

Heteropoly metallophosphoric acid-catalyzed Prins-type cyclizations in the synthesis of functionalized 8-oxabicyclo[5.4.0]undecanes

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Methods and Materials

All reagents and solvents were purchased from Sigma-Aldrich, and used without further purification. Monitoring of the reactions was performed using silica gel TLC plates (silica Merck 60 F254, visualization UV light at 254 and 365 nm). Column chromatography was performed on Merck Kieselgel 60–230 mesh (ASTM).

The microwave syntheses were performed using a Discover® SP System by CEM Corp.

The catalytic hydrogenation processes were performed using a Shaker Hydrogenation Apparatus by Parr Instrument Company.

¹H NMR spectra were recorded on a Varian Mercury Plus 400 instrument (400 MHz operating frequency) at 50 °C. Proton chemical shifts are given in ppm (δ) referenced to solvent residual peak (DMSO-*d*₆ δ = 2.48 ppm) as an internal standard. *J* values are given in Hz.

LC–MS analysis was performed with a Surveyor MSQ instrument by Thermo Fisher Scientific. Chromatographic separation was done on a Phenomenex Onyx Monolithic C18 25×4.6 mm column using gradient elution at ambient temperature. The elution program was as follows: gradient from 100% to 5% of mobile phase A (0.1% solution of formic acid in water) in mobile phase B (0.1% solution of formic acid in acetonitrile), with a flow rate of 1.5 mL min⁻¹. 2 μ l of sample was injected into the system. UV spectra were recorded in the 200–800 nm range. Mass spectra were recorded using atmospheric pressure chemical ionization source in positive and negative polarities.

Experimental

Compound 2

To a vigorously stirred solution of TMS-acetylene (9.8 g, 100 mmol) in dry THF (150 ml) 2.5 M solution of *n*-BuLi in THF (40.0 ml, 100 mmol) was added dropwise at -78 °C under inert atmosphere and the solution was stirred over 0.5 h at -78 °C. Then, BF₃·OEt₂ (14.2 g, 100 mmol) was added at -78 °C. The mixture was stirred another 0.5 h at -78 °C. The solution of epoxide **1** (10.6

g, 50 mmol) in dry THF (50 ml) was added dropwise to the reaction mixture at temperature below -60°C . The resulting mixture was stirred at -60°C over 1 h, warmed to a room temperature and left overnight. Then, 10% K_2CO_3 (wt.) water solution (300 ml) was added and the mixture was stirred vigorously over 1 h. The organic layer was separated and the water layer was extracted with DCM (2x200 ml). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (eluent - hexane/ethyl acetate, 4:1) to give 14.0 g of compound **2**.

Yield ~ 90 %; thick yellow oil.

^1H NMR (400 MHz, DMSO-d_6): δ - 0.25 (9H, s), 1.75 (1H, m), 1.85 (2H, m), 2.00 (2H, m), 2.25 (1H, m), 2.38 (2H, m), 2.75 (1H, m), 3.88 (1H, m), 4.88 (1H, d, $J = 5.0$ Hz), 7.25 (1H, t, $J = 8.5$ Hz), 7.38 (2H, t, $J = 8.5$ Hz), 7.50 (2H, d, $J = 8.5$ Hz).

$[\text{M}+\text{H}]^+ m/z = 312.1$

Anal. $\text{C}_{19}\text{H}_{25}\text{NOSi}$ (311): calc. C 73.26; H 8.09; N 4.50; found C 73.29; H 8.05; N 4.61.

Compound 3

A solution of compound **2** (15.5 g, 50 mmol) and NaOH (3.0 g, 75.0 mmol) in ethanol (80 ml) was stirred over 3 h at room temperature. Then, the reaction mixture was diluted with DCM (350 ml) and washed with solution of HCl (1% wt, 120 ml) and water (2x150 ml). The organic layer was separated, dried over Na_2SO_4 . The solvent was evaporated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (eluent - hexane/ethyl acetate, 2:1) to give 11.9 g of compound **3**.

Yield ~ 100 %; yellow crystalline powder.

^1H NMR (400 MHz, DMSO-d_6): δ - 1.75 (1H, m), 1.85 (2H, m), 2.00 (2H, m), 2.25 (1H, m), 2.30 (1H, m), 2.36 (1H, m), 2.75 (1H, m), 2.97 (1H, m), 3.88 (1H, m), 5.00 (1H, d, $J = 5.0$ Hz), 7.25 (1H, t, $J = 8.5$ Hz), 7.38 (2H, t, $J = 8.5$ Hz), 7.50 (2H, d, $J = 8.5$ Hz).

$[\text{M}+\text{H}]^+ m/z = 240.2$

Anal. $\text{C}_{16}\text{H}_{17}\text{NO}$ (239): calc. C 80.30; H 7.16; N 5.85; found C 80.31; H 7.21; N 5.73.

Compound 4

Compound **3** (11.9 g, 50 mmol) was dissolved in ethyl acetate (300 ml) at room temperature. Lindlar catalyst (0.5 g) and quinoline (0.06 g, 0.5 mmol) were added to the solution. The formed suspension was flushed with argon and placed into Parr shaker-type apparatus. Hydrogenation was completed in 8 h at hydrogen pressure 1 atm and 20°C . Then, the resulting mixture was filtered through the pad of celite. The solvent was evaporated under reduced pressure. The crude

residue was purified by flash chromatography on silica gel (eluent - hexane/ethyl acetate, 2:1) to give 12.0 g of compound **4**.

Yield ~ 100 %; yellow crystalline powder.

^1H NMR (400 MHz, DMSO- d_6): δ – 1.75 (2H, m), 1.85 (2H, m), 2.00 (2H, m), 2.20 (2H, m), 2.40 (1H, m), 3.60 (1H, m), 4.58 (1H, d, J = 5.0 Hz), 5.00 (2H, d/d, J = 12.0 Hz / 6.0 Hz), 5.90 (1H, m), 7.25 (1H, t, J = 8.5 Hz), 7.38 (2H, t, J = 8.5 Hz), 7.50 (2H, d, J = 8.5 Hz).

$[\text{M}+\text{H}]^+ m/z = 242.1$

Anal. $\text{C}_{16}\text{H}_{19}\text{NO}$ (241): calc. C 79.63; H 7.94; N 5.80; found C 79.61; H 7.98; N 5.85.

Compound 6b: 4.4 g; yield 65%; white crystalline solid.

^1H NMR (400 MHz, DMSO- d_6): δ – 1.12 (3H, s), 1.20 (4H, superposition of s (3H) and m (1H)), 1.25 (2H, m), 1.63 (1H, m), 1.75 (4H, superposition of s (3H) and m (1H)), 1.88 (2H, m), 2.12 (2H, m), 2.25 (1H, m), 2.38 (1H, m), 3.50 (1H, 1H, d/d/d, J = 9.7 Hz / 6.6 Hz / 4.9 Hz), 3.75 (1H, t/d/d, J = 12.0 Hz / 8.7 Hz / 4.2 Hz), 7.25 (1H, t, J = 8.5 Hz), 7.37 (2H, t, J = 8.5 Hz), 7.50 (2H, d, J = 8.5 Hz), 7.53 (1H, d, J = 5.0 Hz).

$[\text{M}+\text{H}]^+ m/z = 341.2$

Anal. $\text{C}_{21}\text{H}_{28}\text{N}_2\text{O}_2$ (340): calc. C 74.08; H 8.29; N 8.23; found C 74.10; H 8.27; N 8.14.

Compound 6d: 4.1 g; yield 68%; white crystalline solid.

^1H NMR (400 MHz, DMSO- d_6): δ – 1.10 (3H, s), 1.15 (3H, s), 1.25 (2H, m), 1.75 (2H, m), 1.85 (1H, m), 1.95 (1H, m), 2.05 (2H, m), 2.25 (2H, m), 2.40 (1H, m), 3.40 (2H, m), 4.50 (1H, d, J = 5.0 Hz), 7.25 (1H, t, J = 8.5 Hz), 7.38 (2H, t, J = 8.5 Hz), 7.50 (2H, d, J = 8.5 Hz).

$[\text{M}+\text{H}]^+ m/z = 300.2$

Anal. $\text{C}_{19}\text{H}_{25}\text{NO}_2$ (299): calc. C 76.22; H 8.42; N 4.68; found C 76.24; H 8.47; N 4.59.

Compound 6e: 6.2 g; yield 60%; white crystalline solid.

^1H NMR (400 MHz, DMSO- d_6): δ – 1.20 (5H, m), 1.50 (1H, m), 1.73 (1H, m), 1.75 (3H, s), 1.85 (3H, m), 2.15 (4H, m), 2.35 (1H, m), 3.00 (1H, m), 3.15 (1H, m), 3.50 (1H, m), 3.75 (2H, m), 3.78 (1H, m), 5.00 (2H, s), 7.25 (6H, m), 7.38 (2H, t, J = 8.5 Hz), 7.50 (2H, d, J = 8.5 Hz), 7.62 (1H, d, J = 7.0 Hz).

$[\text{M}+\text{H}]^+ m/z = 516.2$

Anal. $\text{C}_{31}\text{H}_{37}\text{N}_3\text{O}_4$ (515): calc. C 72.21; H 7.23; N 8.15; found C 72.23; H 7.25; N 8.28.

Compounds 7 a-e. General Procedure.

The corresponding nitrile (**6a-e**; ~ 10 mmol) was dissolved in 100 ml MeOH saturated with NH₃ (15-20 wt%). Raney nickel (1.0 g) was pre-washed twice with methanol and resulting suspension was added to the solution. The formed suspension was flushed with argon and placed into Parr shaker-type apparatus. Hydrogenation was completed in about 18 h at a hydrogen pressure 2-3 atm and 20 °C. Then resulting mixture was filtered through the pad of celite. The solvent was evaporated under reduced pressure. A residue was purified by flash chromatography on silica gel (eluent – DCM/methanol, 99:1) to give corresponding amines **7a-e** in a quantitative yield.

Compound 7a: 3.9 g; yield ~ 100 %; colorless thick oil.

¹H NMR (400 MHz, DMSO-d₆): δ – 0.72 (2H, broad peak), 0.87 (1H, m), 1.22 (1H, m), 1.35 (1H, m), 1.60 (3H, m), 1.80 (1H, m), 1.92 (3H, m), 2.00 (1H, m), 2.15 (2H, m), 2.25 (1H, m), 2.60 (2H, m), 3.15 (1H, m), 3.50 (1H, m), 4.25 (1H, m), 7.15 (1H, m), 7.25 (5H, m), 7.32 (2H, m), 7.37 (2H, m), 7.45 (1H, d, *J* = 5.0 Hz). [M+H]⁺ *m/z* = 393.2.

Anal. C₂₅H₃₂N₂O₂ (392): calc. C 76.49; H 8.22; N 7.14; found C 76.47; H 8.25; N 7.29.

Compound 7b: 3.4 g; yield ~ 100 %; colorless thick oil.

¹H NMR (400 MHz, DMSO-d₆): δ – 0.68 (2H, broad peak), 0.78 (1H, m), 1.12 (3H, s), 1.25 (4H, superposition of s (3H) and m (1H)), 1.38 (1H, m), 1.62 (3H, m), 1.75 (1H, m), 1.82 (3H, s), 2.25 (3H, m), 2.75 (1H, m), 3.25 (3H, m), 3.75 (1H, m), 7.15 (1H, m), 7.25 (4H, m), 7.38 (1H, d, *J* = 5.0 Hz). [M+H]⁺ *m/z* = 345.2.

Anal. C₂₁H₃₂N₂O₂ (344): calc. C 73.22; H 9.36; N 8.13; found C 73.25; H 9.32; N 8.02.

Compound 7c: 3.5 g; yield ~ 100 %; colorless thick oil.

¹H NMR (400 MHz, DMSO-d₆): δ – 0.70 (2H, broad peak), 1.00 (1H, m), 1.25 (1H, m), 1.38 (1H, m), 1.50 (2H, m), 1.60 (1H, m), 1.85 (1H, m), 2.05 (2H, m), 2.25 (2H, m), 2.63 (2H, d/d, *J* = 12.0 Hz), 3.13 (1H, m), 3.35 (1H, m), 4.40 (1H, d/d, *J* = 12.0 Hz / 4.0 Hz), 4.58 (1H, d, *J* = 5.0 Hz), 7.16 (1H, m), 7.22 (1H, m), 7.28 (4H, m), 7.32 (4H, m). [M+H]⁺ *m/z* = 352.2.

Anal. C₂₃H₂₉NO₂ (351): calc. C 78.59; H 8.32; N 3.99; found C 78.60; H 8.36; N 4.08.

Compound 7d: 3.0 g; yield ~ 100 %; colorless thick oil.

¹H NMR (400 MHz, CDCl₃): δ – 0.75 (2H, broad peak), 1.00 (1H, m), 1.15 (1H, m), 1.25 (7H, superposition of two s (6H) and m (1H)), 1.30 (2H, m), 1.45 (2H, m), 1.60 (1H, m), 1.85 (3H, m), 2.15 (2H, m), 2.30 (1H, m), 3.25 (1H, m), 3.50 (1H, m), 7.12 (1H, m), 7.25 (4H, m).

[M+H]⁺ *m/z* = 304.2.

Anal. C₁₉H₂₉NO₂ (303): calc. C 75.21; H 9.63; N 4.62; found C 75.23; H 9.62; N 4.54.

Compound 7e: 5.2 g; yield ~ 100 %; colorless thick oil.

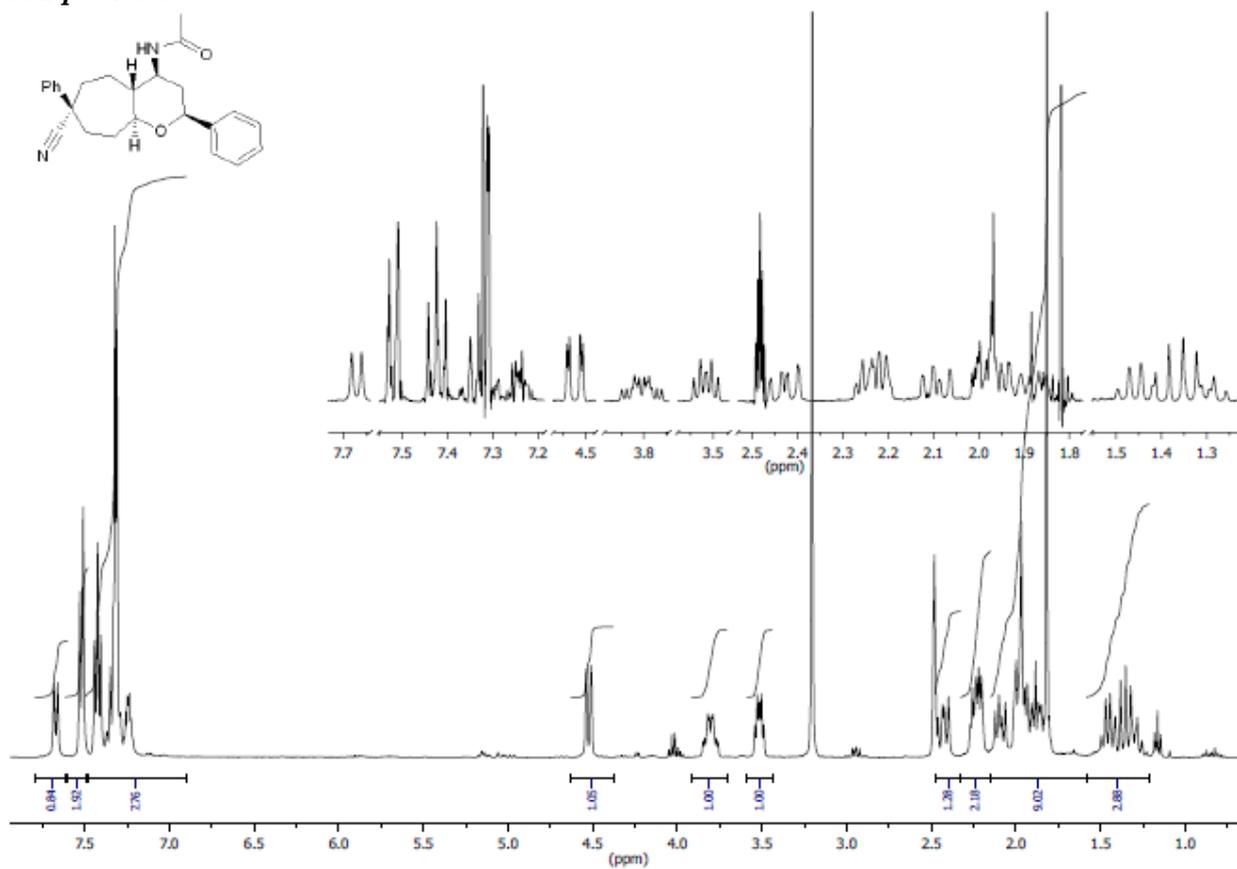
¹H NMR (400 MHz, DMSO-d₆): δ – 0.74 (2H, broad peak), 0.95 (5H, m), 1.45 (2H, m), 1.70 (3H, s), 1.82 (3H, m), 2.10 (4H, m), 2.25 (1H, m), 2.70 (2H, m), 2.90 (1H, m), 3.10 (1H, m), 3.30 (1H, m), 3.45 (2H, m), 3.70 (1H, m), 4.90 (2H, s), 7.15 (6H, m), 7.30 (2H, m), 7.42 (2H, d, *J* = 8.5 Hz), 7.51 (1H, d, *J* = 7.0 Hz).

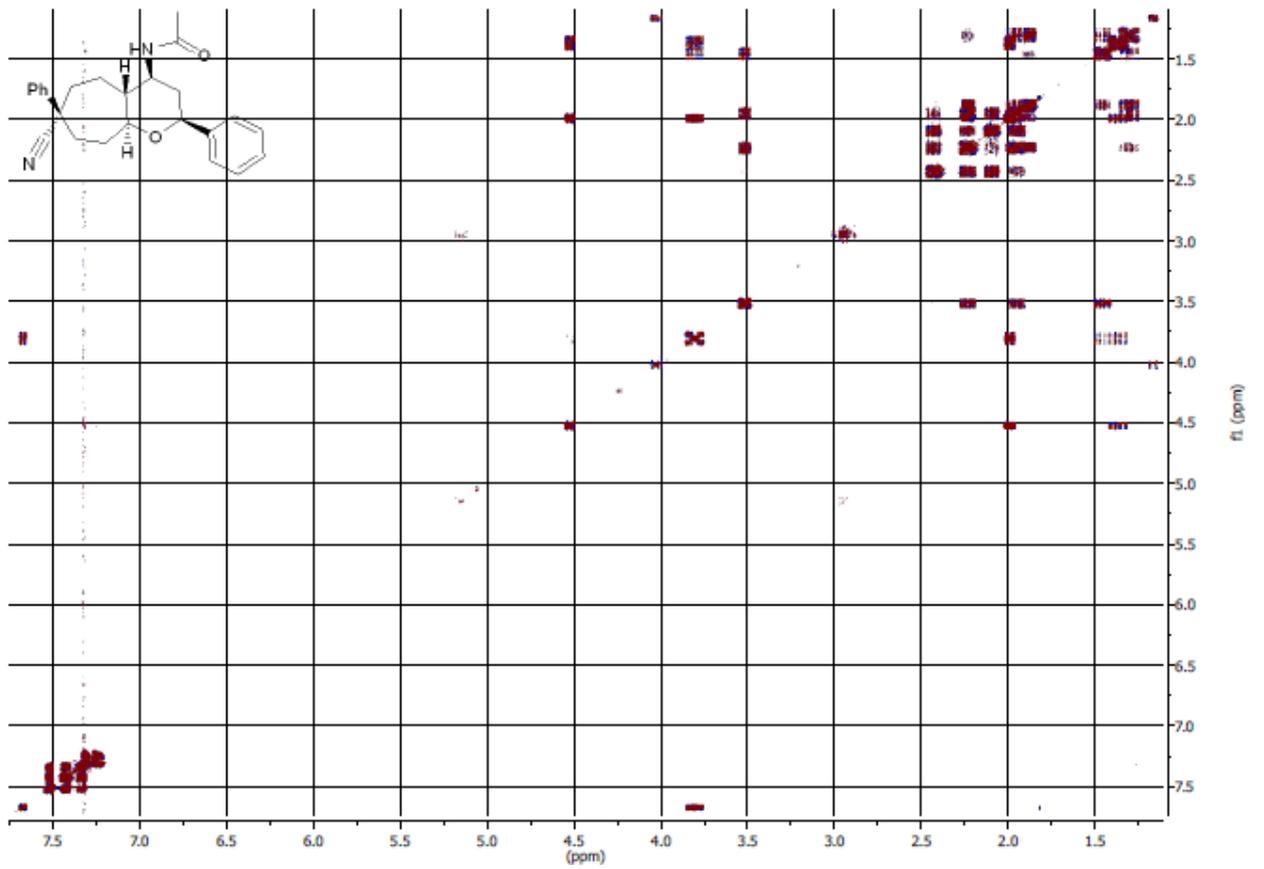
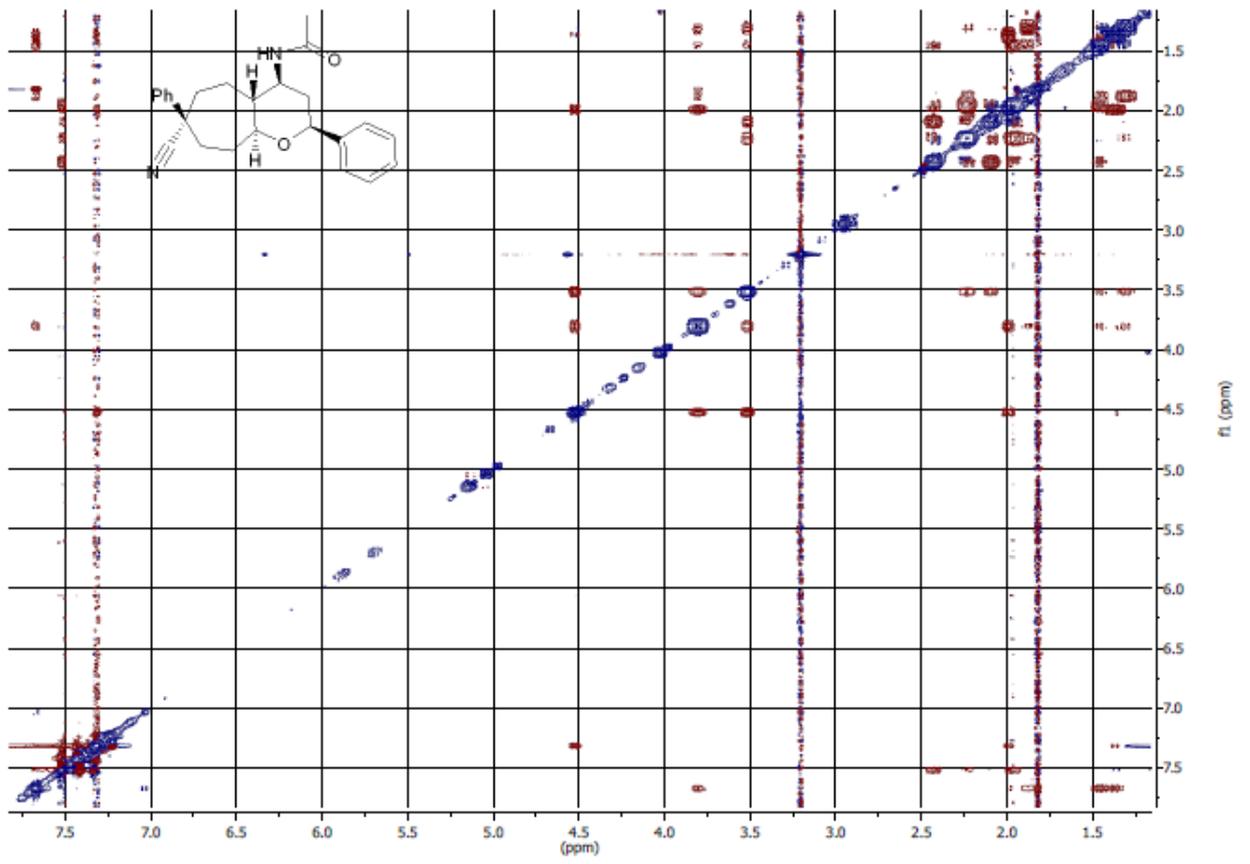
[M+H]⁺ *m/z* = 520.3.

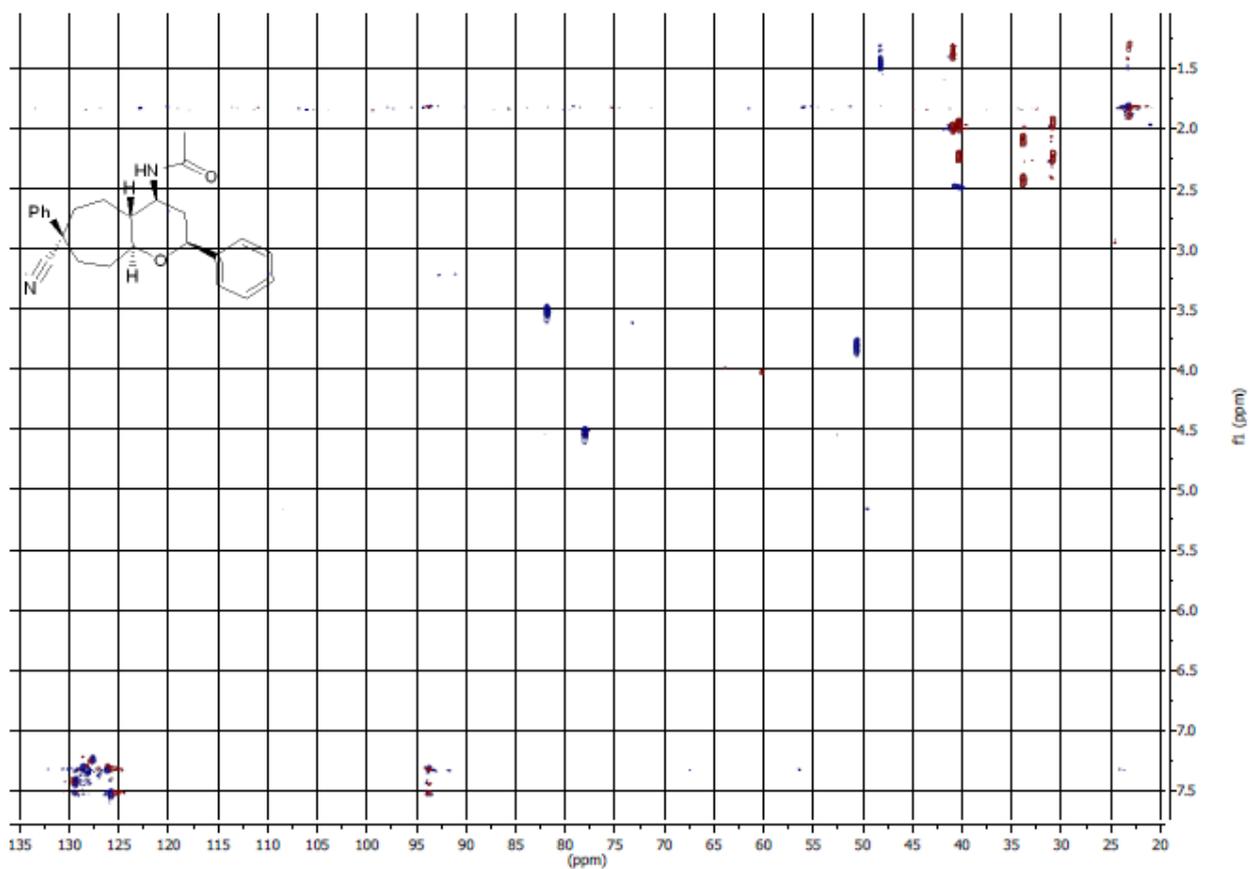
Anal. C₃₁H₄₁N₃O₄ (519): calc. C 71.65; H 7.95; N 8.09; found C 71.68; H 7.97; N 8.17.

Appendix 2D NMR data for compounds 6 a-e

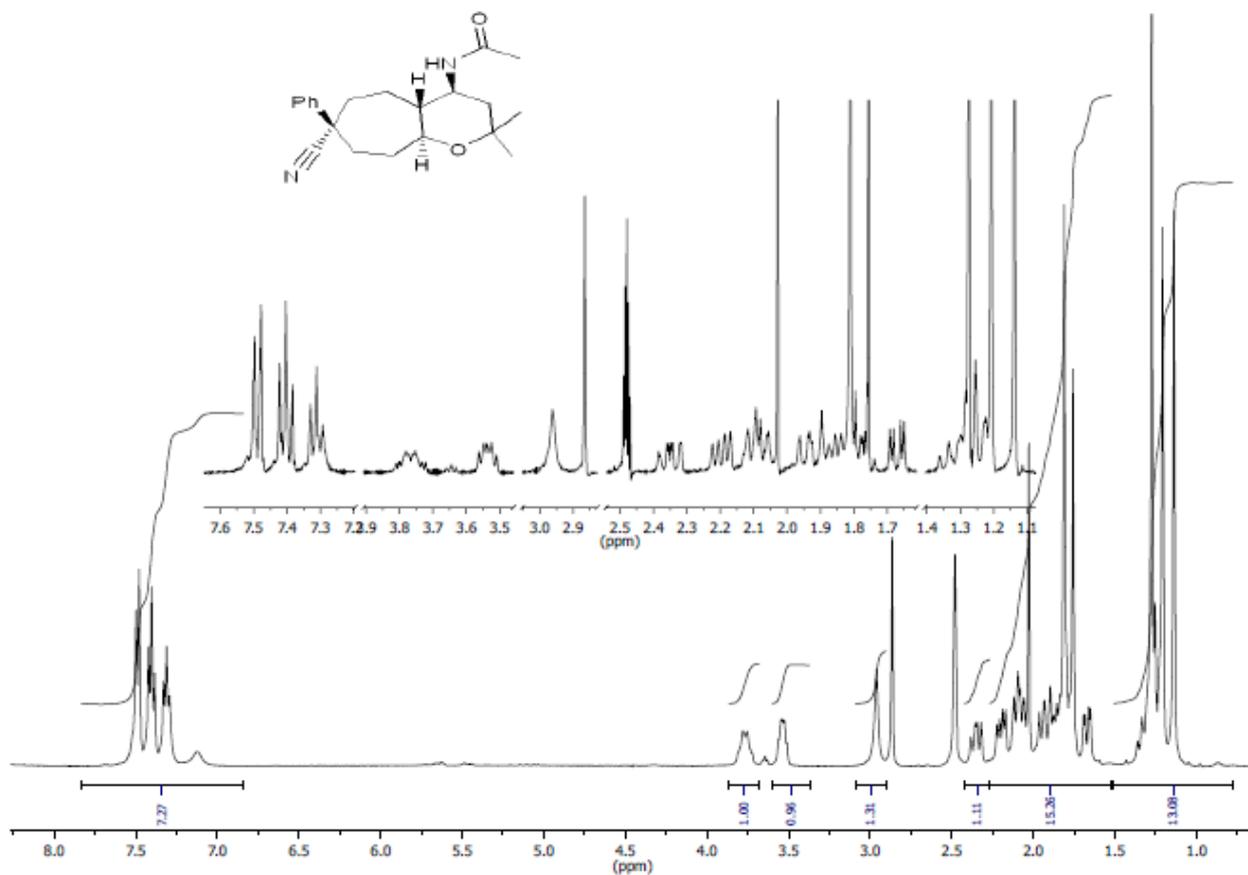
Compound 6a

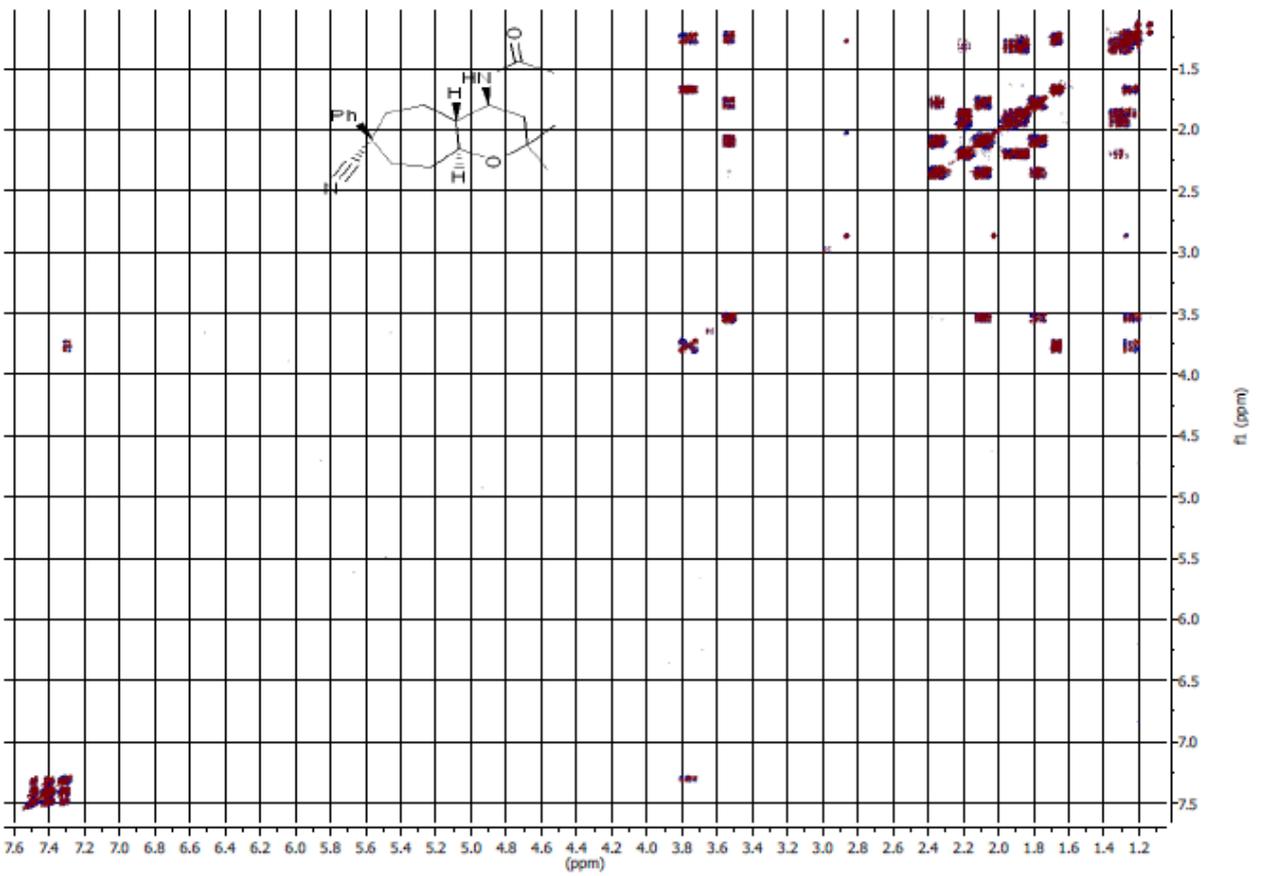
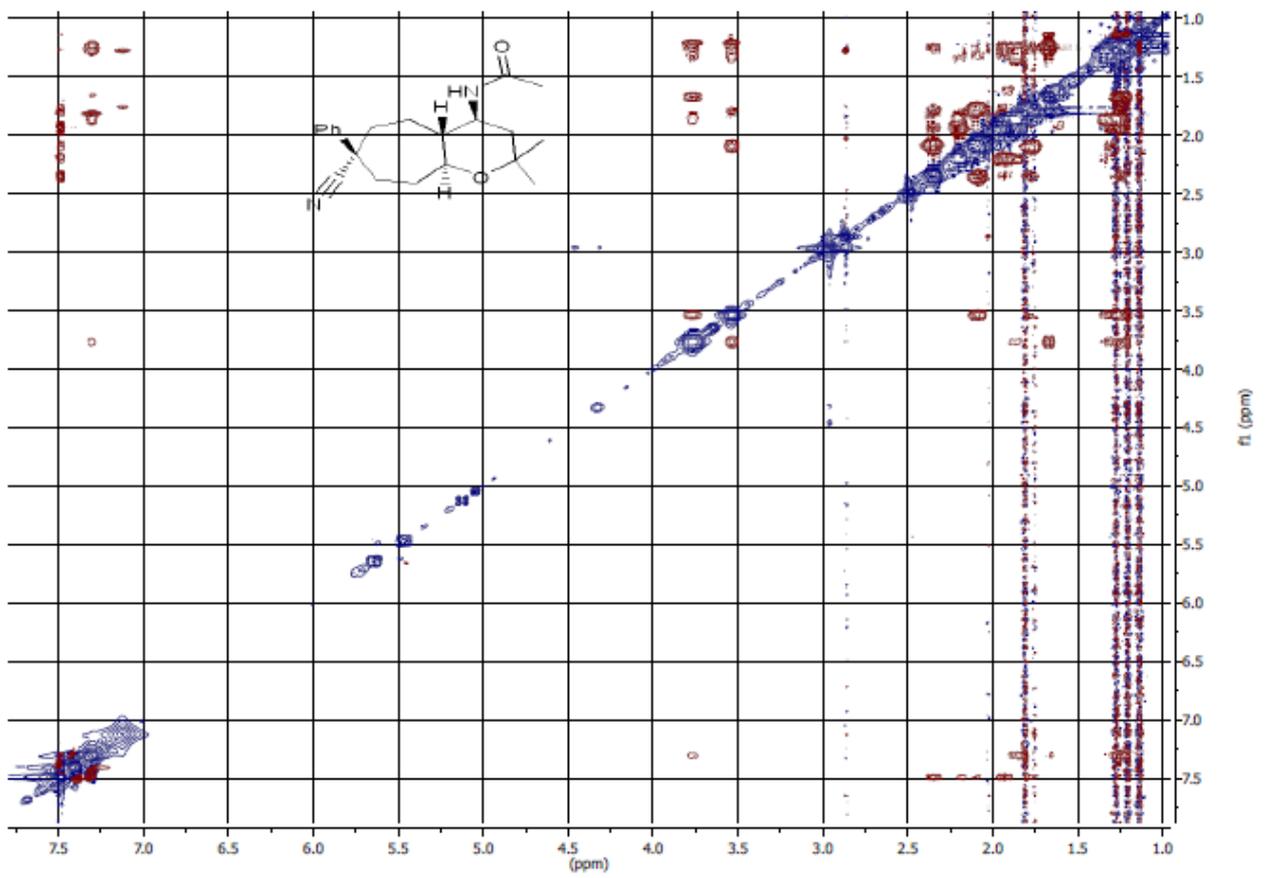


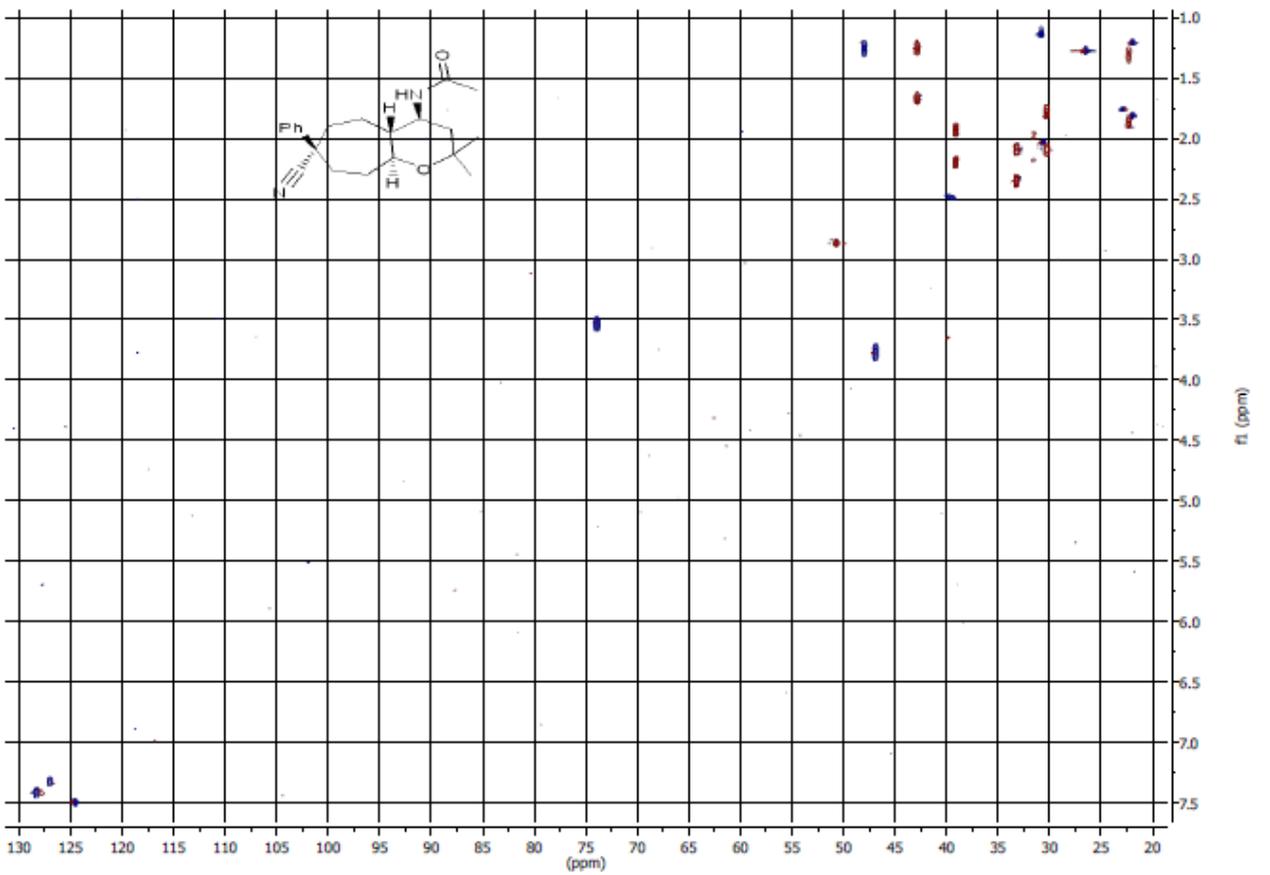
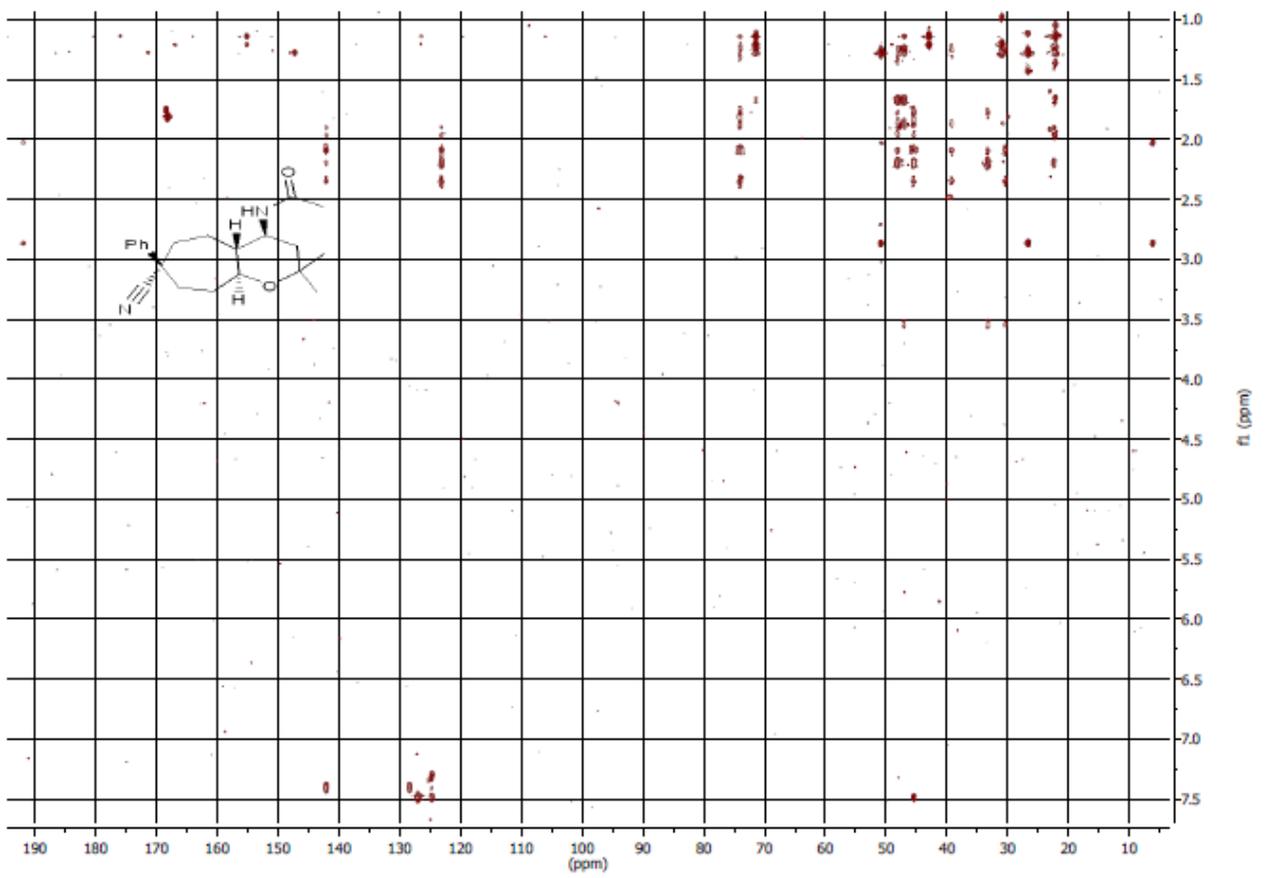




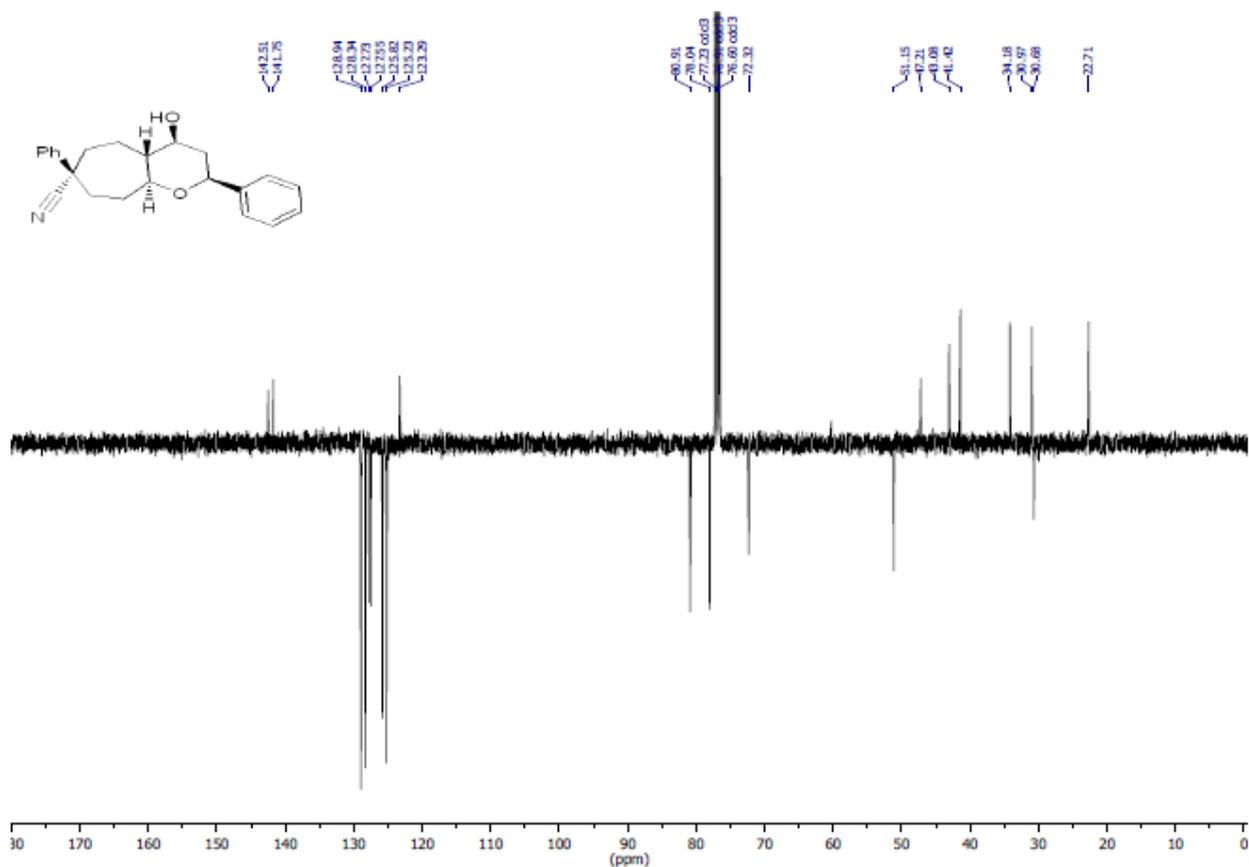
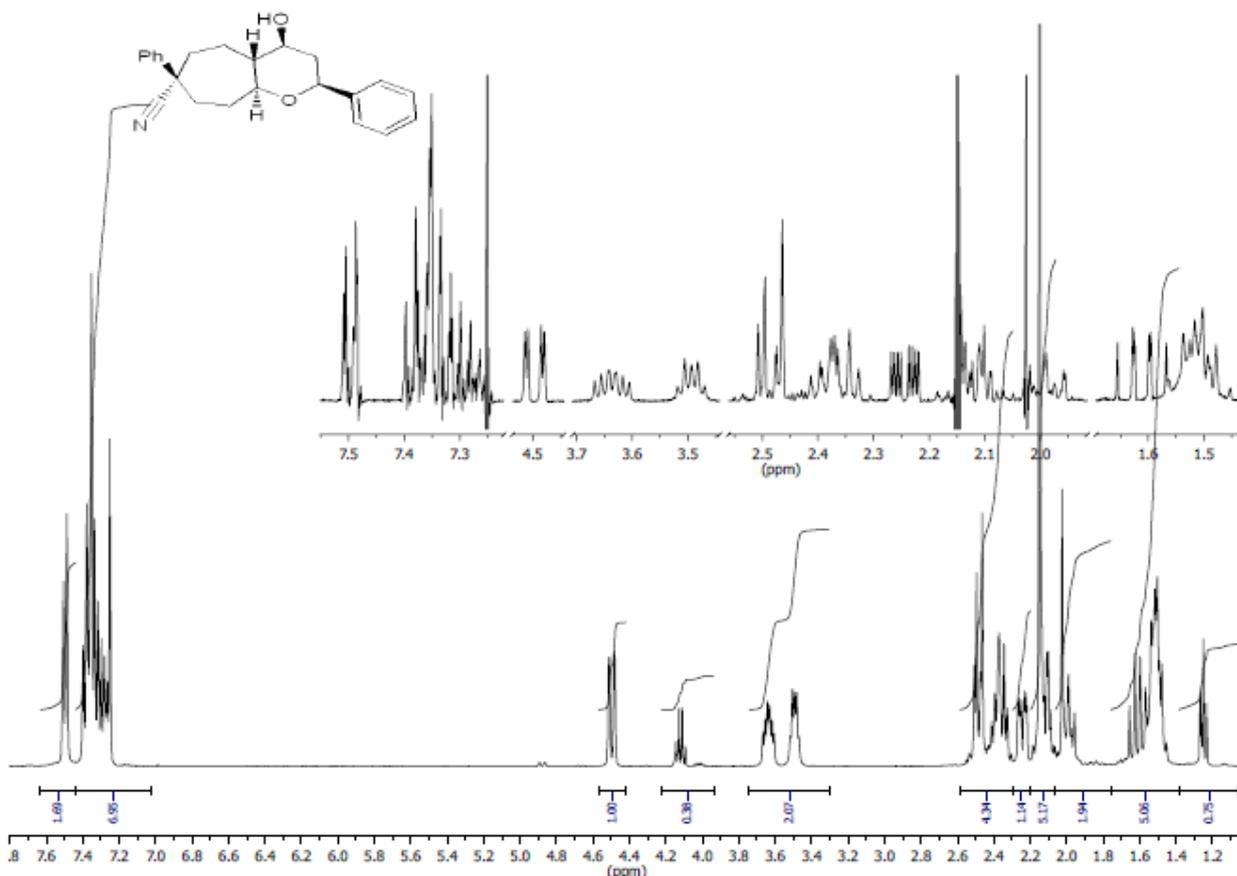
Compound 6b

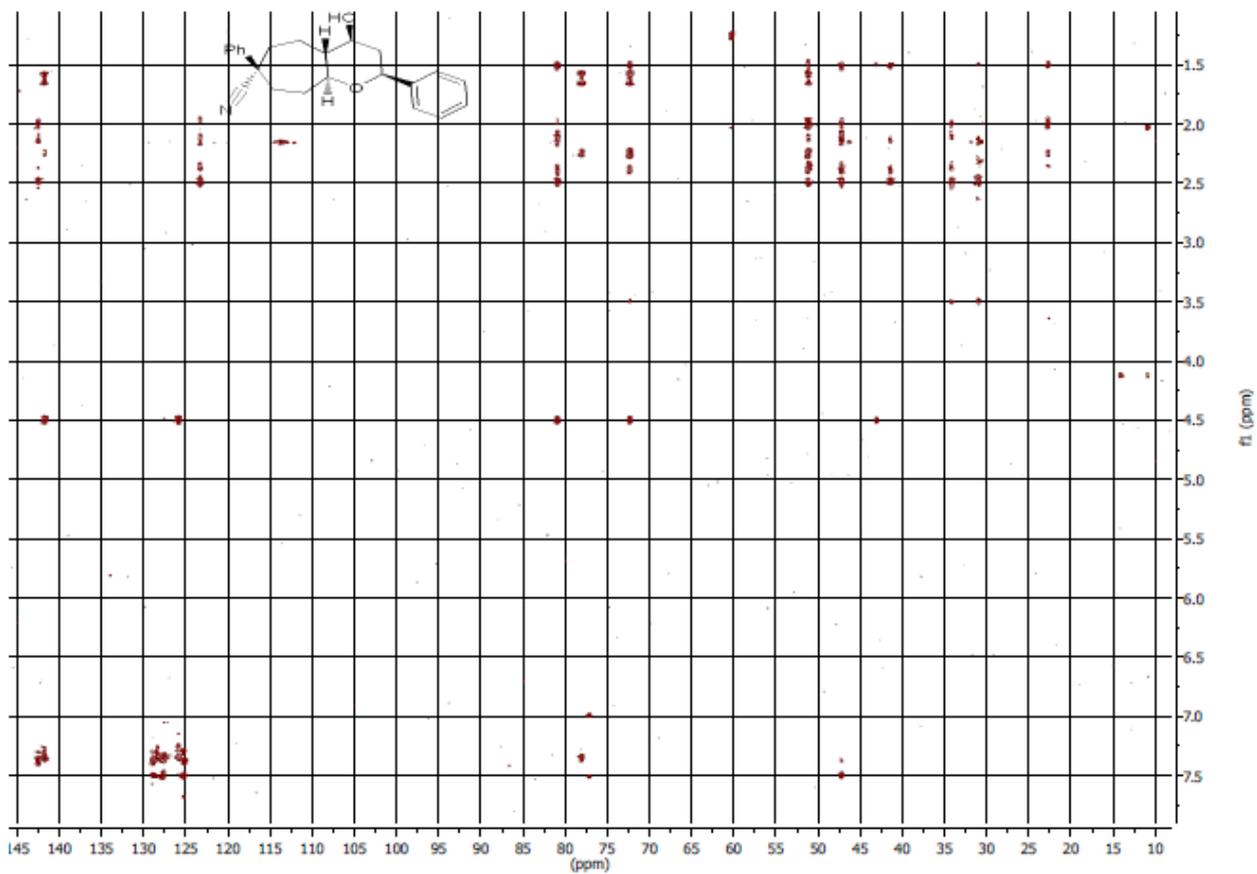
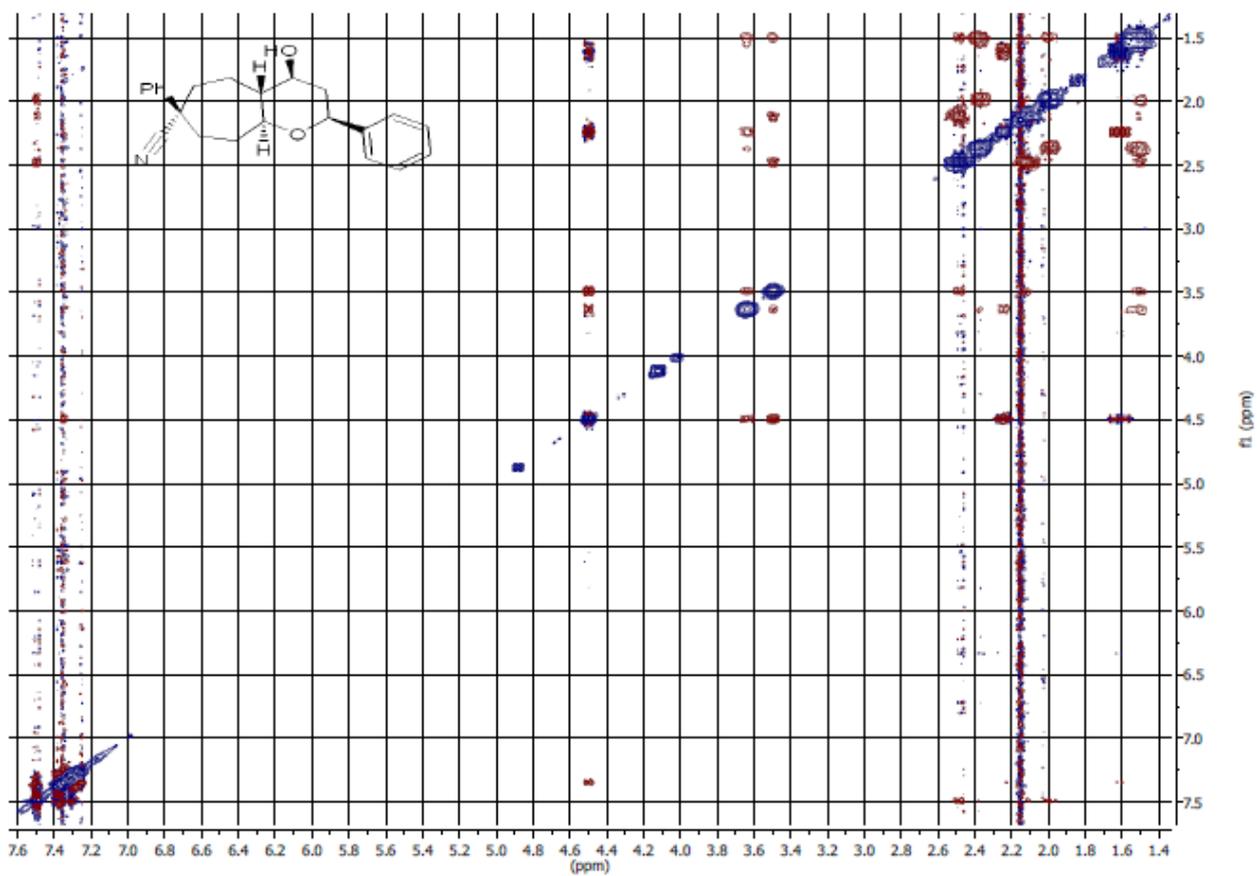


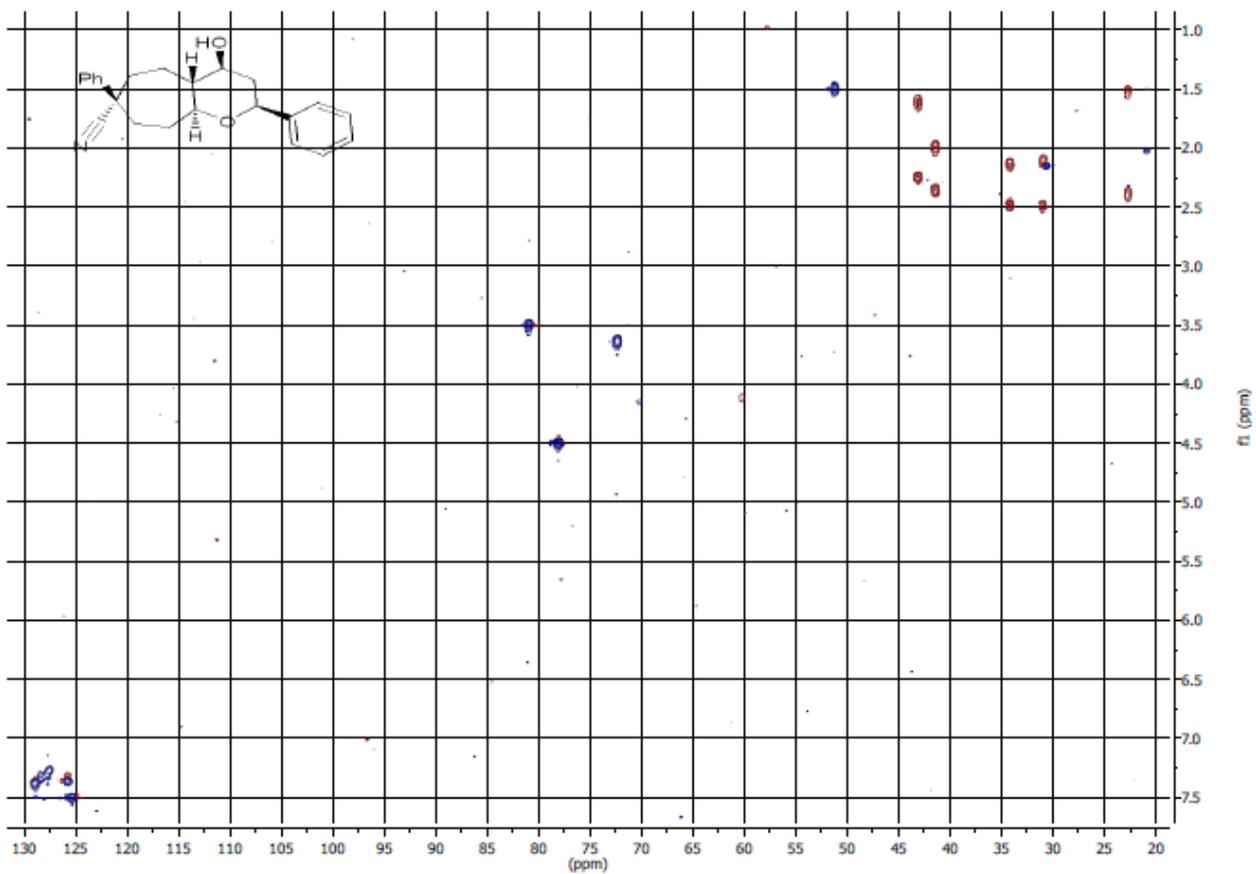




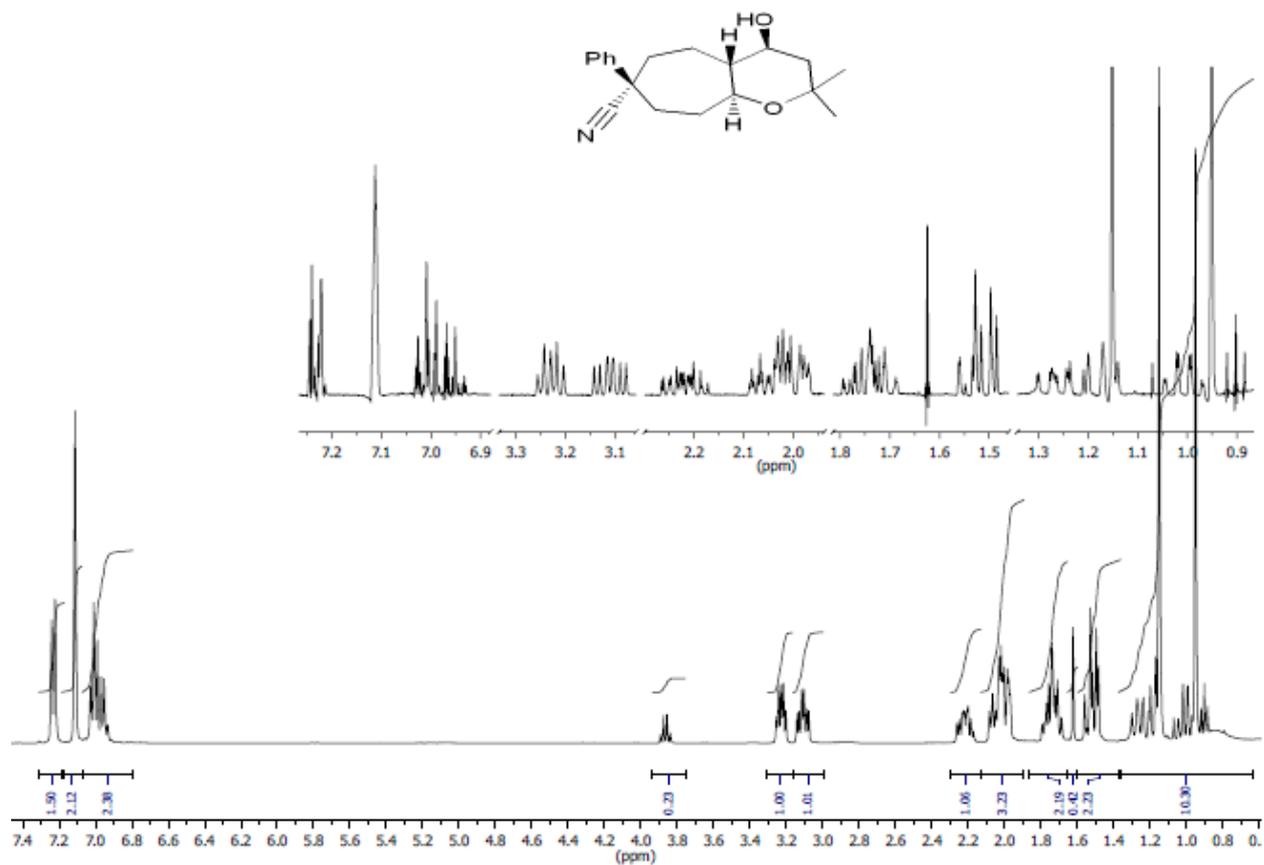
Compound 6c

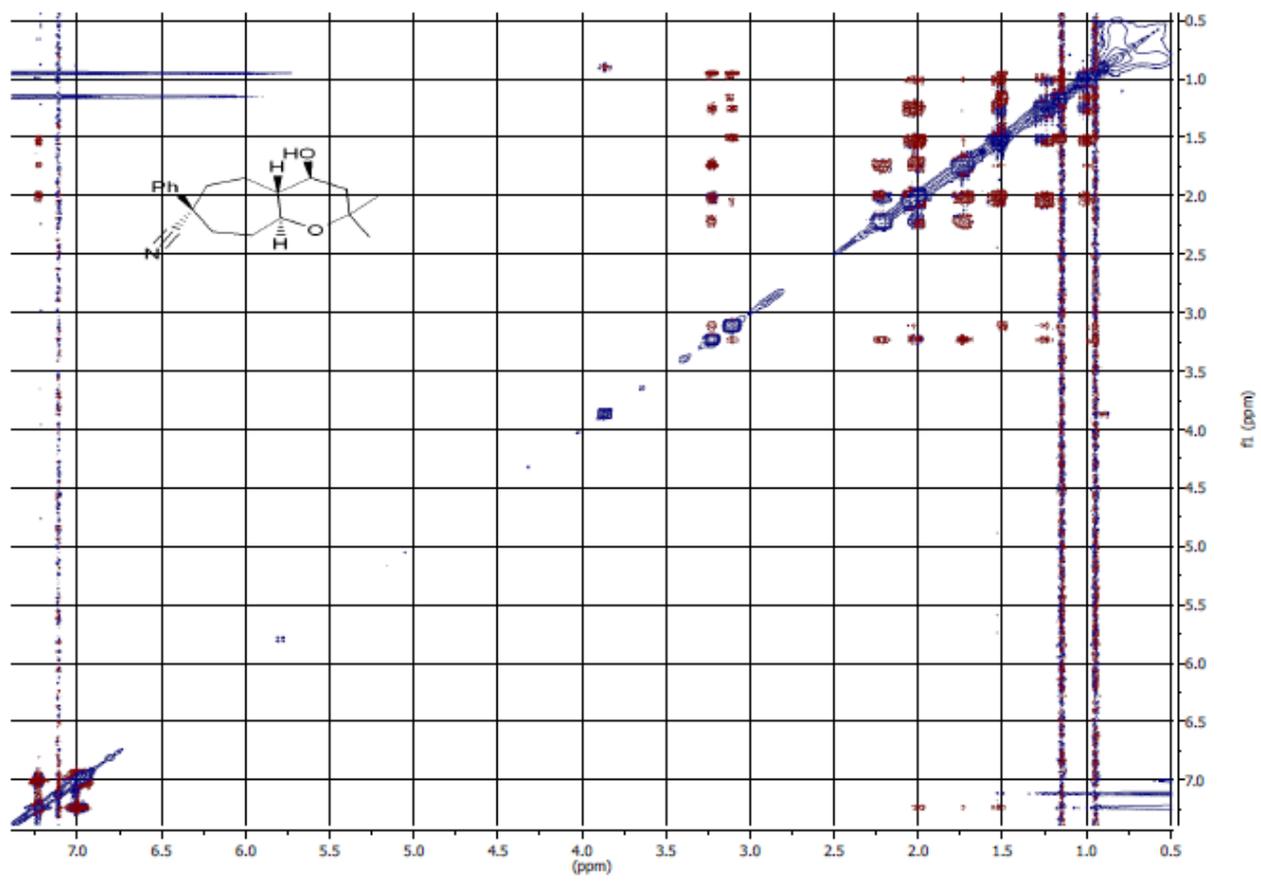
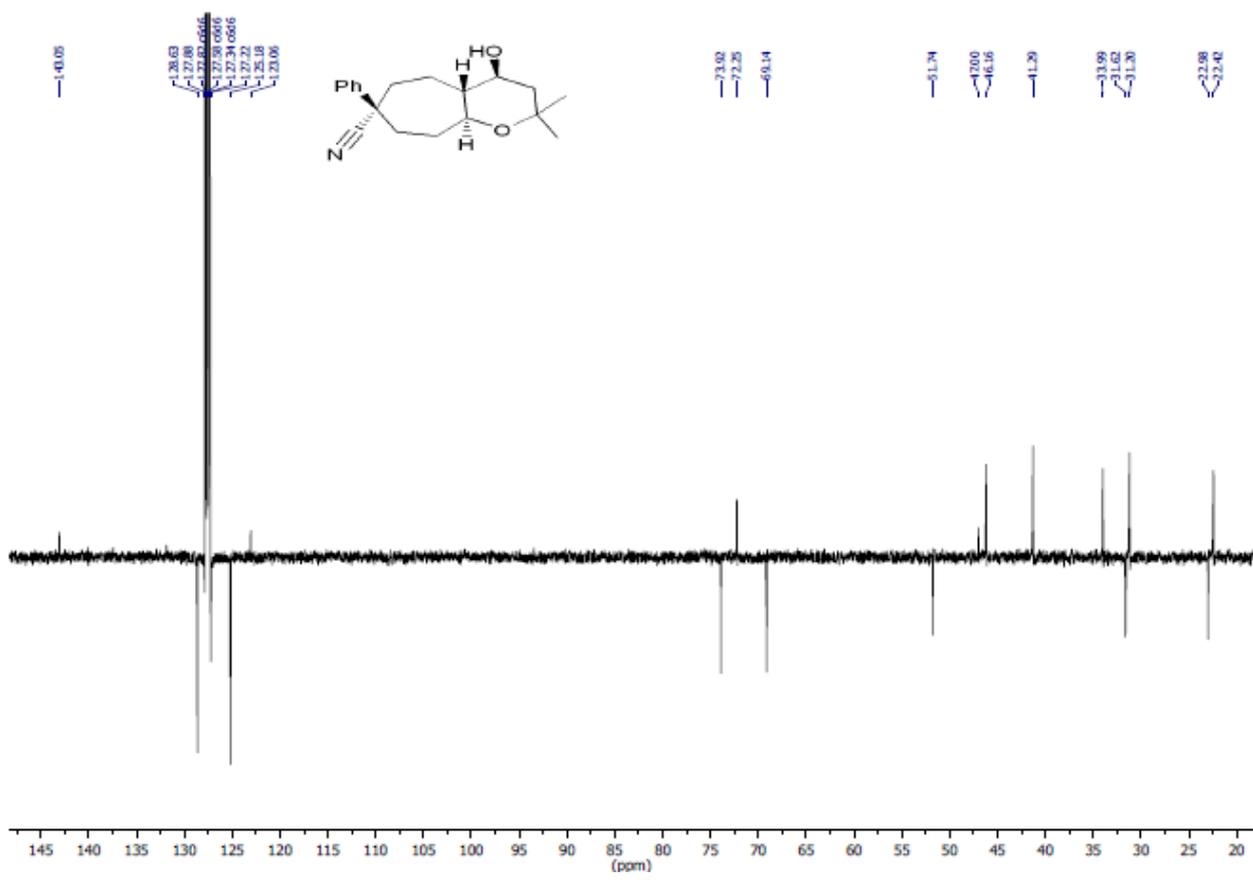


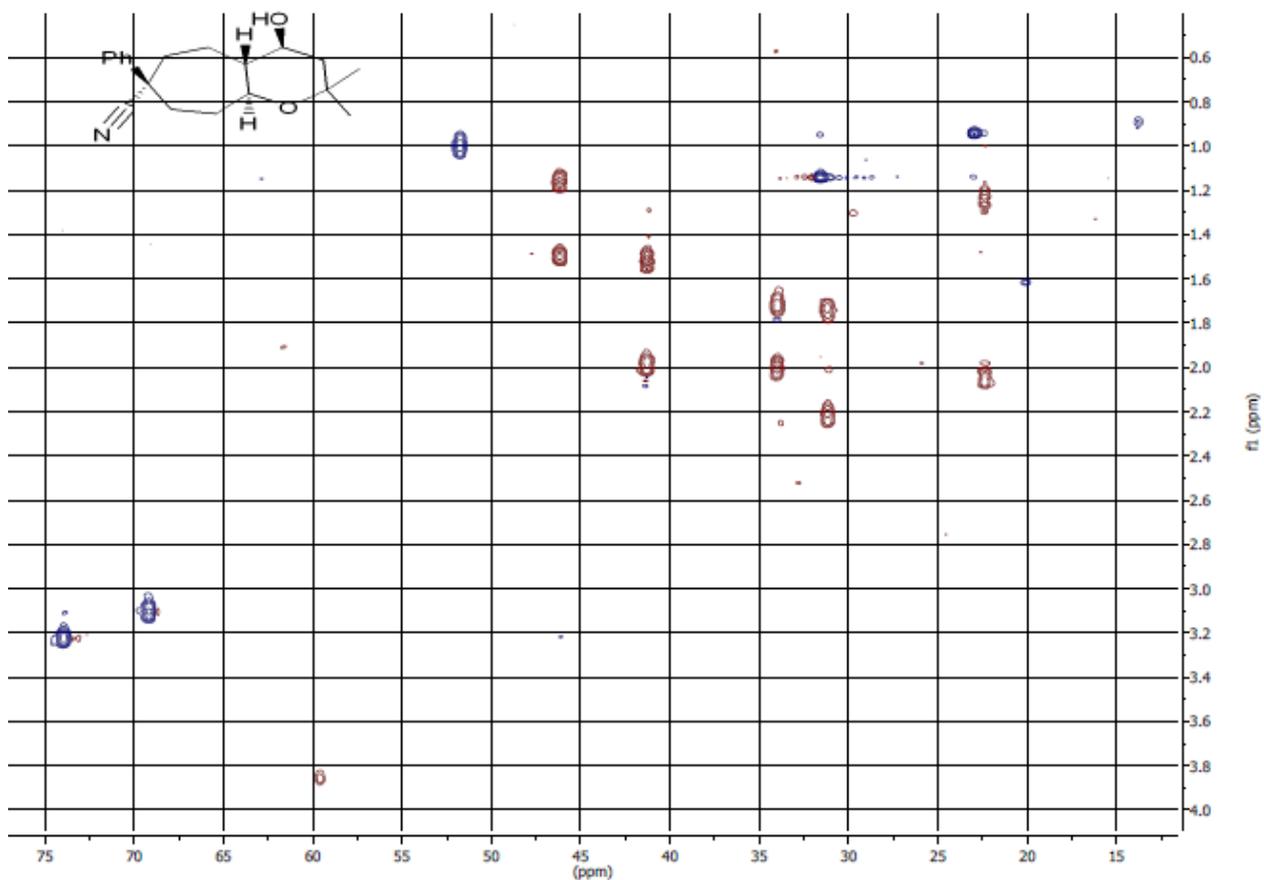




Compound 6d







Compound 6e

