**Supporting Information**

# Aldolase–catalyzed synthesis of conformationally constrained iminocyclitols: Preparation of polyhydroxylated benzopyrrolizidines and cyclohexapyrrolizidines

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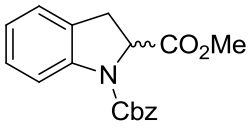
**Materials:** Dihydroxyacetone phosphate (DHAP) was obtained from the cyclic dimer precursor 2,5-diethoxy-*p*-dioxane-2,5-dimethanol-*O*-2[1]-*O*-5[1]-bisphosphate, which was synthesized in our lab using a procedure described by Jung et al.[1] with slight modifications. DHAP is released from the precursor by acidic hydrolysis at 65 ºC.[2] *N*-Cbz-amino aldehydes used in these studies were synthesized in our lab using procedures published in previous works.[3] L-Rhamnulose-1-phosphate aldolase [$Co^{II}$] (RhuA) (3.8 U $mg^{-1}$ of protein) (1U catalyzes the cleavage of 1 μmol of L-rhamnulose-1-phosphate per minute at 25 ºC and pH 7.5 (100 mM Tris·HCl + 150 mM KCl)),[4] L-fuculose-1-phosphate aldolase mutants FucA F131A (0.1 U $mg^{-1}$ of protein), and FucA F131A/F206A (<0.005 U $mg^{-1}$ of protein) were obtained as previously described (1 U cleaves 1 μmol of L-fuculose-1-phosphate per minute at 25 ºC and pH 7.5 (100 mM Tris·HCl + 150 mM KCl)).[3, 5] Acid phosphatase (PA, EC 3.1.3.2, 5.3 U $mg^{-1}$) was from Sigma-Aldrich. Water for analytical HPLC and for the preparation of buffers was obtained from an Arium® Pro Ultrapure Water Purification System (SartoriusStedim Biotech). All other solvents used were of analytical grade.

**General Methodology**. All reagents were used as received from commercial suppliers without further purification. Thin-layer chromatography (TLC) was performed on

Macherey–Nagel Polygram® SIL G/$UV_{254}$ precoated silica gel polyester plates. The products were visualized by exposure to UV light (254 nm), iodine vapours or charring with cerium molybdate stain [aqueous solution of phosphomolybdic acid (2 %), $CeSO_4 \cdot 4H_2O$ (1 %) and $H_2SO_4$ (6 %)]. Column chromatography was performed using 60 M (0.04–0.063 mm) silica gel from Macherey–Nagel. Melting points were determined with a Gallenkamp apparatus. IR spectra were recorded with a Nicolet Avatar 360 FTIR spectrophotometer; *ν*max is given for the main absorption bands. $^1$H- and $^{13}$C-NMR spectra were recorded on Bruker AV-400 (400.13 MHz for 1H and 100.62 MHz for $^{13}$C), Bruker Avance DRX-500 (500.13 MHz for $^1$H and 125.77 MHz for $^{13}$C, and equipped with a TXI cryoprobe) or Bruker Avance-III-600 (600.13 MHz for $^1$H and 150.92 MHz for $^{13}$C) spectrometers. Conventional 1D $^1$H and 1D $^{13}$C, selective 1D TOCSY and selective 1D NOESY and 2D COSY, 2D HSQC, 2D multiplicity-edited HSQC and 2D NOESY experiments were collected using standard Bruker software and acquired under routine conditions. The residual solvent signal was used as the internal standard; chemical shifts ($\delta$) are expressed in parts per million and coupling constants (*J*) in Hertz. High-resolution mass spectra were recorded with a Bruker Microtof-Q spectrometer.

**Synthesis of *N*-benzyloxycarbonyl methyl ester derivatives *rac*-7, (2*S**,3a*S**,7a*S**)-9 and (2*S**,3a*R**,7a*R**)-11.**

**Methyl *N*-(benzyloxycarbonyl)indoline-2-carboxylate (*rac*-7).**

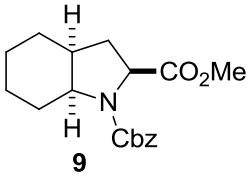



*rac*-**7**

Thionyl chloride (0.97 mL, 13.30 mmol) was added dropwise to an ice-cooled solution of indoline-2-carboxylic acid (*rac*-**6**) (735 mg, 4.51 mmol) in dry methanol (10 mL). The resulting solution was stirred at room temperature for 24 h. The solvent was evaporated and the residue was partitioned between saturated aqueous $NaHCO_3$ (20 mL) and $CH_2Cl_2$ (40 mL). The organic layer was separated and the aqueous phase was extracted with $CH_2Cl_2$ (2 x 40 mL). The combined organic extracts were dried over magnesium sulfate, filtered and evaporated to afford a colorless oil. To an ice-cooled solution of the above residue and *N*,*N*-diisopropylethylamine (1.37 mL, 7.88 mmol) in anhydrous dichloromethane (20 mL) benzyl chloroformate (1.13 mL, 7.90 mmol) was

added dropwise. Once the addition was completed the reaction mixture was stirred at room temperature for 24 h. Then the mixture was washed with saturated aqueous $NaHCO_3$ (10 mL), dried over magnesium sulfate, filtered and the solvent evaporated. The crude was purified by flash chromatography (10 % EtOAc/hexane) to afford the title compound as a white solid (859 mg, 2.76 mmol, 61 % yield). Melting point: 81-83 ºC (lit.[6]: 80.0-80.6 ºC. Spectroscopic data were in agreement with those previously reported.[7] IR (KBr): ν 1758, 1710 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz): δ (duplicated signals are observed for some protons; asterisks indicate those corresponding to the minor rotamer) 7.95 (d, 1H, *J* = 7.6 Hz); 7.57─7.10 (m, 7H); 6.99 (t, 1H, *J* = 7.2 Hz); 5.43─5.27 (m, 1H); 5.22─5.12 (m, 1H); 5.05─4.91 (m, 1H); 3.76* (s, 3H), 3.58 (s, 3H); 3.56─3.46 (m, 1H); 3.17 (d, 1H, *J* = 4.4 Hz), 3.13* (d, 1H, *J* = 4.4 Hz).$^{13}C$ NMR ($CDCl_3$, 100MHz): δ 171.86, 152.13, 142.08, 135.86, 135.86, 128.43, 128.14, 127.99, 127.90, 124.30, 122.96, 114.71, 67.14, 59.95, 52.26, 32.79. HRMS (ESI): calcd. for $C_{18}H_{18}NO_4$ $[M+H]^+$ 312.1230, found 312.1223.

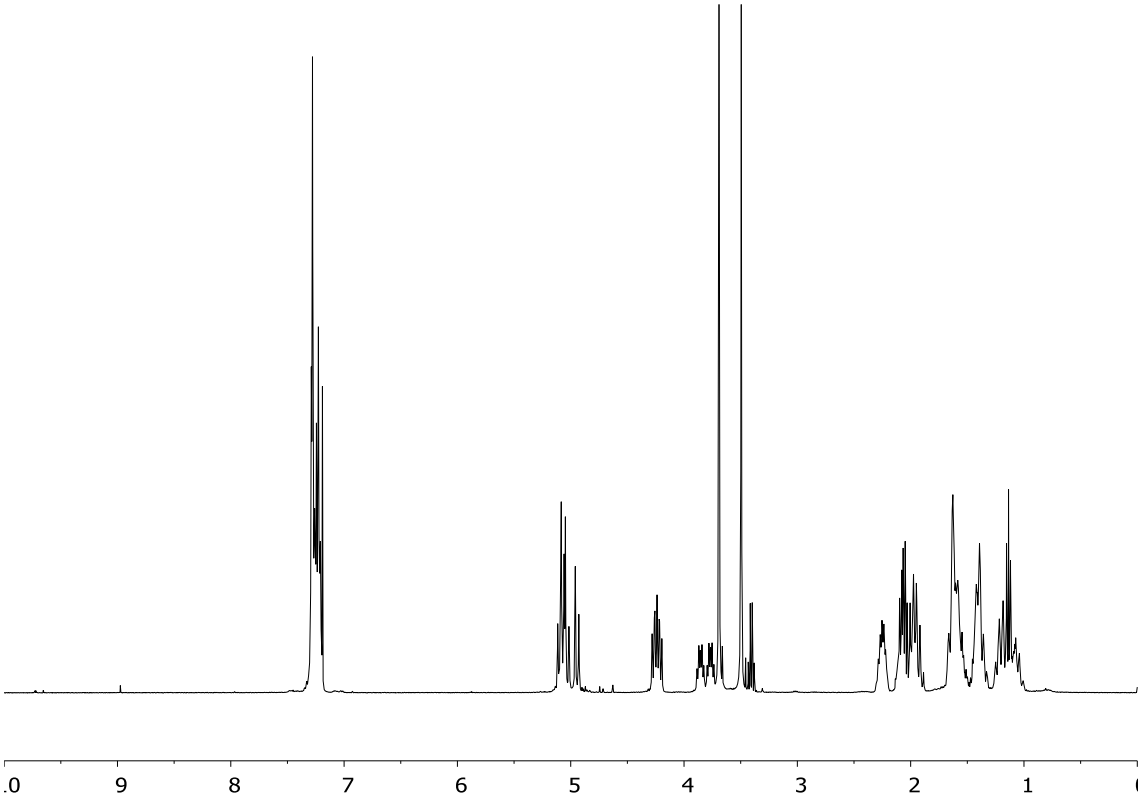
**Methyl (2*S**,3a*S**,7a*S**)-*N*-(benzyloxycarbonyl)octahydroindole-2-carboxylate (9)**



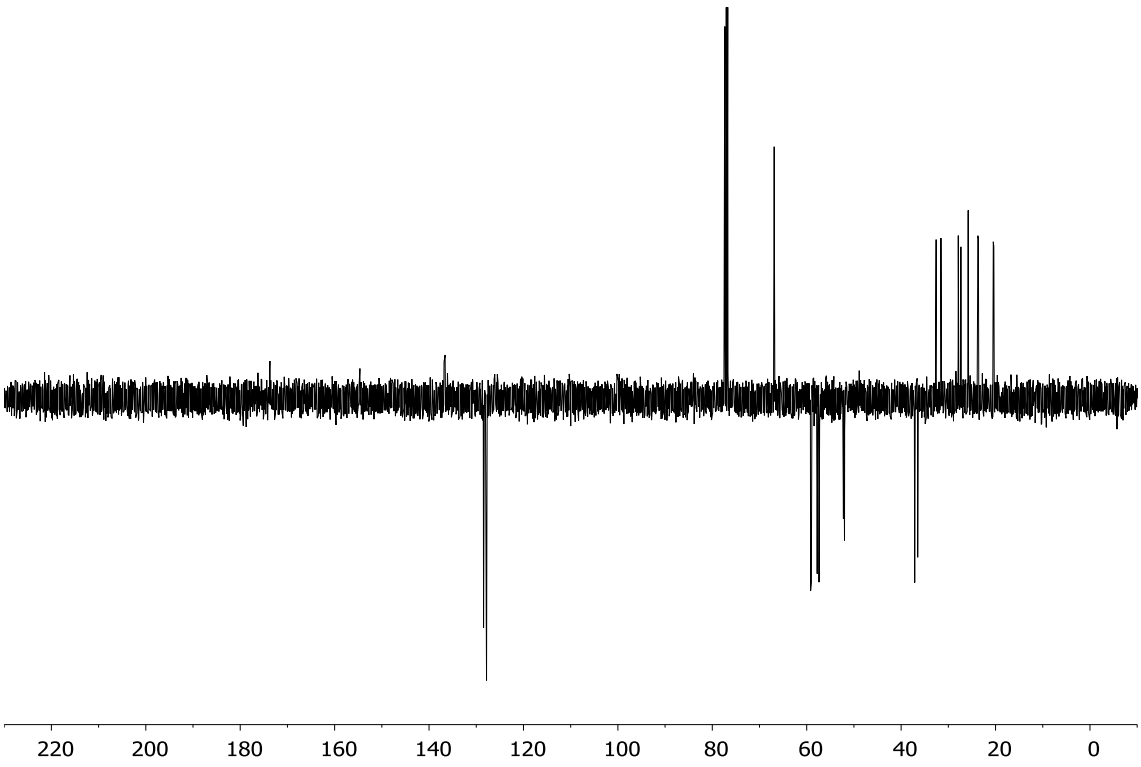

**9**

The title compound was prepared by the general procedure described above starting from (2*S**,3a*S**,7a*S**)-octahydroindole-2-carboxylic acid (**8**) (857 mg, 5.07 mmol) to afford **9** as a white solid (1.13 mg, 3.55 mmol, 70 % yield). Melting point: 50-52 ºC. IR (KBr): ν 1751, 1702 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz): δ (duplicated signals are observed for some protons; asterisks indicate those corresponding to the minor rotamer) 7.38─7.25 (m, 5H); 5.20─4.98 (m, 2H); 4.31 (m, 1H); 3.92* (m, 1H), 3.84 (m, 1H); 3.76 (s, 3H), 3.56* (s, 3H); 2.32 (m, 1H); 2.20─1.95 (m, 3H); 1.76─1.38 (m, 5H); 1.34─1.06 (m, 2H). $^{13}C$ NMR ($CDCl_3$, 100MHz): δ (duplicated signals are observed for most carbons) 173.67, 173.51; 154.71, 154.61; 136.79, 136.57; 128.42, 128.31; 127.86, 127.81; 127.79, 127.73; 66.85, 66.81; 59.13, 58.98; 57.74, 57.35; 52.18, 51.95; 37.08, 36.44; 32.54, 31.52; 27.85, 27.29; 25.75, 25.70; 23.69, 23.59; 20.43, 20.32. HRMS (ESI): calcd. for $C_{18}H_{24}NO_4$ $[M+H]^+$ 318.1700, found 318.1686.

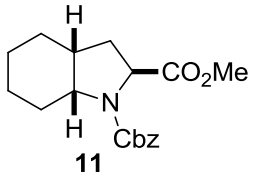
Copy $^{1}$H-NMR compound **9**




Copy $^{13}$C-APT compound **9**



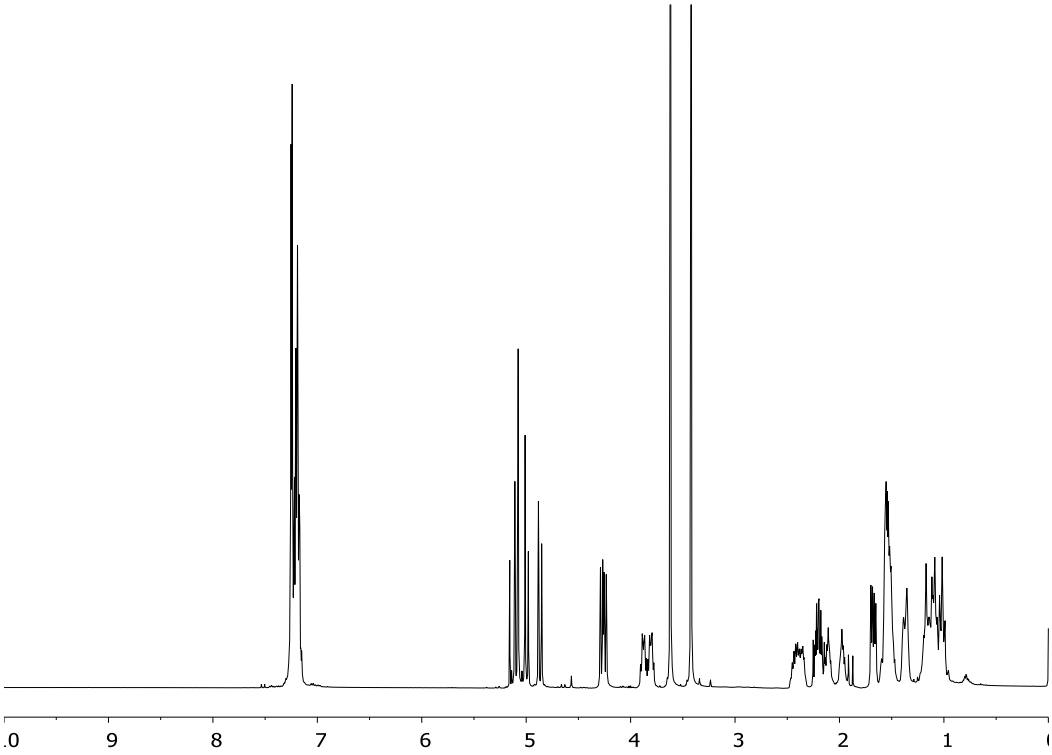
**Methyl (2*S**,3a*R**,7a*R**)-*N*-(benzyloxycarbonyl)octahydroindole-2-carboxylate (11)**



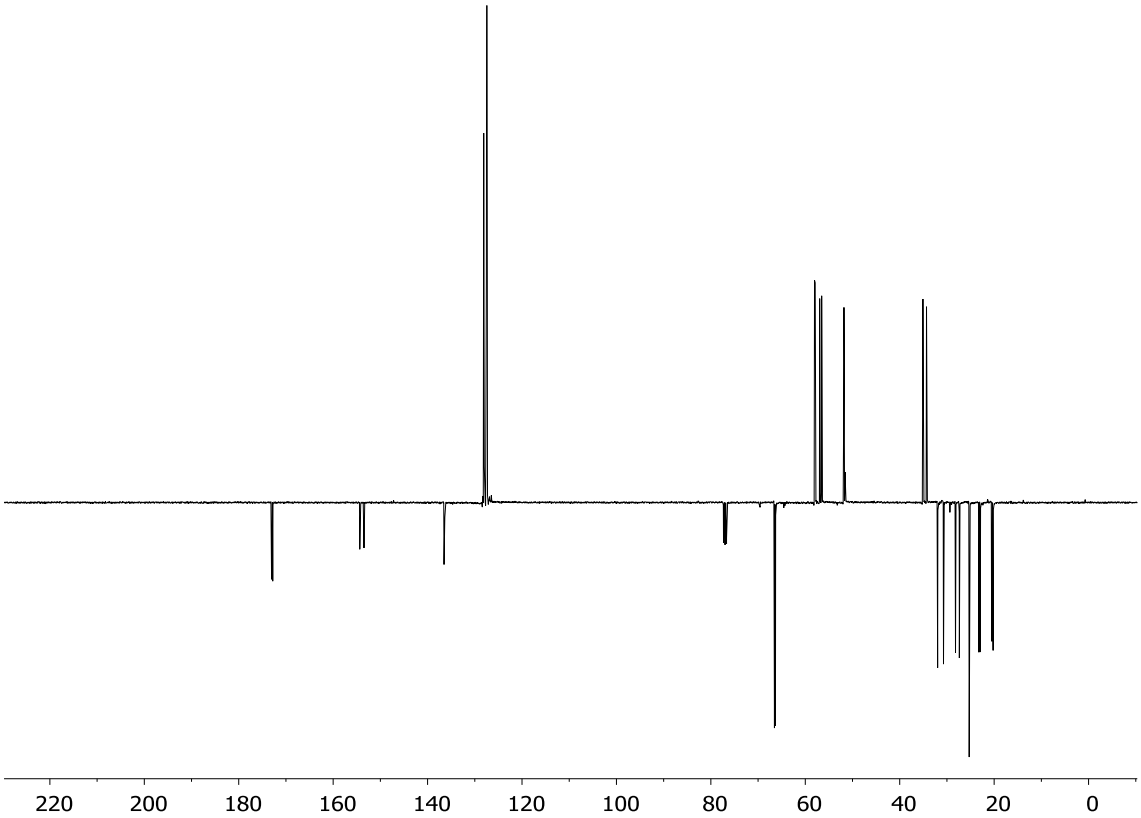

**11**

The title compound was prepared by the general procedure described above starting from (2*S**,3a*R**,7a*R**)-octahydroindole-2-carboxylic acid (**10**) (736 mg, 3.58 mmol) to afford **11** as a colorless oil (840 mg, 2.65 mmol, 74 % yield). IR (neat): ν 1763, 1714 $cm^{-1}$. $^{1}H$ NMR ($CDCl_3$, 400 MHz): δ (duplicated signals are observed for some protons; asterisks indicate those corresponding to the minor rotamer) 7.27─7.14 (m, 5H); 5.16─4.84 (m, 2H); 4.28 (dd, 1H, *J* = 9.6, 1.6 Hz), 4.24* (dd, 1H, *J* = 9.6, 1.6 Hz); 3.88* (m, 1H), 3.81 (m, 1H); 3.62 (s, 3H), 3.42* (s, 3H); 2.47─2.31 (m, 1H); 2.26─2.15 (m, 1H); 2.14─1.93 (m, 1H); 1.71─1.64 (m, 1H); 1.62─1.45 (m, 3H); 1.42─1.32 (m, 1H); 1.23─0.95 (m, 3H). $^{13}C$ NMR ($CDCl_3$, 100MHz): δ (duplicated signals are observed for most carbons) 173.05, 172.79; 154.36, 153.47; 136.52, 136.36; 128.11, 128.01; 127.55, 127.52; 127.45; 66.53, 66.32; 58.05, 57.90; 56.95, 56.53; 51.81, 51.60; 35.09, 34.33; 31.97, 30.73; 28.18, 27.37; 25.28; 23.23, 22.94; 20.53, 20.22. HRMS (ESI): calcd. for $C_{18}H_{24}NO_4$ $[M+H]^+$ 318.1700, found 318.1705.

Copy $^{1}$H-NMR compound **11**

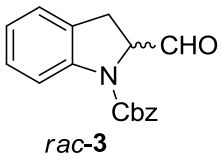



Copy $^{13}$C-APT compound **11**



**Synthesis of aldehyde derivatives (3-5).**

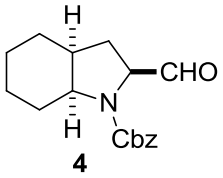
***N*-(benzyloxycarbonyl)indoline-2-carbaldehyde (*rac*-3)**




*rac*-**3**

To a solution of *rac*-**7** (100 mg, 0.32 mmol) in dry tetrahydrofurane (0.94 mL) and dry methanol (0.94 mL) sodium borohydride (61 mg, 1.60 mmol) and calcium chloride (107 mg, 0.96 mmol) were added. The reaction mixture was stirred at room temperature for 2 h. After quenching the reaction with a 5 % aqueous solution of citric acid (10 mL), it was extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with saturated aq $NaHCO_3$ (20 mL). The organic phase was dried, filtered, and concentrated. To a solution of the obtained residue in ethyl acetate (7 mL) 2-iodoxybenzoic acid (185 mg, 0.66 mmol) was added. The reaction mixture was stirred under reflux for 6 h. The resulting suspension was filtered. The organic phase was washed with saturated aq $NaHCO_3$ (20 mL), and with brine (20 mL). Then was dried, filtered, and concentrated to afford *rac*-**3** (85 mg, 0.30 mmol, 95 % yield). The compound was used immediately without further purification.

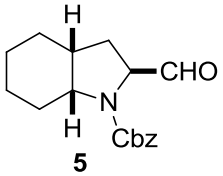
**Methyl (2*S**,3a*S**,7a*S**)-*N*-(benzyloxycarbonyl)octahydroindole-2-carbaldehyde (4)**




**4**

The title compound was prepared by the general procedure described above starting from (2*S**,3a*S**,7a*S**)-**9** (100 mg, 0.32 mmol) to afford (2*S**,3a*S**,7a*S**)-**4** as a colorless oil (60 mg, 0.21 mmol, 66 % yield).

**Methyl (2*S**,3a*R**,7a*R**)-*N*-(benzyloxycarbonyl)octahydroindole-2-carbaldehyde (5)**




**5**

The title compound was prepared by the general procedure described above starting from (2*S**,3a*R**,7a*R**)-**11** (100 mg, 0.32 mmol) to afford (2*S**,3a*R**,7a*R**)-**5** as a colorless oil (66 mg, 0.23 mmol, 73 % yield).

**HPLC analyses**

HPLC analyses were performed on a RP-HPLC cartridge, 250 x 4 mm filled with Lichrosphere 100, RP-18, 5 µm from Merck (Darmstadt, Germany).

Samples (80 µL of the reaction) were withdrawn from the aldol reaction, dissolved in methanol (515 µL) to stop the reaction and analyzed by HPLC. The solvent system used was solvent (A): $H_2O$ 0.1 % (v/v) trifluoroacetic acid (TFA) and solvent (B): AcCN/$H_2O$ 4:1 0.095 % (v/v) TFA, gradient elution from 10 % to 100 % B over 30 minutes, flow rate 1 mL $min^{-1}$, detection 215 nm.

**Enzymatic Aldol additions in analytical scale.**

Analytical scale reactions were conducted in Eppendorf tubes following the procedure described below.

**Enzymatic aldol additions in mixtures water/dimethylformamide 4:1 at 4 ºC. General Procedure.**

The aldehyde *rac*-**3**, **4** or **5** (0.03 mmol) was dissolved in dimethylformamide (100 µL). Then, a dihydroxyacetone phosphate solution (0.04 mmol, 336 µL of a 124 mM solution) at pH 7 and water (64 µL), were added dropwise while stirring at 4 ºC with a vortex mixer. Finally the aldolase, RhuA (0.6 mg of protein, 1.5 U), FucA F131A (0.6 mg of protein, 0.06 U)[3] or FucA F131A/F206A (0.6 mg, 0.003 U)[3], was added and mixed again. The test tubes were stirred (1000 rpm) at 4 ºC for 24 h. Then, the reaction was followed by HPLC as indicated above.

**Enzymatic aldol additions in mixtures water/dimethylformamide 4:1 at 25 ºC. General Procedure.**

The aldehyde *rac*-**3**, **4** or **5** (0.03 mmol) was dissolved in dimethylformamide (100 µL). Then, a dihydroxyacetone phosphate solution (0.04 mmol, 336 µL of a 124 mM solution) at pH 7 and water (64 µL), were added dropwise while stirring at 25 ºC with a vortex mixer. Finally, FucA F131A (0.6 mg of protein, 0.06 U) was added and mixed again. The test tubes were stirred (1000 rpm) at room temperature for 24 h. Then, the reaction was followed by HPLC as indicated above.

**Enzymatic aldol additions in mixtures sodium borate buffer/dimethylformamide 4:1 at 4 ºC. General Procedure.**

The aldehyde *rac*-**3**, **4** or **5** (0.03 mmol) was dissolved in dimethylformamide (100 µL). Then, a dihydroxyacetone phosphate solution (0.04 mmol, 336 µL of a 124 mM solution) at pH 7 and sodium borate buffer (117 µL of a 100 mM solution) at pH 7.5, were added dropwise while stirring at 25 ºC with a vortex mixer. Finally, FucA F131A (0.6 mg of protein, 0.06 U) was added and mixed again. The test tubes were stirred (1000 rpm) at 4 ºC for 24 h. Then, the reaction was followed by HPLC as indicated above.

**Enzymatic aldol additions in mixtures water/dimethylformamide 4:1 at 4 ºC. Effect of enzyme content. General Procedure.**

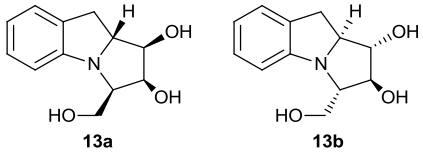
The aldehyde *rac*-**3**, **4** or **5** (0.03 mmol) was dissolved in dimethylformamide (100 µL). Then, a dihydroxyacetone phosphate solution (0.04 mmol, 336 µL of a 124 mM solution) at pH 7 and water (64 µL), were added dropwise while stirring at 25 ºC with a vortex mixer. Finally, FucA F131A (1.2 mg of protein, 0.12 U) was added and mixed again. The test tubes were stirred (1000 rpm) at 4 ºC for 24 h. Then, the reaction was followed by HPLC as indicated above.

It was found that increasing the amount of enzyme the yields were not improved. On the contrary, the results (not shown) indicate that the use of higher amount of enzyme was detrimental, since a decrease in the conversion was observed. This is likely due to DHAP degradation and the ensuing retroaldol reaction to re-establish the equilibrium position decreasing the conversion to aldol adduct and reducing the yield. This was observed before in other reactions.[8] Moreover, it must be consider also that the DHAP degradation increased with the amount of FucA.[9]

**Enzymatic aldol additions at preparative scale.**

Preparative aldol enzymatic-catalyzed reactions were conducted in 100 mL Erlenmeyer flasks following the procedure described below.

**Synthesis of (1*R*,2*S*,3*R*,9a*R*)- (13a) and (1*S*,2*S*,3*S*,9a*S*)-3-(hydroxymethyl)-2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-a]indole-1,2-diol (13b).**




**13a** **13b**

Aldehyde *rac*-**3** (200 mg, 0.69 mmol) was dissolved in dimethylformamide (2.35 mL) and cooled to 0 ºC. Then, a dihydroxyacetone phosphate solution (0.92 mmol, 8 mL of a 115 mM solution, at pH 7, freshly prepared) and sodium borate buffer (2.5 mL of a 100 mM solution, at pH 7.5) were added under vigorous agitation. Then, FucA F131A (15.4 mg of protein, 1.51 U) was added and mixed again. The reaction was shaken (1000 rpm) at 4 ºC for 24 h. Then, methanol (120 mL) was added, and the denatured enzyme filtered on Celite. The methanol of the filtrate was evaporated and the excess of aldehyde was removed by extractions with diethylether (3 x 10 mL). To the aqueous solution of the product obtained (12 mL), citrate buffer 2 M, pH 4.5 (3 mL) was added and treated with acid phosphatase (12 mg) for 12 h. Then, methanol (120 mL) was added, and the denatured enzyme filtered on Celite. The methanol of the filtrate was then evaporated and the unphosphorylated product was extracted with ethyl acetate (3x 20 mL). Then, the combined organic phases were dried over sodium sulfate, filtered and the solvent evaporated. The crude was purified by flash chromatography (silica: EtOAc/hexane 1:1) to afford a mixture of **12a** and **12b** as a white solid (46 mg, 0.12 mmol, 18 % overall yield).

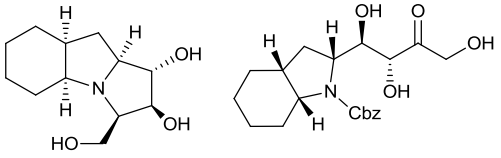
To a solution of **12a** and **12b** mixture in methanol (24 mL) palladium on charcoal (46 mg) was added. The reaction mixture was stirred under hydrogen gas (50 psi) overnight at room temperature. After removal of the catalyst by filtration through Celite, the crude was purified by flash chromatography (silica; EtOAc) to afford **13a** (9 mg, 0.04 mmol, 12 % overall yield) and; **13b** (8 mg, 0.04 mmol, 11 % overall yield) as brown solids.

**13a:** $^{1}$H NMR (400 MHz, MeOD) δ 7.06–7.04 (m, 2H), 6.75–6.80 (m, 2H), 4.21 (t, *J* = 4.6 Hz, 1H), 3.96 (m, 2H), 3.96 (dd, *J* = 11.2, 7.0 Hz, 1H), 3.49 (dd, *J* = 9.5, 4.4 Hz, 1H), 3.43 (m, 1H), 3.13 (m, 2H). $^{13}$C NMR (101 MHz, MeOD) δ 128.6, 125.9, 121.4,

112.1, 76.9, 74.5, 71.5, 67.5, 63.4, 32.4. HRMS (ESI): calcd. for $C_{12}H_{15}NNaO_3$ $[M+Na]^+$ 249.0451, found 249.0441.

**13b:** $^1$H NMR (400 MHz, MeOD) δ 7.12–7.08 (m, 2H), 6.79 (m, 2H), 3.93 (dd, *J* = 8.1, 7.2 Hz, 1H), 3.88 (dd, *J* = 8.1, 7.2 Hz, 1H), 3.73 (m, 1H), 3.71 (dd, *J* = 11.2, 3.6 Hz, 1H), 3.52 (dd, *J* = 9.5, 8.0 Hz, 1H), 3.05 (m, 1H), 3.03 (m, 2H). $^{13}$C NMR (101 MHz, MeOD) δ 128.6, 125.8, 121.0, 111.6, 80.4, 79.9, 73.2, 67.9, 65.1, 32.8. HRMS (ESI): calcd. for $C_{12}H_{16}NO_3$ $[M+H]^+$ 222.1130, found 222.1125.

**Synthesis of (1*S*,2*S*,3*R*,4a*S*,8a*S*,9a*S*)-3-(hydroxymethyl)decahydro-1*H*-pyrrolo[1,2-a]indole-1,2-diol (15) and (2*R*,3a*R*,7a*R*)-*N*-(benzyloxycarbonyl)-2-[(1'*R*,2'*R*)-1,2,4-trihydroxy-3-oxobutyl]octahydroindole (14b).**




Aldehyde (2*S**,3a*S**,7a*S**)-**4** (300 mg, 1.04 mmol) was dissolved in dimethylformamide (3.5 mL) and cooled to 0 ºC. Then, a dihydroxyacetone phosphate solution (1.14 mmol, 12.7 mL of a 90 mM solution, at pH 7, freshly prepared) and sodium borate buffer (4.2 mL of a 100 mM solution, at pH 7.5) were added under vigorous agitation. Then, FucA F131A (24.5 mg of protein, 2.40 U) was added and mixed again. The reaction was shaken (1000 rpm) at 4 ºC for 24 h. Then, methanol (204 mL) was added, and the denatured enzyme filtered on Celite. The methanol of the filtrate was evaporated under vacuum and the excess of aldehyde was removed by extractions with diethylether (3 x 15 mL). To the aqueous solution of the product obtained (20 mL), citrate buffer 2 M, pH 4.5 (5 mL) was added and treated with acid phosphatase (12 mg) for 12 h. Then, methanol (200 mL) was added, and the denatured enzyme filtered on Celite. The methanol of the filtrate was evaporated and the unphosphorylated product was removed by extractions with ethyl acetate (3x 30 mL). Then, the combined organic phases were dried over sodium sulfate, filtered and the solvent evaporated. The crude was purified by flash chromatography (silica; EtOAc/hexane 1:1) to afford **14a** (91 mg, 0.24 mmol, 46 % overall yield) and **14b** (105 mg, 0.28 mmol, 54 % overall yield) as a white solids.

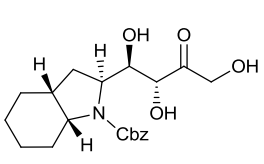
To a solution of **14a** in methanol (48 mL) palladium on charcoal (91 mg) was added. The reaction mixture was stirred under hydrogen gas (50 psi) overnight at room temperature. After removal of the catalyst by filtration through Celite, the crude was

purified by flash chromatography (eluent: dichlorometane/methanol/acetic acid 85:10:5) to afford **15** as a brown solid (41 mg, 0.18 mmol, 35 % overall yield).

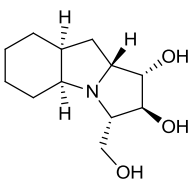
**14b**:(Two conformations due to the Cbz rotamers) **Major**: $^{1}$H NMR (600 MHz, MeOD, 273 K) δ 7.29–7.42 (m, 5H), 5.05–5.14 (m, 2H), 4.60 (d, *J* = 19.3 Hz, 1H), 4.44 (dd, *J* = 1.9, 8.7 Hz, 1H), 4.43 (d, *J* = 19.0 Hz, 1H), 4.07 (m, 1H), 4.01 (d, *J* = 8.7 Hz, 1H), 3.85 (m, 1H), 2.25 (m, 1H), 2.24 (m, 1H), 1.84 (m, 1H), 1.79 (m, 1H), 1.74 (m, 1H), 1.69 (m, 1H),1.67 (m, 1H), 1.40 (m, 1H),1.57 (m, 1H), 1.18 (m, 1H). $^{13}$C NMR (151 MHz, MeOD) δ 212.4, 156.8, 138.4, 129.7–129.0, 76.8, 69.3, 67.8, 61.9, 59.4, 37.6, 29.1, 27.3, 25.2, 21.8. **Minor**: $^{1}$H NMR (600 MHz, MeOD, 273 K) δ 7.29–7.42 (m, 5H), 5.17–5.10 (m, 2H), 4.53 (d, *J* = 19.3 Hz, 1H), 4.35 (dd, *J* = 1.9, 8.7 Hz, 1H), 4.33 (d, *J* = 19.0 Hz, 1H), 4.13 (m, 1H), 3.96 (d, *J* = 8.7 Hz, 1H), 3.84 (m, 1H), 2.25 (m, 1H), 2.24 (m, 1H), 1.84 (m, 1H), 1.79 (m, 1H), 1.74 (m, 1H), 1.69 (m, 1H),1.67 (m, 1H), 1.40 (m, 1H),1.57 (m, 1H), 1.18 (m, 1H). $^{13}$C NMR (151 MHz, MeOD) δ 212.3, 157.0, 138.2, 129.7–129.0, 76.7, 70.2, 67.9, 67.6, 61.9, 61.5, 59.9, 37.3, 28.7, 27.2, 27.2(2), 25.3, 21.8. HRMS (ESI): calcd. for $C_{20}H_{28}NO_6$ $[M+H]^+$ 378.1917, found 378.1915. HRMS (ESI): calcd. for $C_{20}H_{28}NO_6Na$ $[M+Na]^+$ 400.1736, found 400.1734.

**15:**$^{1}$H NMR (600 MHz, MeOD) δ 4.28 (dd, *J* = 8.3, 6.1 Hz, 1H), 3.93 (dd, *J* = 8.3, 4.3 Hz, 1H), 3.82 (m, 1H), 3.77 (t, *J* = 8.0 Hz, 1H), 3.64 (t, *J* = 7.4 Hz, 1H), 3.46 (q, *J* = 7.6 Hz, 1H), 2.20 (dt, *J* = 12.9, 6.7, 6.7 Hz, 1H), 2.09 (m, 1H), 2.02 (m, 1H), 2.00 (m, 1H), 1.79 (m, 3H), 1.66 (m, 2H), 1.41 (m, 1H), 1.23 (m, 1H), 1.22 (m, 1H). $^{13}$C $^{13}$C NMR (101 MHz, MeOD) δ 82.7, 79.5, 68.4, 66.3, 65.5, 47.2, 45.7, 37.2, 31.8, 31.5, 25.11. HRMS (ESI): calcd. for $C_{12}H_{21}NNaO_3$ $[M+Na]^+$ 250.1419, found 250.1411. HRMS (ESI): calcd. for $C_{12}H_{22}NO_3$ $[M+H]^+$ 250.1600, found 250.1597.

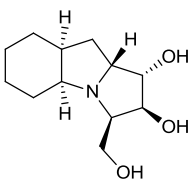
**Synthesis of (2*S*,3a*R*,7a*R*)-*N*-(benzyloxycarbonyl)-2-[(1'*R*,2'*R*)-1,2,4-trihydroxy-3-oxobutyl]octahydroindole (16), (1*S*,2*S*,3*S*,4a*S*,8a*S*,9a*R*)- (18a), (1*S*,2*S*,3*R*,4a*S*,8a*S*,9a*R*)- (18b), (1*R*,2*S*,3*R*,4a*S*,8a*S*,9a*R*)- (18c) and (1*R*,2*S*,3*S*,4a*S*,8a*S*,9a*R*)-3-(hydroxymethyl)decahydro-1*H*-pyrrolo[1,2-a]indole-1,2-diol (18d).**



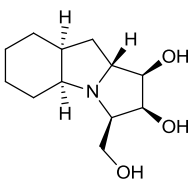

16



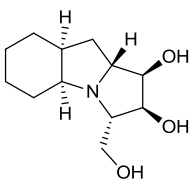

18a




18b




18c




18d

Aldehyde (2*S**,3a*R**,7a*R**)-**5** (296 mg, 1.03 mmol) was dissolved in dimethylformamide (3.44 mL) and cooled to 0 ºC. Then, a dihydroxyacetone phosphate solution (1.14 mmol, 12.7 mL of a 90 mM solution, at pH 7, freshly prepared) and sodium borate buffer (4.2 mL of a 100 mM solution, at pH 7.5) were added under vigorous agitation. Then, FucA F131A (24 mg of protein, 2.35 U) was added and mixed again. The reaction was shaken (1000 rpm) at 4 ºC for 24 h. Then, methanol (204 mL) was added, and the denatured enzyme filtered on Celite. Once the methanol of the filtrate was evaporated, the excess of aldehyde was removed by extractions with diethylether (3 x 15 mL). To the aqueous solution of the product obtained (20 mL), citrate buffer 2 M, pH 4.5 (5 mL) was added and treated with acid phosphatase (12 mg) for 12 h. Then, methanol (200 mL) was added, and the denatured enzyme filtered on Celite. The methanol of the filtrate was evaporated and the unphosphorylated product was removed by extractions with ethyl acetate (3x 30 mL). Then, the combined organic phases were dried over sodium sulfate, filtered and the solvent evaporated. The crude was purified by flash chromatography (silica; EtOAc/hexane 1:1) to afford **16** (31 mg, 0.08 mmol, 16 % overall yield) and **17a** and **17b** as a 70:30 mixture (38 mg, 0.10 mmol, 19 % overall yield) as a white solids.

To a solution of the **17a** and **17b** mixture in methanol (20 mL) palladium on charcoal (38 mg) was added. The reaction mixture was stirred under hydrogen gas (50 psi) overnight at room temperature. After removal of the catalyst by filtration through Celite, the crude was purified by flash chromatography (silica; dichlorometane/methanol/acetic acid 85:10:5) to afford **18a** (10 mg, 0.04 mmol, 9 % overall yield) and a mixture of **18a**, **18b**, **18c** and **18d** in a 1:4:3:1 ratio (8 mg, 0.04 mmol, 7 % overall yield).

**16**:(Two conformations due to the Cbz rotamers) **Major:** $^{1}$H NMR (600 MHz, MeOD) δ 7.42–7.28 (m, 5H), 5.14–5.05 (m, 2H), 4.55 (d, *J* = 19.1 Hz, 1H), 4.39 (d, *J* = 19.0 Hz, 1H), 4.35 (dd, *J* = 8.0, 1.8 Hz, 1H), 4.09 (dt, *J* = 9.5, 1.3, 1.3 Hz, 1H), 3.77 (m, 1H), 2.59 (m, 1H), 2.05 (m, 1H), 2.02 (m, 1H), 1.91 (m, 1H), 1.71 (m, 1H), 1.62 (m, 1H), 1.44 (m, 1H), 1.37 (m, 1H), 1.30 (m, 1H), 1.13 (m, 1H). $^{13}$C NMR (151 MHz, MeOD) δ 211.2, 155.3, 136.7, 129.7–129.1, 77.2, 72.2, 68.0, 67.9, 60.2, 59.2, 37.5, 28.9, 28.8, 27.2, 25.0, 21.6. **Minor**: $^{1}$H NMR (600 MHz, MeOD) δ $^{1}$H NMR (600 MHz, MeOD) δ 7.42–7.28 (m, 5H), 5.17–5.10 (m, 2H), 4.48 (d, *J* = 19.1 Hz, 1H), 4.28 (d, *J* = 19.1 Hz, 1H), 4.24 (dd, *J* = 8.5, 1.6 Hz, 1H), 4.15 (dt, *J* = 9.4, 1.3, 1.3 Hz, 1H), 4.01 (d, *J* = 8.5 Hz, 1H), 3.77 (m, 1H), 2.59 (m, 1H), 2.05 (m, 1H), 2.02 (m, 1H), 1.91 (m, 1H), 1.71 (m,

1H), 1.62 (m, 1H), 1.44 (m, 1H), 1.37 (m, 1H), 1.30 (m, 1H), 1.13 (m, 1H). $^{13}$C NMR (151 MHz, MeOD) δ 212.7, 156.8, 138.4, 129.7–129.1, 77.1, 73.3, 67.9, 67.7, 59.6, 59.5, 36.9, 28.5, 28.4, 27.6, 24.8, 21.9. HRMS (ESI): calcd. for $C_{20}H_{28}NO_6$ $[M+H]^+$ 378.1917, found 378.1918. HRMS (ESI): calcd. for $C_{20}H_{28}NO_6Na$ $[M+Na]^+$ 400.1736, found 400.1737.

**18a:** $^1$H NMR (500 MHz, $CD_3OD$) δ 4.45 (dt, *J* = 8.7, 6.7 Hz, 1H), 4.06 (dd, *J* = 7.2, 5.6 Hz, 1H), 4.00–3.97 (m, 3H), 3.92 (m, 1H), 3.53 (m, 1H), 2.45 (m, 1H), 2.26 (m, 1H), 1.93 (m, 1H), 1.91 (m, 1H), 1.86 (m, 1H), 1.85 (m, 1H), 1.66 (m, 1H), 1.60 (m, 1H), 1.50 (m, 1H),1.47 (m, 1H), 1.44 (m, 1H). $^{13}$C NMR (101 MHz, $CD_3OD$) δ 77.6, 75.3, 70.5, 69.6, 63.7, 58.2, 40.2, 31.7, 26.8, 26.7, 22.7, 22.6. HRMS (ESI): calcd. for $C_{12}H_{22}NO_3$ $[M+H]^+$ 228.1600, found 228.1598.

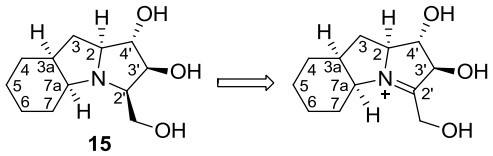
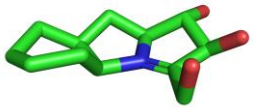
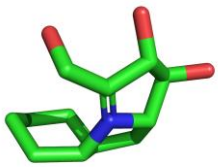
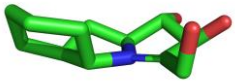
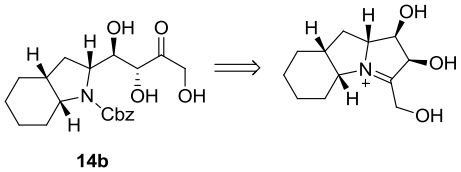
**18b**: $^1$H NMR (500 MHz, $CD_3OD$) δ 4.51 (m, 1H), 4.19 (m, 1H), 4.10 (m, 1H), 4.02 (m, 2H), 3.73 (dt, *J* = 11.6, 6.0, 6.0 Hz, 1H), 3.56 (ddd, *J* = 9.0, 6.3, 2.8 Hz, 1H), 2.70 (m, 1H), 2.11 (m, 2H), 1.96 (m, 1H), 1.77 (m, 1H), 1.68 (m, 1H), 1.58 (m, 1H), 1.76 (m, 1H), 1.50 (m, 1H), 1.46 (m, 1H), 1.28 (m, 1H). $^{13}$C NMR (101 MHz, $CD_3OD$) δ 78.1, 76.1, 71.4, 71.1, 67.0, 59.1, 37.7, 26.3, 26.2, 25.6, 23.8, 20.7. HRMS (ESI): calcd. for $C_{12}H_{22}NO_3$ $[M+H]^+$ 228.1600, found 228.1600.

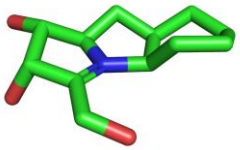
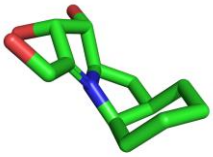
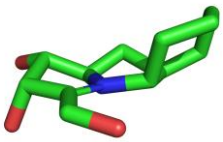
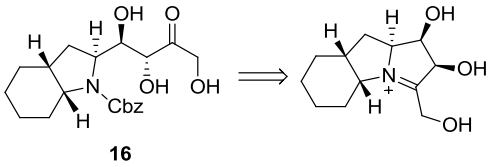
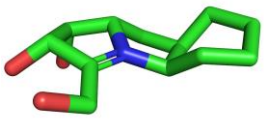
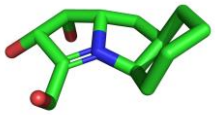
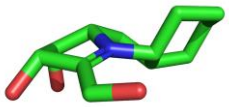
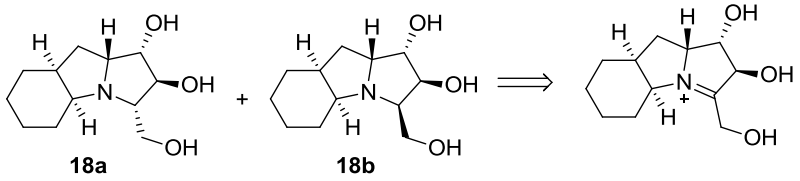
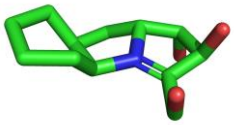
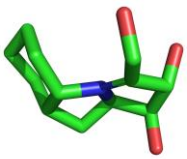
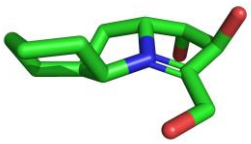
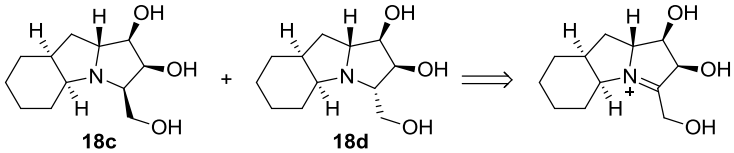
**18c:** $^1$H NMR (500 MHz, $CD_3OD$) δ 4.03 (t, *J* = 9.3 Hz, 1H), 3.94 (m, 1H), 3.92 (m, 1H), 3.87 (m, 1H), 3.85 (m, 1H), 3.72 (m, 1H), 3.37 (m, 1H), 2.66 (m, 1H), 2.28 (m, 1H), 2.04 (m, 1H), 1.90 (m, 1H), 1.73 (m, 1H), 1.71 (m, 1H), 1.68 (m, 1H), 1.37 (m, 1H). $^{13}$C NMR (101 MHz, $CD_3OD$) δ 80.3, 76.4, 73.6, 71.0, 69.5, 59.3, 36.5, 31.9, 25.4, 23.9, 22.8, 21.4. **18d:** $^1$H NMR (500 MHz, $CD_3OD$) δ 4.24 (m, 1H), 4.19 (m, 1H), 4.18 (m, 1H),4.08 (m, 1H), 4.06 (m, 1H), 4.02 (m, 1H), 3.96 (m, 1H), 2.49 (m, 1H), 2.33 (m, 1H), 2.21 (m, 1H), 2.03 (m, 1H),1.79 (m, 1H), 1.70 (m, 1H), 1.56 (m, 1H), 1.31 (m, 1H). $^{13}$C NMR (101 MHz, $CD_3OD$) δ 79.2, 79.0, 77.3, 69.8, 64.5, 56.5, 39.9, 34.3, 26.7, 25.4, 23.7, 20.2. HRMS of the mixture (ESI): calcd. for $C_{12}H_{22}NO_3$ $[M+H]^+$ 228.1600, found 228.1599.

*In silico* conformational analysis.

An *in silico* conformational analysis of the iminium cation intermediates before the reductive amination from compounds a) **14a**, b) **17a**, c) **17b**, d) **14b** and e) **16** was carried out by using density functional theory (DFT) calculations (Spartan'10; Wavefunction, Inc.; Irvine, CA, 2010).[10]. For this purpose, we initially consider three possibly conformers for the *cis* fused six-five membered rings: *cis*-$^{7}B_{4}$-$E_{3a}$, *cis*-$^{7}C_{4}$-$E_{3a}$ and *cis*-$^{7}C_{4}$-$E_{7a}$ (Table 1). Then, the structures were minimized at the B3LYP/6-31G* level.

**Table 1S**. Minimum energy of the three possibly conformers for the *cis* fused six-five membered rings: *cis*-$^{7}B_{4}$-$E_{3a}$, *cis*-$^{7}C_{4}$-$E_{3a}$ and *cis*-$^{7}C_{4}$-$E_{7a}$. The conformational analysis of the compounds which differed mainly in the orientation of the fused six-five membered rings, with a *cis* ring fusion and a $^{7}B_{4}$-$E_{3a}$ boat or $^{7}C_{4}$-$E_{3a}$ and $^{7}C_{4}$-$E_{7a}$ chair structure. Among these, the most stable stereoisomer adopted a *cis*-$^{7}C_{4}$-$E_{7a}$ disposition in all cases.

| | | | |
|---|---|---|---|
| a) |  **15** | | |
| Conformer |  *cis*-$^{7}B_{4}$-$E_{3a}$ |  *cis*-$^{7}C_{4}$-$E_{3a}$ |  *cis*-$^{7}C_{4}$-$E_{7a}$ |
| Energy (au) | –749.485358 | –749.486136 | –749.489712 |
| Kcal mol$^{-1}$ | + 2.73 | + 2.24 | 0 |
| b) |  **14b** | | |

| Conformer |  *cis*-$^{7}B_{4}$-$E_{3a}$ |  *cis*-$^{7}C_{4}$-$E_{3a}$ |  *cis*-$^{7}C_{4}$-$E_{7a}$ |
|---|---|---|---|
| Energy (au) | –749.484158 | –749.484902 | –749.488686 |
| Kcal mol$^{-1}$ | + 2.84 | + 2.37 | 0 |
| c) |  **16** | | |
| Conformer |  *cis*-$^{7}B_{4}$-$E_{3a}$ |  *cis*-$^{7}C_{4}$-$E_{3a}$ |  *cis*-$^{7}C_{4}$-$E_{7a}$ |
| Energy (au) | –749.490284 | –749.488751 | –749.496475 |
| Kcal mol$^{-1}$ | + 3.88 | + 4.85 | 0 |
| d) |  **18a** **18b** | | |
| Conformer |  *cis*-$^{7}B_{4}$-$E_{3a}$ |  *cis*-$^{7}C_{4}$-$E_{3a}$ |  *cis*-$^{7}C_{4}$-$E_{7a}$ |
| Energy (au) | –749.482348 | –749.483718 | –749.485479 |
| Kcal mol$^{-1}$ | + 1.96 | + 1.11 | 0 |
| e) |  **18c** **18d** | | |

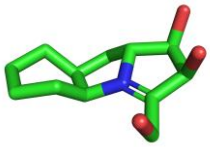
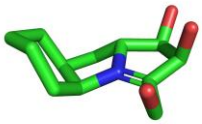
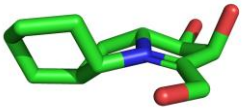
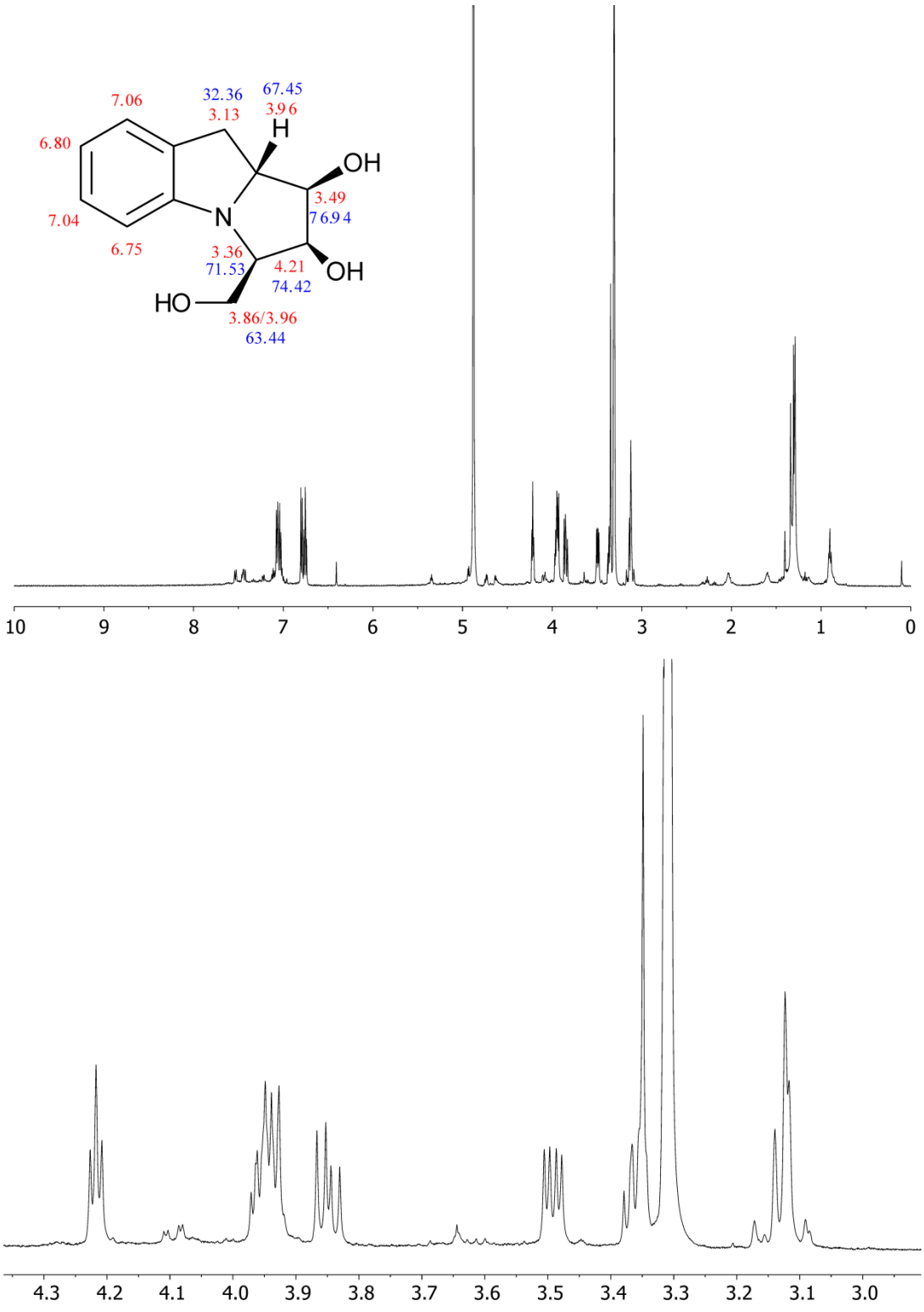
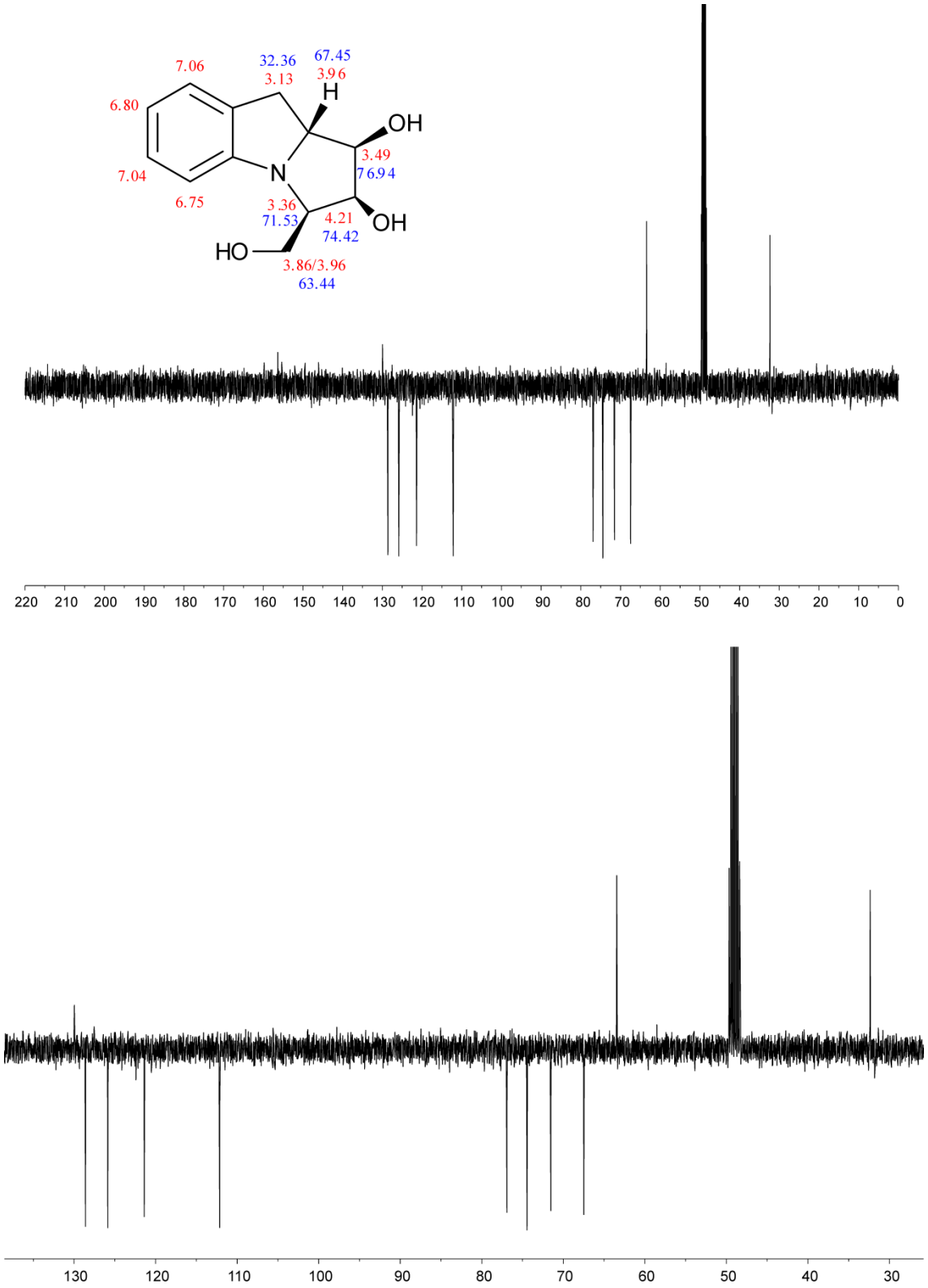
| Conformer |  *cis*-$^{7}B_{4}$-$E_{3a}$ |  *cis*-$^{7}C_{4}$-$E_{3a}$ |  *cis*-$^{7}C_{4}$-$E_{7a}$ |
|---|---|---|---|
| Energy (au) | –749.483093 | –749.483895 | –749.489727 |
| Kcal mol$^{-1}$ | + 4.16 | + 3.66 | 0 |

**Figure 1S**. NMR spectra ($CD_3OD$) of **13a**: a) $^{1}H$; b) $^{13}C$-DEPT; c) 2D $^{1}H$-$^{1}H$ COSY; d) 2D $^{1}H$-$^{13}C$ Multiplicity-edited HSQC and e) 2D $^{1}H$-$^{1}H$ NOESY.

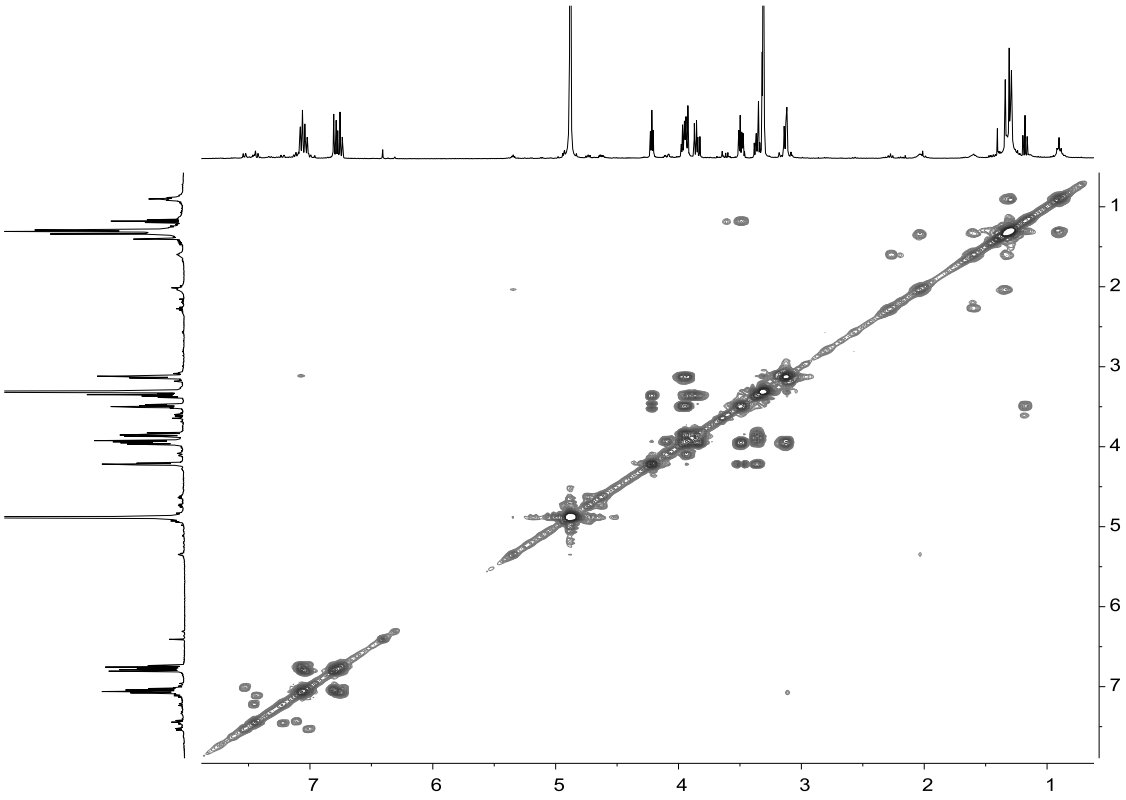
a)



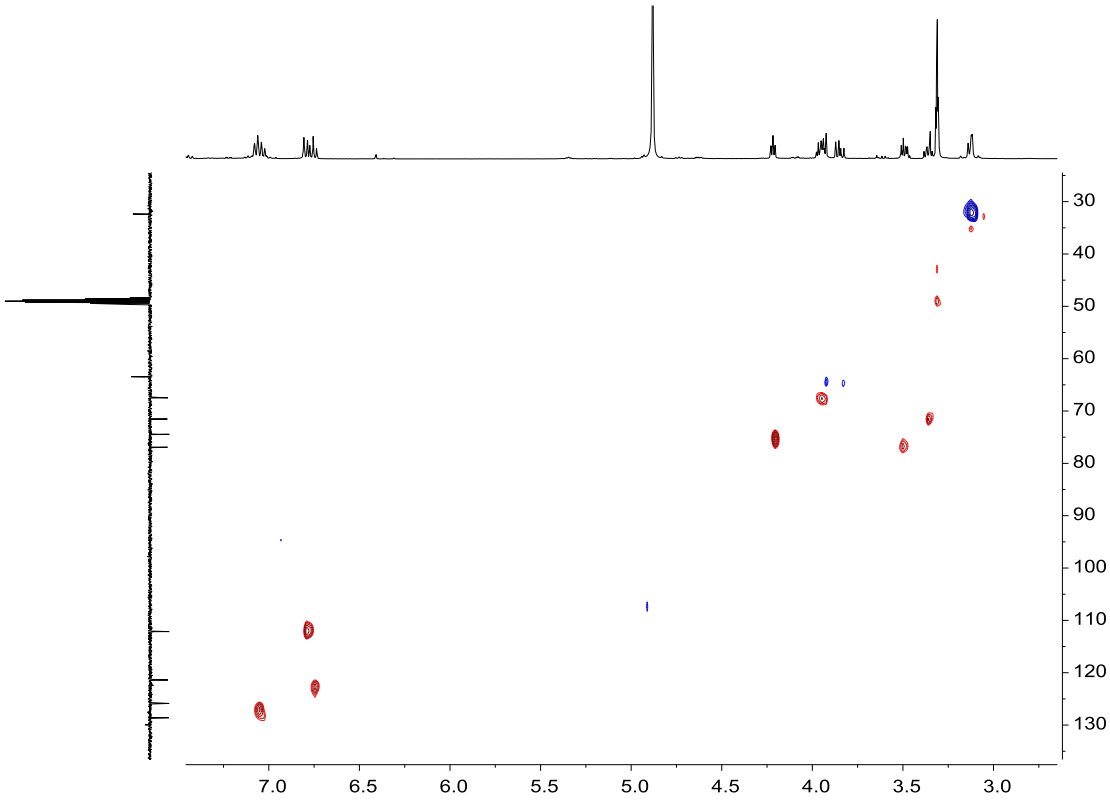
b)


7.06
32.36
3.13
67.45
3.96
H
6.80
OH
3.49
76.94
7.04
N
6.75
3.36
71.53
4.21
74.42
OH
HO
3.86/3.96
63.44
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
130 120 110 100 90 80 70 60 50 40 30

c)


1
2
3
4
5
6
7
7
6
5
4
3
2
1

d)


30
40
50
60
70
80
90
100
110
120
130
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0

e)

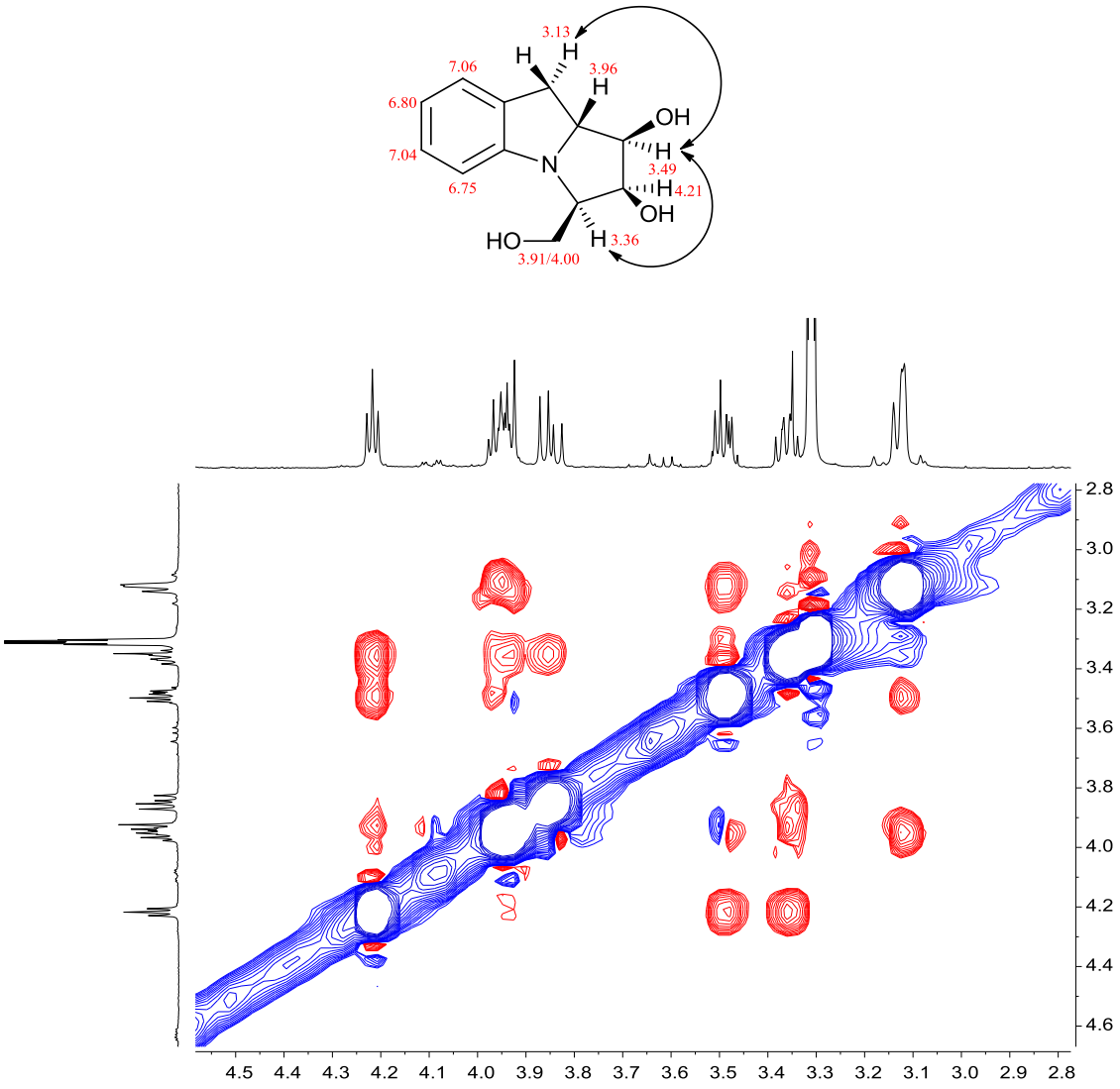
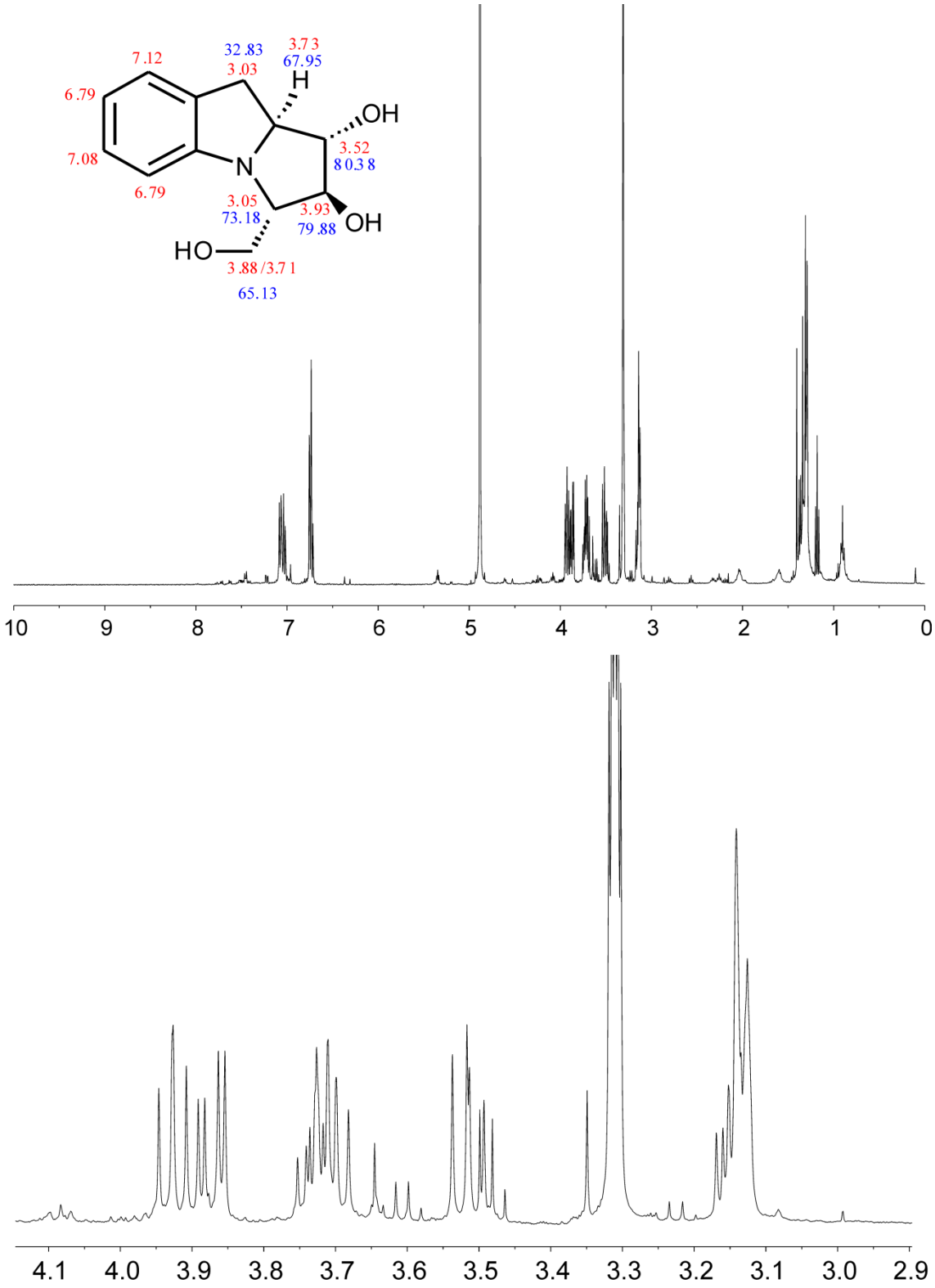
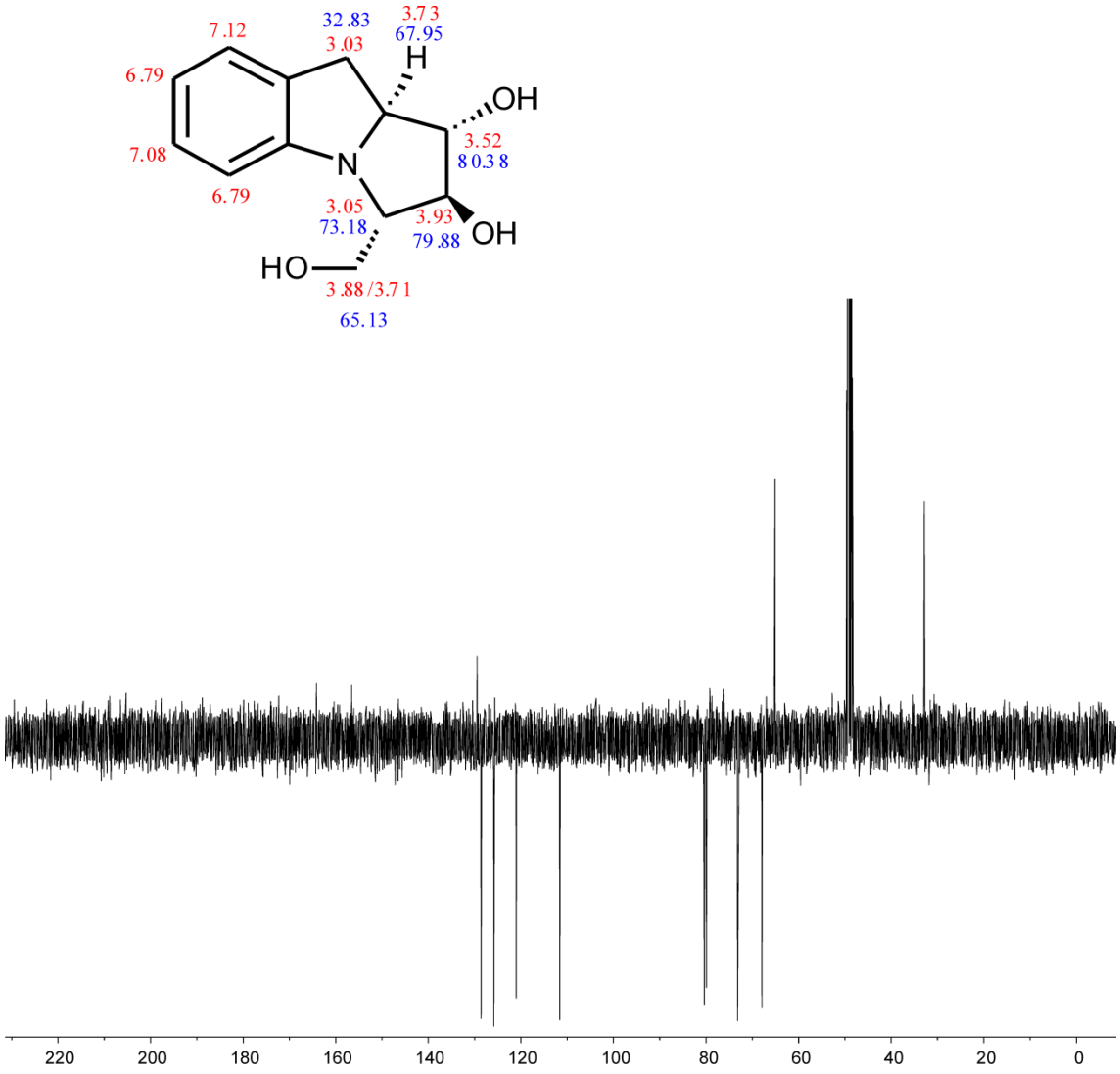

3.13
H
H
7.06
3.96
H
6.80
OH
7.04
N
H
3.49
H
4.21
6.75
OH
HO
H
3.36
3.91/4.00
2.8
3.0
3.2
3.4
3.6
3.8
4.0
4.2
4.4
4.6
4.5 4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8

**Figure 2S**. NMR spectra ($CD_3OD$) of **13b**: a) $^{1}H$; b) $^{13}C$-DEPT; c) 2D $^{1}H$-$^{1}H$ COSY; d) 2D $^{1}H$-$^{13}C$ Multiplicity-edited HSQC and e) 2D $^{1}H$-$^{1}H$ NOESY.

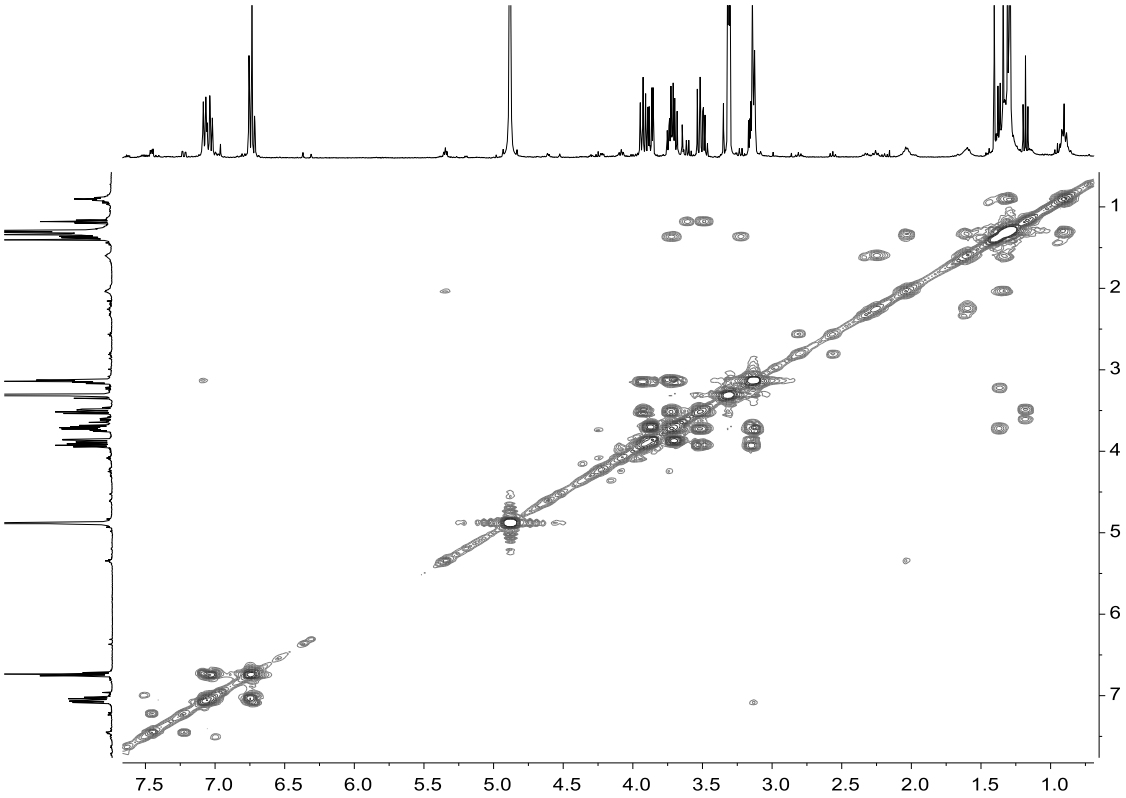
a)



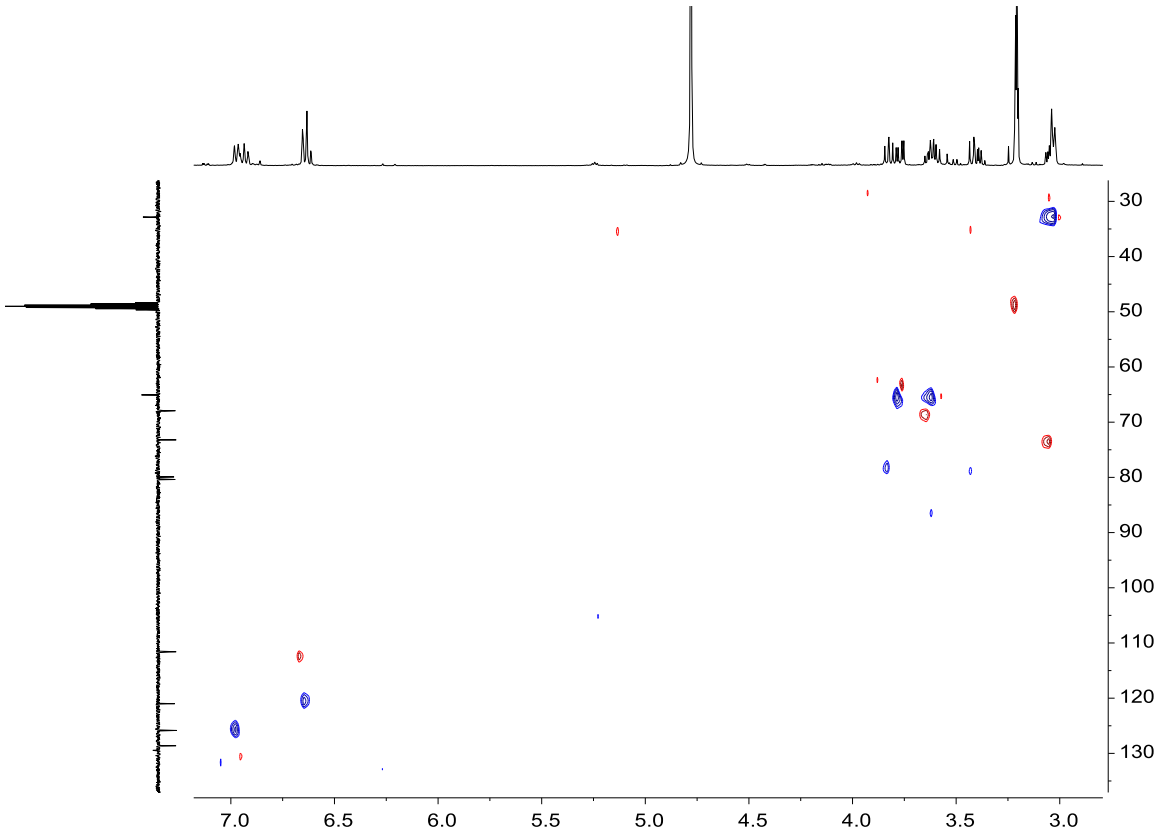
b)


7.12
32.83
3.03
3.73
67.95
H
OH
6.79
7.08
N
3.52
80.38
6.79
3.05
73.18
3.93
79.88
OH
HO
3.88/3.71
65.13
220
200
180
160
140
120
100
80
60
40
20
0

c)


1
2
3
4
5
6
7
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

d)


30
40
50
60
70
80
90
100
110
120
130
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0

e)

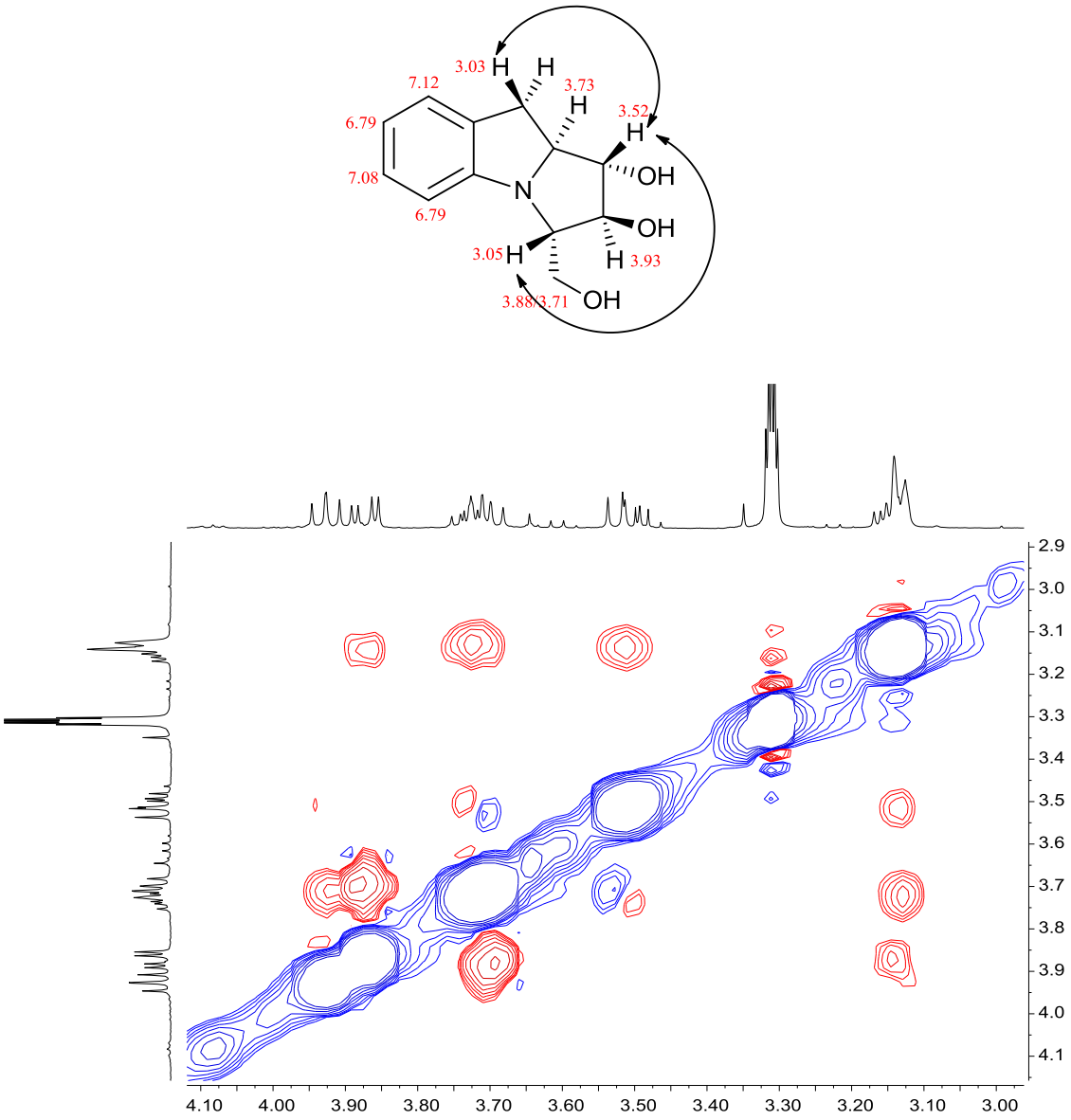
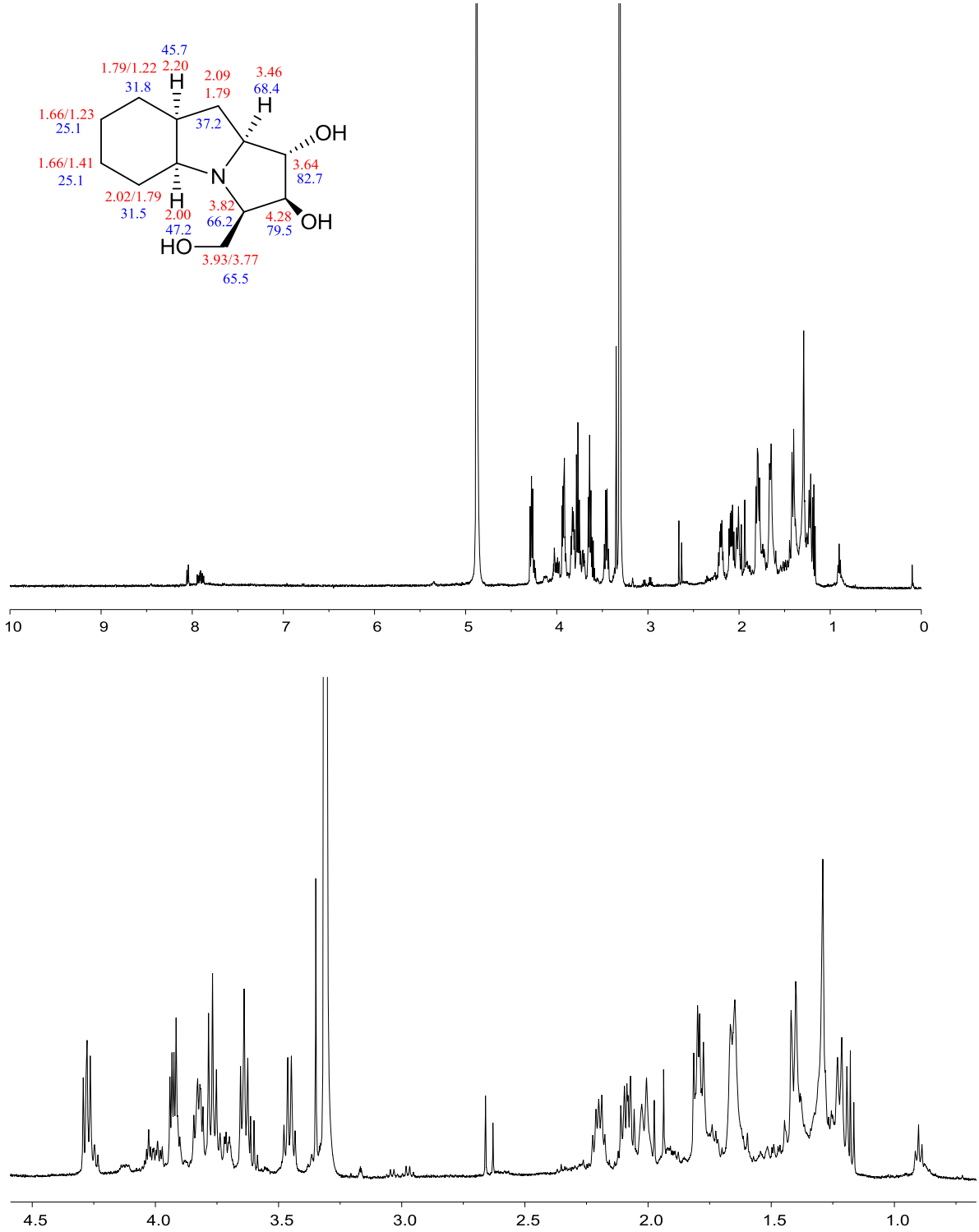
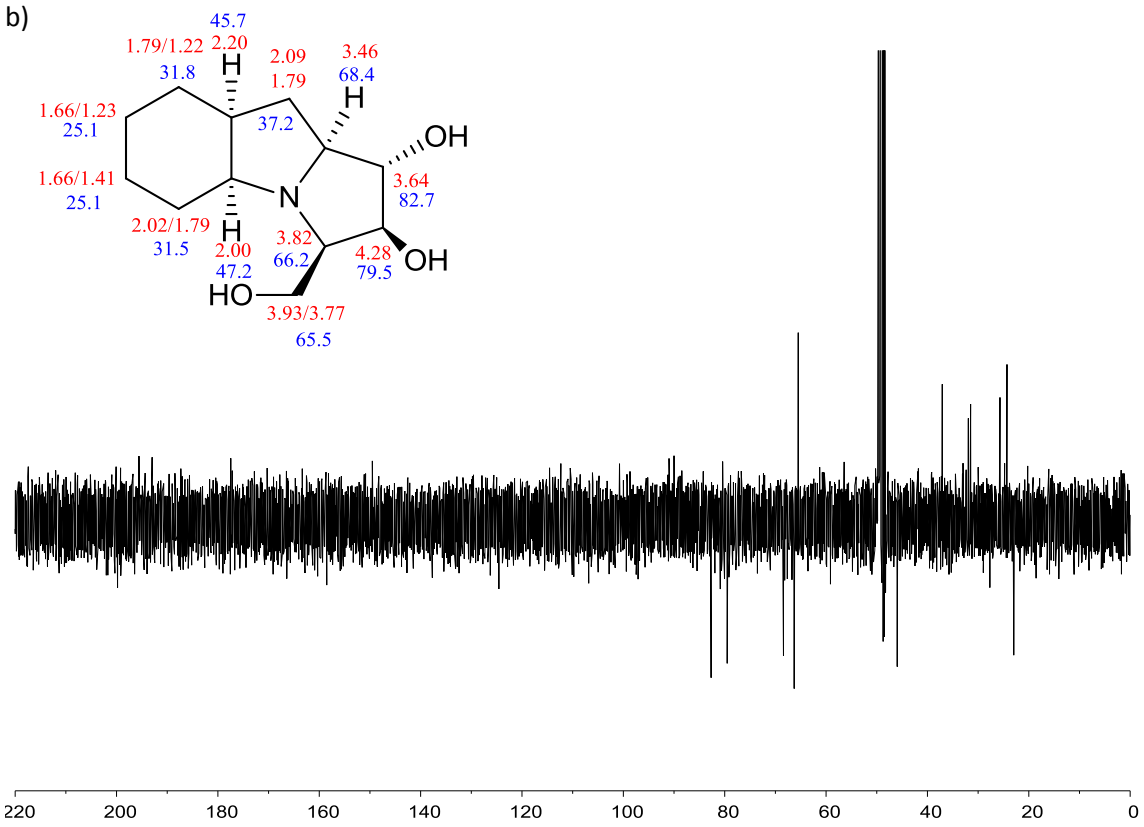

3.03
H
H
3.73
H
3.52
H
7.12
6.79
7.08
6.79
N
OH
OH
3.05
H
H
3.93
3.88/3.71
OH
2.9
3.0
3.1
3.2
3.3
3.4
3.5
3.6
3.7
3.8
3.9
4.0
4.1
4.10
4.00
3.90
3.80
3.70
3.60
3.50
3.40
3.30
3.20
3.10
3.00

**Figure 3S**. NMR spectra ($CD_3OD$) of **15**: a) $^{1}H$; b) $^{13}C$-DEPT; c) 2D $^{1}H$-$^{1}H$ COSY; d) 2D $^{1}H$-$^{13}C$ Multiplicity-edited HSQC and e) 2D $^{1}H$-$^{1}H$ NOESY.

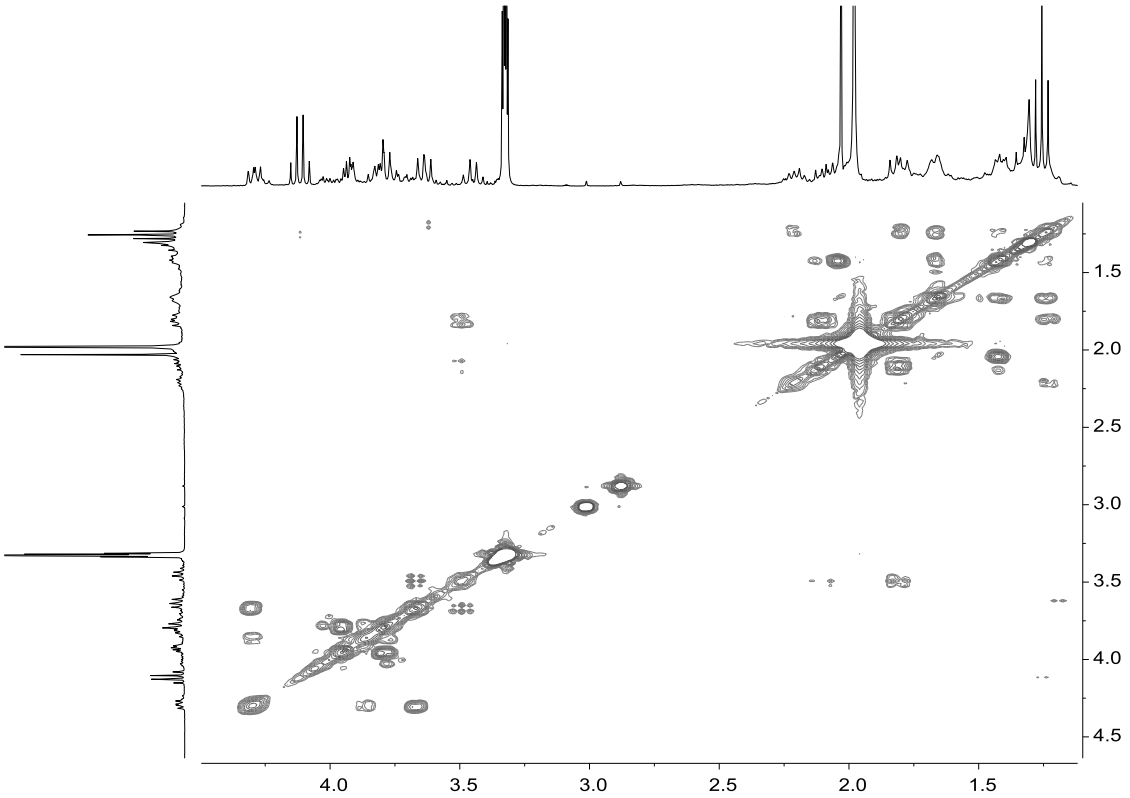
a)



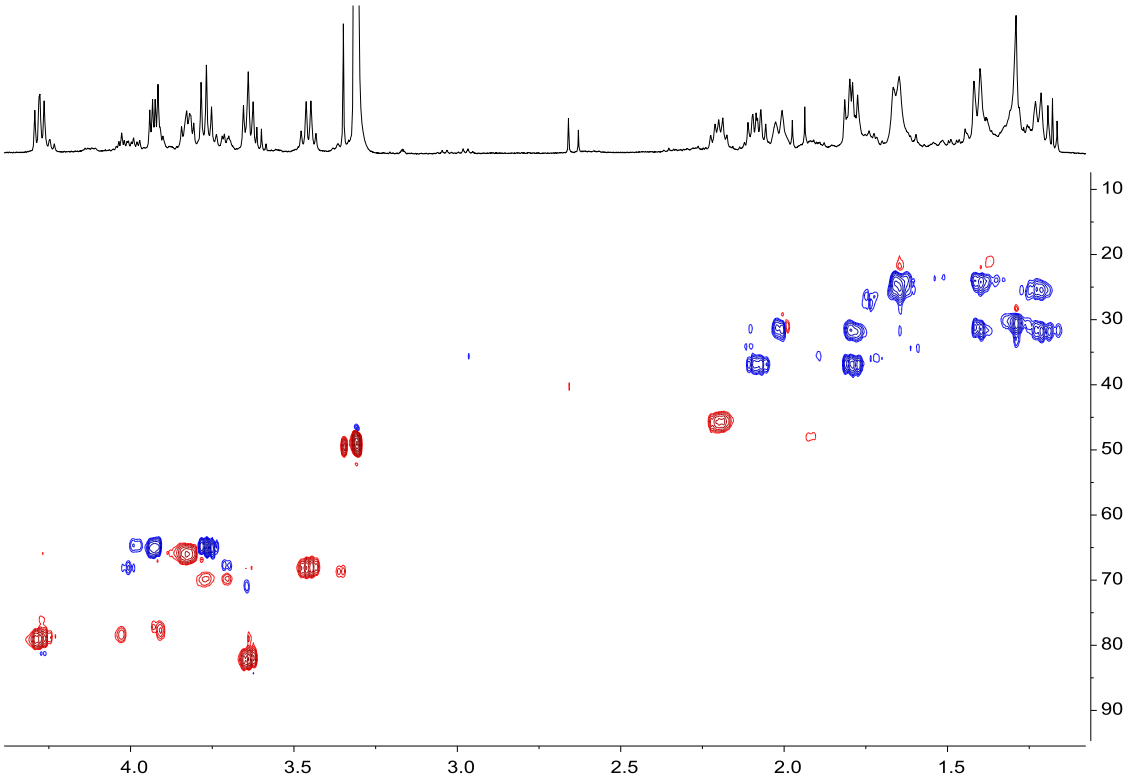
b)


45.7
1.79/1.22
2.20
31.8
H
2.09
1.79
3.46
68.4
H
1.66/1.23
25.1
37.2
OH
1.66/1.41
25.1
N
3.64
82.7
2.02/1.79
31.5
H
2.00
47.2
3.82
66.2
4.28
79.5
OH
HO
3.93/3.77
65.5
220
200
180
160
140
120
100
80
60
40
20
0

c)


1.5
2.0
2.5
3.0
3.5
4.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5

d)


10
20
30
40
50
60
70
80
90
4.0
3.5
3.0
2.5
2.0
1.5

e)

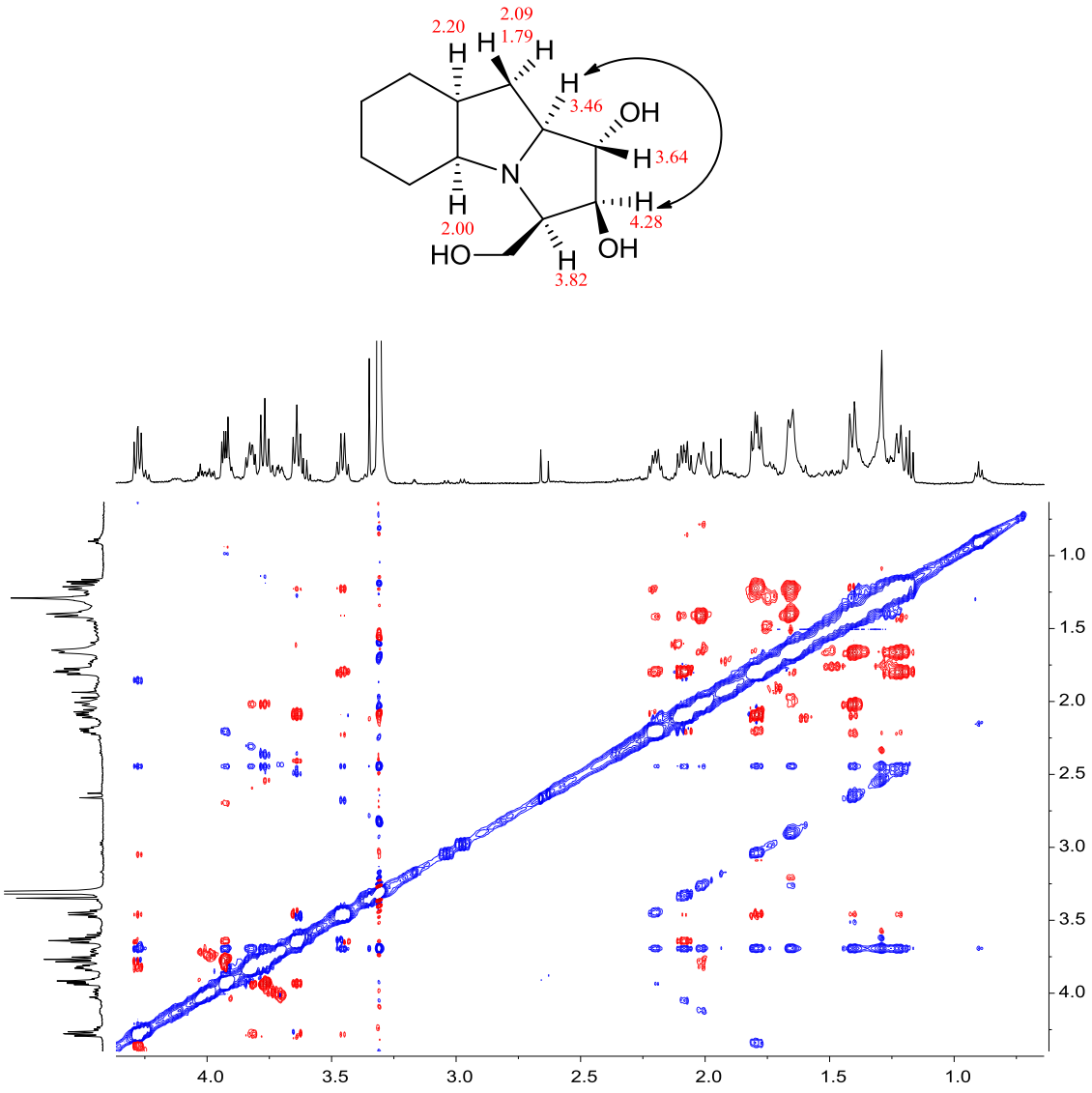
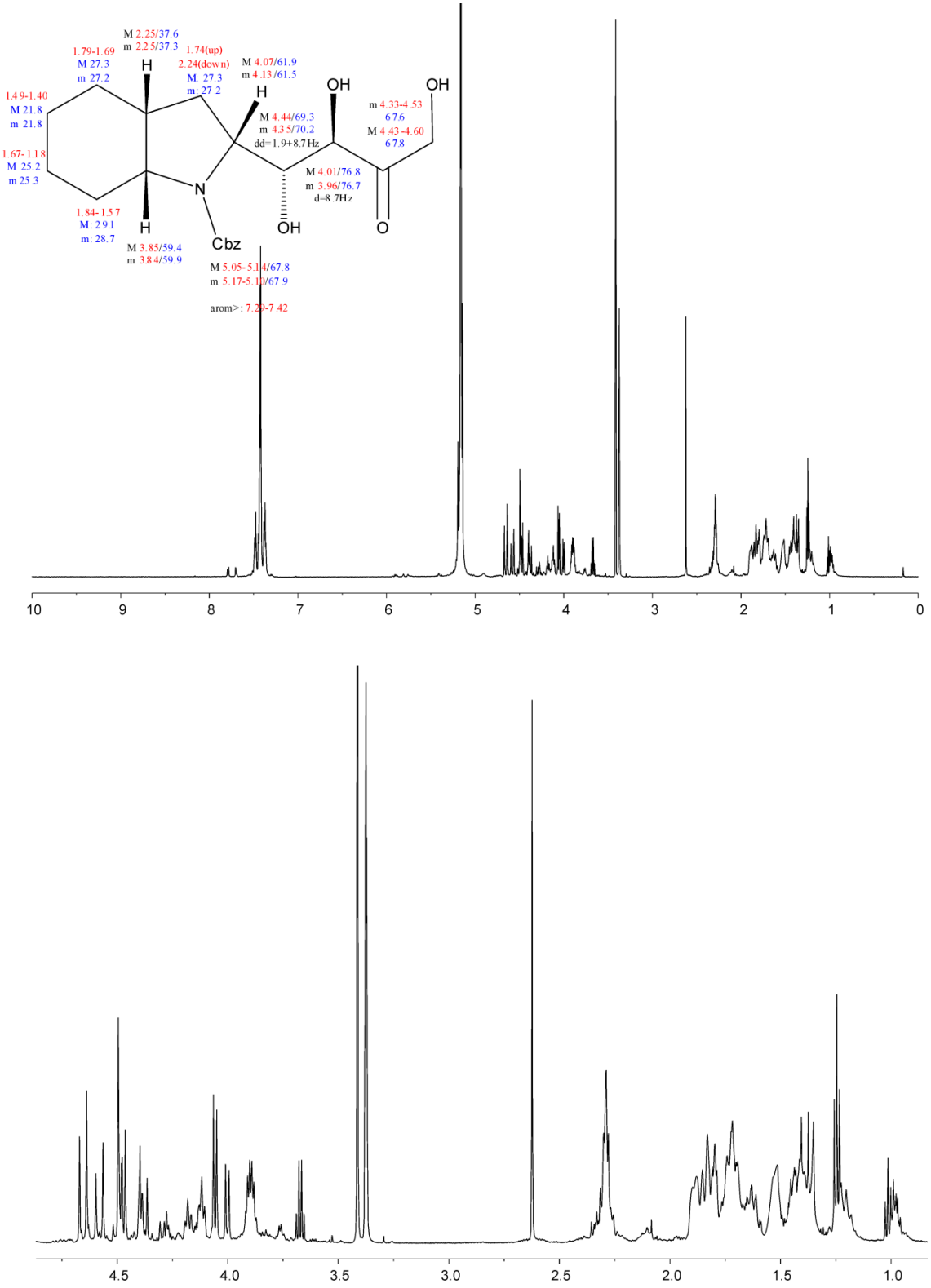
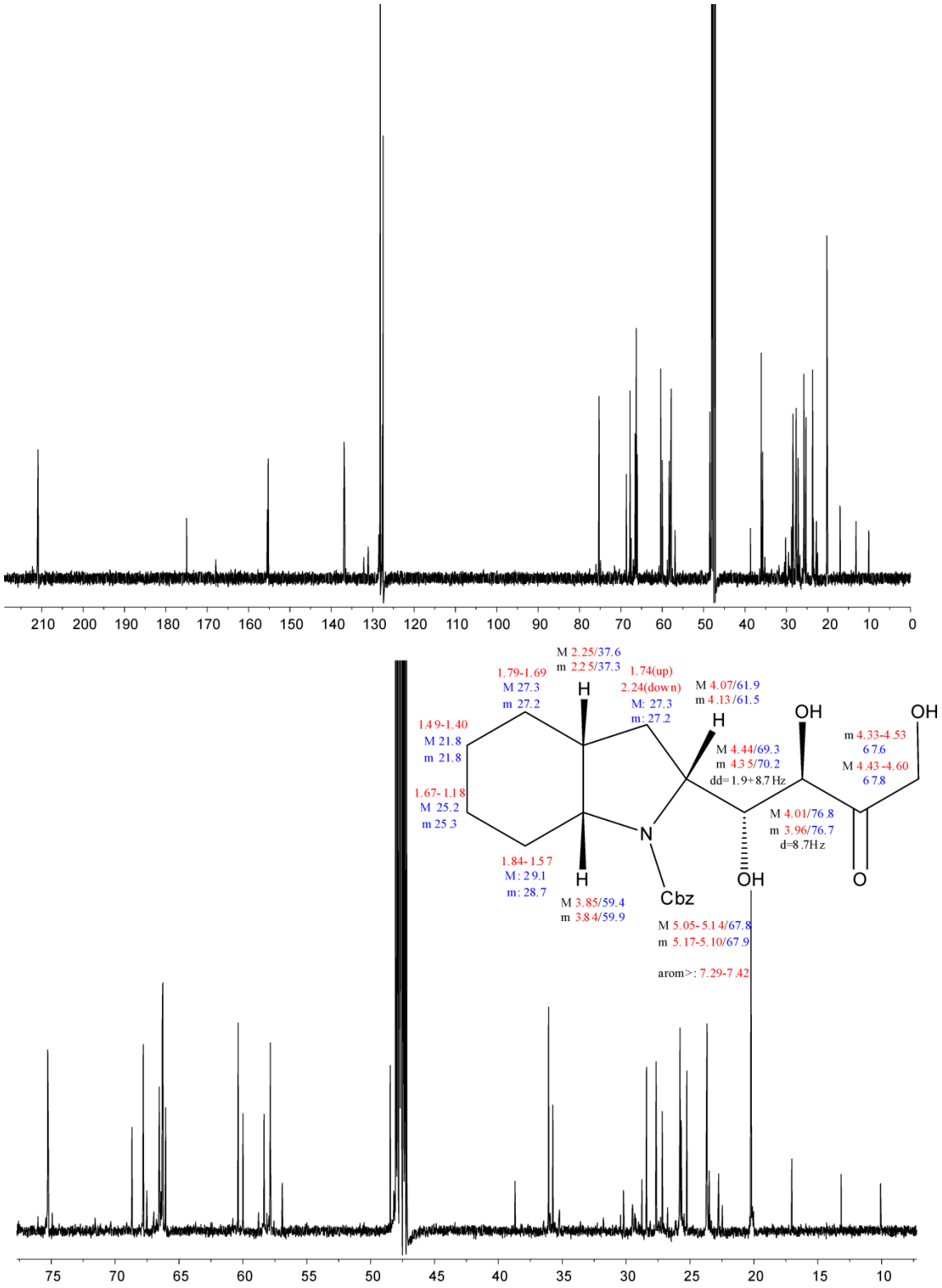

2.20
2.09
1.79
H
H
H
H
3.46
OH
H
3.64
N
H
2.00
H
4.28
HO
OH
H
3.82
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.0
3.5
3.0
2.5
2.0
1.5
1.0

**Figure 4S**. NMR spectra ($CD_3OD$) of **14b** at 273.5 K: a) $^{1}H$; b) $^{13}C$; c) 2D $^{1}H$-$^{1}H$ COSY; d) 2D $^{1}H$-$^{13}C$ Multiplicity-edited HSQC and e) 2D $^{1}H$-$^{1}H$ NOESY. (two conformers were observed corresponding to Cbz rotamers)

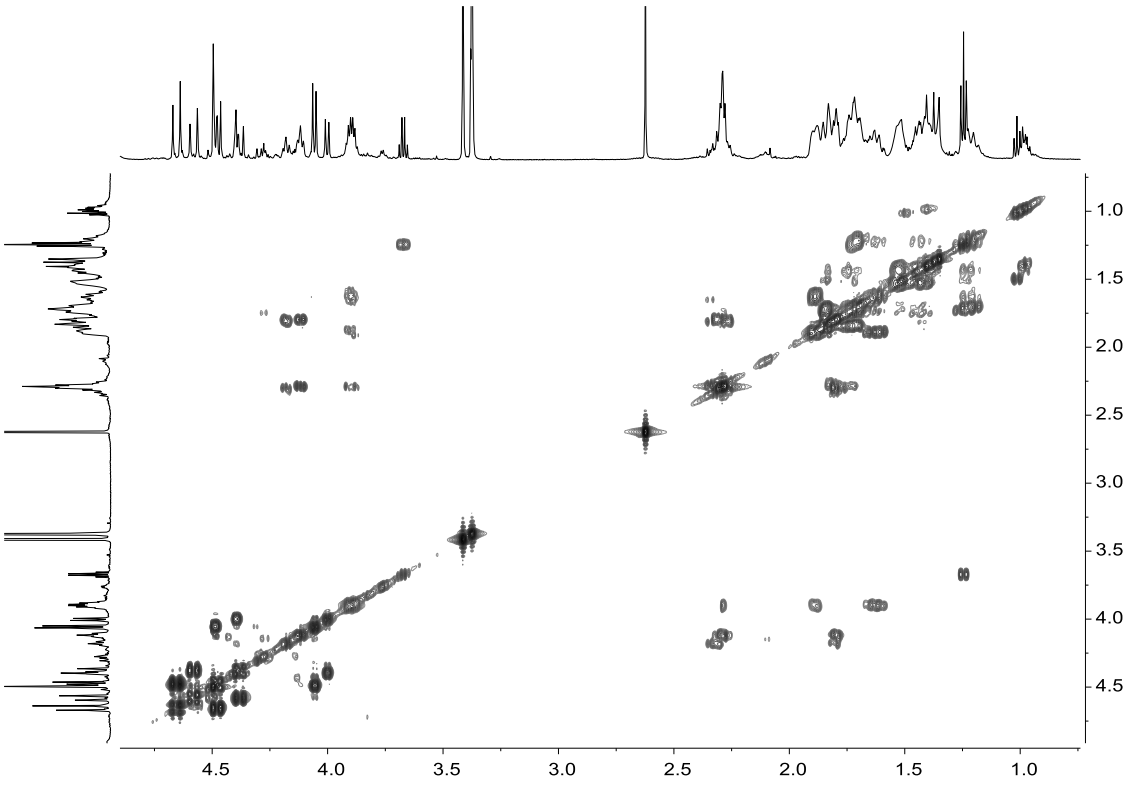
a)



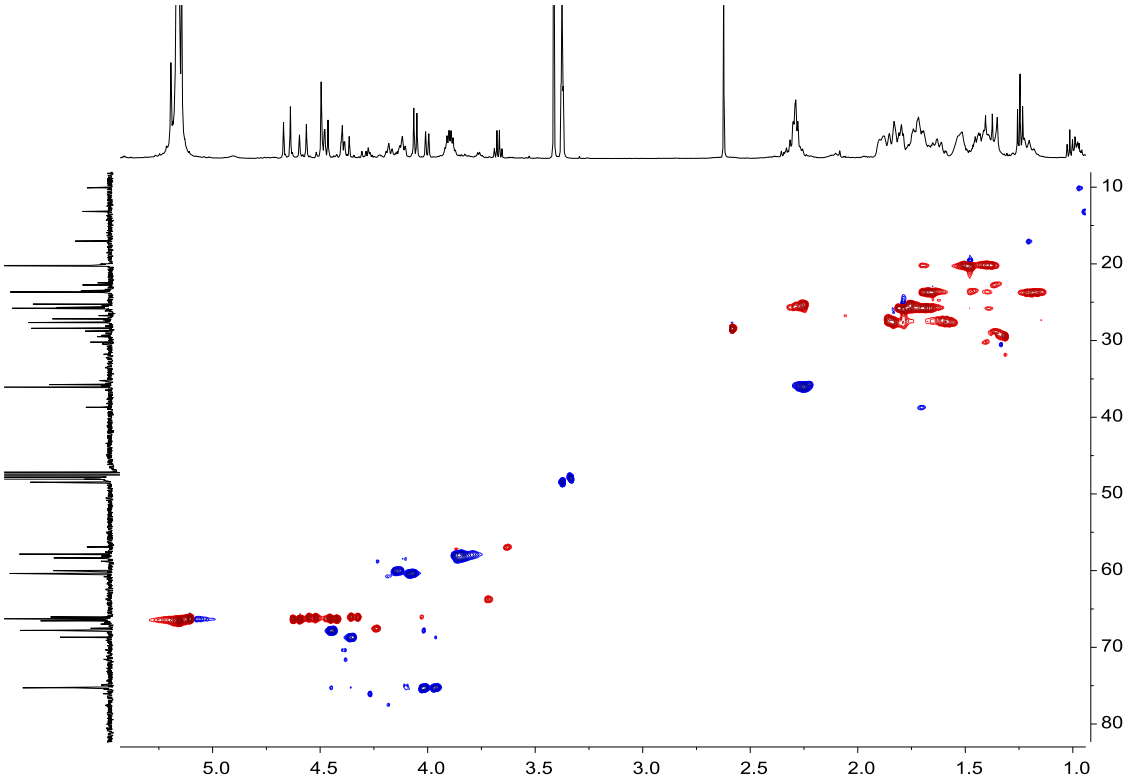
b)


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
M 2.25/37.6
m 2.25/37.3
1.79-1.69
M 27.3
m 27.2
1.74(up)
2.24(down)
M: 27.3
m: 27.2
M 4.07/61.9
m 4.13/61.5
H
OH
OH
m 4.33-4.53
67.6
M 4.43-4.60
67.8
1.49-1.40
M 21.8
m 21.8
M 4.44/69.3
m 4.35/70.2
dd=1.9+8.7Hz
1.67-1.18
M 25.2
m 25.3
M 4.01/76.8
m 3.96/76.7
d=8.7Hz
N
1.84-1.57
M: 29.1
m: 28.7
H
OH
O
M 3.85/59.4
m 3.84/59.9
Cbz
M 5.05-5.14/67.8
m 5.17-5.10/67.9
arom>: 7.29-7.42
75 70 65 60 55 50 45 40 35 30 25 20 15 10

c)


1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0

d)


10
20
30
40
50
60
70
80
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0

e)

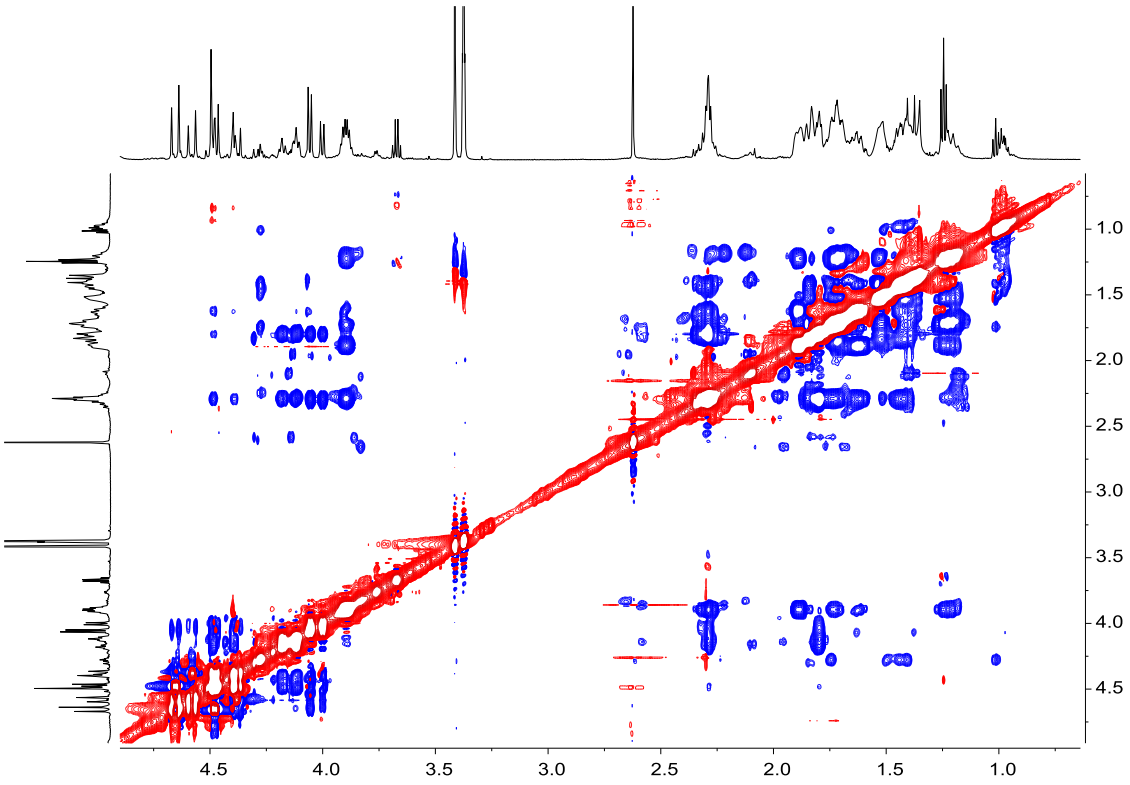
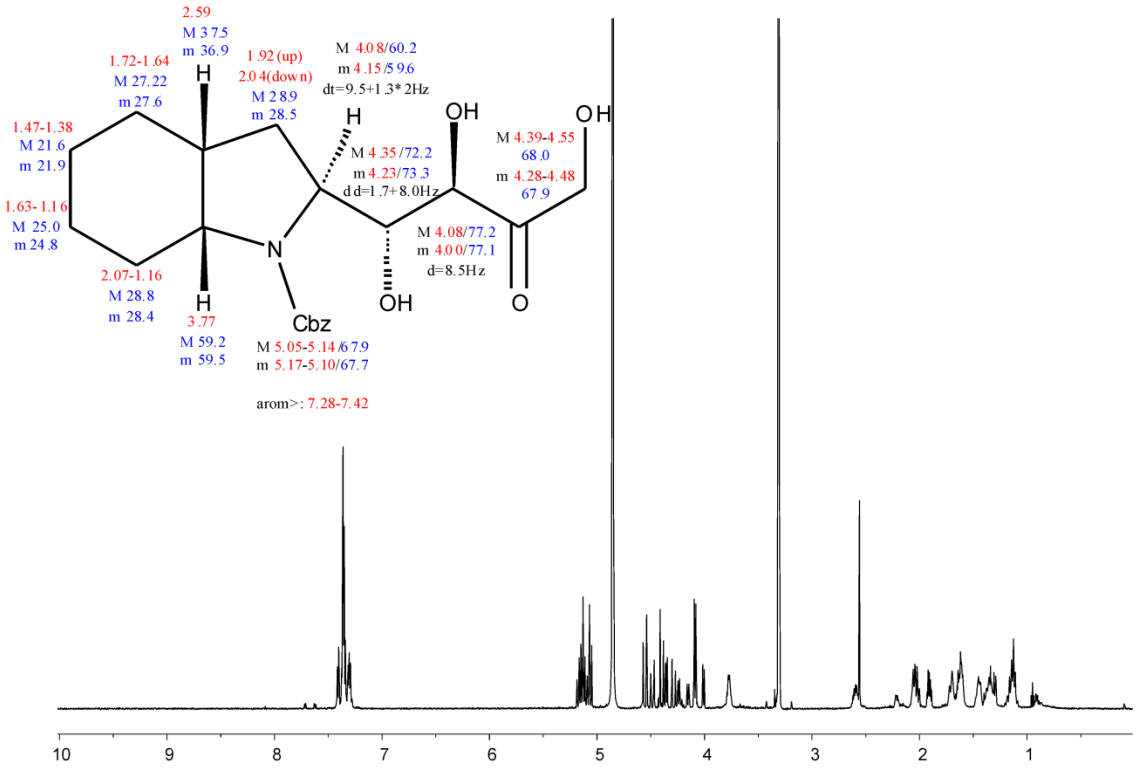
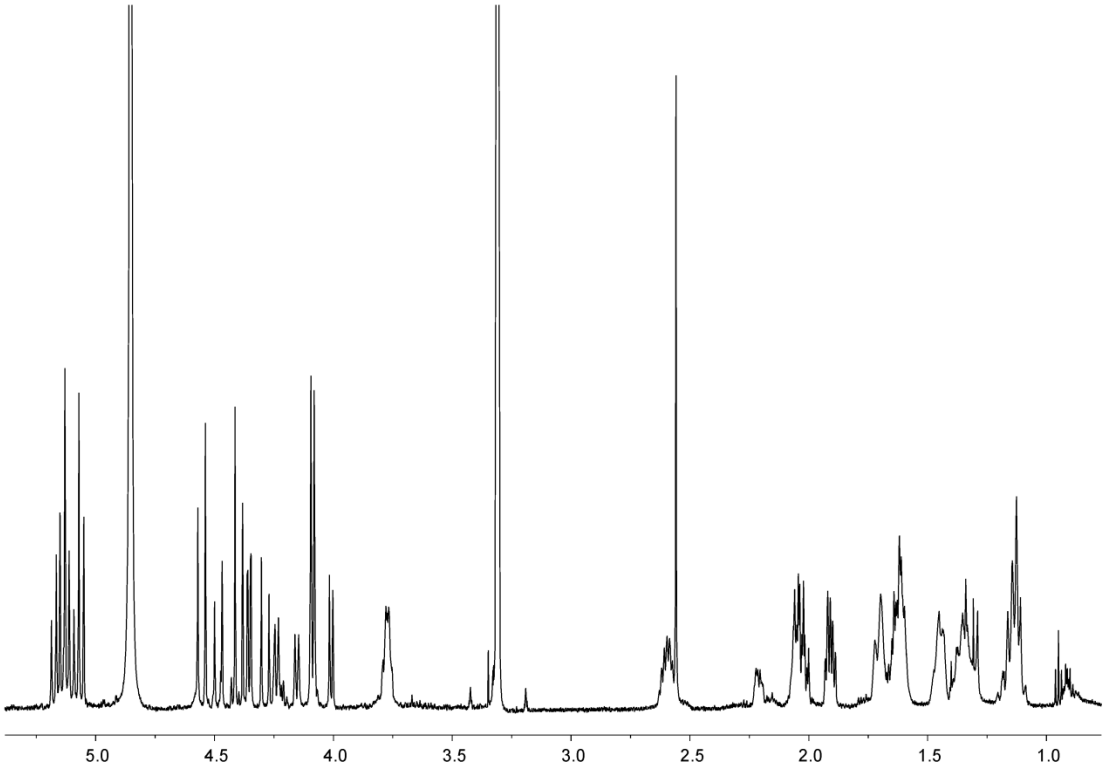


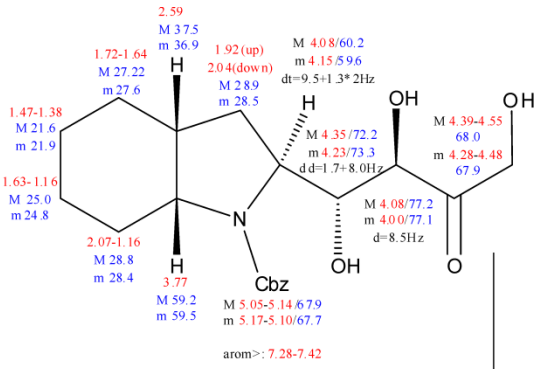
**Figure 5S**. NMR spectra ($CD_3OD$) of **16** at 273.5 K: a) $^{1}H$; b) $^{13}C$; c) 2D $^{1}H$-$^{1}H$ COSY; d) 2D $^{1}H$-$^{13}C$ Multiplicity-edited HSQC and e) 2D $^{1}H$-$^{1}H$ NOESY.

a)

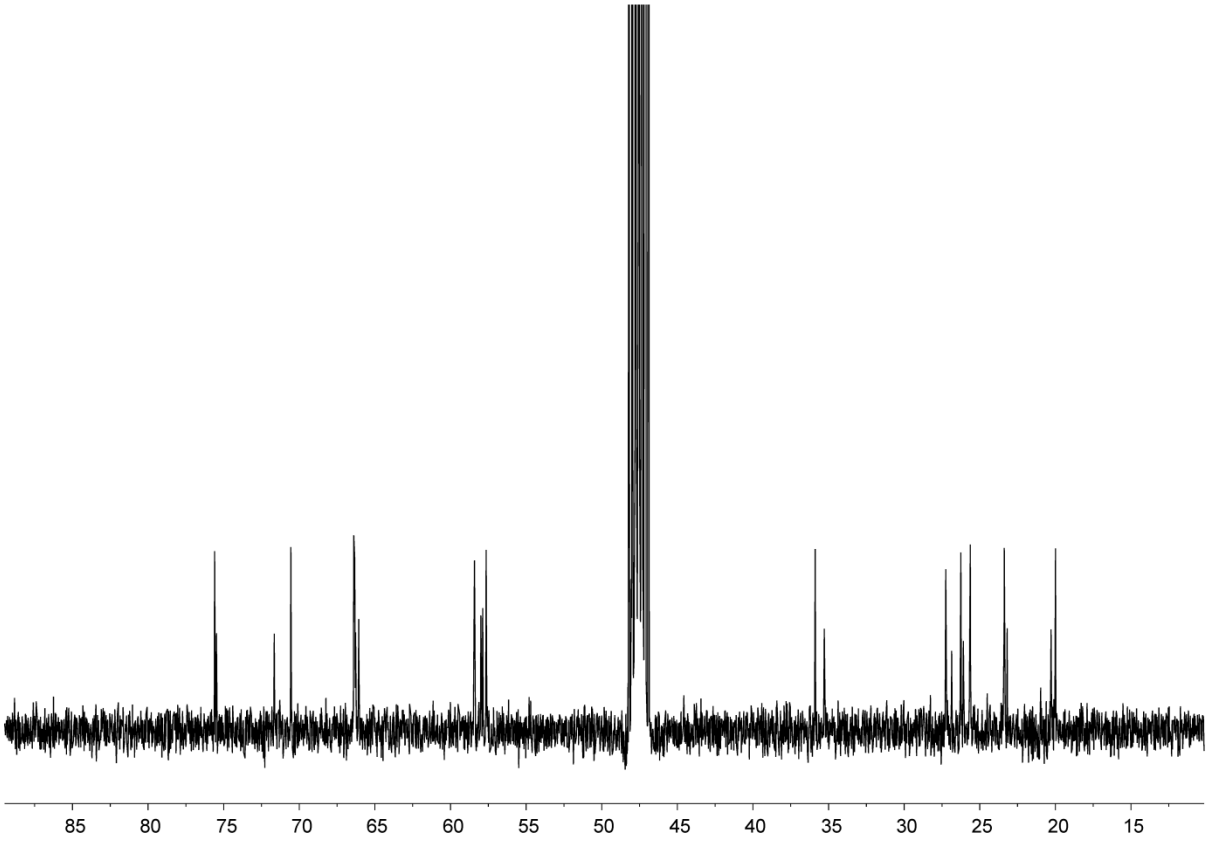


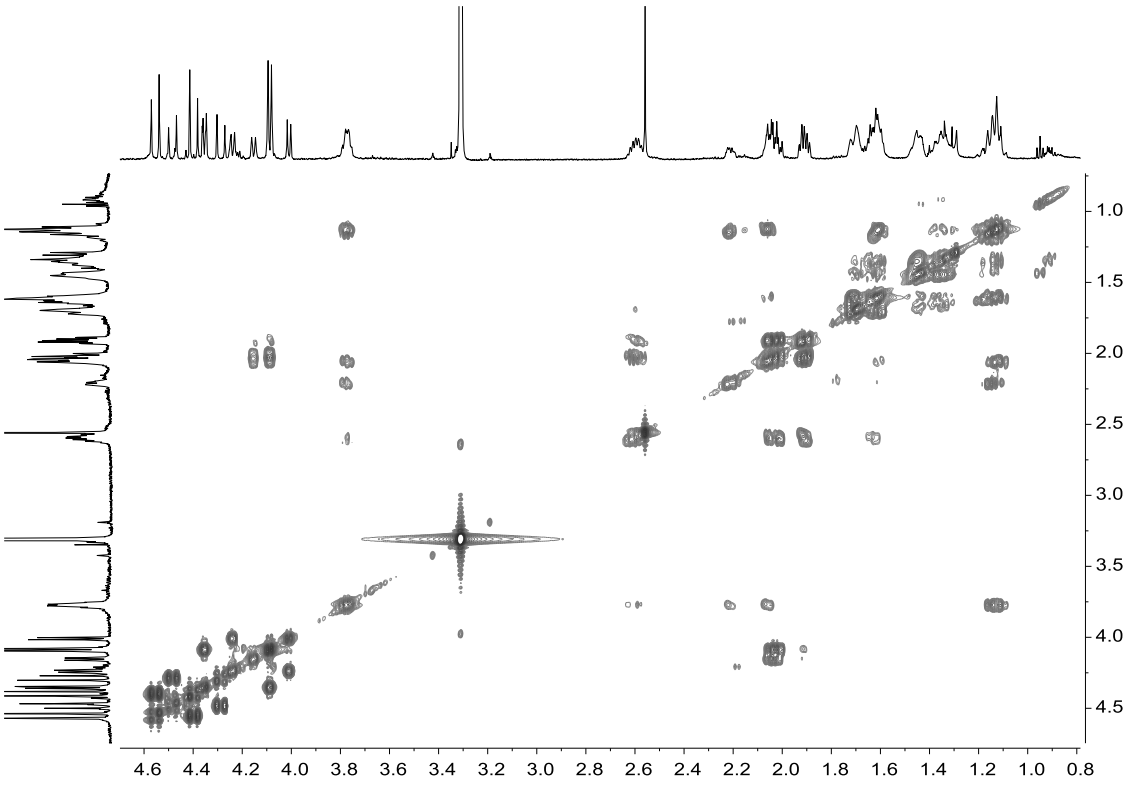

b)


2.59
M 37.5
m 36.9
1.72-1.64
M 27.22
m 27.6
1.92(up)
2.04(down)
M 28.9
m 28.5
M 4.08/60.2
m 4.15/59.6
dt=9.5+1.3*2Hz
1.47-1.38
M 21.6
m 21.9
H
OH
OH
M 4.39-4.55
68.0
m 4.28-4.48
67.9
M 4.35/72.2
m 4.23/73.3
dd=1.7+8.0Hz
1.63-1.16
M 25.0
m 24.8
N
M 4.08/77.2
m 4.00/77.1
d=8.5Hz
2.07-1.16
M 28.8
m 28.4
H
OH
O
3.77
M 59.2
m 59.5
Cbz
M 5.05-5.14/67.9
m 5.17-5.10/67.7
arom>: 7.28-7.42

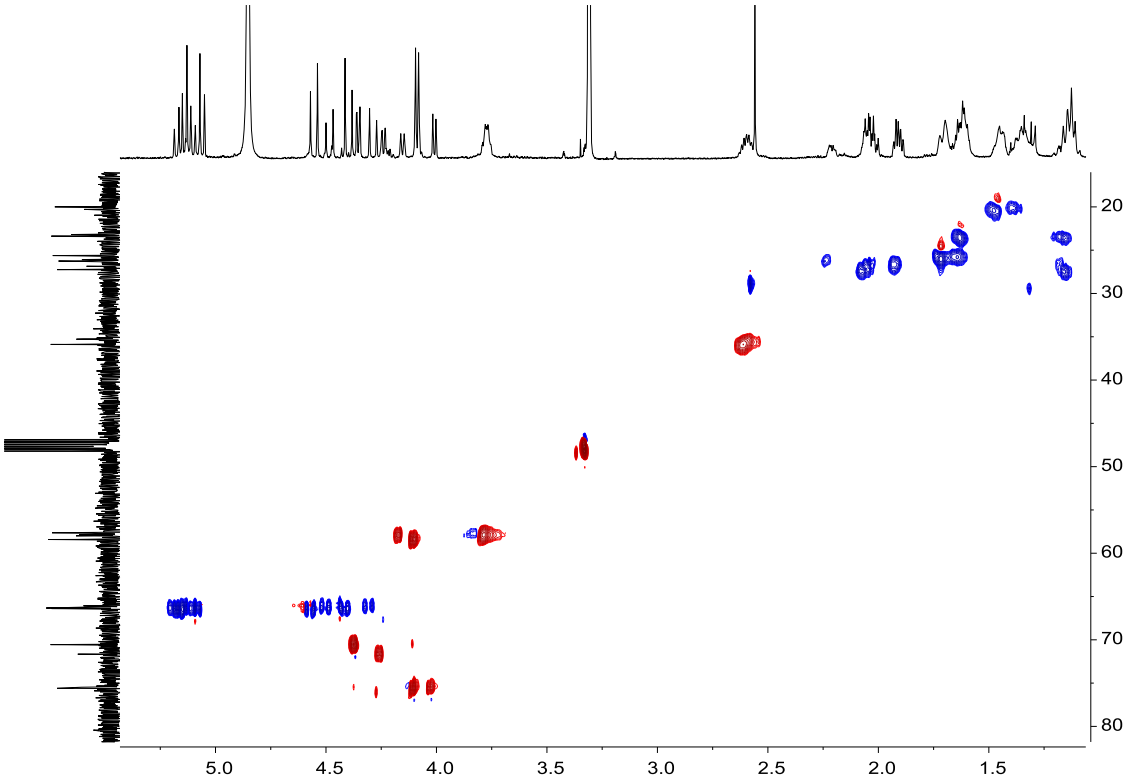

220
200
180
160
140
120
100
80
60
40
20
0


85
80
75
70
65
60
55
50
45
40
35
30
25
20
15

c)


1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
4.6 4.4 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 1.2 1.0 0.8

d)


20
30
40
50
60
70
80
5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5

e)

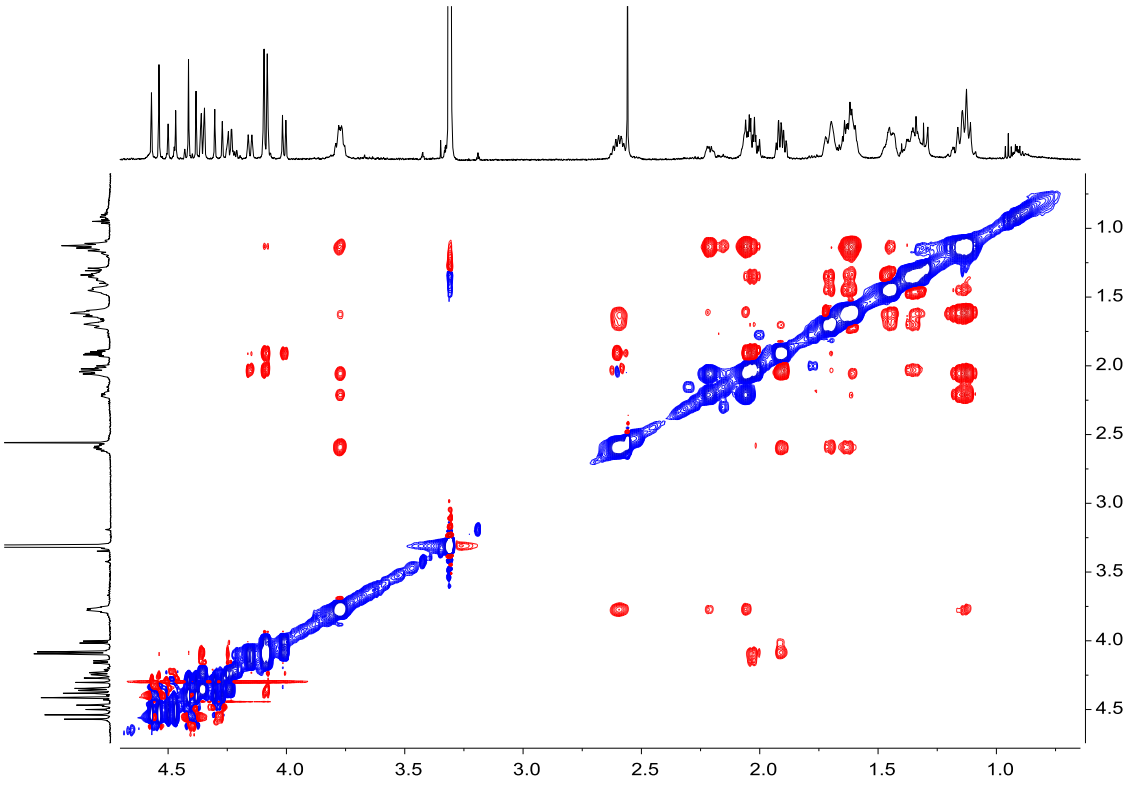
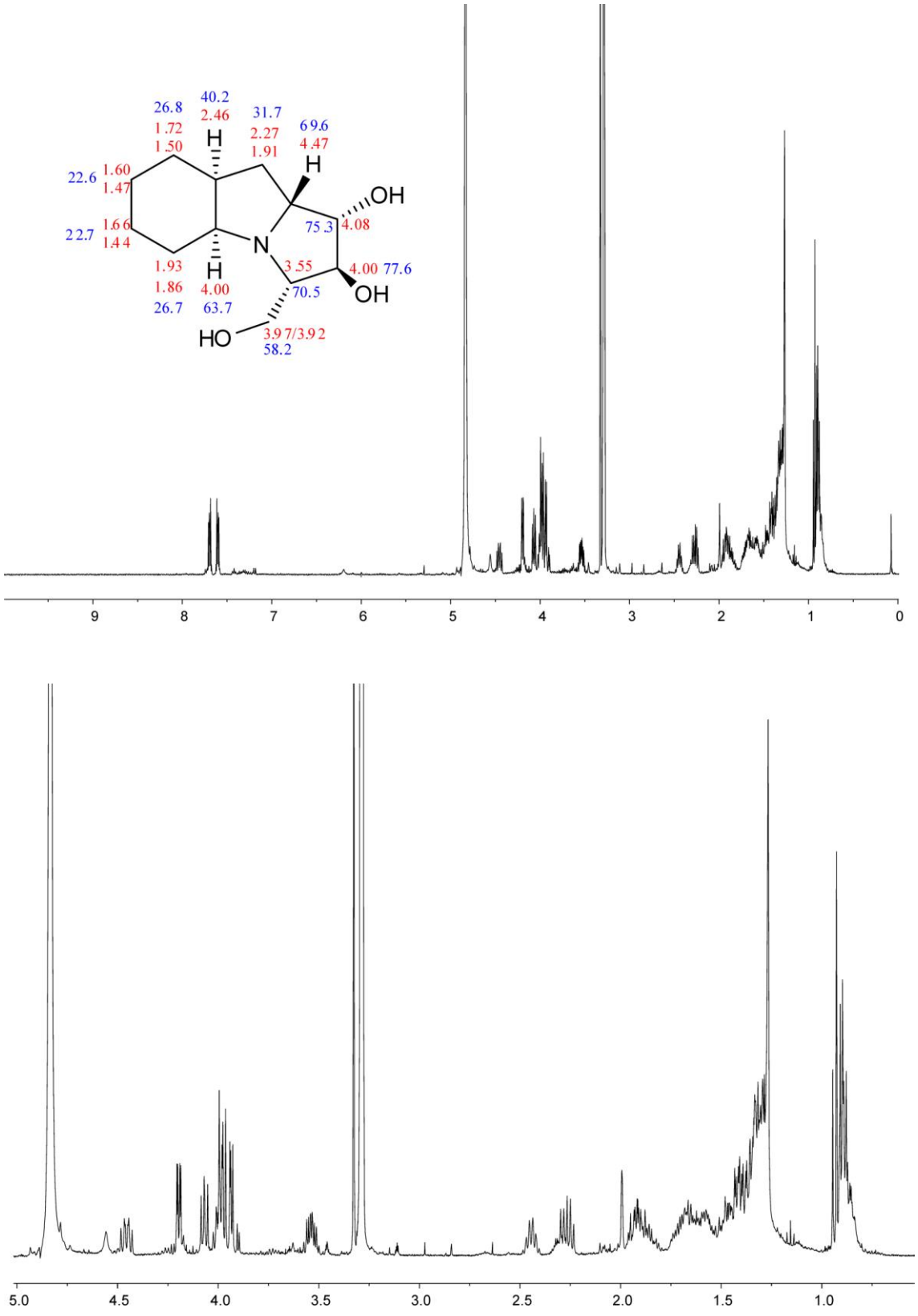
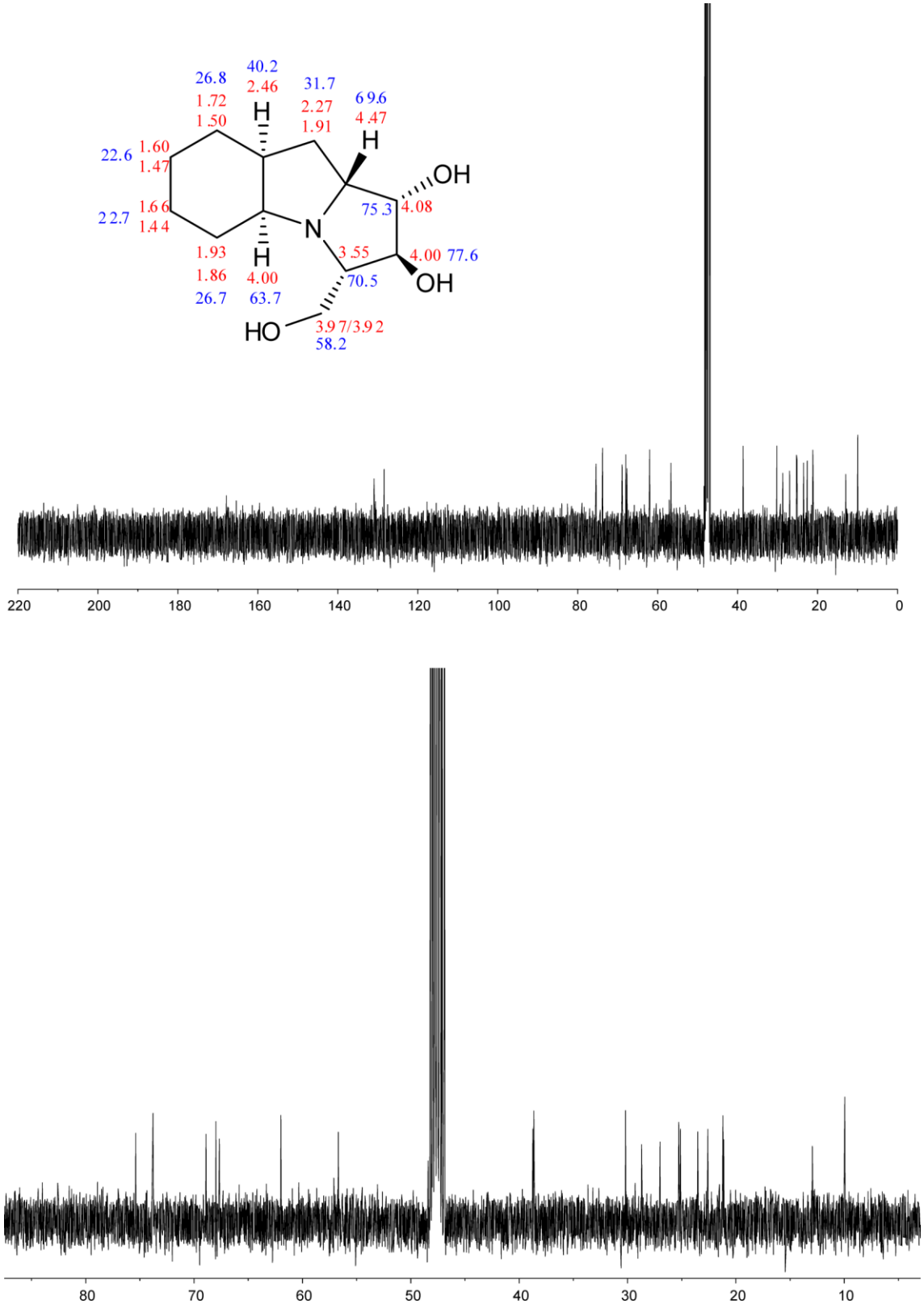


**Figure 6S**. NMR spectra ($CD_3OD$) of **18a**: a) $^{1}H$; b) $^{13}C$; c) 2D $^{1}H$-$^{1}H$ COSY; d) 2D $^{1}H$-$^{13}C$ Multiplicity-edited HSQC and e) 2D $^{1}H$-$^{1}H$ NOESY.

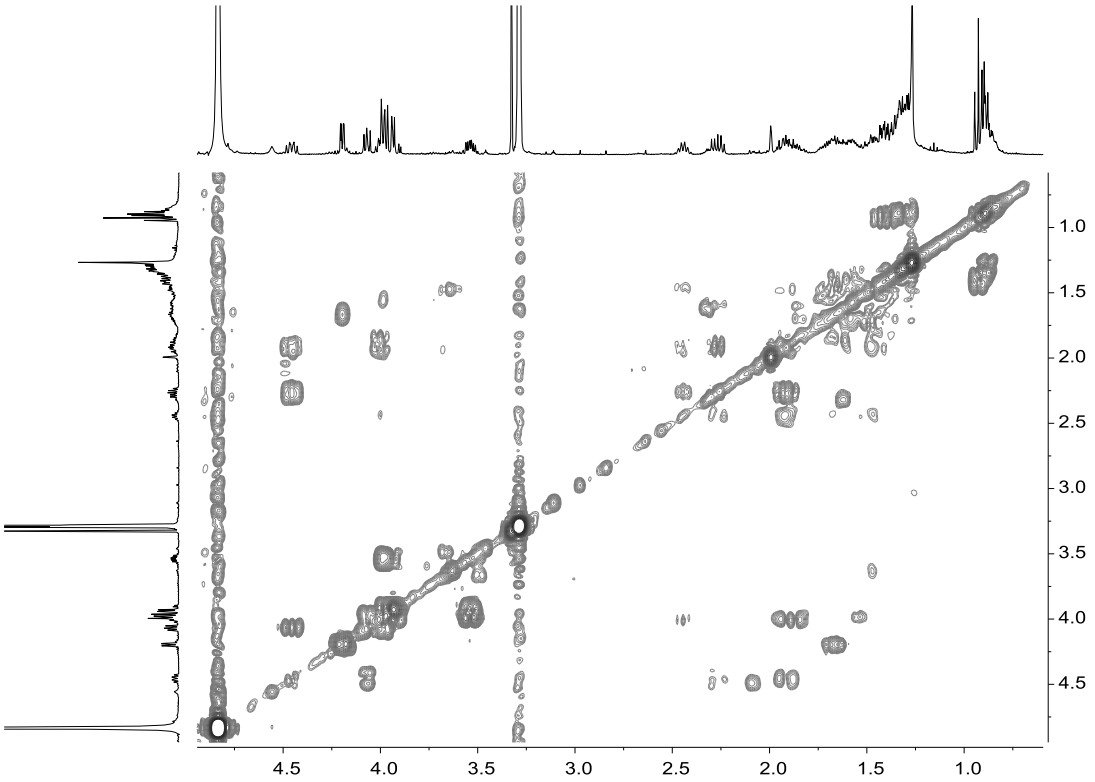
a)



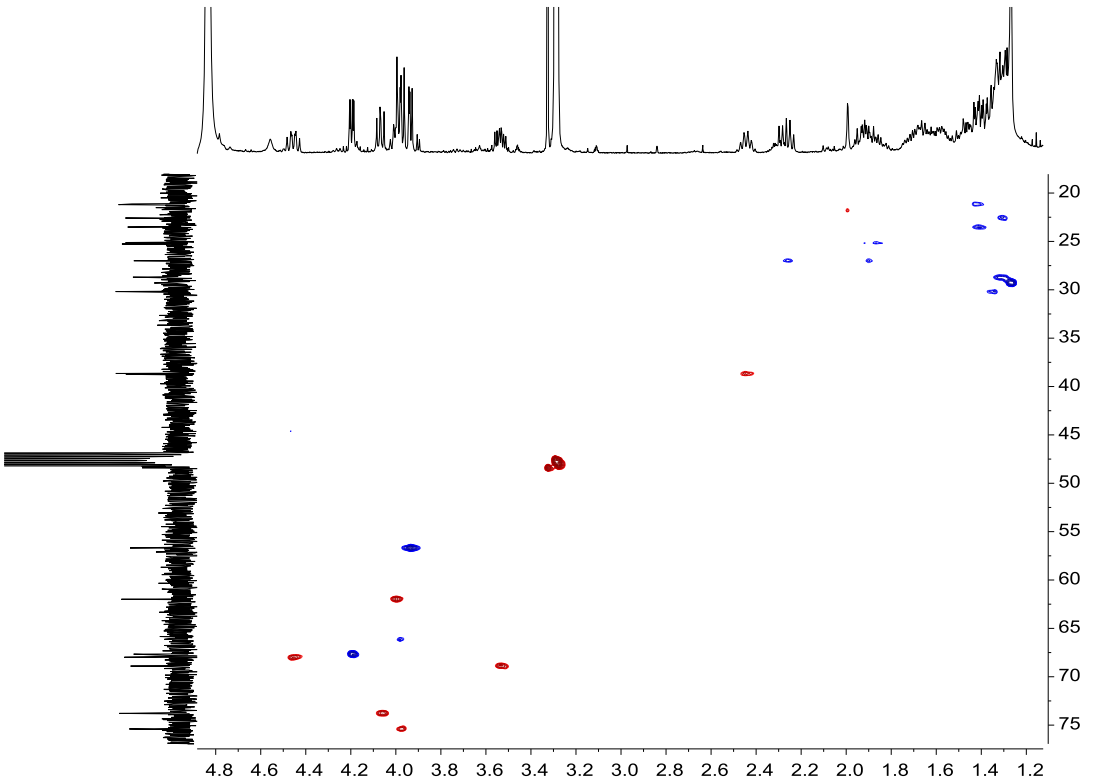
b)


26.8
1.72
1.50
40.2
2.46
H
31.7
2.27
1.91
69.6
4.47
H
22.6
1.60
1.47
OH
75.3
4.08
22.7
1.66
1.44
N
1.93
1.86
26.7
H
4.00
63.7
3.55
70.5
4.00
77.6
OH
HO
3.97/3.92
58.2
220
200
180
160
140
120
100
80
60
40
20
0
80
70
60
50
40
30
20
10

c)


1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0

d)


20
25
30
35
40
45
50
55
60
65
70
75
4.8
4.6
4.4
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
1.2

e)

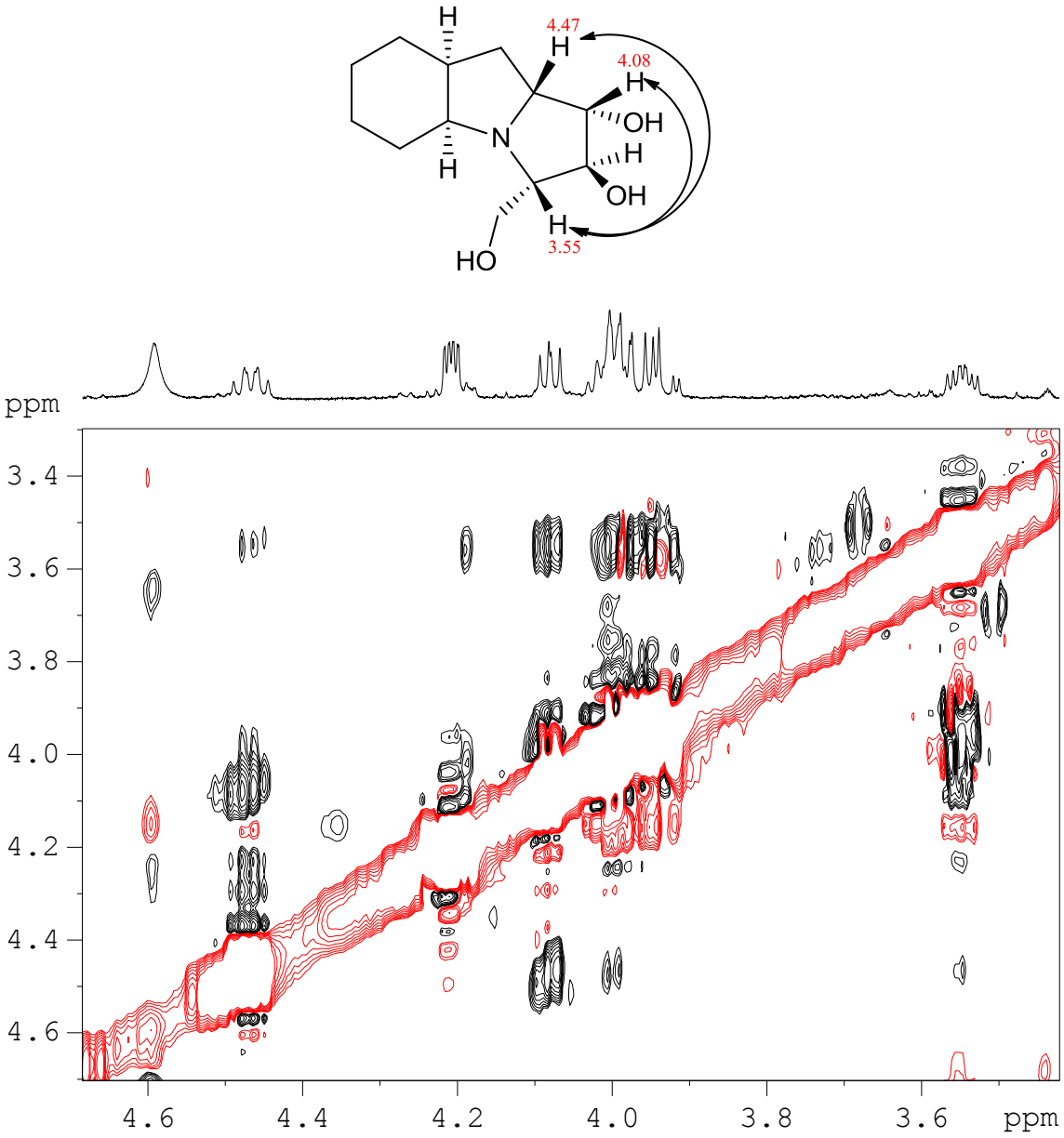
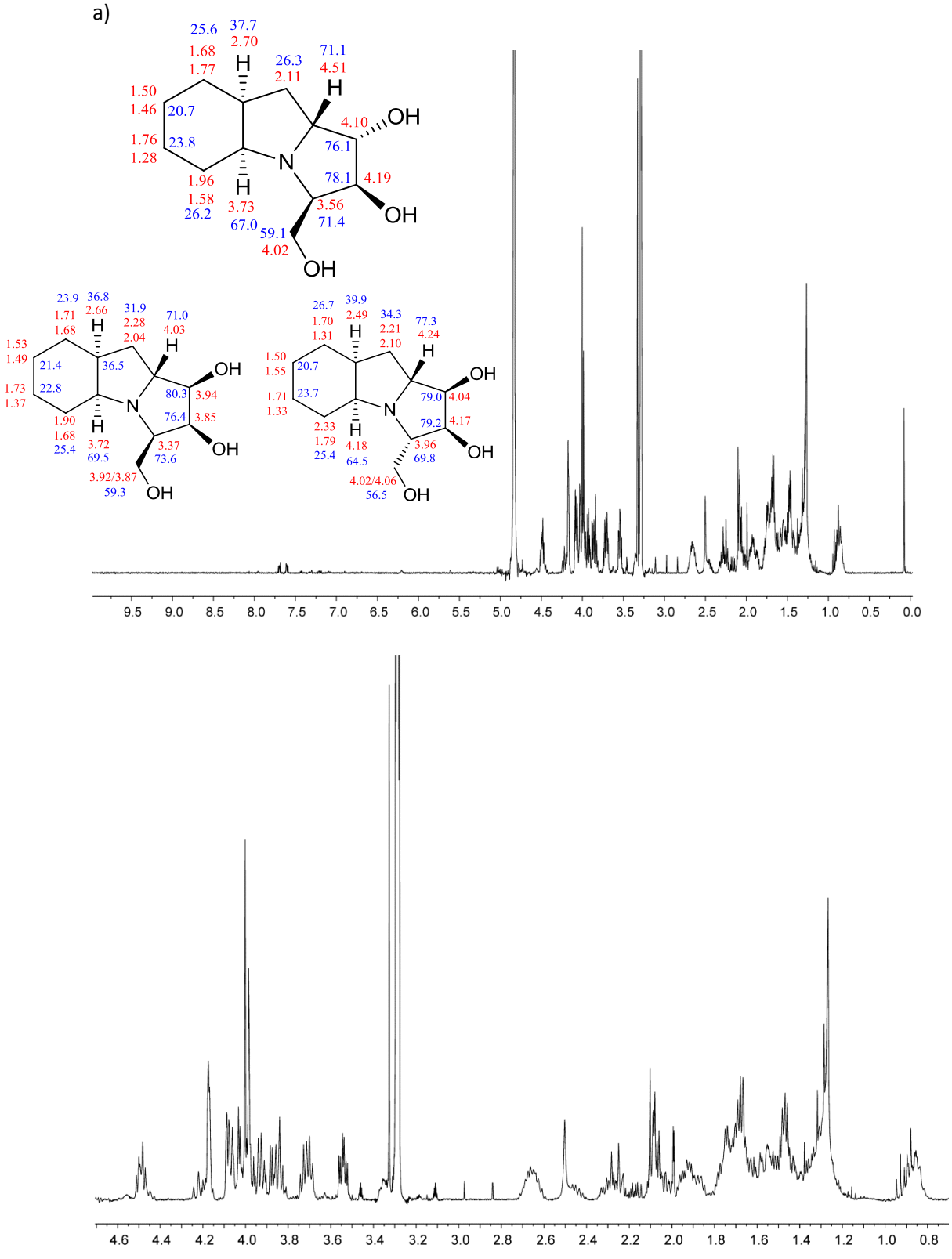
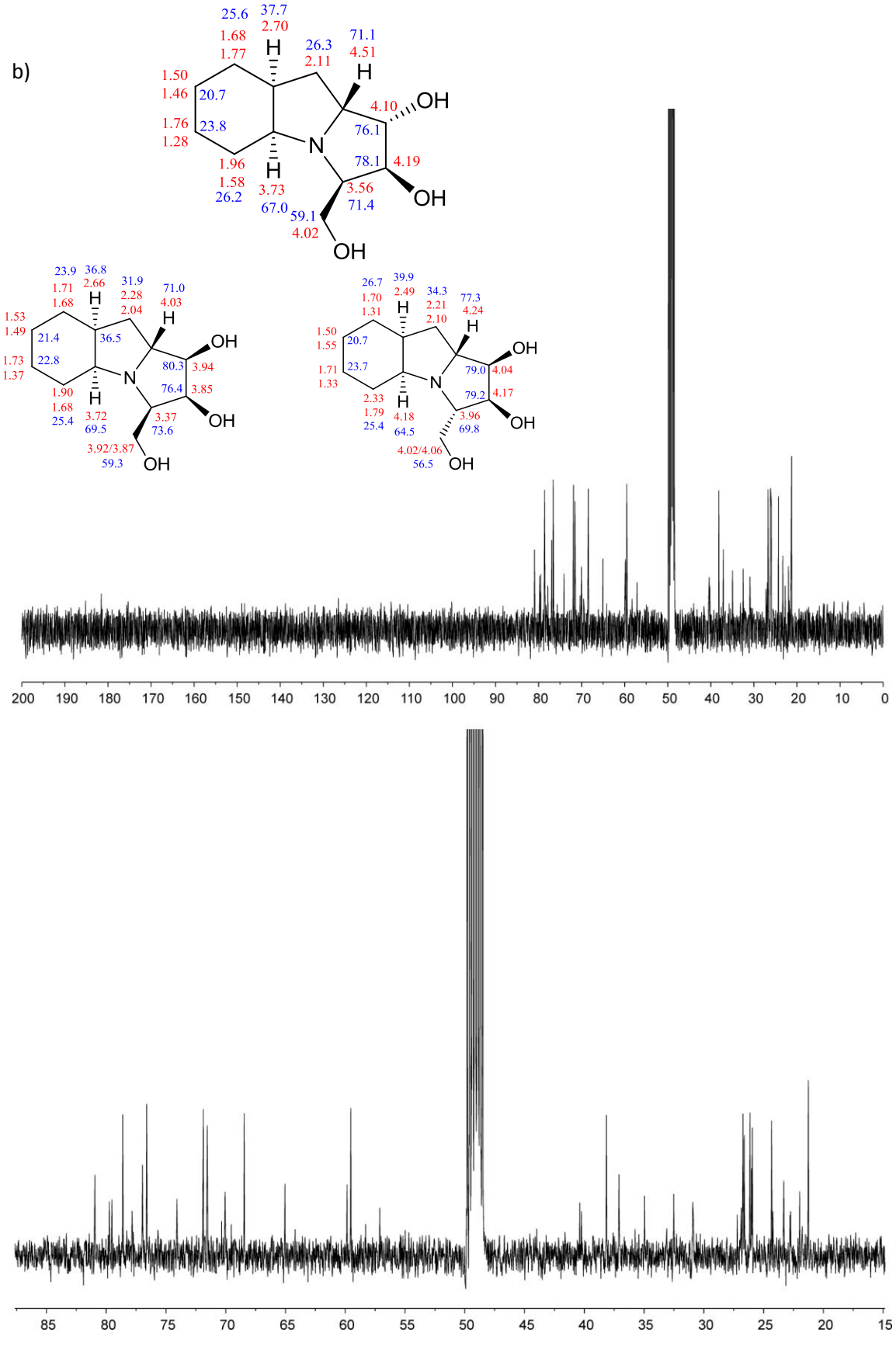

H
4.47
H
4.08
H
OH
H
OH
N
H
H
3.55
HO
ppm
3.4
3.6
3.8
4.0
4.2
4.4
4.6
4.6
4.4
4.2
4.0
3.8
3.6
ppm

**Figure 7S**. NMR spectra ($CD_3OD$) of a mixture containing **18a** (see Figure 6S for assignation)**, 18b**, **18c** and **18d**. Each individual compound have been fully characterized using the following experiments: a) $^{1}H$; b) $^{13}C$; c) 2D $^{1}H$-$^{1}H$ COSY, d) 2D $^{1}H$-$^{13}C$ Multiplicity-edited HSQC, e) 2D $^{1}H$-$^{13}C$ HSQC, f) 2D $^{1}H$-$^{1}H$ NOESY, g) 2D $^{1}H$-$^{1}H$ TOCSY and h) 2D $^{1}H$-$^{13}C$ HSQC-TOCSY.

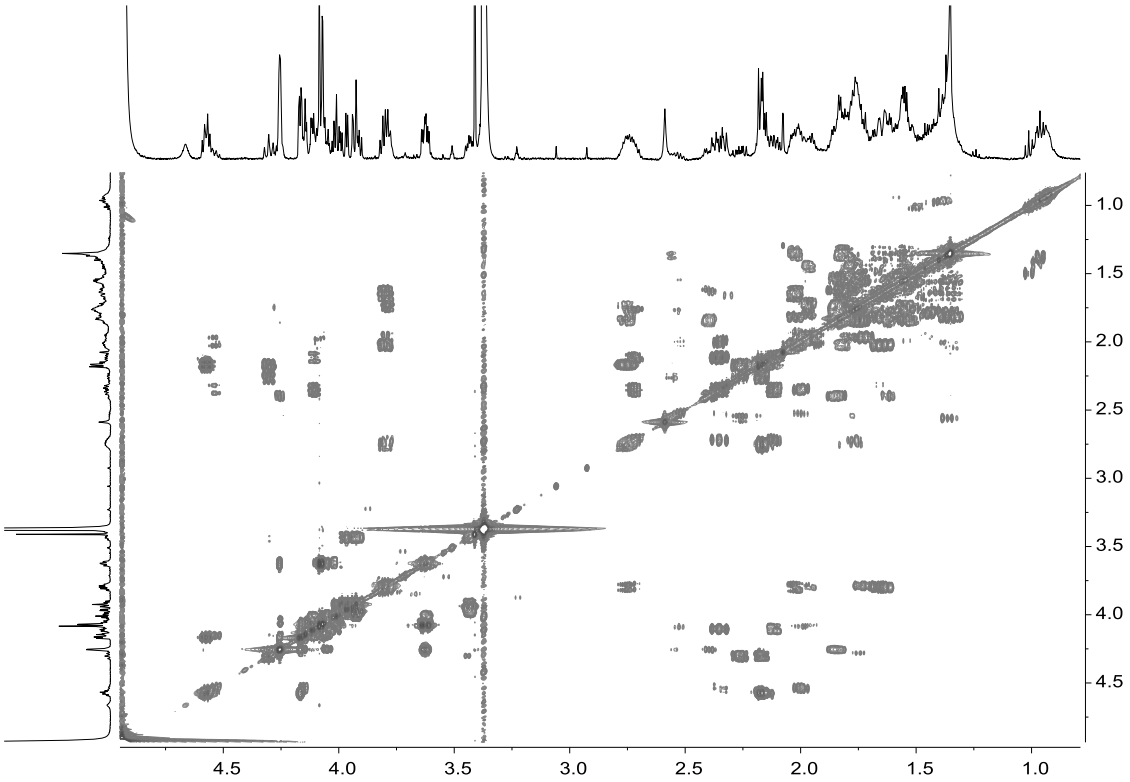
a)



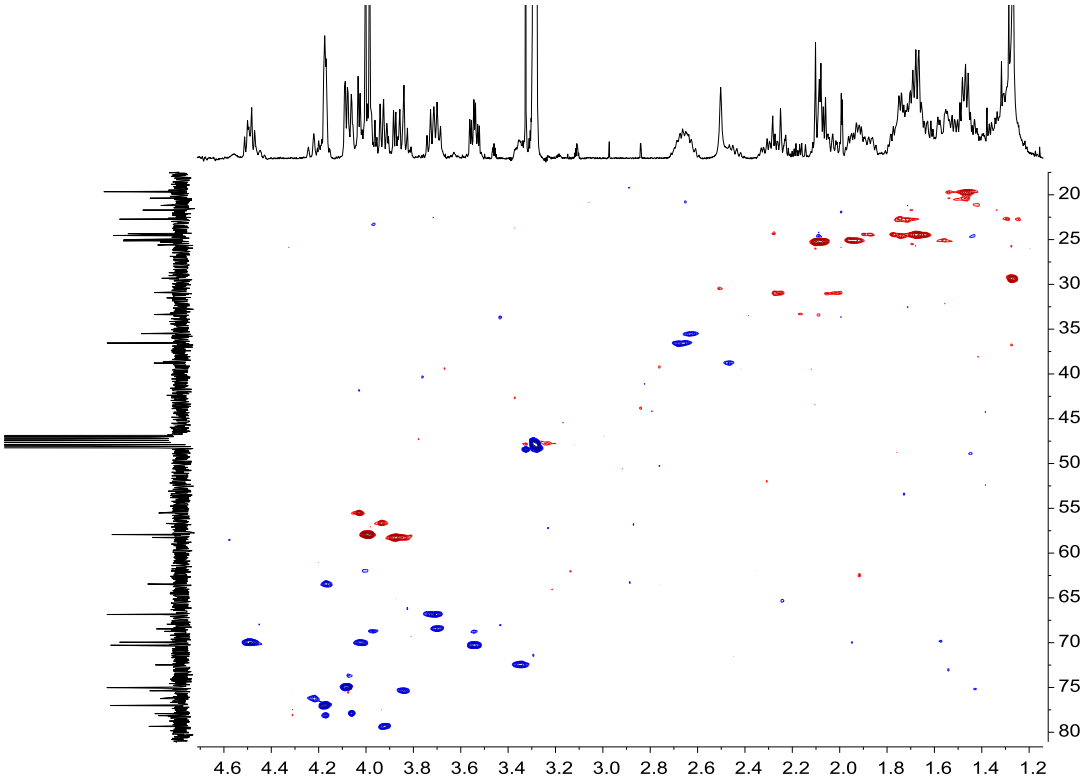
b)


25.6
37.7
1.68
2.70
1.77
H
26.3
2.11
71.1
4.51
H
1.50
1.46
20.7
4.10
OH
1.76
1.28
23.8
76.1
N
78.1
4.19
1.96
1.58
26.2
H
3.73
67.0
3.56
71.4
OH
59.1
4.02
OH
23.9
36.8
1.71
2.66
31.9
2.28
71.0
4.03
1.68
H
2.04
H
1.53
1.49
21.4
36.5
OH
1.73
1.37
22.8
80.3
3.94
N
76.4
3.85
1.90
1.68
25.4
H
3.72
69.5
3.37
73.6
OH
3.92/3.87
59.3
OH
26.7
39.9
1.70
2.49
34.3
2.21
77.3
4.24
1.31
H
2.10
H
1.50
1.55
20.7
OH
1.71
1.33
23.7
79.0
4.04
N
2.33
1.79
25.4
H
4.18
64.5
79.2
4.17
3.96
69.8
OH
4.02/4.06
56.5
OH
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
85 80 75 70 65 60 55 50 45 40 35 30 25 20 15

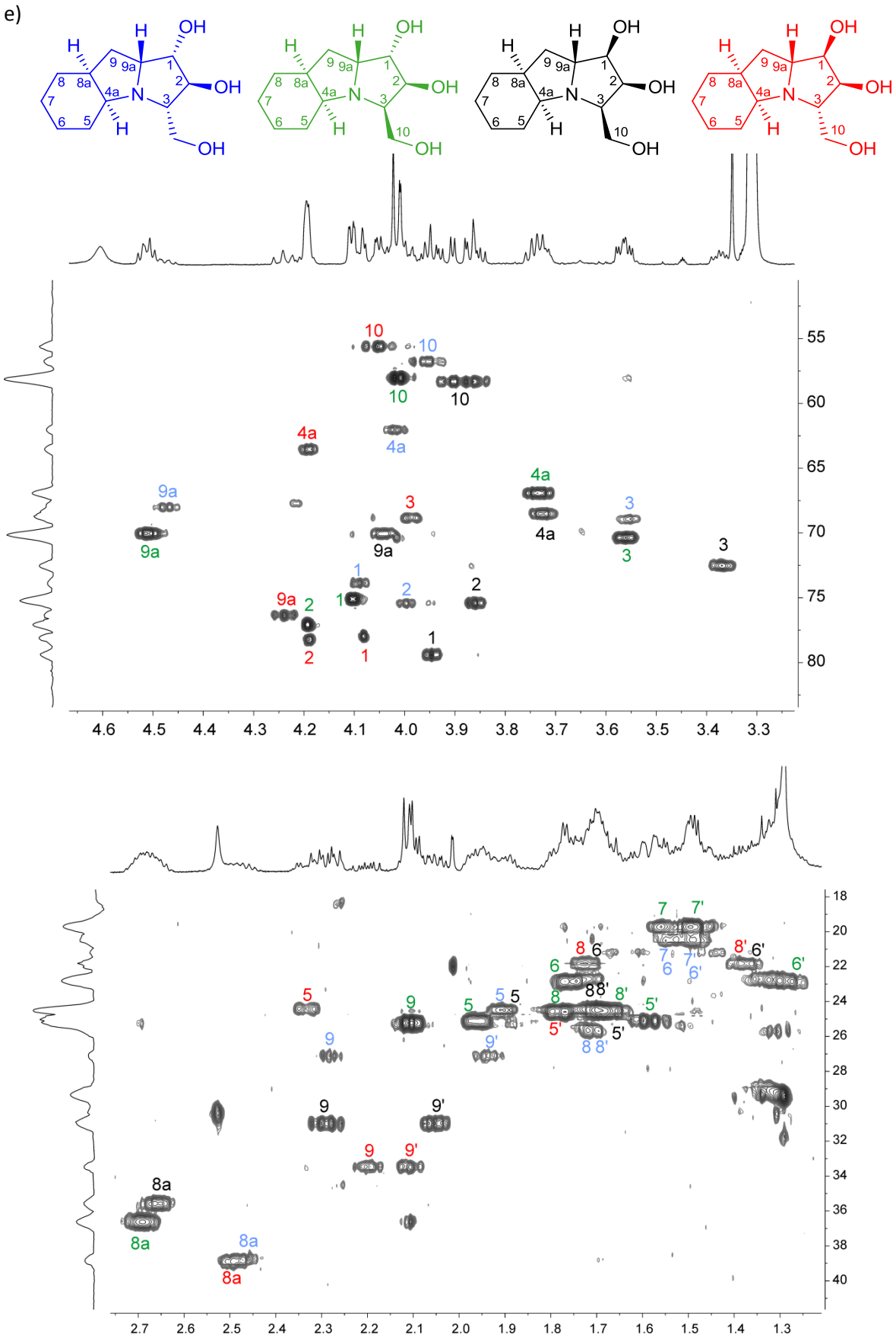
c)


1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0

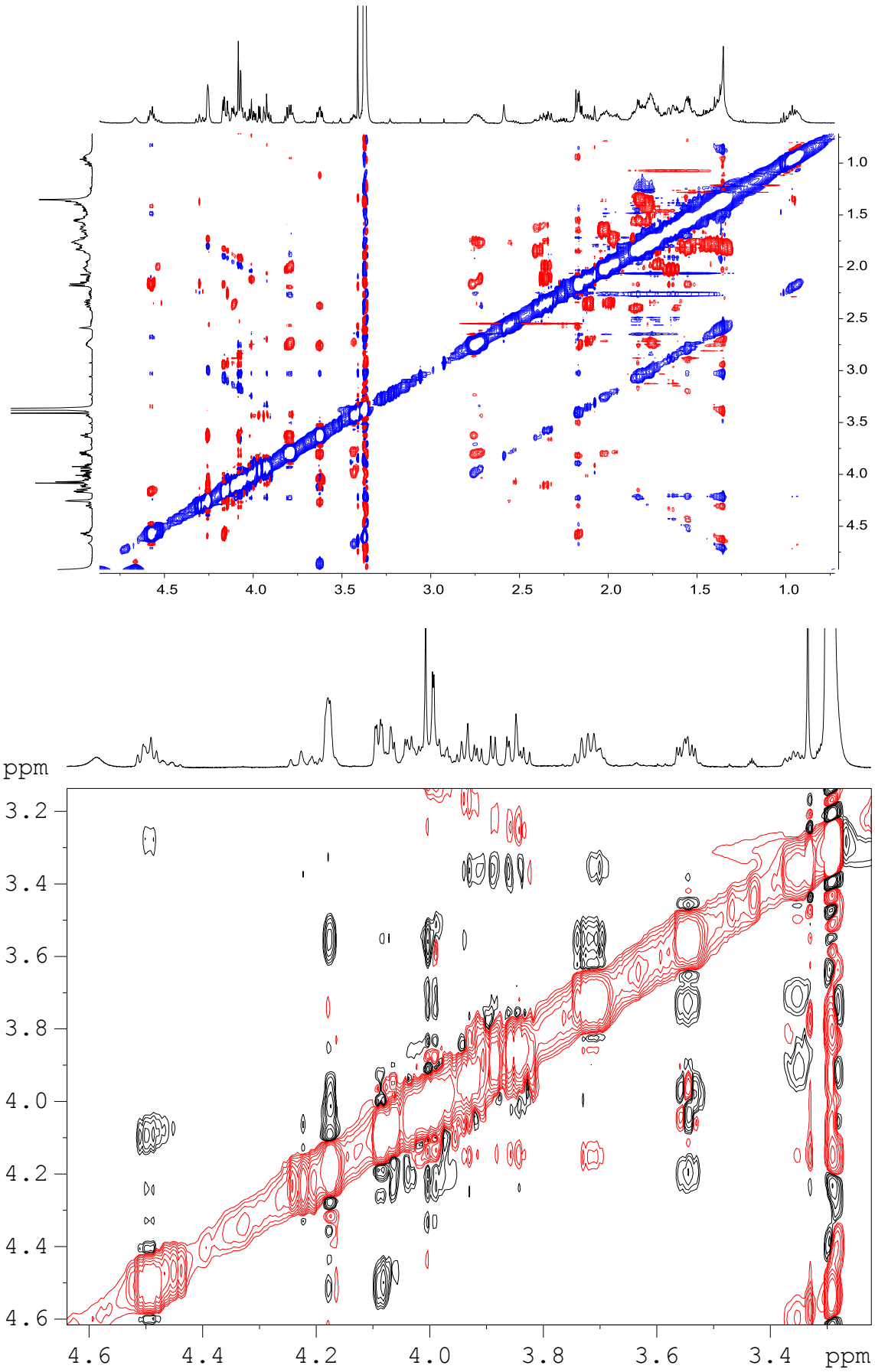
d)


20
25
30
35
40
45
50
55
60
65
70
75
80
4.6
4.4
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
1.2

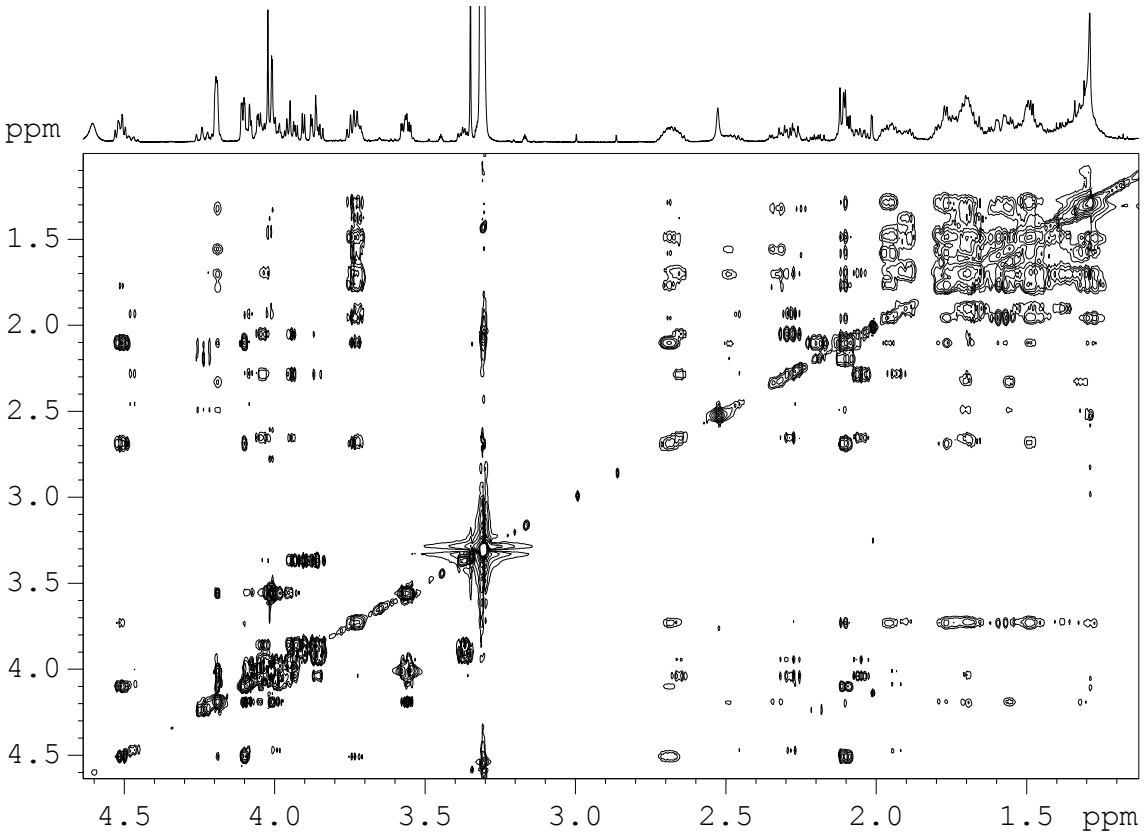
e)



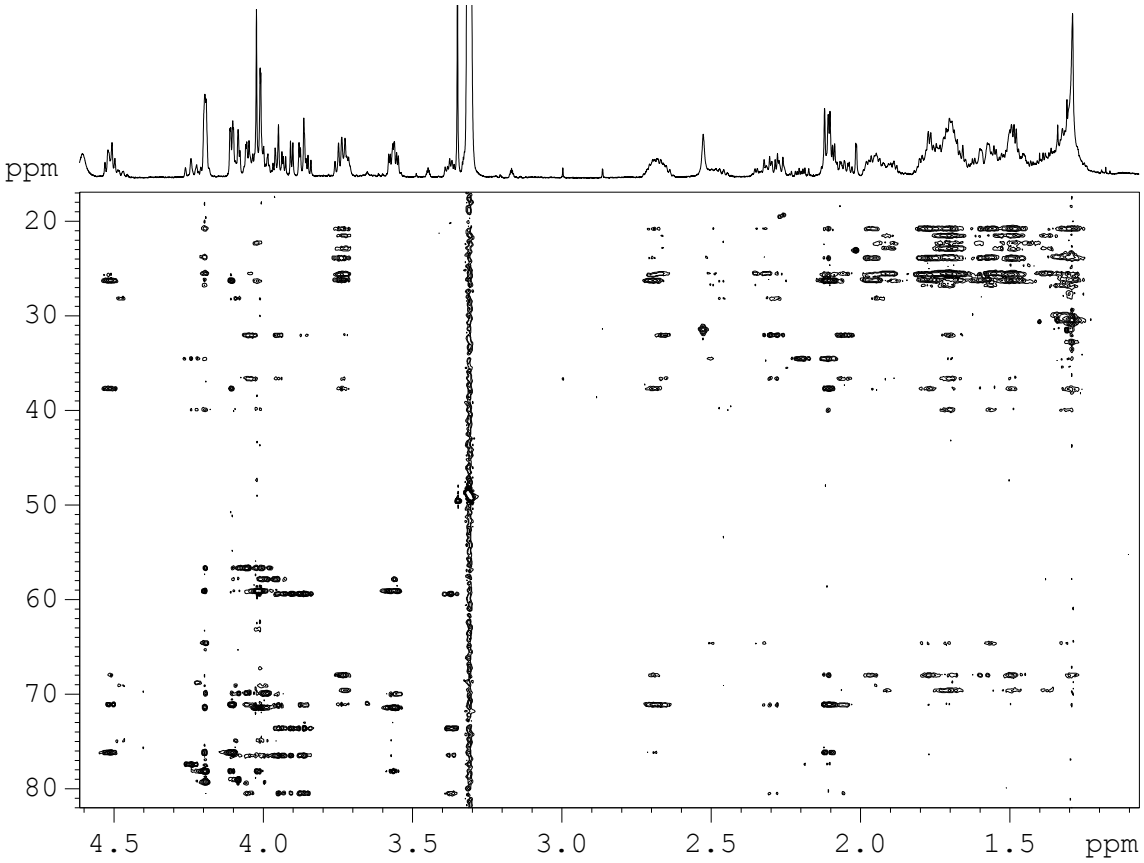
f)



g)


ppm
1.5
2.0
2.5
3.0
3.5
4.0
4.5
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

h)


ppm
20
30
40
50
60
70
80
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

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