Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.


**Supplementary Information**

# Novel Spirocyclic Systems *via* a Multicomponent Aza-Diels-Alder Reaction

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## Supplementary Tables

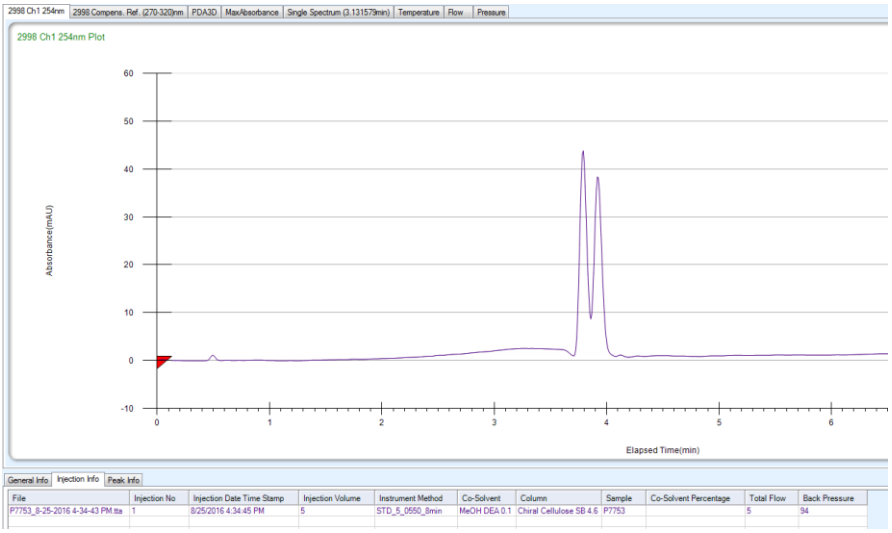
**Supplementary Table 1 Crystal difraction parameters for 9e.**

| | |
|---|---|
| Formula | $C_{17}$ $H_{26}$ $N_2$ $O_5$ S |
| F. W. | 370.46 |
| Crys. Sys. | Monoclinic |
| Space group | P21/c |
| a [Å] | 15.5689(12) |
| b [Å] | 10.3588(6) |
| c [Å] | 11.1945(7) |
| α[°] | 90 |
| β[°] | 92.692(6) |
| γ[°] | 90 |
| V [$Å^3$] | 1803.4(2) |
| Z | 4 |
| Dcalc.[$g/cm^3$] | 1.364 |
| μ [$mm^{-1}$] | 0.210 |
| F(000) | 792 |
| θ range [°.] | 2.68 – 25.68 |
| Refls. Colled. | 53810 |
| Rint | 0.1587 |
| GOF on F2 | 0.893 |
| Final R1 | 0.0398 |
| Final wR2 | 0.0829 |

## Supplementary Figures

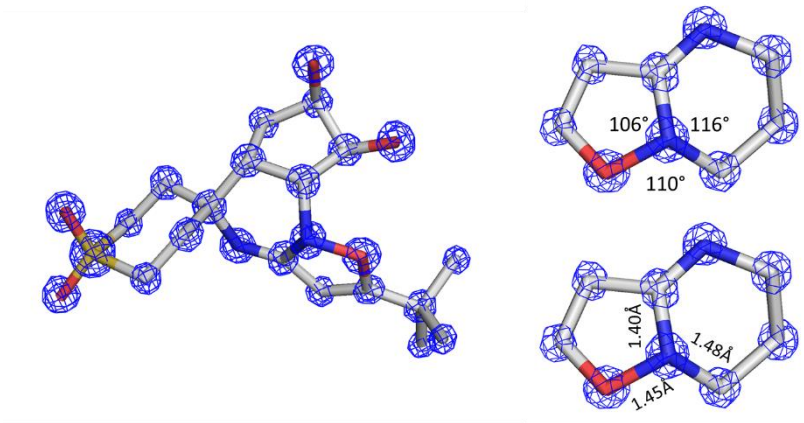
**Supplementary Figure 1 Chiral HPLC analysis of 9i.**

Compound **9i** (3.2 mg/mL in MeOH), vol. inj. 5 µL, CHIRAL ART Cellulose-SB column (4.6 mm*150 mm, 5 uM) with MeOH 0.1% DEA, Gradient 5-50%, Flow 5 ml/min.

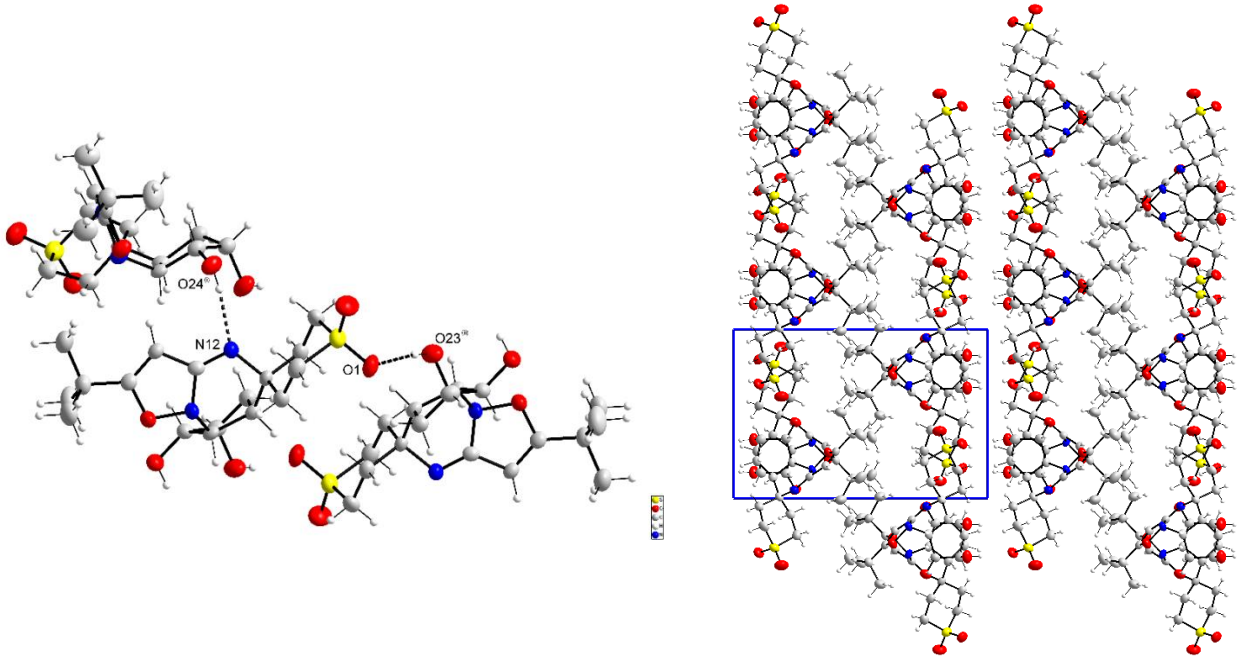


**Supplementary Figure 2 (a) 3Fo-2Fc electron density map of 9e contoured at 3σ, and relevant C-N bond angles and distances. (b) The hydrogen bond network of 9e molecules building up the crystal lattice is displayed. (c) The unit cell contains four molecules.**

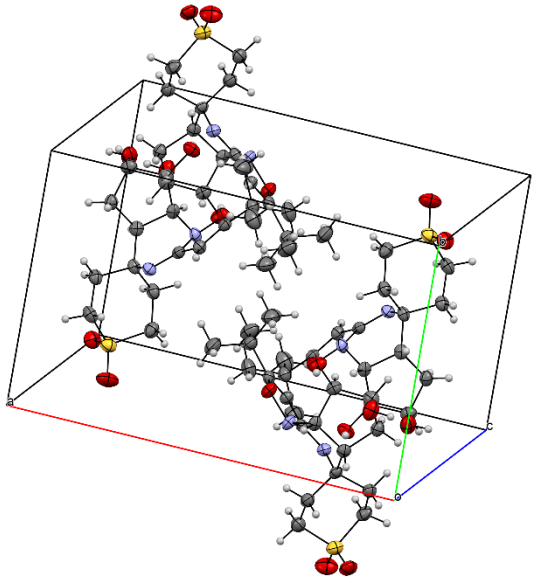
**a**




**b**




**c**

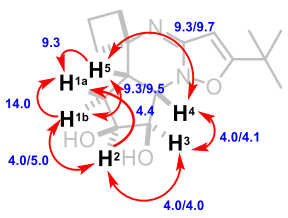


**Supplementary Figure 3 $^{1}$H NMR summary for 8b, 8d, 8k and 9e.**

Despite the rigid construction of the tricyclic products, the inherent conformational flexibility of the cyclopentane ring led to great intermolecular variability in proton coupling constants,[1] in accordance with Povarov literature (see Supplementary Figure 4). The nOe interactions observed in **8b**, **8d** and **8k** matched **9e**'s, and their structures were assigned by analogy to the crystal structure of **9e** (Figure 2 and Supplementary Figure 2). Examples with a five-membered heterocycle as ring A, with or without a nitrogen bridgehead, displayed $H^4$-$H^5$ scalar couplings between 10 and 7 Hz, in accordance with literature values, whereas six-membered heterocycles (**8j**, **8h**, **8i**), presented unusually low scalar couplings around 4 Hz. Interestingly, examples bearing a five-membered heterocycle ring A and a nitrogen bridgedhead, showed $H^4$-$H^3$ coupling constants ~4.5 Hz, whereas every other example showed spin couplings <2 Hz.

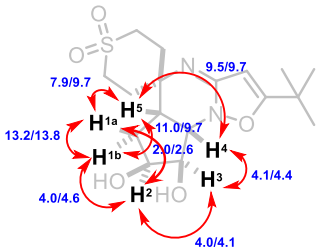
**2D COSY and $^{1}$H coupling constants (in blue)**

**8b**



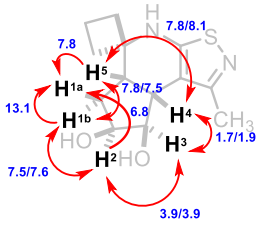

| | | | |
|---|---|---|---|
| **H$^{1a}$** | 1.85 | m | - |
| **H$^{1b}$** | 1.43 | ddd | 14.0, 9.5, 5.0 |
| **H$^{2}$** | 3.89 | app dt | 4.4, 4.0 |
| **H$^{3}$** | 3.75 | app t | 4.0 |
| **H$^{4}$** | 4.26 | dd | 9.7, 4.1 |
| **H$^{5}$** | 3.14 | app q | 9.3 |

**9e**



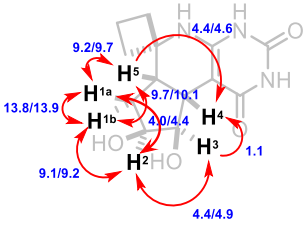

| | | | |
|---|---|---|---|
| **H$^{1a}$** | 1.82 | ddd | 13.2, 7.9, 2.0 |
| **H$^{1b}$** | 1.48 | ddd | 13.8, 11.0, 4.6 |
| **H$^{2}$** | 3.93 | app dt | 2.6, 4.0 |
| **H$^{3}$** | 3.75 | app t | 4.1 |
| **H$^{4}$** | 4.22 | dd | 9.5, 4.4 |
| **H$^{5}$** | 2.90 | app q | 9.7 |

**8d**




| | | | |
|---|---|---|---|
| **H$^{1a}$** | 1.85 | m | - |
| **H$^{1b}$** | 1.72 | app dt | 13.1, 7.5 |
| **H$^{2}$** | 3.86 | ddd | 7.6, 6.8, 3.9 |
| **H$^{3}$** | 3.99 | dd | 3.9, 1.9 |
| **H$^{4}$** | 3.18 | dd | 8.1, 1.7 |
| **H$^{5}$** | 3.09 | app q | 7.8 |

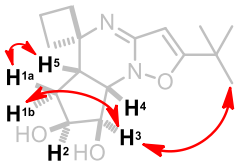
**8k**



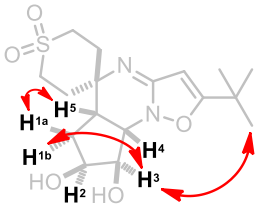

| | | | |
|---|---|---|---|
| **H$^{1a}$** | 1.62 | ddd | 13.8, 9.2, 4.0 |
| **H$^{1b}$** | 1.82 | ddd | 13.9, 10.1, 9.2 |
| **H$^{2}$** | 4.32 | app dt | 9.1, 4.4 |
| **H$^{3}$** | 3.97 | dd | 4.9, 1.1 |
| **H$^{4}$** | 3.54 | app d | 4.4 |
| **H$^{5}$** | 3.04 | app dt | 4.6, 9.7 |

**2D NOESY correlations (in red)**

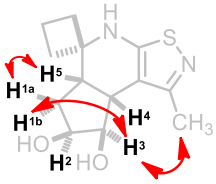
**8b**



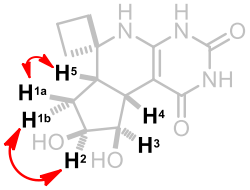
**9e**



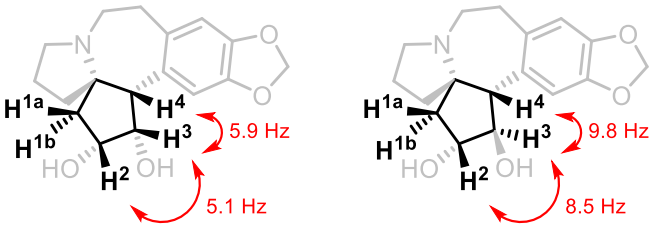
**8d**



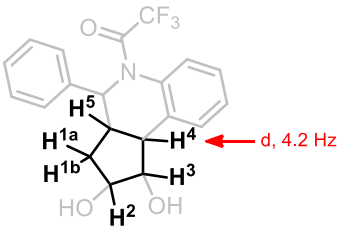
**8k**



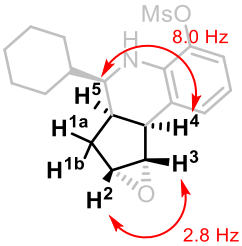
**Supplementary Figure 4 $^{1}$H NMR information on related tricyclic systems available in the literature.**



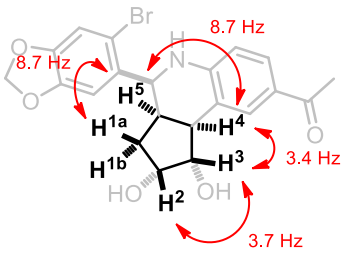

**Ref.** [2]




**Ref.** [3]



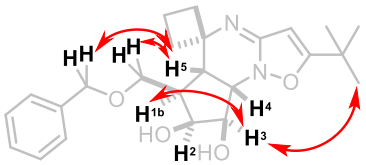

**Ref.** [4]




**Ref.** [5]

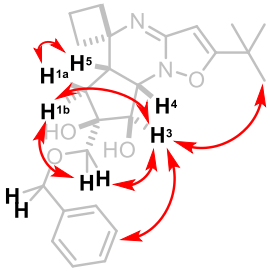
**Supplementary Figure 5 2D NOESY summary for 11a, 11b and 11c.**

**11a**



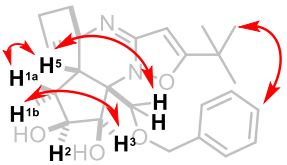

$H^2$ and $H^3$ lack nOe interaction with benzylic and ethereal -$CH_2$ groups. $H^{1b}$ lacks nOe interaction with $H^4$.

**11b**



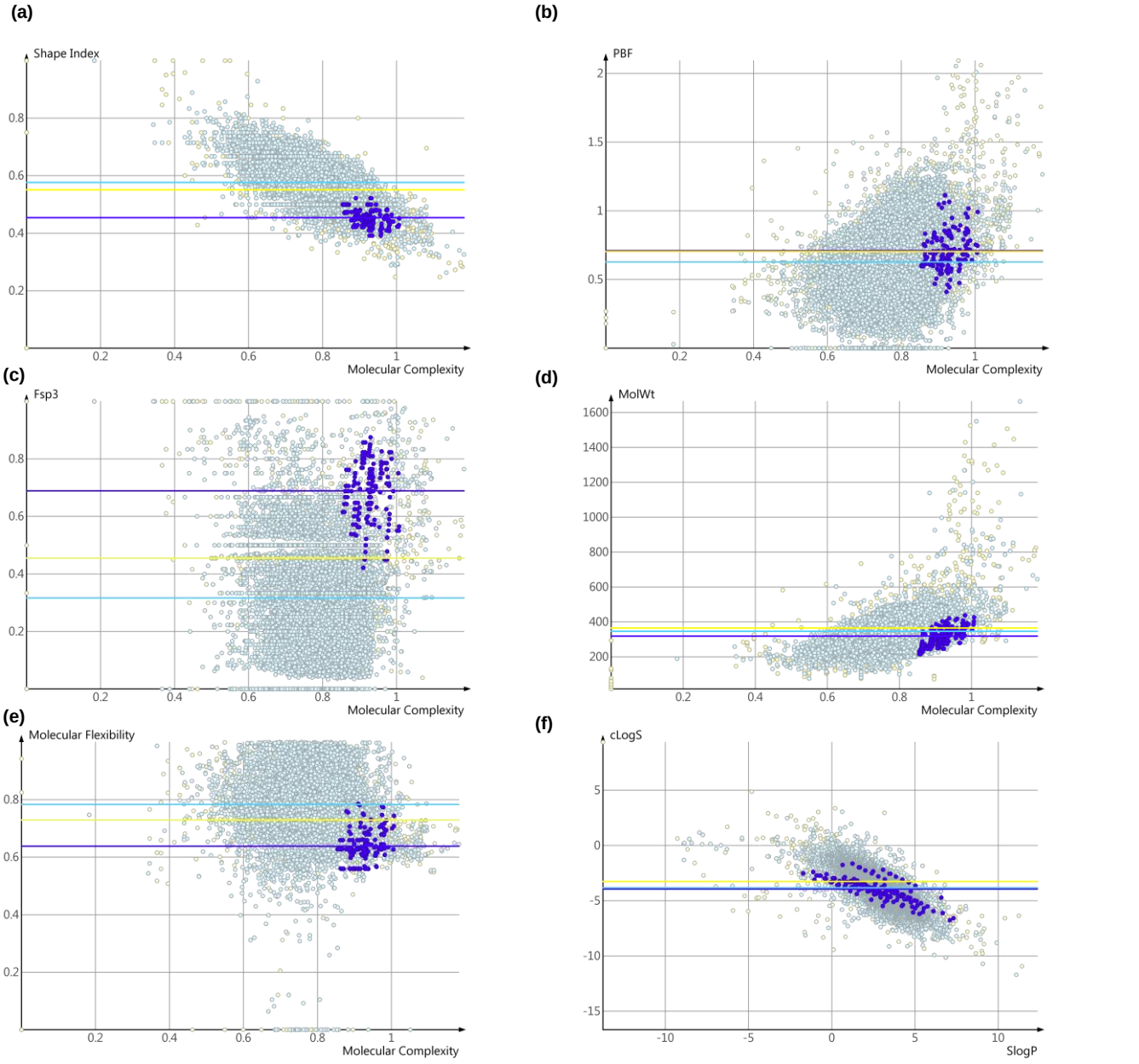

$H^4$ and $H^5$ lack nOe interaction with benzylic and ethereal -$CH_2$ groups.

**11c**




$H^2$ and $H^3$ lack nOe interaction with benzylic and ethereal -$CH_2$ groups.

**Supplementary Figure 6 Comparison of some General Lead/Drug-Likeness Criteria between a theoretical DOLE set in dark blue (162 compounds), an in house primary screening set in light blue (LCBKI, ~11000 compounds), and approved drugs in light yellow (DrugBank, ~1700 compounds). No filters applied. (a) Molecular Shape Index, (b) Plane of Best Fit, (c) Fraction sp3, (d) Molecular weight, (e) Molecular Flexibility vs. Molecular Complexity, (f) cLogS vs. SLogP. Molecular Shape Index: Spherical < 0.5 < Linear; Molecular Flexibility: Low < 0.5 < High; Molecular Complexity: Low < 0.5 < High.**



## Crystallography Experimental Section

### Crystallography Experimental Procedure

A crystal of **9e** was recovered from an NMR tube containing a MeOD solution of **9e**. The crystal was glued to a thin glass fiber and mounted on a Bruker D8 4-circle diffractometer equipped with a photon 100 detector. The detector distance was 50 mm and the data collection was carried out at 291K. Several different phiscans as well as omega scans were done to record all unique reflections. The intensity data were processed using CrysAlisPro (Rigaku) due to the problems with resolving the twinning with the APEX 3 software. Direct methods using SHELXS were used to solve the structure and refinement was performed using SHELXL.[6] Hydrogen atoms were fixed on calculated positions using HFIX options in SHELXL. The **9e** reflection data was measured to 0.83 Å resolution, but the number of significant reflections decreased below 1 Å resolution, a fact known from many sxtl investigations. The data set fulfilled "Sheldrick rule" that 50% of the reflections between 1.0 and 1.2 Å resolution should be significantly observed. The final structure is of high quality (Supplementary Table 1). The only aberration is the rather high internal R value, but this is partly related to the fact that the reflection data came from two individuals of the twinned crystal and partly to the rather high amount of nonsignificant reflections, 46% on average. This amount did of course increase below 1.0 Å resolution, thus contributing to the internal R-value. The structure was analysed and pictures were produced using Mercury, Coot and Pymol.[7-9] The coordinates and structure factors have been deposited in the Cambridge Structural Database under CCDC number CCDC 1541016.

## Computational Chemistry Experimental Section

### Molecular Property Calculations

For each molecule, a single, neutralized, 3D minimized conformation was generated using Ligprep, as implemented in Schrödinger Suite (Schrödinger Release 2017-1: LigPrep, Schrödinger, LLC, New York, NY, 2017). The OPLS3 force field was used for minimizations. The Plane of Best Fit was then calculated for each 3D molecule using the Erlwood nodes as implemented in Knime 3.3.1 (https://www.knime.org/), while the other structural descriptors were calculated using DataWarrior 4.5.1 (http://www.openmolecules.org/datawarrior/index.html).

## Synthetic Chemistry Experimental Section

### General Information

All commercial reagents and solvents were used without further purification. All starting material ketones, amines and catalysts are commercially available. Cyclopentadiene was cracked and distilled prior to use. Analytical thin-layer chromatography was performed on silica gel 60 F-254 plates (E. Merck) and visualized under a UV lamp. Flash column chromatography was performed in a Biotage® SP4 MPLC system using Merck silica gel 60Å (40-63 mm mesh). $^{1}H$ and $^{13}C$ NMR spectra were recorded on a Bruker DRX-400 or a Bruker Avance III 600 MHz spectrometer. Chemical shifts are expressed in parts per million (ppm) and referenced to the residual solvent peak. Analytical LC-MS were performed on an Agilent MSD mass spectrometer connected to an Agilent 1100 system with: Method B1090A: Column ACE 3 C8 (50 x 3.0 mm); $H_2O$ (+ 0.1% TFA) and MeCN were used as mobile phases at a flow rate of 1 mL/min, with a gradient time of 3.0 min; or Method 0597X3: Column Xterra MSC18 (50 x 3.0 mm); $H_2O$ (containing 10 mM $NH_4HCO_3$; pH = 10) and MeCN were used as mobile phases at a flow rate of 1 mL/min, with a gradient time of 3.0 min. For LC-MS, detection was made by UV (254 or 214 nm) and MS (ESI+). All final compounds were assessed to be >95% pure by LC-MS analysis.

### Typical procedure for the synthesis of products

**Step 1**

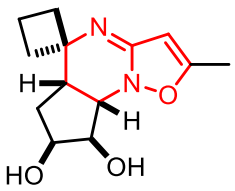
A solution of trifluoroacetic acid (0.6 mmol, 1 eq) in acetonitrile (1 mL) was added to a solution of heterocyclic amine (0.6 mmol, 1 eq) in acetonitrile (0.5 mL), followed by sequential addition of a solution of ketone (0.66 mmol, 1.1 eq) and yttrium (III) triflate (0.3 mmol, 0.5 eq) in acetonitrile (1 mL). The mixture was stirred at room temperature for one minute, followed by addition of a solution of cyclopentadiene (1.2 mmol, 2 eq) in in acetonitrile (0.5 mL) (total reaction volume 3 mL), and subsequently stirred at the indicated temperature, until the amine starting material was consumed (determined by LC-MS). In some instances, additional ketone, yttrium (III) triflate and cyclopentadiene were added. The resulting mixture was concentrated *in vacuo*, passed through a silica pad and used in the next step without any further purification.

**Step 2**

The crude mixture from Step 1 was dissolved in acetone (2 mL) at 0 °C, treated with *N*-methylmorpholine *N*-oxide (1.2 mmol, 2 eq), followed by osmium tetroxide solution (2.5 wt. % in tert-butanol, 0.240 mmol, 0.4 eq) in water (2 mL). The reaction mixture was allowed to warm to room temperature, and stirred until the starting material was consumed (determined by LC-MS). In some instances, additional osmium tetroxide and *N*-methylmorpholine *N*-oxide were added. The reaction was quenched with QuadraPure® IMDAZ resin (3-fold excess in respect to the total amount of osmium used) and stirred at room temperature for 30 minutes. The resin was filtered off and the reaction mixture was concentrated *in vacuo*. The resulting residue was purified by flash column chromatography.

**Product characterization**

**8a**

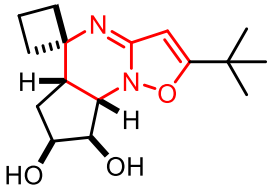


**(5a'S,7'R,8'S,8a'S)-2'-Methyl-6',7',8',8a'-tetrahydro-5a'H-spiro[cyclobutane-1,5'-cyclopenta[e]isoxazolo[2,3-a]pyrimidine]-7',8'-diol**

Step 1: Room temperature, 18 h.

Step 2: After 24 h, an additional portion of $OsO_4$ and NMO was added. Total reaction time 48 h. The reaction mixture was purified by flash chromatography (5-10% MeOH / DCM). Obtained as an off-white amorphous solid (112 mg, 75% yield). $^1$H NMR (400 MHz, MeOD) δ = 6.13 (q, J = 0.8 Hz, 1H), 4.45 (dd, J = 7.8, 2.6 Hz, 1H), 4.07 (dd, J = 4.3, 2.7 Hz, 1H), 3.90 (dt, J = 6.0, 4.0, 1H), 3.35 (dt, J = 10.2, 8.2 Hz, 1H), 2.38 (d, J = 0.7 Hz, 3H), 2.30 – 2.14 (m, 3H), 2.11 – 2.01 (m, 1H), 1.95 – 1.81 (m, 3H), 1.48 (ddd, J = 13.8, 10.3, 6.1 Hz, 1H). $^{13}$C NMR (101 MHz, MeOD) δ = 174.5, 156.5, 95.6, 77.2, 72.5, 66.0, 57.0, 43.3, 36.7, 32.8, 31.9, 14.3, 12.6. LC-MS (ESI+) m/z: 251 $[M+H]^+$. HRMS (ESI+): exact mass calculated for $[M+H]^+$ ($C_{13}H_{18}N_2O_3$) requires m/z 251.1390, found m/z 251.1387.

**8b**

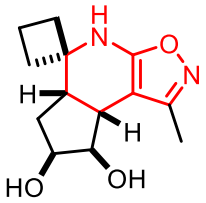


**(5a'S,7'R,8'S,8a'S)-2'-(Tert-butyl)-6',7',8',8a'-tetrahydro-5a'H-spiro[cyclobutane-1,5'-cyclopenta[e]isoxazolo[2,3-a]pyrimidine]-7',8'-diol**

Step 1: Room temperature, 18 h.

Step 2: Total reaction time 18 h. Obtained as an amorphous off-white solid (154 mg, 88% yield). $^1$H NMR (600 MHz, MeOD) δ = 5.58 (s, 1H), 4.26 (dd, J = 9.7, 4.1 Hz, 1H), 3.89 (app dt, J = 4.4, 4.0 Hz, 1H), 3.75 (app t, J = 4.0 Hz, 1H), 3.14 (app q, J = 9.3 Hz, 1H), 2.31 – 2.08 (m, 3H), 1.99 – 1.80 (m, 4H), 1.43 (ddd, J = 14.0, 9.5, 5.0 Hz, 1H). $^{13}$C NMR (DEPT135, 101 MHz, MeOD) δ = 182.4 (-C), 162.3 (-C), 94.2 (-CH), 77.8 (-CH), 73.5 (-CH), 67.5 (-CH), 60.0 (-C), 43.1 (-CH), 35.4 (-$CH_2$), 34.2 (-C), 33.5 (-$CH_2$), 33.3 (-$CH_2$), 28.2 (-$CH_3$), 15.4 (-$CH_2$). LC-MS (ESI+) *m/z:* 293 $[M+H]^+$. HRMS (ESI+): exact mass calculated for $[M+H]^+$ ($C_{16}H_{24}N_2O_3$) requires m/z 293.1860, found m/z 293.1861.

**8c**

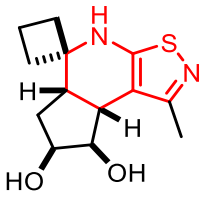


**(5a'S,7'R,8'S,8a'R)-1'-Methyl-4',5a',6',7',8',8a'-hexahydrospiro[cyclobutane-1,5'-cyclopenta[d]isoxazolo[5,4-b]pyridine]-7',8'-diol**

Step 1: Room temperature, 18 h.

Step 2: Total reaction time 18 h. Obtained as an amorphous off-white solid (134 mg, 89% yield). $^1$H NMR (400 MHz, MeOD) δ = 4.07 (dd, J = 4.0, 1.5 Hz, 1H), 3.93 (ddd, J = 8.2, 6.8, 4.0 Hz, 1H), 3.12 – 3.05 (m, 1H), 3.03 (dd, J = 6.9, 1.0 Hz, 1H), 2.23 – 2.18 (m, 1H), 2.15 (s, 3H), 2.14 – 2.08 (m, 1H), 2.03 – 1.95 (m, 1H), 1.91 (dd, J = 11.4, 8.4 Hz, 1H), 1.86 – 1.78 (m, 2H), 1.75 – 1.69 (m, 2H). $^{13}$C NMR (101 MHz, MeOD) δ = 167.6, 159.7, 89.1, 77.7, 73.7, 59.9, 43.4, 39.6, 37.3, 33.4, 32.1, 13.9, 10.9. LC-MS (ESI+) *m/z:* 251 $[M+H]^+$. HRMS (ESI+): exact mass calculated for $[M+H]^+$ ($C_{13}H_{18}N_2O_3$) requires m/z 251.1390, found m/z 251.1387.

**8d**

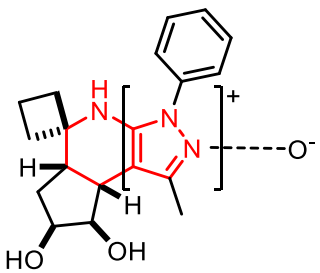


**(5a'S,7'R,8'S,8a'R)-1'-Methyl-4',5a',6',7',8j',8a'-hexahydrospiro[cyclobutane-1,5'-cyclopenta[d]isothiazolo[5,4-b]pyridine]-7',8'-diol**

Step 1: After 24 h, an additional portion of ketone, yttrium (III) triflate and cyclopentadiene was added. Total reaction time 4 days.

Step 2: Total reaction time 18 h. Obtained as an amorphous beige solid (128 mg, 80% yield). $^1$H NMR (400 MHz, MeOD) δ = 3.99 (dd, *J* = 3.9, 1.9 Hz, 1H), 3.86 (ddd, *J* = 7.6, 6.8, 3.9 Hz, 1H), 3.18 (dd, *J* = 8.1, 1.7 Hz, 1H), 3.18 (dd, *J* = 8.1, 1.7 Hz, 1H), 2.30 (s, 3H), 2.18 – 2.09 (m, 2H), 2.04 – 1.95 (m, 1H), 1.91 – 1.79 (m, 4H), 1.72 (app dt, *J* = 13.1, 7.5 Hz, 1H). $^{13}$C NMR (DEPT135, 101 MHz, MeOD) δ = 167.9 (-C), 165.8 (-C), 114.7 (-C), 79.4 (-CH), 73.5 (-CH), 60.4 (-C), 43.2 (-CH), 41.9 (-CH), 36.5 (-$CH_2$), 33.6 (-$CH_2$), 32.7 (-$CH_2$), 18.4 (-$CH_3$), 13.9 (-$CH_2$). LC-MS (ESI+) *m/z:* 267 $[M+H]^+$. HRMS (ESI+): exact mass calculated for $[M+H]^+$ ($C_{13}H_{18}N_2O_2S$) requires m/z 267.1162, found m/z 267.1161.

**8e**

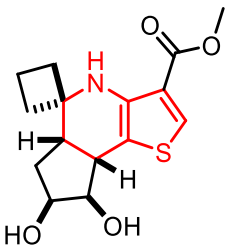


**(5a'S,7'R,8'S,8a'R)-1'-methyl-3'-phenyl-4',5a',6',7',8',8a'-hexahydro-3'H-spiro[cyclobutane-1,5'-cyclopenta[d]pyrazolo[3,4-b]pyridine]-7',8'-diol *N*-oxide**

Step 1: After 24 h, an additional portion of ketone, yttrium (III) triflate and cyclopentadiene was added, followed by additional portions every 24 h. Total reaction time 4 days.

Step 2: After 24 h, an additional portion of $OsO_4$ and NMO was added. Total reaction time 48 h. The reaction mixture was purified by flash chromatography (5-10% MeOH / DCM). Obtained as an amorphous off-white solid (197 mg, 96% yield). $^1$H NMR (400 MHz, MeOD) δ = 7.69 – 7.54 (m, 5H), 3.88 (app t, J = 3.1 Hz, 1H), 3.25 (app q, J = 8.1 Hz, 1H), 3.15 (app t, J = 9.8 Hz, 1H), 3.09 (dd, J = 9.9, 3.3 Hz, 1H), 2.59 – 2.46 (m, 1H), 2.37 (s, 1H), 2.33 – 2.24 (m, 1H), 2.05 (dd, J = 14.0, 8.1 Hz, 1H), 2.01 – 1.84 (m, 1H), 1.09 (ddd, J = 14.1, 10.8, 3.4 Hz, 1H). $^{13}$C NMR (101 MHz, MeOD) δ = 170.7, 163.8, 136.1, 131.3, 131.3, 125.6, 86.3, 76.4, 73.0, 64.6, 42.1, 40.9, 34.7, 31.1, 15.0, 13.0. LC-MS (ESI+) *m/z:* 342 $[M+H]^+$. HRMS (ESI+): exact mass calculated for $[M+H]^+$ ($C_{19}H_{23}N_3O_3$) requires m/z 342.1812, found m/z 342.1814.

**8f**

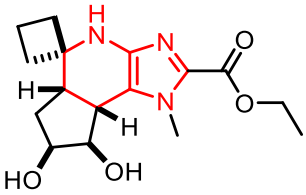


**(5a'S,7'R,8'S,8a'S)-Methyl 7',8'-dihydroxy-4',5a',6',7',8',8a'-hexahydrospiro[cyclobutane-1,5'-cyclopenta[d]thieno[3,2-b]pyridine]-3'-carboxylate**

Step 1: Room temperature, 18 h.

Step 2: After 24 h, an additional portion of $OsO_4$ and NMO was added, followed by additional portions every 24 h. Total reaction time 4 days. The reaction mixture was purified by flash chromatography (5-10% MeOH / DCM). Obtained as an amorphous off-white solid (50 mg, 27% yield). $^1$H NMR (400 MHz, MeOD) δ = 7.93 (s, 1H), 3.98 (dd, J = 3.9, 1.9 Hz, 1H), 3.89 – 3.85 (m, 1H), 3.83 (s, 3H), 3.24 (dd, J = 7.6, 0.9 Hz, 1H), 3.12 (dt, J = 10.1, 7.4 Hz, 1H), 2.18 – 1.96 (m, 3H), 1.89 – 1.68 (m, 6H). $^{13}$C NMR (101 MHz, MeOD) δ = 165.1, 143.4, 132.2, 122.4, 114.2, 80.9, 73.8, 58.0, 51.9, 43.8, 43.1, 38.0, 34.3, 32.2, 13.8. LC-MS (ESI+) *m/z:* 310 $[M+H]^+$. HRMS (ESI+): exact mass calculated for $[M+H]^+$ ($C_{15}H_{19}NO_4S$) requires m/z 310.1108, found m/z 310.1109.

**8h**

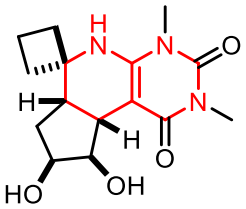


**(5a'S,7'R,8'S,8a'R)-Ethyl 7',8'-dihydroxy-1'-methyl-4',5a',6',7',8',8a'-hexahydro-1'H-spiro[cyclobutane-1,5'-cyclopenta[d]imidazo[4,5-b]pyridine]-2'-carboxylate**

Step 1: Room temperature, 18 h.

Step 2: Total reaction time 48 h. The reaction mixture was purified by flash chromatography (5-10% MeOH / DCM). Obtained as an amorphous off-white solid (124 mg, 64% yield). $^1$H NMR (400 MHz, MeOD) δ = 4.33 (q, J = 7.1 Hz, 2H), 3.95 (s, 3H), 3.92 – 3.88 (m, 1H), 3.23 (dd, J = 8.2, 2.6 Hz, 1H), 3.17 (app q, J = 8.5 Hz, 1H), 2.13 – 2.07 (m, 1H), 1.99 – 1.96 (m, 1H), 1.87 – 1.78 (m, 2H), 1.77 – 1.69 (m, 1H), 1.36 (t, J = 7.1 Hz, 3H). $^{13}$C NMR (101 MHz, MeOD) δ = 159.9, 144.5, 132.3, 119.6, 79.5, 73.7, 61.9, 59.9, 44.8, 40.4, 36.6, 34.3, 33.4, 32.4, 14.6, 13.8. LC-MS (ESI+) *m/z:* 322 $[M+H]^+$. HRMS (ESI+): exact mass calculated for $[M+H]^+$ ($C_{15}H_{21}N_3O_4$) requires m/z 322.1761, found m/z 322.1761.

**8j**

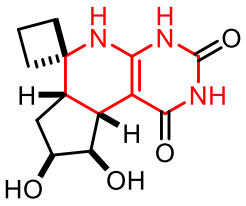


**(6a'S,8'R,9'S,9a'R)-8',9'-Dihydroxy-2',4'-dimethyl-5',6a',7',8',9',9a'-hexahydrospiro[cyclobutane-1,6'-cyclopenta[4,5]pyrido[2,3-d]pyrimidine]-1',3'(2'H,4'H)-dione**

Step 1: 50 °C. After 24 h, an additional portion of ketone, yttrium (III) triflate and cyclopentadiene was added, followed by additional portions every 24 h. Total reaction time 2 days.

Step 2: Total reaction time 18 h. The reaction mixture was purified by flash chromatography (5-15% MeOH / DCM). Obtained as an amorphous off-white solid (131 mg, 71% yield). $^1$H NMR (400 MHz, MeOD) δ = 4.34 (dt, J = 4.5, 9.3 Hz, 1H), 4.21 (dd, J = 5.0, 1.2 Hz, 1H), 3.69 – 3.60 (m, 1H), 3.57 (app d, J = 4.5 Hz, 1H), 3.33 (s, 3H), 3.25 (s, 3H), 3.06 (dt, J = 4.6, 9.7 Hz, 1H), 2.50 – 2.39 (m, 1H), 2.03 – 1.92 (m, 2H), 1.85 – 1.76 (m, 1H), 1.77 – 1.66 (m, 2H), 1.60 (ddd, J = 13.9, 10.1, 9.2 Hz, 1H). $^{13}$C NMR (101 MHz, MeOD) δ = 164.1, 152.8, 150.5, 88.5, 77.2, 72.3, 58.5, 44.7, 39.5, 36.8, 34.9, 29.8, 29.2, 28.1, 15.4. LC-MS (ESI+) *m/z:* 308 $[M+H]^+$. HRMS (ESI+): exact mass calculated for $[M+H]^+$ ($C_{15}H_{21}N_3O_4$) requires m/z 308.1605, found m/z 308.1603.

**8k**

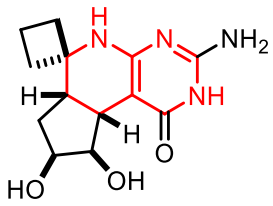


**(6a'S,8'R,9'S,9a'R)-8',9'-Dihydroxy-5',6a',7',8',9',9a'-hexahydrospiro[cyclobutane-1,6'-cyclopenta[4,5]pyrido[2,3-d]pyrimidine]-1',3'(2'H,4'H)-dione**

Step 1: 50 °C. After 24 h, an additional portion of ketone, yttrium (III) triflate and cyclopentadiene was added, followed by additional portions every 24 h. Total reaction time 3 days.

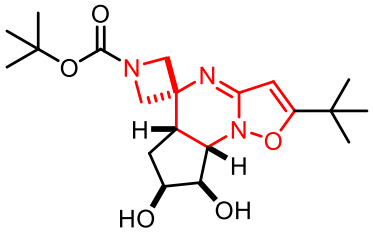
Step 2: Total reaction time 18 h. The reaction mixture was purified by flash chromatography (5-25% MeOH / DCM). Obtained as an amorphous white solid (45 mg, 27% yield). $^1$H NMR (400 MHz, MeOD) δ = 4.33 (dt, J = 4.4, 9.1 Hz, 1H), 3.97 (dd, J = 4.9, 1.1 Hz, 1H), 3.63 (ddd, J = 11.7, 9.7, 5.2 Hz, 1H), 3.54 (app d, J = 4.4 Hz, 1H), 3.04 (app dt, J = 4.6, 9.7 Hz, 1H), 2.46 – 2.36 (m, 1H), 2.03 – 1.89 (m, 2H), 1.82 (ddd, J = 13.9, 10.1, 9.2 Hz, 1H), 1.76 – 1.68 (m, 2H), 1.62 (ddd, J = 13.9, 9.2, 4.0 Hz, 1H). $^{13}$C NMR (101 MHz, MeOD) δ = 166.4 (-C), 152.3 (-C), 150.8 (-C), 87.4 (-C), 77.6 (-CH), 72.5 (-CH), 58.0 (-CH), 44.8 (-CH), 38.9 (-C), 37.0 (-$CH_2$), 35.0 (-$CH_2$), 28.8 (-$CH_2$), 15.5 (-$CH_2$). LC-MS (ESI+) *m/z:* 280 $[M+H]^+$. HRMS (ESI+): exact mass calculated for $[M+H]^+$ ($C_{13}H_{17}N_3O_4$) requires m/z 280.1292, found m/z 280.1293.

**8l**



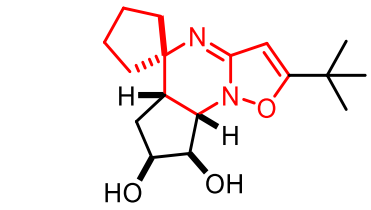
**(6a'S,8'R,9'S,9a'R)-3'-Amino-8',9'-dihydroxy-5',6a',7',8',9',9a'-hexahydrospiro[cyclobutane-1,6'-cyclopenta[4,5]pyrido[2,3-d]pyrimidin]-1'(2'H)-one**
Step 1: 50 °C. After 24 h, an additional portion of ketone, yttrium (III) triflate and cyclopentadiene was added, followed by additional portions every 24 h. Total reaction time 3 days.
Step 2: Total reaction time 18 h. The reaction mixture was purified by flash chromatography (5-25% MeOH / DCM). Obtained as an amorphous white solid (53 mg, 32% yield). $^{1}$H NMR (400 MHz, MeOD) δ = 4.32 (dt, J = 4.4, 8.4 Hz, 1H), 4.01 (app d, J = 4.6 Hz, 1H), 3.70 (app q, J = 9.9 Hz, 1H), 3.54 (d, J = 3.9 Hz, 1H), 3.01 (dt, J = 4.5, 9.4 Hz, 1H), 2.38 (app q, J = 9.7 Hz, 1H), 2.01 – 1.89 (m, 2H), 1.83 – 1.68 (m, 3H), 1.64 – 1.53 (m, 1H). $^{13}$C NMR (101 MHz, MeOD) δ = 165.1, 160.7, 154.9, 90.0, 77.8, 72.8, 58.0, 44.8, 39.7, 37.1, 34.9, 29.0, 15.7. LC-MS (ESI+) *m/z:* 279 $[M+H]^+$. HRMS (ESI+): exact mass calculated for $[M+H]^+$ ($C_{13}H_{18}N_4O_3$) requires m/z 279,1452, found m/z 279,1447.

**9a**



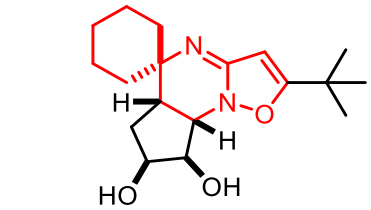
**(5a'S,7'R,8'S,8a'S)-Tert-butyl 2'-(tert-butyl)-7',8'-dihydroxy-6',7',8',8a'-tetrahydro-5a'H-spiro[azetidine-3,5'-cyclopenta[e]isoxazolo[2,3-a]pyrimidine]-1-carboxylate**
Step 1: Room temperature, 18 h.
Step 2: Total reaction time 18 h. The reaction mixture was purified by flash chromatography (0-5% MeOH / DCM). Obtained as an amorphous beige solid (85 mg, 36% yield). $^{1}$H NMR (400MHz, MeOD) δ = 5.56 (s, 1H), 4.23 (dd, J = 10.0, 4.5 Hz, 1H), 4.01 (dd, J = 17.0, 8.5 Hz, 2H), 3.94 – 3.86 (m, 2H), 3.68 (app t, J = 4.3 Hz, 1H), 3.63 – 3.55 (m, 1H), 3.15 (dd, J = 18.1, 9.0 Hz, 1H), 1.96 (ddd, J = 13.2, 8.4, 3.0 Hz, 1H), 1.44 (s, 9H), 1.30 (s, 9H). $^{13}$C NMR (101MHz, MeOD) δ = 183.3, 165.6, 158.1, 94.4, 81.1, 78.2, 73.4, 67.3, 66.4, 62.6, 55.7, 42.2, 34.1, 33.1, 28.6, 28.2. LC-MS (ESI+) *m/z:* 394 $[M+H]^+$. HRMS (ESI+): exact mass calculated for $[M+H]^+$ ($C_{20}H_{31}N_3O_5$) requires m/z 394.2336, found m/z 394,2342.

**9b**



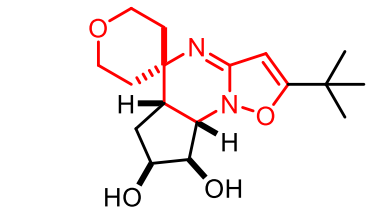
**(5aS,7R,8S,8aS)-2-(Tert-butyl)-6,7,8,8a-tetrahydro-5aH-spiro[cyclopenta[e]isoxazolo[2,3-a]pyrimidine-5,1'-cyclopentane]-7,8-diol**
Step 1: Room temperature, 18 h.
Step 2: Total reaction time 18 h. The reaction mixture was purified by flash chromatography (0-5% MeOH / DCM). Obtained as an amorphous white solid (131 mg, 71% yield). $^{1}$H NMR (400MHz, MeOD) δ = 5.47 (s, 1H), 4.17 (dd, J = 9.8, 4.4 Hz, 1H), 3.89 (dd, J = 7.3, 4.5 Hz, 1H), 3.75 (app t, J = 4.3 Hz, 1H), 2.74 (dd, J = 18.2, 9.7 Hz, 1H), 1.84 (ddd, J = 13.7, 8.2, 3.0 Hz, 2H), 1.77 – 1.56 (m, 7H), 1.49 (ddd, J = 18.7, 9.7, 4.7 Hz, 1H), 1.29 (s, 9H). $^{13}$C NMR (101MHz, MeOD) δ = 181.6, 162.1, 94.3, 77.9, 73.5, 67.9, 66.1, 44.0, 38.7, 38.3, 34.3, 34.0, 28.3, 25.2, 24.8. LC-MS (ESI+) *m/z:* 307 $[M+H]^+$. HRMS (ESI+): exact mass calculated for $[M+H]^+$ ($C_{17}H_{26}N_2O_3$) requires m/z 307.2016, found m/z 307,2016.

**9c**



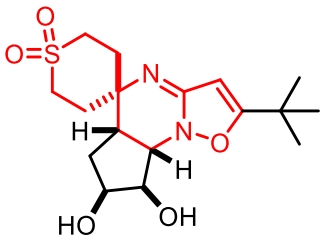
**(5a'S,7'R,8'S,8a'S)-2'-(Tert-butyl)-6',7',8',8a'-tetrahydro-5a'H-spiro[cyclohexane-1,5'-cyclopenta[e]isoxazolo[2,3-a]pyrimidine]-7',8'-diol**
Step 1: Room temperature, 18 h.
Step 2: Total reaction time 18 h. The reaction mixture was purified by flash chromatography (0-5% MeOH / DCM). Obtained as an amorphous white solid (178 mg, 92%). $^{1}$H NMR (400MHz, MeOD) δ = 5.51 (s, 1H), 4.18 (dd, J = 9.5, 4.1 Hz, 1H), 3.91 (dd, J = 7.1, 4.4 Hz, 1H), 3.76 (app t, J = 4.1 Hz, 1H), 2.87 (dd, J = 18.4, 9.7 Hz, 1H), 1.80 – 1.67 (m, 3H), 1.65 – 1.39 (m, 10H), 1.30 (s, 9H). $^{13}$C NMR (101MHz, MeOD) δ = 180.9, 161.0, 94.6, 77.8, 73.3, 67.4, 56.5, 43.3, 36.9, 34.0, 33.8, 33.0, 28.3, 27.2, 23.6, 23.1. LC-MS (ESI+) *m/z:* 321 $[M+H]^+$. HRMS (ESI+): exact mass calculated for $[M+H]^+$ ($C_{18}H_{28}N_2O_3$) requires m/z 321.2173, found m/z 321.2173.

**9d**



**(5aS,7R,8S,8aS)-2-(Tert-butyl)-2',3',5',6,6',7,8,8a-octahydro-5aH-spiro[cyclopenta[e]isoxazolo[2,3-a]pyrimidine-5,4'-pyran]-7,8-diol**
Step 1: Room temperature, 18 h.
Step 2: Total reaction time 18 h. The reaction mixture was purified by flash chromatography (0-5% MeOH / DCM). Obtained as an amorphous white solid (155 mg, 80% yield). $^{1}$H NMR (600MHz, MeOD) δ = 5.51 (s, 1H), 4.20 (dd, J = 9.7, 4.3 Hz, 1H), 3.93 (dd, J = 11.2, 2.4 Hz, 1H), 3.90 (dd, J = 6.7, 4.0 Hz, 1H), 3.77 (dt, J = 11.4, 3.9 Hz, 1H), 3.73 (app t, J = 4.1 Hz, 1H), 3.68 (dd, J = 7.8, 2.8 Hz, 2H), 2.75 (dd, J = 18.3, 9.8 Hz, 1H), 1.86 (ddd, J = 14.2, 4.9, 2.6 Hz, 1H), 1.79 (ddd, J = 13.5, 8.0, 2.6 Hz, 1H), 1.71 – 1.61 (m, 3H), 1.56 (ddd, J = 7.3, 5.1, 2.8 Hz, 1H), 1.47 (ddd, J = 14.0, 10.6, 4.6 Hz, 1H), 1.30 (s, 9H). $^{13}$C NMR (101MHz, MeOD) δ = 181.5, 161.9, 94.6, 77.8, 73.2, 67.4, 65.4, 65.0, 54.3, 44.8, 36.6, 34.8, 34.1, 32.7, 28.3. LC-MS (ESI+) *m/z:* 323 $[M+H]^+$. HRMS (ESI+): exact mass calculated for $[M+H]^+$ ($C_{17}H_{26}N_2O_4$) requires m/z 323.1965, found m/z 323.1961.

**9e**

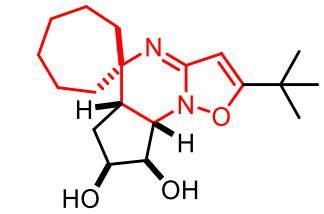


**(5aS,7R,8S,8aS)-2-(Tert-butyl)-7,8-dihydroxy-2',3',5',6,6',7,8,8a-octahydro-5aH-spiro[cyclopenta[e]isoxazolo[2,3-a]pyrimidine-5,4'-thiopyran] 1',1'-dioxide**

Step 1: Room temperature, 18 h.

Step 2: Total reaction time 18 h. The reaction mixture was purified by flash chromatography (0-10% MeOH / DCM). Obtained as an amorphous white solid (185 mg, 83% yield). A crystal of **9e** was recovered from an NMR tube containing a MeOD solution of **9e**. Mp: >210°C (decomp). $^{1}$H NMR (600MHz, MeOD) δ = 5.55 (s, 1H), 4.22 (dd, J = 9.5, 4.4 Hz, 1H), 3.93 (app dt, J = 2.6, 4.0 Hz, 1H), 3.75 (app t, J = 4.1 Hz, 1H), 3.49 (ddd, J = 14.6, 11.5, 4.9 Hz, 1H), 3.19 (td, J = 14.0, 3.1 Hz, 1H), 2.99 (ddd, J = 11.9, 7.5, 3.6 Hz, 1H), 2.87 (app q, J = 9.7 Hz, 1H), 2.77 (dd, J = 18.4, 9.7 Hz, 1H), 2.47 (dt, J = 9.5, 5.0 Hz, 1H), 2.14 – 2.00 (m, 4H), 1.82 (ddd, J = 13.2, 7.9, 2.0 Hz, 1H), 1.48 (ddd, J = 13.8, 11.0, 4.6 Hz, 1H), 1.31 (s, 9H). $^{13}$C NMR (DEPT 135, 101MHz, MeOD) δ = 181.8 (-C), 162.7 (-C), 94.8 (-CH), 78.0 (-CH), 73.2 (-CH), 67.3 (-CH), 54.4 (-C), 48.6 (-$CH_2$), 48.2 (-$CH_2$), 44.0 (-CH), 34.4 (-$CH_2$), 34.1 (-C), 33.4 (-$CH_2$), 31.4 (-$CH_2$), 28.2 (-$CH_3$). LC-MS (ESI+) *m/z:* 371 $[M+H]^+$. HRMS (ESI+): exact mass calculated for $[M+H]^+$ ($C_{17}H_{26}N_2O_5S$) requires m/z 371.1635, found m/z 371.1631.

**9f**

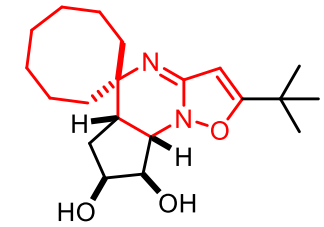


**(5a'S,7'R,8'S,8a'S)-2'-(Tert-butyl)-6',7',8',8a'-tetrahydro-5a'H-spiro[cycloheptane-1,5'-cyclopenta[e]isoxazolo[2,3-a]pyrimidine]-7',8'-diol**

Step 1: Total reaction time 18 h.

Step 2: After 24 h, an additional portion of $OsO_4$ and NMO was added. Total reaction time 48 h. The reaction mixture was purified by flash chromatography (2-7% MeOH / DCM). Obtained as an amorphous white solid (139 mg, 69% yield). $^{1}$H NMR (400MHz, MeOD) δ = 6.14 (s, 1H), 4.53 (dd, J = 7.4, 1.9 Hz, 1H), 4.21 (dd, J = 4.5, 2.3 Hz, 1H), 4.02 (td, J = 5.2, 2.9 Hz, 1H), 3.19 (app dt, J = 11.4, 7.5 Hz, 1H), 1.95 – 1.78 (m, 5H), 1.74 – 1.53 (m, 9H), 1.39 (s, 9H). $^{13}$C NMR (101MHz, MeOD) δ = 183.7, 155.3, 92.8, 76.7, 72.2, 66.7, 59.7, 49.8, 44.9, 39.1, 37.8, 34.7, 33.1, 30.7, 30.6, 28.1, 22.8, 22.8. LC-MS (ESI+) *m/z:* 335 $[M+H]^+$. HRMS (ESI+): exact mass calculated for $[M+H]^+$ ($C_{19}H_{30}N_2O_3$) requires m/z 335.2329, found m/z 335.2330.

**9g**

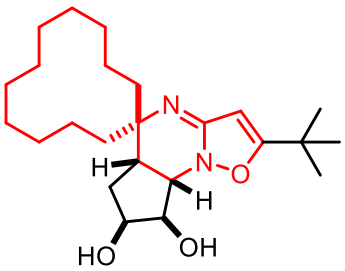


**(5a'S,7'R,8'S,8a'S)-2'-(Tert-butyl)-6',7',8',8a'-tetrahydro-5a'H-spiro[cyclooctane-1,5'-cyclopenta[e]isoxazolo[2,3-a]pyrimidine]-7',8'-diol**

Step 1: After 24 h, an additional portion of ketone, yttrium (III) triflate and cyclopentadiene was added, and the temperature was raised to 60 °C, followed by additional portions every 24 h. Total reaction time 5 days.

Step 2: After 24 h, an additional portion of $OsO_4$ and NMO was added. Total reaction time 48 h. The reaction mixture was purified by flash chromatography (5-10% MeOH / DCM). Obtained as a yellow oil (111 mg, 53% yield). $^{1}$H NMR (400MHz, MeOD) δ = 6.18 (s, 1H), 4.54 (dd, J = 7.3, 2.0 Hz, 1H), 4.22 (dd, J = 4.6, 2.3 Hz, 1H), 4.02 (td, J = 5.7, 3.2 Hz, 1H), 3.19 (app dt, J = 11.3, 7.6 Hz, 1H), 1.91 (ddd, J = 13.5, 7.5, 2.8 Hz, 1H), 1.86 – 1.80 (m, 4H), 1.74 – 1.52 (m, 11H), 1.37 (s, 9H). $^{13}$C NMR (101MHz, MeOD) δ = 183.7, 154.9, 92.8, 76.8, 72.3, 66.9, 59.4, 43.9, 34.8, 34.2, 33.2, 32.0, 29.5, 28.7, 28.2, 26.1, 22.8, 22.7. LC-MS (ESI+) *m/z:* 349 $[M+H]^+$. HRMS (ESI+): exact mass calculated for $[M+H]^+$ ($C_{20}H_{32}N_2O_3$) requires m/z 349.2486, found m/z 349.2487.

**9h**

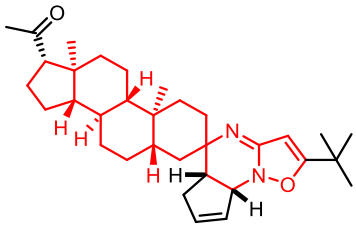


**(5a'S,7'R,8'S,8a'S)-2'-(Tert-butyl)-6',7',8',8a'-tetrahydro-5a'H-spiro[cyclododecane-1,5'-cyclopenta[e]isoxazolo[2,3-a]pyrimidine]-7',8'-diol**

Step 1: After 24 h, an additional portion of ketone, yttrium (III) triflate and cyclopentadiene was added, and the temperature was raised to 60 °C, followed by additional portions every 24 h. Total reaction time 4 days.

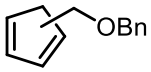
Step 2: After 24 h, an additional portion of $OsO_4$ and NMO was added. Total reaction time 48 h. The reaction mixture was purified by flash chromatography (2-8% MeOH / DCM). Obtained as a brown oil (187 mg, 77% yield). $^{1}$H NMR (400MHz, MeOD) δ = 6.15 (s, 1H), 4.56 (dd, J = 7.6, 1.9 Hz, 1H), 4.16 (dd, J = 4.6, 2.4 Hz, 1H), 4.03 (td, J = 5.1, 3.0 Hz, 1H), 3.08 (dt, J = 11.5, 7.6 Hz, 1H), 1.97 – 1.85 (m, 2H), 1.74 – 1.63 (m, 3H), 1.56 – 1.40 (m, 17H), 1.39 (s, 9H). $^{13}$C NMR (101MHz, MeOD) δ = 183.9, 155.3, 92.7, 76.8, 72.4, 66.9, 59.1, 43.5, 34.8, 32.8, 31.7, 31.4, 28.2, 28.2, 27.3, 27.0, 27.0, 23.5, 23.5, 23.0, 23.0, 19.9, 19.6. LC-MS (ESI+) *m/z:* 405 $[M+H]^+$. HRMS (ESI+): exact mass calculated for $[M+H]^+$ ($C_{24}H_{40}N_2O_3$) requires m/z 405.3112, found m/z 405.3112.

**9i**



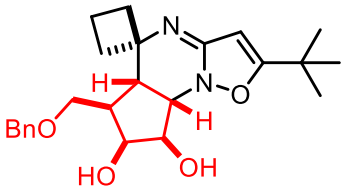
**1-((5S,8R,9S,10S,13S,14S,17S)-2'-(Tert-butyl)-10,13-dimethyl-1,2,4,5,6,6',7,8,8a',9,10,11,12,13,14,15,16,17-octadecahydro-5a'H-spiro[cyclopenta[a]phenanthrene-3,5'-cyclopenta[e]isoxazolo[2,3-a]pyrimidin]-17-yl)ethanone** (mixture of 2 diastereomers)
Step 1: Run at 0.2 mmol scale. Room temperature, 18 h. The reaction mixture was purified by flash chromatography (0-5% MeOH / DCM). Obtained as an amorphous yellow solid (91 mg, 90% yield). $^{1}$H NMR (400MHz, MeOD) δ = 6.25 – 6.21 (m, 1H), 6.09 – 6.04 (m, 1H), 5.24 (app dt, J = 7.6, 1.9 Hz, 1H), 2.98 (app q, J = 8.1 Hz, 1H), 2.65 (t, J = 8.8 Hz, 1H), 2.57 – 2.49 (m, 1H), 2.29 – 2.20 (m, 1H), 2.17 – 2.13 (m, 1H), 2.12 (s, 1.3H), 2.12 (s, 1.7H), 2.09 – 2.02 (m, 1H), 2.00 – 1.84 (m, 1H), 1.80 – 1.38 (m, 13H), 1.36 (s, 8H), 1.34 – 0.93 (m, 7H), 0.91 (s, 1.3H), 0.90 (s, 1.7H), 0.62 (s, 3H). $^{13}$C NMR (DEPT 135, 101MHz, MeOD) δ = 212.3 (-C), 184.2 (-C), 157.0 (-C x 2), 140.7 (-CH x 2), 126.2 (-CH), 92.9 (-CH), 65.4 (-CH x 2), 64.7 (-CH), 57.8 (-CH), 56.4 (-C x 2), 55.3 (-CH x 2), 49.9 (-CH), 45.3 (-C x 2), 45.3 (-C x 2), 42.5 (-CH), 41.8 (-CH), 40.0 ($-CH_2$), 37.7 ($-CH_2$), 36.8 ($-CH_2$), 36.8 (-C), 36.7 (-CH), 36.7 (-CH), 34.9 (-C), 34.7 ($-CH_2$), 34.3 ($-CH_2$), 33.0 ($-CH_2$), 33.0 ($-CH_2$), 32.9 ($-CH_2$), 31.6 ($-CH_3$), 30.9 ($-CH_2$), 30.3 ($-CH_2$), 29.3 ($-CH_2$), 29.1 ($-CH_2$), 28.1 ($-CH_3$), 25.3 ($-CH_2$), 23.7 ($-CH_2$), 22.1 ($-CH_2$), 13.8 ($-CH_3$), 11.3 ($-CH_3$). LC-MS (ESI+) *m/z:* 505 $[M+H]^+$. HRMS (ESI+): exact mass calculated for $[M+H]^+$ ($C_{33}H_{48}N_2O_2$) requires m/z 505.3789, found m/z 505.3788.

**10**



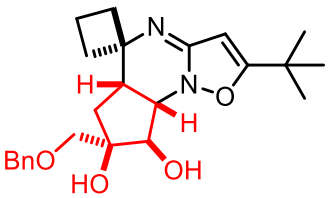
**((Cyclopentadien-1-ylmethoxy)methyl)benzene** (mixture of **10a**, **10b** and **10c**)
Chloromethyl benzyl ether (330 µL, 376 mg, 2.40 mmol) was added to a stirred solution of cyclopentadienyl sodium salt (2M in THF, 1.32 ml, 233 mg, 2.64 mmol) in DMF (3 ml) at -40 °C and stirred for 1.5 h. The reaction mixture was quenched 0 °C with water (5 ml), extracted with hexane (2×5 ml), washed with water (5 ml), dried ($MgSO_4$) and evaporated under a stream of $N_2$ to give the crude alkylated CPD as a mixture of regioisomers **10a**, **10b** and **10c**. LC-MS (ESI+) *m/z:* 187 $[M+H]^+$. The crude residue was dissolved in MeCN (3 ml) and used immediately in Step 1, or stored at -20 °C for 24 or 48 h, and used in Step 1.
Step 1: Room temperature, 7 h.
Step 2: After 24 h, an additional portion of $OsO_4$ and NMO was added. Total reaction time 48 h. The reaction mixture was purified by flash chromatography (0-10% MeOH / DCM) and the following three compounds were isolated (See Scheme 3 for yields):

**11a**



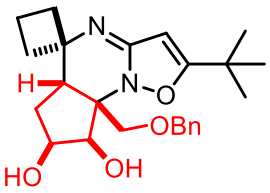
**(5a'S,6'R,7'S,8'R,8a'S)-6'-((benzyloxy)methyl)-2'-(tert-butyl)-6',7',8',8a'-tetrahydro-5a'H-spiro[cyclobutane-1,5'-cyclopenta[e]isoxazolo[2,3-a]pyrimidine]-7',8'-diol**
The combined fractions were concentrated *in vacuo* and triturated with hexane. Obtained as an amorphous white solid. $^{1}$H NMR (400 MHz, MeOD) δ 7.39 – 7.26 (m, 5H), 6.18 (s, 1H), 4.58 (d, J = 8.2, 3.4 Hz, 1H), 4.56 (s, 2H), 4.13 (app t, J = 3.8 Hz, 1H), 3.88 (dd, J = 7.0, 4.1 Hz, 1H), 3.78 (dd, J = 9.5, 5.7 Hz, 1H), 3.69 (dd, J = 9.4, 6.5 Hz, 1H), 3.00 (app t, J = 7.8 Hz, 1H), 2.60 – 2.52 (m, 1H), 2.41 – 2.33 (m, 1H), 2.20 – 1.97 (m, 4H), 1.93 – 1.84 (m, 1H), 1.38 (s, 9H). $^{13}$C NMR (DEPT 135, 101MHz, MeOD) δ 184.8 (-C), 157.7 (-C), 139.4 (-C), 129.5 (-CH), 129.1 (-CH), 128.9 (-CH), 92.9 (-CH), 76.0 (-CH), 74.4 ($-CH_2$), 73.5 (-CH), 70.5 ($-CH_2$), 66.0 (-CH), 58.8 (-C), 46.0 (-CH), 43.5 (-CH), 35.9 (-C), 34.9 ($-CH_2$), 31.9 ($-CH_2$), 28.1 ($-CH_3$), 15.3 ($-CH_2$). LC-MS (ESI+) *m/z:* 413 $[M+H]^+$. HRMS (ESI+): exact mass calculated for $[M+H]^+$ ($C_{24}H_{32}N_2O_4$) requires m/z 413.2435, found m/z 413.2434.

**11b**



**(5a'S,7'R,8'R,8a'S)-7'-((benzyloxy)methyl)-2'-(tert-butyl)-6',7',8',8a'-tetrahydro-5a'H-spiro[cyclobutane-1,5'-cyclopenta[e]isoxazolo[2,3-a]pyrimidine]-7',8'-diol**
Obtained as a clear oil (See Scheme 3 for yields). $^{1}$H NMR (400 MHz, MeOD) δ 7.34 – 7.26 (m, 3H), 7.25 – 7.21 (m, 2H), 6.17 (s, 1H), 4.59 (dd, *J* = 8.3, 3.0 Hz, 1H), 4.48 (s, 2H), 4.08 (d, *J* = 3.1 Hz, 1H), 3.43 (d, *J* = 9.2 Hz, 1H), 3.44 – 3.35 (m, 1H), 3.36 (d, *J* = 9.2 Hz, 1H), 2.35 – 2.29 (m, 3H), 2.18 (dt, *J* = 12.7, 8.8 Hz, 1H), 2.03 – 1.90 (m, 3H), 1.72 (dd, *J* = 13.6, 12.5 Hz, 1H), 1.30 (s, 9H). $^{13}$C NMR (DEPT 135, 101MHz, MeOD) δ 184.6 (-C), 156.4 (-C), 139.5 (-C), 129.5 (-CH), 128.8 (-CH), 128.6 (-CH), 92.8 (-CH), 79.3 (-CH), 77.4 (-C), 74.4 ($-CH_2$), 73.1 ($-CH_2$), 68.0 (-CH), 57.0 (-C), 42.5 (-CH), 36.4 ($-CH_2$), 34.8 ($-CH_2$), 34.8 (-C), 31.6 ($-CH_2$), 28.1 ($-CH_3$), 14.5 ($-CH_2$). LC-MS (ESI+) *m/z:* 413 $[M+H]^+$. HRMS (ESI+): exact mass calculated for $[M+H]^+$ ($C_{24}H_{32}N_2O_4$) requires m/z 413.2435, found m/z 413.2437.

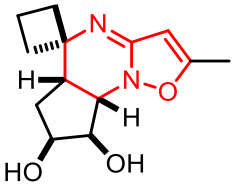
**11c**

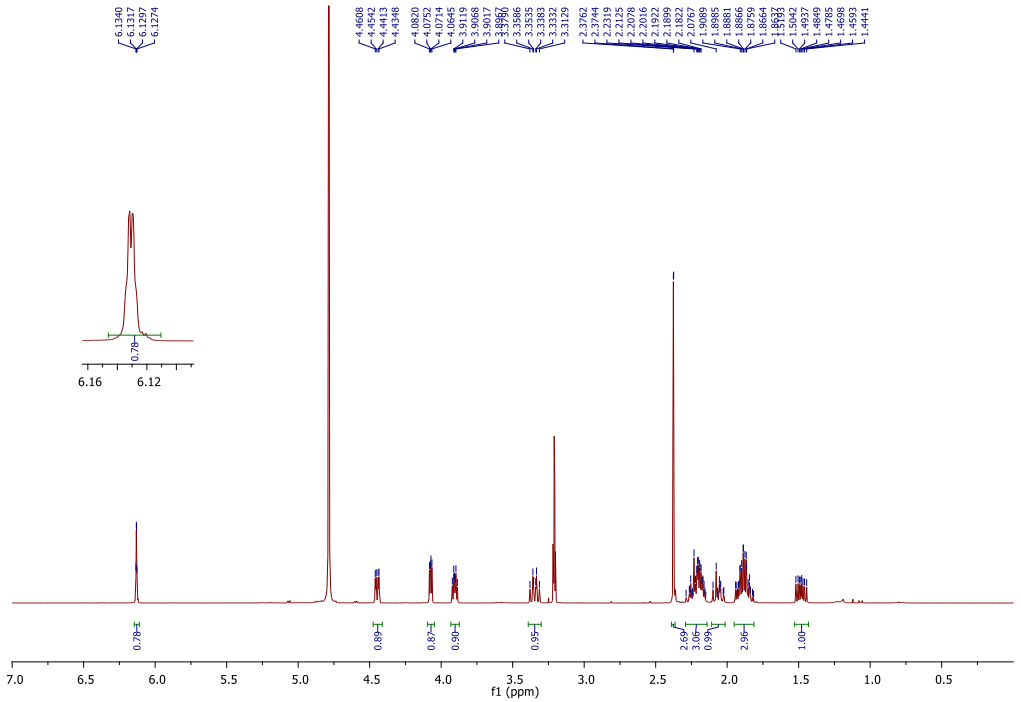


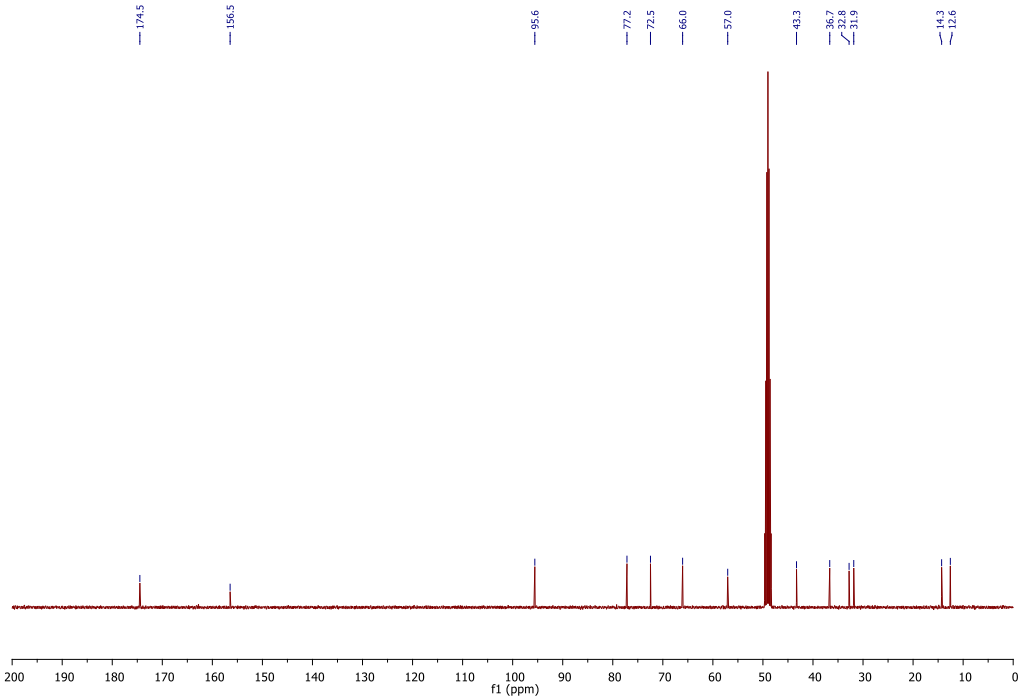

**(5a'R,7'S,8'R,8a'R)-8a'-((benzyloxy)methyl)-2'-(tert-butyl)-6',7',8',8a'-tetrahydro-5a'H-spiro[cyclobutane-1,5'-cyclopenta[e]isoxazolo[2,3-a]pyrimidine]-7',8'-diol**
Obtained as a clear oil (See Scheme 3 for yields). $^{1}$H NMR (400 MHz, MeOD) δ = 7.35 – 7.25 (m, 5H), 6.20 (s, 1H), 4.61 (d, J = 11.9, 1H), 4.53 (d, J = 11.9, 1H), 4.10 (d, J = 10.7, 1H), 4.00 – 3.93 (m, 2H), 3.82 (d, J = 10.7, 1H), 3.27 (dd, J = 10.8, 8.3, 1H), 2.63 – 2.55 (m, 1H), 2.43 – 2.34 (m, 1H), 2.26 – 2.16 (m, 1H), 2.07 – 1.96 (m, 3H), 1.92 – 1.80 (m, 1H), 1.52 (ddd, J = 13.7, 11.0, 5.1, 1H), 1.36 (s, 9H). $^{13}$C NMR (DEPT 135, 101MHz, MeOD) δ = 183.6 (-C), 156.8 (-C), 137.5 (-C), 127.9 (-CH), 127.4 (-CH), 91.5 (-CH), 78.2 (-CH), 73.8 (-C), 72.9 (-$CH_2$), 70.5 (-CH), 69.6 (-$CH_2$), 57.9 (-C), 46.9 (-CH), 36.1 (-$CH_2$), 33.4 (-C), 31.5 (-$CH_2$), 31.1 (-$CH_2$), 26.6 (-$CH_3$), 13.5 (-$CH_2$). LC-MS (ESI+) *m/z:* 413 $[M+H]^+$. HRMS (ESI+): exact mass calculated for $[M+H]^+$ ($C_{24}H_{32}N_2O_4$) requires m/z 413.2435, found m/z 413.2435.

## NMR spectra

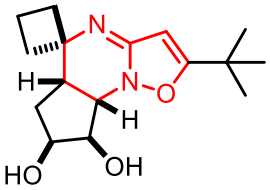
### $^{1}H$ and $^{13}C$ NMR spectra of 8a in MeOD

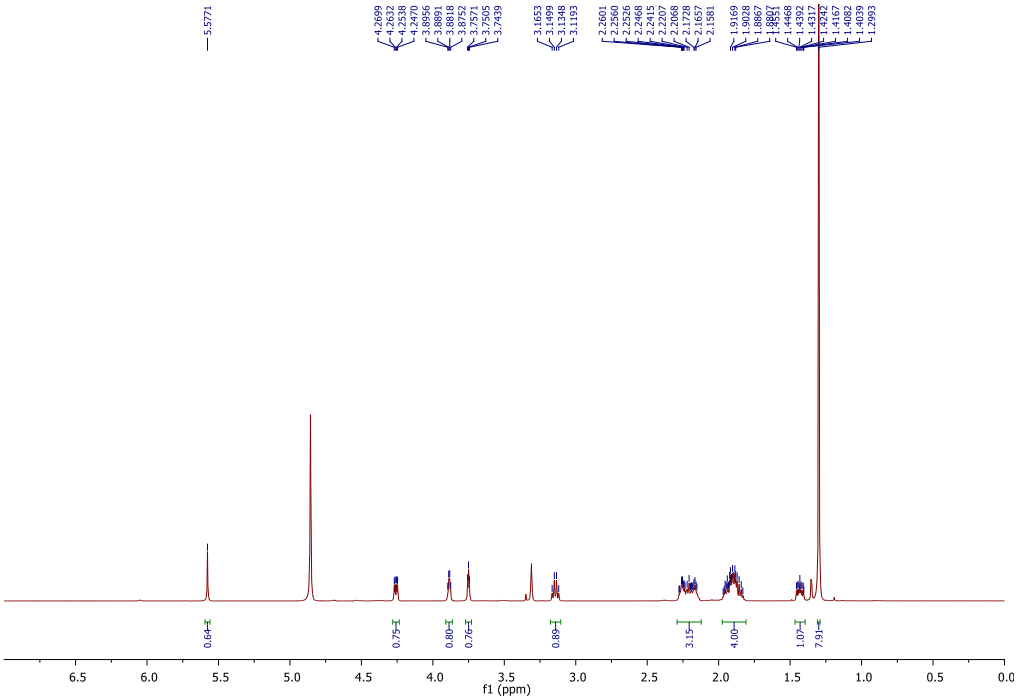


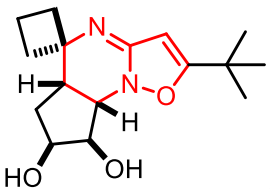



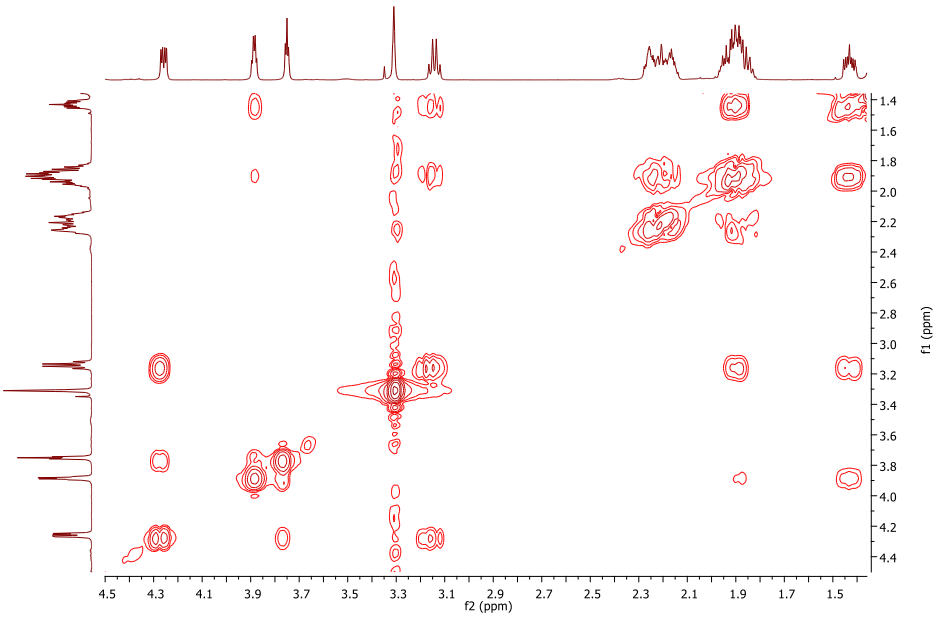
**$^{1}$H, COSY, NOESY, $^{13}$C and DEPT135 spectra of 8b in MeOD**

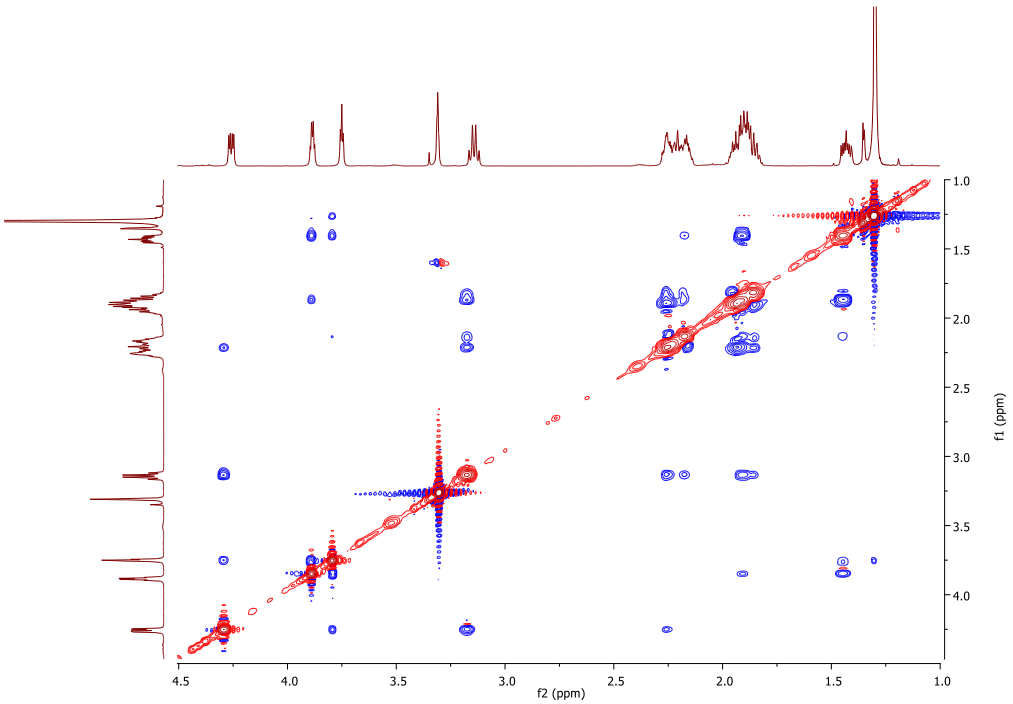


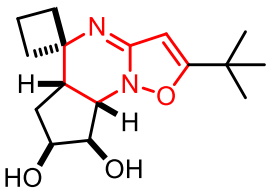





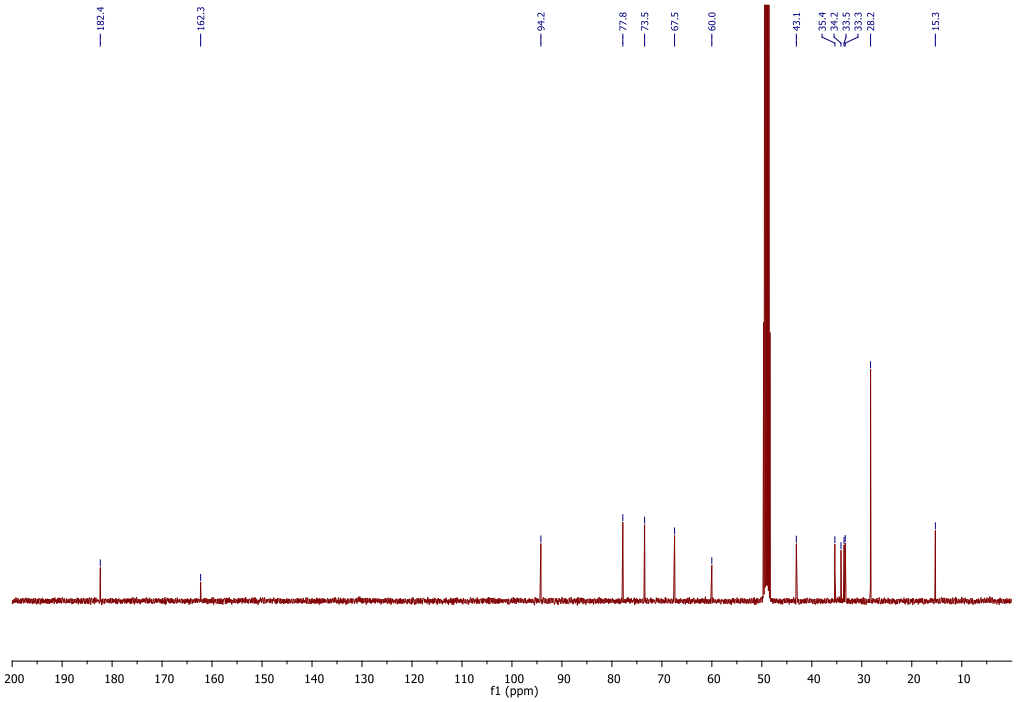

**8b**

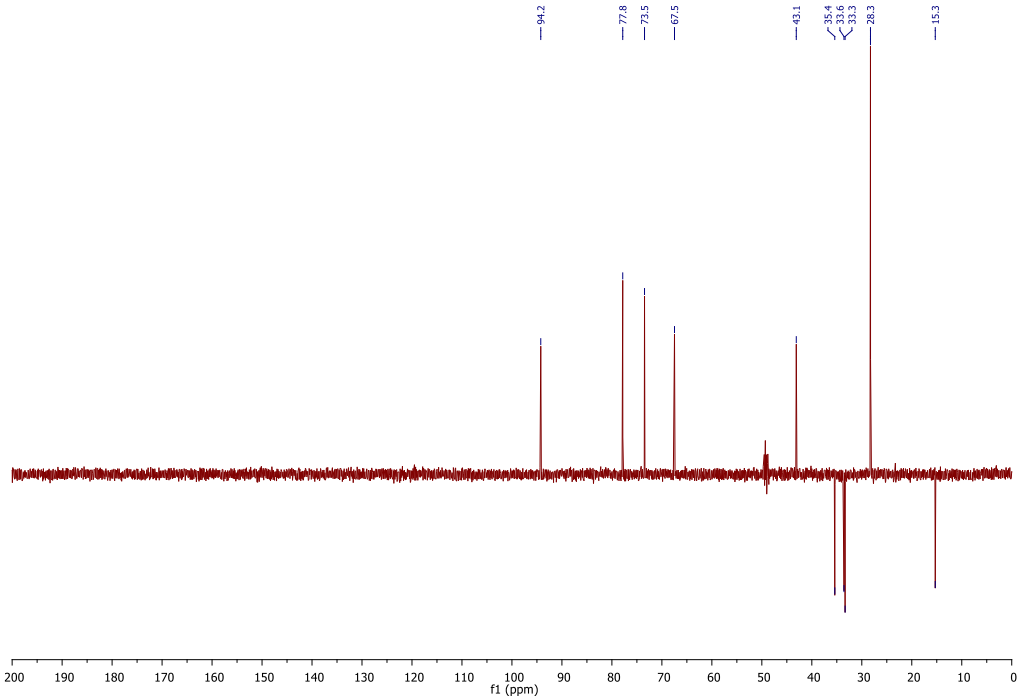


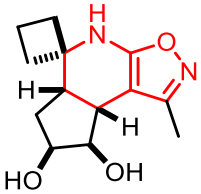

N
H
N
O
H
HO
OH

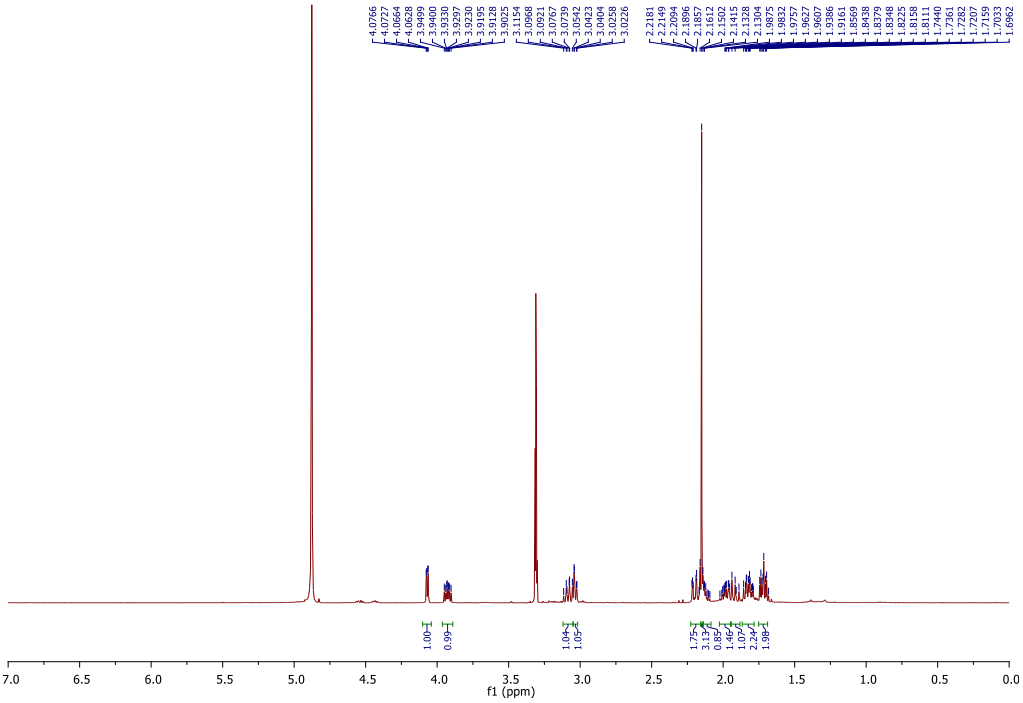
**8b**

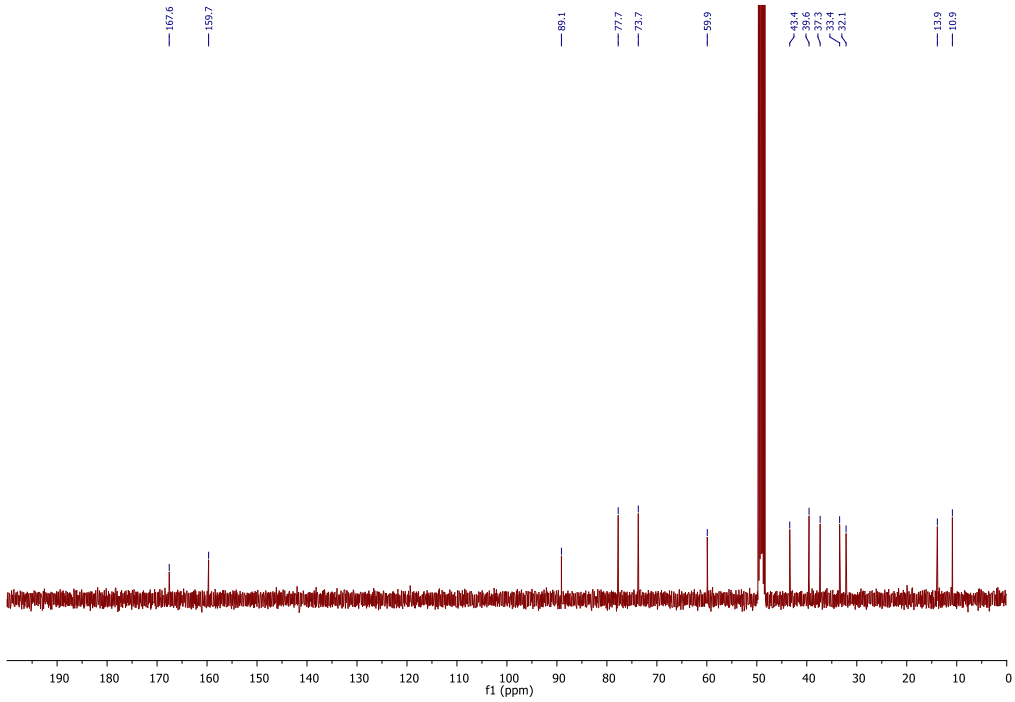

182.4
162.3
94.2
77.8
73.5
67.5
60.0
43.1
35.4
34.2
33.5
33.3
28.2
15.3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


94.2
77.8
73.5
67.5
43.1
35.4
33.6
33.3
28.3
15.3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

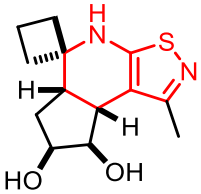
**$^{1}$H and $^{13}$C NMR spectra of 8c in MeOD**

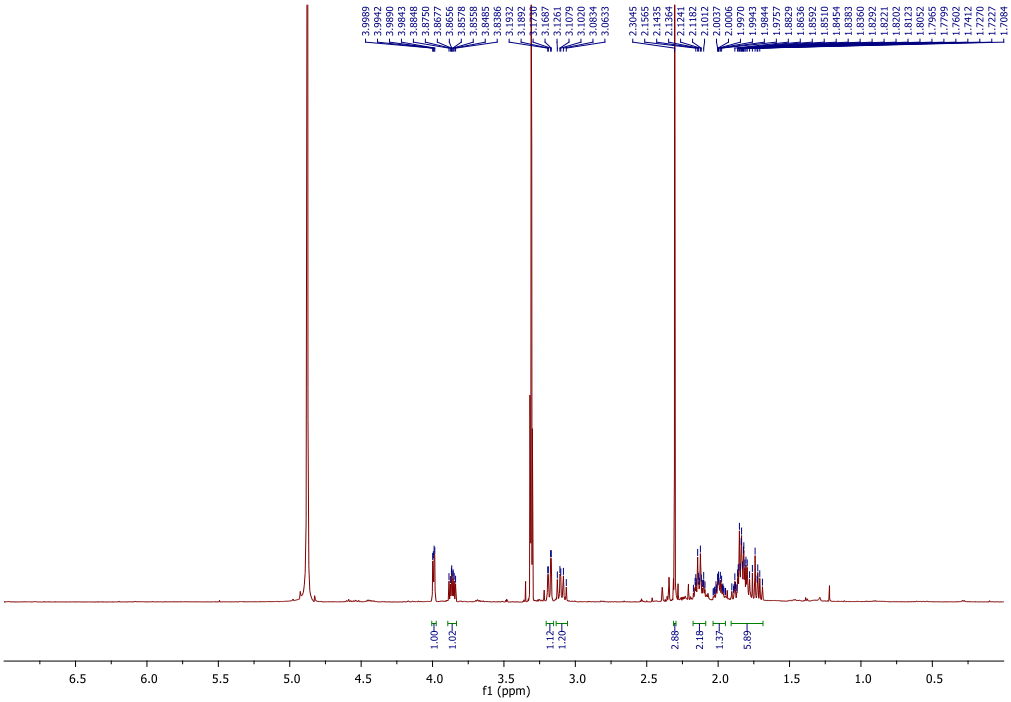


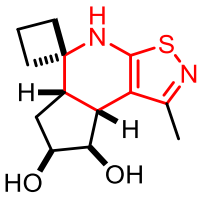



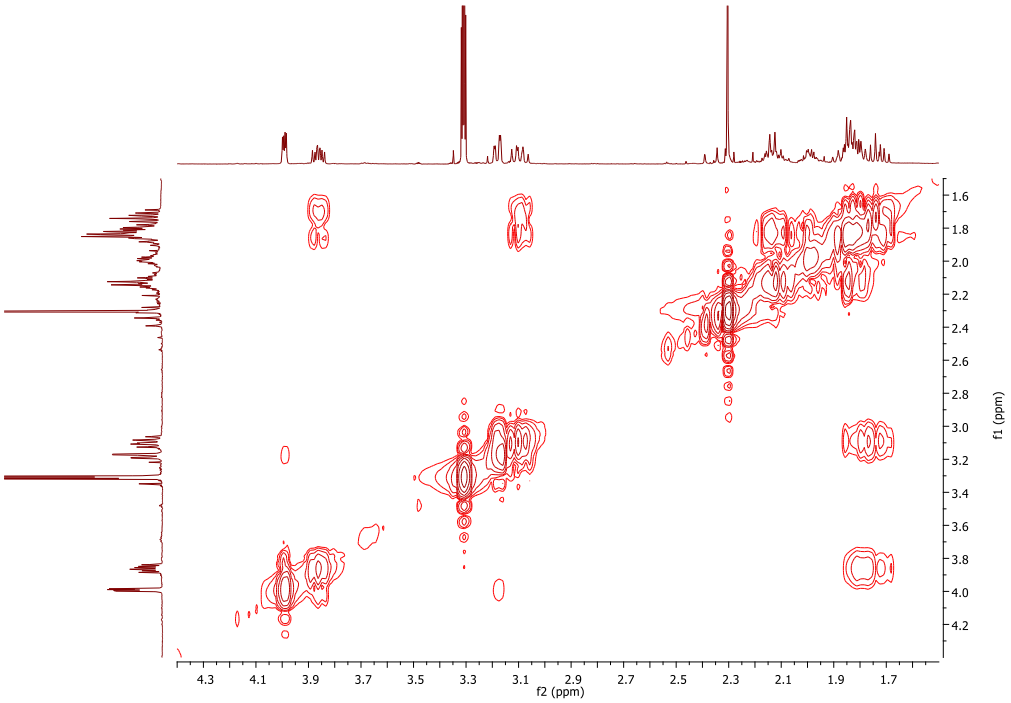
**$^{1}$H, COSY, NOESY, $^{13}$C and DEPT135 spectra of 8d in MeOD**

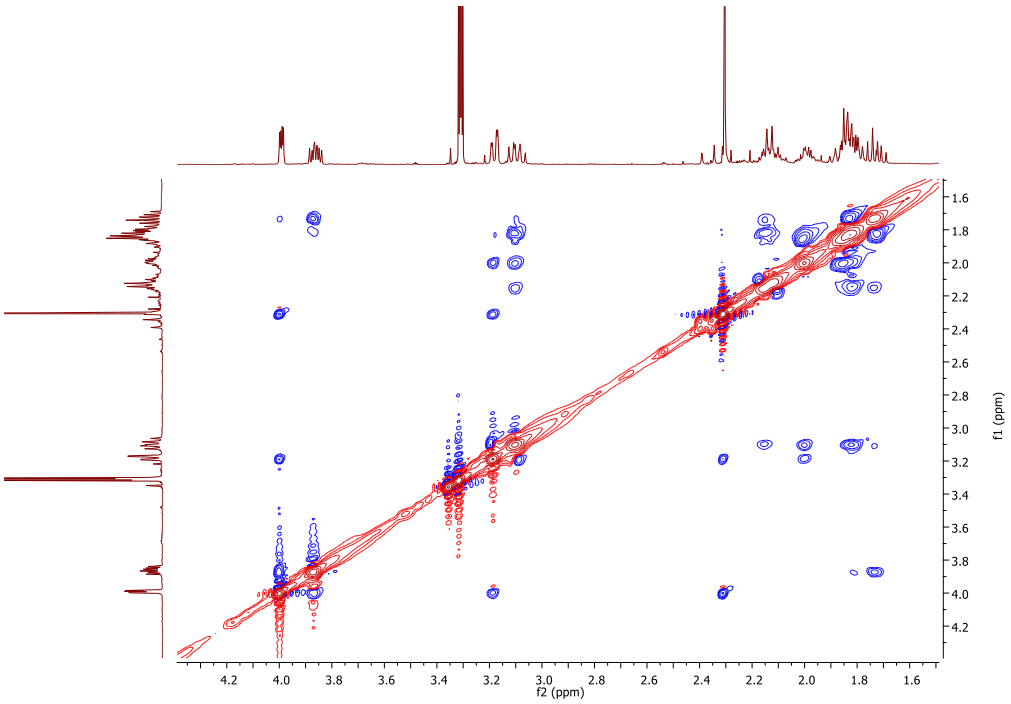


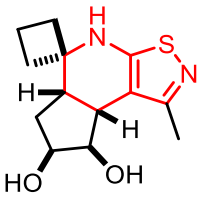





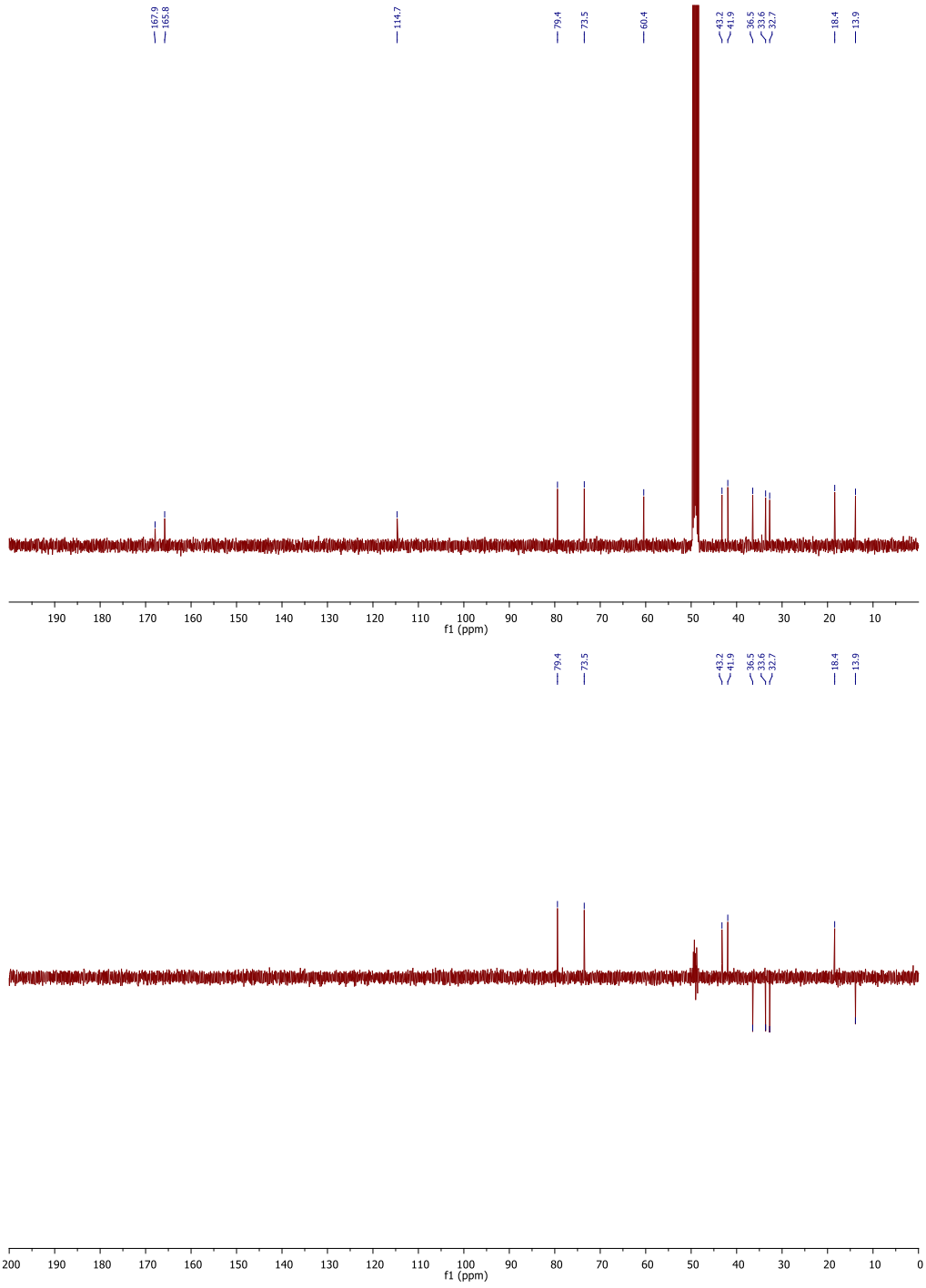

**8d**



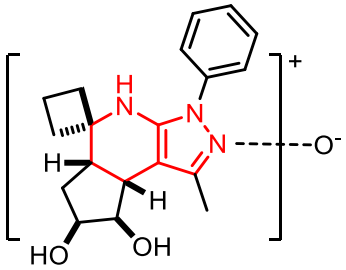



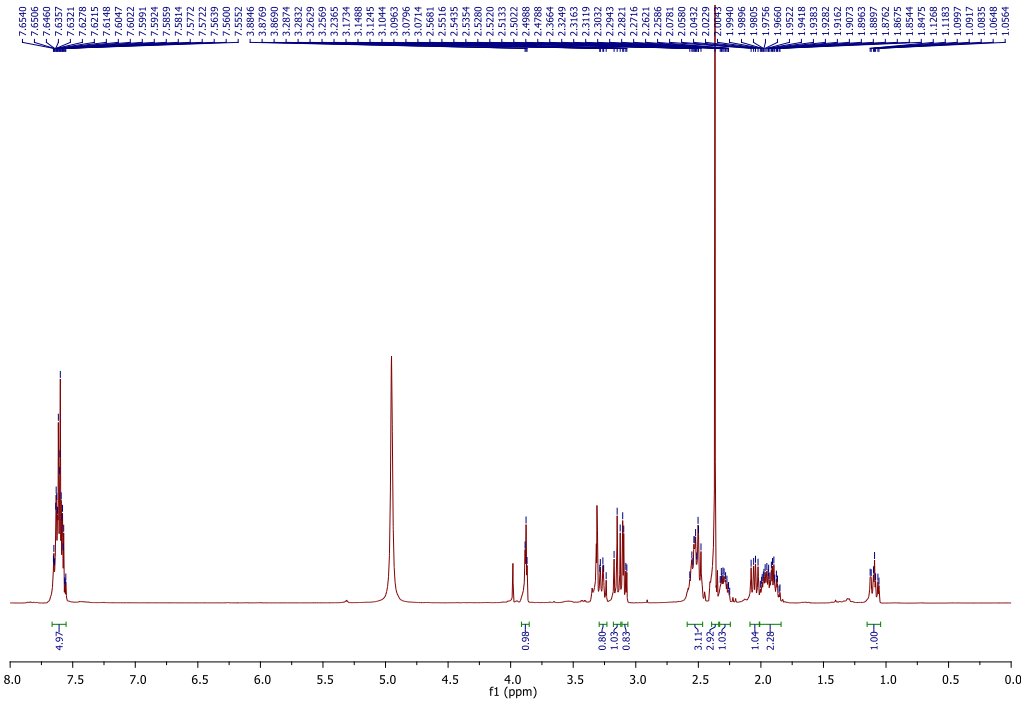

H
N
S
N
H
H
HO
OH

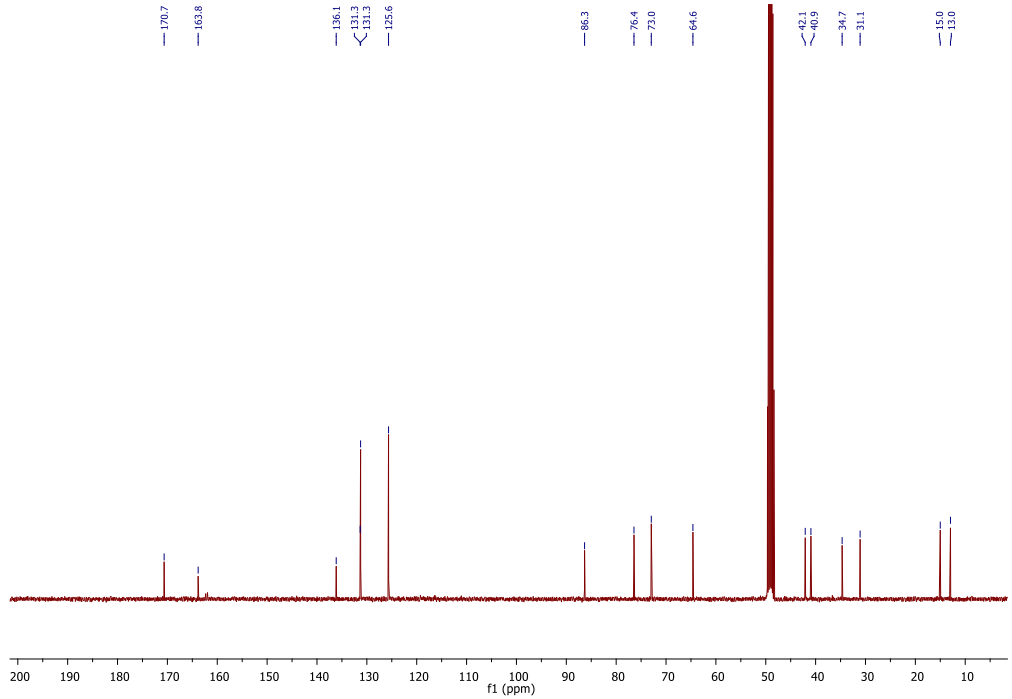
**8d**


167.9
165.8
114.7
79.4
73.5
60.4
43.2
41.9
36.5
33.6
32.7
18.4
13.9
f1 (ppm)

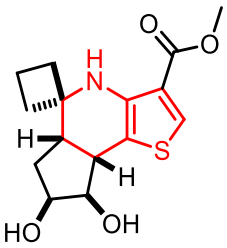
**$^{1}$H and $^{13}$C NMR spectra of 8e in MeOD**

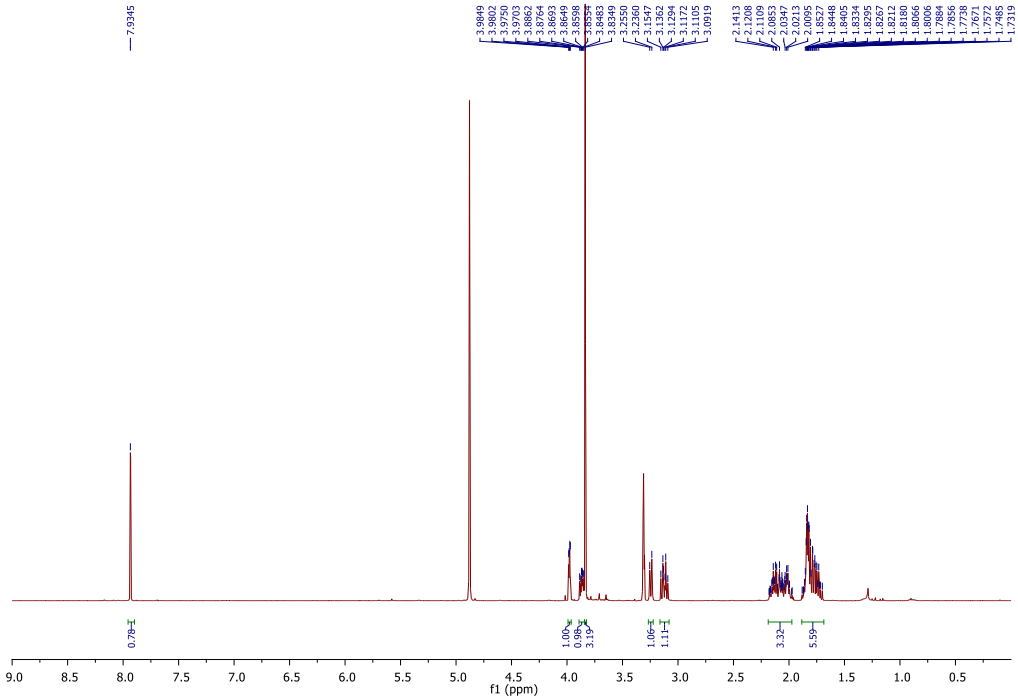


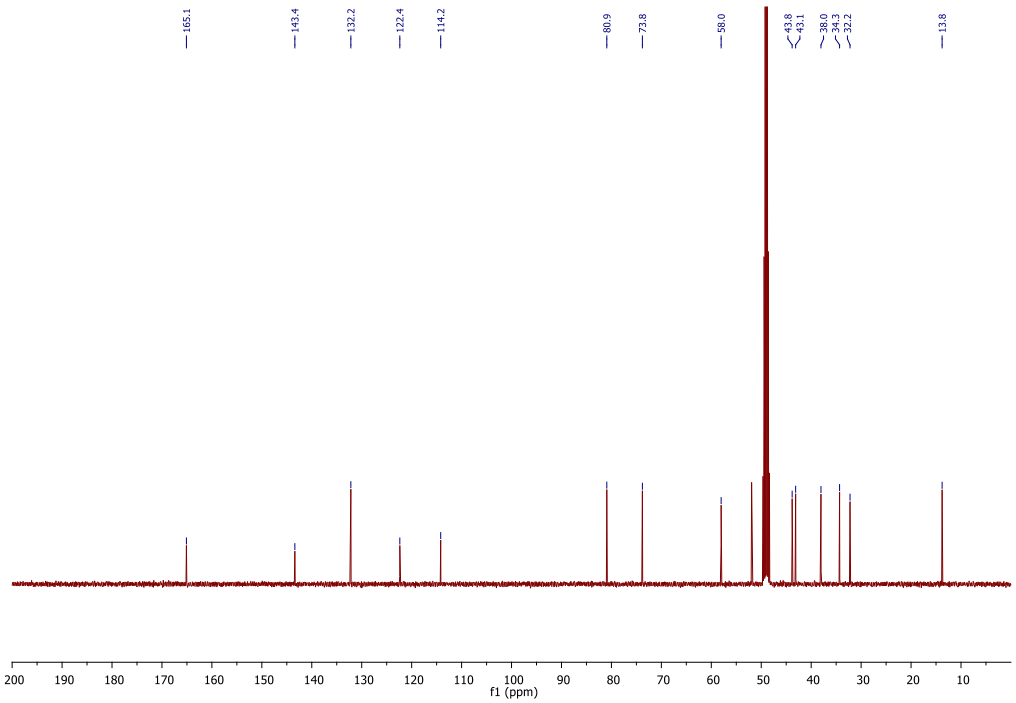



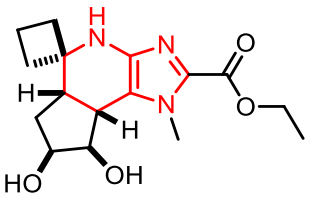
**$^{1}$H and $^{13}$C NMR spectra of 8f in MeOD**

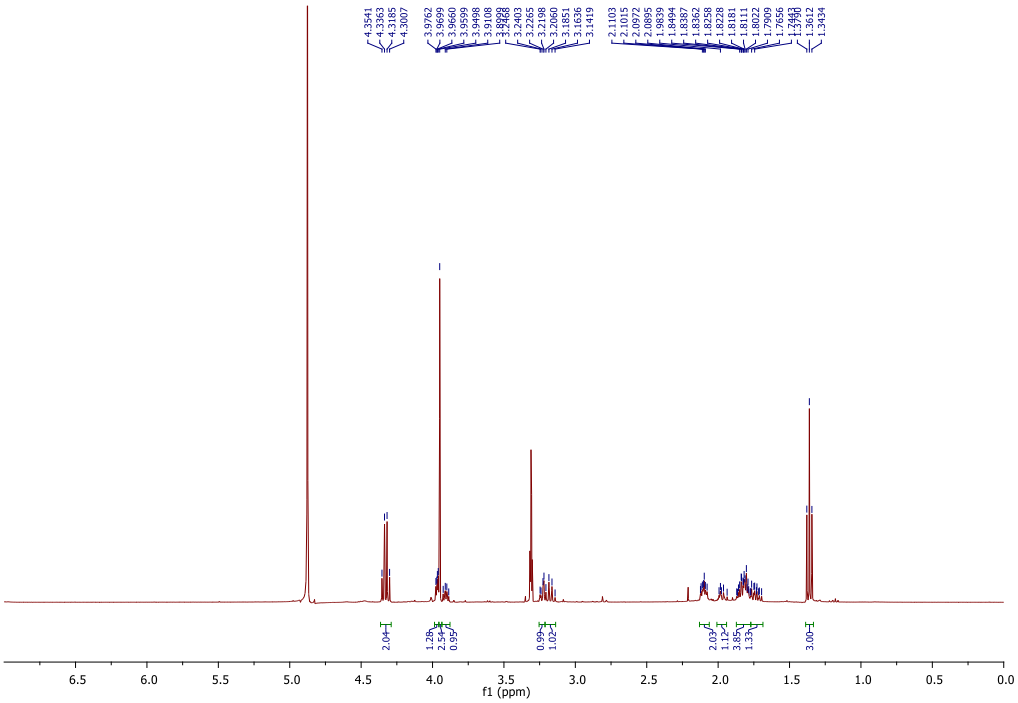


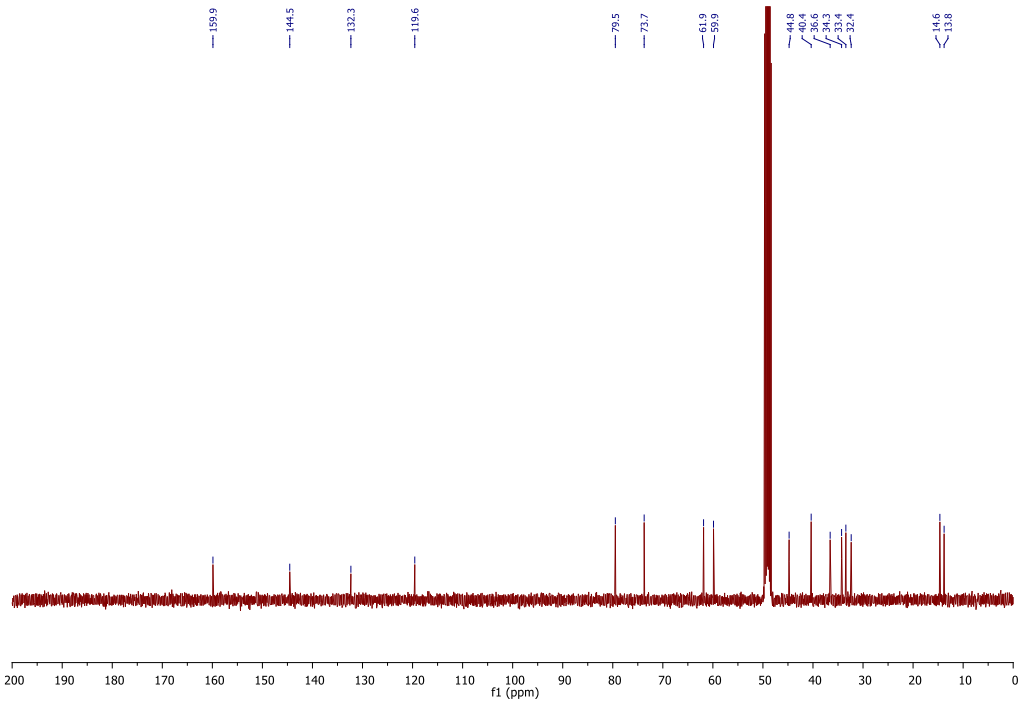



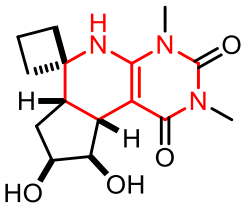
**$^{1}H$ and $^{13}C$ NMR spectra of 8h in MeOD**

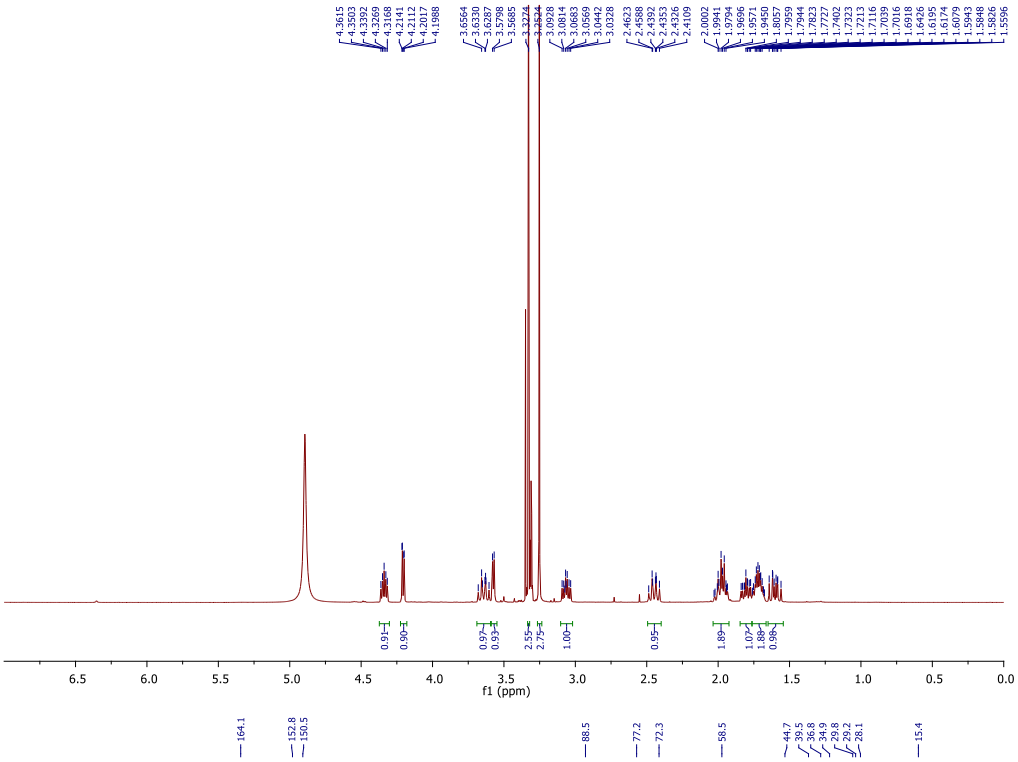


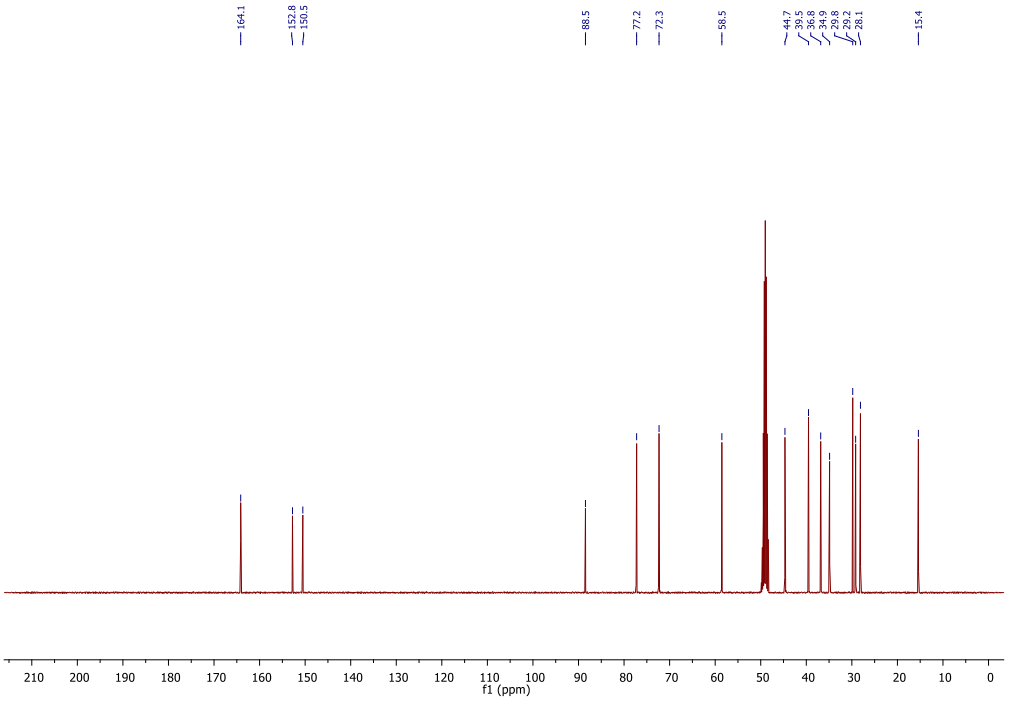



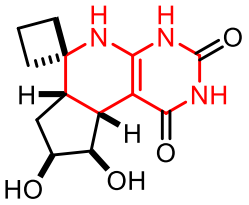
**$^{1}$H and $^{13}$C NMR spectra of 8j in MeOD**

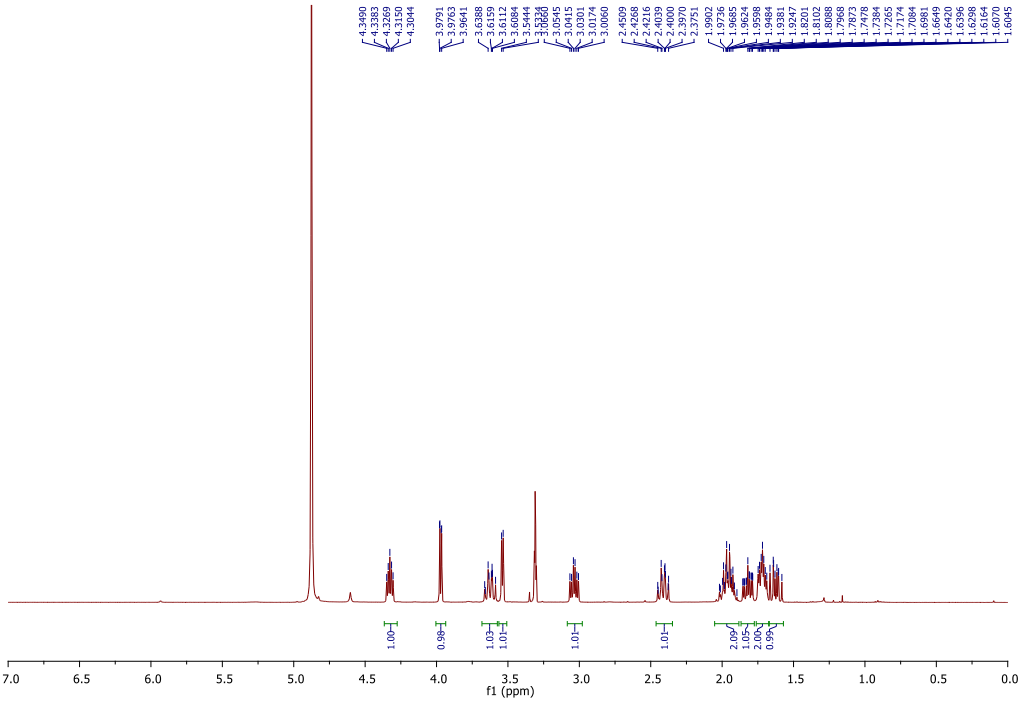


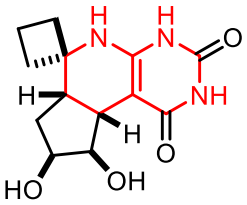



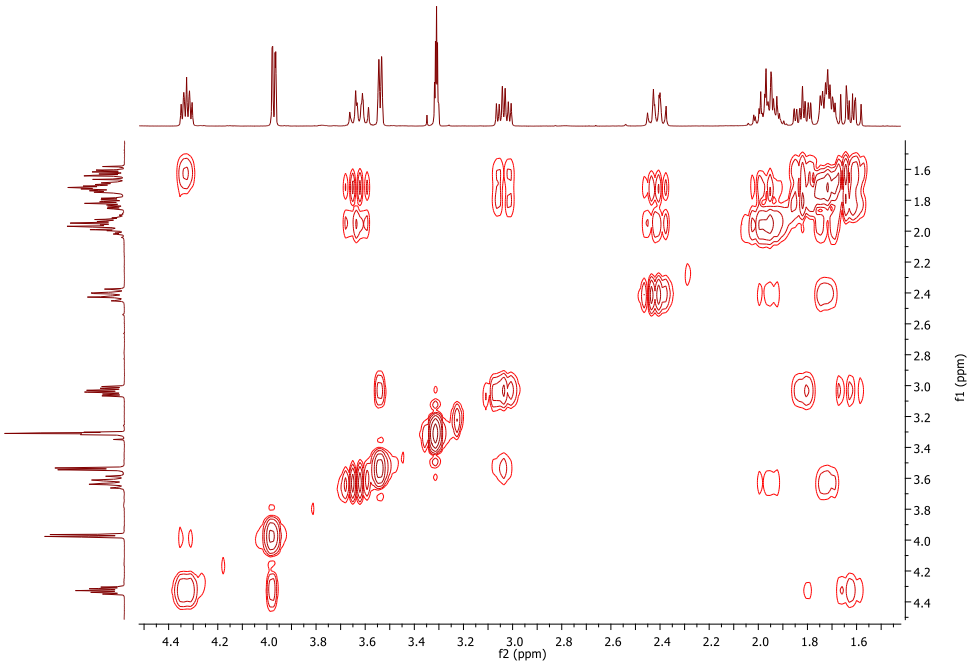
**$^{1}$H, COSY, NOESY, $^{13}$C and DEPT135 spectra of 8h in MeOD**

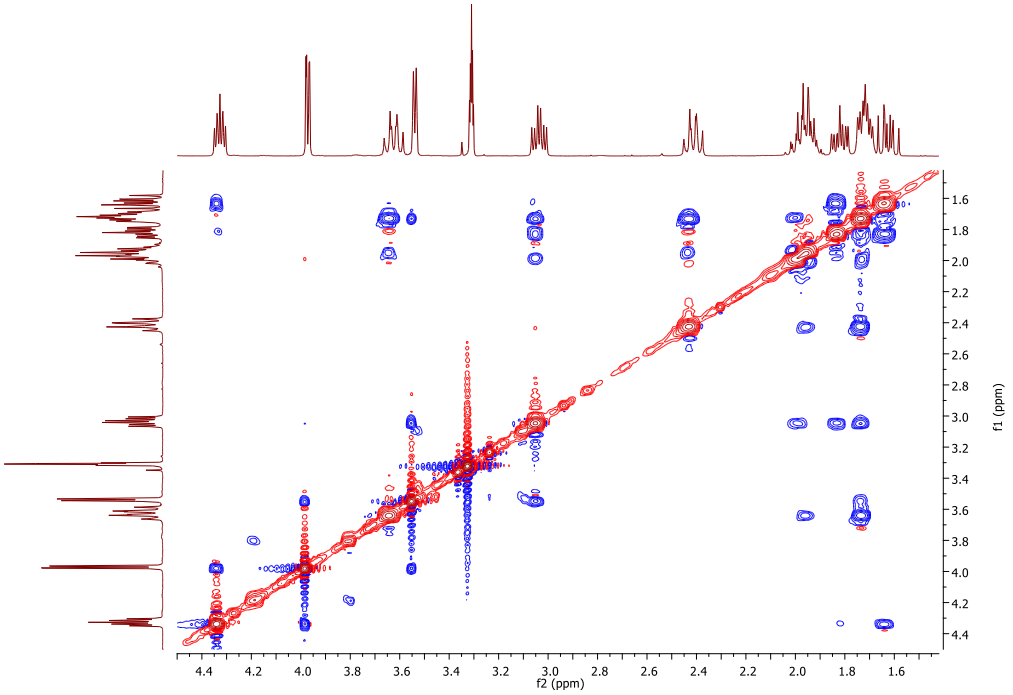


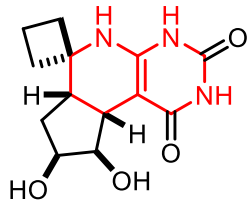





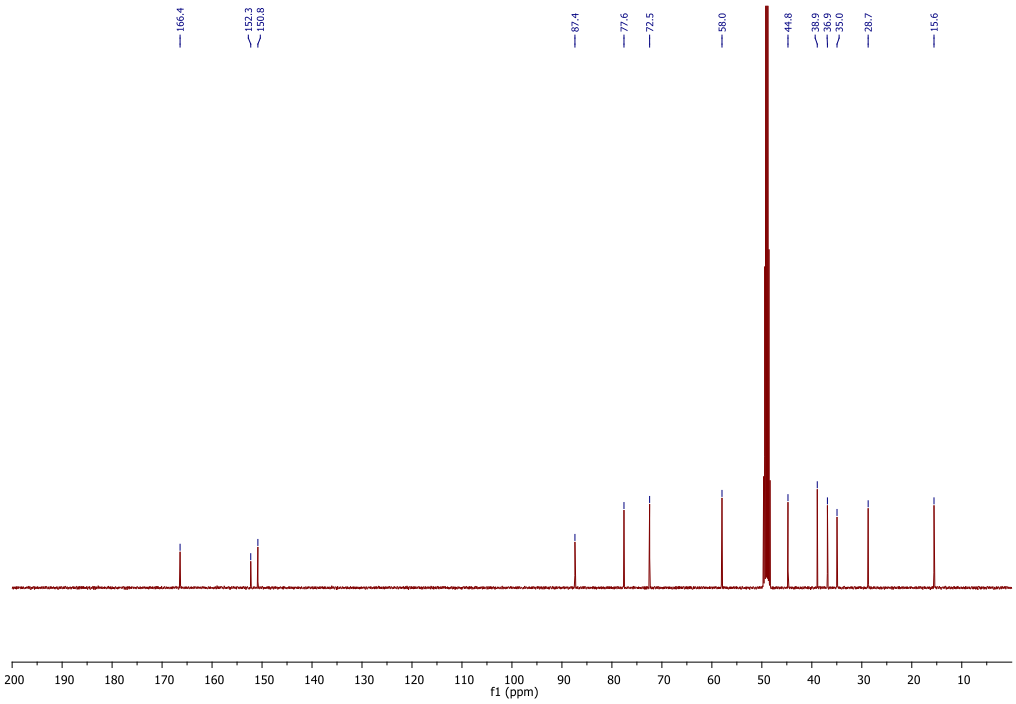

**8h**

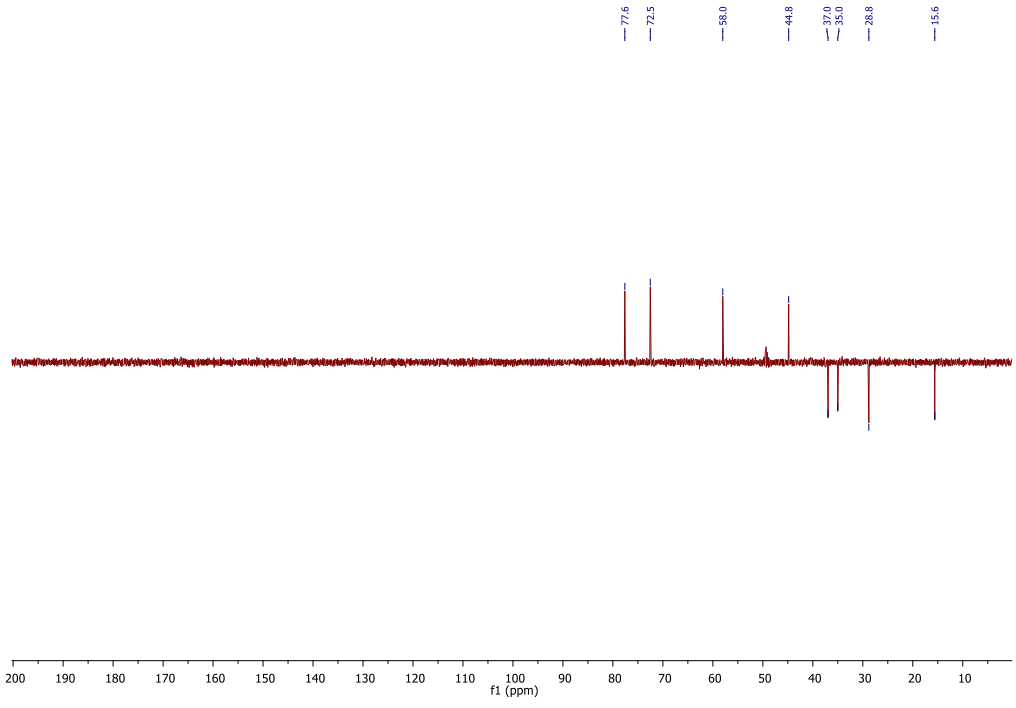


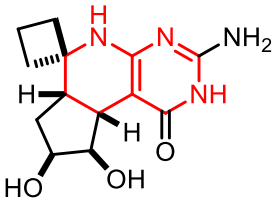

H
N
H
N
O
NH
H
O
HO
OH

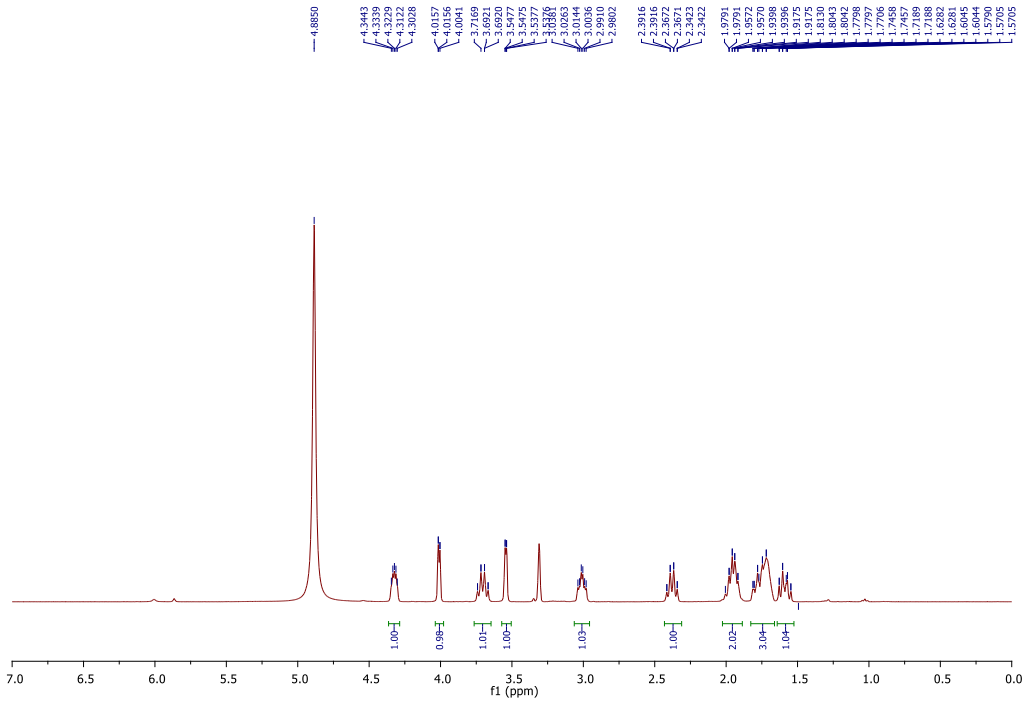
**8h**

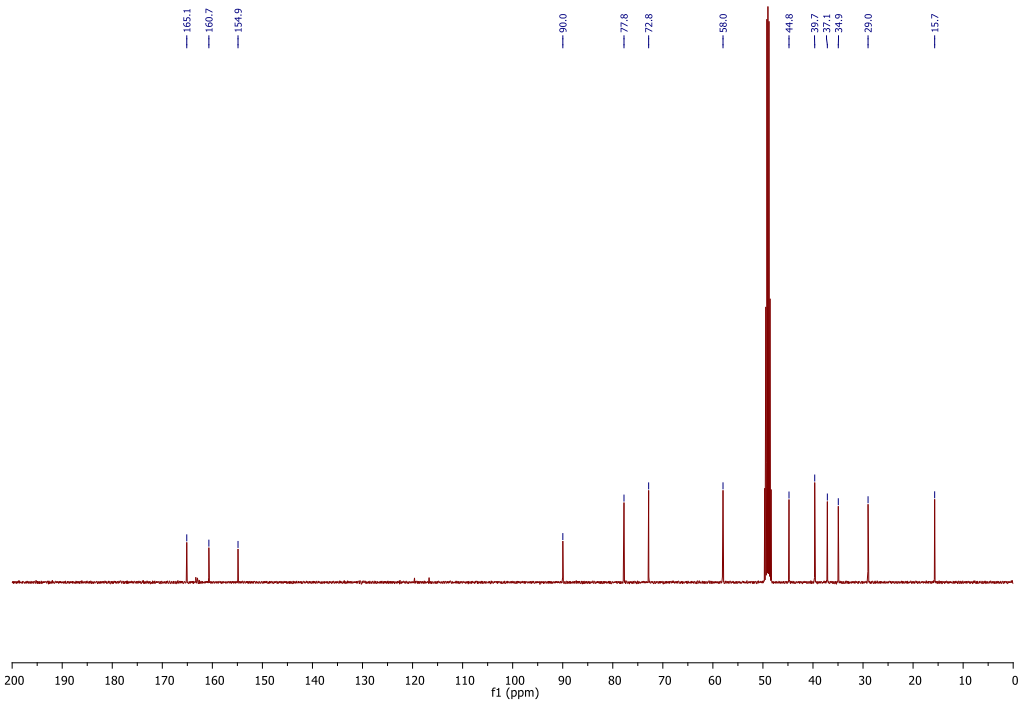

166.4
152.3
150.8
87.4
77.6
72.5
58.0
44.8
38.9
36.9
35.0
28.7
15.6
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


77.6
72.5
58.0
44.8
37.0
35.0
28.8
15.6
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

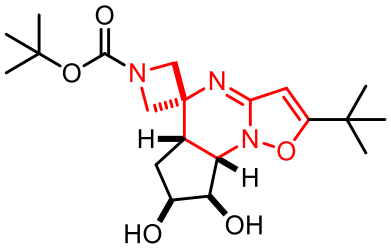
**$^{1}$H and $^{13}$C NMR spectra of 8l in MeOD**

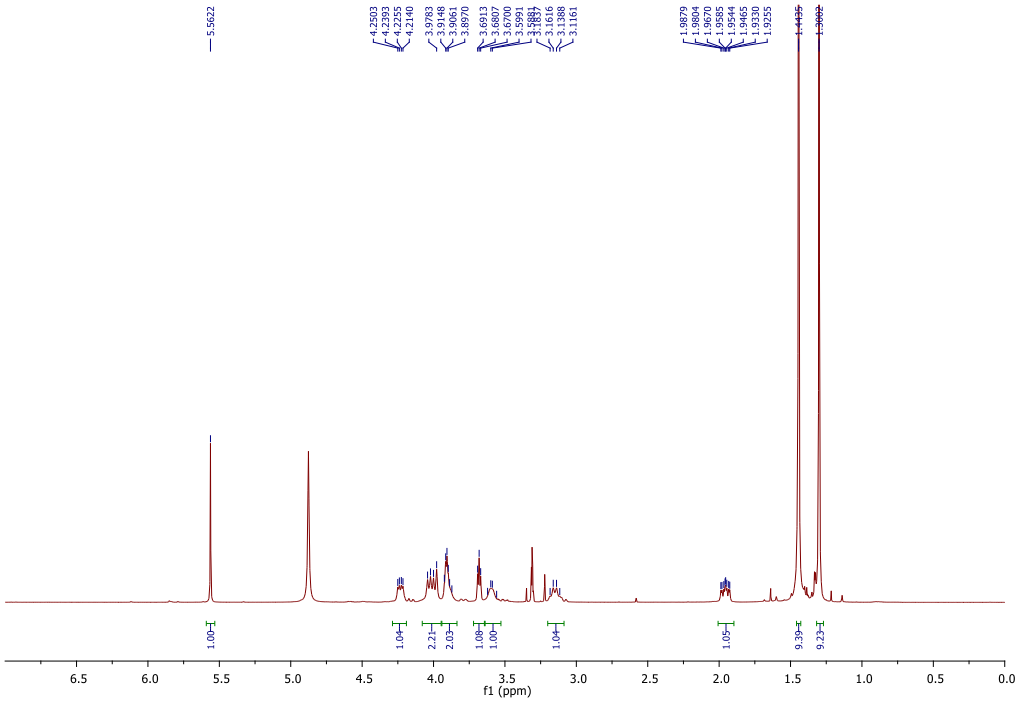


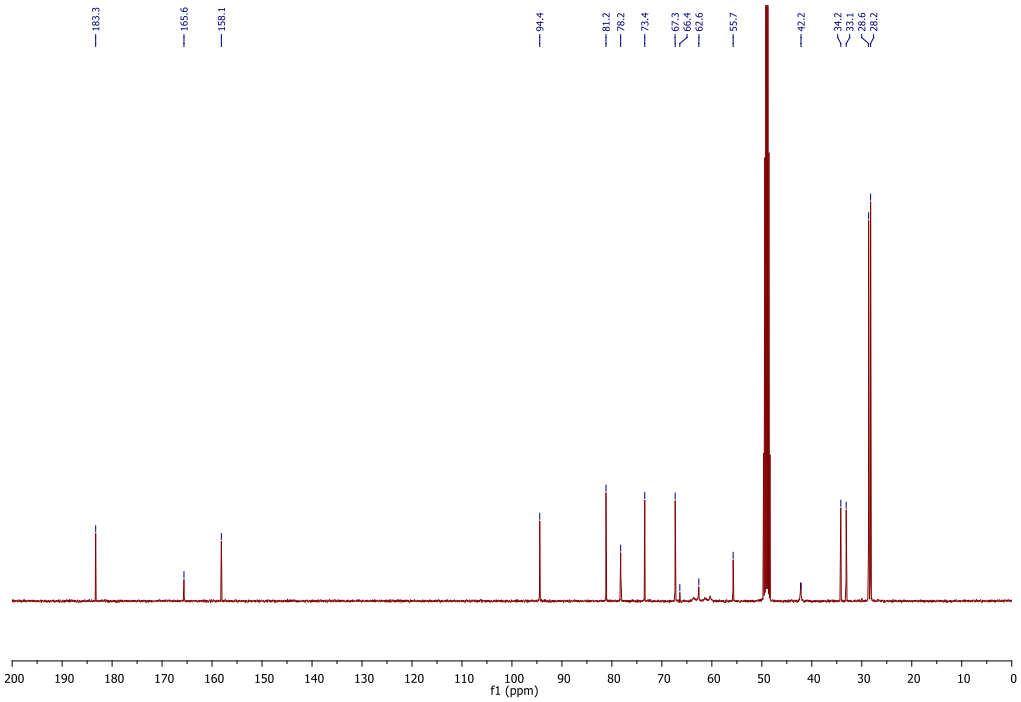



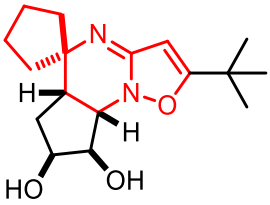
**$^{1}$H and $^{13}$C NMR spectra of 9a in MeOD**

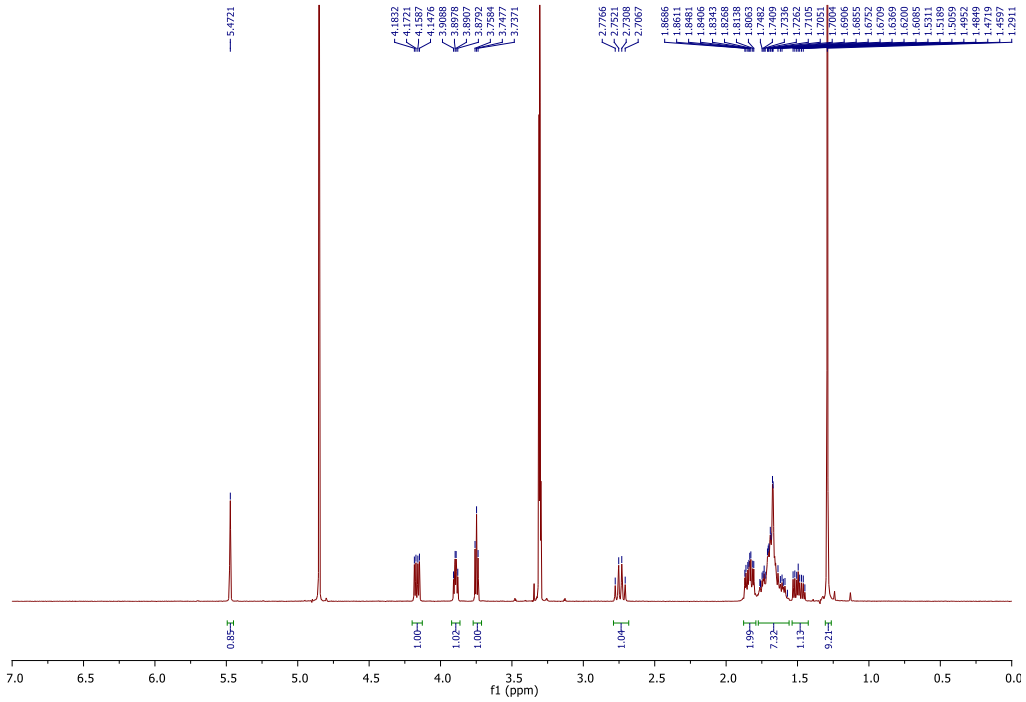


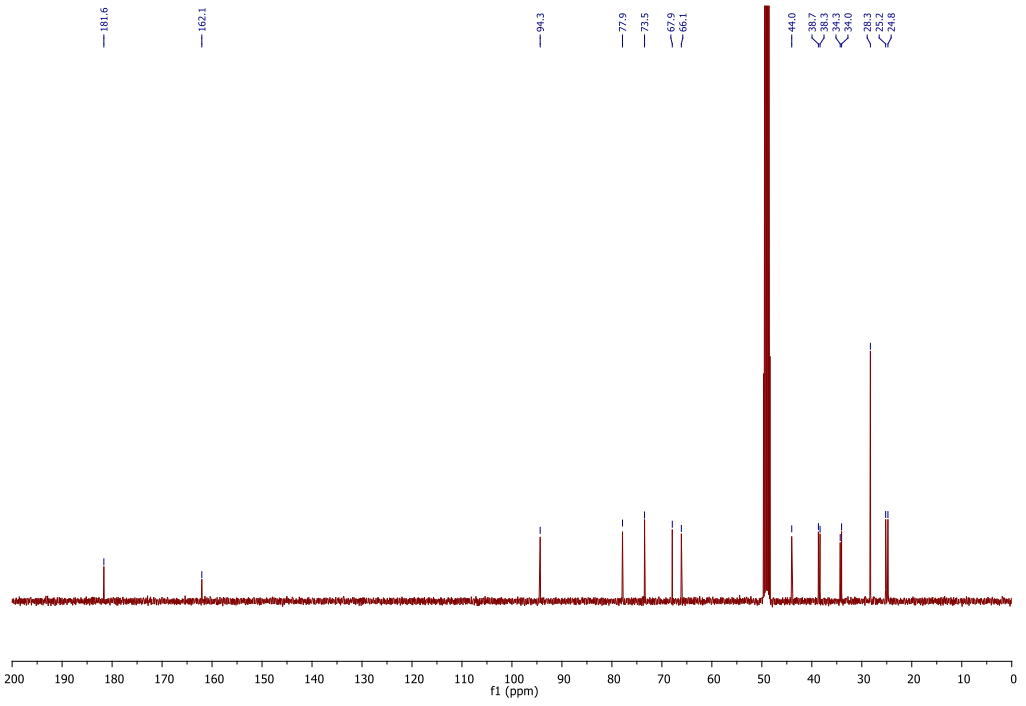



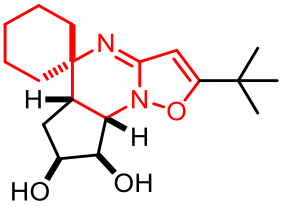
**$^{1}$H and $^{13}$C NMR spectra of 9b in MeOD**

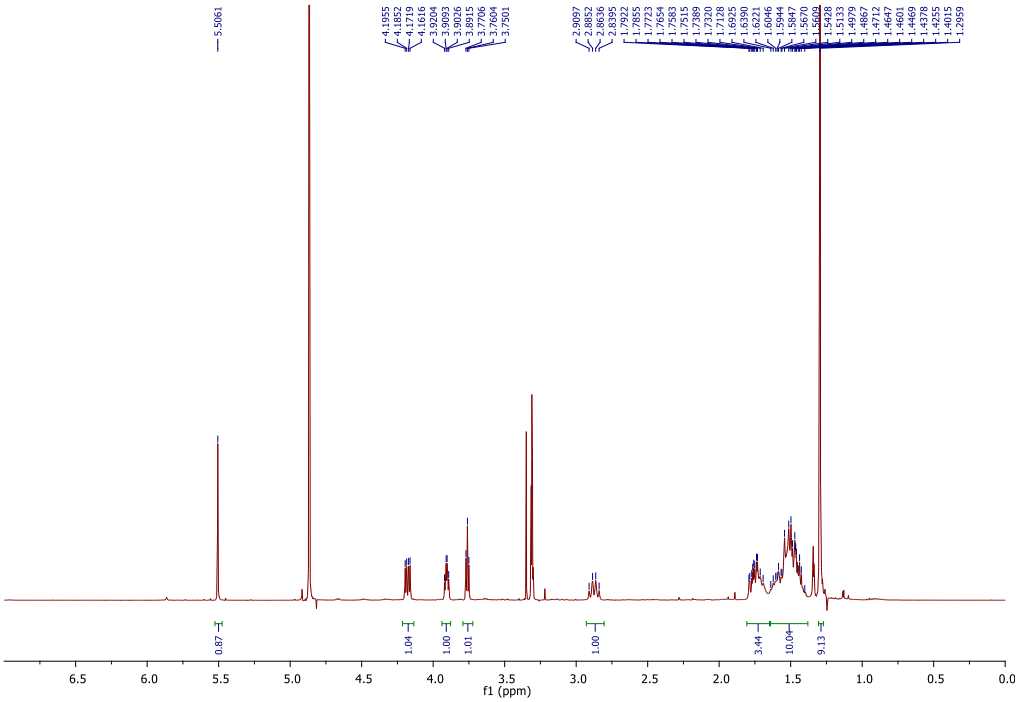


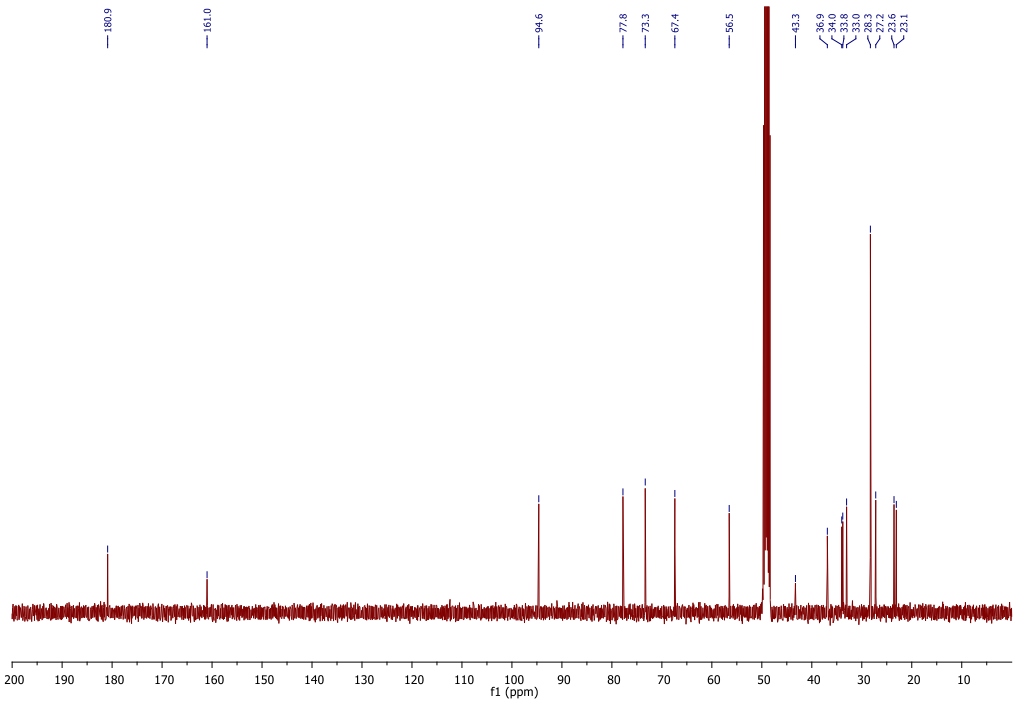



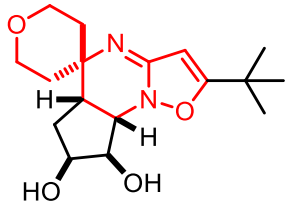
**$^{1}$H and $^{13}$C NMR spectra of 9c in MeOD**

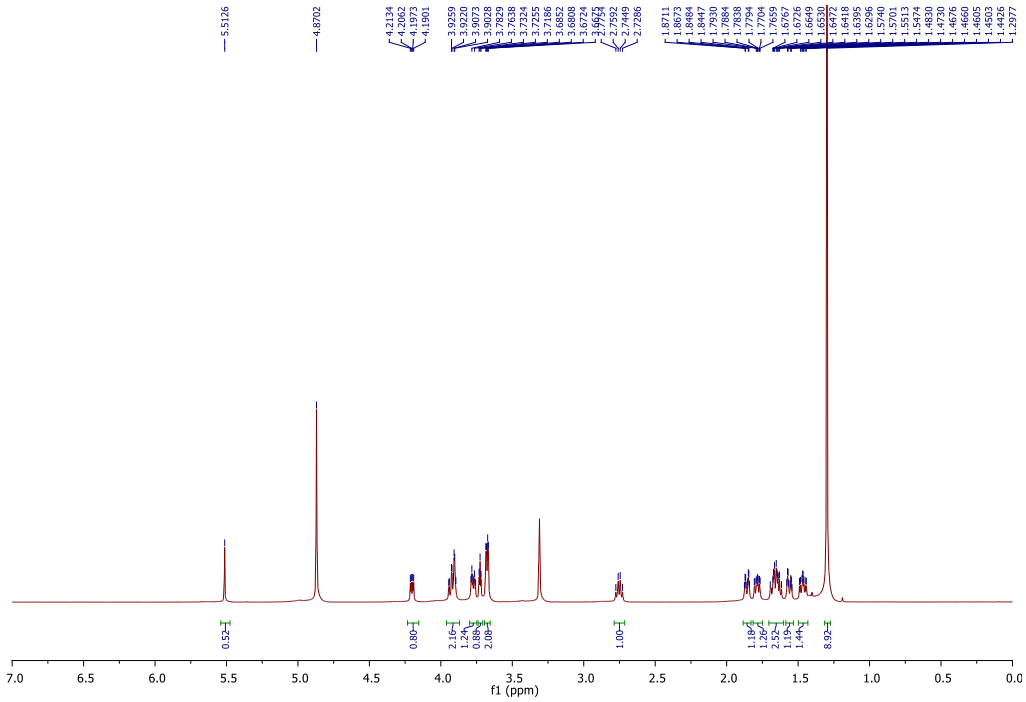


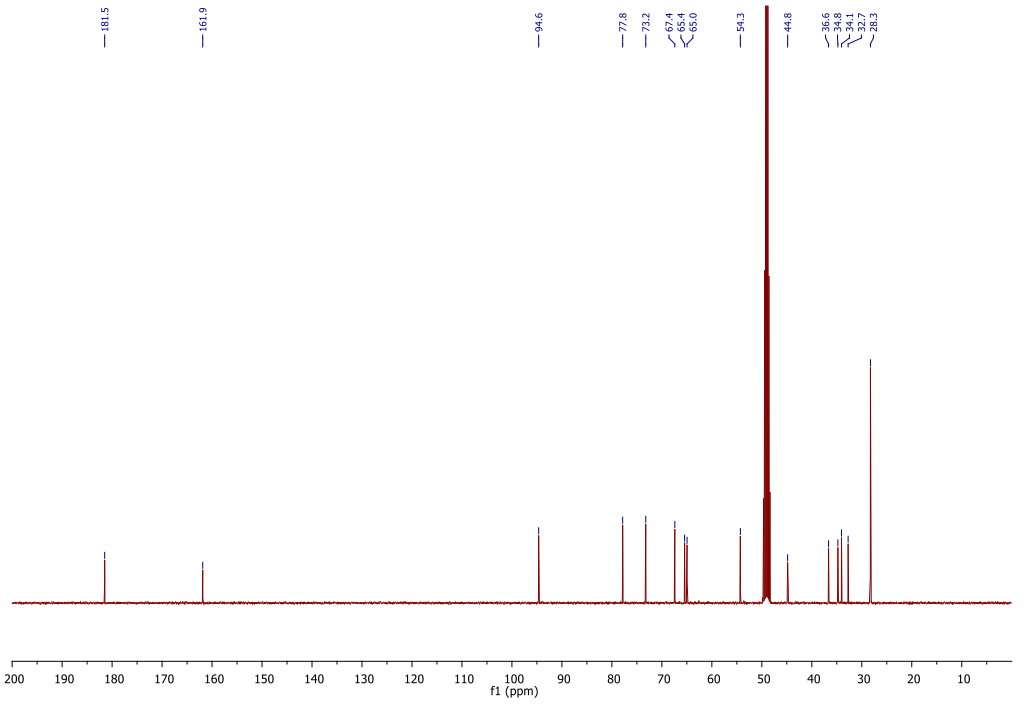



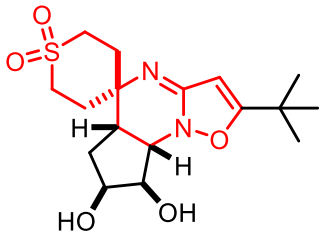
**$^{1}$H and $^{13}$C NMR spectra of 9d in MeOD**

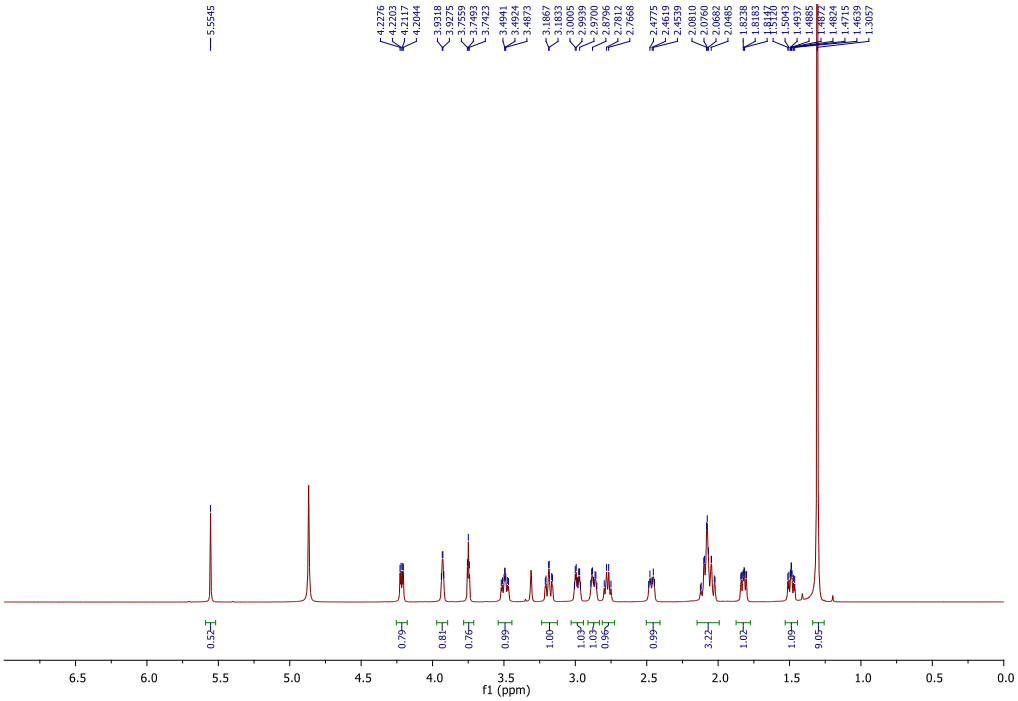


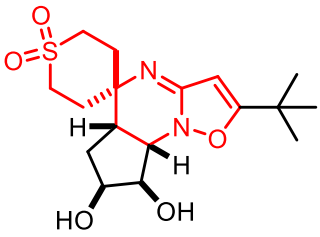



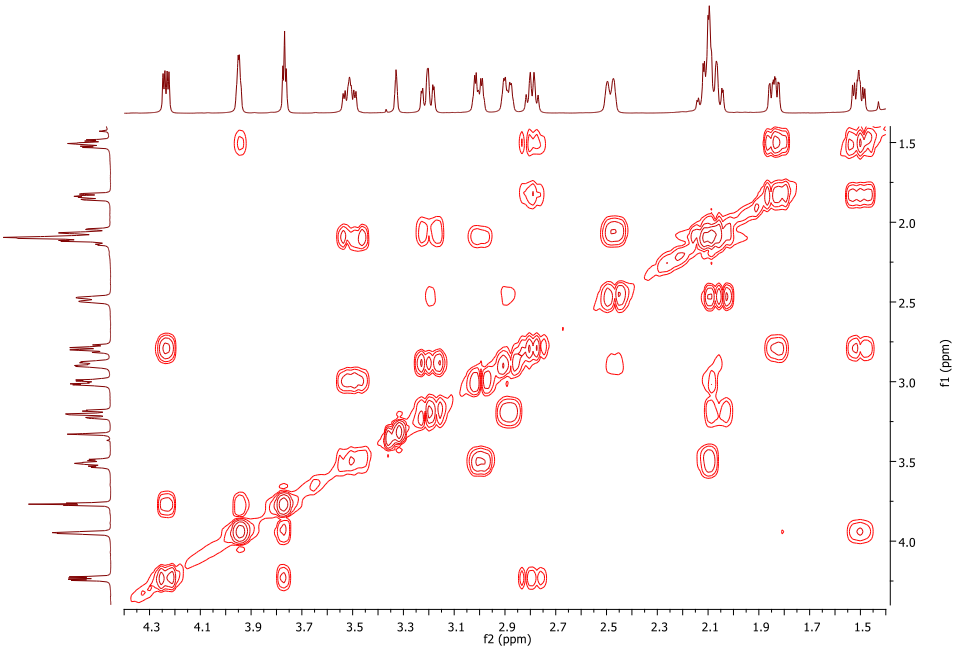
**$^{1}$H, COSY, NOESY, $^{13}$C and DEPT135 spectra of 9e in MeOD**

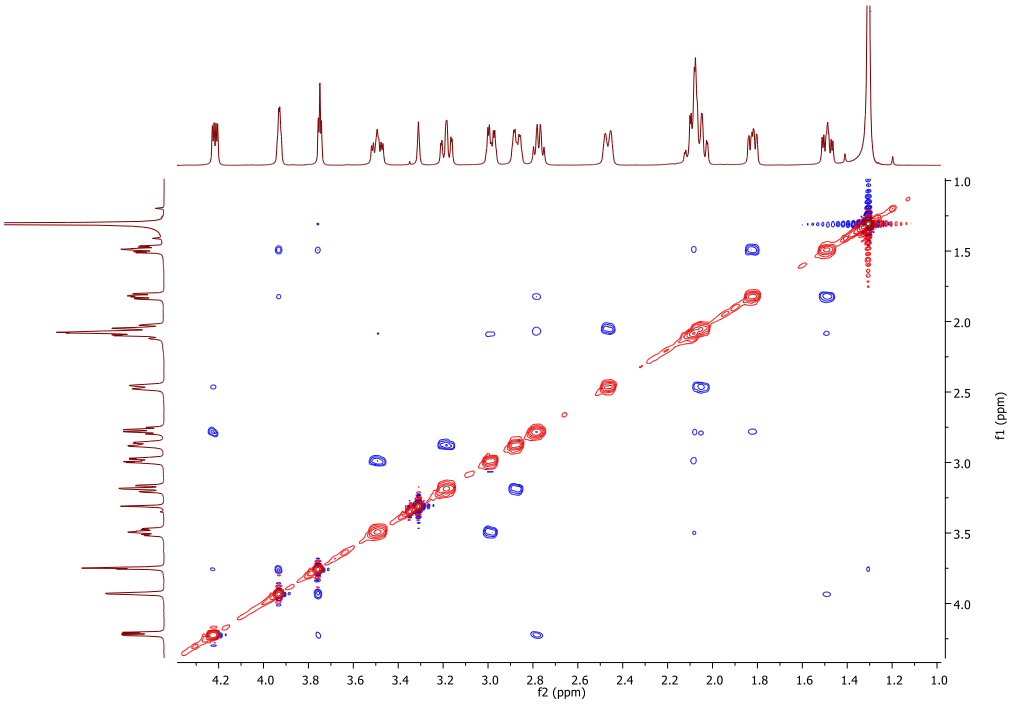


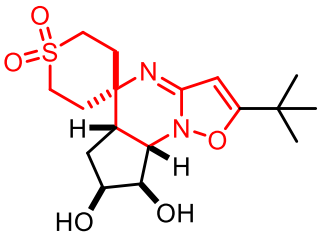



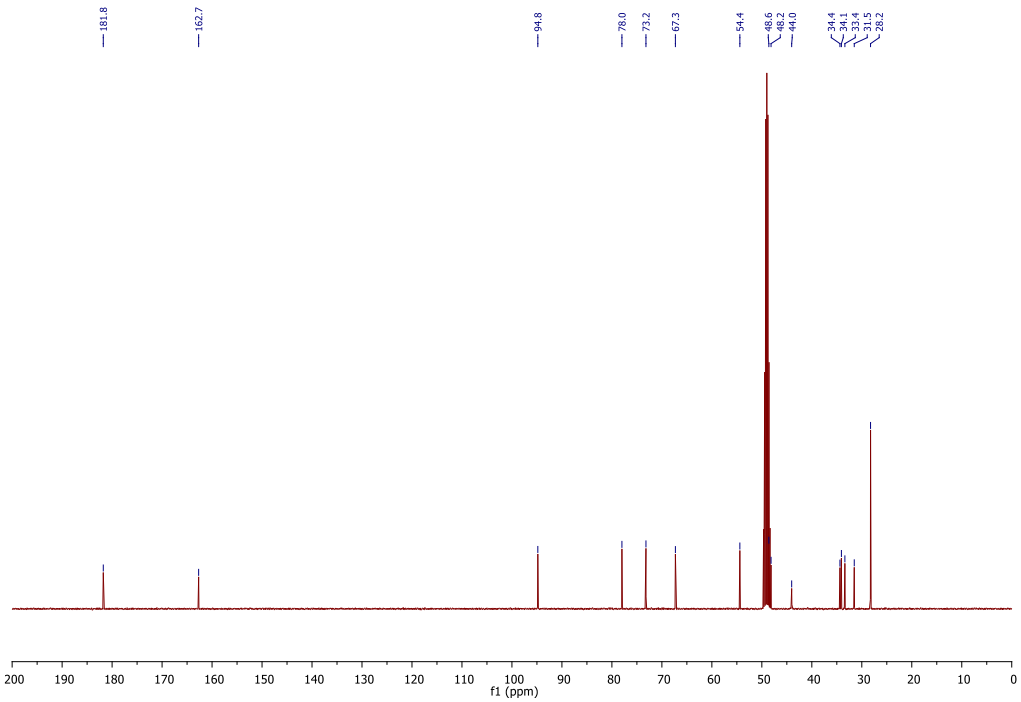

O
O=S
N
H
N
O
H
HO
OH

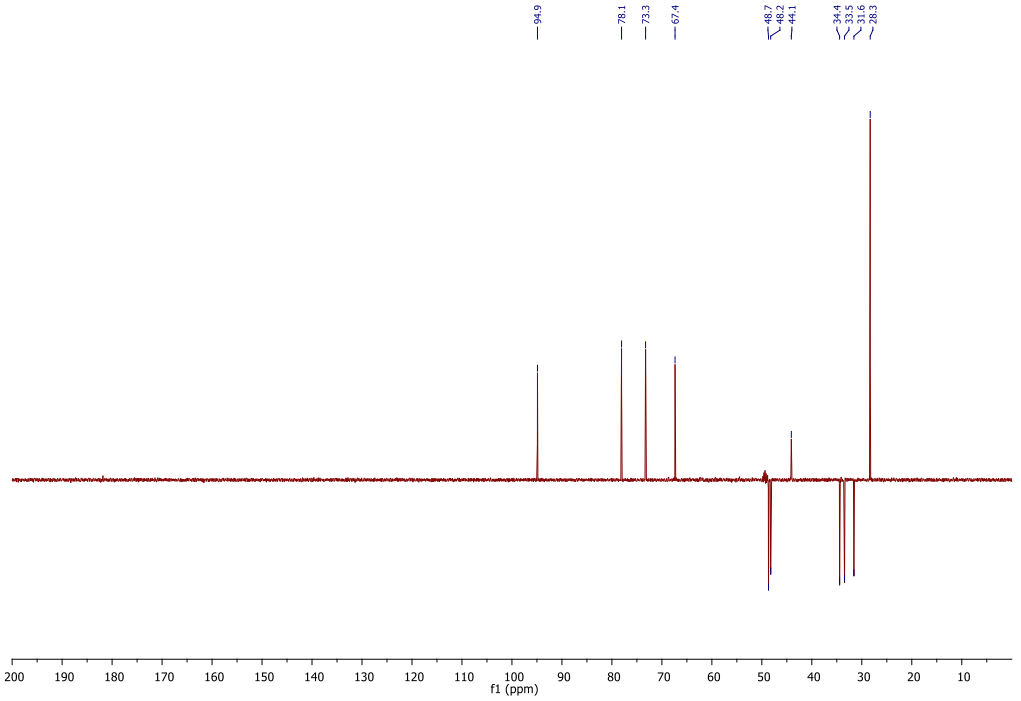
**9e**


1.5
2.0
2.5
3.0
3.5
4.0
f1 (ppm)
4.3
4.1
3.9
3.7
3.5
3.3
3.1
2.9
2.7
2.5
2.3
2.1
1.9
1.7
1.5
f2 (ppm)

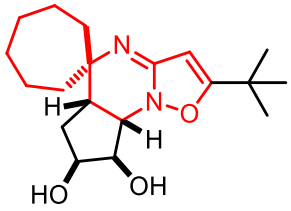

1.0
1.5
2.0
2.5
3.0
3.5
4.0
f1 (ppm)
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
f2 (ppm)

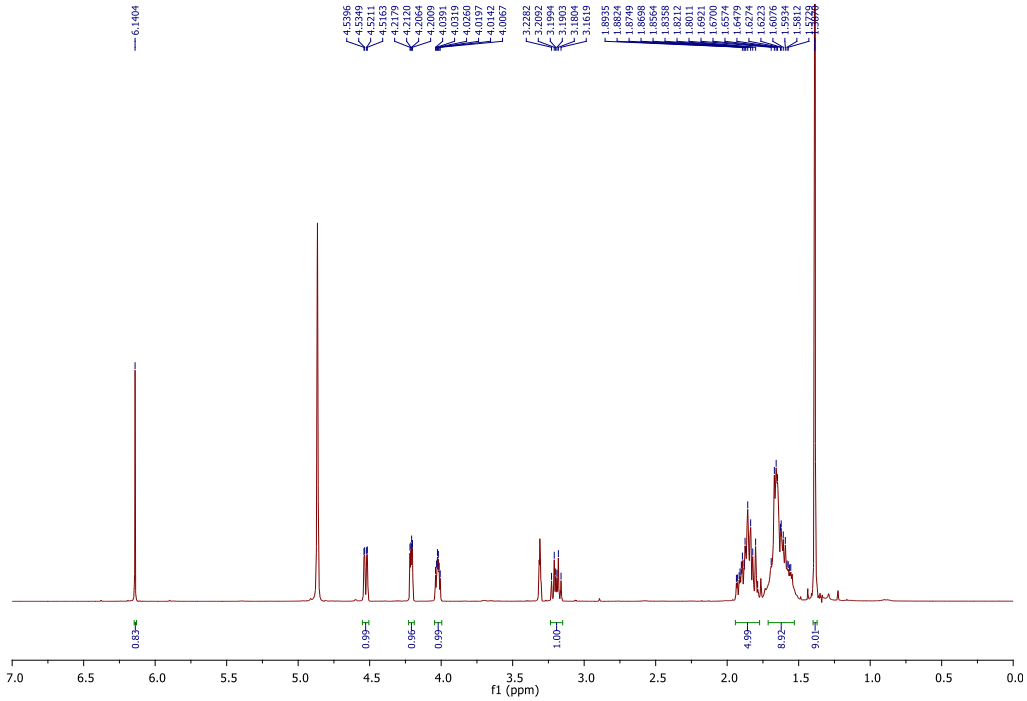

O
O
S
N
H
N
O
H
HO
OH

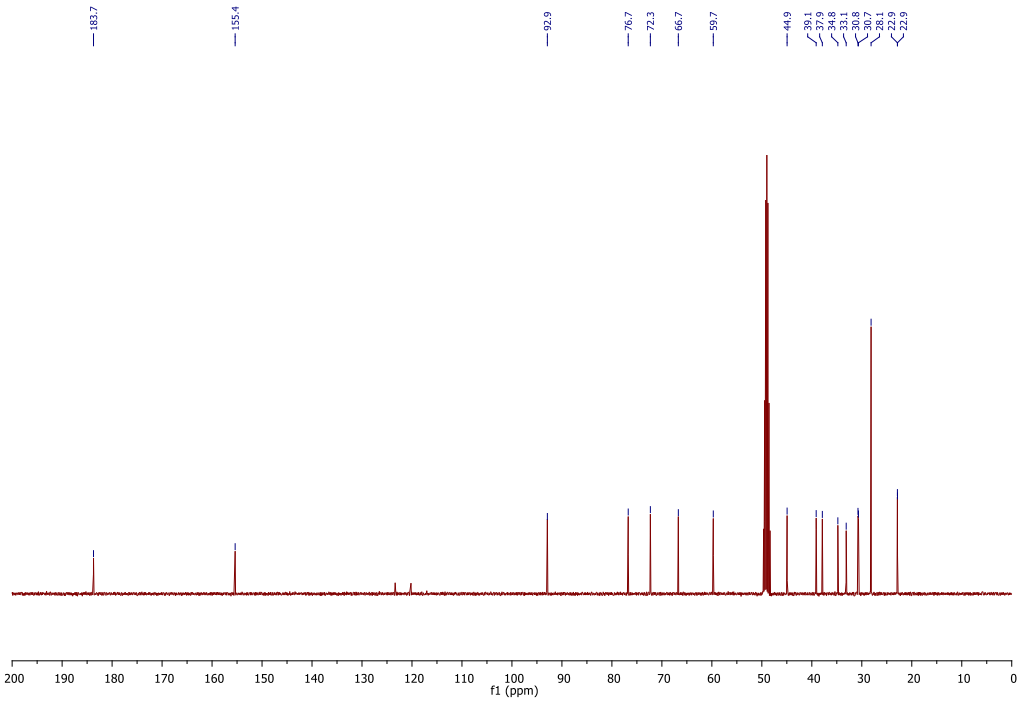

181.8
162.7
94.8
78.0
73.2
67.3
54.4
48.6
48.2
44.0
34.4
34.1
33.4
31.5
28.2
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


94.9
78.1
73.3
67.4
48.7
48.2
44.1
34.4
33.5
31.6
28.3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

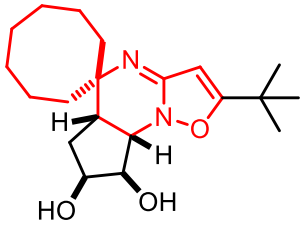
**$^{1}$H and $^{13}$C NMR spectra of 9f in MeOD**

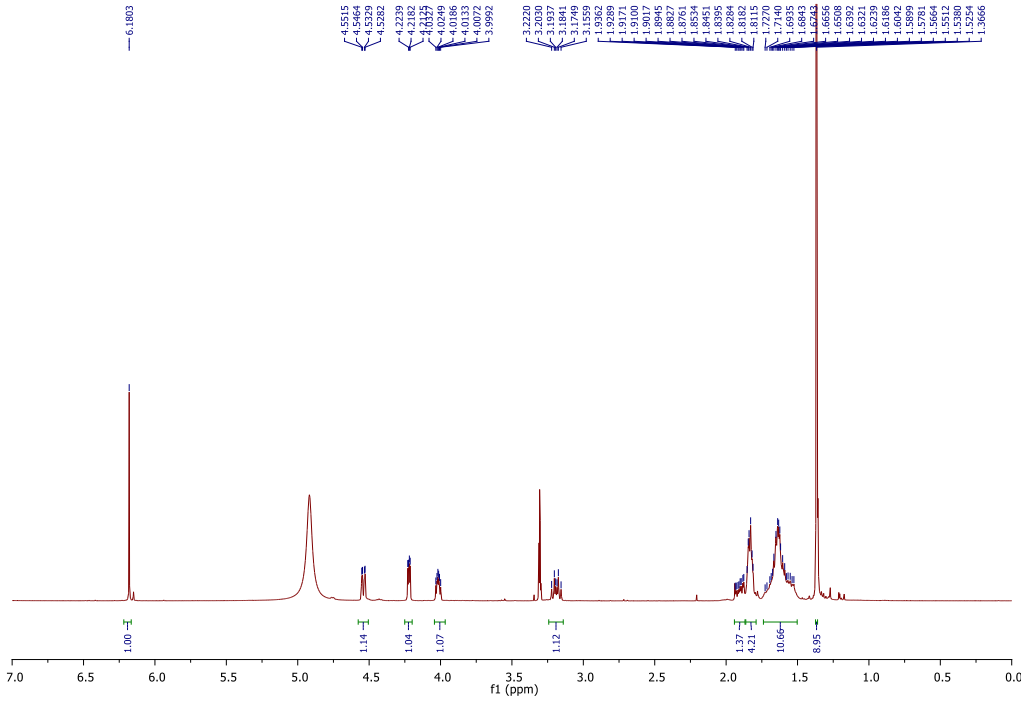


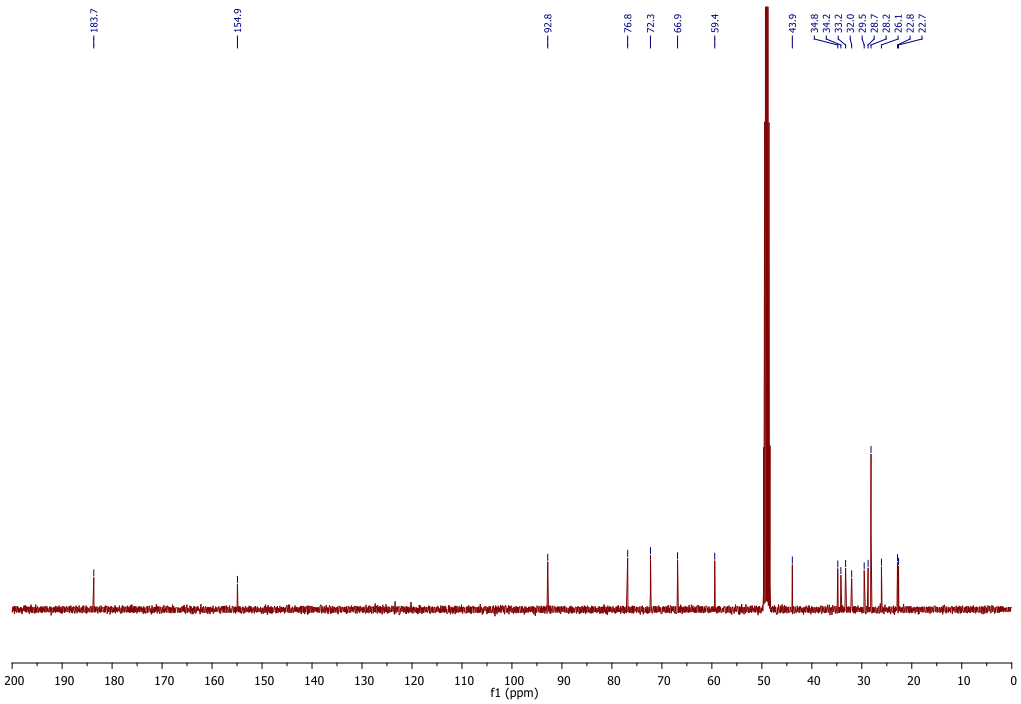



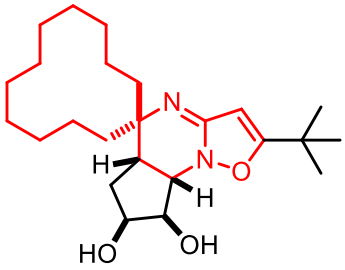
**$^{1}$H and $^{13}$C NMR spectra of 9g in MeOD**

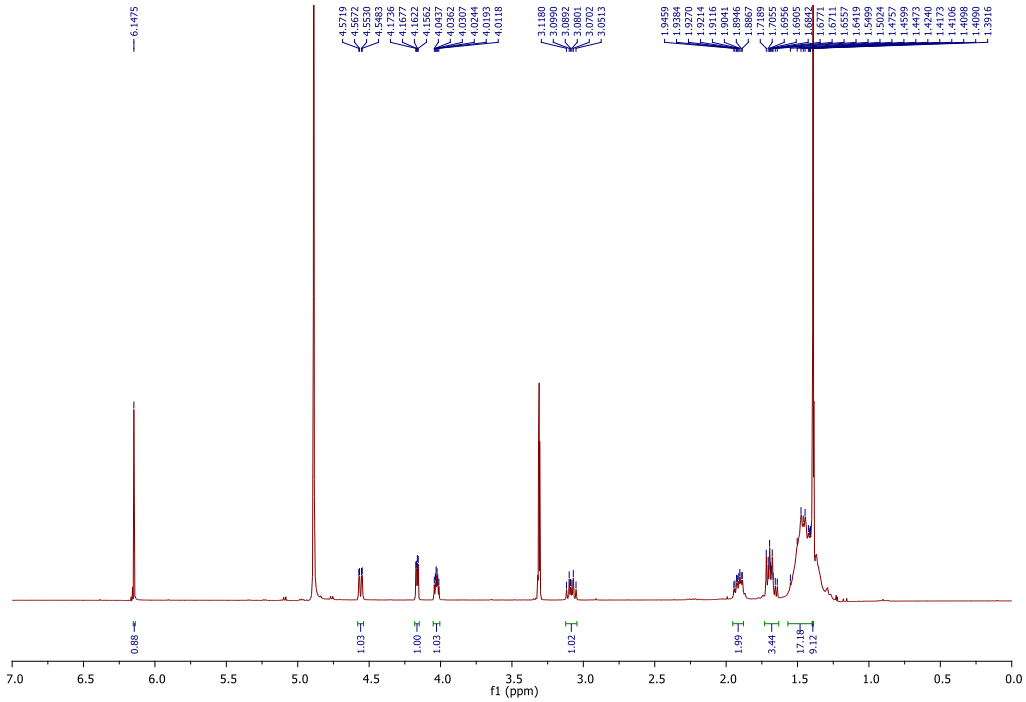


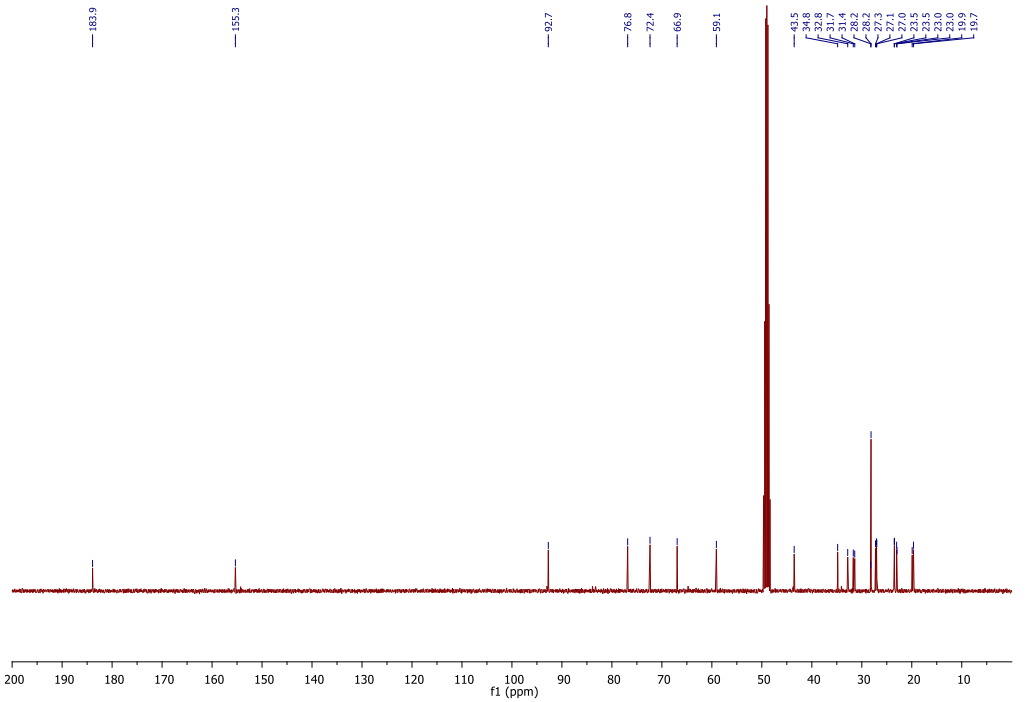



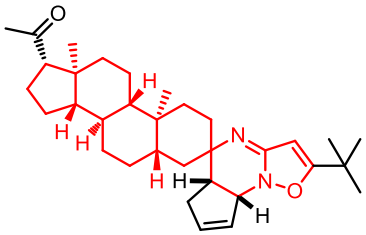
**$^{1}$H and $^{13}$C NMR spectra of 9h in MeOD**

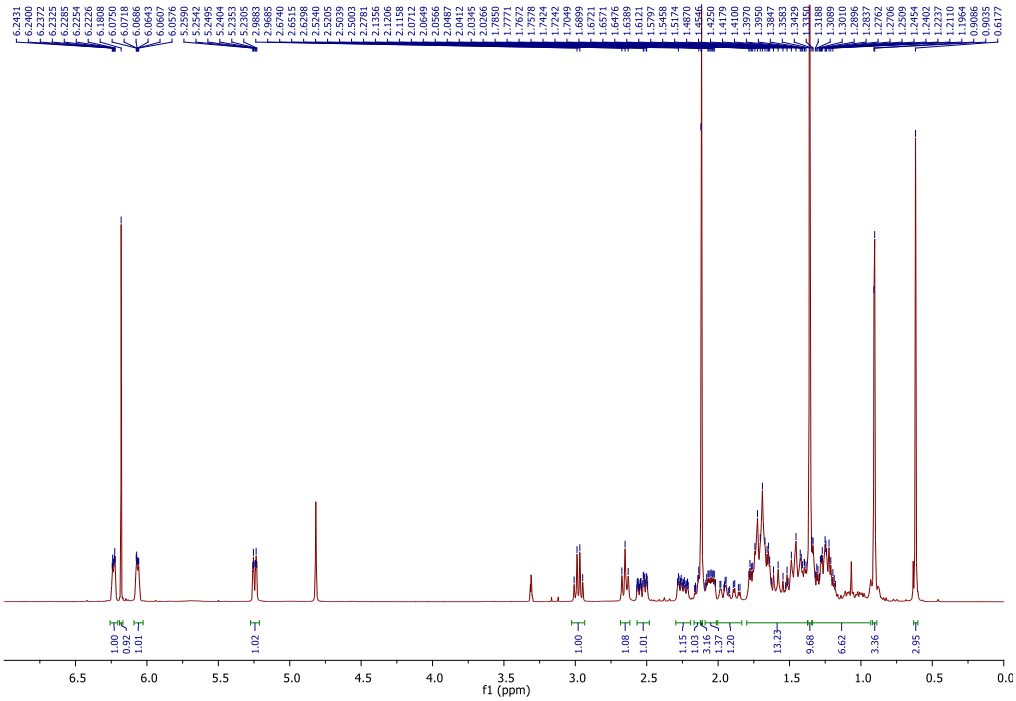


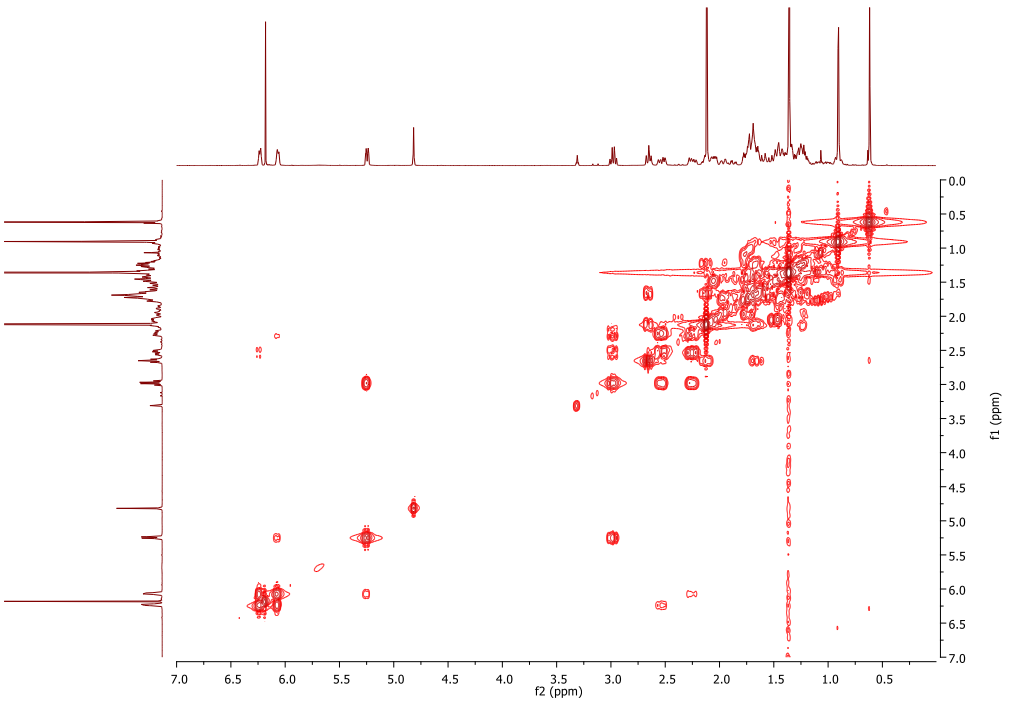



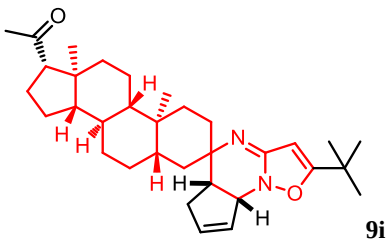



**$^{1}$H, COSY, $^{13}$C and DEPT135 spectra of 9i in MeOD**

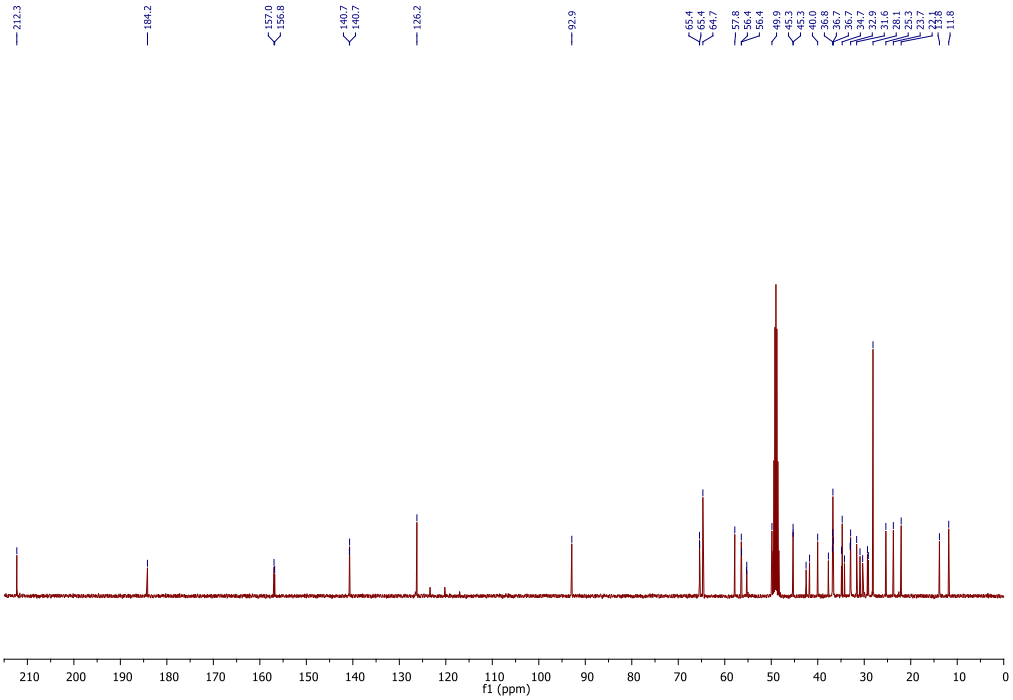


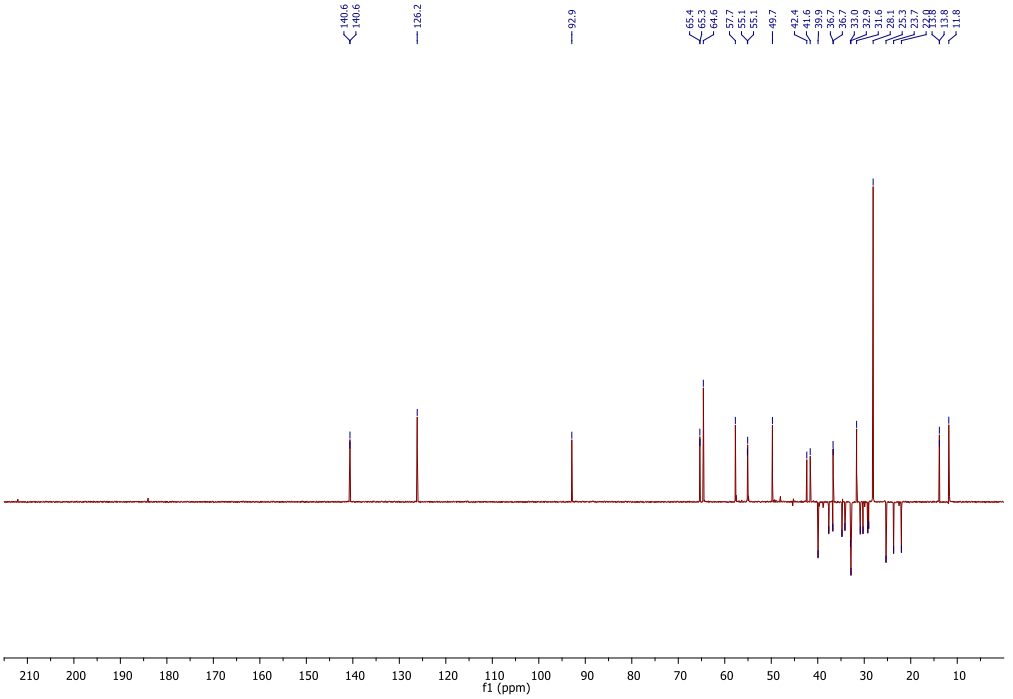



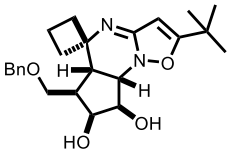


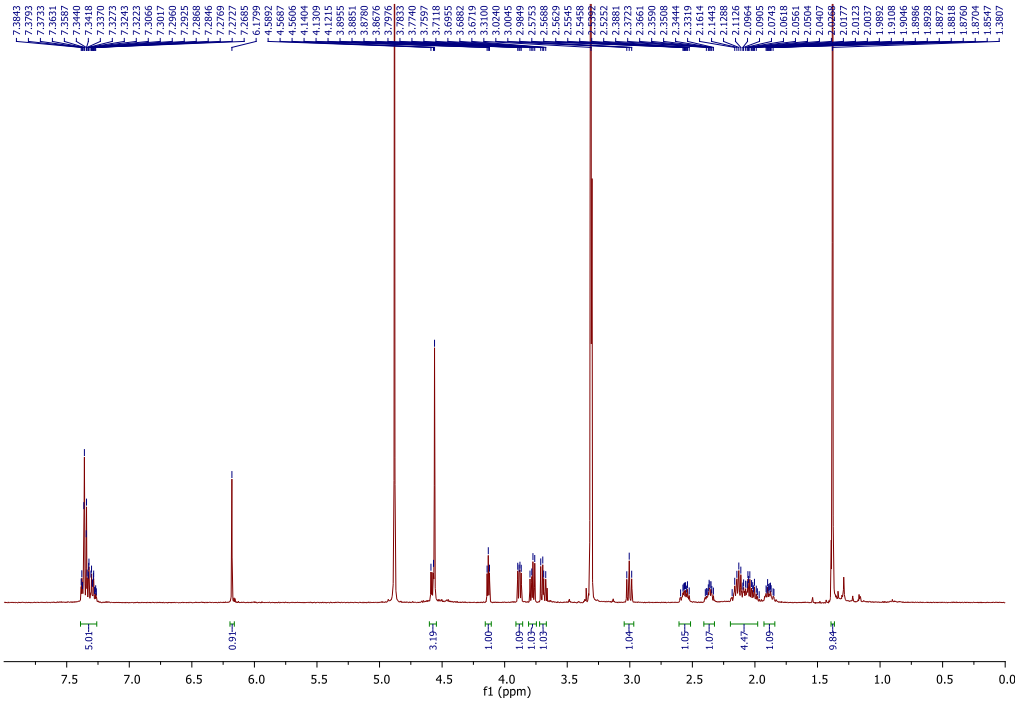
**9i**

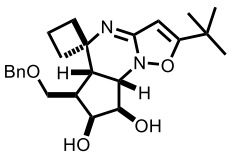

212.3
184.2
157.0
156.8
140.7
140.7
126.2
92.9
65.4
65.4
64.7
57.8
56.4
56.4
49.9
45.3
45.3
40.0
36.8
36.7
36.7
34.7
32.9
31.6
28.1
25.3
23.7
22.0
13.8
11.8
f1 (ppm)


140.6
140.6
126.2
92.9
65.4
65.3
64.6
57.7
55.1
55.1
49.7
42.4
41.6
39.9
36.7
36.7
33.0
32.9
31.6
28.1
25.3
23.7
22.0
13.8
11.8
f1 (ppm)

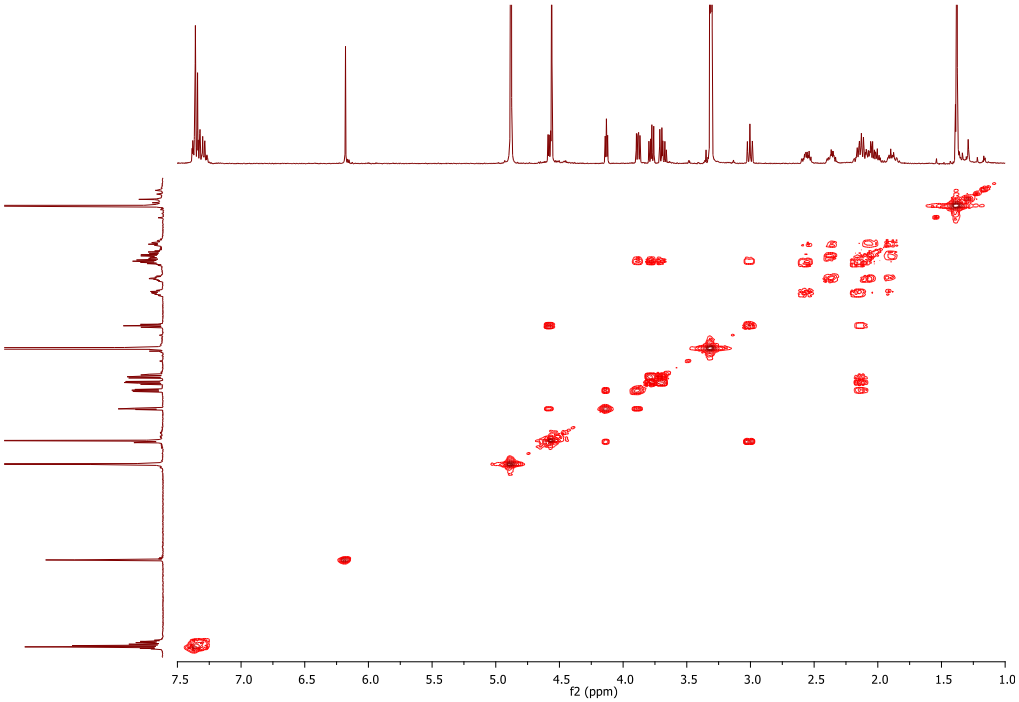
**$^{1}$H, COSY, NOESY, $^{13}$C and DEPT135 spectra of 11a in MeOD**

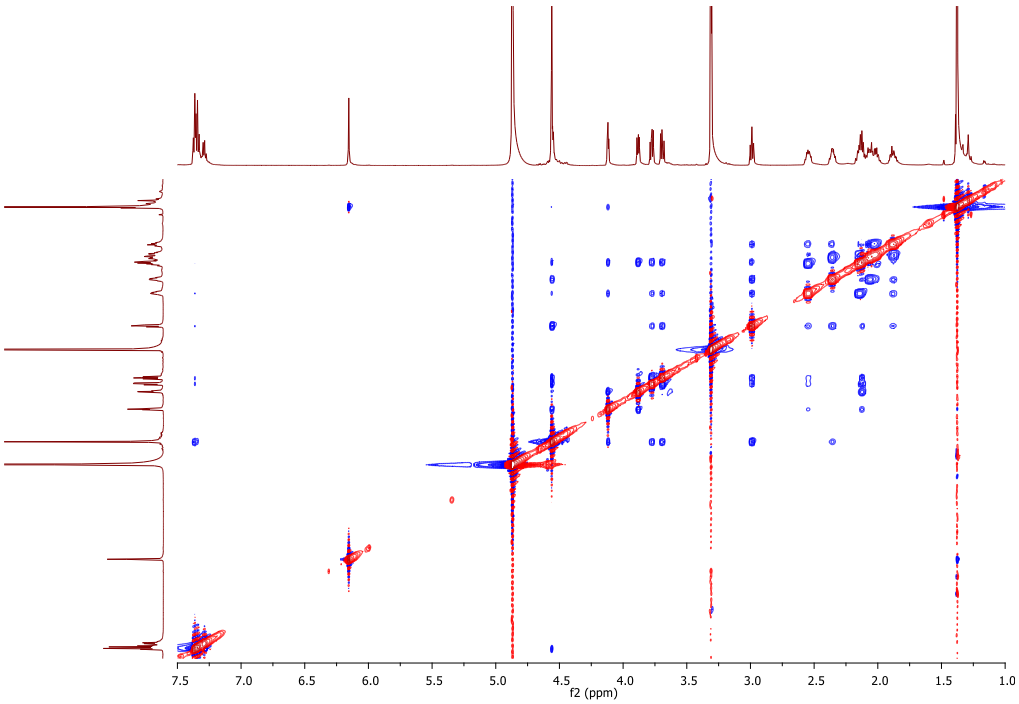


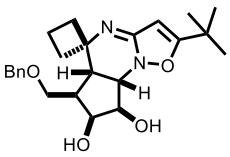




BnO
H
N
N
O
H
OH
HO

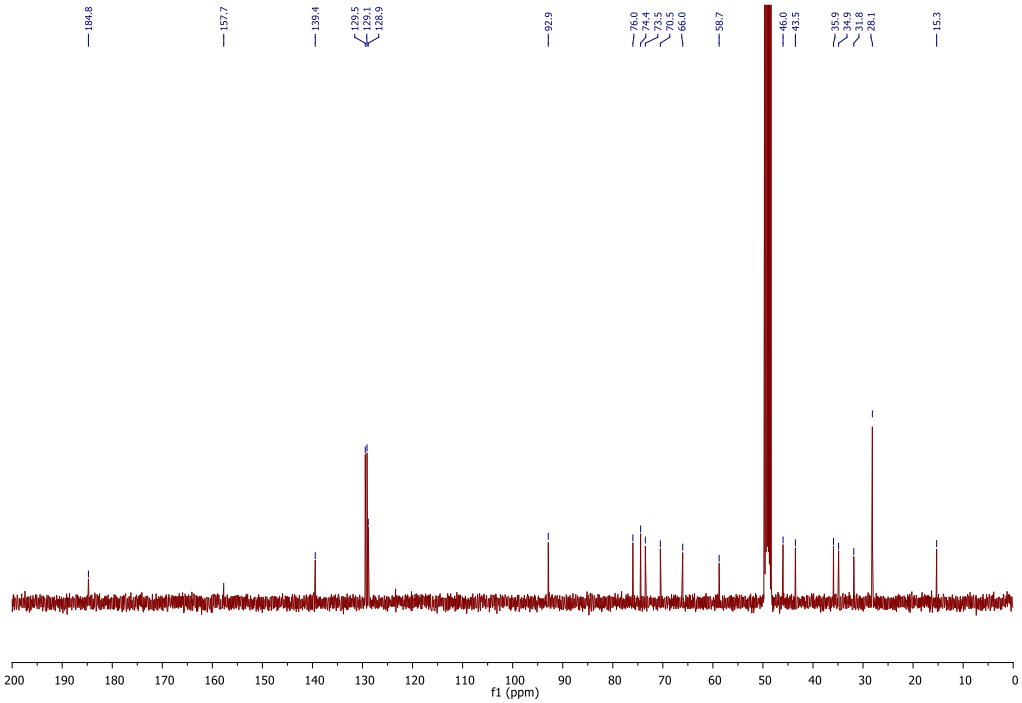
**11a**

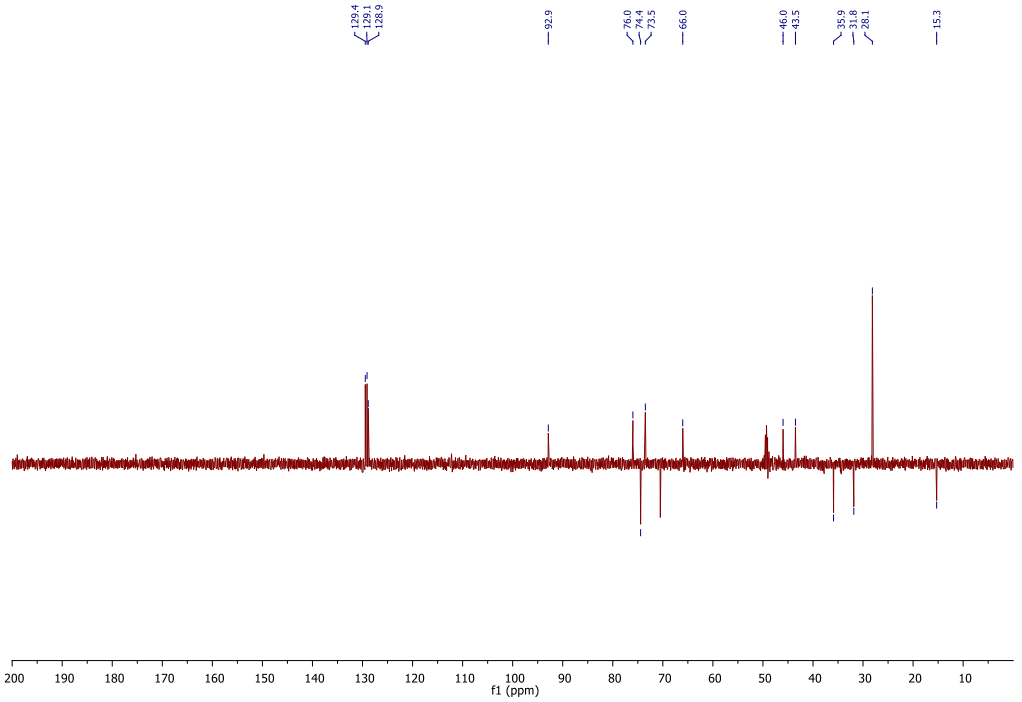

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f2 (ppm)


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
f2 (ppm)

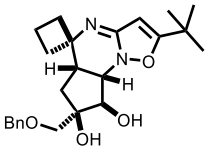

BnO
H
N
N
O
H
OH
HO

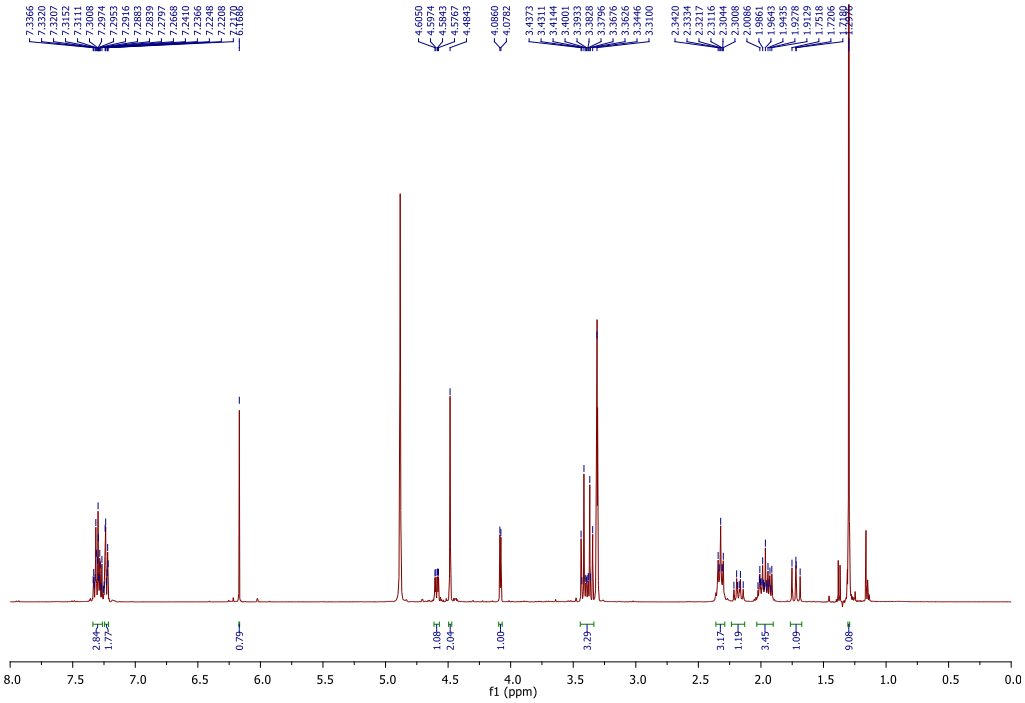
**11a**

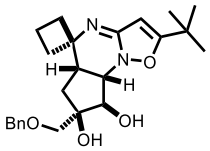

184.8
157.7
139.4
129.5
129.1
128.9
92.9
76.0
74.4
73.5
70.5
66.0
58.7
46.0
43.5
35.9
34.9
31.8
28.1
15.3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


129.4
129.1
128.9
92.9
76.0
74.4
73.5
66.0
46.0
43.5
35.9
31.8
28.1
15.3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

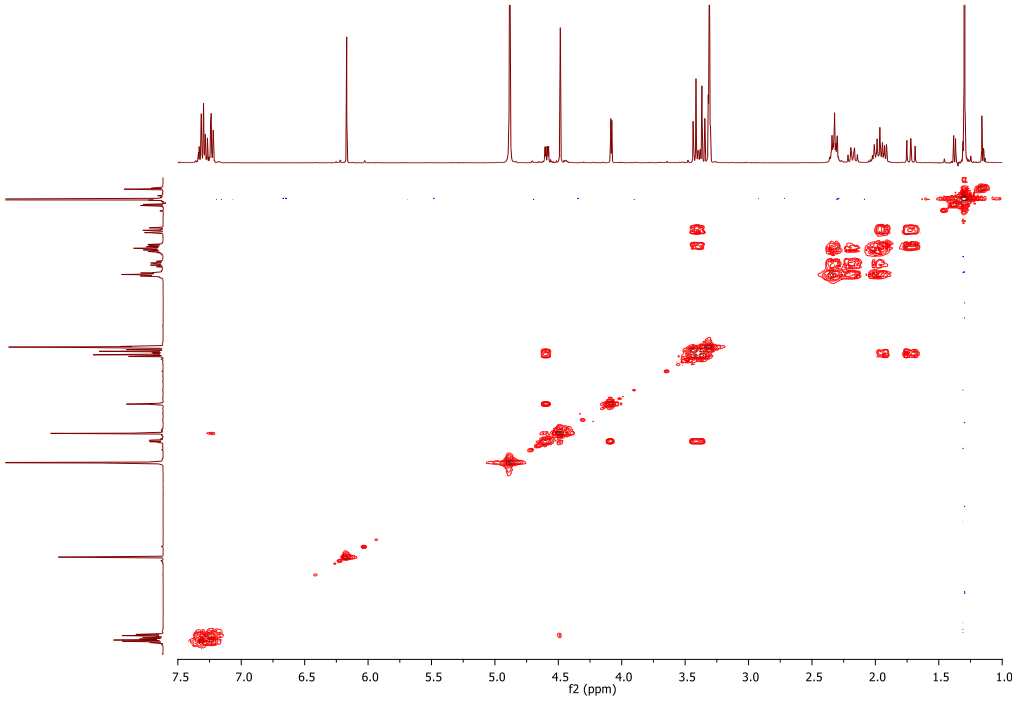
**$^{1}$H, COSY, NOESY, $^{13}$C and DEPT135 spectra of 11b in MeOD**

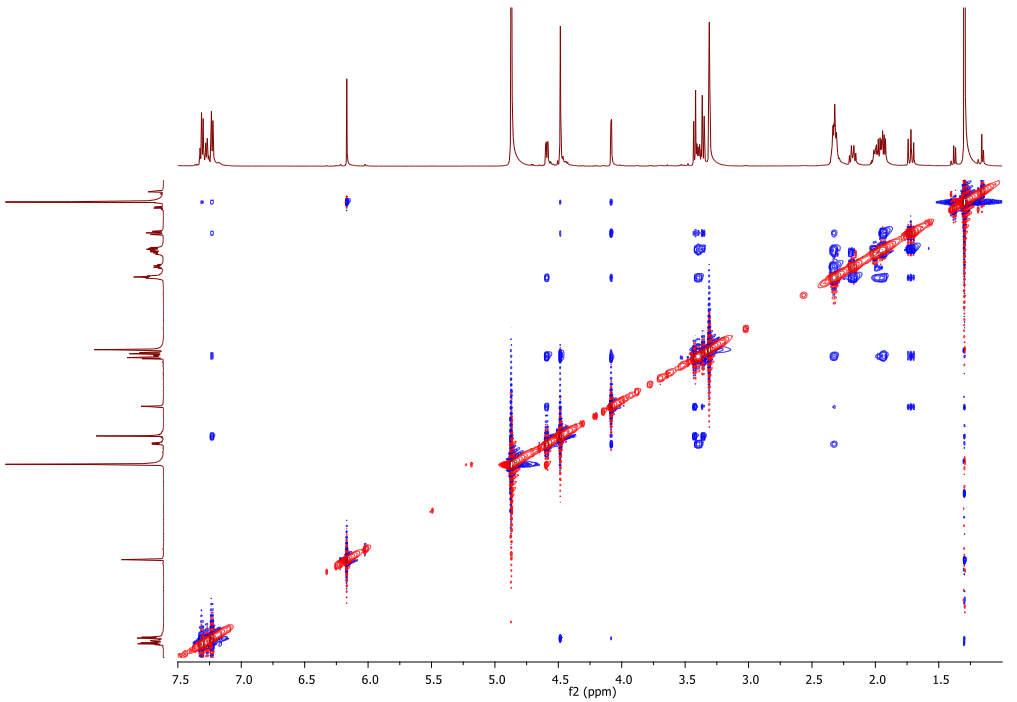


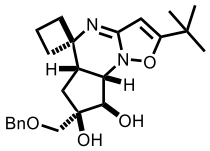




N
N
O
H
H
BnO
OH
OH

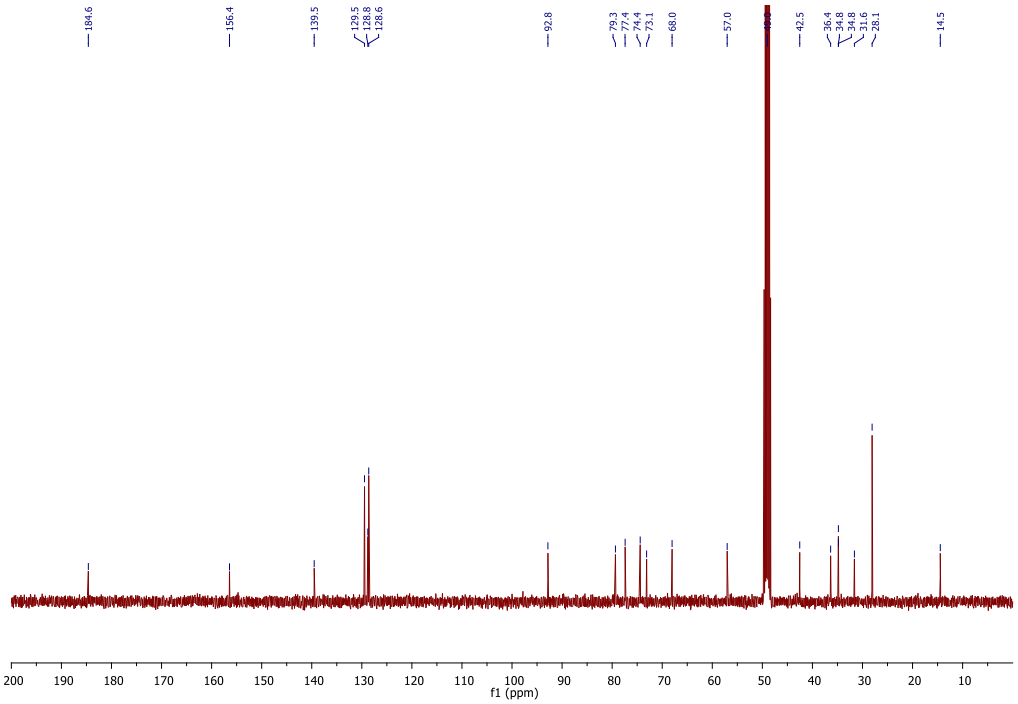
**11b**

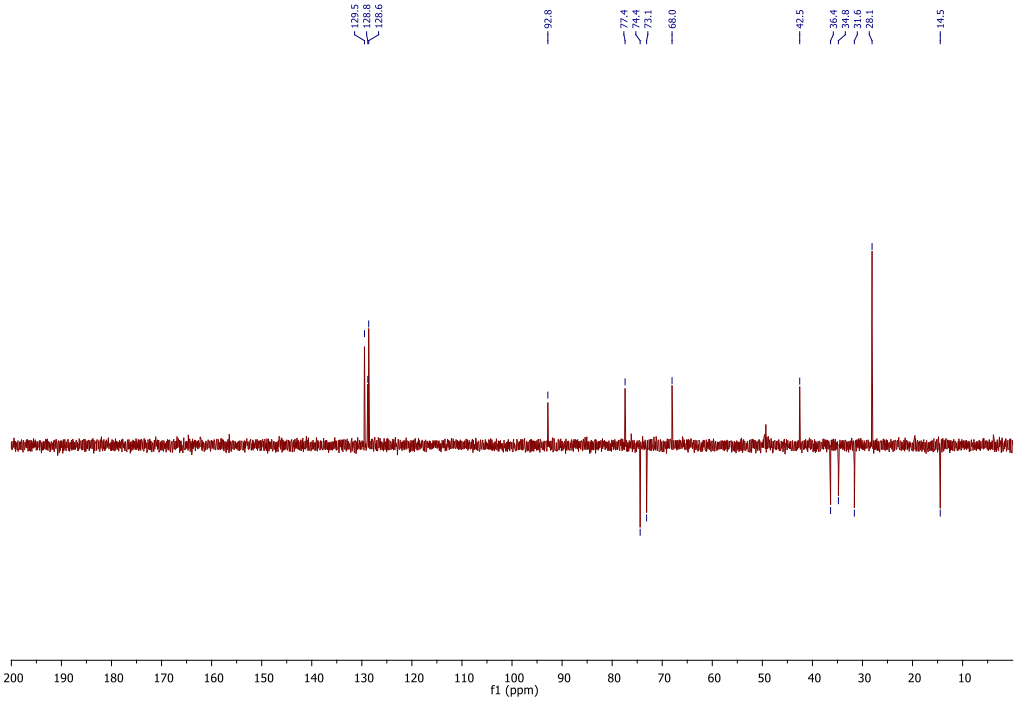

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f2 (ppm)


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
f2 (ppm)

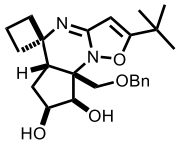

N
H
N
O
H
BnO
OH
OH

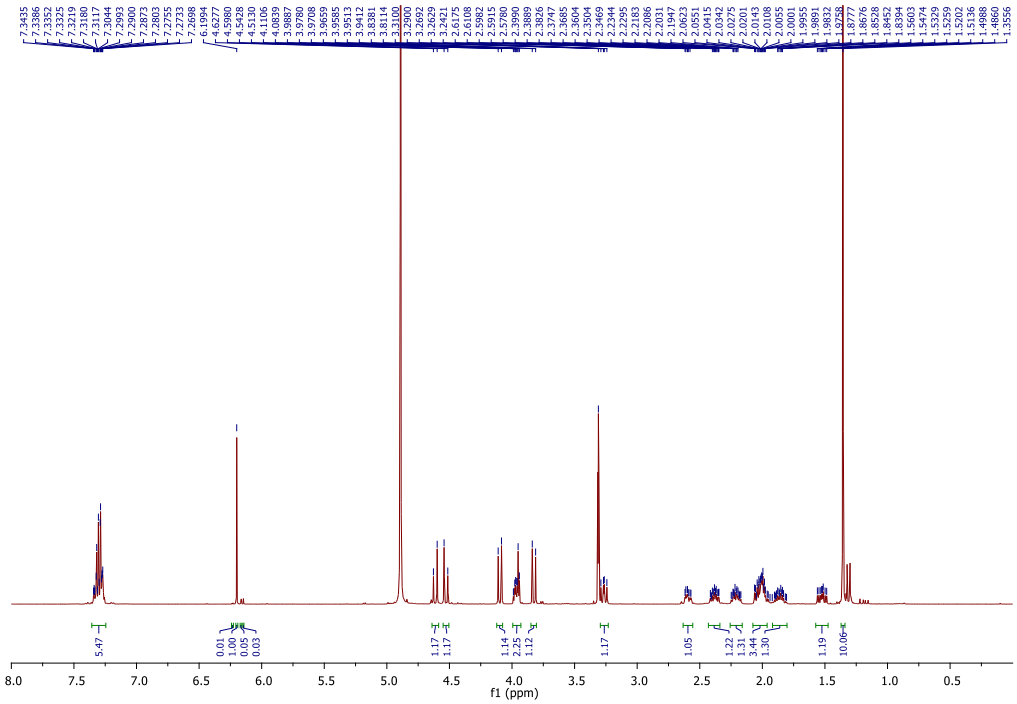
**11b**

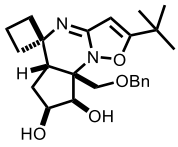

184.6
156.4
139.5
129.5
128.8
128.6
92.8
79.3
77.4
74.4
73.1
68.0
57.0
42.5
36.4
34.8
31.6
28.1
14.5
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


129.5
128.8
128.6
92.8
77.4
74.4
73.1
68.0
42.5
36.4
34.8
31.6
28.1
14.5
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

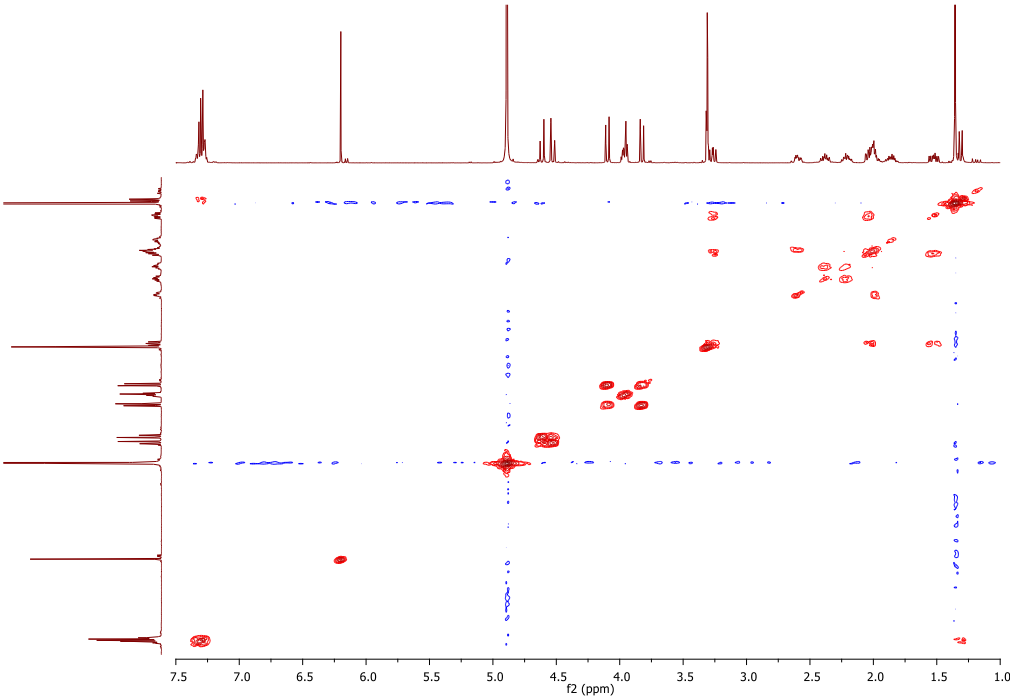
**$^{1}$H, COSY, NOESY, $^{13}$C and DEPT135 spectra of 11c in MeOD**

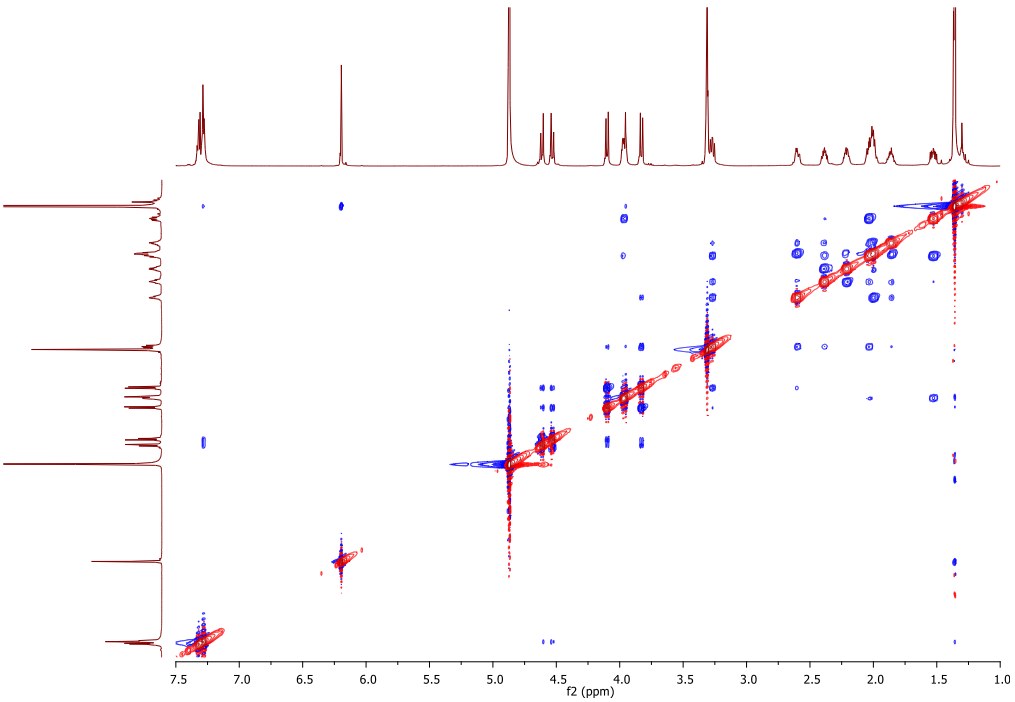


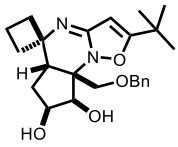




N
N
O
H
OBn
OH
HO

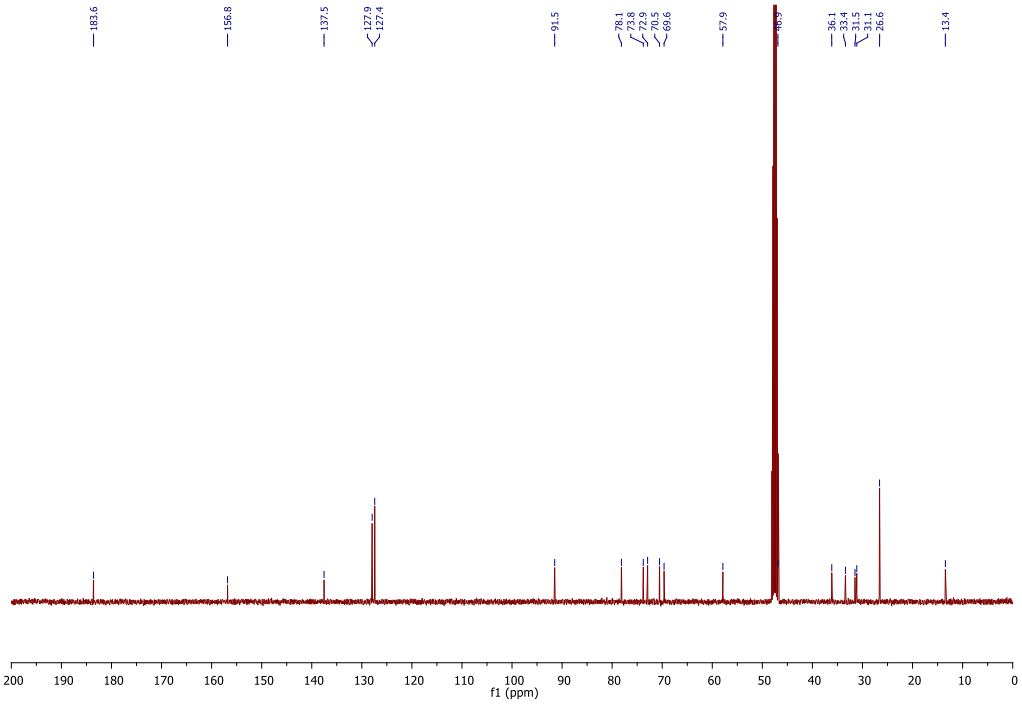
**11c**

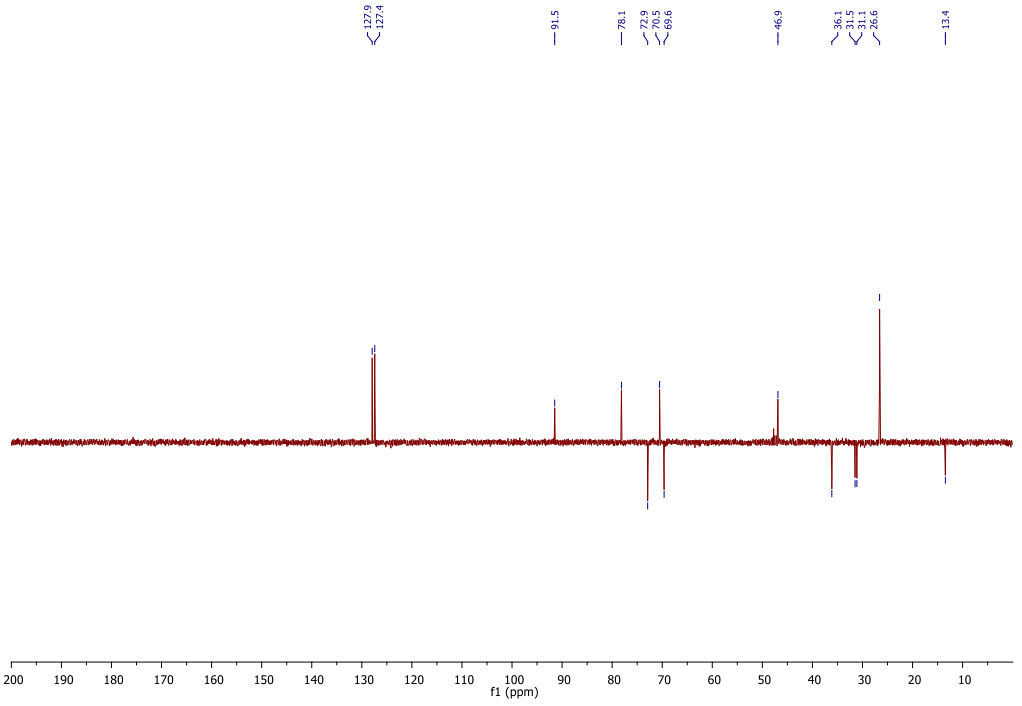

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f2 (ppm)


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
f2 (ppm)


N
N
O
H
OBn
OH
HO

**11c**


183.6
156.8
137.5
127.9
127.4
91.5
78.1
73.8
72.9
70.5
69.6
57.9
46.9
36.1
33.4
31.5
31.1
26.6
13.4
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


127.9
127.4
91.5
78.1
72.9
70.5
69.6
46.9
36.1
31.5
31.1
26.6
13.4
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

## Supplementary References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