	4.27 (d, *J* = 8.7)
5	4.17 (dd, *J* = 8.2, 4.7)	4.16 (dd, 1H, *J* = 7.3, 4.5 Hz)
6α	3.23 (dd, *J* = 15.3, 4.7)	3.22 (dd, *J* = 15.1, 5.0)
6β	2.75 (d, *J* = 15.3)	2.76 – 2.71 (m, 1H)
9	7.68 (dd, *J* = 7.6, 1.2)	7.67 (m)
10	7.25 (ddd, *J* = 7.2, 7.2, 1.2)	7.24 (ddd, *J* = 7.1, 7.1, 1.1)
11	7.29 (ddd, *J* = 7.2, 7.2, 1.2)	7.29 (ddd, *J* = 7.1, 7.1, 1.1)
12	7.57 (dd, *J* = 7.6, 1.2)	7.57 (dd, J_2 = 1.7 Hz, The other doublet is embedded in the solvent peak)
14α	2.22 (ddd, *J* = 12.9, 9.4, 1.2)	2.22 (ddd, *J* = 12.3, 9.5, 1.3)
14β	1.47 (dd, *J* = 12.9, 2.4)	1.47 (dd, *J* = 13.0, 2.4)
15	2.73 (m)	2.71 (br s)
16	2.32 (d, *J* = 8.2)	2.31 (d, *J* = 7.8)
17	9.87 (s)	9.83 (s)
18	1.32 (d, *J* = 6.5)	1.31 (d, *J* = 6.7)
19	2.51 (ddd, *J* = 14.7, 6.5, 6.5)	2.55 – 2.45 (m, 1H),
20	1.57 (ddd, *J* = 14.7, 8.8, 5.3 Hz)	1.57 (dd, *J* = 14.2, 8.2 Hz)
21a	3.75 (dd, *J* = 11.4, 8.8)	} 3.81 – 3.70 (m)
21b	3.82 (dd, *J* = 11.4, 5.3)	
21-OH	6.18 (br s)	6.18 (br s)
N_a-H	11.90 (br, s)	11.81 (br s)

[a]The numbering and the assignment of the protons follows that from the literature.[2] [b]Values are in ppm (δ). The multiplicities and coupling constants (*J* in Hz) are in parentheses.

Table 2. Comparison of the ^{13}C NMR Data for Natural[2] and Synthetic 19(*S*),20(*R*)-Dihydroperaksine-17-al **1** in Pyridine-d_5[a]

^{13}C NMR [a]	^{13}C Natural (150.6 MHz)[a, b]	^{13}C Synthetic (75 MHz)[b]
2	140.1 (C)	141.2 (C)
3	53.0 (CH)	54.1 (CH)
5	44.5 (CH)	45.6 (CH)
6	27.8 (CH_2)[c]	29.2 (CH_2)
7	104.4 (C)	105.6 (C)
8	128.6 (C)	129.8 (C)
9	118.4 (CH)	119.6 (CH)
10	119.4 (CH)	120.5 (CH)
11	121.3(CH)	122.4 (CH)
12	111.8 (CH)	112.9 (CH)
13	137.7 (C)	138.9 (C)
14	28.0 (CH_2)[c]	29.6 (CH_2)
15	26.6 (CH)	27.7 (CH)
16	54.6 (CH)	55.9 (CH)
17	204.4 (CH)	205.6 (CH)
18	18.7 (CH_3)	19.9 (CH_3)
19	55.7 (CH)	57.0 (CH)
20	41.9 (CH)	43.1 (CH)
21	62.3 (CH_2)	63.5 (CH_2)

[a]The numbering and the assignment of the carbons follows that from the literature.[2] [b]Values are in ppm (δ).

[c]Assignments may be interchanged.

Table 3. Comparison of the ^{1}H NMR Spectral Data for Natural[2] and Synthetic 19(*S*),20(*R*)-Dihydroperaksine **2** in Pyridine-d_5[a]

Proton[a]	^{1}H Natural (400 MHz)[a, b]	^{1}H Synthetic (300 MHz)[b]
3	4.51 (d, *J* = 9.6)	4.26 (d, *J* = 8.9)
5	3.58 (m)	3.34 (dd, *J* = 7.7, 4.9)
6α	3.39 (dd, *J* = 15.1, 4.8)	3.23 (dd, *J* = 14.8, 4.9)
6β	3.11 (d, *J* = 15.1)	3.04 (d, *J* = 15.0)
9	7.66 (dd, *J* = 7.2, 1.4)	7.68 (dd, *J* = 7.8, 1.8)
10	7.23 (ddd, *J* = 7.2, 7.2, 1.4)	7.29 – 7.23 (m)
11	7.27 (ddd, *J* = 7.2, 7.2, 1.4)	
12	7.58 (dd, *J* = 7.2, 1.4)	7.57 (dd, J_2 = 1.7 Hz, The other doublet is embedded in the solvent peak)
14α	2.33 (ddd, *J* = 13.0, 9.6, 1.4)	2.22 (ddd, *J* = 12.4, 10.4, 1.3)
14β	1.54 (dd, *J* = 13.0, 3.1)	1.45 (m)
15	2.48 (m)	2.49 (br s)
16	2.12 (m)	2.11 (dd, *J* = 15.1, 8.0)
17a	4.01 (m)	4.07 – 4.01 (m)
17b	4.01 (m)	
18	1.52 (d, *J* = 6.5)	1.39 (d, *J* = 6.7)
19	2.81 (ddd, *J* = 14.7, 6.5, 6.5)	2.64 – 2.55 (m)
20	2.07 (ddd, *J* = 14.7, 7.9, 5.8)	1.97 (dd, *J* = 14.4, 7.8 Hz)
21a	3.81 (dd, *J* = 10.9, 7.9)	3.92 – 3.79 (m)
21b	3.87 (dd, *J* = 10.6, 5.8)	
17-OH	5.58 (br s)	6.10 (br s)
21-OH	6.18 (br s)	
N_a-H	12.02 (br s)	11.79 (br s)

[a]The numbering and the assignment of the protons follows that from the literature.[2] [b]Values are in ppm (δ). The multiplicities and coupling constants (*J* in Hz) are in parentheses.

Table 4. Comparison of the ^{13}C NMR Data for Natural[2] and Synthetic 19(*S*),20(*R*)-Dihydroperaksine **2** in Pyridine-d_5.[a]

^{13}C NMR[a]	^{13}C Natural (100 MHz)[a, b]	^{13}C Synthetic (75 MHz)
2	139.3 (C)	142.2 (C)
3	53.4 (CH)	54.5 (CH)
5	49.7 (CH)	50.3 (CH)
6	27.4 (CH_2)	29.2 (CH_2)
7	105.0 (C)	106.4 (C)
8	128.5 (C)	130.0 (C)
9	118.5 (CH)	119.6 (CH)
10	119.3 (CH)	120.3 (CH)
11	121.3 (CH)	122.1 (CH)
12	111.9 (CH)	112.9 (CH)
13	137.8 (C)[c]	138.8 (C)
14	29.8 (CH_2)	31.3 (CH_2)
15	27.7 (CH)	28.8 (CH)
16	43.9 (CH)	45.4 (CH)
17	63.0 (CH_2)	64.3 (CH_2)
18	18.6 (CH_3)	20.4 (CH_3)
19	57.5 (CH)	58.0 (CH)
20	40.2 (CH)	41.4 (CH)
21	62.9 (CH_2)	64.3 (CH_2)

[a]The numbering and the assignment of the carbon atoms follow from the literature.[2] [b]Values are in ppm (δ).

[c]Assignments may be interchanged.

X-ray Structural Analysis and Methods for 14

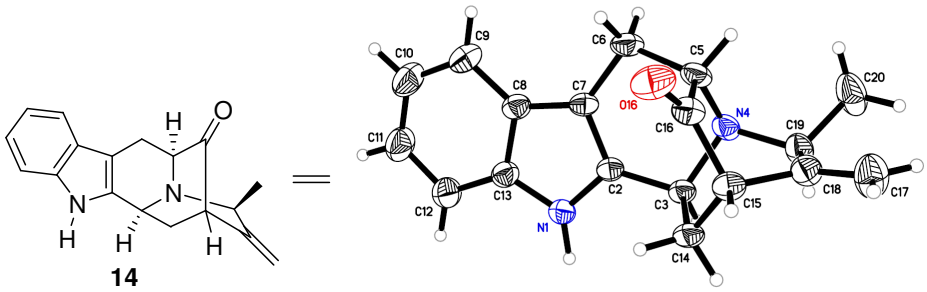


Figure S1: Displacement ellipsoid plot of (6*S*,8*S*,11a*S*)-8-methyl-9-methylene-6,8,9,10,11a,12-hexahydro-6,10-methanoindolo-[3,2-*b*]quinolizin-11(5*H*)-one **(14)** (sarp--agine numbering not followed)

X-ray Crystal methods for 14

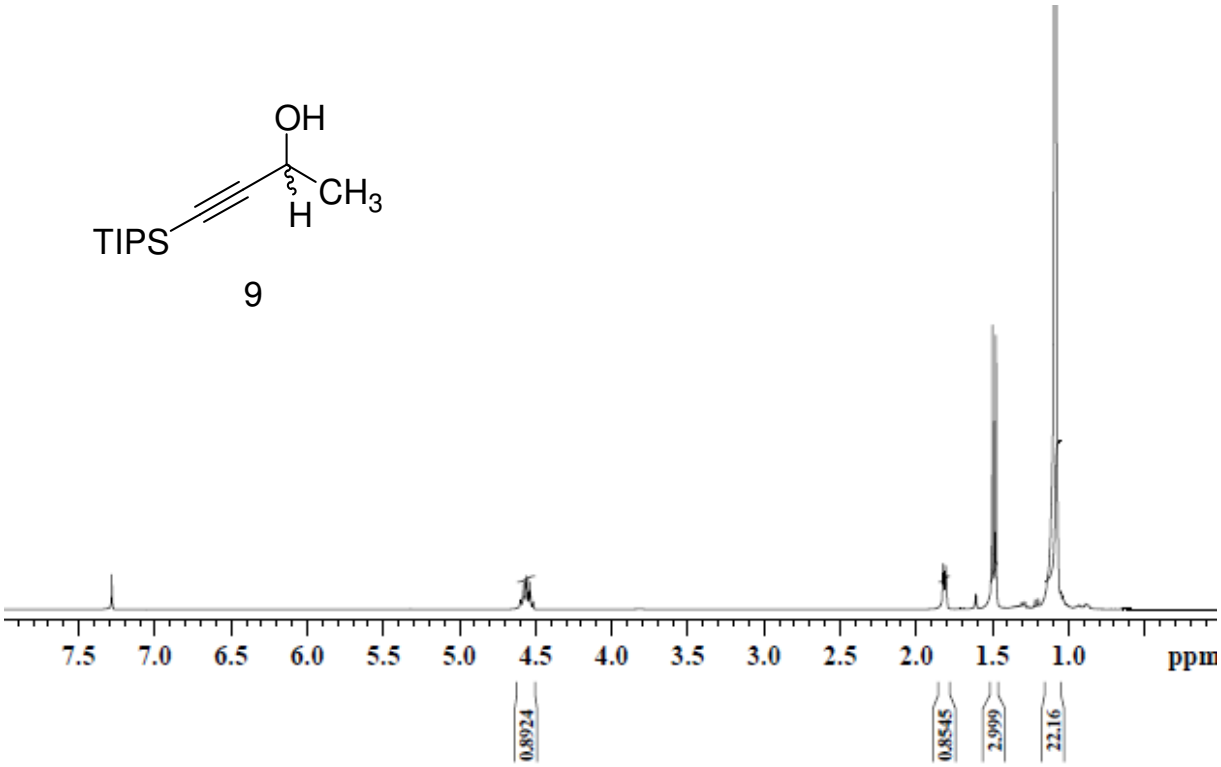
The 0.51 x 0.21 x 0.13 mm^3 crystal of **14** was monoclinic in space group $P2_1$ with unit cell dimensions a = 9.821(4) Å, b = 7.317(3) Å, c = 10.846(4), and b = 108.497(5)°. Data were 99.8% complete to 25.00° q. The asymmetric unit contains a single molecule. Single-crystal x-ray diffraction data on **14** was collected at 295 °K using MoKa radiation (l = 0.71073 Å) and a Bruker APEX 2 CCD area detector. The sample was prepared for data collection by coating with high viscosity microscope oil (Paratone-N, Hampton Research). The oil-coated crystal was mounted on a MicroMesh mount (MiTeGen, Inc.) and transferred immediately to the diffractometer. Corrections were applied for Lorentz, polarization, and absorption effects. The structure was solved by direct methods and refined by full-matrix least squares on F^2 values using the programs found in the SHELXTL suite (Bruker, SHELXTL v6.10, 2000, Bruker AXS Inc., Madison, WI). Parameters refined included atomic coordinates and anisotropic thermal parameters for

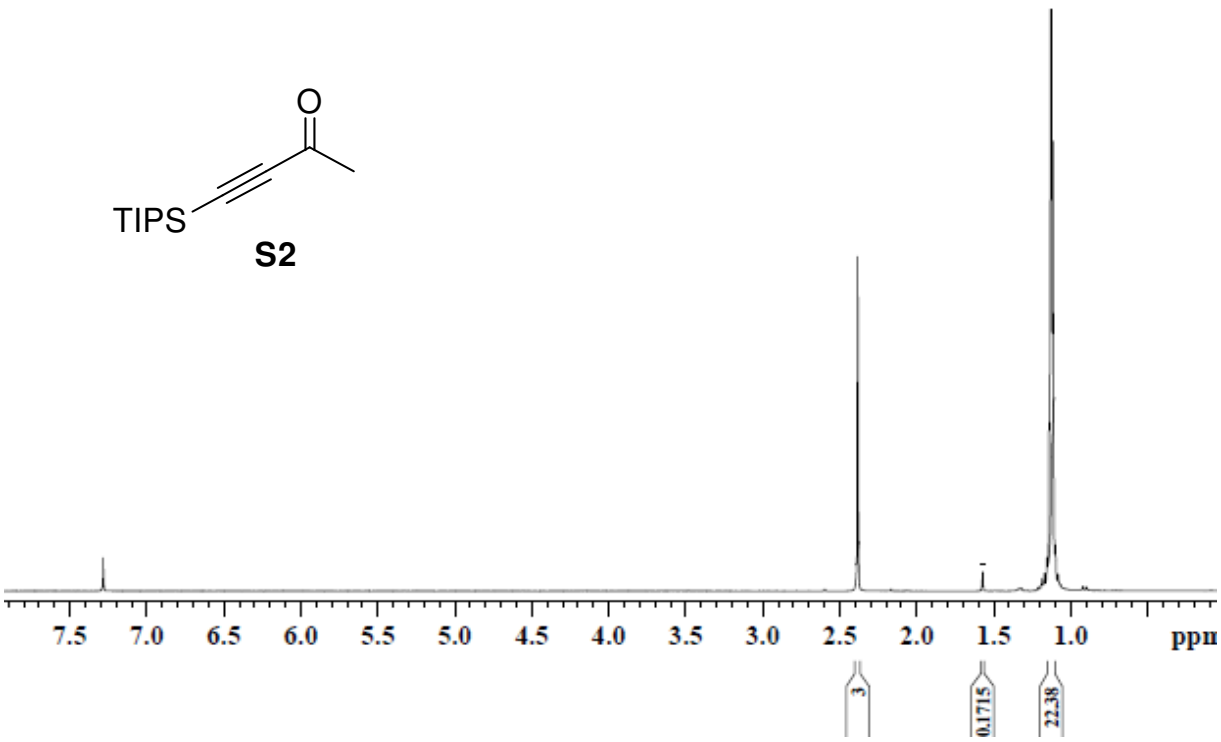
all non-hydrogen atoms. Hydrogen atoms on carbons were included using a riding model [coordinate shifts of C applied to H atoms] with C-H distance set at 0.96 Å.

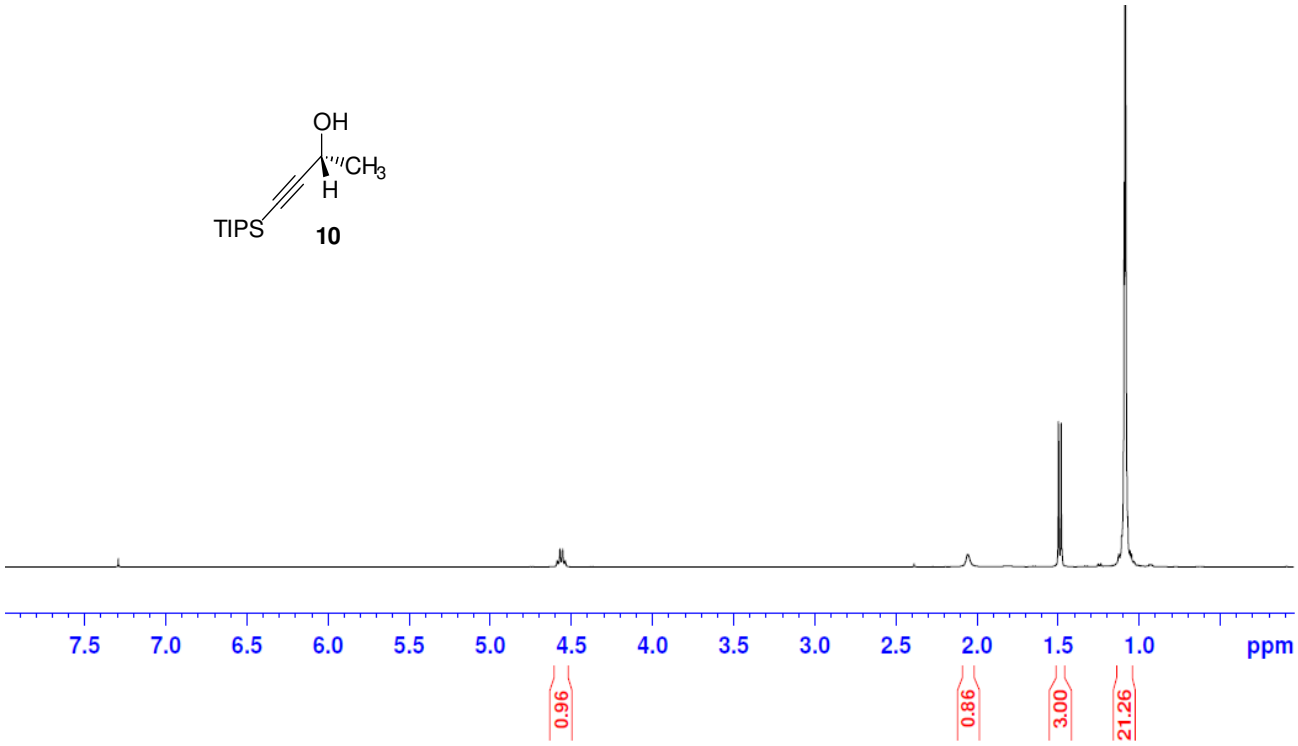
References:

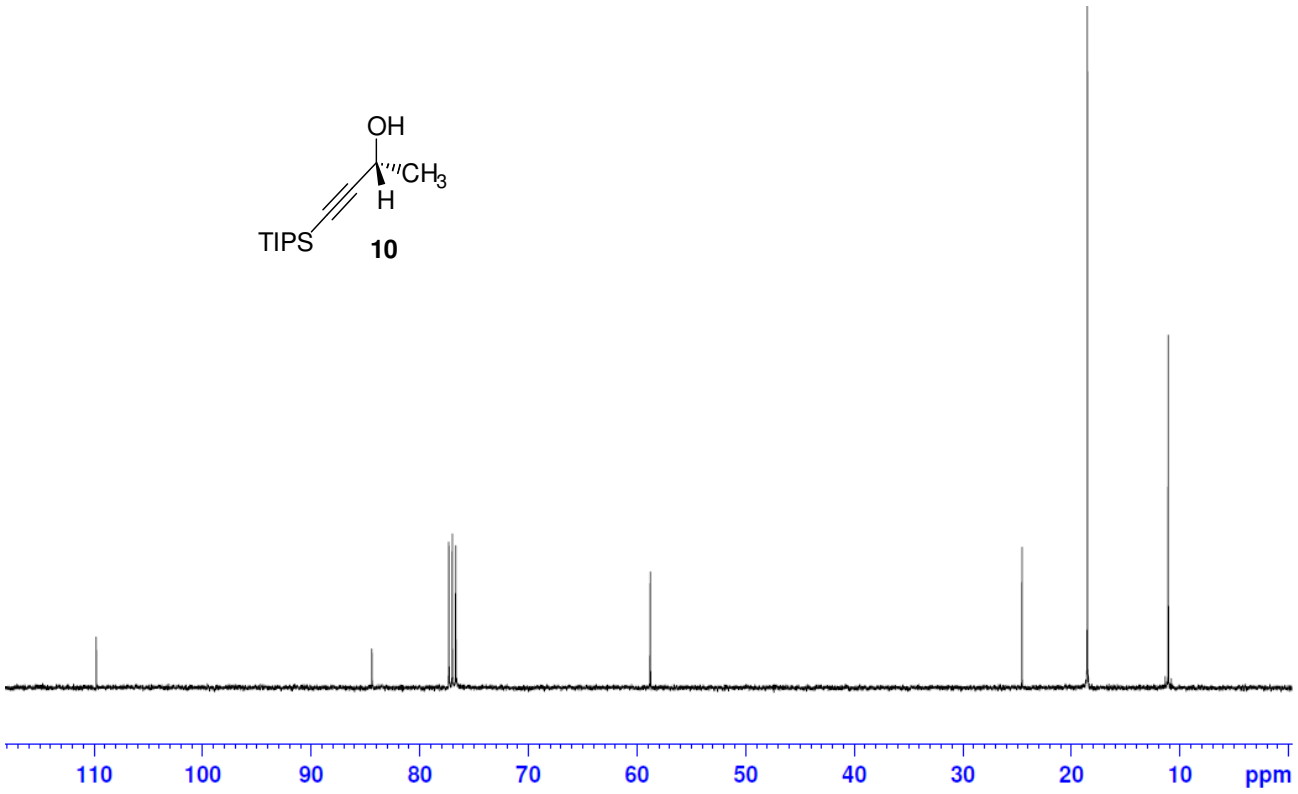
1) Li, J. J.; Limberakis, C.; Pflum, D. A. *Modern Organic Synthesis in the Laboratory*, Oxford University Press, Inc: New York, NY, 2007, Chapter 1, pp 17-20.
2) Sheludko, Y.; Gerasimenko, I.; Kolshorn, H.; Stöckigt, J. *J. Nat. Prod.* **2002**, *65*, 1006.
3) The racemic TIPS alcohol (**9**) was prepared following the procedure of: Jones, G. B.; Wright, J. M.; Plourde II, G. W.; Hynd, G.; Huber, R. S.; Mathews, J. E. *J. Am. Chem. Soc.* **2000**, *122*, 1937.
4) (a) The synthesis of catalyst **A** and asymmetric Noyori reduction was carried out following the preparation of (*S*)-acetylenic alcohol by: Marshall, J. A.; Eidam, P.; Eidam, H. S. *Org. Synth.* **2007**, *84*, 120. (b) Helal, C. J.; Magriotis, P. A.; Corey, E. J. *J. Am. Chem. Soc*. **1996**, *118*, 10938.
5) Burgess, K.; Jennings, J. D. *J. Am. Chem. Soc*. **1990**, *112*, 7434.
6) Yu, P.; Wang, T.; Li, J.; Cook, J. M. *J. Org. Chem.* **2000**, *65*, 3173.

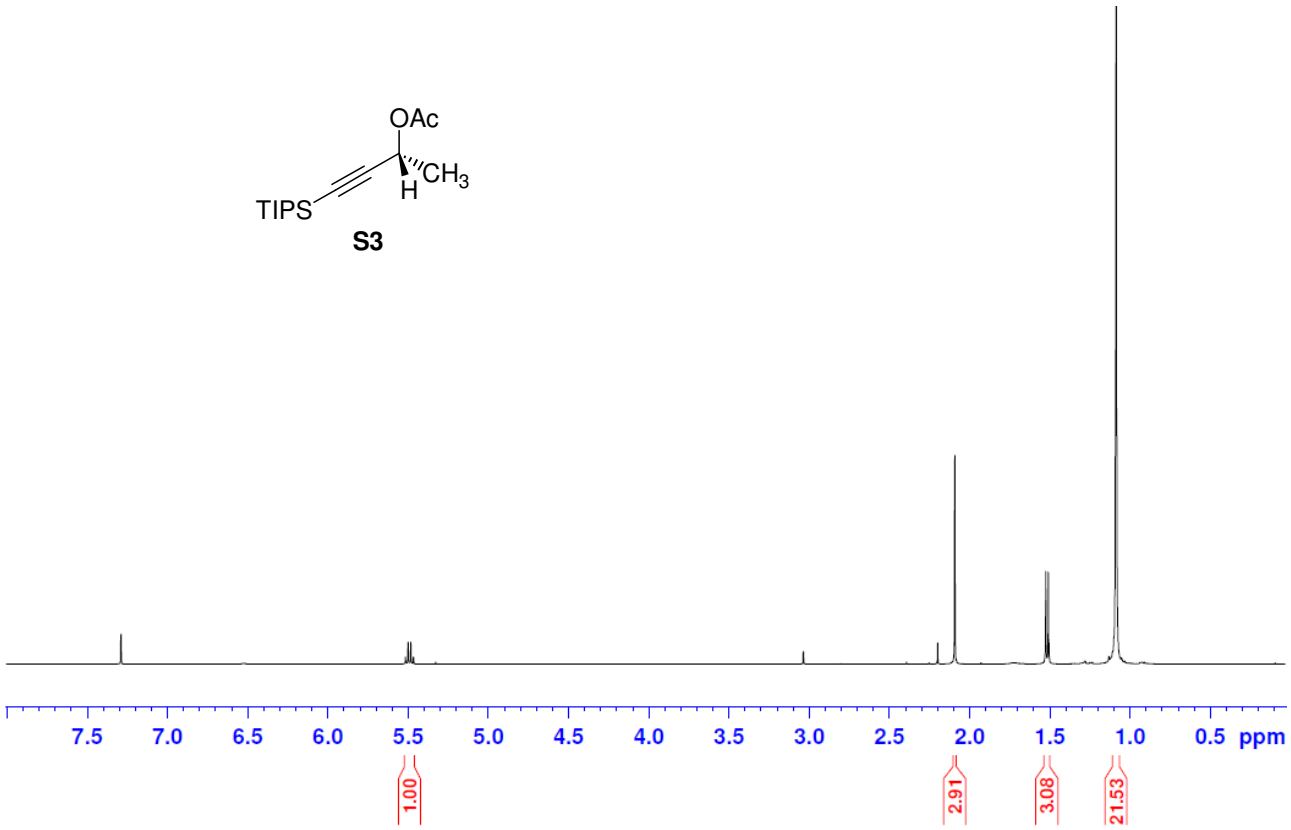
Copies of ^{1}H and ^{13}C NMR Spectra:

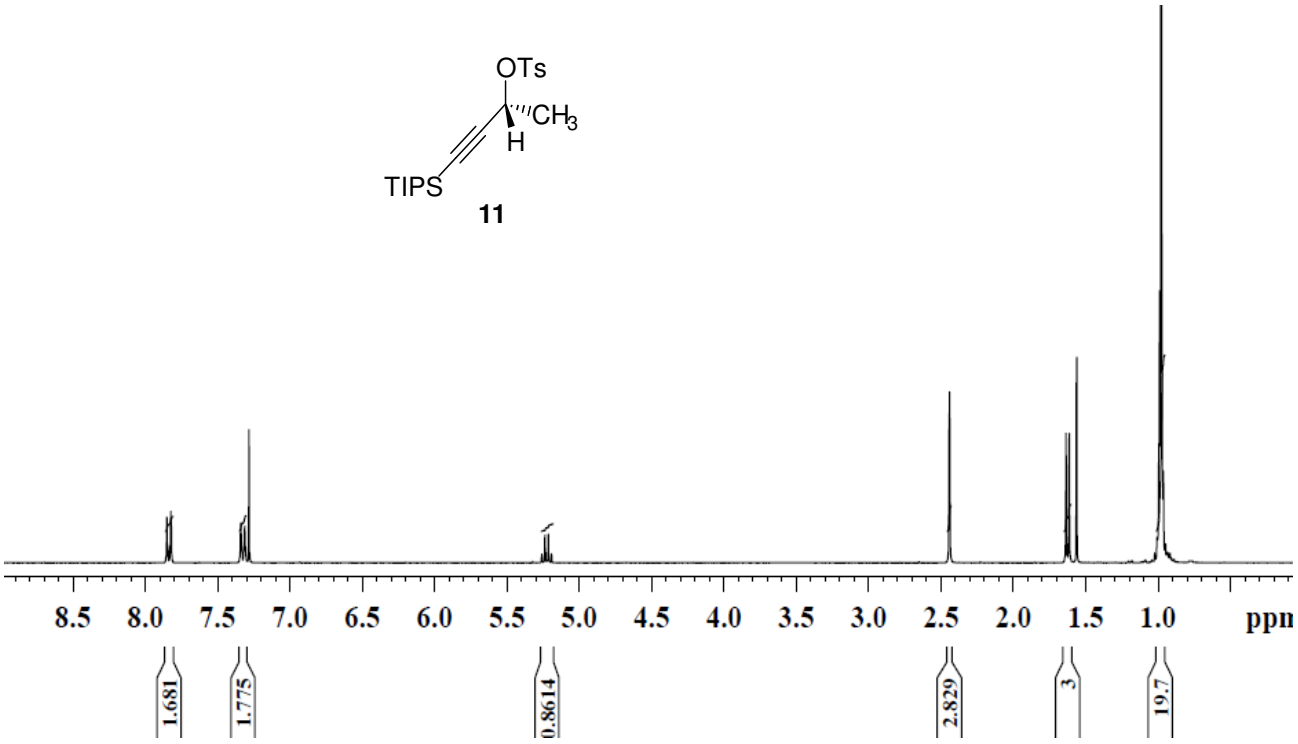


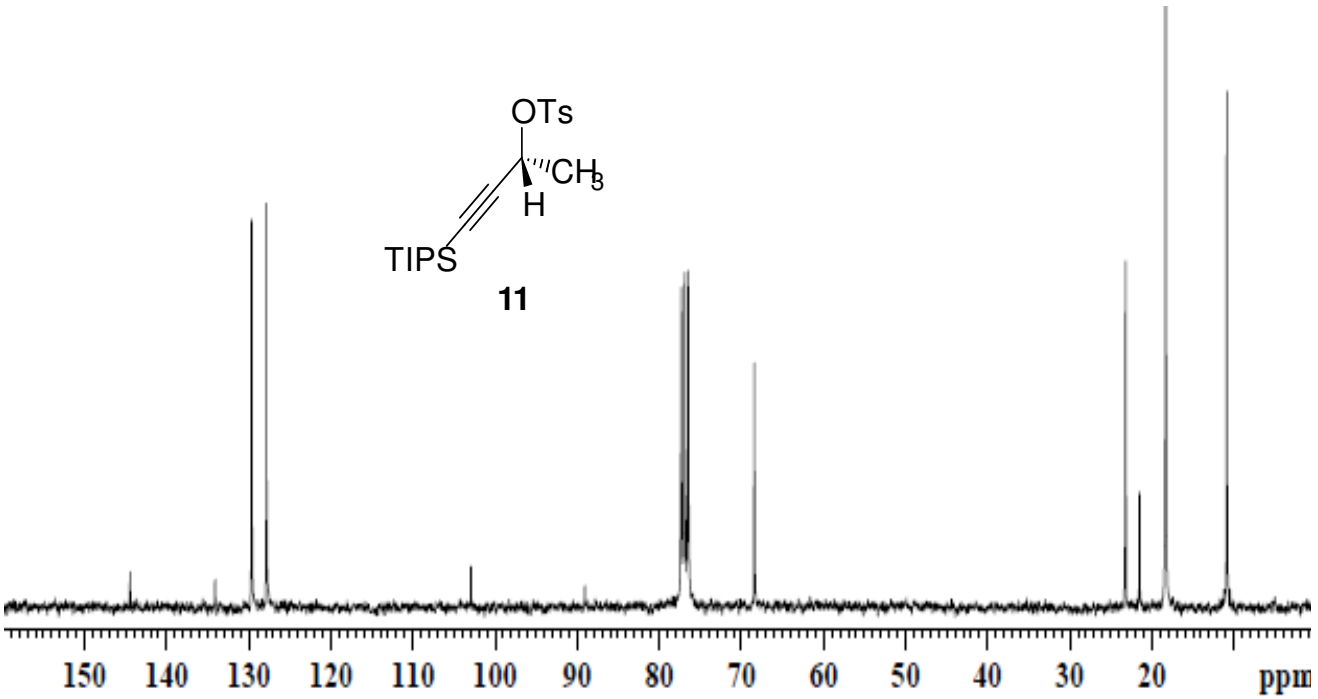


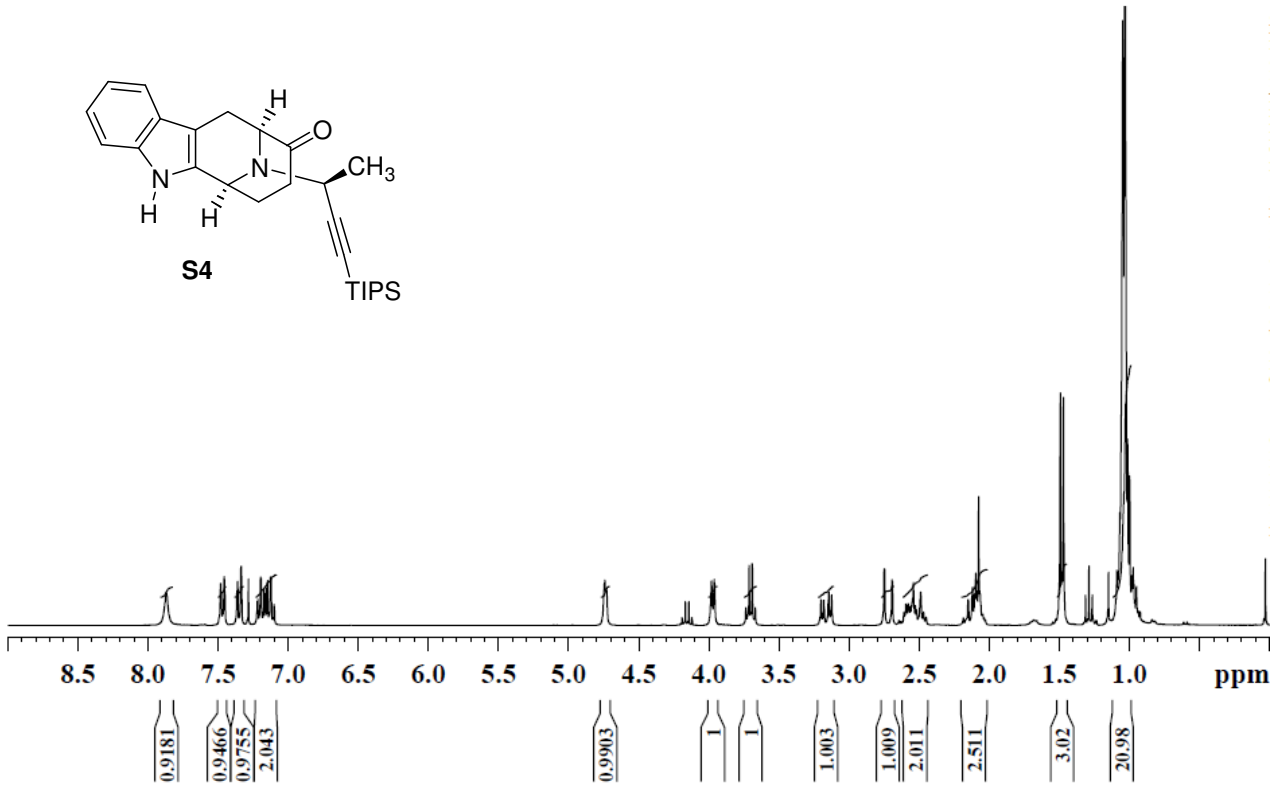

OH
CH3
H
TIPS
10
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
0.96
0.86
3.00
21.26


OH
CH3
H
TIPS
10
110
100
90
80
70
60
50
40
30
20
10
ppm

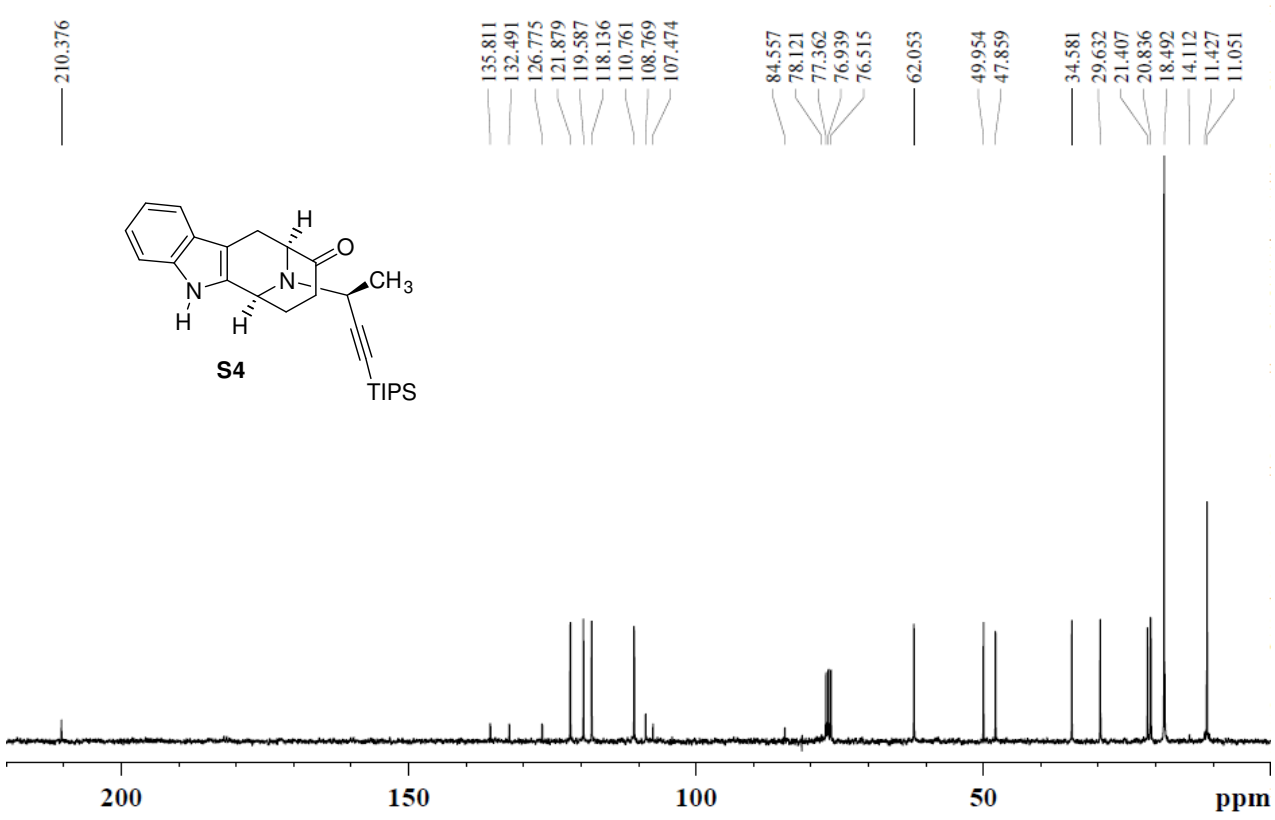

OAc
CH3
H
TIPS
S3
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
2.91
3.08
21.53

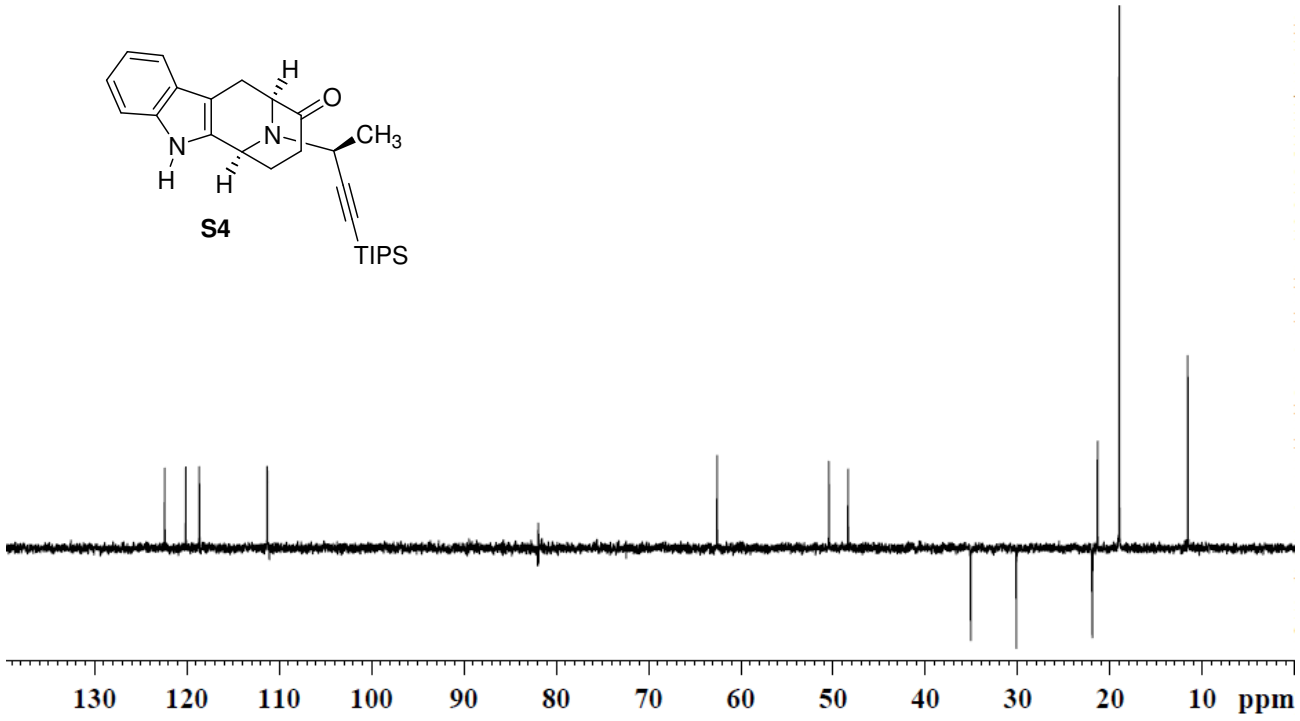

OTs
CH3
H
TIPS
11
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.681
1.775
0.8614
2.829
3
19.7

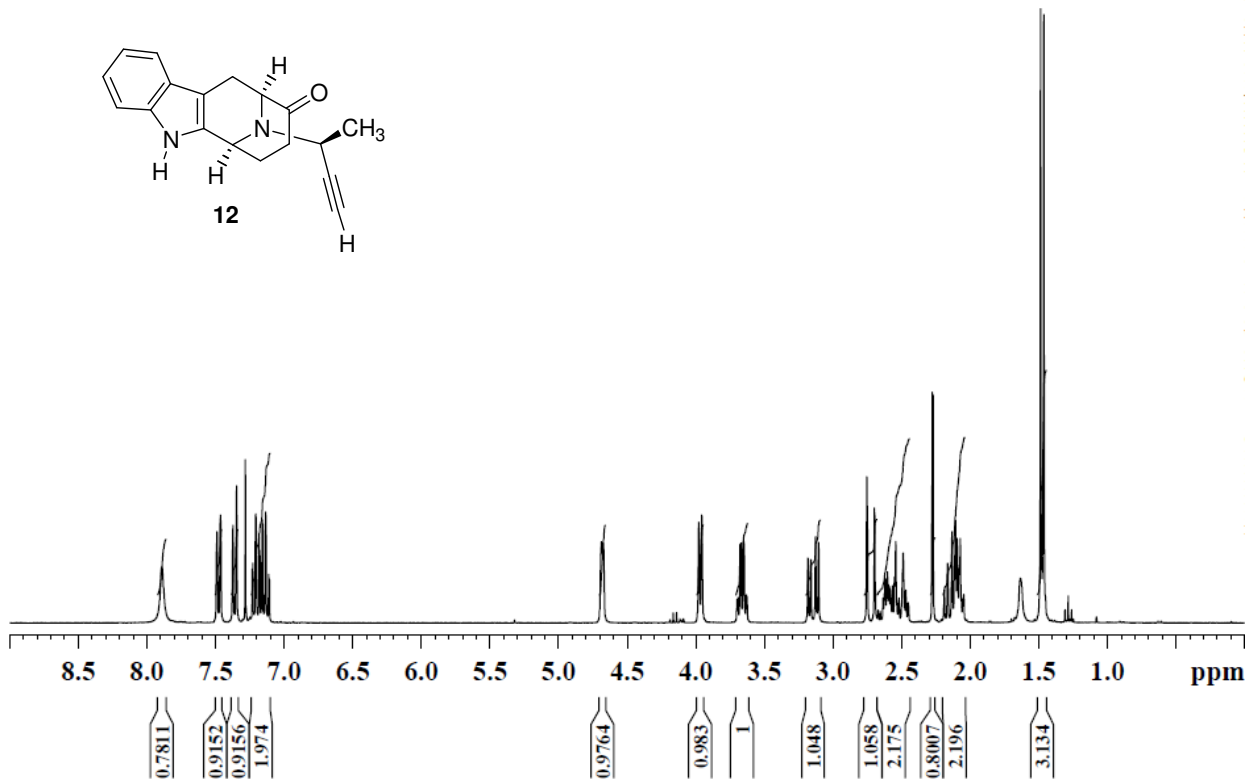

OTs
CH3
H
TIPS
11
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

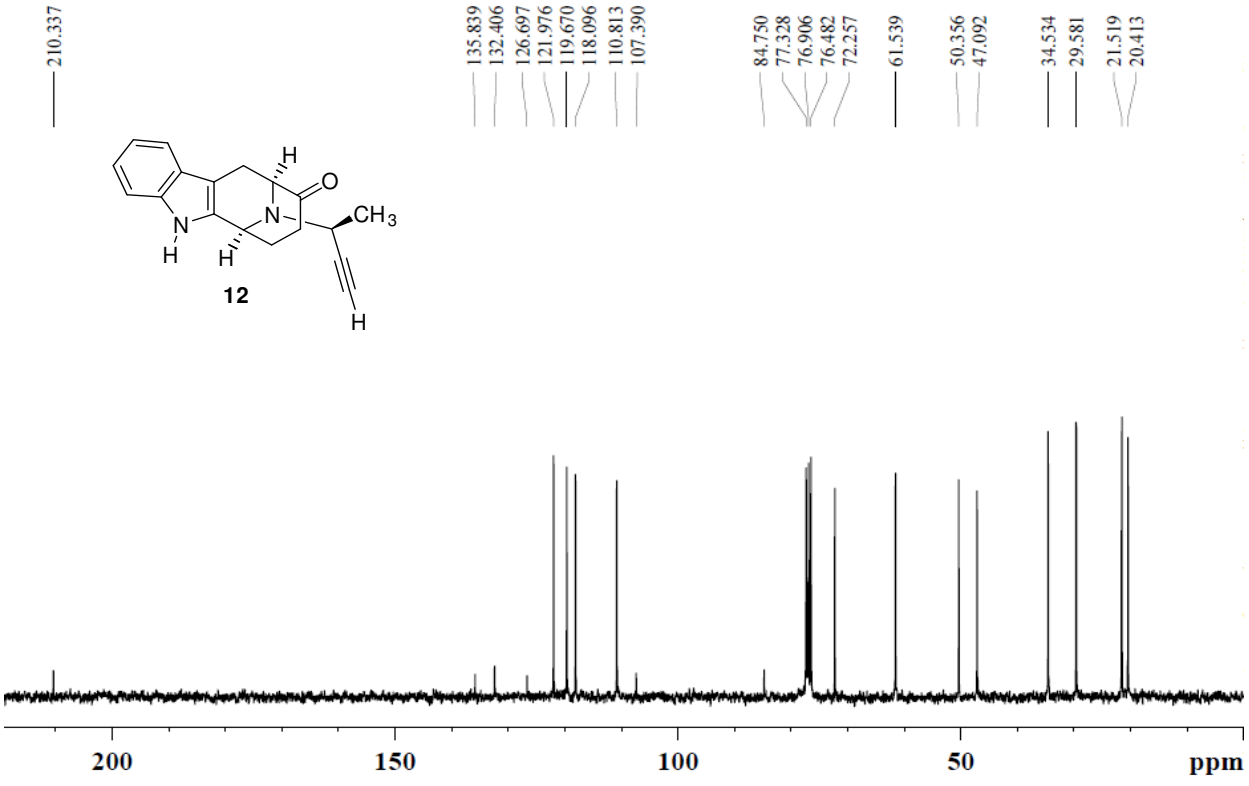

H
O
N
CH3
N
H
H
TIPS
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
0.9181
0.9466
0.9755
2.043
0.9903
1
1
1.003
1.009
2.011
2.511
3.02
20.98

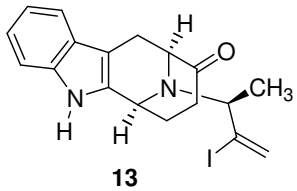
S4


210.376
135.811
132.491
126.775
121.879
119.587
118.136
110.761
108.769
107.474
84.557
78.121
77.362
76.939
76.515
62.053
49.954
47.859
34.581
29.632
21.407
20.836
18.492
14.112
11.427
11.051
H
O
N
CH3
N
H
H
S4
TIPS
200
150
100
50
ppm

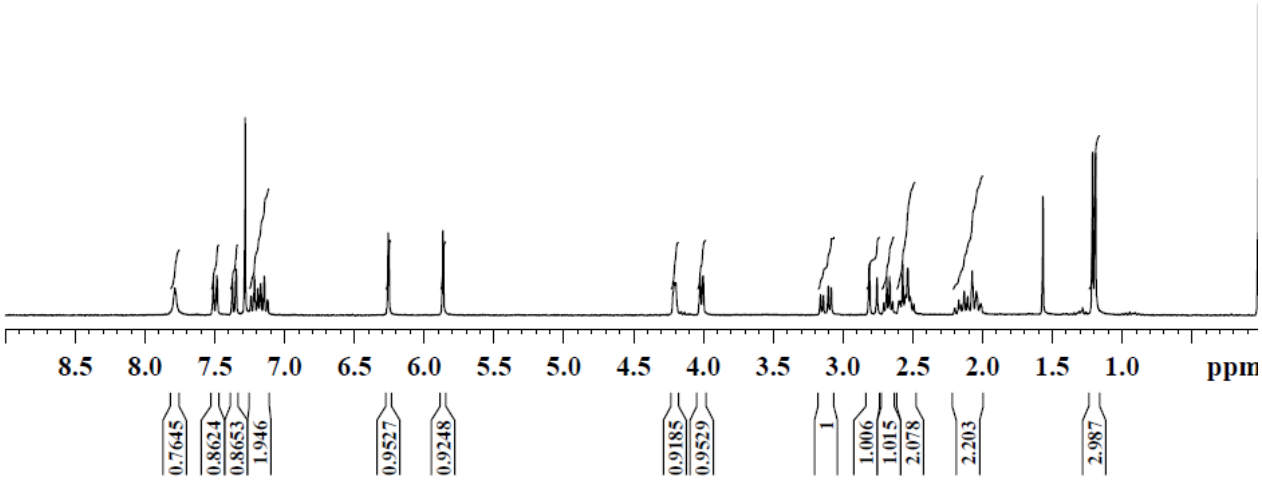

H
O
N
CH3
N
H
H
S4
TIPS
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

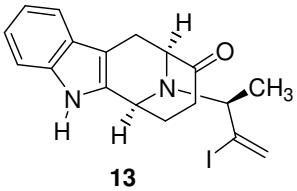

12
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
0.7811 0.9152 0.9156 1.974 0.9764 0.983 1 1.048 1.058 2.175 0.8007 2.196 3.134


210.337
135.839 132.406 126.697 121.976 119.670 118.096 110.813 107.390
84.750 77.328 76.906 76.482 72.257
61.539
50.356 47.092
34.534 29.581 21.519 20.413
12
200 150 100 50 ppm

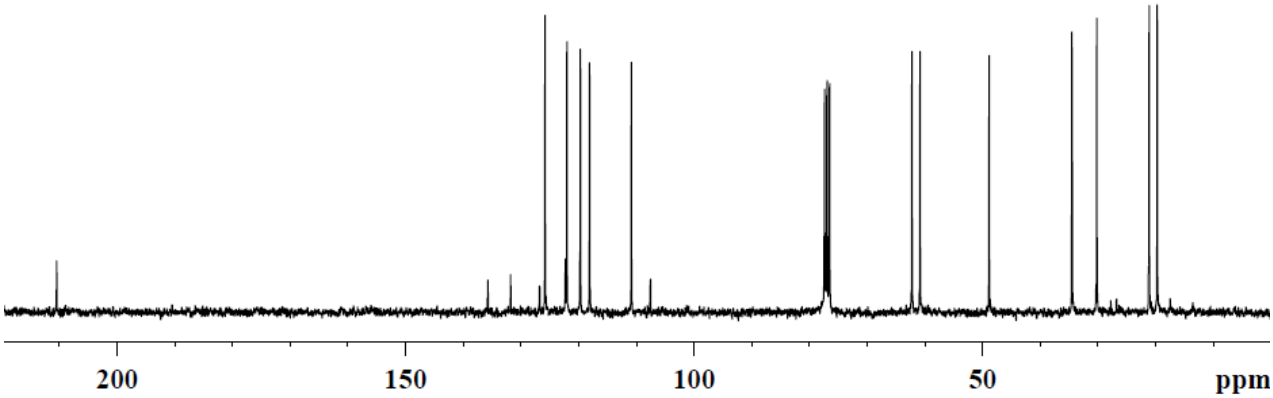

H
O
N
CH3
N
H
H
I

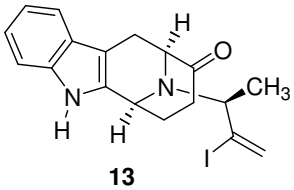
13


8.5
8.0
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
ppm
0.7645
0.8624
0.8653
1.946
0.9527
0.9248
0.9185
0.9529
1
1.006
1.015
2.078
2.203
2.987

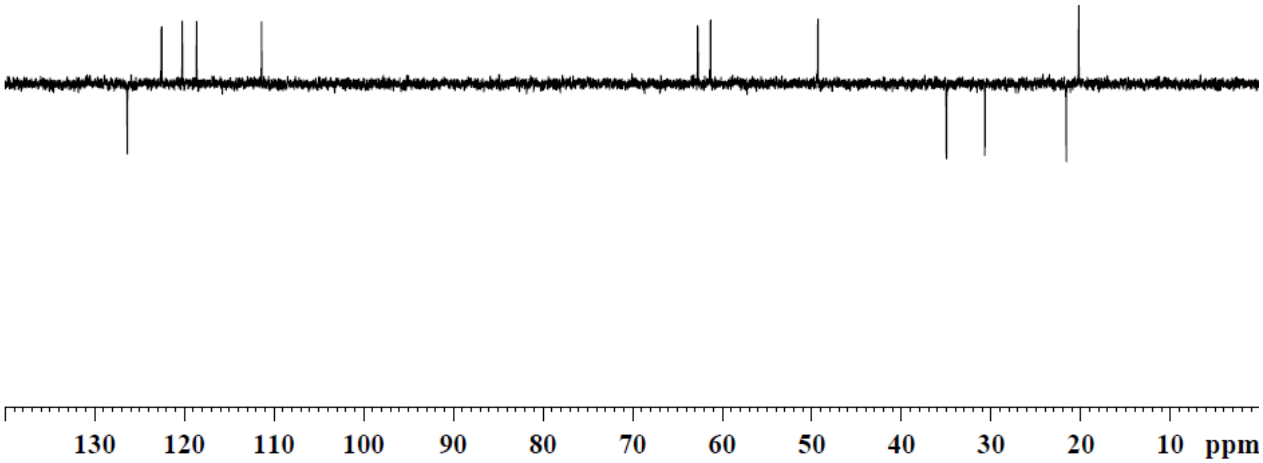

H
O
N
CH3
N
H
H
I

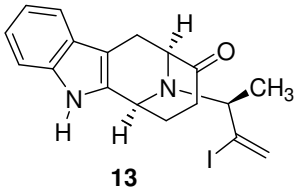
13


200
150
100
50
ppm

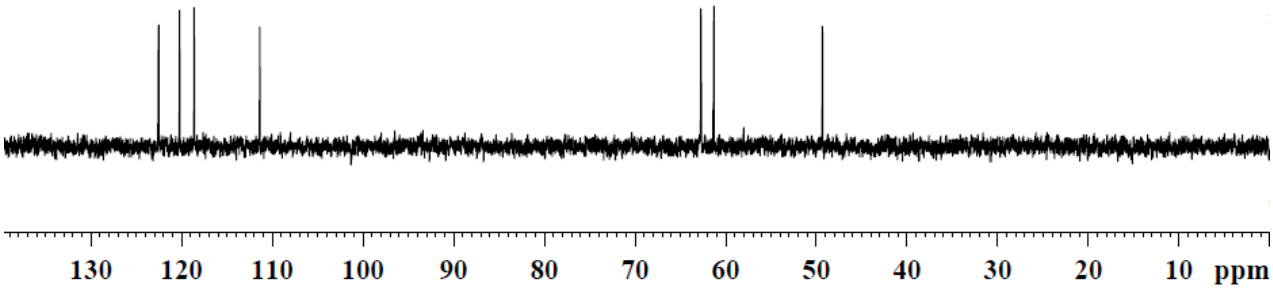

H
O
N
CH3
N
H
H
I

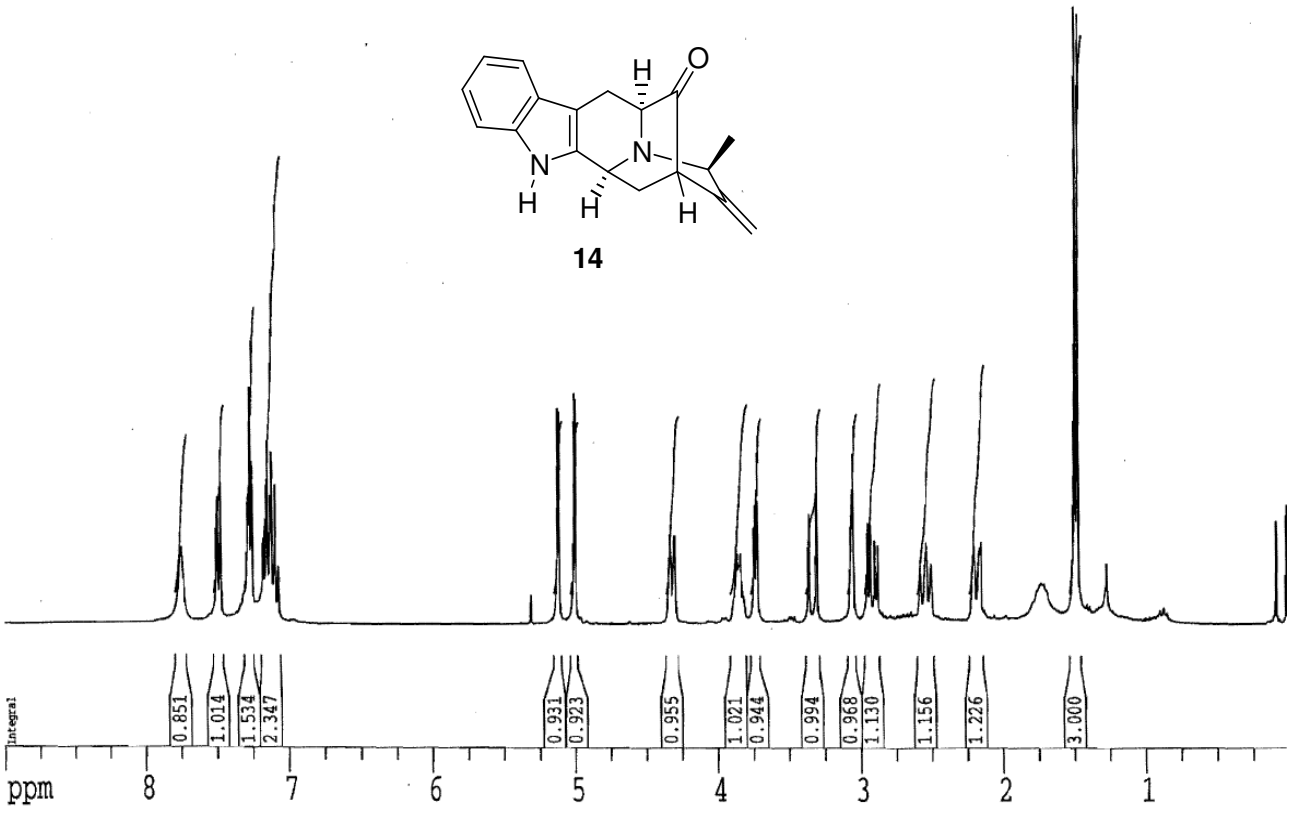
13

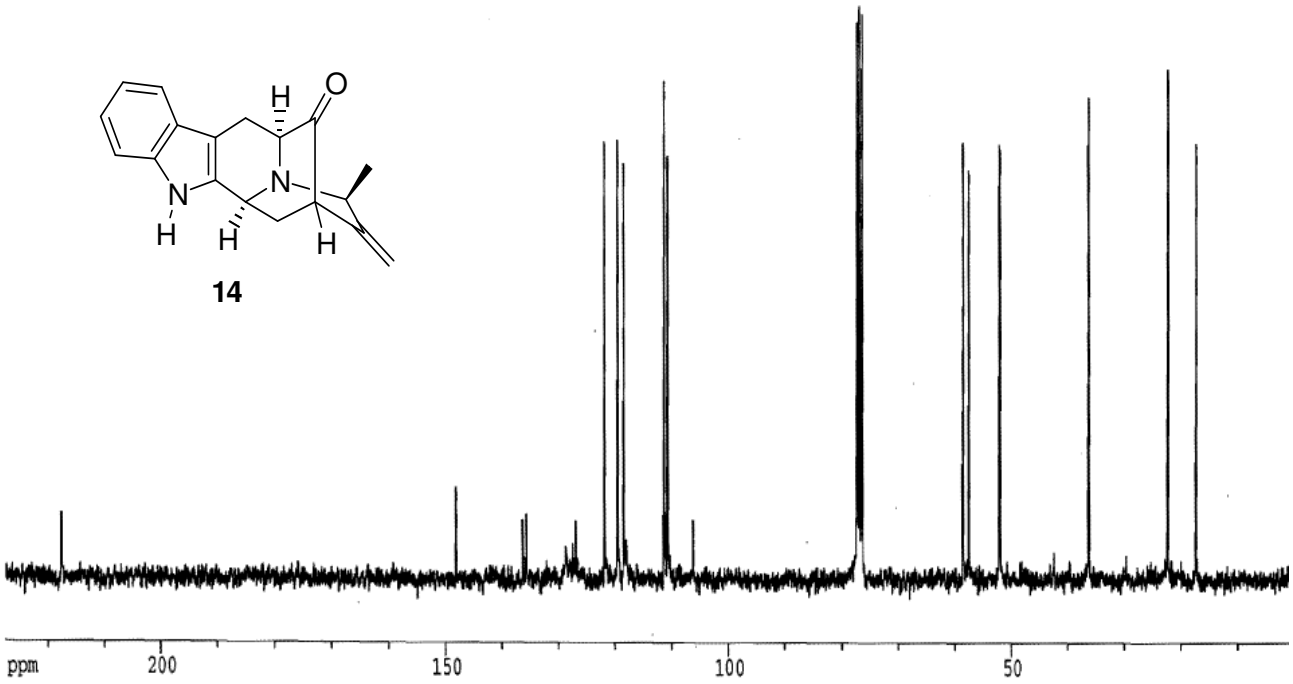

130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

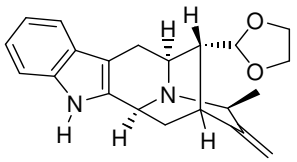

H
O
N
CH3
N
H
H
I

13

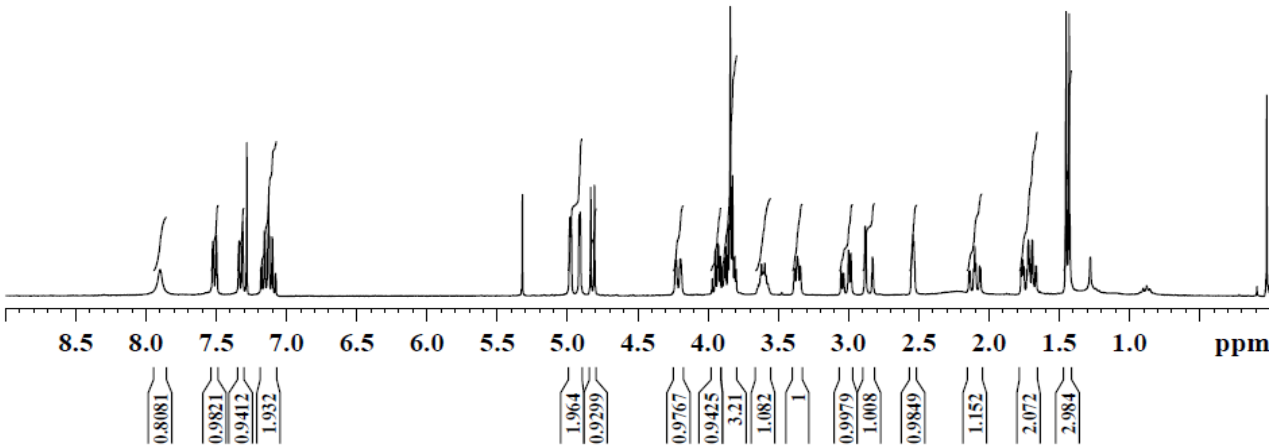

130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

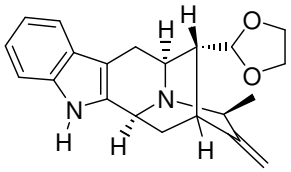

H
O
N
H
N
H
H
H
14
Integral
0.851
1.014
1.534
2.347
0.931
0.923
0.955
1.021
0.944
0.994
0.968
1.130
1.156
1.226
3.000
ppm
8
7
6
5
4
3
2
1


H
O
N
H
N
H
H
H
14
ppm
200
150
100
50

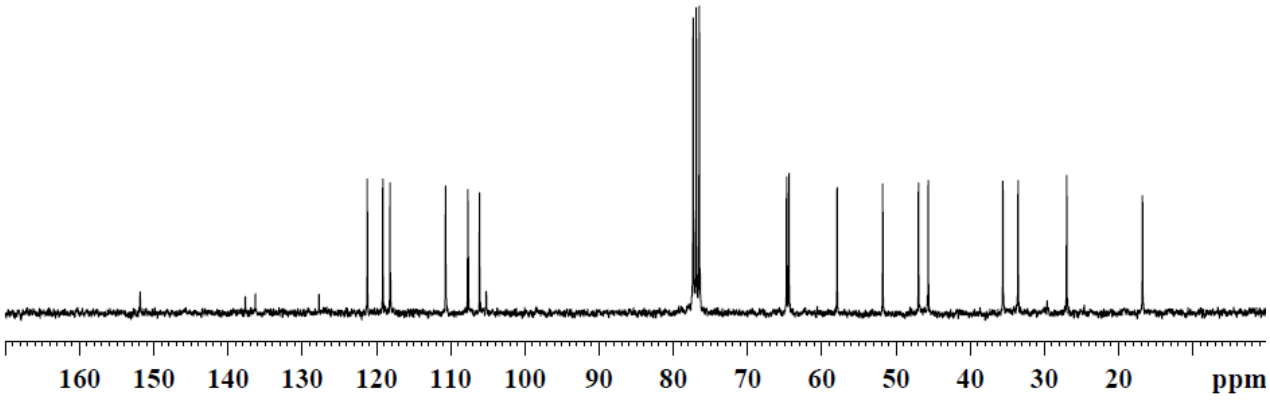


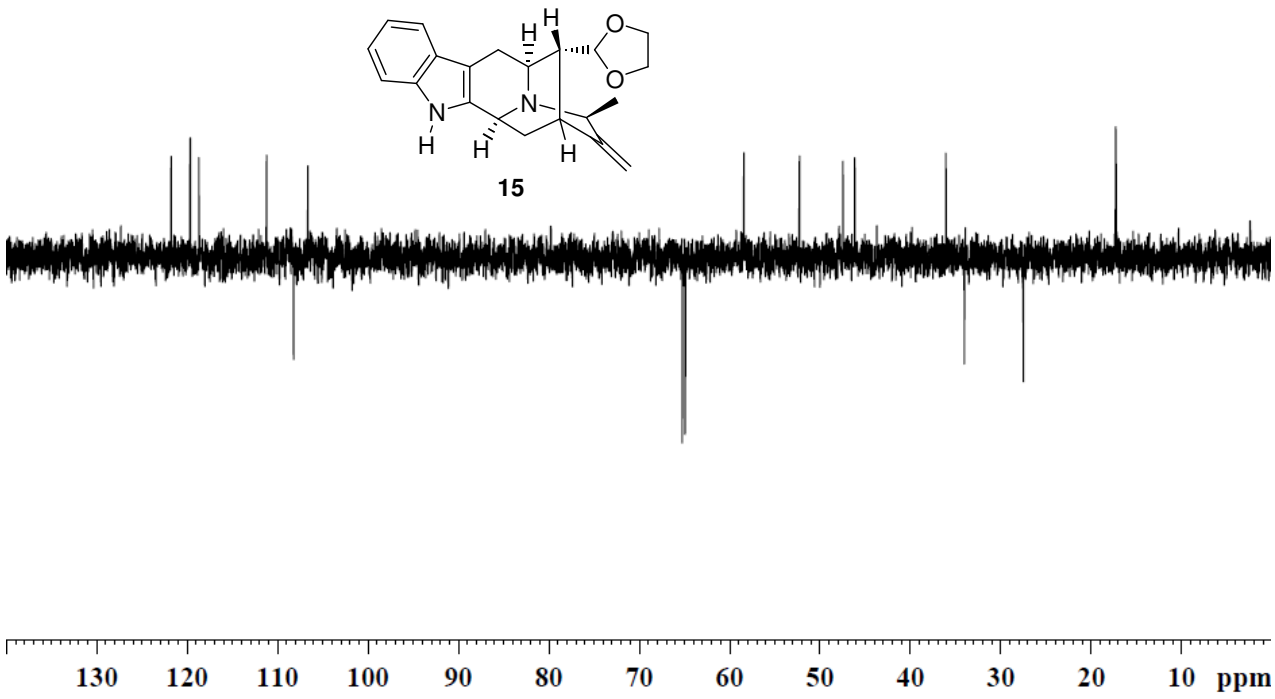
15

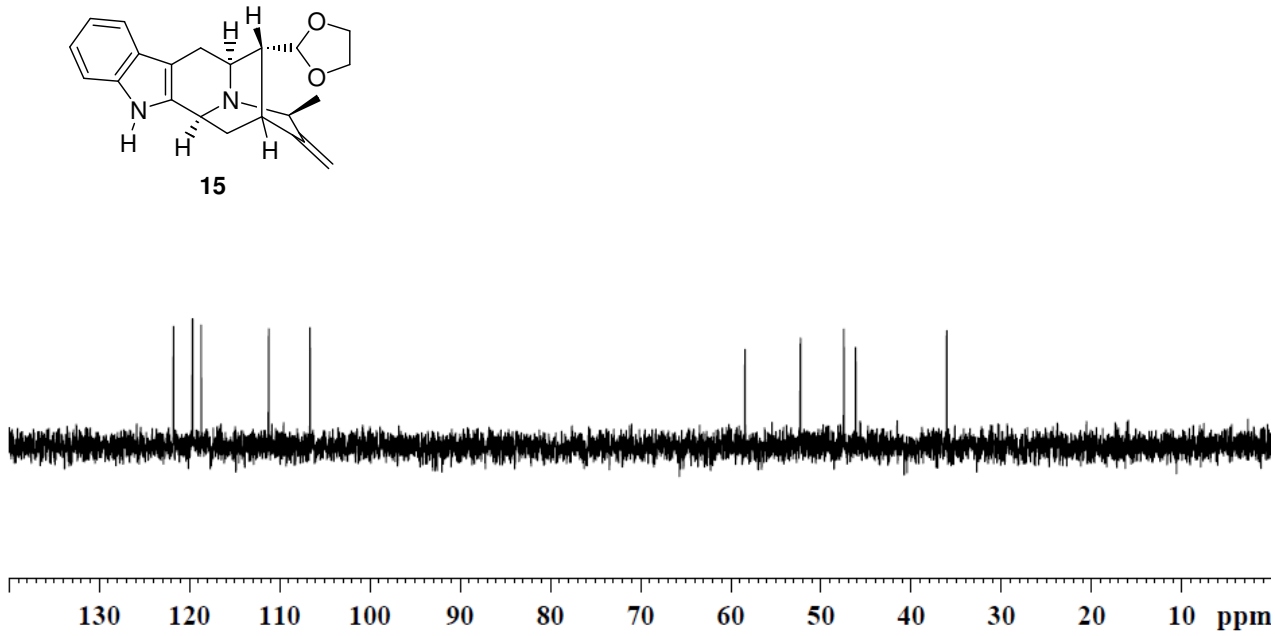

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
0.8081
0.9821
0.9412
1.932
1.964
0.9299
0.9767
0.9425
3.21
1.082
1
0.9979
1.008
0.9849
1.152
2.072
2.984

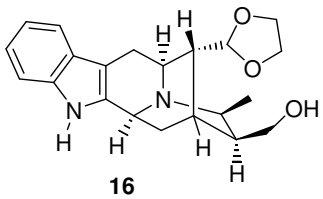


15

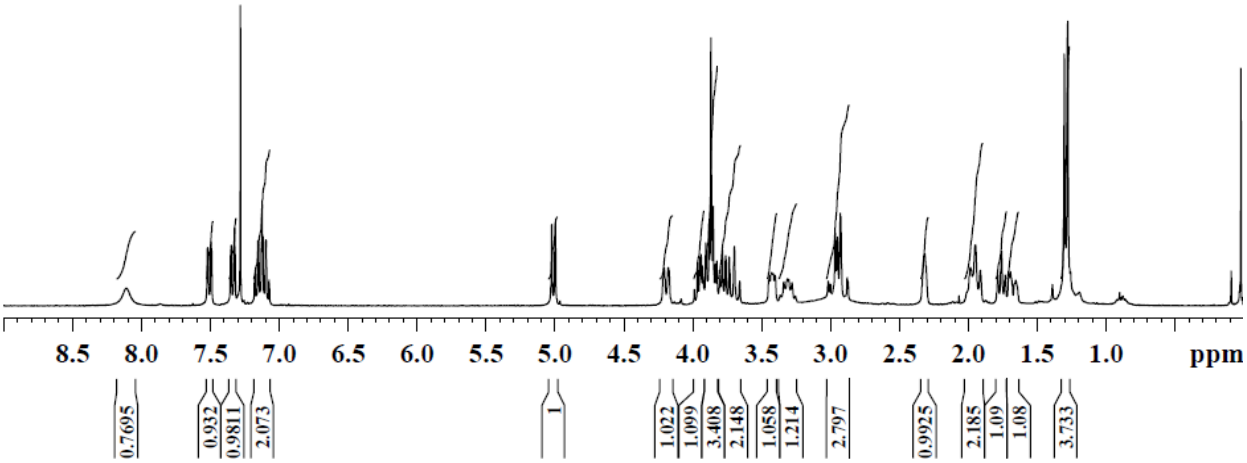

160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

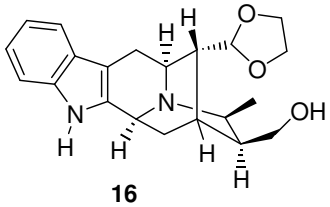

H
H
O
O
N
N
H
H
H
15
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


H
H
O
O
N
N
H
H
H
15
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

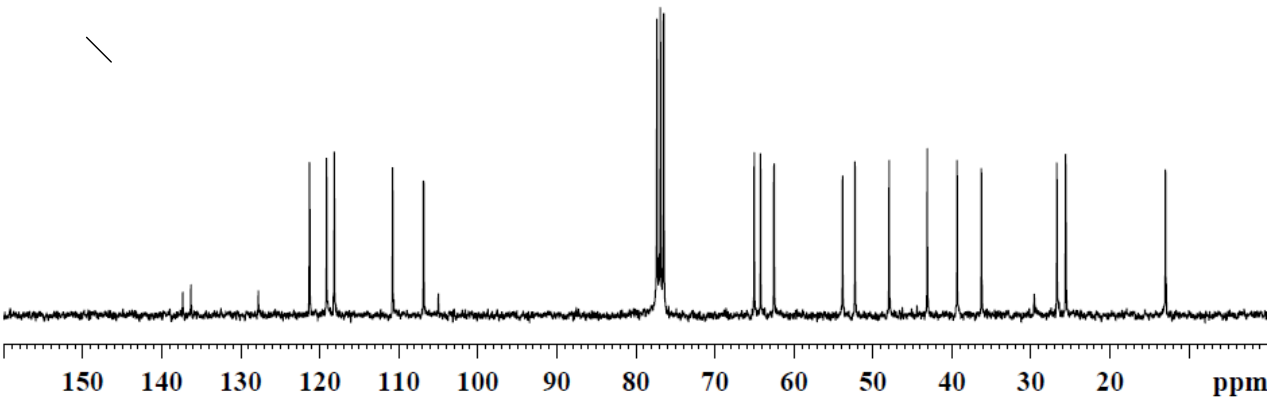

H
O
H
O
N
N
H
OH
H
H
H
H

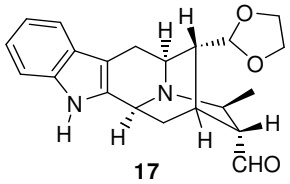
16


8.5
8.0
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
ppm
0.7695
0.932
0.9811
2.073
1
1.022
1.099
3.408
2.148
1.058
1.214
2.797
0.9925
2.185
1.09
1.08
3.733

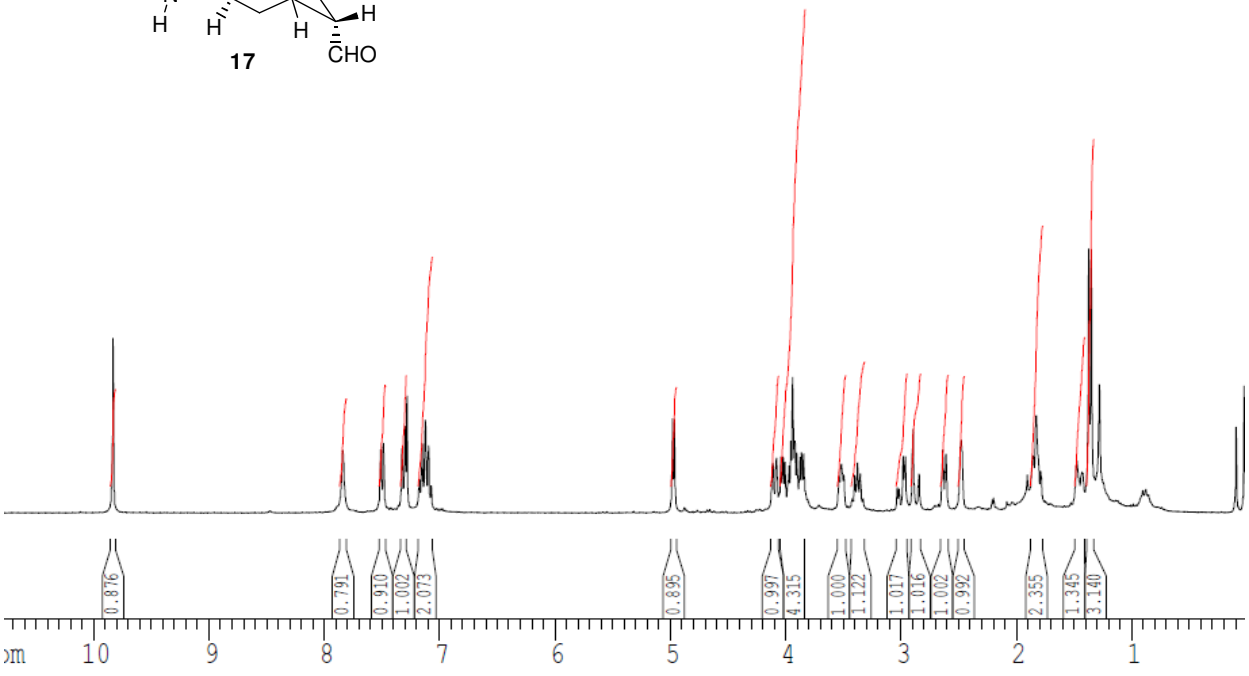

H
O
H
O
N
N
H
OH
H
H
H
H

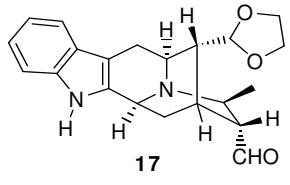
16


150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


H
O
O
N
H
N
H
H
H
H
CHO

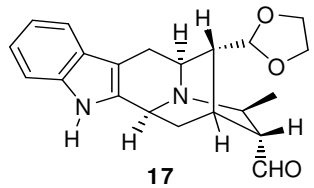
17


0.876
0.791
0.910
1.002
2.073
0.895
0.997
4.315
1.000
1.122
1.017
1.016
1.002
0.992
2.355
1.345
3.140
ppm
10
9
8
7
6
5
4
3
2
1

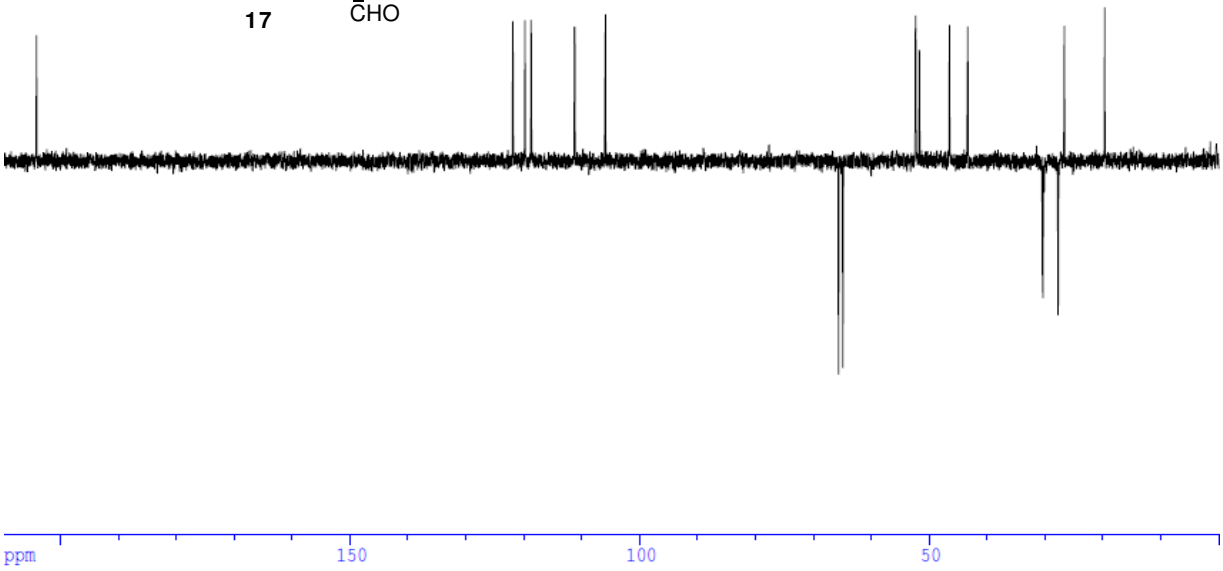

H
O
O
N
H
N
H
H
H
H
CHO

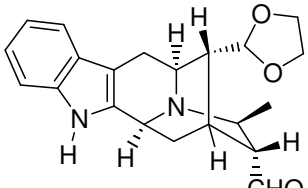
17

ppm
180
160
140
120
100
80
60
40
20

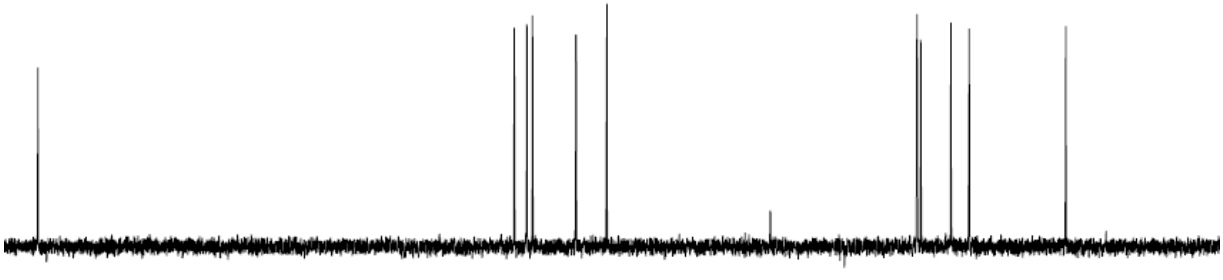


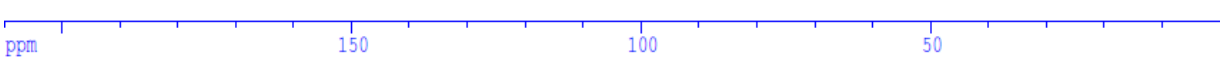
17

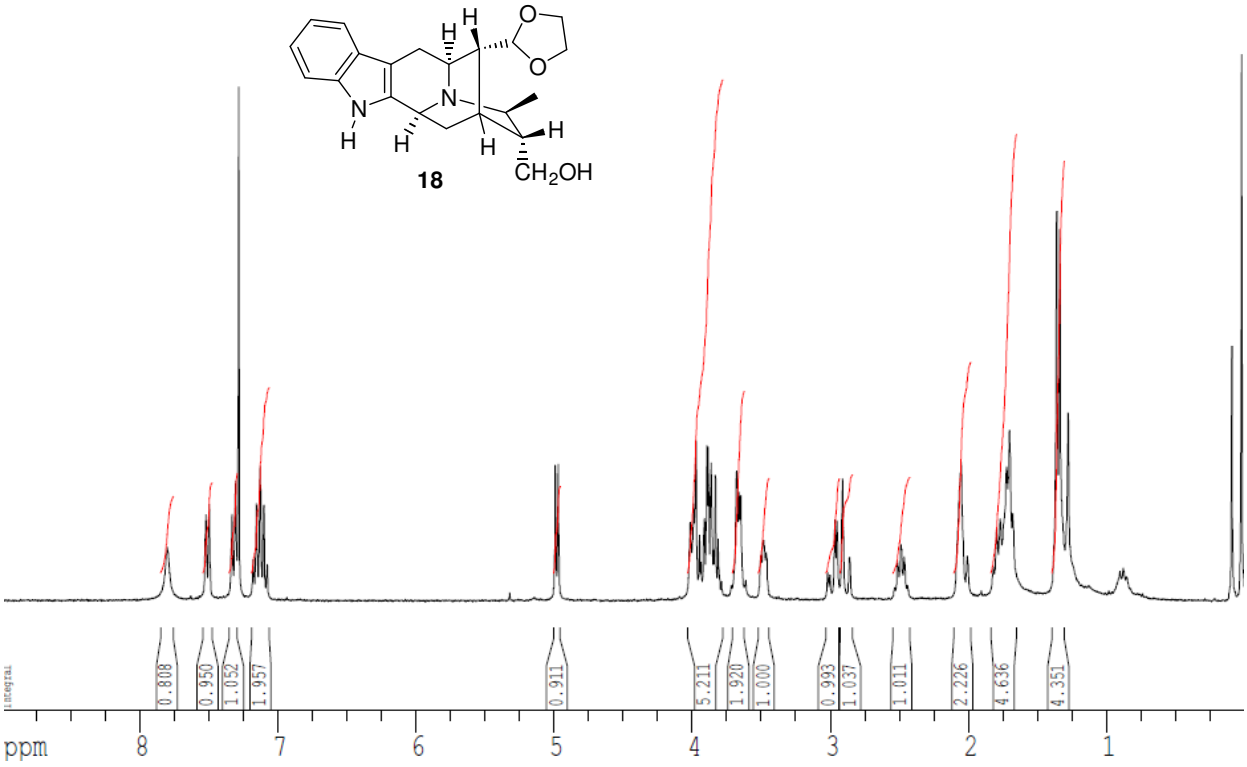


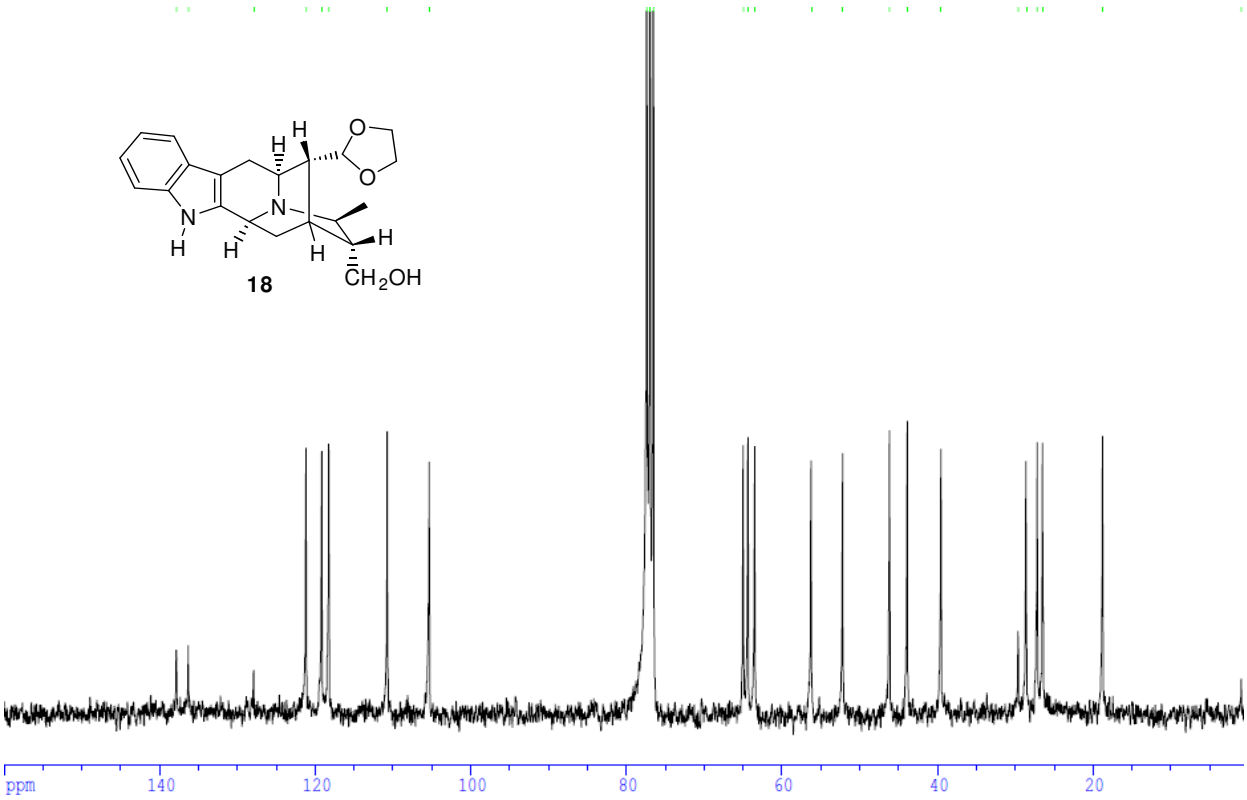


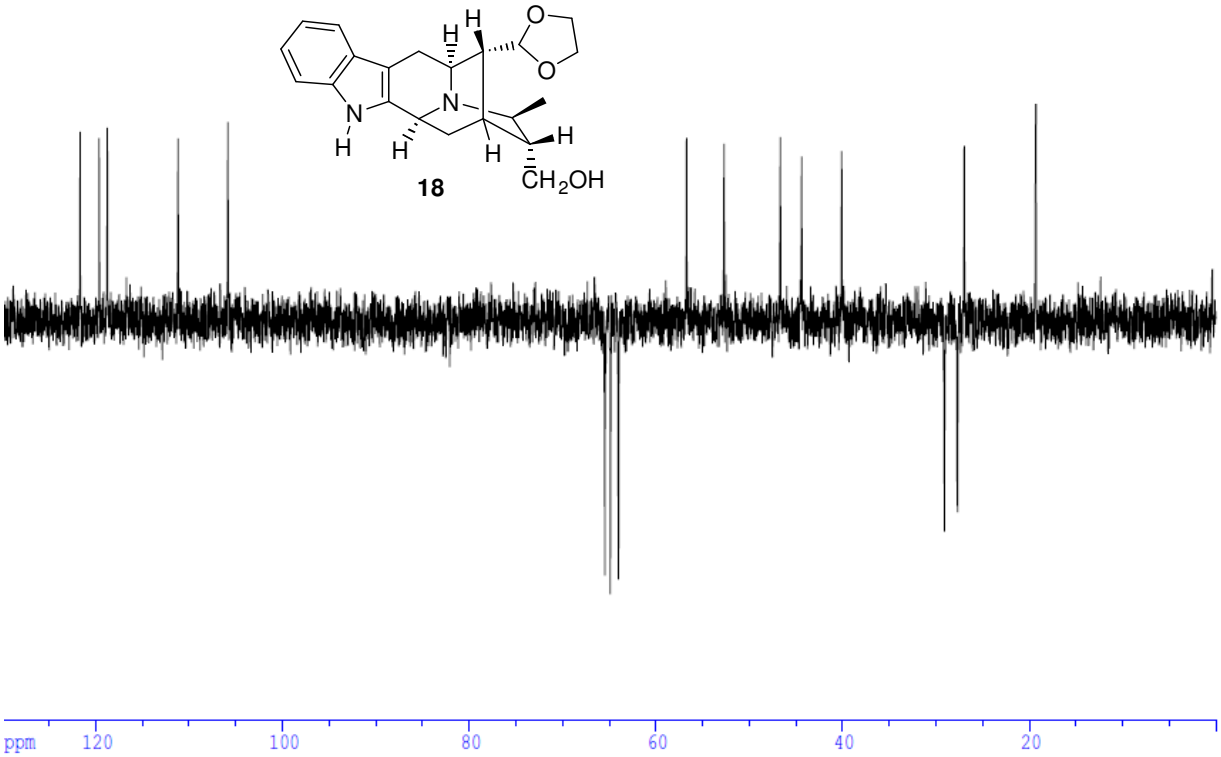
17

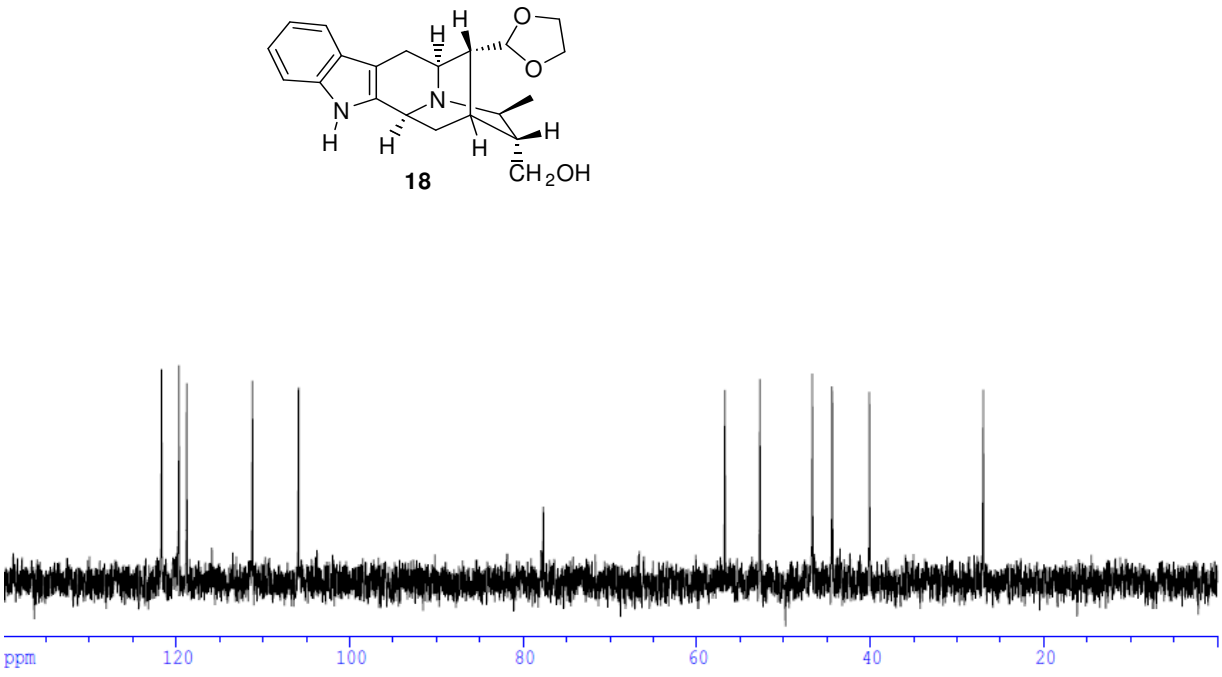


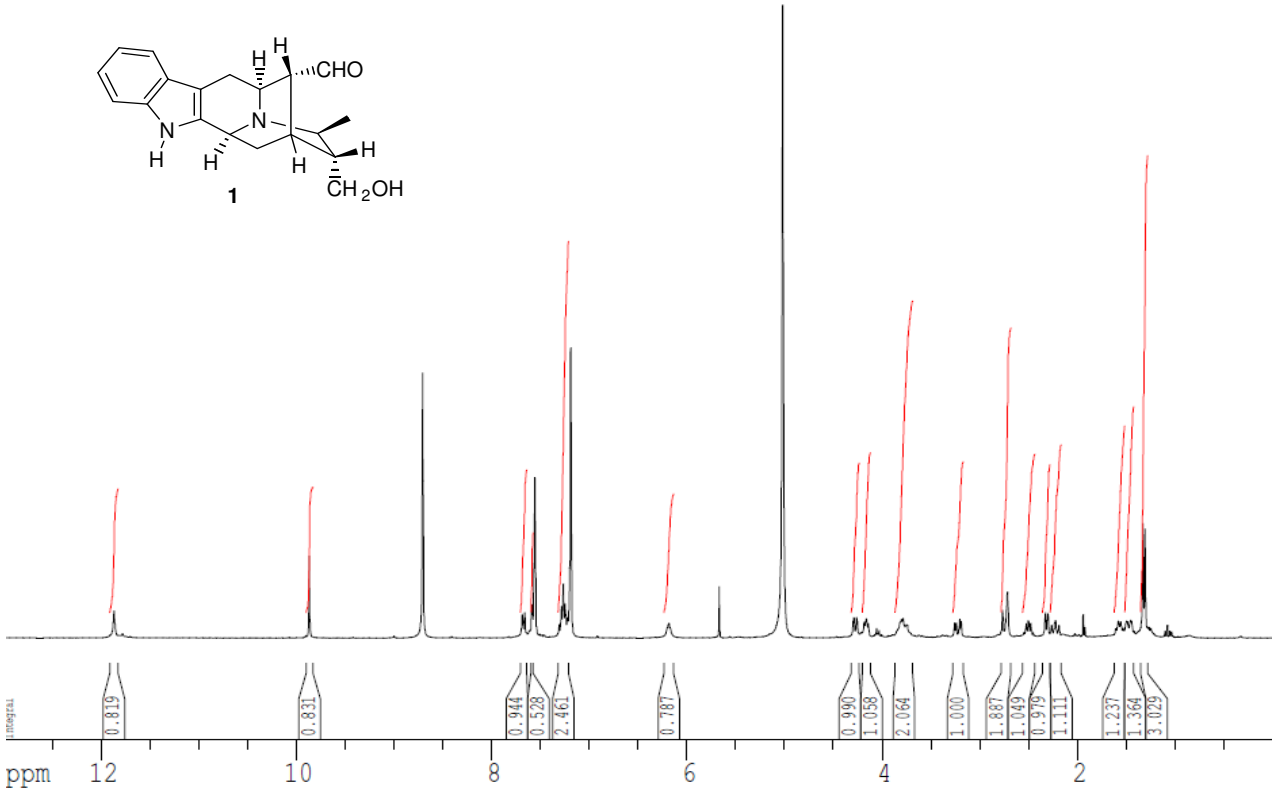



18
0.808
0.950
1.052
1.957
0.911
5.211
1.920
1.000
0.993
1.037
1.011
2.226
4.636
4.351
ppm
8
7
6
5
4
3
2
1

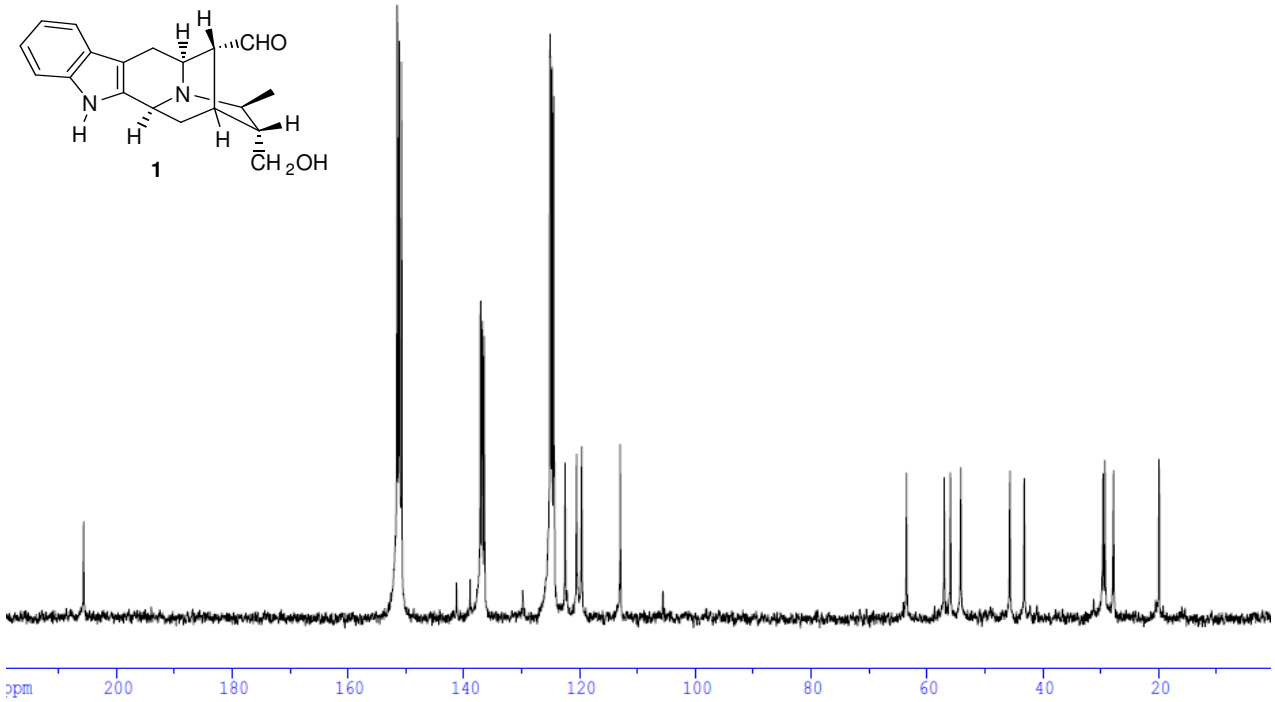

18
ppm
140
120
100
80
60
40
20

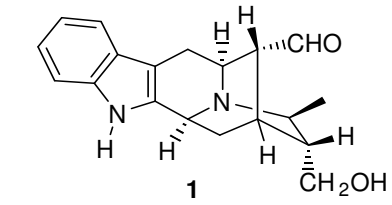

H
O
O
N
H
N
H
H
H
H
CH2OH
18
ppm
120
100
80
60
40
20


H
O
O
N
H
N
H
H
H
H
CH2OH
18
ppm
120
100
80
60
40
20

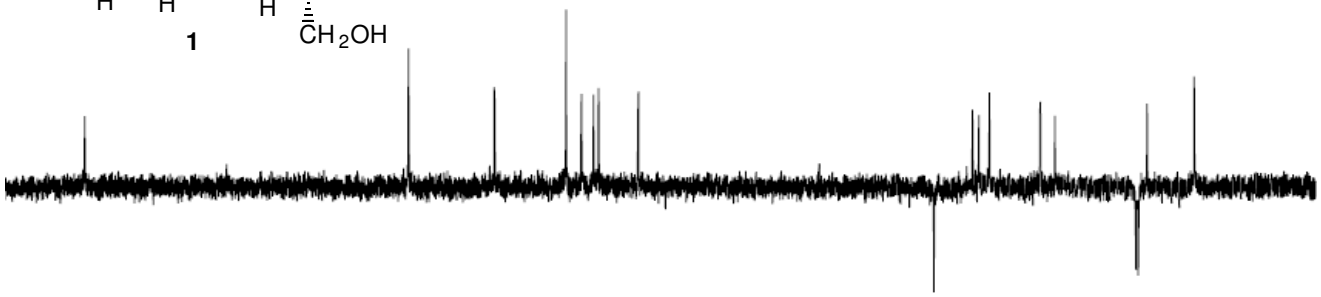


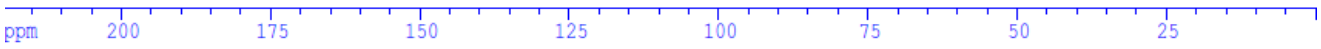
There are EtOAc peaks in the spectrum.

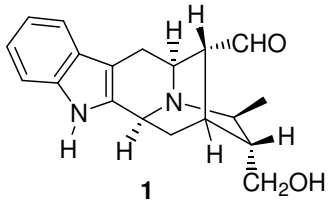



H
CHO
N
H
N
H
H
H
H
CH2OH

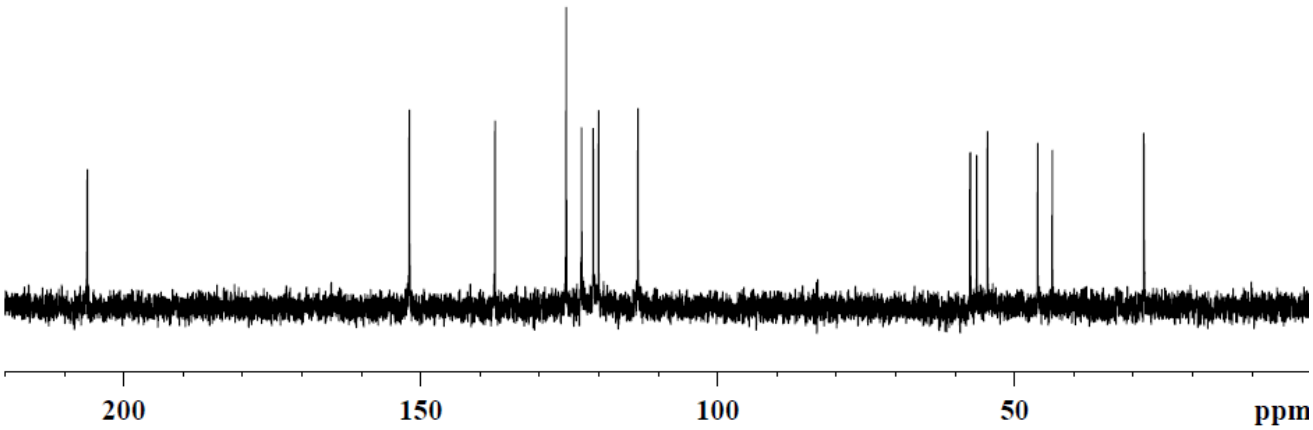
1

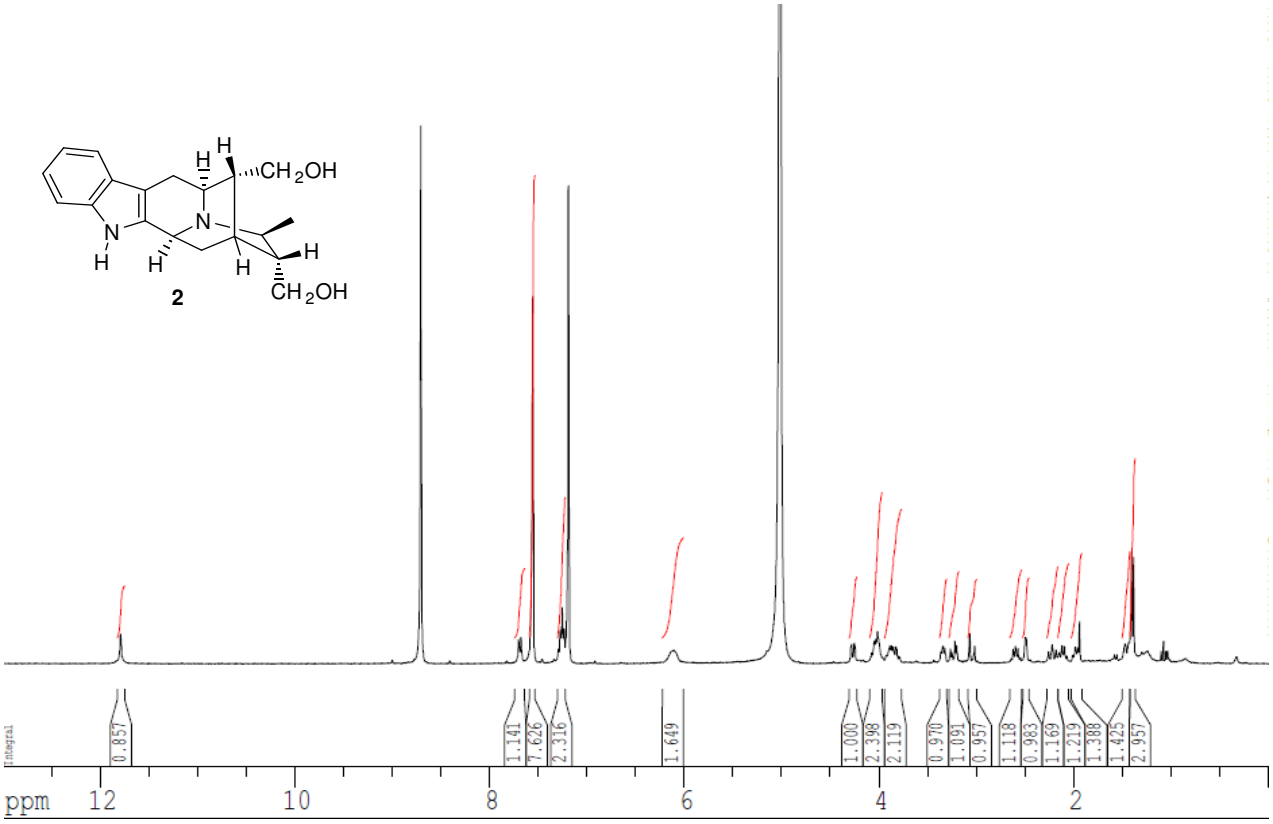


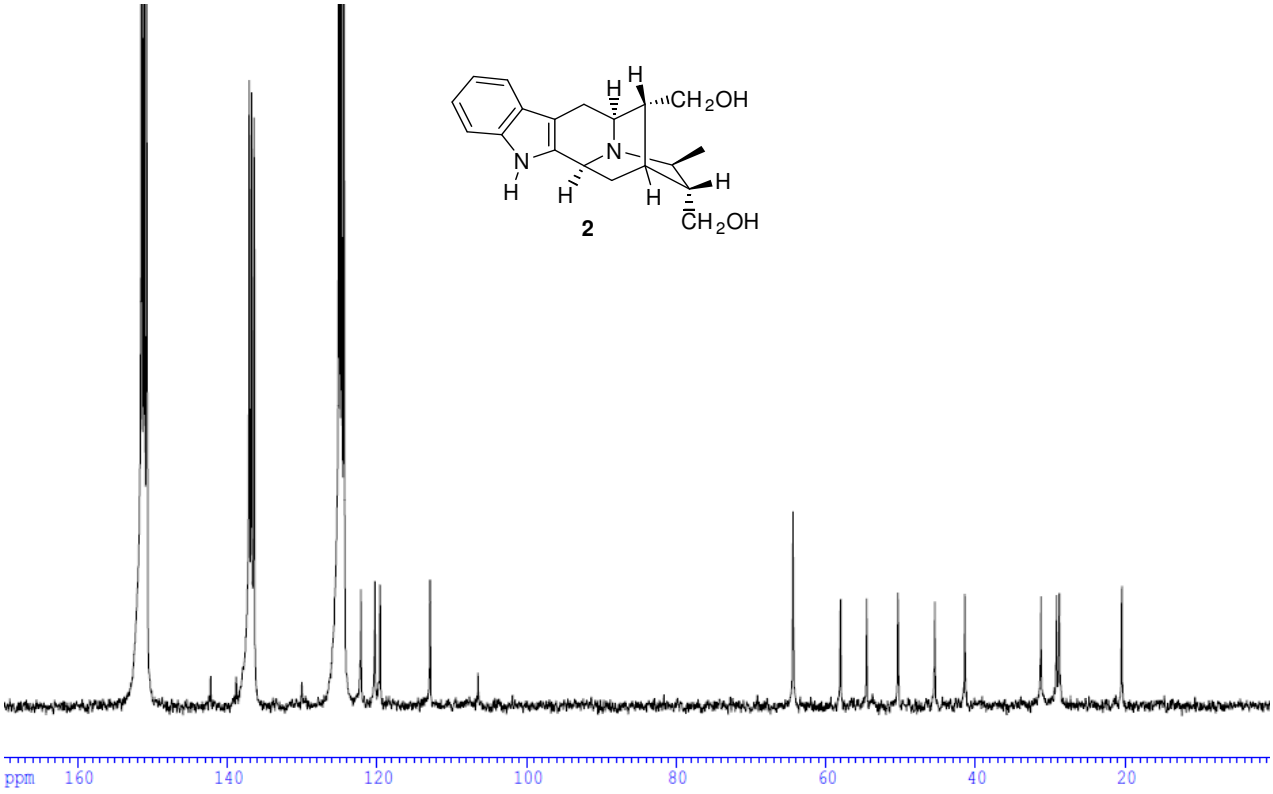

ppm
200
175
150
125
100
75
50
25

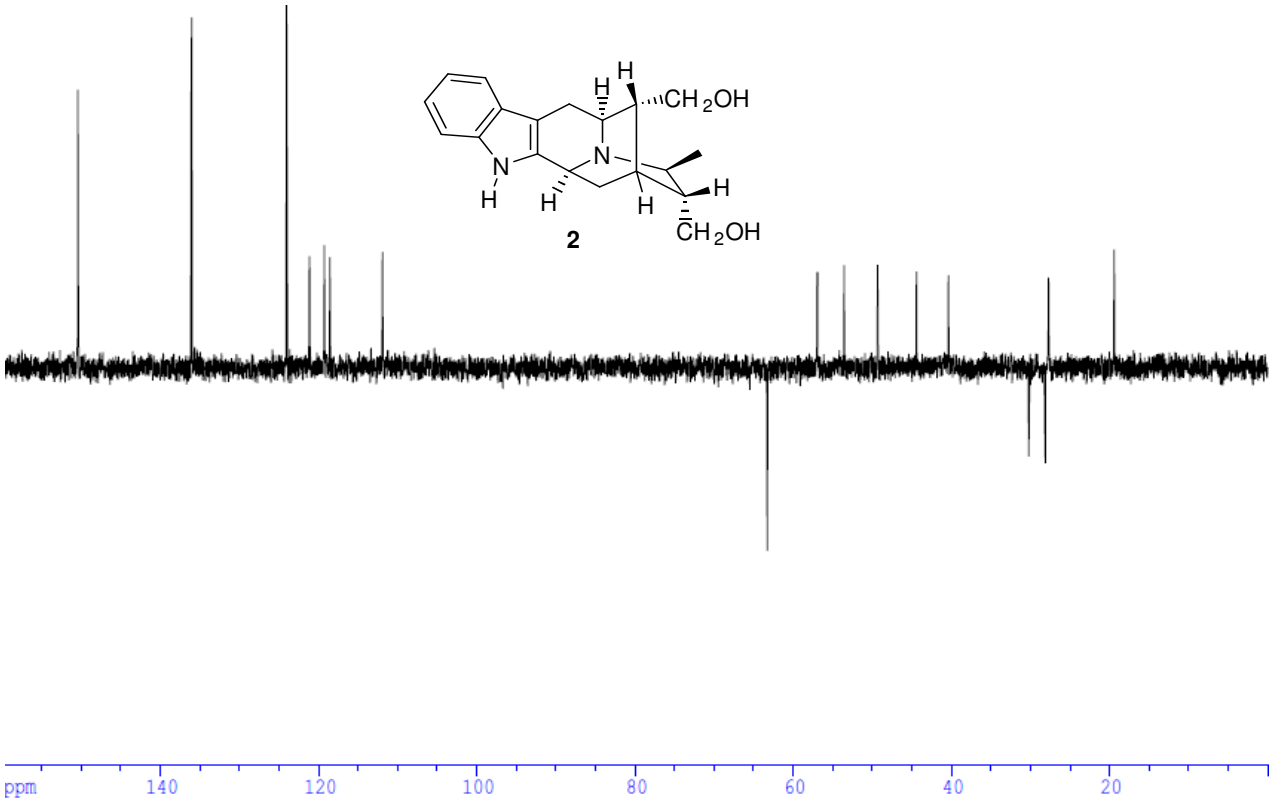

H
CHO
N
H
N
H
H
H
CH2OH

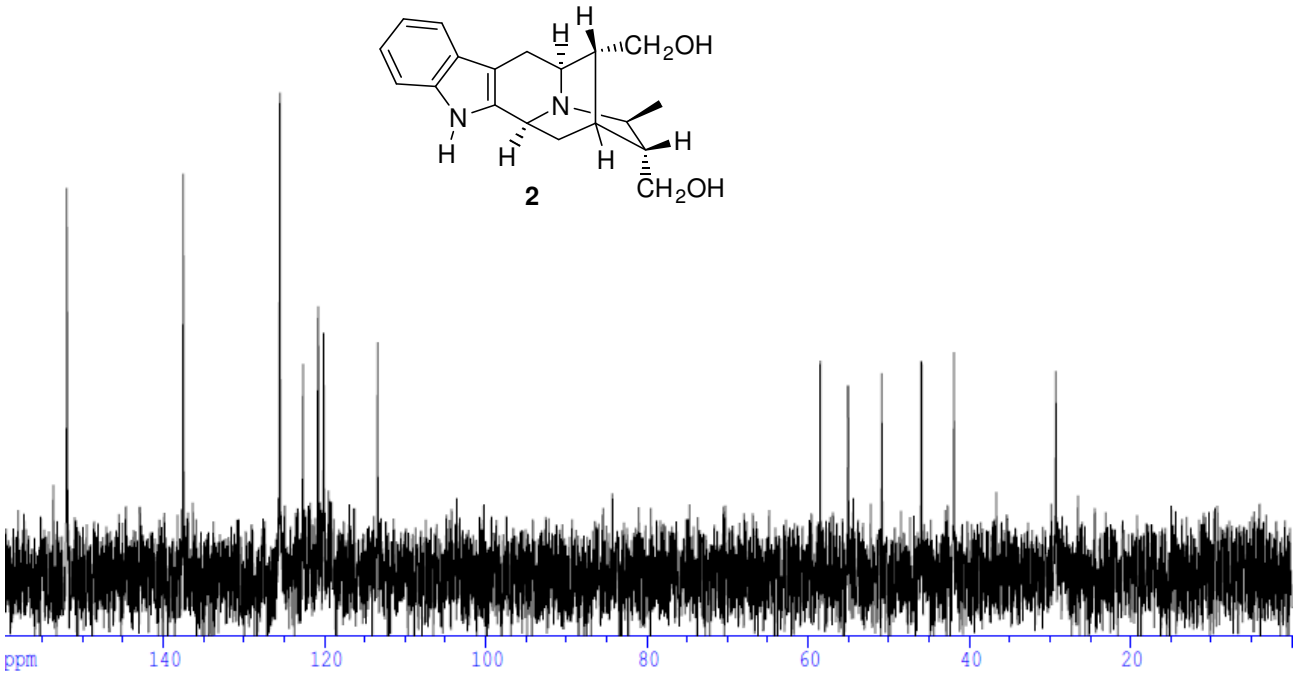
1


200
150
100
50
ppm


CH2OH
N
H
H
H
H
CH2OH
2
Integral
0.857
1.141
7.626
2.316
1.649
1.000
2.398
2.119
0.970
1.091
0.957
1.118
0.983
1.169
1.219
1.388
1.425
2.957
ppm
12
10
8
6
4
2

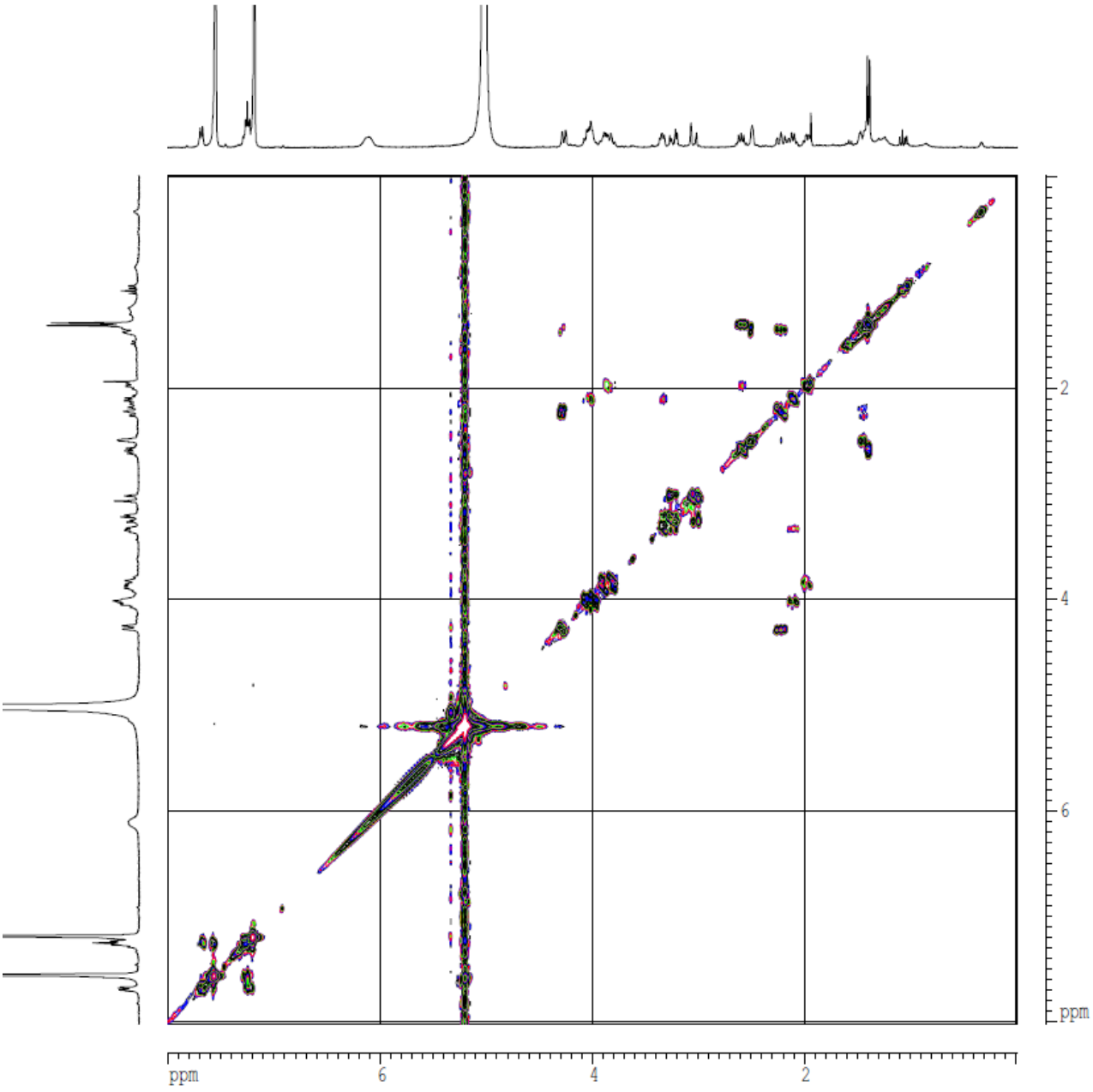

CH2OH
N
H
H
H
H
CH2OH
2
ppm
160
140
120
100
80
60
40
20


H
H
CH2OH
N
N
H
H
H
H
CH2OH
2
ppm
140
120
100
80
60
40
20

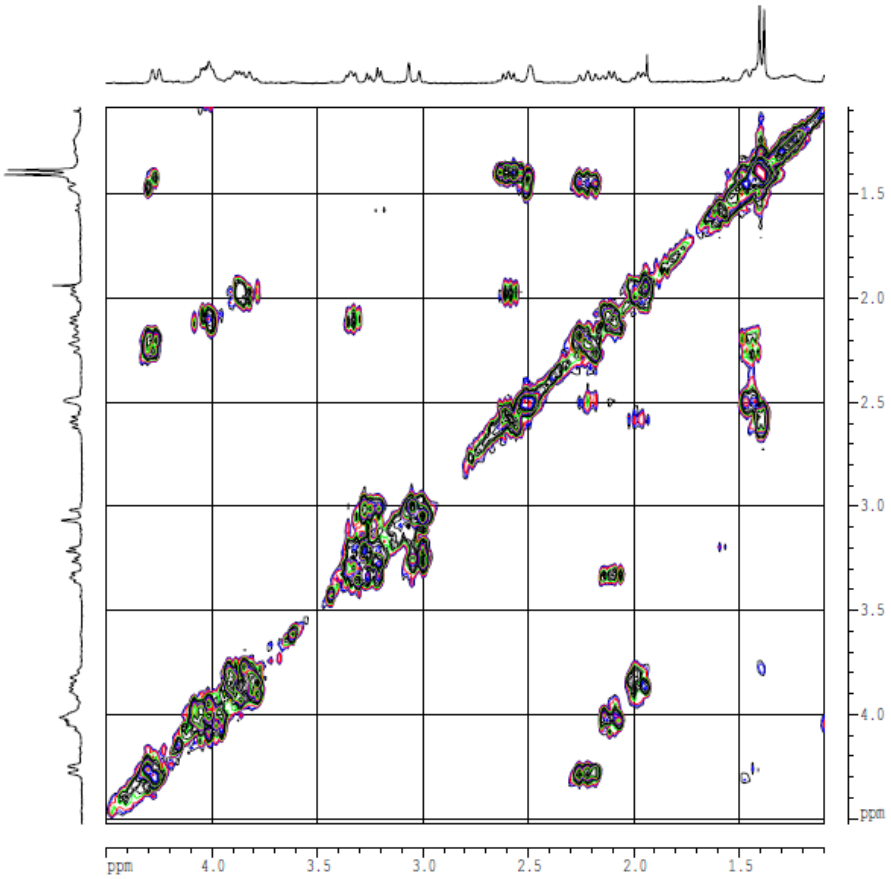

H
H
CH2OH
N
N
H
H
H
H
CH2OH
2
ppm
140
120
100
80
60
40
20

Copies of Correlation Experiments for Compound 2:

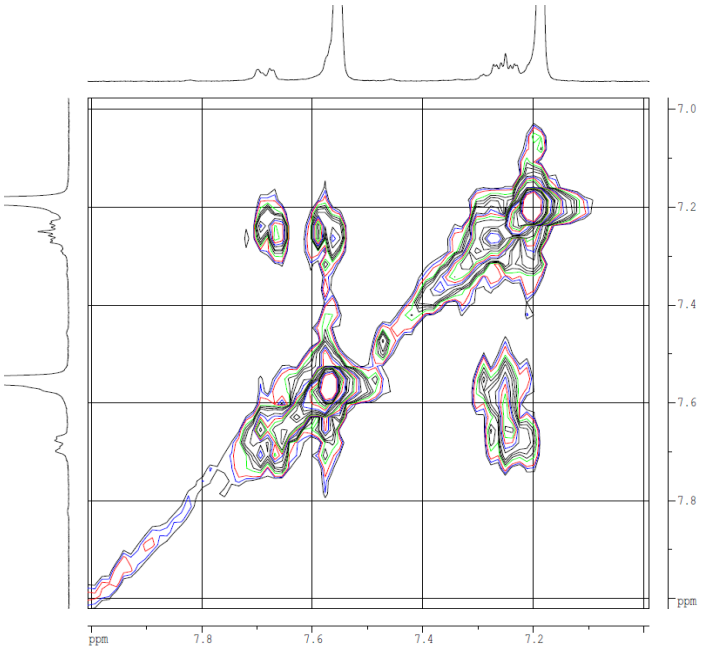
COSY Spectrum for **2**



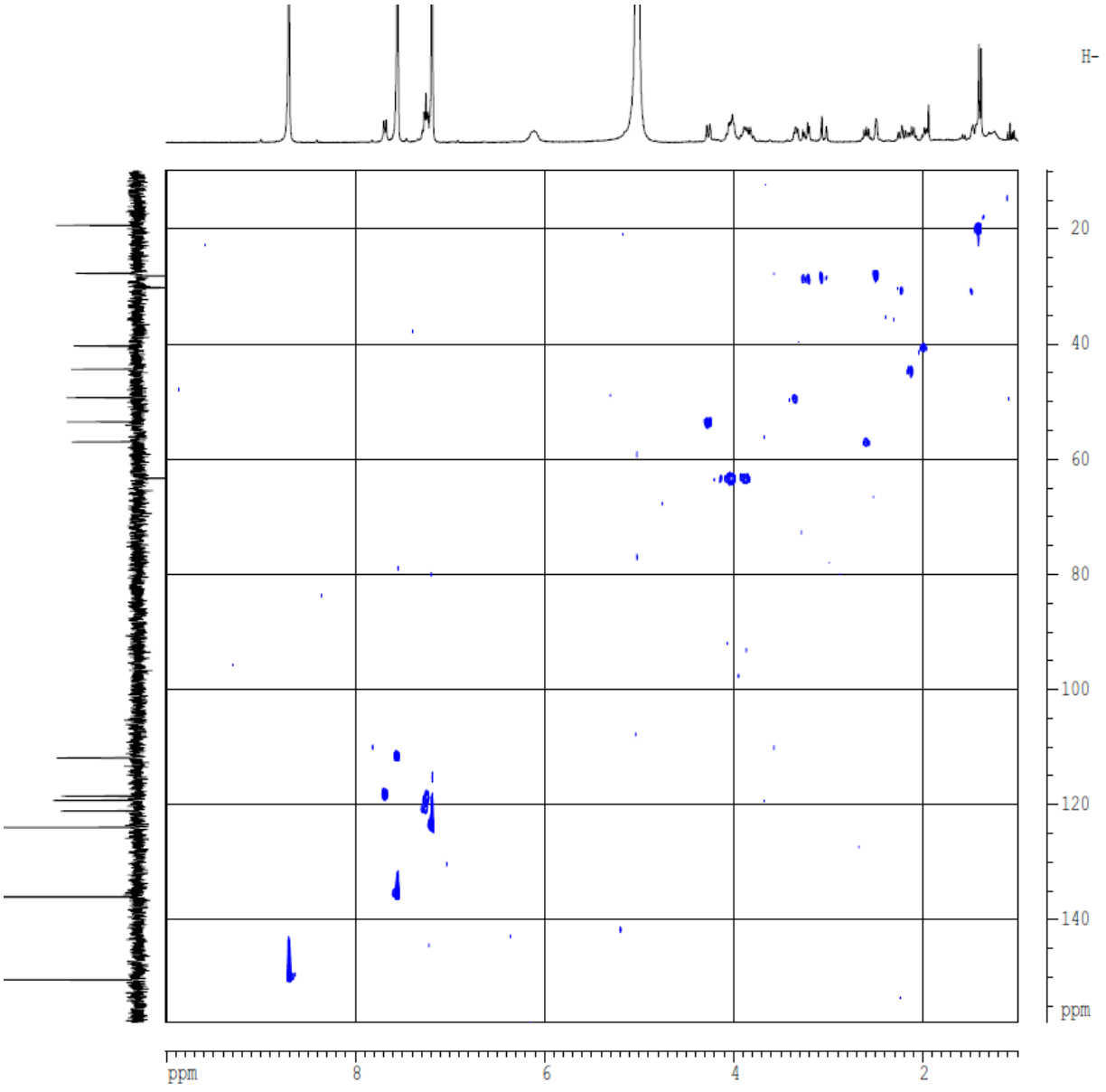
Aliphatic region of COSY Spectrum for **2**



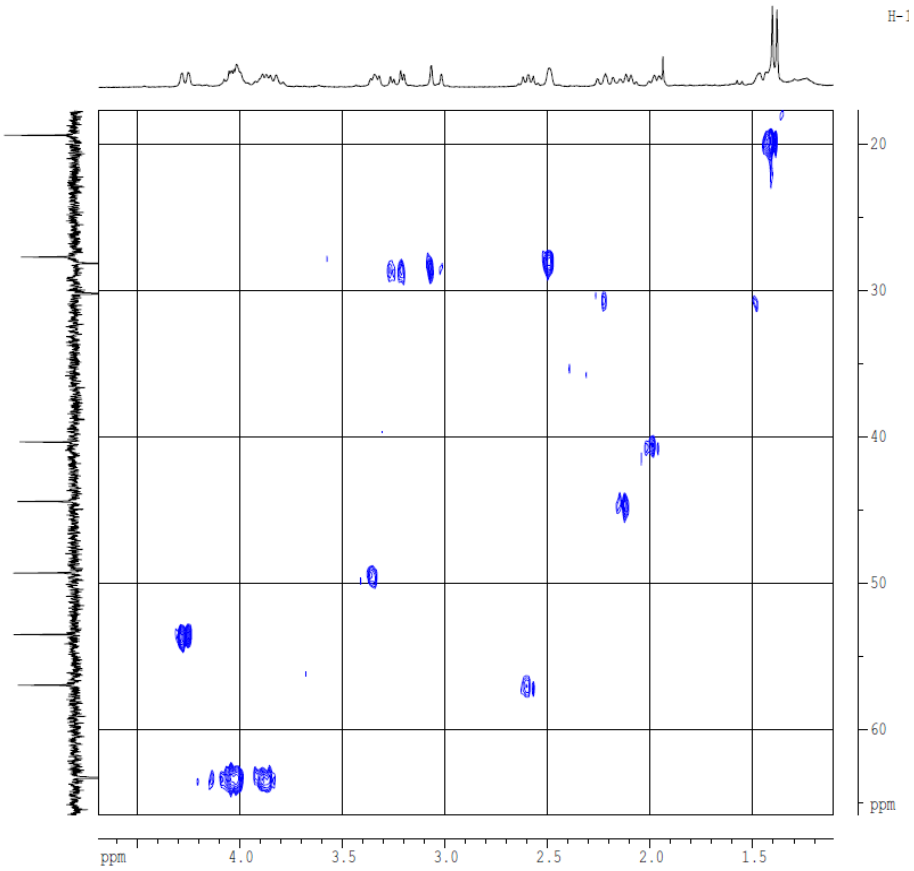
Benzene region of COSY Spectrum for **2**



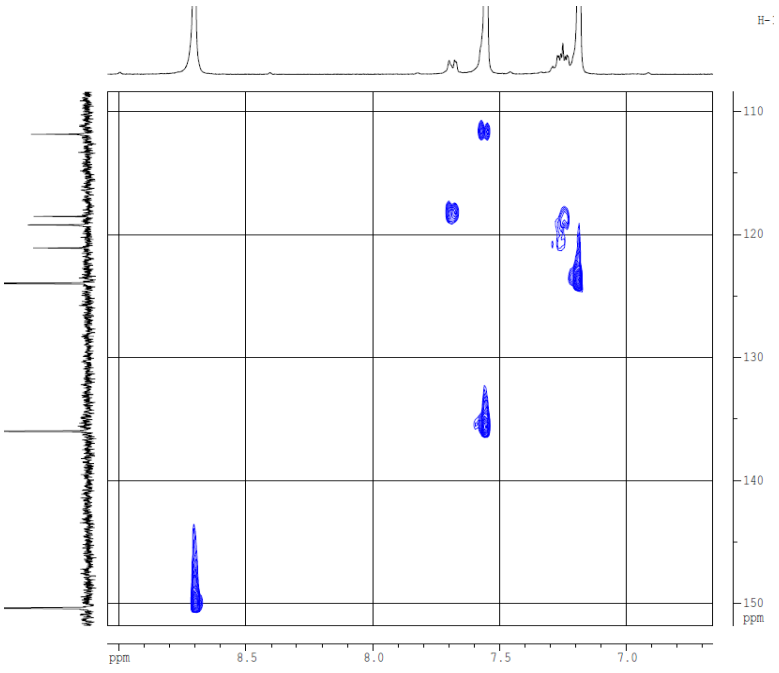
HSQC Spectrum for **2**



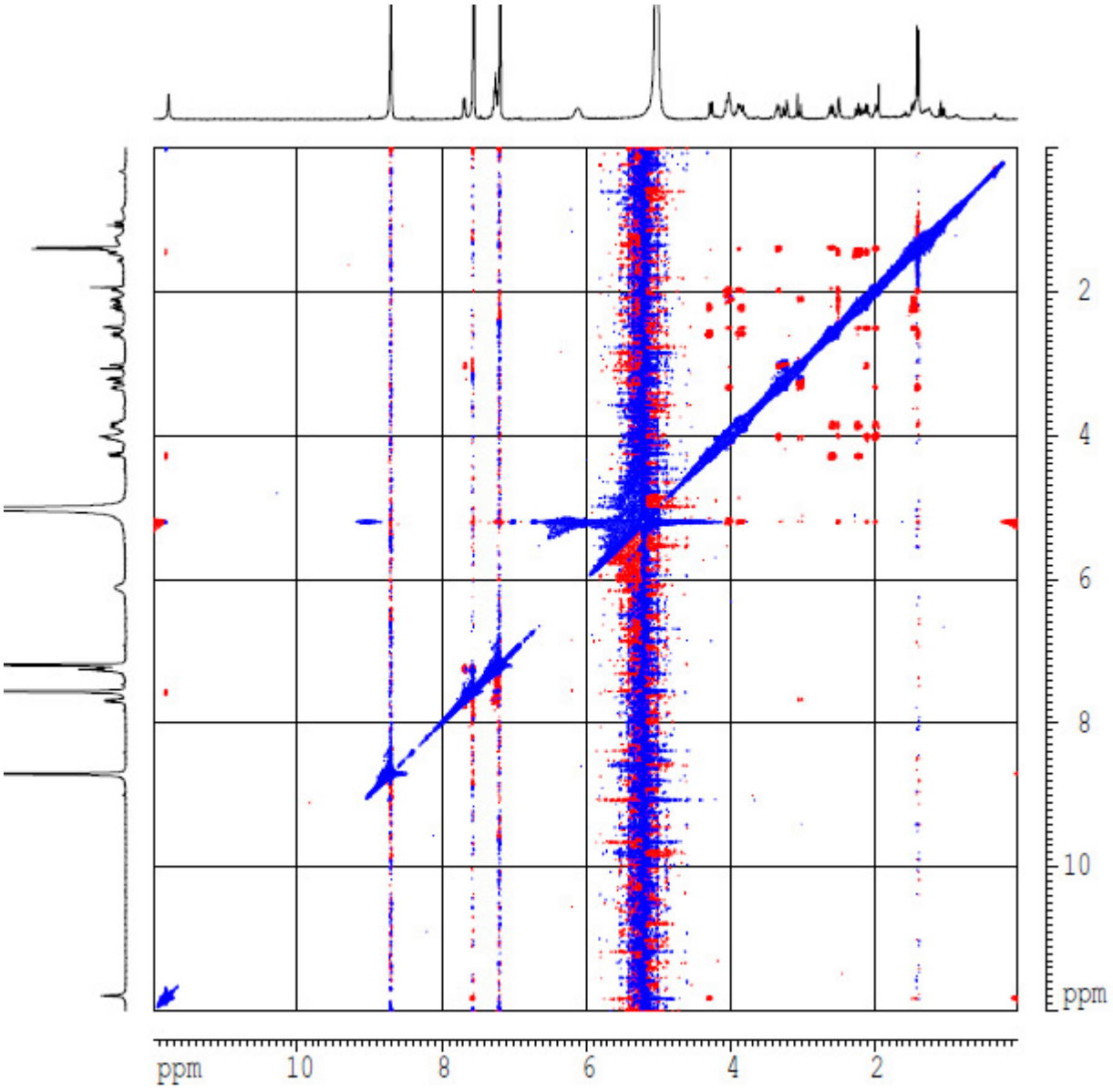
Aliphatic region of HSQC Spectrum for **2**



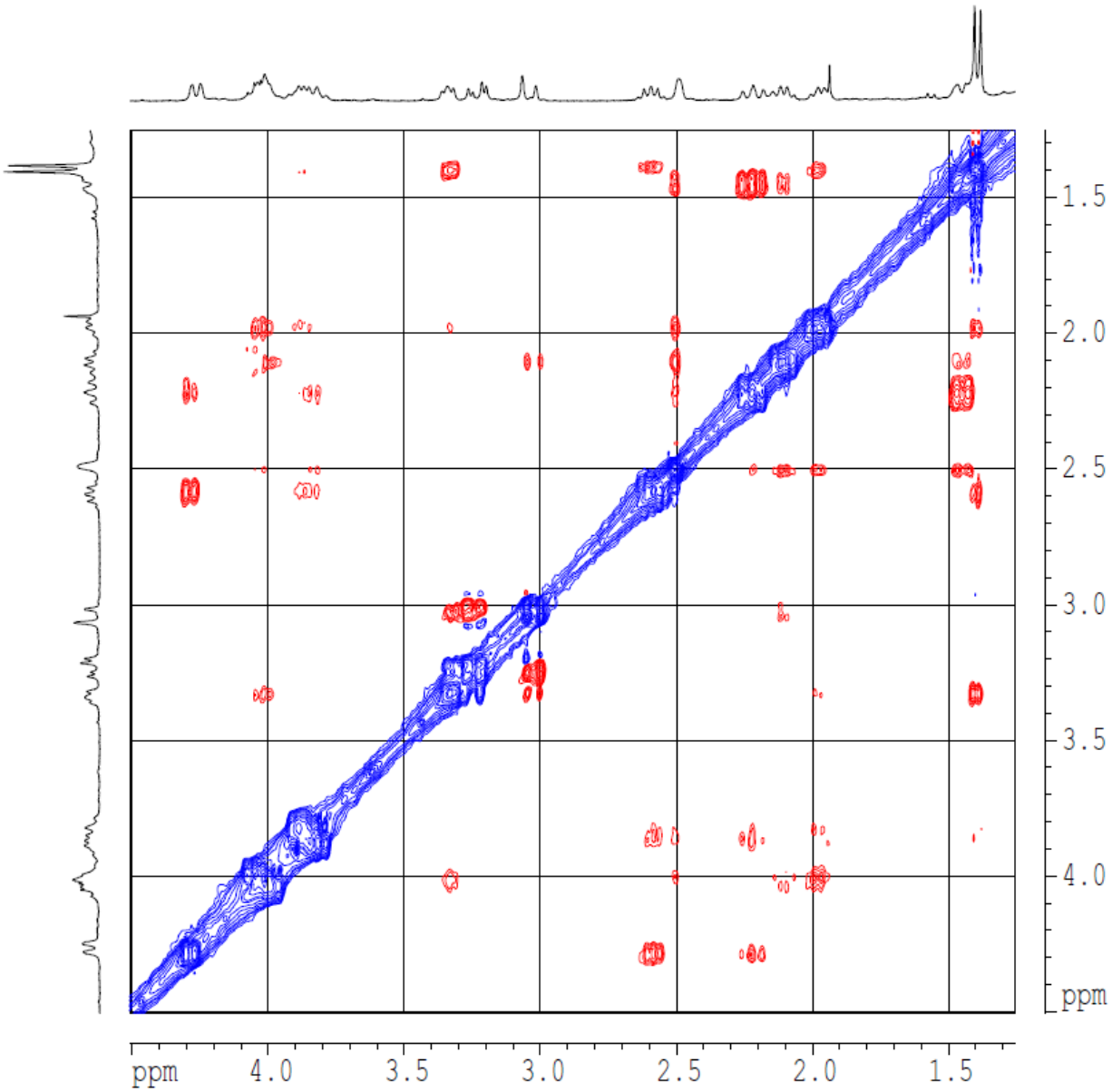
Benzene region of HSQC Spectrum for **2**



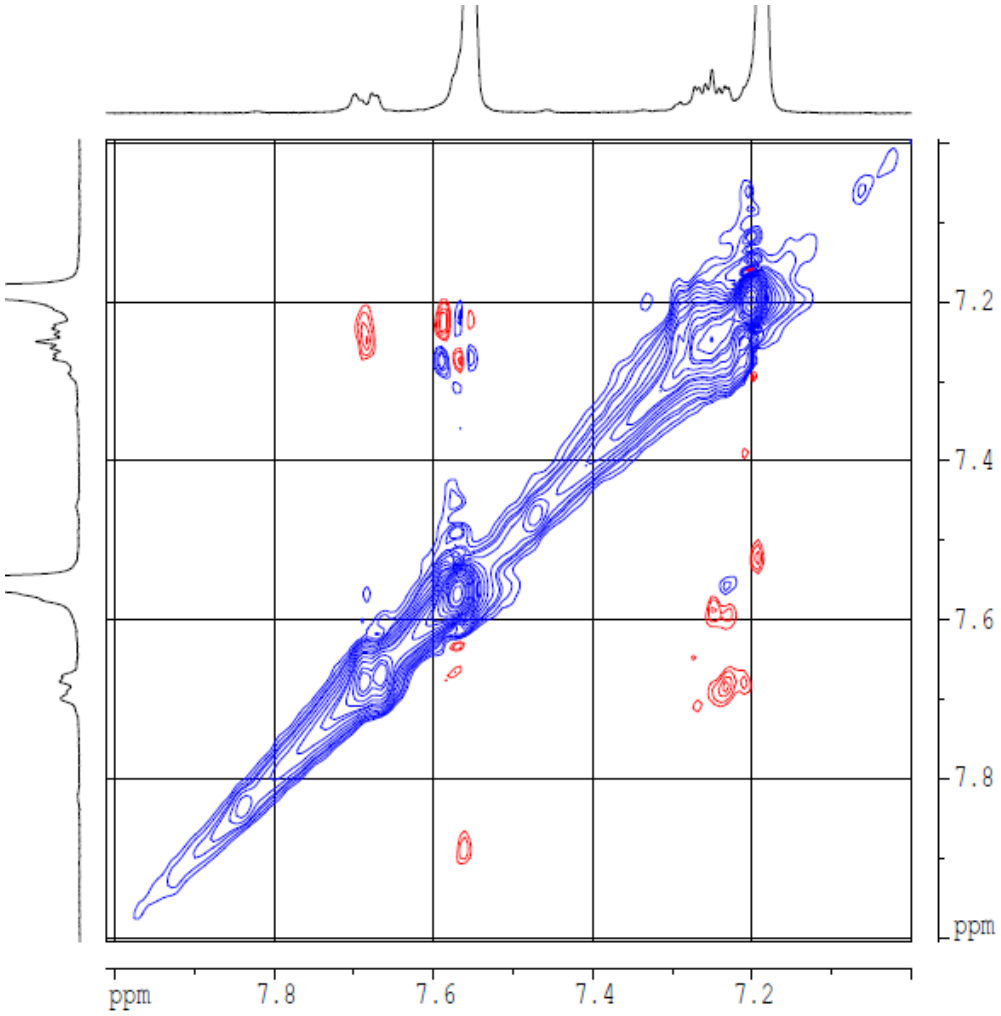
2D NOESY Spectrum for 2



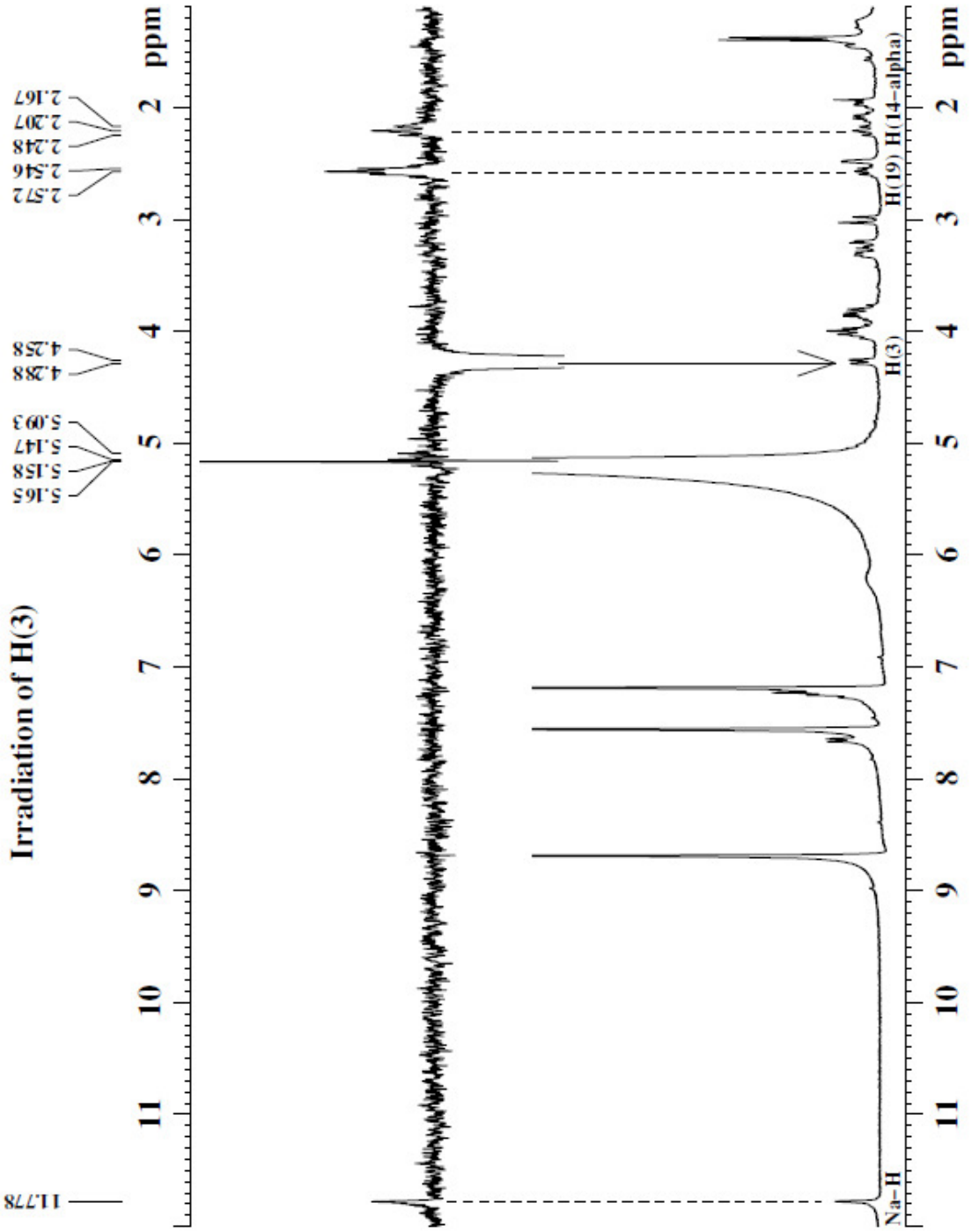
Aliphatic region of 2D NOESY Spectrum for **2**

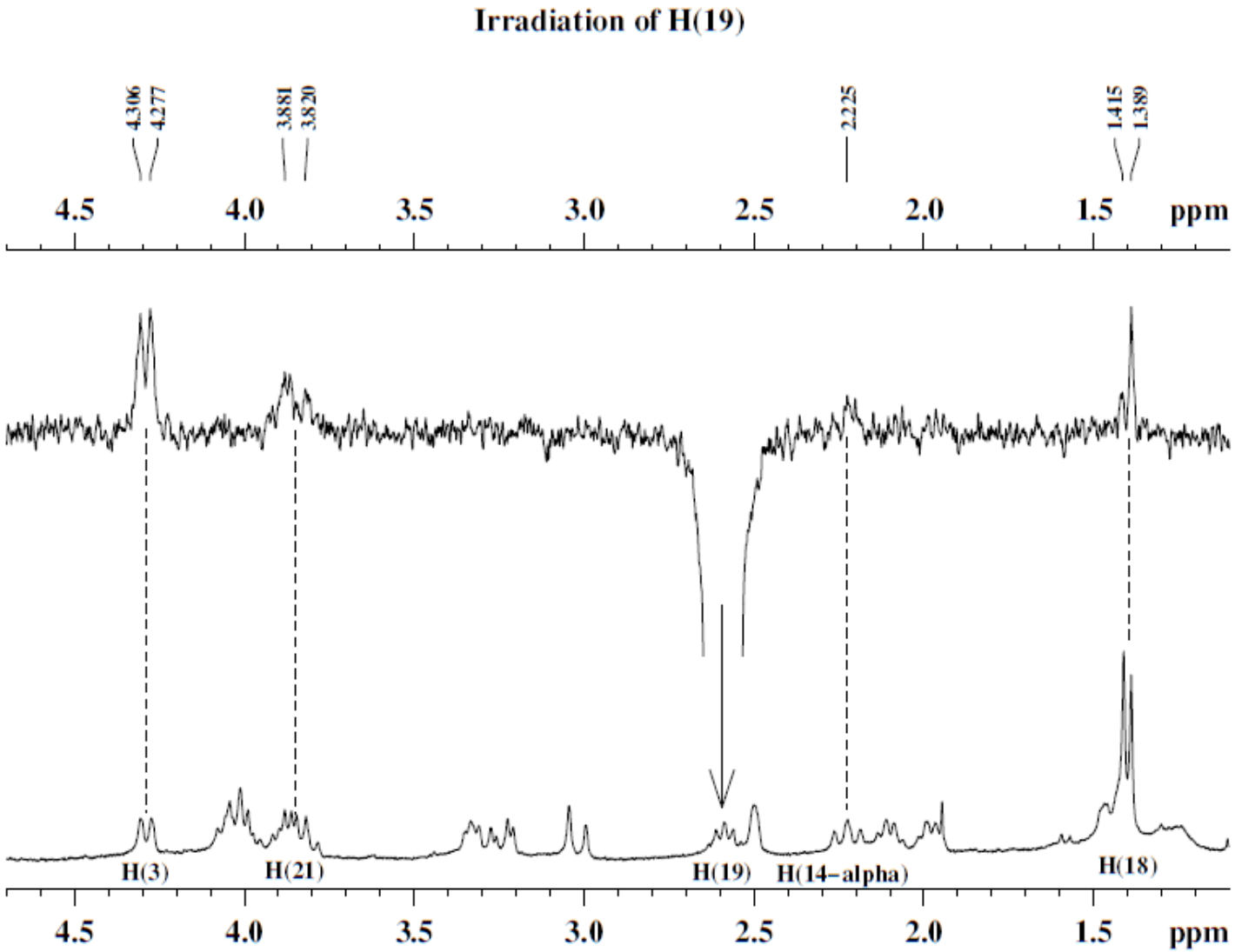


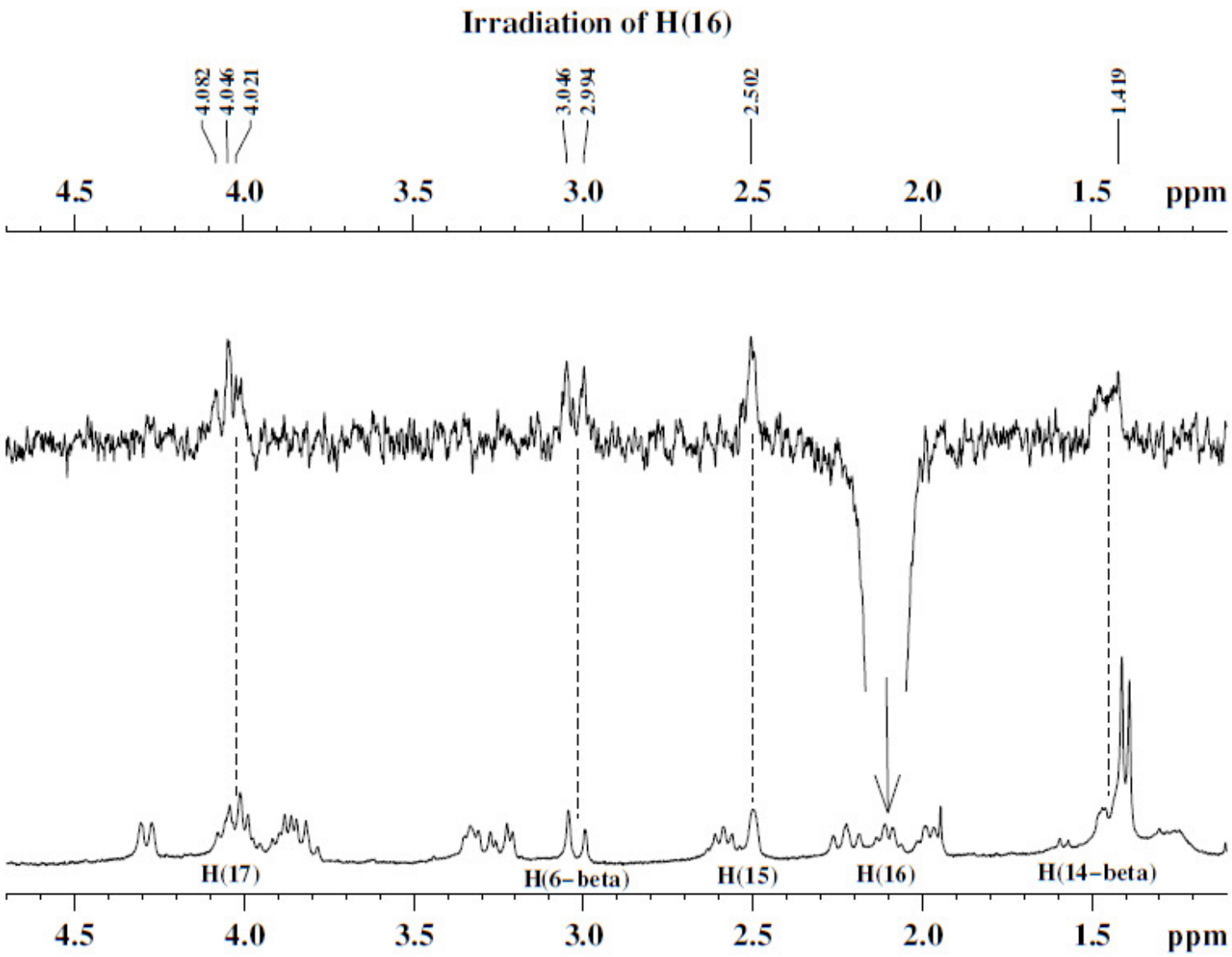
Benzene region of 2D NOESY Spectrum for **2**

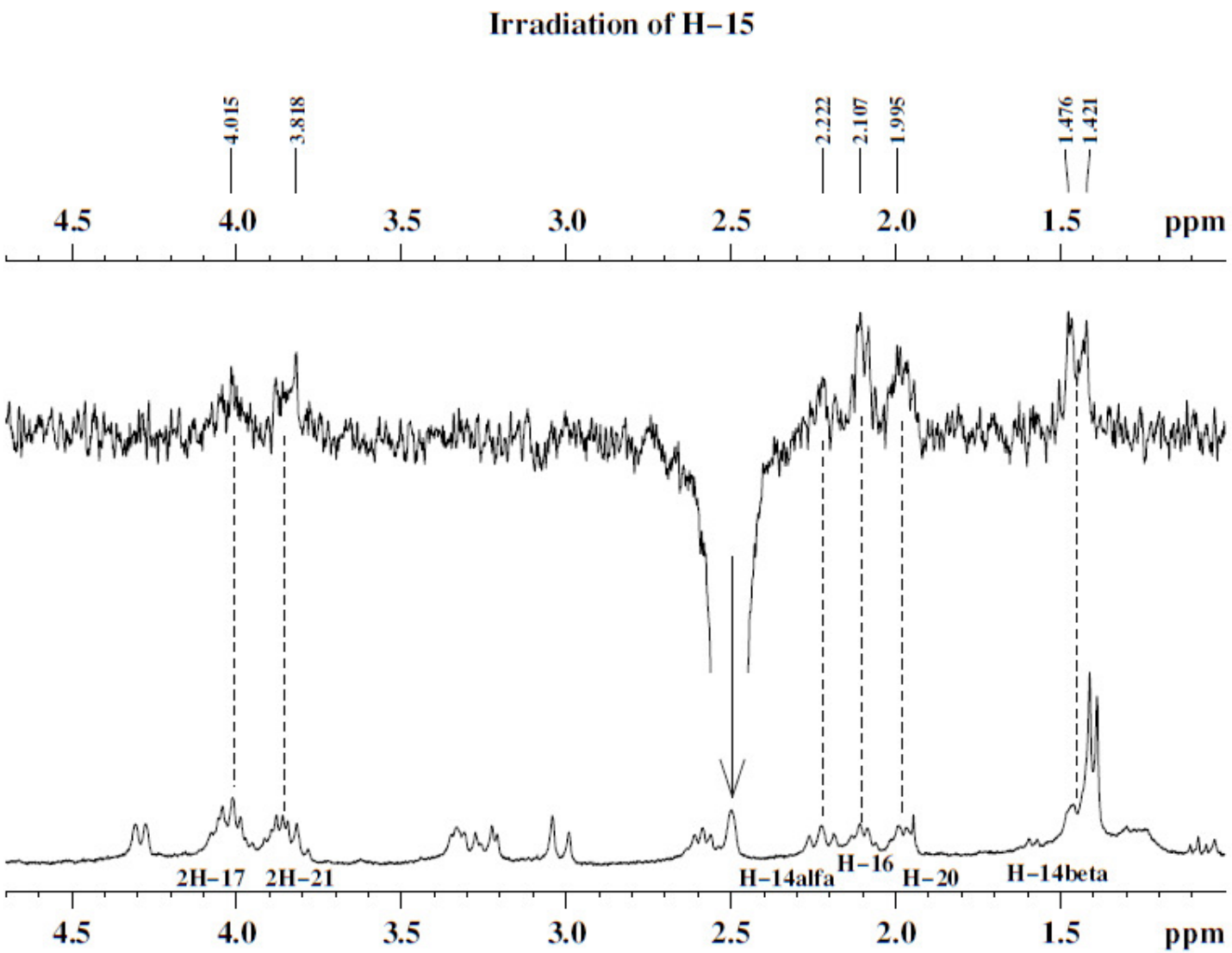


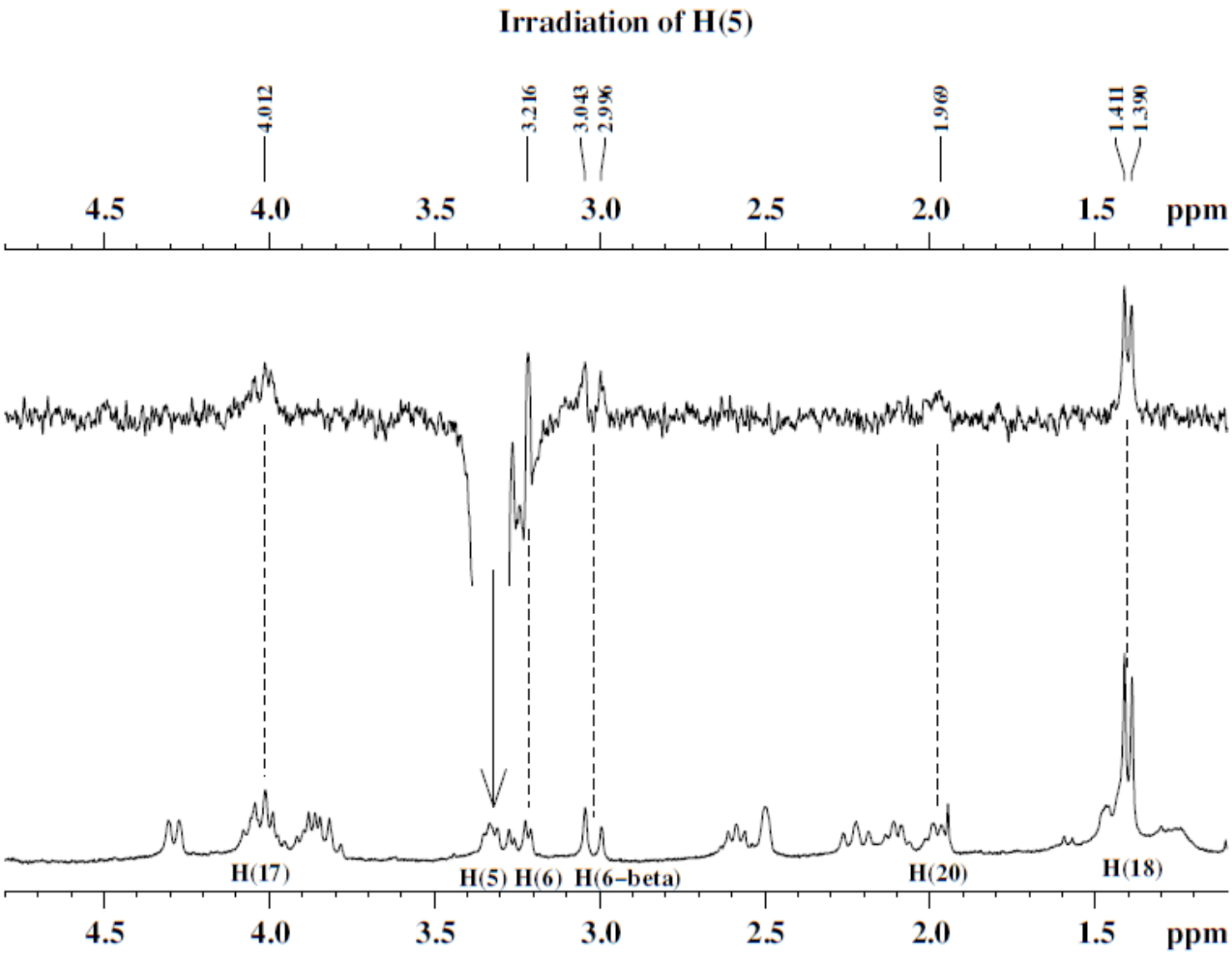
1D NOE Data for 2:

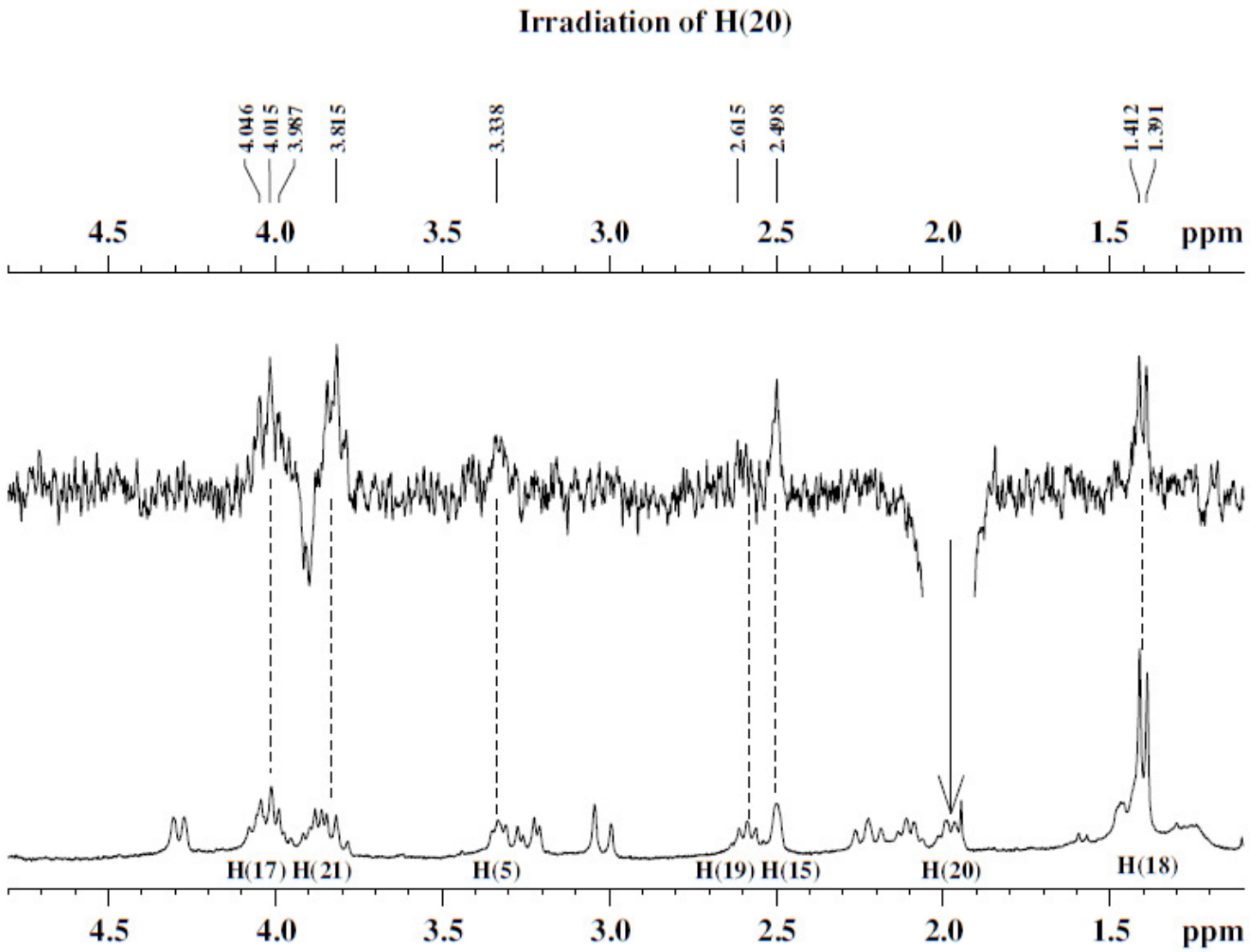



Irradiation of H(19)
4.306
4.277
3.881
3.820
2.225
1.415
1.389
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
H(3)
H(21)
H(19)
H(14-alpha)
H(18)
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm


Irradiation of H(16)
4.082
4.046
4.021
3.046
2.994
2.502
1.419
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
H(17)
H(6−beta)
H(15)
H(16)
H(14−beta)


Irradiation of H–15
4.015
3.818
2.222
2.107
1.995
1.476
1.421
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
2H–17
2H–21
H–14alfa
H–16
H–20
H–14beta
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm


Irradiation of H(5)
4.012
3.216
3.043
2.996
1.969
1.411
1.390
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
H(17)
H(5)
H(6)
H(6–beta)
H(20)
H(18)


Irradiation of H(20)
4.046
4.015
3.987
3.815
3.338
2.615
2.498
1.412
1.391
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
H(17) H(21)
H(5)
H(19) H(15)
H(20)
H(18)

The relative assignment of the peaks by Stöckigt et al.[2] was confirmed by COSY and HSQC experiments. The methyl group (3H-18) detected as a three proton doublet showed strong connectivity only to H-19, while H-19 showed strong coupling with 3H-18 and H-20. The protons of the hydroxyl carbon atoms at C-21 and C-17 were coupled to H-20 and H-16, respectively, while H-16 showed connectivity to H-5 and 2H-17. The two protons, which resonated at carbon atom C-6 showed a connection only between themselves in the COSY spectrum. The α and β assignment for the protons at C-6 was confirmed by 2D NOE and 1D NOE experiments. The coupling signals between 2H-6 and H-5 fell on the contour lines. The α and β assignment for the protons at C-14 was confirmed by a COSY spectrum as H-14α which showed coupling to H-14β (strong), H-15 (weak) and H-3 (strong), whereas H-14β was coupled to H-14α (strong) and H-15 (strong). It showed no coupling with the proton at H-3.

Figure S2. Selected 2D NOEs of 19(*S*),20(*R*)-Dihydroperaksine **2**

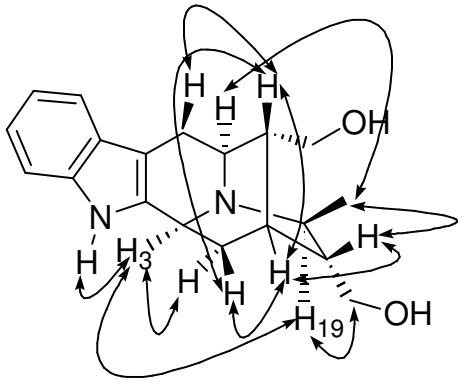
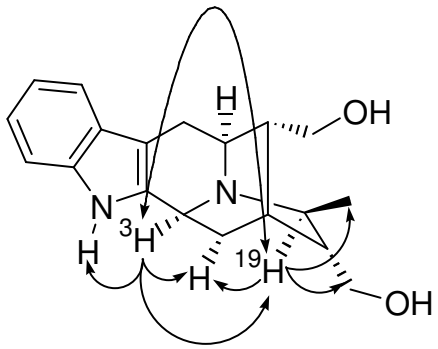
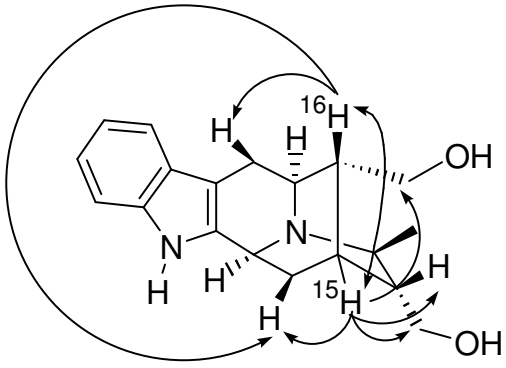


Figure S3. 1D NOEs Observed after Irradiation of Protons at H-3 and H-19



Analysis of the 2D NOESY experiments (Figure S2) was further confirmed, as indicated by 1D NOESY experiments. Good NOEs were found between H-3 and H-14α (strong), H-19 (strong) and the indole N_a-H proton. The irradiation of the proton at C-3 resulted in the enhancement of the signals at H-14α, H-19 and the indole N_a-H, indicating that the protons at H-3 and H-19 (see Figure S3) were located in the α position. These results were supported by examination of the 2D NOE spectrum for H-19 which exhibited cross peaks at H-3 (strong), 2H-21 (strong) and H-18 (strong), while irradiation of the proton at C-19 resulted in enhancement of the signals at H-3, 2H-21, H-14α and H-18 (see Figure S3).

Figure S4. 1D NOEs Observed after the Irradiation of the Protons at H-16 and H-15



The *R*-configuration at C-16 was confirmed by observation of NOEs between H-16 and H-14β (strong), H-15 (strong), H-6β (strong) and 2H-17 (weak). This was further supported by NOE signal enhancements between H-16 and H-14β, H-15, H-6β and 2H-17 (see Figure S4). The β-position of H-16 and *S*-configuration at H-15 were further determined by observation of the 2D NOEs between H-15 and H-14β (strong), H-20 (strong), H-16 (strong), H14α (weak), 2H-17 (slight) and 2H-21 (slight). In addition, irradiation of H-15 lead to enhancement of the signals at H-16, H-14β, 2H-21, H-20 and 2H-17 (see Figure S4).

The 2D NOE signals were observed between H-5 and 3H-18 (strong), 2H-17 (strong), H-20 (weak) and to H-6β (weak). The signal for H-6α fell on the contour lines. The strong NOE between H-5 and H-18 and a weak NOE between H-5 and H-20 indicated the proton at C-5 was located in the α position while the methyl group located at C-18 and the proton at C-20 were found to be β. The irradiation of the proton at C-5 enhanced the signals of 2H-17, 2H-6α,β, H-20 and 3H-18 (see Figure S5). The location of NOE signals between H-20 and 3H-18 (strong), H-15 (strong), 2H-17 (strong), H-5 (weak) and 2H-21 (weak), in addition to the irradiation of H-20 which enhanced signals at 3H-18, H-15, 2H-17, 2H-21, H-5 (weak) and H-19 (slight), confirmed β stereochemistry for H-20. The protons at C-21 exhibited cross peaks in the 2D NOE spectrum with H-19 (strong), H-14α (strong), H-20 (weak) and H-15 (weak), which indicated an α-position for the two protons of the -CH_2 group at C-21. In summary, the 2D COSY, NOESY and 1D NOE experiments support the structure is in complete agreement with that of natural 19(*S*),20(*R*)-dihydroperaksine **2**.[2]

Figure S5. 1D NOEs Observed after the Irradiation of the Protons at H-5 and H-20