Preparation of Structurally Diverse Compounds from the Natural Product Lycorine

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Figure S1. Complete Compound Set…..……..……S2

Figure S2. Comprehensive Synthetic Scheme.…….……..S3

Computational Analysis……..…….S4

Materials and Methods…….……S9

Experimental Procedures……...S10

References……..……..……..S50

NMR Spectra……S51

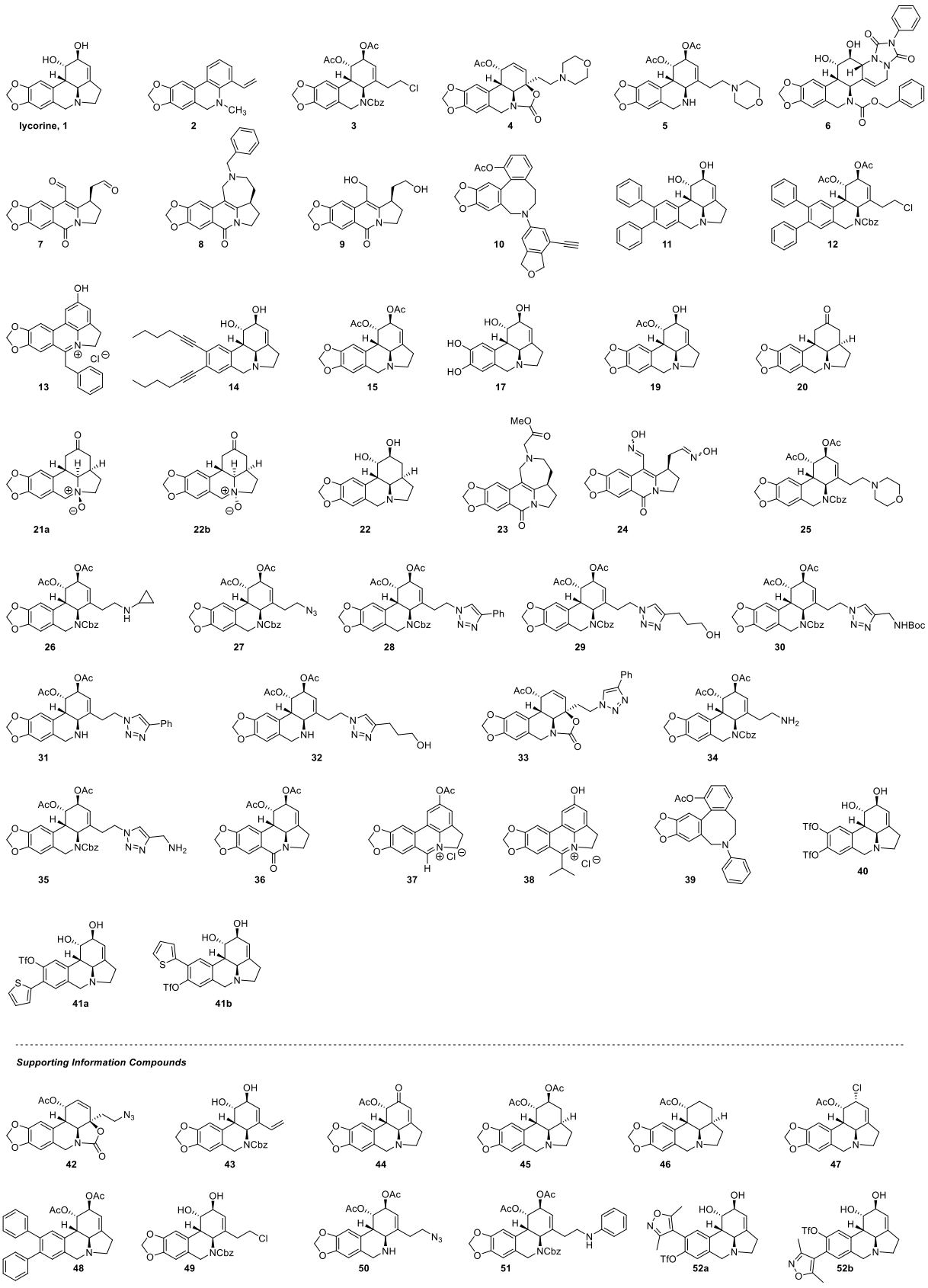


Figure S1. Complete lycorine compound set.

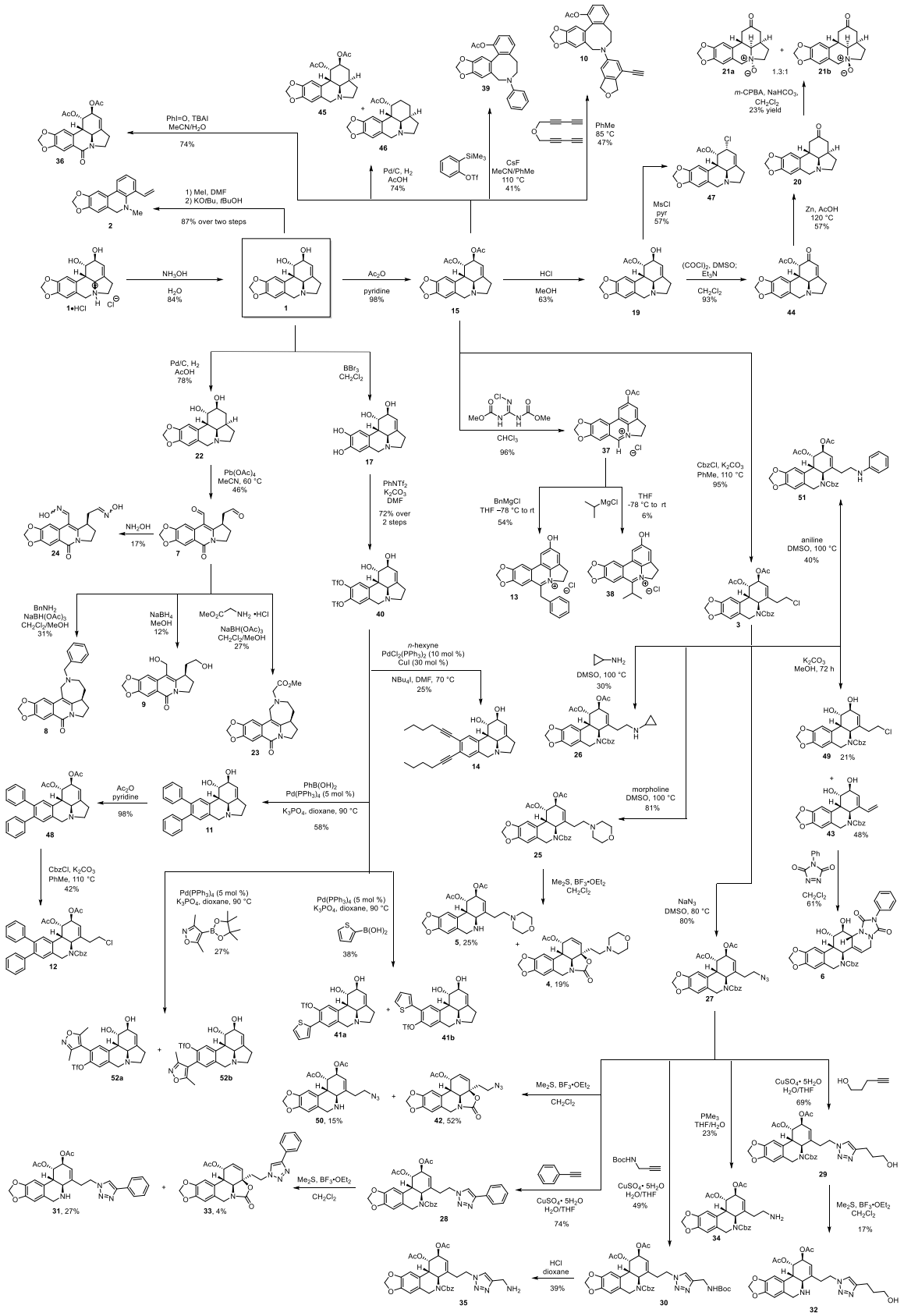


Figure S2. Comprehensive synthetic scheme.

Computational Analysis

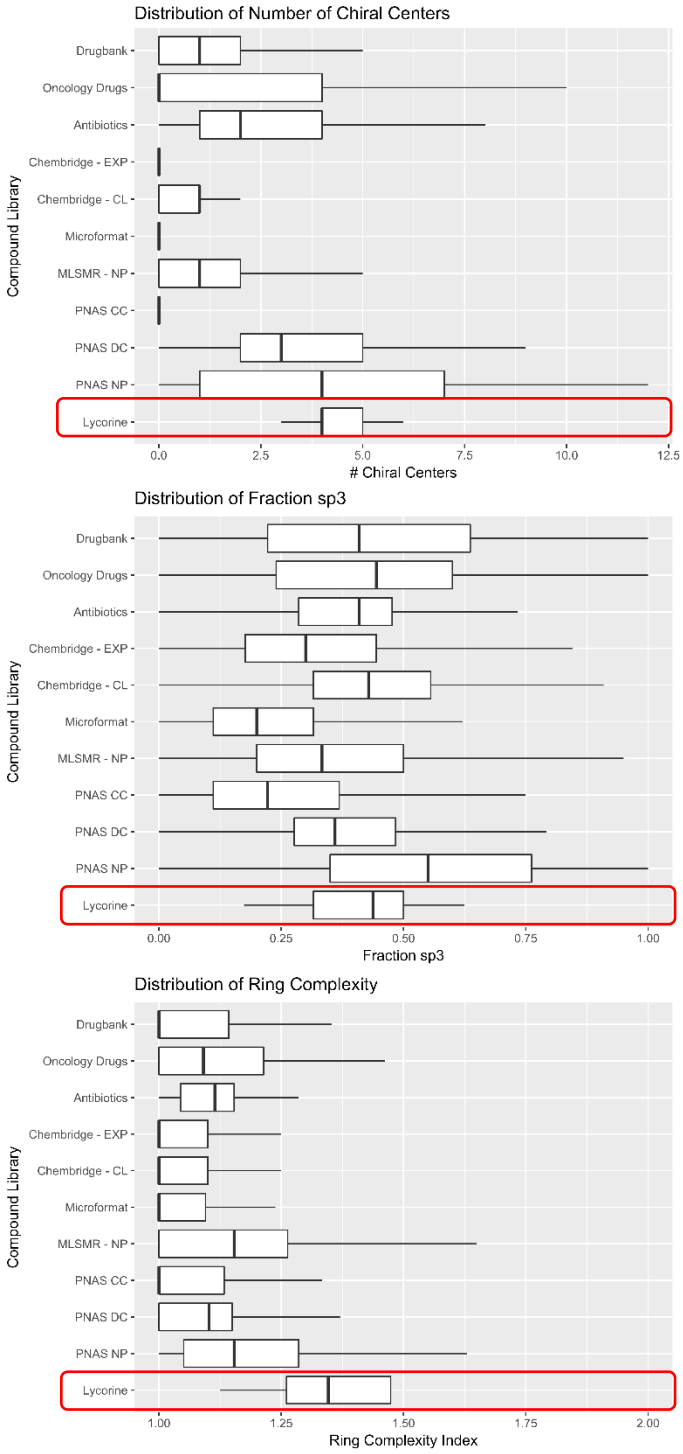


Figure S3. Histograms of selected physicochemical properties of approved drugs (including oncology and antibacterial subsets), commercial screening libraries (including those composed of natural products), and the set of lycorine compounds synthesized herein.

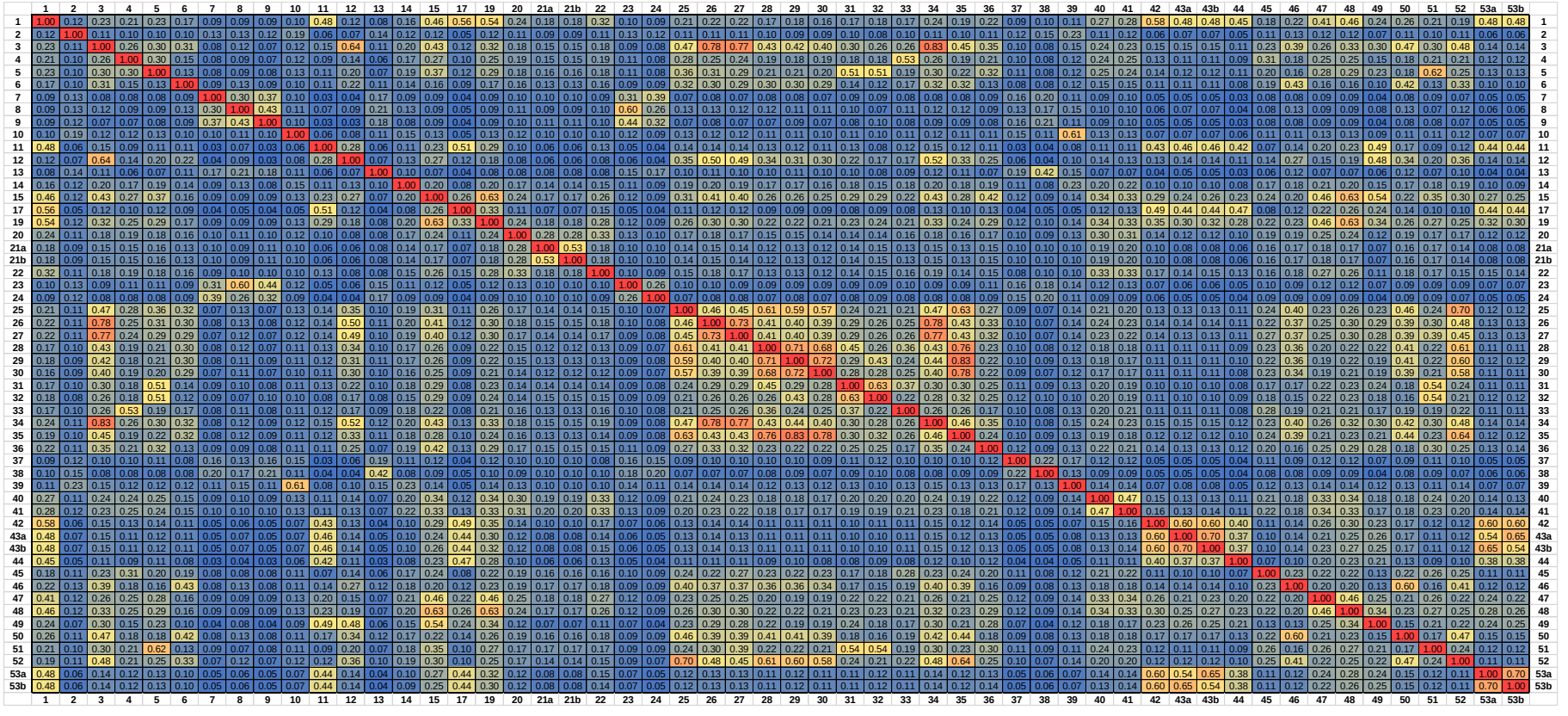


Figure S4. Tanimoto similarity matrix for the 52-compound set (and lycorine). The Tanimoto coefficient was calculated using Canvas (Schrödinger) version 3.5.011 using ECFP radial molecular fingerprints. The table was shaded using the color scale depicted to the right.

Computational Methods:
Details of the computational methods for each parameter is found at https://github.com/HergenrotherLab/ctd-pleuro

Data Set Sources for Figure S3

- Drugbank: Drugbank website (https://www.drugbank.ca/).
- Oncology Drugs: NCI Approved Oncology Drugs Set VIII (https://wiki.nci.nih.gov/display/NCIDTPdata/Compound+Sets).
- Antibiotics: O'Shea and Moser *J. Med. Chem.* **2008**, *51*, 2871–2878.[1]
- Chembridge-EXP: ChemBridge website (http://www.chembridge.com/).
- Chembridge-CL: ChemBridge website (http://www.chembridge.com/).
- Microformat: ChemBridge website (http://www.chembridge.com/).
- MLSMR-NP: PubChem website (https://pubchem.ncbi.nlm.nih.gov/).
- PNAS CC: Clemons *et al*. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 18787–18792.[2]
- PNAS DC: Clemons *et al*. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 18787–18792.[2]
- PNAS NP: Clemons *et al*. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 18787–18792.[2]
- Lycorine: Lycorine and the 52 derivatives described herein

The number of stereogenic centers were calculated in Canvas 2.2 (Schrodinger, New York) using the Ligfilter Descriptor "Num_chiral_centers" in the Molecular Properties application. Globularity was calculated using Entryway (www.entry-way.org). The following Python program (ctd_score.py) calculates several relevant molecular descriptors given a properly formatted sdf file. The ctd_score.py requires RDKit, an open-source collection of cheminformatics software.

The program is run from the command line with the following syntax:

```
> python ctd_score.py FILENAME.sdf
```

where FILENAME.sdf is a collection of molecules to be calculated. A new file is written with "descr.sdf" appended to the end of the filename.

```
#
# calculation of molecular descriptors and complexity index
#
# Implements RDKit
#
# Bryon Drown, May 2015
# Updated Oct. 9, 2015
# University of Illinois, Urbana-Champaign
#
#

import sys
from rdkit import Chem
from rdkit.Chem import Descriptors
from rdkit.ML.Descriptors import MoleculeDescriptors
from collections import defaultdict
from collections import OrderedDict

def calcRingDescriptors(m):
  nBonds = m.GetNumBonds()
  nAtoms = m.GetNumAtoms()
```

```
  cyclomatic = nBonds - nAtoms + 1
  if(cyclomatic < 1): return

  ri = m.GetRingInfo()
  if(ri.NumRings() < 1): return
  # get total ring path and nBondRings
  totalRing = 0
  Bonds = []
  Bridges = []
  for ring in ri.BondRings():
    for id in ring:
      if (ri.NumBondRings(id) > 1):
        Bridges.append(id)
      totalRing+=1
      Bonds.append(id)

  # remove duplicates, then get length
  nBondRings = len(OrderedDict.fromkeys(Bonds).keys())
  nBridgeEdges = len(OrderedDict.fromkeys(Bridges).keys())

  # get nAtomRings
  Atoms=[]
  for ring in ri.AtomRings():
    for id in ring:
      Atoms.append(id)
  nAtomRings=len(OrderedDict.fromkeys(Atoms).keys())

  # descriptors
  ringFusionDensity = 2 * float(nBridgeEdges) / float(nAtomRings)
  ringComplexityIndex = float(totalRing) / float(nAtomRings)
  molecularCyclizedDegree = float(nAtomRings) / float(nAtoms)
  nRingSystems = (nBonds - nBondRings) - (nAtoms - nAtomRings) + 1
  if(nRingSystems < 1):
    ringFusionDegree = 0
  else:
    ringFusionDegree = float(cyclomatic) / float(nRingSystems)

  # set props
  m.SetProp('TotalRing',str(totalRing))
  m.SetProp('NumBridges',str(nBridgeEdges))
  m.SetProp('nBondRings',str(nBondRings))
  m.SetProp('nAtomRings',str(nAtomRings))
  m.SetProp('ringFusionDensity',str(ringFusionDensity))
  m.SetProp('ringFusionDegree',str(ringFusionDegree))
  m.SetProp('ringComplexityIndex',str(ringComplexityIndex))
  m.SetProp('molecularCyclizedDegree',str(molecularCyclizedDegree))
  m.SetProp('NumRingSystems',str(nRingSystems))

  return

if __name__=='__main__':
    file_in  = sys.argv[1]
    file_out = file_in+".descr.sdf"
    ms = [x for x in Chem.SDMolSupplier(file_in) if x is not None]
```

```
ms_wr = Chem.SDWriter(file_out)

nms= ('BalabanJ','BertzCT','FractionCSP3','MolWt','RingCount')
calc = MoleculeDescriptors.MolecularDescriptorCalculator(nms)

for i in range(len(ms)):
  descrs = calc.CalcDescriptors(ms[i])
  calcRingDescriptors(ms[i])
  for x in range(len(descrs)):
    ms[i].SetProp(str(nms[x]),str(descrs[x]))
  ms_wr.write(ms[i])
```

Three-dimensional histograms plotting Fsp3 and the number of stereogenic centers were prepared in OriginPro 2015 (OriginLab, Northampton, MA) using the 2D Frequency Count/Binning feature. The number of stereogenic centers was set to X and bin range was set to “Bin Centers”. The minimum bin center was set to 0, the max bin center was set to 8, and the bin size was set to 1. Outliers greater than or equal to the maximum were included and the output binning order was set to descending. Fsp3 was set to Y and the bin range was set to “Bin Centers”. The minimum bin center was set to 0, the max bin center was set to 1, and the bin size was set to 0.1. Outliers greater than or equal to the maximum were included and the output binning order was set to ascending. The quantity to compute was set to “Count”. The resulting data set was then exported to Excel (Microsoft, Redmond WA) and plotted in a 3D column plot (number stereogenic centers = series, Fsp3 = category).

For the Tanimoto Similarity Analysis (Figure S4), compound structures were converted to .sdf library format in ChemDraw (Cambridgesoft, Cambridge, MA). Tanimoto similarity coefficients were calculated using Canvas (Schrödinger, New York, NY), using the Similarity/Distance Matrix application with radial (ECFP) molecular fingerprints. The resulting values were exported to Excel (Microsoft, Redmond, WA) where a heatmap was generated using a three-color scale set to 0.0 (blue), 0.5 (yellow), and 1.0 (red).

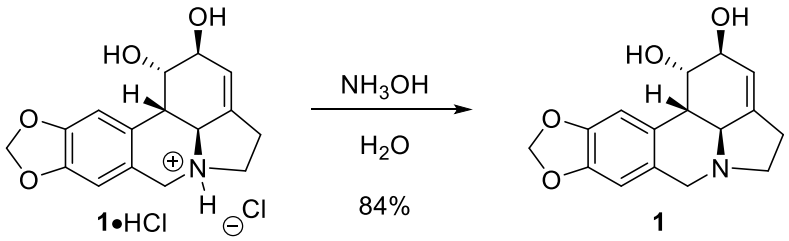
Materials and Methods

Lycorine•HCl (≥98% purity) was purchased from Vesino Industrial Co. Ltd. (Tianjin, China). All reagents were used as received. Commercially available chemicals were purchased from either Sigma-Aldrich Chemical Company (Milwaukee, WI), Alfa Aesar (Ward Hill, MA), Oakwood Chemical (Estill, SC), or TCI America (Portland, OR).

Reactions were performed without rigorous exclusion of air and water unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed on 0.2 mm coated Science silica gel (EM 60-F254) plates. Visualization was accomplished with UV light (254 nm) and exposure to either ceric ammonium molybdate (CAM), *para*-anisaldehyde, or $KMnO_4$ solution followed by heating. Preparatory HPLC purification was performed on a Teledyne ISCO ACCQPrep Hp125 system under the conditions specified.

^1H NMR Spectra were obtained on either a Bruker 500 MHz, Varian Inova 400 MHz, 500 MHz, or 600 MHz NMR instrument; ^{13}C spectra were recorded on a Bruker 500 MHz (at 126 MHz) or Varian Inova 600 MHz (at 151 MHz) NMR instrument. Chemical shifts (^1H and ^{13}C) are reported in parts per million and referenced to the residual solvent peak (for $CDCl_3$, δ = 7.26 ppm, 77.0 ppm respectively). The following designations are used to describe multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), m (multiplet), br (broad), app (apparent). High-resolution mass spectrometry data were acquired by the School of Chemical Sciences Mass Spectrometry Laboratory Facility, University of Illinois at Urbana-Champaign. Compound purity was assessed at 254 or 280 nm UV absorption on an Agilent 1260 Infinity LC system with an Agilent 6230 TOF MS.

Experimental Procedures



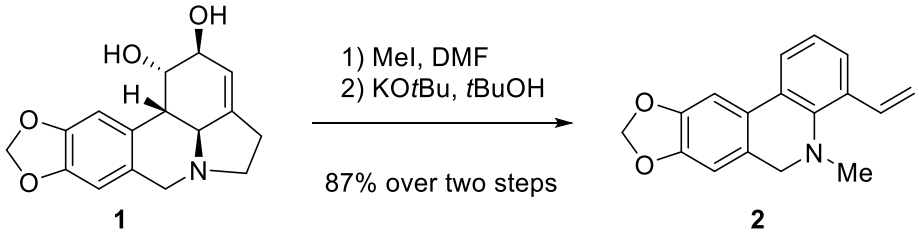
Lycorine free base (**1**)[3]

Lycorine hydrochloride (2.67 g, 8.25 mmol, 1.0 equiv) was dissolved in deionized water (200 mL, 0.04 mM), then saturated aqueous ammonium hydroxide (60 mL, 890 mmol, 110 equiv) was added. White needle crystals immediately began to form, and the solution was kept at room temperature for 16 hr, then cooled to 5 °C for 6 hr. The white needles were then filtered, washing with cold water, and dried to yield lycorine free base (**1**) (2.00 g, 84% recovery).

^{1}H NMR (500 MHz, DMSO-d_6) δ 6.80 (s, 1H), 6.68 (s, 1H), 5.95 (dd, J = 7.1, 1.0 Hz, 2H), 5.43–5.30 (m, 1H), 4.86 (d, J = 6.2 Hz, 1H), 4.76 (d, J = 3.9 Hz, 1H), 4.37–4.18 (m, 1H), 4.01 (d, J = 14.1 Hz, 1H), 3.97 (ddt, J = 6.5, 3.4, 1.7 Hz, 1H), 3.41–3.27 (m, 1H), 3.25–3.14 (m, 1H), 2.60 (d, J = 10.6 Hz, 1H), 2.42 (dddd, J = 18.9, 9.7, 7.7, 2.1 Hz, 1H), 2.20 (dd, J = 8.7 Hz, 1H).

^{13}C NMR (126 MHz, DMSO-d_6) δ 145.6, 145.2, 141.6, 129.7, 129.6, 118.5, 107.0, 105.0, 100.5, 71.7, 70.2, 60.8, 56.7, 53.3, 40.2, 28.1.

HRMS (*m*/*z*) [M + H]+ calcd for $C_{16}H_{18}NO_4$, 288.1230; found, 288.1238.



5-methyl-4-vinyl-5,6-dihydro-[1,3]dioxolo[4,5-j]phenanthridine (**2**)[3]

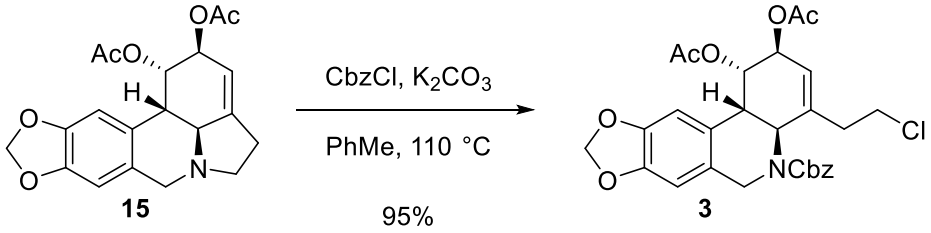
In a round bottom flask, lycorine (601 mg, 2.09 mmol, 1.0 equiv) was dissolved in DMF (12 mL, 0.17 M). Iodomethane (0.80 mL, 12.9 mmol, 6.1 equiv) was added, and the reaction mixture was stirred at room temperature for 12 h. Methanol (5 mL) was then added to quench, and the solvent was removed under vacuum. The crude mixture was then redissolved in *t*-BuOH (20 mL, 0.1 M), KO*t*Bu (2.20 g, 19.6 mmol, 9.4 equiv) was added, and the mixture was heated to 90 °C for 4 h. The reaction was cooled to room temperature and poured into saturated aqueous NH_4Cl (100 mL). Et_2O was added, and the layers were separated. The aqueous layer was extracted twice with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and

concentrated. Purification by silica gel column chromatography (5:1 Hexanes/EtOAc) afforded **2** as a colorless oil (478 mg, 87% over two steps).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.50 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.37–7.26 (m, 2H), 7.18 (t, *J* = 7.7 Hz, 1H), 6.74 (s, 1H), 6.01 (s, 2H), 5.78 (dd, *J* = 17.8, 1.5 Hz, 1H), 5.35 (dd, *J* = 11.0, 1.5 Hz, 1H), 4.06 (s, 2H), 2.54 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 147.4, 147.3, 145.2, 133.5, 133.2, 129.2, 126.4, 125.9, 124.9, 124.3, 122.7, 114.3, 107.1, 103.7, 100.9, 54.8, 41.6.

HRMS (*m*/*z*) [M + H]+ calcd for $C_{17}H_{16}NO_2$, 266.1176; found, 266.1176.



(1S,2S,4aS,11bS)-5-((benzyloxy)carbonyl)-4-(2-chloroethyl)-1,2,4a,5,6,11b-hexahydro-[1,3]dioxolo[4,5-j]phenanthridine-1,2-diyl diacetate (**3**)

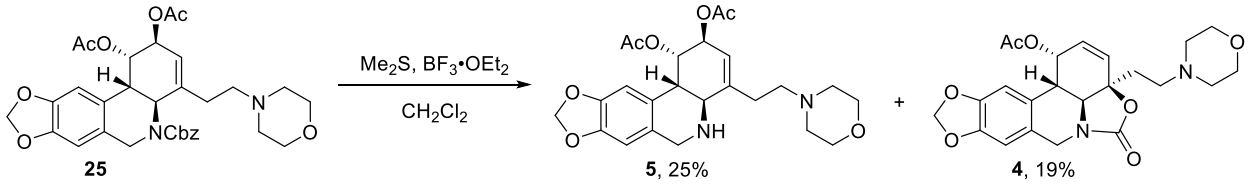
In an oven-dried 200 mL round bottom flask, **15** (524 mg, 1.41 mmol, 1.0 equiv) was dissolved in toluene (60 mL, 0.02 M). Then potassium bicarbonate (3.0 g, 21.1 mmol, 15 equiv) and benzyl chloroformate (2.0 mL, 14 mmol, 10 equiv) were added, and the mixture was heated 110 °C for 16 hr. After cooling to room temperature, toluene and water were added, and the layers were separated. The organic layer was washed with water three times and once with brine. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Silica gel column chromatography (100% $CHCl_3$–1% MeOH in $CHCl_3$) afforded **3** as a yellow oil (727 mg, 95% yield).

Note: The carbamate protecting group results in rotamers, which coalesce at 100 °C, but not sufficiently to resolve all of the ^{13}C signals. Therefore, the cooled spectrum of the same sample at –40 °C (resulting in rotameric products) is reported below.

^{1}H NMR (600 MHz, Toluene-d_8 100 °C) δ 7.11–6.96 (m, 5H), 6.95 (s, 1H), 6.77 (s, 1H), 5.84 (s, 1H), 5.61 (s, 1H), 5.37–5.28 (m, 3H), 4.93 (dd, 2H), 4.23–3.48 (m, 2H), 3.34 (t, *J* = 7.0 Hz, 2H), 2.60 (ddd, *J* = 14.1, 6.7, 6.7 Hz, 1H), 2.49–2.35 (m, 1H), 2.14–2.00 (m, 2H), 1.67 (s, 3H), 1.47 (s, 3H).

^{13}C NMR (151 MHz, Toluene-d_8 –40 °C) δ 169.3, 169.25, 169.19, 168.8, 156.4, 155.6, 147.2, 147.0, 146.6, 146.5, 141.85, 141.81, 137.02, 136.97, 136.3, 135.8, 128.14, 128.10, 127.5, 127.4, 127.2, 127.0, 126.8, 126.5, 125.2, 119.0, 118.4, 106.7, 106.1, 105.5, 105.1, 100.8, 69.5, 69.0, 67.9, 67.1, 67.0, 66.7, 64.5, 56.5, 55.9, 50.9, 50.4, 43.2, 42.8, 36.5, 36.2, 35.9, 35.5, 20.2, 19.8, 19.7.

HRMS (*m*/*z*) [M + Na]+ calcd for $C_{28}H_{28}NO_8NaCl$, 564.1396; found, 564.1414.



In a one-dram vial equipped with a septum, under inert atmosphere **25** (62 mg, 0.105 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (2.0 mL, 0.05 M) and Me_2S (0.19 mL, 2.59 mmol, 25 equiv) was added. Next, boron trifluoride diethyl etherate (0.13 mL, 1.05 mmol, 10 equiv) was added and the resulting mixture was stirred for 2 hr before saturated sodium bicarbonate (1 mL) was added to quench the reaction stirring for 10 minutes. Next, CH_2Cl_2 and saturated sodium bicarbonate were added, the layers separated, and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The resulting crude product was then purified by preparatory HPLC (C18 20x250mm, 10–100% ACN in H_2O) to afford **5** (12.1 mg, 25%) as a colorless oil and **4** (8.9 mg, 19%) as a yellow oil.

(1S,2S,4aS,11bS)-4-(2-morpholinoethyl)-1,2,4a,5,6,11b-hexahydro-[1,3]dioxolo[4,5-j]phenanthridine-1,2-diyl diacetate (**5**)

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.76 (s, 1H), 6.50 (s, 1H), 5.90 (d, *J* = 1.4 Hz, 2H), 5.66 (s, 1H), 5.63 (s, 1H), 5.10 (d, *J* = 4.7 Hz, 1H), 4.11 (d, *J* = 16.9 Hz, 1H), 4.03 (d, *J* = 16.7 Hz, 1H), 3.71 (t, *J* = 4.7 Hz, 4H), 3.46 (d, *J* = 9.8 Hz, 1H), 2.95 (d, *J* = 10.2 Hz, 1H), 2.67–2.44 (m, 7H), 2.36 (ddd, *J* = 13.7, 8.8, 5.6 Hz, 1H), 2.08 (s, 3H), 1.94 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.0, 169.7, 146.4, 146.2, 145.9, 129.8, 126.9, 118.8, 106.0, 104.9, 100.8, 69.0, 67.9, 67.0, 57.3, 53.7, 53.2, 49.6, 40.4, 30.3, 21.1, 20.9.

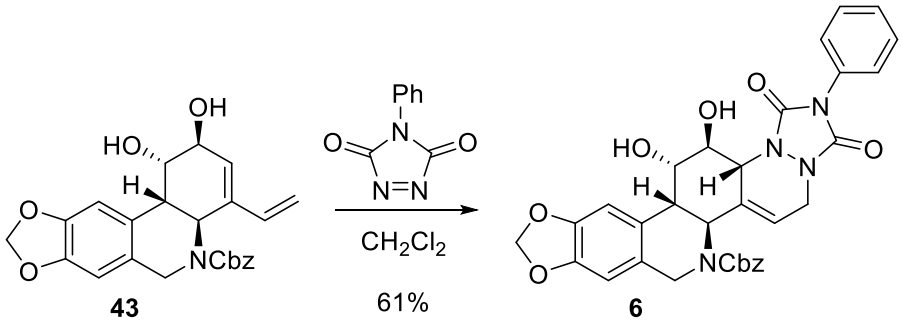
HRMS (*m*/*z*) [M + H]+ calcd for $C_{24}H_{31}N_2O_7$, 459.2126; found, 459.2125.

(1R,3aR,3a1S,12bS)-3a-(2-morpholinoethyl)-5-oxo-3a,3a1,7,12b-tetrahydro-1H,5H-[1,3]dioxolo[4,5-j]oxazolo[5,4,3-de]phenanthridin-1-yl acetate (**4**)

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.66 (s, 1H), 6.58 (s, 1H), 6.47 (dd, *J* = 9.9, 6.2 Hz, 1H), 6.13 (d, *J* = 9.9 Hz, 1H), 5.98 (dd, *J* = 11.9, 1.4 Hz, 2H), 5.77 (dd, *J* = 6.2, 2.4 Hz, 1H), 4.84 (d, *J* = 16.7 Hz, 1H), 4.39 (d, *J* = 16.5 Hz, 1H), 3.79 (d, *J* = 10.6 Hz, 1H), 3.72 (t, *J* = 4.7 Hz, 4H), 2.86 (ddd, *J* = 10.7, 2.4, 1.2 Hz, 1H), 2.54–2.42 (m, 6H), 2.14–2.05 (m, 2H), 1.99 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 157.7, 147.1, 147.0, 130.9, 129.6, 125.9, 125.3, 106.8, 104.8, 101.3, 78.2, 66.7, 62.9, 55.5, 53.7, 53.0, 44.4, 39.6, 35.1, 20.8.

HRMS (*m*/*z*) [M + H]+ calcd for $C_{23}H_{27}N_2O_7$, 443.1813; found, 443.1825.



43 **6**

Benzyl (6bS,13bS,14S,15S,15aR)-14,15-dihydroxy-1,3-dioxo-2-phenyl-2,3,5,8,13b,14,15,15a-octahydro-1H-[1,2,4]triazolo[1',2':1,2]pyridazino[3,4-c][1,3]dioxolo[4,5-j]phenanthridine-7(6bH)-carboxylate (**6**)

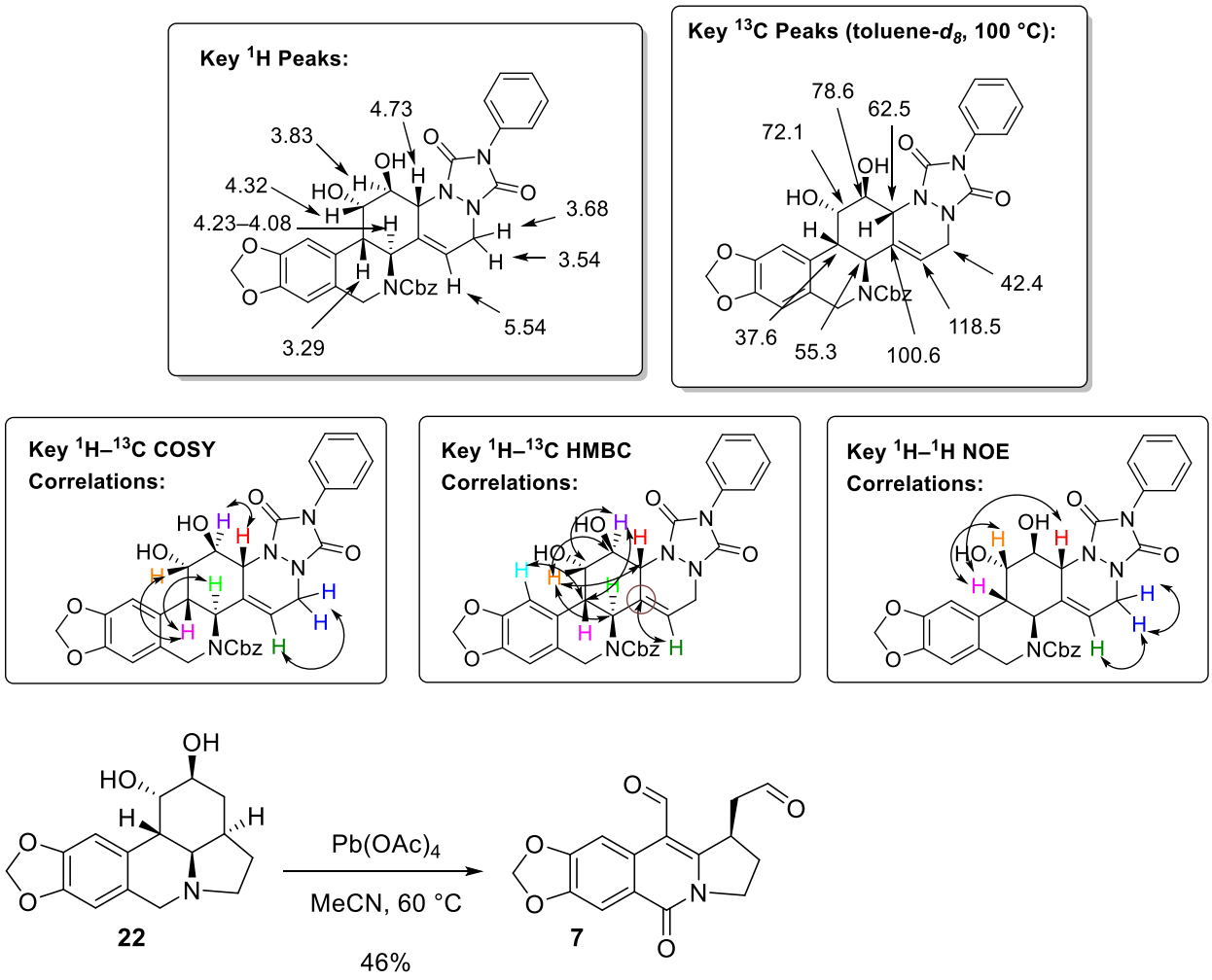
In a 1 dram vial, **43** (24.4 mg, 0.058 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (1.0 mL, 0.06 M). 4-phenyl-1,2,4-triazoline-3,5-dione (15.2 mg, 0.087 mmol, 1.5 equiv) was added, and the mixture was stirred at room temperature for 4.5 hr, before being concentrated under vacuum. Silica gel column chromatography (2–5% MeOH in $CHCl_3$) afforded **6** as a white solid (21.0 mg, 61%).

Note: The carbamate protecting group results in rotamers, which coalesce at 100 °C, but not sufficiently to resolve all of the ^{13}C signals. Therefore, the cooled spectrum of the same sample at –30 °C (resulting in rotameric products) is reported below. Poor solubility of **6** in toluene at lower temperatures necessitated the change in solvents.

^1H NMR (600 MHz, Toluene-d_8, 100 °C) δ 7.69–7.58 (m, 2H), 7.15 (t, J = 7.8 Hz, 2H), 7.08–6.99 (m, 4H), 6.98–6.91 (m, 2H), 6.63 (s, 1H), 6.24 (s, 1H), 5.54 (s, 1H), 5.40 (dd, J = 8.9, 1.5 Hz, 2H), 4.94 (d, J = 11.9 Hz, 1H), 4.87 (d, J = 16.2 Hz, 1H), 4.83 (d, J = 12.0 Hz, 1H), 4.73 (s, 1H), 4.31 (s, 1H), 4.23–4.08 (m, 2H), 3.83 (d, J = 6.3 Hz, 1H), 3.68 (d, J = 16.9 Hz, 1H), 3.54 (d, J = 16.4 Hz, 1H), 3.29 (d, J = 12.1 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$, –30 °C) δ 156.1, 155.6, 154.2, 152.9, 151.2, 151.0, 146.96, 146.95, 146.6, 146.5, 135.6, 134.5, 130.4, 130.2, 129.7, 129.6, 129.6, 129.0, 129.0, 128.8, 128.72, 128.69, 128.6, 128.5, 128.3, 128.2, 127.6, 127.1, 125.8, 124.9, 118.7, 118.6, 106.7, 106.4, 105.6, 105.5, 101.3, 78.4, 72.1, 68.9, 67.5, 62.4, 61.9, 55.0, 54.4, 51.1, 50.8, 42.5, 42.3, 37.3, 36.4.

HRMS (*m*/*z*) [M + H]+ calcd for $C_{32}H_{29}N_4O_8$, 597.1980; found, 597.1990.



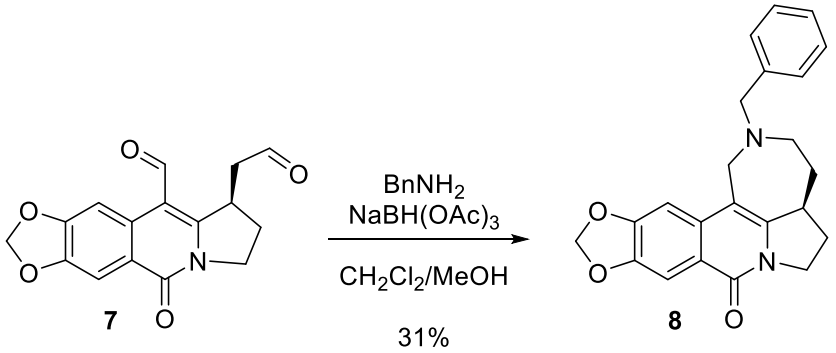
(R)-5-oxo-9-(2-oxoethyl)-5,7,8,9-tetrahydro-[1,3]dioxolo[4,5-g]pyrrolo[1,2-b]isoquinoline-10-carbaldehyde (**7**)

In a 20 mL vial, acetonitrile (7 mL, 0.1 M) was added to **22**•4AcOH (392 mg, 0.74 mmol, 1.0 equiv). Lead (IV) acetate (1.3 g, 4.0 equiv) was then added at room temperature and stirred for 10 min until bubbling had ceased. The reaction mixture was then heated to 60 °C for 4.5 hr, before being cooled to room temperature and concentrated under vacuum. The crude reaction mixture was purified directly by silica gel column chromatography (2–5% MeOH in $CHCl_3$), giving **7** as a yellow oil (103 mg, 46%) of sufficient purity to carry on to the next step. Note: the yield and purity of this reaction is variable, ranging from 10–50%, possibly due to instability of dialdehyde **7**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.21 (s, 1H), 9.85 (s, 1H), 8.27 (s, 1H), 7.73 (s, 1H), 6.13 (s, 2H), 4.55 (ddd, *J* = 12.4, 8.4, 4.2 Hz, 1H), 4.48 (dd, *J* = 12.8, 9.1 Hz, 1H), 4.03 (ddd, *J* = 12.8, 11.4, 6.9 Hz, 1H), 3.74 (dd, *J* = 13.8, 7.0 Hz, 1H), 2.98–2.86 (m, 2H), 2.47 (ddd, *J* = 20.8, 12.7, 9.6 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 198.4, 187.2, 160.6, 158.0, 153.5, 148.1, 132.4 120.5, 108.9, 105.4, 102.6, 102.4, 47.9, 46.9, 37.1, 27.5.

HRMS (*m*/*z*) [M + H]+ calcd for $C_{16}H_{14}NO_5$, 300.0866; found, 300.0879.



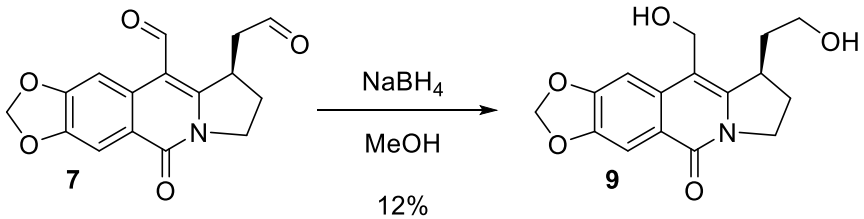
(S)-2-benzyl-2,3,4,4a,5,6-hexahydro-[1,3]dioxolo[4',5':4,5]benzo[1,2-f]azepino[3,4,5-hi]indolizin-8(1H)-one (**8**)

Dialdehyde **7** (60 mg, 0.20 mmol, 1.0 equiv) was dissolved in a 4:1 mixture of CH_2Cl_2/MeOH (4 mL, 0.05 M) in a 20 mL vial. Benzylamine (28 µL, 0.27 mmol, 1.3 equiv) was added, followed by sodium triacetoxyborohydride (212 mg, 1.0 mmol, 5.0 equiv). The reaction mixture was stirred at room temperature for 14 h, before being quenched by the addition of saturated aqueous $NaHCO_3$. CH_3Cl was also added, and the aqueous layer was extracted twice with $CHCl_3$. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Silica gel column chromatography (2–5% MeOH in $CHCl_3$) provided **8** as a yellow oil (23.2 mg, 31% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.35–7.27 (m, 5H), 6.50 (s, 1H), 6.02 (dd, *J* = 13.8, 1.3 Hz, 2H), 4.41 (ddd, *J* = 12.2, 9.4, 2.6 Hz, 1H), 4.02–3.88 (m, 2H), 3.80–3.70 (m, 2H), 3.69–3.60 (m, 2H), 3.12–2.91 (m, 2H), 2.45 (dtd, *J* = 12.9, 8.3, 2.6 Hz, 1H), 2.03–1.71 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 160.0, 151.8, 146.5, 145.0, 139.0, 134.7, 129.0, 128.4, 127.2, 120.4, 109.0, 105.5, 101.6, 100.2, 60.3, 56.6, 51.3, 47.4, 43.2, 32.2, 29.2.

HRMS (*m*/*z*) [M + H]+ calcd for $C_{23}H_{23}N_2O_3$, 375.1703; found, 375.1703.



(R)-9-(2-hydroxyethyl)-10-(hydroxymethyl)-8,9-dihydro-[1,3]dioxolo[4,5-g]pyrrolo[1,2-b]isoquinolin-5(7H)-one (**9**)

In a 25 mL round bottom flask, **7** (137 mg, 0.46 mmol, 1.0 equiv) was dissolved in methanol (8 mL, 0.05 M). The reaction mixture was cooled to 0 °C, sodium borohydride

(158 mg, 4.2 mmol, 9.0 equiv) was added, and it was stirred at 0 °C for 1 hr then warmed to room temperature for 1.5 hr. The reaction mixture was concentrated under vacuum, and the crude residue was purified by silica gel column chromatography (2–10% MeOH in $CHCl_3$) to afford **9** as a white solid (16 mg, 12%).

^{1}H NMR (500 MHz, 3:1 $CDCl_3$/CD_3OD) δ 7.65 (s, 1H), 7.29 (s, 1H), 6.06 (s, 2H), 4.72 (dd, *J* = 30.3, 12.4 Hz, 2H), 4.33 (dd, *J* = 12.5, 9.0 Hz, 1H), 3.97 (td, *J* = 11.9, 6.8 Hz, 1H), 3.80–3.59 (m, 3H), 2.25 (tt, *J* = 12.3, 8.8 Hz, 1H), 2.08 (dd, *J* = 12.9, 6.7 Hz, 1H), 1.92–1.73 (m, 2H).

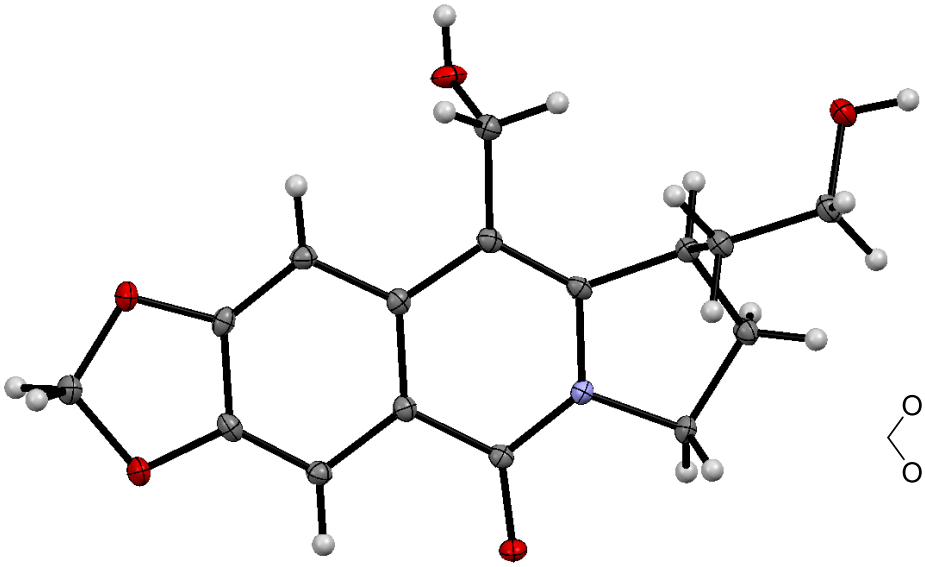
^{13}C NMR (151 MHz, 3:1 $CDCl_3$/CD_3OD) δ 160.8, 152.4, 147.3, 145.2, 135.6, 120.3, 110.6, 104.5, 101.8, 101.6, 59.4, 57.6, 46.7, 38.7, 36.5, 26.8.

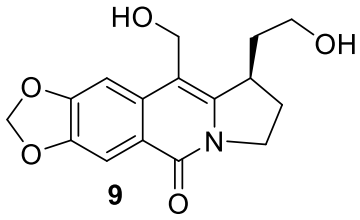
HRMS (*m*/*z*) [M + H]+ calcd for $C_{16}H_{18}NO_5$, 304.1179; found, 304.1183.

Figure S5. Thermal ellipsoid depiction of diol **9**

Crystals suitable for X-ray diffraction were grown by liquid/liquid diffusion between a 3:1 $CDCl_3$/MeOD mixture and hexanes (insoluble).

The complete data for this structure are on file with the CCDC under entry CCDC 1853000.

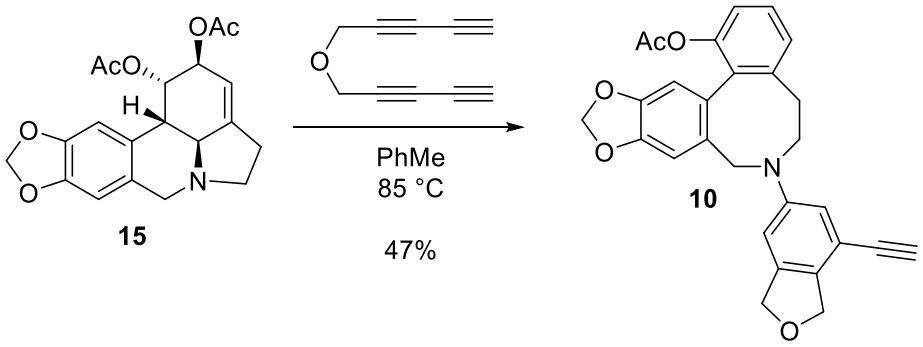




9

Empirical formula: $C_{16}H_{17}NO_5$
a: 5.060 Å
b: 15.797 Å
c: 8.402 Å
α (alpha): 90.00 °
β (beta): 103.84 °
γ (gamma): 90.00 °
Volume: 652.10 Å^3

Space group: $P2_1$
Calculated density: 1.545 g/cm^3
Color: colourless
Z: 2
Temperature: -173.0 °C
Formula weight: 303.315 g/mole
R(F): 0.0248
$R_w(F^2)$: 0.0636



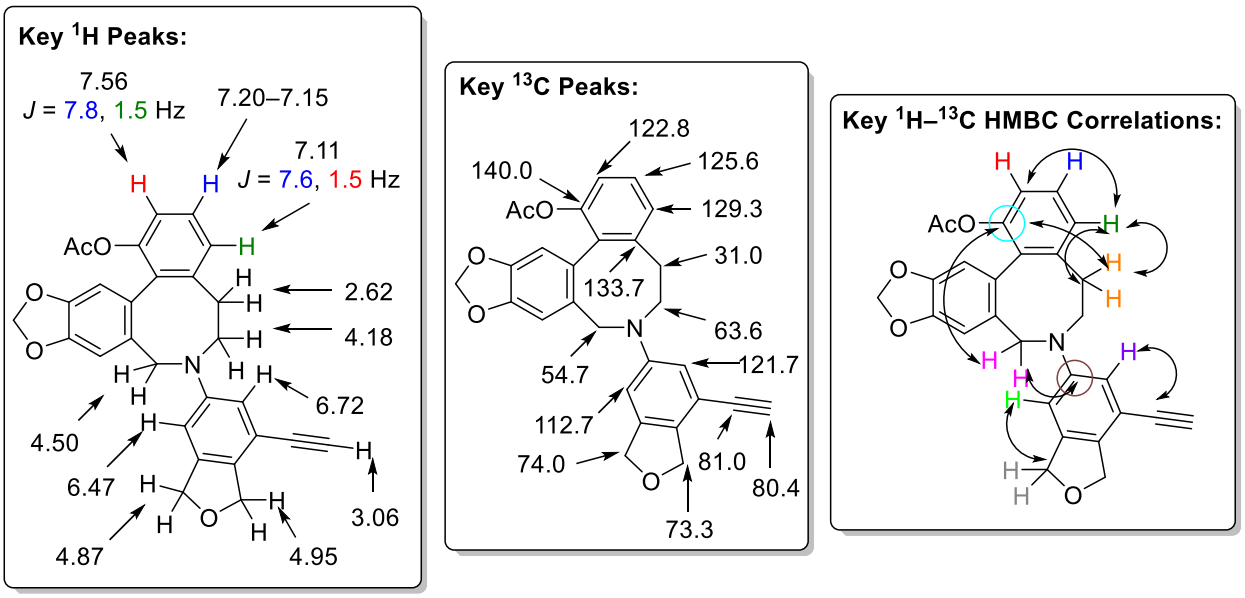
7-(7-ethynyl-1,3-dihydroisobenzofuran-4-yl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4',5':4,5] benzo[1,2-c]benzo[e]azocin-1-yl acetate (**10**)

In a 1 dram vial, diacetyl lycorine (16.8 mg, 0.045 mmol, 1.0 equiv) and 5-(penta-2,4-diyn-1-yloxy)penta-1,3-diyne (6.4 mg, 0.045 mmol, 1.0 equiv) were dissolved in toluene (0.5 mL, 0.1 M) and heated to 85 °C for 24 hr. The reaction mixture was concentrated under vacuum, followed by purification by silica gel column chromatography (0–2% MeOH in $CHCl_3$) to afford **10** (9.6 mg, 47%) as an orange solid.

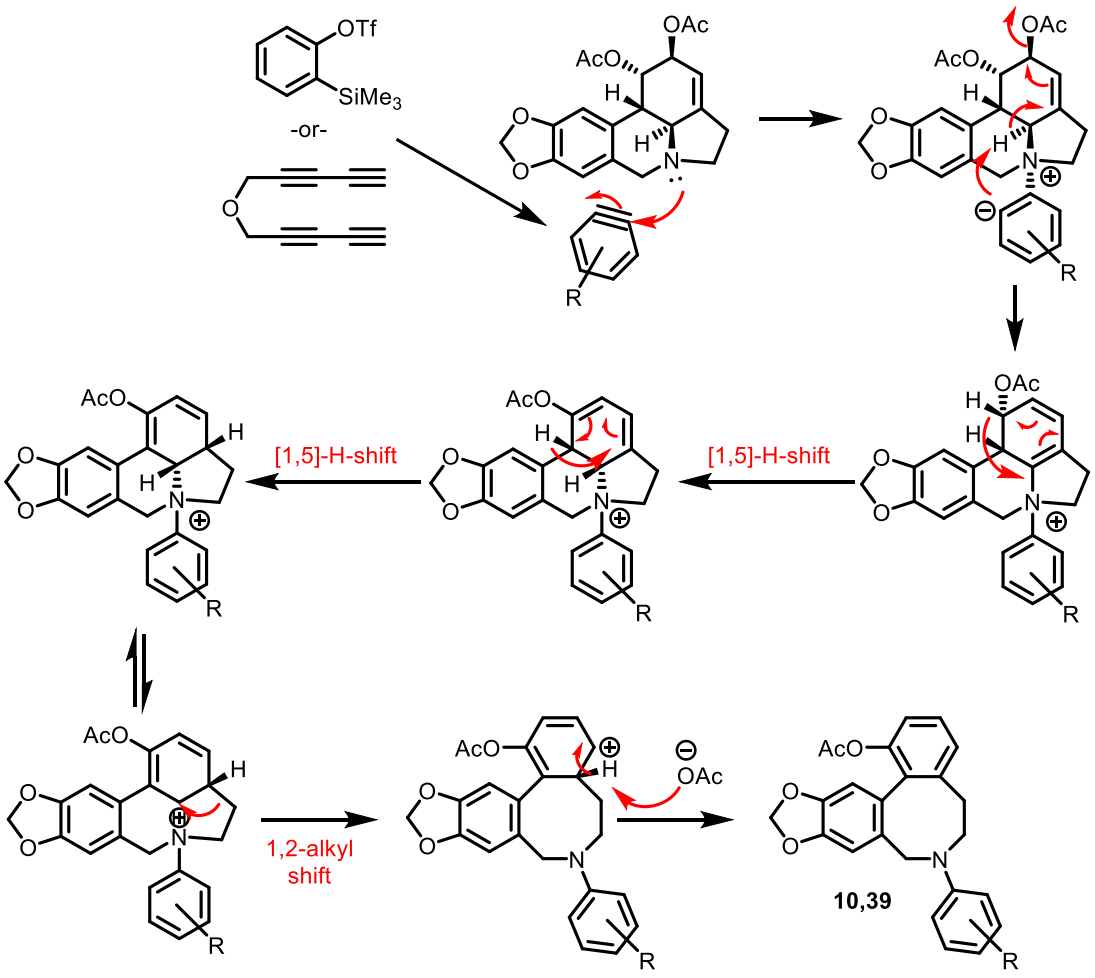
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.20–7.15 (m, 2H), 7.11 (dd, *J* = 7.6, 1.5 Hz, 1H), 6.72 (d, *J* = 2.0 Hz, 1H), 6.54 (s, 1H), 6.47 (s, 1H), 5.86 (s, 2H), 4.95 (d, *J* = 4.2 Hz, 2H), 4.87 (s, 2H), 4.50 (s, 2H), 4.18 (t, *J* = 7.0 Hz, 2H), 3.06 (s, 1H), 2.62 (t, *J* = 7.0 Hz, 2H), 1.92 (s, 3H).

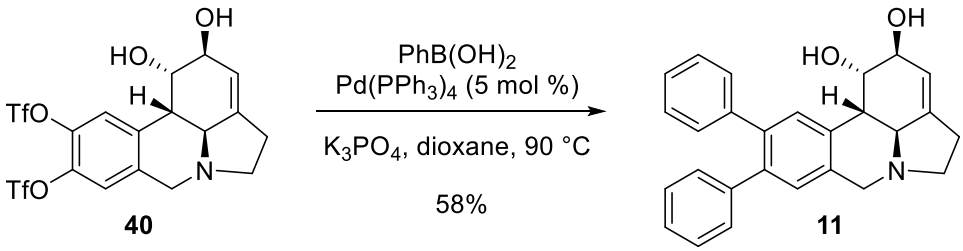
^{13}C NMR (126 MHz, $CDCl_3$) δ 171.0, 148.6, 147.7, 147.4, 140.6, 140.0, 134.9, 133.7, 131.4, 129.3, 127.6, 126.4, 125.6, 122.8, 121.7, 115.9, 112.7, 106.4, 104.0, 101.1, 81.0, 80.4, 74.0, 73.3, 63.6, 54.7, 31.0, 21.0.

HRMS (*m*/*z*) [M – H]+ calcd for $C_{28}H_{22}NO_5$, 452.1492; found, 452.1498.



Proposed Mechanism for Benzyne Product Formation:





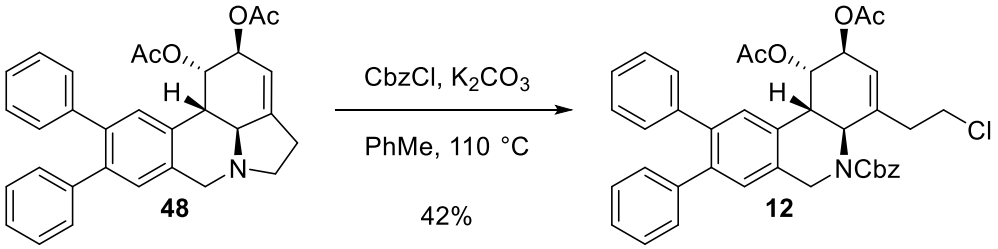
(1S,2S,3a1S,11bS)-9,10-diphenyl-2,3a1,4,5,7,11b-hexahydro-1H-pyrrolo[3,2,1-de]phenanthridine-1,2-diol (**11**)

In a dry 20 mL vial equipped with a septum, ditriflate **40** (341 mg, 0.63 mmol, 1.0 equiv), phenylboronic acid (200 mg, 1.64 mmol, 2.6 equiv), $Pd(PPh_3)_4$ (37 mg, 0.032 mmol, 0.05 equiv), and K_3PO_4 (538 mg, 2.53 mmol, 4.0 equiv) were dissolved in dry and degassed 1,4-dioxane (10 mL, 0.6 M) under N_2. The reaction mixture was heated to 90 °C for 16 h. After cooling to room temperature, sat. aqueous $NaHCO_3$ and $CHCl_3$ were added, and the layers were separated. The aqueous layer was extracted three times with $CHCl_3$, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. Silica gel column chromatography (5–20% MeOH/$CHCl_3$) afforded **11** as a tan solid (144 mg, 58%).

^{1}H NMR (500 MHz, 3:1 $CDCl_3$/CD_3OD) δ 7.36 (s, 1H), 7.17–6.98 (m, 11H), 5.55 (s, 1H), 4.55 (s, 1H), 4.27 (d, *J* = 14.6 Hz, 1H), 4.18–3.98 (m, 1H), 3.66 (d, *J* = 14.5 Hz, 1H), 3.35 (dd, *J* = 8.3, 7.9 Hz, 1H), 2.93 (d, *J* = 11.1 Hz, 1H), 2.78 (d, *J* = 10.7 Hz, 1H), 2.70–2.48 (m, 2H), 2.40 (dd, *J* = 18.1, 9.0 Hz, 1H).

^{13}C NMR (126 MHz, 3:1 $CDCl_3$/CD_3OD) δ 142.1, 141.3, 141.1, 139.1, 138.7, 134.8, 133.9, 129.8, 129.7, 129.4, 127.81, 127.77, 126.9, 126.41, 126.39, 118.1, 71.8, 70.4, 61.1, 56.6, 53.8, 39.8, 28.1.

HRMS (*m*/*z*) [M + H]+ calcd for $C_{27}H_{26}NO_2$, 396.1958; found, 396.1979.



(1S,2S,4aS,10bS)-5-((benzyloxy)carbonyl)-4-(2-chloroethyl)-8,9-diphenyl-1,2,4a,5,6,10b-hexahydrophenanthridine-1,2-diyl diacetate (**12**)

In a 50 mL round bottom flask, **48** (94 mg, 0.20 mmol, 1.0 equiv) was dissolved in toluene (9.8 mL, 0.02 M). K_2CO_3 (406 mg, 2.9 mmol, 15 equiv) and benzyl chloroformate (0.28 mL, 2.0 mmol, 10 equiv) were then added, and the reaction mixture was heated to reflux under N_2 for 20 h. H_2O and toluene were added, and the layers were separated. The aqueous layer was extracted twice with toluene, and the combined organic layers were

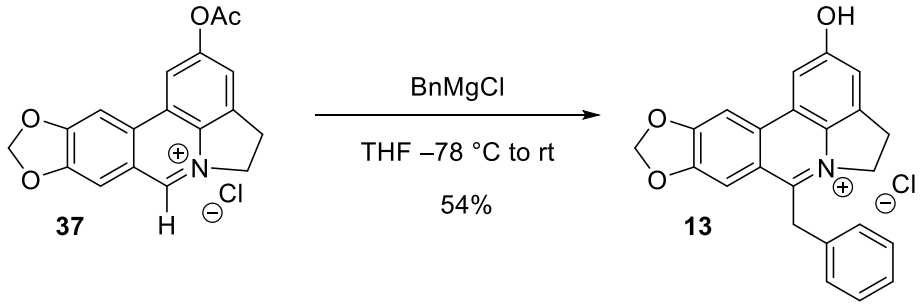
washed with brine, dried over $MgSO_4$, filtered, and concentrated. Silica gel column chromatography (100% $CHCl_3$) afforded **12** (54 mg, 42%) as a tan solid.

Note: The carbamate protecting group results in rotamers, which coalesce at 100 °C, but not sufficiently to resolve all of the ^{13}C signals. Therefore, the cooled spectrum of the same sample at –30 °C (resulting in rotameric products) is reported below. Poor solubility of **12** in toluene at lower temperatures necessitated the change in solvents.

^1H NMR (600 MHz, Toluene-d_8) δ 7.50 (s, 1H), 7.14 (d, J = 7.6 Hz, 2H), 7.07–7.01 (m, 6H), 7.00–6.93 (m, 9H), 6.09 (s, 1H), 5.66 (s, 1H), 5.34 (d, J = 3.1 Hz, 1H), 4.98 (d, J = 12.5 Hz, 1H), 4.93 (d, J = 12.4 Hz, 1H), 4.27 (s, 2H), 3.79 (s, 1H), 3.44–3.28 (m, 2H), 2.66 (dt, J = 14.0, 6.6 Hz, 1H), 2.46 (s, 1H), 1.66 (s, 3H), 1.50 (s, 3H).

^{13}C NMR (151 MHz, Chloroform-d) δ 170.5, 170.41, 170.37, 170.1, 157.1, 155.8, 142.0, 141.8, 140.63, 140.60, 140.59, 140.53, 139.4, 139.3, 139.0, 138.8, 136.0, 135.3, 133.9, 133.3, 133.1, 132.7, 129.9, 129.8, 129.8, 129.0, 128.7, 128.6, 128.51, 128.49, 128.40, 128.37, 128.23, 128.17, 128.14, 128.12, 128.0, 127.9, 127.80, 127.77, 126.83, 126.80, 126.77, 118.9, 118.2, 69.0, 68.6, 68.5, 67.5, 66.7, 66.6, 64.2, 56.1, 55.9, 51.1, 50.7, 43.5, 43.0, 36.5, 36.1, 35.5, 21.6, 21.37, 21.35, 21.1.

HRMS (*m*/*z*) [M + Na]+ calcd for $C_{39}H_{36}ClNO_6Na$, 672.2123; found, 672.2124.



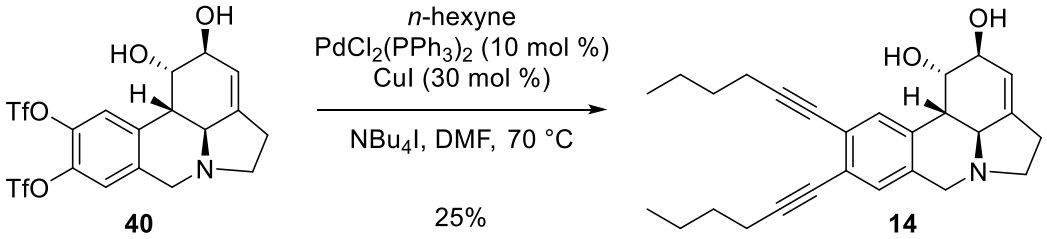
7-benzyl-2-hydroxy-4,5-dihydro-[1,3]dioxolo[4,5-j]pyrrolo[3,2,1-de]phenanthridin-6-ium chloride (**13**)

In a 20 mL vial under N_2 **37** (45.2 mg, 0.123 mmol, 1.0 equiv) was dissolved in tetrahydrofuran (4 mL, 0.03 M) and stirred 5 minutes before cooling to –78 °C and adding benzylmagnesium chloride (1.0 M in Me-THF, 0.55 mL, 4.5 equiv). The solution was stirred 30 minutes at –78 °C before warming to room temperature and stirring 16 hr. The reaction was quenched by the addition of methanol, concentrated under vacuum, and the crude mixture was purified by silica gel column chromatography (2% MeOH in $CHCl_3$) to yield **13** (26 mg, 54%) as an orange solid.

^1H NMR (500 MHz, 3:1 $CDCl_3$/CD_3OD) δ 8.00 (s, 1H), 7.73 (s, 1H), 7.62 (s, 1H), 7.34–7.25 (m, 4H), 7.07 (d, J = 7.0 Hz, 2H), 6.32 (s, 2H), 5.16–5.02 (m, 2H), 4.86 (s, 2H), 3.76–3.67 (m, 2H).

^{13}C NMR (126 MHz, 3:1 $CDCl_3/CD_3OD$) δ 161.4, 155.8, 151.4, 151.3, 137.8, 133.4, 132.9, 131.0, 129.8, 128.2, 128.1, 124.9, 122.8, 117.6, 105.5, 104.2, 103.6, 101.9, 55.3, 35.6, 27.3.

HRMS (*m*/*z*) [M]+ calcd for $C_{23}H_{18}NO_3$, 356.1281; found, 356.1282.



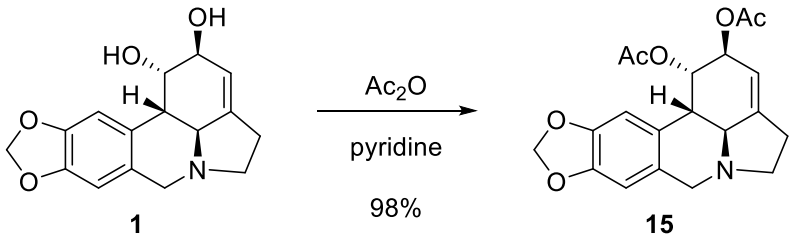
(1S,2S,3a1S,11bS)-9,10-di(hex-1-yn-1-yl)-2,3a1,4,5,7,11b-hexahydro-1H-pyrrolo[3,2,1-de]phenanthridine-1,2-diol (**14**)

Ditriflate **40** (177 mg, 0.328 mmol, 1.0 equiv), tetrabutylammonium iodide (364 mg, 1.00 mmol, 3.0 equiv), $PdCl_2(PPh_3)_2$ (23 mg, 0.033 mmol, 0.1 equiv), and CuI (19 mg, 0.10 mmol, 0.3 equiv) were weighed out into a 20 mL oven-dried vial equipped with a septum, which was then pumped/backfilled with N_2 three times. Dry, degassed DMF (5.0 mL, 0.07 M) and Et_3N (1.0 mL, 0.33 M) were added and the reaction was stirred at room temperature for 5 min. 1-Hexyne (0.15 mL, 1.31 mmol, 4.1 equiv) was then added, and the vial was heated to 70 °C for 7 h. After cooling to room temperature, sat. aqueous $NaHCO_3$ and $CHCl_3$ were added, and the layers were separated. The aqueous layer was extracted three times with $CHCl_3$, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. Silica gel column chromatography (5–20% MeOH/$CHCl_3$) afforded **14** (33 mg, 25%) as a white solid.

^{1}H NMR (500 MHz, 3:1 $CDCl_3/CD_3OD$) δ 7.37 (s, 1H), 7.11 (s, 1H), 5.54 (s, 1H), 4.50 (s, 1H), 4.15 (d, *J* = 14.8 Hz, 1H), 4.10 (s, 1H), 3.53 (d, *J* = 14.8 Hz, 1H), 3.31 (td, *J* = 8.5, 7.7, 1.6 Hz, 1H), 2.83 (d, *J* = 10.9 Hz, 1H), 2.70–2.58 (m, 2H), 2.53 (dddd, *J* = 17.0, 9.6, 7.6, 2.0 Hz, 1H), 2.42 (td, *J* = 6.9, 3.4 Hz, 4H), 2.37 (dd, *J* = 17.7, 8.9 Hz, 1H), 1.56 (dt, *J* = 12.1, 6.9 Hz, 4H), 1.54–1.41 (m, 4H), 0.92 (t, *J* = 7.2 Hz, 6H).

^{13}C NMR (126 MHz, 3:1 $CDCl_3/CD_3OD$) δ 142.3, 135.3, 134.5, 130.6, 128.4, 125.0, 124.6, 118.3, 93.8, 79.6, 79.4, 71.9, 70.5, 61.0, 56.6, 53.8, 40.1, 31.01, 30.99, 28.3, 22.1, 19.4, 13.7.

HRMS (*m*/*z*) [M + H]+ calcd for $C_{27}H_{34}NO_2$, 404.2584; found, 404.2580.



1 **15**

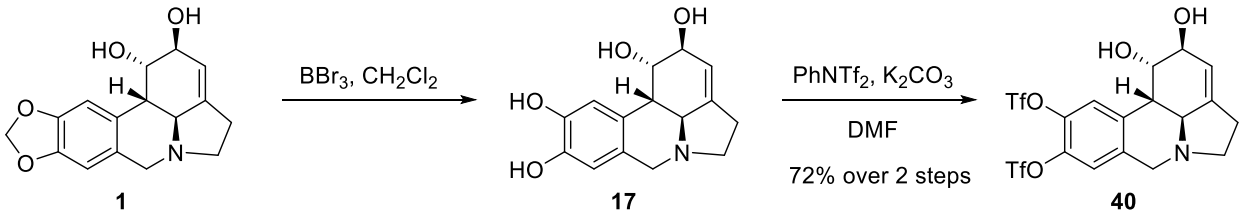
Diacetyl lycorine (**15**)[3]

Lycorine free base (**1**) (2.57 g, 8.9 mmol, 1.0 equiv), pyridine (30 mL, 0.3 M), and acetic anhydride (8.5 mL, 77 mmol, 8.7 equiv) were stirred at 50 °C for 13 h. After cooling the reaction to room temperature, methanol (19 mL) was added, and the reaction was stirred at room temperature for 3.5 h. The solvents were then removed under vacuum, and the resulting crude material was purified by silica gel column chromatography (3:1 CH_2Cl_2/EtOAc) afforded diacetyl lycorine (**15**) as an off-white solid (3.26 g, 98%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.74 (s, 1H), 6.57 (s, 1H), 5.91 (s, 2H), 5.78–5.67 (m, 1H), 5.59–5.46 (m, 1H), 5.25 (dp, *J* = 3.5, 1.8 Hz, 1H), 4.15 (d, *J* = 14.1 Hz, 1H), 3.53 (d, *J* = 14.0 Hz, 1H), 3.36 (dt, *J* = 9.3, 5.1 Hz, 1H), 2.87 (d, *J* = 10.4 Hz, 1H), 2.78 (d, *J* = 10.6 Hz, 1H), 2.65 (ddd, *J* = 8.4, 3.9, 2.1 Hz, 2H), 2.40 (dd, *J* = 8.7 Hz, 1H), 2.07 (s, 3H), 1.94 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.0, 169.7, 146.5, 146.3, 146.1, 129.4, 126.6, 113.9, 107.3, 105.1, 101.0, 70.9, 69.2, 61.2, 56.9, 53.6, 40.5, 28.7, 21.1, 20.9.

HRMS (*m*/*z*) [M + H]+ calcd for $C_{20}H_{22}NO_6$, 372.1442; found, 372.1448.



1 **17** **40**

(1S,2S,3a1S,11bS)-2,3a1,4,5,7,11b-hexahydro-1H-pyrrolo[3,2,1-de]phenanthridine-1,2,9,10-tetraol (**17**)[4]

In a dry 100 mL round bottom flask under N_2, lycorine free base (1.01 g, 3.5 mmol, 1.0 equiv) and CH_2Cl_2 (30 mL, 0.11 M) were cooled to 0 °C. Boron tribromide (1M in CH_2Cl_2, 8.1 mL, 2.3 equiv) was added dropwise, and the reaction was stirred at 0 °C for 2 h, before MeOH (25 mL) was added and the reaction was stirred at room temperature for 10 min. The reaction mixture was then concentrated under vacuum to yield **17** as a yellow solid, which was carried onto the next reaction without further purification. For characterization and biological testing, **17** could be purified by preparatory HPLC (HILIC amide 20x150mm, 95–50% [ACN with 10 mM NH_4OAc] in [H_2O with 10mM NH_4OAc) to yield **17**•2HOAc as a yellow solid.

^{1}H NMR (500 MHz, 3:1 $CDCl_3/CD_3OD$) δ 6.82 (s, 1H), 6.56 (s, 1H), 5.66 (s, 1H), 4.47 (s, 1H), 4.18 (s, 1H), 4.10 (d, *J* = 13.8 Hz, 1H), 3.89 (d, *J* = 13.9 Hz, 1H), 3.49–3.39 (m, 2H), 3.04 (dd, *J* = 8.4, 8.3 Hz, 1H), 2.82 (d, *J* = 11.3 Hz, 1H), 2.78–2.70 (m, 1H), 2.71–2.60 (m, 1H), 1.93 (s, 6H, ($^{-}$OCOC*H*$_3$)$_2$).

^{13}C NMR (126 MHz, 3:1 $CDCl_3/CD_3OD$) δ 177.9, 144.6, 143.8, 138.4, 125.6, 123.4, 120.3, 114.1, 111.6, 71.0, 69.4, 60.9, 53.5, 49.5, 37.4, 28.3, 22.7.

HRMS (*m*/*z*) [M + H]+ calcd for $C_{15}H_{18}NO_4$, 276.1230; found, 276.1235.

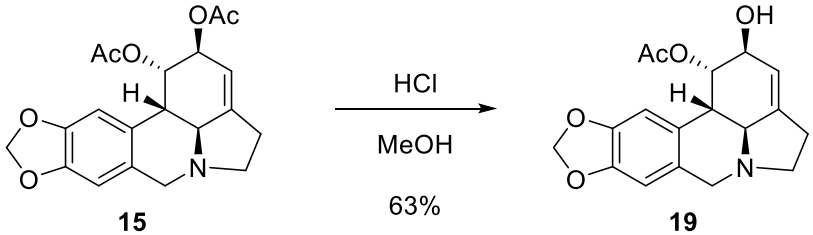
(1S,2S,3a1S,11bS)-1,2-dihydroxy-2,3a1,4,5,7,11b-hexahydro-1H-pyrrolo[3,2,1-de]phenanthridine-9,10-diyl bis(trifluoromethanesulfonate) (**40**)

The crude mixture above was dissolved in DMF (35 mL, 0.1 M), and then $PhNTf_2$ (3.13 g, 8.8 mmol, 2.5 equiv) and K_2CO_3 (1.21 g, 8.8 mmol, 2.5 equiv) were added. The reaction was stirred at room temperature for 21 h, before the DMF was removed under vacuum. The resulting crude mixture was purified directly by silica gel column chromatography (5–10% MeOH/$CHCl_3$) to provide **40** as a yellow solid (1.35 g, 72% over 2 steps).

^{1}H NMR (500 MHz, 3:1 $CDCl_3/CD_3OD$) δ 7.46 (s, 1H), 7.21 (s, 1H), 5.57 (s, 1H), 4.44 (s, 1H), 4.26 (d, *J* = 15.2 Hz, 1H), 4.13 (s, 1H), 3.64 (d, *J* = 15.2 Hz, 1H), 3.35 (dd, *J* = 17.9, 8.9 Hz, 1H), 2.89 (d, *J* = 10.6 Hz, 1H), 2.73 (d, *J* = 10.7 Hz, 1H), 2.71–2.48 (m, 2H), 2.42 (dd, *J* = 9.0 Hz, 1H).

^{13}C NMR (151 MHz, 3:1 $CDCl_3/CD_3OD$) δ 141.6, 138.7, 138.50, 138.48, 138.2, 121.9, 118.47 (q, *J* = 320.6 Hz) 118.46 (q, *J* = 320.7 Hz), 120.3, 118.2, 71.8, 70.2, 60.1, 56.0, 53.5, 40.3, 28.1.

HRMS (*m*/*z*) [M + H]+ calcd for $C_{17}H_{16}NO_8$, 540.0216; found, 540.0219.



15 **19**

(1S,2S,3a1S,12bS)-2-hydroxy-2,3a1,4,5,7,12b-hexahydro-1H-[1,3]dioxolo[4,5-j]pyrrolo[3,2,1-de]phenanthridin-1-yl acetate (**19**)[4]

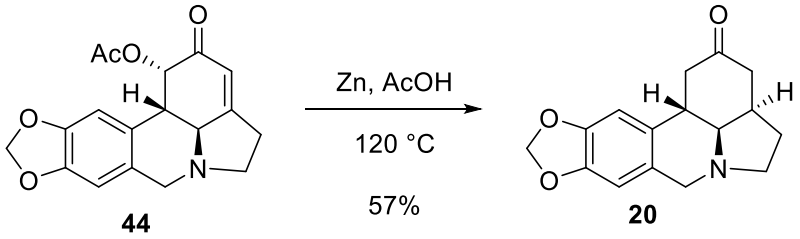
In a 500 mL round bottom flask, concentrated aqueous hydrochloric acid (26 mL, 0.13 M) was added to a suspension of **15** (1.27 g, 3.42 mmol, 1.0 equiv) in methanol (131 mL, 0.026 M). The mixture was then heated to 55 °C for 1 hr, and then cooled to room temperature. Saturated aqueous $NaHCO_3$ was added until gas evolution ceased and the pH was ~8–9. CH_2Cl_2 was added, and the layers were separated. The aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with brine,

dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by column chromatography (10:1 EtOAc/MeOH) to yield **19** as a white solid (715 mg, 63% yield).

^{1}H NMR (500 MHz, 3:1 $CDCl_3$/CD_3OD) δ 6.59 (s, 1H), 6.43 (s, 1H), 5.76 (dd, *J* = 4.4, 1.3 Hz 2H), 5.50 (bs, 1H), 5.42 (ddt, *J* = 3.4, 2.3, 1.4 Hz, 1H), 3.97 (s, 2H), 3.42 (d, *J* = 14.1 Hz, 1H), 3.25–3.14 (m, 1H), 2.69 (dd, *J* = 19.4, 10.7 Hz, 2H), 2.58–2.39 (m, 2H), 2.30 (dd, *J* = 17.9, 8.9 Hz, 1H), 1.78 (s, 3H).

^{13}C NMR (126 MHz, 3:1 $CDCl_3$/CD_3OD) δ 171.0, 146.7, 146.4, 142.3, 128.6, 126.9, 117.8, 107.2, 104.8, 101.0, 72.4, 69.0, 61.6, 56.7, 53.5, 38.6, 28.2, 20.8.

HRMS (*m*/*z*) [M + H]+ calcd for $C_{18}H_{20}NO_5$, 330.1336; found, 330.1335.



44 **20**

(3aS,3a1R,12bS)-3a,3a1,4,5,7,12b-hexahydro-1H-[1,3]dioxolo[4,5-j]pyrrolo[3,2,1-de]phenanthridin-2(3H)-one (**20**)

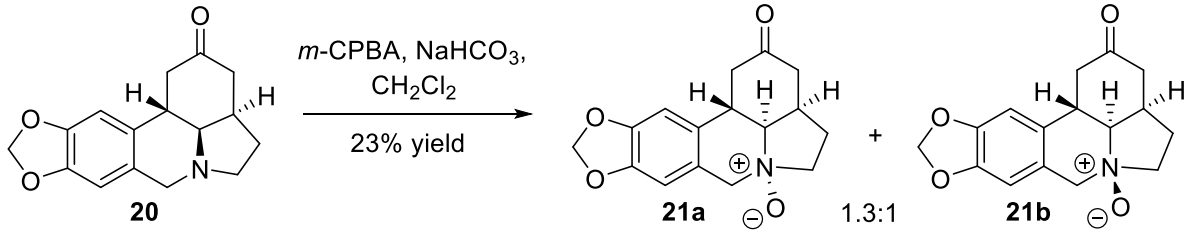
Ketone **44** (706 mg, 2.16 mmol, 1.0 equiv) was dissolved in glacial acetic acid (78 mL, 0.03 M) in a 250 mL round bottom flask. Unactivated Zn dust (3.26 g, 49.9 mmol, 23 equiv) was added, and the mixture was heated to 120 °C for 4 h. The reaction mixture was then cooled and filtered through celite, washing with water and $CHCl_3$. Saturated aqueous $NaHCO_3$ and solid $NaHCO_3$ was added until gas evolution ceased, and pH of the aqueous layer was 8–9. The layers were separated, and the aqueous layer was extracted three times with $CHCl_3$. The combined organic layers were dried over $MgSO_4$, filtered and conc. Purification by column chromatography (2–5% MeOH in $CHCl_3$) afforded **20** as a white solid (331 mg, 57% yield).

*Note: Upon treatment with CD_3OD, exchange of deuterium at the α-position(s) is observed (time-dependent).

^{1}H NMR (600 MHz, DMSO-d_6) δ 6.74 (s, 1H), 6.68 (s, 1H), 5.90 (dd, *J* = 8.1, 1.1 Hz, 2H), 3.92 (d, *J* = 14.3 Hz, 1H), 3.62 (d, *J* = 13.7 Hz, 1H), 3.12 (ddd, *J* = 14.0, 8.1, 4.1 Hz, 1H), 2.94 (ddd, *J* = 8.7, 6.3, 2.4 Hz, 1H), 2.89 (dd, *J* = 18.2, 4.1 Hz, 1H), 2.55–2.43 (m, 1H), 2.43–2.33 (m, 3H), 2.29 (dd, *J* = 14.1, 5.6 Hz, 1H), 2.04 (dddd, *J* = 13.2, 7.7, 5.3, 2.4 Hz, 1H), 1.93 (dd, *J* = 18.2, 13.7 Hz, 1H), 1.51 (ddt, *J* = 11.9, 9.5, 6.8 Hz, 1H).

^{13}C NMR (151 MHz, DMSO-d_6) δ 211.6, 145.7, 145.3, 132.3, 129.0, 106.9, 105.4, 100.6, 64.0, 55.1, 52.7, 43.7, 39.0, 35.7, 32.6, 32.1.

HRMS (*m*/*z*) [M + H]+ calcd for $C_{16}H_{18}NO_3$, 272.1281; found, 272.1282.



In a 20 mL vial equipped with a septum, **20** (150 mg, 0.55 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (11 mL, 0.05 M), sodium bicarbonate (279 mg, 3.32 mmol, 6 equiv) was added, and the mixture was cooled to 0 °C. Next, *m*-CPBA (310 mg, 1.38 mmol, 2.5 equiv) was added and stirred at 0 °C for 3.5 hr. The solvent was removed by vacuum and the resulting crude mixture was purified by preparatory HPLC (C18 20x250mm, 10–100% ACN in H_2O) to afford **21a** as a white solid (21 mg, 13%) and **21b** as a white solid (16 mg, 10%).

(3aR,3a1R,6R,12bS)-2-oxo-2,3,3a,3a1,4,5,7,12b-octahydro-[1,3]dioxolo[4,5-j]pyrrolo[3,2,1-de]phenanthridine 6(1H)-oxide (**21a**)

^{1}H NMR (500 MHz, 3:1 $CDCl_3/CD_3OD$) δ 6.89 (s, 1H), 6.65 (s, 1H), 5.98 (s, 2H), 4.52 (d, *J* = 13.8 Hz, 1H), 4.44 (d, *J* = 13.7 Hz, 1H), 3.87–3.62 (m, 2H), 3.33 (s, 1H), 3.09 (td, *J* = 12.8, 4.5 Hz, 2H), 2.97 (dd, *J* = 18.0, 4.2 Hz, 1H), 2.78 (dtd, *J* = 13.5, 8.9, 7.2 Hz, 1H), 2.69–2.51 (m, 2H), 2.38 (dd, *J* = 18.0, 13.4 Hz, 1H), 1.90 (ddd, *J* = 10.8, 5.2, 5.2 Hz, 1H).

^{13}C NMR (126 MHz, 3:1 $CDCl_3/CD_3OD$) δ 208.1, 148.3, 146.6, 130.9, 123.3, 108.9, 103.8, 101.2, 82.2, 68.4, 68.0, 41.2, 38.1, 34.1, 31.8, 30.1.

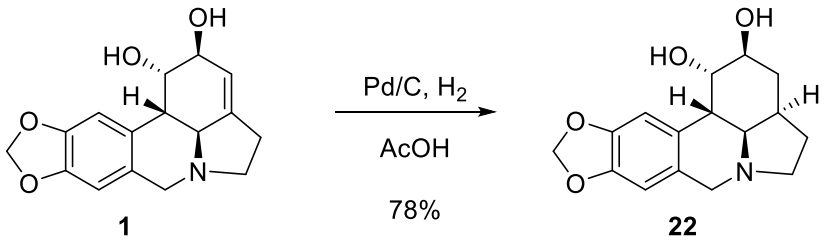
HRMS (*m*/*z*) [M + H]+ calcd for $C_{16}H_{18}NO_4$, 288.1230; found, 288.1225.

(3aR,3a1R,6S,12bS)-2-oxo-2,3,3a,3a1,4,5,7,12b-octahydro-[1,3]dioxolo[4,5-j]pyrrolo[3,2,1-de]phenanthridine 6(1H)-oxide (**21b**)

^{1}H NMR (500 MHz, 3:1 $CDCl_3/CD_3OD$) δ 6.70 (s, 1H), 6.59 (s, 1H), 5.94 (d, *J* = 2.3 Hz, 2H), 4.71–4.50 (m, 2H), 4.30–4.18 (m, 1H), 3.85 (dd, *J* = 10.3, 6.3 Hz, 1H), 3.55 (td, *J* = 11.3, 4.6 Hz, 1H), 3.45 (ddd, *J* = 12.7, 10.2, 6.1 Hz, 1H), 3.08 (dd, *J* = 18.3, 4.5 Hz, 1H), 2.82–2.69 (m, 1H), 2.60 (ddq, *J* = 13.2, 8.0, 2.4 Hz, 1H), 2.57–2.50 (m, 1H), 2.46 (ddt, *J* = 12.7, 8.1, 6.3 Hz, 1H), 2.37 (ddd, *J* = 12.8, 8.7, 6.1 Hz, 1H), 2.22 (dd, *J* = 18.3, 14.7 Hz, 1H).

^{13}C NMR (126 MHz, 3:1 $CDCl_3/CD_3OD$) δ 210.7, 147.6, 147.2, 129.8, 123.0, 107.4, 105.1, 101.7, 75.4, 69.1, 68.3, 43.7, 37.7, 30.8, 30.0, 29.9.

HRMS (*m*/*z*) [M + H]+ calcd for $C_{16}H_{18}NO_4$, 288.1230; found, 288.1248.



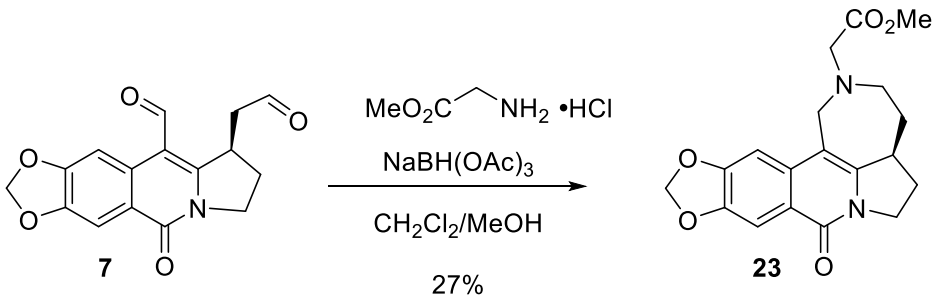
Dihydrolycorine (**22**)

In a high-pressure reactor, lycorine (507 mg, 1.76 mmol, 1.0 equiv) was dissolved in acetic acid (6 mL, 0.3 M). Pd/C (5% by weight, 120 mg) was added, the reactor was flushed with N_2, and then charged with H_2 (300 psi). The reaction was stirred at room temperature for 20 h, flushed with N_2 again, and filtered through a pad of celite, washing with MeOH. The filtrate was concentrated under vacuum to yield **22**•4AcOH (854 mg, 91%), which could be used for diol cleavage reaction without further purification. To isolate the free base of **22**, **22**•2AcOH (530 mg, 1.3 mmol) was dissolved in H_2O (15 mL). Upon addition of saturated aqueous ammonium hydroxide (17 mL), white crystals precipitated, which after filtration and drying yielded **22** (320 mg, 86% recovery, 78% overall yield).

^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 6.81 (s, 1H), 6.65 (s, 1H), 5.93 (s, 2H), 4.79 (d, *J* = 4.1 Hz, 1H, –O**H**), 4.66 (d, *J* = 4.8 Hz, 1H, –O**H**), 4.19 (dt, *J* = 4.7, 2.3 Hz, 1H), 3.81 (d, *J* = 15.0 Hz, 1H), 3.72–3.65 (m, 2H), 2.81 (td, *J* = 8.4, 2.8 Hz, 1H), 2.70 (d, *J* = 11.0 Hz, 1H), 2.58–2.51 (m, 2H), 2.16 (td, *J* = 8.8, 5.8 Hz, 1H), 1.96–1.86 (m, 2H), 1.68 (dq, *J* = 12.0, 8.6 Hz, 1H), 1.37 (ddd, *J* = 13.4, 8.8, 7.6 Hz, 1H).

^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ 145.8, 145.3, 131.8, 130.0, 107.0, 106.0, 100.8, 74.2, 71.2, 59.0, 54.9, 53.5, 36.7, 34.0, 33.4, 31.0.

HRMS (*m*/*z*) [M + H]+ calcd for $C_{16}H_{20}NO_4$, 290.1387; found, 290.1391.



Methyl(S)-2-(8-oxo-3,4,4a,5,6,8-hexahydro-[1,3]dioxolo[4',5':4,5]benzo[1,2-f]azepino [3,4,5-hi]indolizin-2(1H)-yl)acetate (**23**)

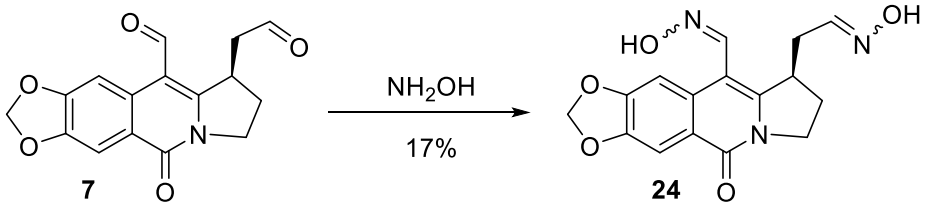
Dialdehyde **7** (104 mg, 0.35 mmol, 1.0 equiv) was dissolved in a 4:1 mixture of CH_2Cl_2/MeOH (7 mL, 0.05 M) in a 20 mL vial. Glycine methyl ester hydrochloride (57 mg,

0.45 mmol, 1.3 equiv) was added, followed by sodium triacetoxyborohydride (368 mg, 1.7 mmol, 5.0 equiv). The reaction mixture was stirred at room temperature for 14 h, before being quenched by the addition of saturated aqueous $NaHCO_3$. CH_3Cl was also added, and the aqueous layer was extracted twice with $CHCl_3$. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Silica gel column chromatography (2–5% MeOH in $CHCl_3$) provided **23** as an orange oil (33.2 mg, 27% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (s, 1H), 6.95 (s, 1H), 6.03 (s, 2H), 4.37 (ddd, *J* = 12.1, 9.3, 2.6 Hz, 1H), 4.24 (d, *J* = 15.7 Hz, 1H), 4.04–3.84 (m, 2H), 3.71 (s, 3H), 3.59 (dt, *J* = 14.5, 9.0 Hz, 1H), 3.42 (d, *J* = 4.2 Hz, 2H), 3.17 (dt, *J* = 13.0, 4.0 Hz, 1H), 3.14–3.04 (m, 1H), 2.43 (dddd, *J* = 12.8, 8.8, 7.8, 2.6 Hz, 1H), 1.89–1.74 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.6, 159.9, 152.1, 146.7, 144.9, 134.7, 120.3, 108.5, 105.6, 101.7, 99.9, 51.8, 51.2, 47.3, 43.2, 41.3, 31.7, 29.2, 23.0.

HRMS (*m*/*z*) [M + H]+ calcd for $C_{19}H_{21}N_2O_5$, 357.1445; found, 357.1447.



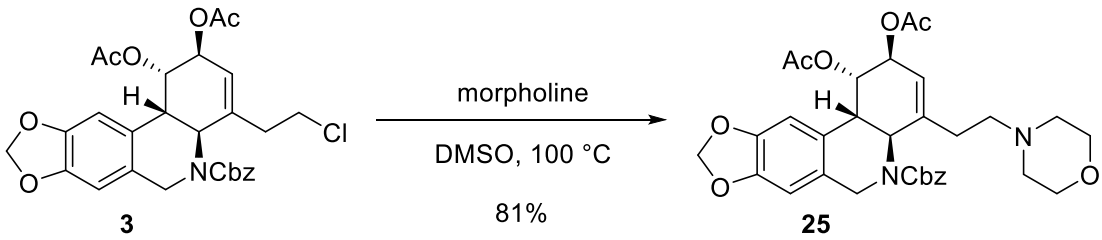
(R)-2-(10-((hydroxyimino)methyl)-5-oxo-5,7,8,9-tetrahydro-[1,3]dioxolo[4,5-g]pyrrolo[1,2-b]isoquinolin-9-yl)acetaldehyde oxime (**24**)

In a 50 mL flask equipped with a reflux condenser, dialdehyde **7** (103 mg, 0.34 mmol, 1.0 equiv) was dissolved in EtOH (6.9 mL, 0.05 M). Sodium acetate (226 mg, 2.76 mmol, 8.0 equiv) and hydroxylamine hydrochloride (192 mg, 2.76 mmol, 8.0 equiv) were added, and the reaction was heated to 75 °C for 2.25 hr. The reaction mixture was then cooled to room temperature, and saturated aqueous $NaHCO_3$ and $CHCl_3$ were added. The layers were separated, and the aqueous layer was extracted twice with $CHCl_3$. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Silica gel column chromatography (5–10% MeOH in $CHCl_3$) afforded **24** as a mixture of (*E*)- and (*Z*)-oxime isomers as a white solid (19.7 mg, 17%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.47/11.13/11.11/11.06/10.96/10.63 (s, 2H), 8.38/8.34/8.25/8.19 (s, 1H), 7.68/7.58/7.53 (s, 1H), 7.38/7.29 (t, *J* = 5.9 Hz, 1H), 6.84/6.72 (t, *J* = 5.3 Hz, 1H), 6.18/6.16 (s, 2H), 4.23 (dt, *J* = 12.4, 8.9 Hz, 1H), 4.13–3.99 (m 1H), 3.97–3.88 (m, 1H), 2.57 (ddd, *J* = 16.1, 10.6, 5.8 Hz, 1H), 2.47–2.36 (m, 1H), 2.31–2.19 (m, 1H), 2.00 (ddd, *J* = 20.1, 12.9, 6.8 Hz, 1H).

^{13}C NMR (151 MHz, DMSO-d_6) δ 159.0, 152.3, 152.2, 149.0, 148.7, 147.8, 147.5, 147.2, 147.2, 146.5, 146.2, 132.5, 132.5, 120.71, 120.66, 104.55, 104.53, 104.3, 104.1, 103.6, 103.5, 102.6, 47.0, 33.5, 29.0, 26.7, 26.1.

HRMS (*m*/*z*) [M + H]+ calcd for $C_{16}H_{16}N_3O_5$, 330.1084; found, 330.1097.



3 **25**

(1S,2S,4aS,11bS)-5-((benzyloxy)carbonyl)-4-(2-morpholinoethyl)-1,2,4a,5,6,11b-hexahydro-[1,3]dioxolo[4,5-j]phenanthridine-1,2-diyl diacetate (**25**)

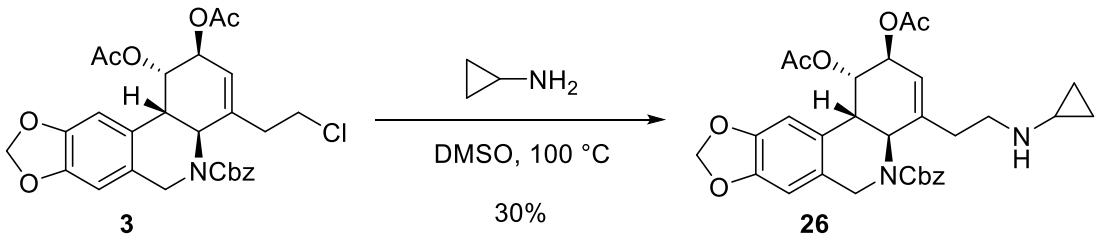
In a 20 mL vial **3** (129 mg, 0.24 mmol, 1.0 equiv) was dissolved in DMSO (4.8 mL, 0.05 M), and morpholine (0.21 mL, 240 mmol, 10 equiv) was then added. The solution was heated to 100 °C for 16 hr. After cooling to room temperature, saturated sodium bicarbonate, water, and $CHCl_3$ were added, and the layers separated. The aqueous layer was extracted with $CHCl_3$ five times, and the combined organic layers were dried over $MgSO_4$, filtered and concentrated. Purification by silica gel column chromatography (0–5% MeOH in $CHCl_3$) afforded **25** as a white foam (114 mg, 81%).

Note: The carbamate protecting group results in rotamers, which coalesce at 100 °C, but not sufficiently to resolve all of the ^{13}C signals. Therefore, the cooled spectrum of the same sample at –30 °C (resulting in rotameric products) is reported below. Poor solubility of **25** in toluene at lower temperatures necessitated the change in solvents.

^1H NMR (600 MHz, Toluene-d_8, 100 °C) δ 7.13–6.91 (m, 5H), 6.80 (s, 1H), 6.45–6.20 (m, 1H), 5.87 (s, 1H), 5.69 (s, 1H), 5.34 (dd, *J* = 14.6, 1.6 Hz, 2H), 5.31 (s, 1H), 5.01–4.87 (m, 2H), 4.19 (bs, 2H), 3.50 (t, *J* = 4.6 Hz, 4H), 2.48–2.24 (m, 5H), 2.19 (dd, *J* = 6.0, 3.4 Hz, 4H), 2.08 (dq, *J* = 4.5, 2.0 Hz, 1H), 1.69 (s, 3H), 1.47 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$, –30 °C) δ 170.5, 170.33, 170.28, 170.2, 157.0, 155.7, 146.91, 146.85, 146.4, 146.2, 143.90, 143.85, 136.1, 135.3, 128.7, 128.6, 128.4, 128.3, 128.2, 128.1, 128.0, 127.7, 127.0, 126.7, 116.5, 115.8, 106.6, 106.2, 105.7, 105.3, 101.3, 101.2, 69.3, 68.9, 68.4, 67.2, 67.03, 66.95, 66.8, 57.4, 57.1, 56.42, 56.38, 53.69, 53.66, 51.3, 50.9, 36.4, 35.3, 30.3, 30.1, 21.6, 21.5, 21.4, 21.25, 21.15.

HRMS (*m*/*z*) [M + H]+ calcd for $C_{32}H_{37}N_2O_9$, 593.2494; found, 593.2485.



3 **26**

(1S,2S,4aS,11bS)-5-((benzyloxy)carbonyl)-4-(2-(cyclopropylamino)ethyl)-1,2,4a,5,6,11b-hexahydro-[1,3]dioxolo[4,5-j]phenanthridine-1,2-diyl diacetate (**26**)

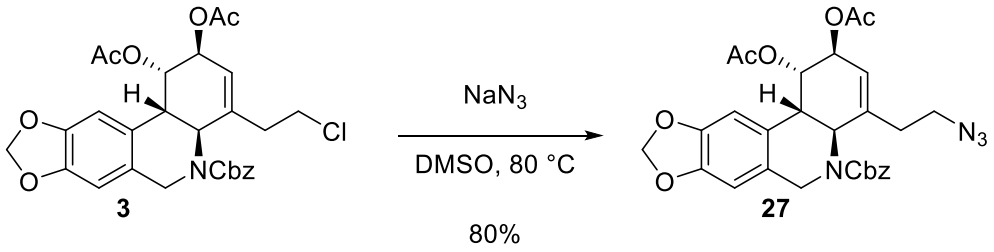
In a 20 mL vial **3** (102 mg, 0.19 mmol, 1.0 equiv) was dissolved in DMSO (3.8 mL, 0.05 M), and morpholine (0.13 mL, 190 mmol, 10 equiv) was then added. The solution was heated to 100 °C for 16 hr. After cooling to room temperature, saturated sodium bicarbonate, water, and $CHCl_3$ were added, and the layers separated. The aqueous layer was extracted with $CHCl_3$ five times, and the combined organic layers were dried over $MgSO_4$, filtered and concentrated. Purification by silica gel column chromatography (0–2% MeOH in $CHCl_3$) afforded **26** (31 mg, 30%) as a light yellow solid.

Note: The carbamate protecting group results in rotamers, which coalesce at 100 °C, but not sufficiently to resolve all of the ^{13}C signals. Therefore, the cooled spectrum of the same sample at –30 °C (resulting in rotameric products) is reported below. Poor solubility of **26** in toluene at lower temperatures necessitated the change in solvents.

^1H NMR (600 MHz, Toluene-d_8, 100 °C) δ 8.03 (s, 1H), 7.11 (d, J = 7.9 Hz, 1H), 7.03–6.98 (m, 2H), 6.98–6.94 (m, 2H), 6.80 (s, 1H), 6.27 (s, 1H), 5.86 (s, 1H), 5.65 (s, 1H), 5.33 (dd, J = 14.4, 1.6 Hz, 2H), 5.28 (s, 1H), 5.05–4.90 (m, 3H), 4.41 (s, 2H), 3.67 (s, 2H), 2.99 (s, 1H), 2.44 (d, J = 58.5 Hz, 2H), 1.87 (s, 1H), 1.68 (s, 3H), 1.56 (s, 3H), 0.58–0.02 (m, 5H).

^{13}C NMR (151 MHz, $CDCl_3$, –30 °C) δ 173.2, 170.6, 170.42, 170.40, 170.2, 164.18, 164.16, 157.25, 157.23, 156.1, 146.83, 146.79, 146.3, 146.2, 142.93, 142.89, 136.1, 135.4, 128.65, 128.62, 128.58, 128.5, 128.43, 128.41, 128.39, 128.3, 128.22, 128.19, 127.99, 127.98, 127.9, 127.54, 127.46, 126.9, 126.6, 118.0, 117.3, 106.9, 106.4, 105.7, 105.4, 101.2, 69.4, 69.0, 68.4, 67.2, 67.0, 66.8, 55.7, 55.5, 51.4, 50.9, 41.5, 41.3, 36.3, 35.2, 31.6, 31.5, 28.4, 25.9, 23.0, 21.64, 21.62, 21.4, 21.1, 21.04, 21.00, 10.4, 7.2, 5.1, 5.0.

HRMS (*m*/*z*) [M + H]+ calcd for $C_{31}H_{35}N_2O_8$, 563.2388; found, 563.2374.



(1S,2S,4aS,11bS)-4-(2-azidoethyl)-5-((benzyloxy)carbonyl)-1,2,4a,5,6,11b-hexahydro-[1,3]dioxolo[4,5-j]phenanthridine-1,2-diyl diacetate (**27**)

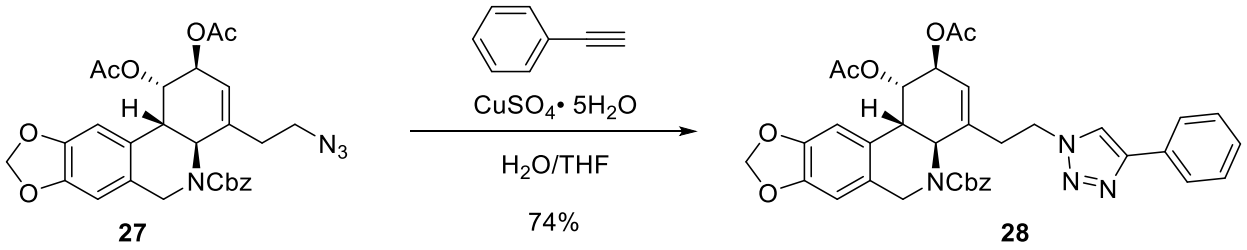
In a 50 mL round bottom flask, **3** (250 mg, 0.461 mmol, 1.0 equiv) was dissolved in DMSO (9.2 mL, 0.05 M). Sodium azide (295 mg, 4.61 mol, 10 equiv) was added and the reaction heated at 80 °C for 16 h. After cooling the reaction to room temperature water and $CHCl_3$ were added and the layers were separated. The aqueous layer was extracted three times with $CHCl_3$ and then the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification by silica gel column chromatography (0–5% MeOH in $CHCl_3$) afforded **27** as a yellow oil (202 mg, 80% yield).

Note: The carbamate protecting group results in rotamers, which coalesce at 100 °C, but not sufficiently to resolve all of the ^{13}C signals. Therefore, the cooled spectrum of the same sample at –40 °C (resulting in rotameric products) is reported below.

^{1}H NMR (600 MHz, Toluene-d_8, 100 °C) δ 7.09–6.96 (m, 5H), 6.95 (s, 1H), 6.78 (s, 1H), 6.26 (bs, 1H), 5.85 (s, 1H), 5.63 (s, 1H), 5.33 (dd, *J* = 14.9, 1.6 Hz, 2H), 5.30 (bs, 1H), 4.92 (dd, *J* = 25.3, 12.5 Hz, 2H), 4.15 (bs, 2H), 3.53 (bs, 1H), 3.13–2.83 (m, 2H), 2.37 (dt, *J* = 13.9, 6.7 Hz, 1H), 2.29–2.16 (m, 1H), 1.68 (s, 3H), 1.48 (s, 3H).

^{13}C NMR (151 MHz, Toluene-d_8, –40 °C) δ 169.8, 169.40, 169.36, 169.3, 168.9, 168.7, 158.0, 156.3, 155.6, 147.2, 147.1, 146.7, 146.5, 146.2, 144.9, 142.4, 142.3, 137.0, 136.3, 135.8, 127.1, 126.8, 125.2, 118.5, 117.9, 106.7, 106.2, 105.5, 105.1, 104.7, 100.83, 100.81, 69.5, 69.0, 67.9, 67.2, 67.1, 66.8, 56.6, 56.0, 53.8, 50.9, 50.5, 49.6, 49.2, 36.5, 35.5, 32.6, 32.4, 20.2, 19.85, 19.81.

HRMS (*m*/*z*) [M + Na]+ calcd for $C_{28}H_{28}N_4O_8Na$, 571.1799; found, 571.1790.



27 **28**

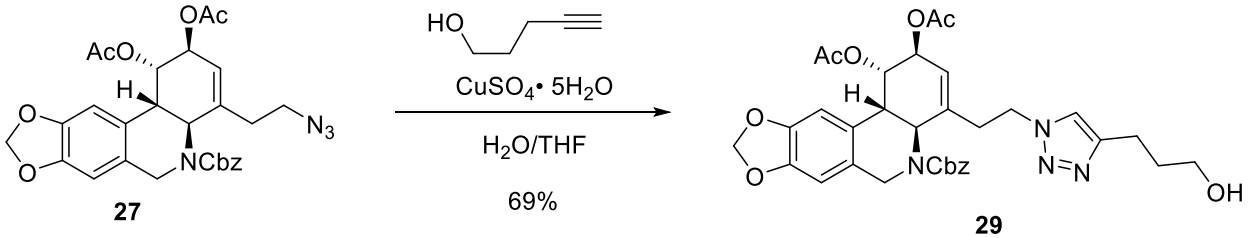
In a 1 dram vial equipped with a septum, **27** (180 mg, 0.33 mmol, 1.0 equiv) was dissolved in a 1:1 H_2O/THF mixture (1 mL, 0.3 M). Phenylacetylene (45 µL, 0.36 mmol, 1.1 equiv), $CuSO_4$•$5H_2O$ (17 mg, 0.066 mmol, 0.2 equiv),and sodium ascorbate (133 mg, 0.66 mmol, 2.0 equiv) were added, and the mixture was stirred at room temperature for 16 h. CH_2Cl_2 and brine were then added, and the layers were separated. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Silica gel column chromatography (0–2% MeOH in $CHCl_3$) afforded **28** as a yellow oil (157 mg, 74%)

Note: The carbamate protecting group results in rotamers, which coalesce at 100 °C, but not sufficiently to resolve all of the ^{13}C signals. Therefore, the cooled spectrum of the same sample at –30 °C (resulting in rotameric products) is reported below. Poor solubility of **28** in toluene at lower temperatures necessitated the change in solvents.

^{1}H NMR (600 MHz, Toluene-d_8,100 °C) δ 7.75 (d, *J* = 8.3 Hz, 1H), 7.16 (t, *J* = 7.7 Hz, 2H), 7.12–6.93 (m, 9H), 6.75 (s, 1H), 6.42–6.20 (m, 1H), 5.79 (s, 1H), 5.51 (s, 1H), 5.32 (dd, *J* = 18.1, 1.5 Hz, 2H), 5.19–5.11 (m, 1H), 4.95 (dd, *J* = 23.8, 12.4 Hz, 2H), 4.23–4.11 (m, 2H), 4.06 (s, 1H), 2.67 (s, 1H), 2.50 (s, 1H), 2.08 (dt, *J* = 4.4, 2.2 Hz, 2H), 1.64 (s, 3H), 1.55 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$, –30 °C) δ 170.60, 170.57, 170.5, 170.4, 170.1, 169.9, 158.3, 157.1, 156.1, 147.82, 147.77, 147.75, 147.0, 146.9, 146.5, 146.3, 141.0, 140.9, 135.9, 135.3, 129.0, 128.75, 128.69, 128.5, 128.43, 128.38, 128.1, 127.84, 127.79, 126.6, 126.3, 125.55, 125.51, 119.6, 119.3, 119.2, 119.0, 118.3, 106.8, 106.7, 106.3, 105.6, 105.3, 104.7, 101.30, 101.28, 69.0, 68.6, 68.5, 68.3, 68.0, 67.4, 66.5, 66.4, 55.8, 55.4, 53.5, 51.3, 50.9, 48.7, 48.3, 39.0, 36.3, 35.2, 34.5, 34.3, 21.5, 21.4, 21.1, 21.00, 20.96, 20.9.

HRMS (*m*/*z*) [M + H]+ calcd for $C_{36}H_{35}N_4O_8$, 651.2449; found, 651.2440.



(1S,2S,4aS,11bS)-5-((benzyloxy)carbonyl)-4-(2-(4-(3-hydroxypropyl)-1H-1,2,3-triazol-1-yl)ethyl)-1,2,4a,5,6,11b-hexahydro-[1,3]dioxolo[4,5-j]phenanthridine-1,2-diyl diacetate (**29**)

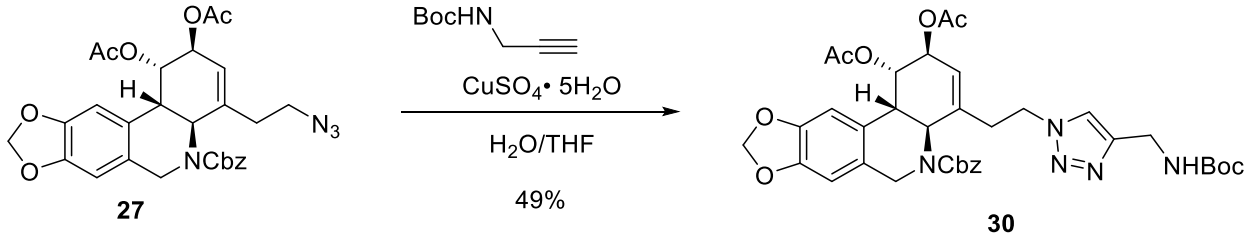
In a 1 dram vial equipped with a septum, **27** (20 mg, 0.037 mmol, 1.0 equiv) was dissolved in a 1:1 H_2O/THF mixture (0.2 mL, 0.3 M). 4-pentyn-1-ol (4 µL, 0.041 mmol, 1.1 equiv), $CuSO_4$•$5H_2O$ (2.2 mg, 0.007 mmol, 0.2 equiv) and sodium ascorbate (18 mg, 0.074 mmol, 2.0 equiv) were added, and the mixture was stirred at room temperature for 16 h. CH_2Cl_2 and brine were then added, and the layers were separated. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Silica gel column chromatography (0–2% MeOH in $CHCl_3$) afforded **29** (16 mg, 69%) as a light yellow solid.

Note: The carbamate protecting group results in rotamers, which coalesce at 100 °C, but not sufficiently to resolve all of the ^{13}C signals. Therefore, the cooled spectrum of the same sample at –30 °C (resulting in rotameric products) is reported below. Poor solubility of **29** in toluene at lower temperatures necessitated the change in solvents.

^{1}H NMR (600 MHz, Toluene-d_8, 100 °C) δ 7.11–6.94 (m, 6H), 6.76 (s, 1H), 6.65 (s, 1H), 6.40–6.26 (m, 1H), 5.78 (s, 1H), 5.40 (s, 1H), 5.34 (d, *J* = 15.4 Hz, 2H), 5.14 (s, 1H), 4.94 (dd, *J* = 24.4, 12.5 Hz, 2H), 4.14 (dt, *J* = 14.2, 7.2 Hz, 2H), 3.97 (s, 1H), 3.45 (t, *J* = 6.1 Hz, 2H), 2.64 (t, *J* = 7.2 Hz, 3H), 2.39 (s, 1H), 2.08 (p, *J* = 2.2 Hz, 2H), 1.75 (p, *J* = 6.6 Hz, 2H), 1.68 (s, 3H), 1.67 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$, –30 °C) δ 170.61, 170.55, 170.5, 170.2, 158.4, 157.1, 156.1, 147.6, 147.5, 147.3, 147.2, 147.0, 146.9, 146.5, 146.3, 140.94, 140.90, 135.9, 135.2, 128.8, 128.7, 128.5, 128.4, 128.1, 127.8, 126.6, 126.3, 120.7, 120.5, 118.9, 118.1, 106.7, 106.3, 105.6, 105.3, 101.3, 69.1, 68.7, 68.5, 67.4, 66.6, 66.4, 61.58, 61.56, 55.6, 55.3, 51.3, 50.9, 48.4, 48.1, 40.8, 39.0, 36.3, 35.2, 34.4, 31.6, 22.10, 22.07, 21.6, 21.2, 21.12, 21.09.

HRMS (*m*/*z*) [M + H]+ calcd for $C_{33}H_{37}N_4O_9$, 633.2555; found, 633.2571.



27 **30**

(1S,2S,4aS,11bS)-5-((benzyloxy)carbonyl)-4-(2-(4-(((tert-butoxycarbonyl)amino)methyl)-1H-1,2,3-triazol-1-yl)ethyl)-1,2,4a,5,6,11b-hexahydro-[1,3]dioxolo[4,5-j]phenanthridine-1,2-diyl diacetate (**30**)

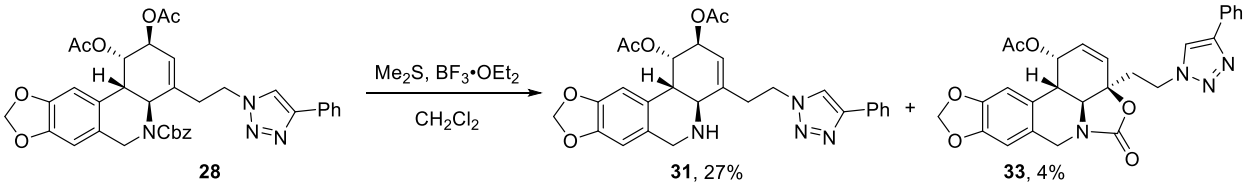
In a 20 mL vial equipped with a septum, **27** (260 mg, 0.474 mmol, 1.0 equiv) was dissolved in a 1:1 H_2O/THF mixture (1.6 mL, 0.3 M). *N*-Boc-propargylamine (82 mg, 0.521 mmol, 1.1 equiv), $CuSO_4$•$5H_2O$ (25 mg, 0.095 mmol, 0.2 equiv) and sodium ascorbate (190 mg, 0.95 mmol, 2.0 equiv) were added, and the mixture was stirred at room temperature for 16 h. CH_2Cl_2 and brine were then added, and the layers were separated. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Silica gel column chromatography (0–5% MeOH in $CHCl_3$) afforded **30** as a white solid (258 mg, 89% purity by LC-MS analysis, 69%). Further purification for biological testing was carried out by preparatory HPLC on 86 mg of the above material ((C18 20x250mm, 10–100% ACN in H_2O)), to yield 55 mg analytically pure **30** as a white solid (49% yield overall).

Note: The carbamate protecting group results in rotamers, which coalesce at 100 °C, but not sufficiently to resolve all of the ^{13}C signals. Therefore, the cooled spectrum of the same sample at –30 °C (resulting in rotameric products) is reported below. Poor solubility of **30** in toluene at lower temperatures necessitated the change in solvents.

^1H NMR (600 MHz, Toluene-d_8, 100 °C) δ 7.11–6.94 (m, 6H), 6.87 (s, 1H), 6.77 (s, 1H), 6.29 (s, 1H), 5.80 (s, 1H), 5.40 (s, 1H), 5.33 (d, *J* = 14.5 Hz, 2H), 5.15 (s, 1H), 4.95 (dd, *J* = 22.1, 12.5 Hz, 2H), 4.63 (s, 1H), 4.22–4.15 (m, 3H), 4.06 (dt, *J* = 13.9, 7.2 Hz, 1H), 3.96 (s, 1H), 3.51 (s, 1H), 2.58 (s, 1H), 2.39 (s, 1H), 1.69 (s, 3H), 1.65 (s, 3H), 1.39 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$, –30 °C) δ 170.6, 170.52, 170.46, 170.4, 170.1, 170.0, 157.0, 156.1, 155.88, 155.86, 147.0, 146.9, 146.5, 146.3, 145.6, 145.5, 141.0, 140.9, 136.0, 135.9, 135.2, 128.75, 128.68, 128.53, 128.46, 128.4, 128.1, 128.0, 127.9, 127.83, 127.81, 126.6, 126.3, 121.7, 121.6, 118.8, 118.1, 106.7, 106.3, 105.6, 105.3, 101.30, 101.28, 79.97, 79.96, 69.0, 68.6, 68.5, 68.2, 68.1, 68.0, 67.5, 66.4, 66.3, 55.8, 55.5, 53.4, 51.3, 50.9, 49.5, 48.6, 48.2, 45.5, 39.0, 36.3, 36.03, 35.98, 35.2, 34.5, 34.4, 34.2, 28.4, 21.5, 21.4, 21.3, 21.2, 21.14, 21.12.

HRMS (*m*/*z*) [M + H]+ calcd for $C_{36}H_{42}N_5O_{10}$, 704.2926; found, 704.2926.



In a one-dram vial equipped with a septum, under inert atmosphere **28** (100 mg, 0.154 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (2.2 mL, 0.07 M) and Me_2S (0.28 mL, 3.85 mmol, 25 equiv) was added. Next, boron trifluoride diethyl etherate (0.19 mL, 1.54 mmol, 10 equiv) was added and the resulting mixture was stirred for 2 hr before saturated sodium bicarbonate (1 mL) was added to quench the reaction stirring for 10 minutes. Next, CH_2Cl_2 and saturated sodium bicarbonate were added, the layers separated, and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The resulting crude product was then purified by preparatory HPLC (C18 10x250mm, 10–100% [ACN with 0.1% formic acid] in [H_2O with 0.1% formic acid]) to afford **31** (21.5 mg, 27%) as a colorless oil and **33** (3.3 mg, 4%) as a white solid.

(1S,2S,4aS,11bS)-4-(2-(4-phenyl-1H-1,2,3-triazol-1-yl)ethyl)-1,2,4a,5,6,11b-hexahydro-[1,3]dioxolo[4,5-j]phenanthridine-1,2-diyl diacetate (**31**)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.81–7.75 (m, 2H), 7.40 (dd, *J* = 8.4, 6.9 Hz, 2H), 7.32 (dd, *J* = 7.4, 7.3 Hz, 1H), 6.73 (s, 1H), 6.52 (s, 1H), 5.92 (d, *J* = 1.4 Hz, 2H), 5.65–5.55 (m, 2H), 4.99–4.93 (m, 1H), 4.72–4.62 (m, 2H), 4.23 (d, *J* = 16.5 Hz, 1H), 4.14 (d, *J* = 16.1 Hz, 1H), 3.67 (d, *J* = 10.2 Hz, 1H), 3.13–3.07 (m, 2H), 2.82 (dt, *J* = 14.6, 7.2 Hz, 1H), 1.95 (s, 3H), 1.91 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.0, 169.5, 147.8, 146.9, 146.7, 140.7, 130.4, 128.9, 128.2, 127.5, 125.9, 125.7, 122.7, 119.6, 106.1, 104.9, 101.0, 68.3, 66.9, 53.0, 48.7, 48.4, 39.4, 34.1, 20.8, 20.7.

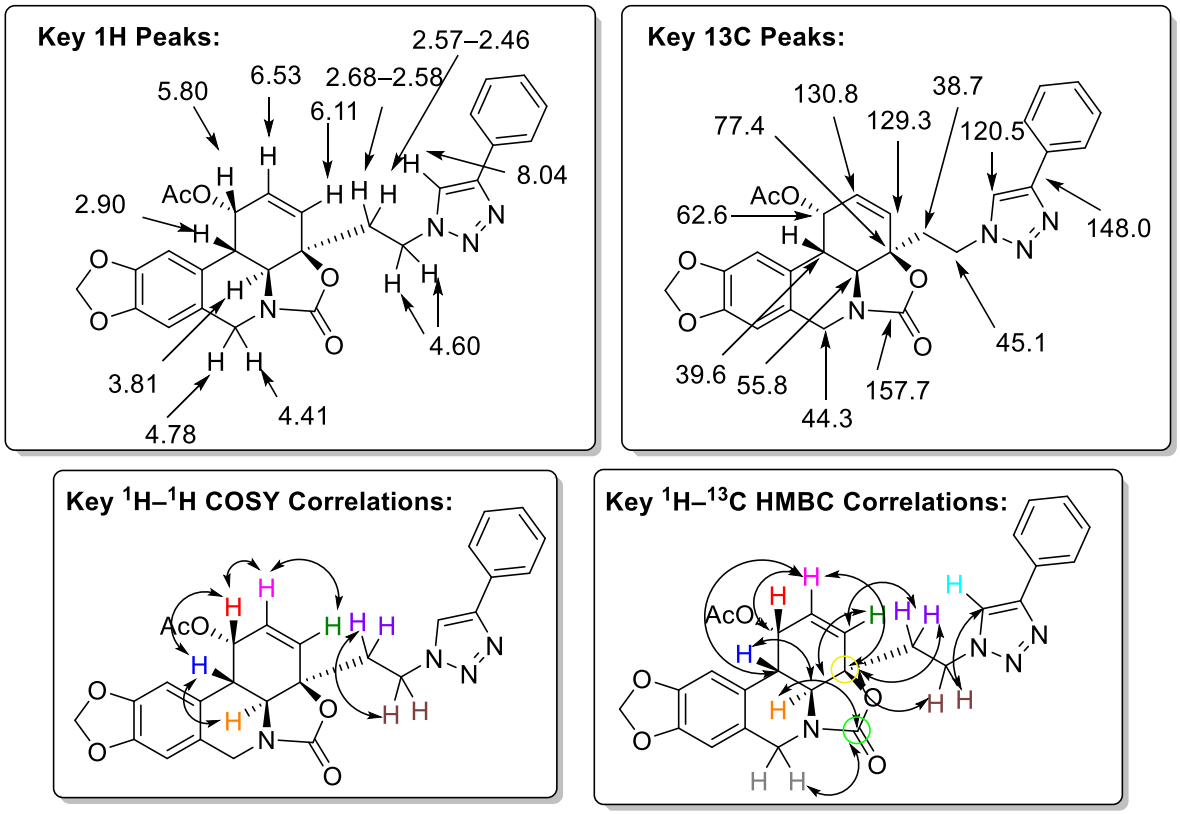
HRMS (*m*/*z*) [M + H]+ calcd for $C_{28}H_{29}N_4O_6$, 517.2082; found, 517.2083.

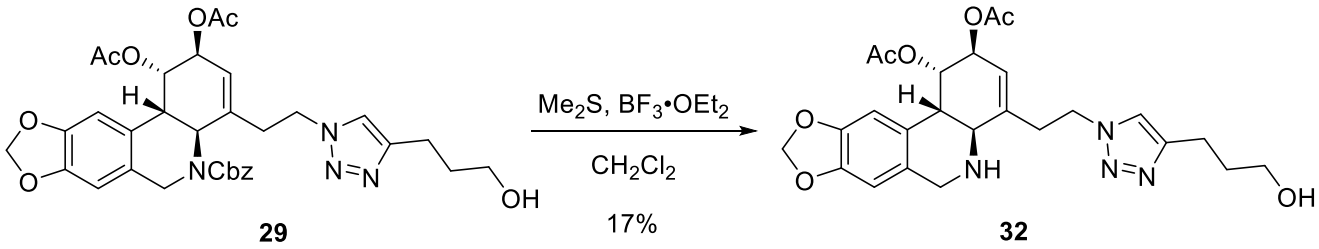
(1R,3aR,3a1S,12bS)-5-oxo-3a-(2-(4-phenyl-1H-1,2,3-triazol-1-yl)ethyl)-3a,3a1,7,12b-tetrahydro-1H,5H-[1,3]dioxolo[4,5-j]oxazolo[5,4,3-de]phenanthridin-1-yl acetate (**33**)

^{1}H NMR (500 MHz, 3:1 $CDCl_3$/CD_3OD) δ 8.04 (s, 1H), 7.78–7.74 (m, 2H), 7.43–7.39 (m, 2H), 7.36–7.30 (m, 1H), 6.66 (s, 1H), 6.57 (s, 1H), 6.53 (dd, *J* = 9.9, 6.2 Hz, 1H), 6.11 (d, *J* = 9.9 Hz, 1H), 5.95 (dd, *J* = 11.1, 1.3 Hz, 2H), 5.80 (dd, *J* = 6.3, 2.4 Hz, 1H), 4.78 (d, *J* = 16.6 Hz, 1H), 4.60 (dd, *J* = 8.5, 7.3 Hz, 2H), 4.41 (d, *J* = 16.5 Hz, 1H), 3.81 (d, *J* = 10.7 Hz, 1H), 2.90 (ddd, *J* = 10.7, 2.2, 1.2 Hz, 1H), 2.68–2.58 (m, 1H), 2.57–2.46 (m, 1H), 2.01 (s, 3H).

^{13}C NMR (126 MHz, 3:1 $CDCl_3$/CD_3OD) δ 170.8, 157.7, 148.0, 147.213, 147.210, 130.8, 129.9, 129.3, 128.9, 128.4, 125.6, 125.4, 124.8, 120.5, 106.8, 104.7, 101.3, 77.4, 62.6, 55.8, 45.1, 44.3, 39.6, 38.7, 20.4.

HRMS (*m*/*z*) [M + H]+ calcd for $C_{27}H_{25}N_4O_6$, 501.1769; found, 501.1755.





29 **32**

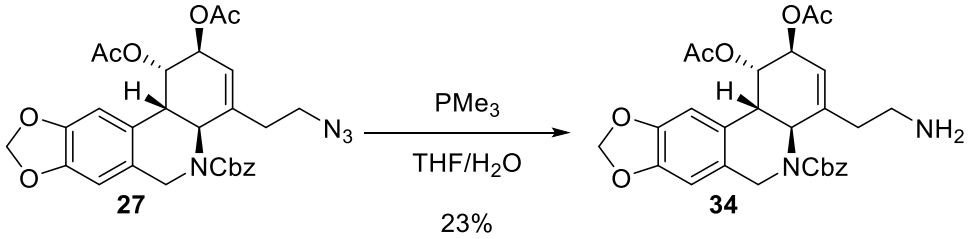
(1S,2S,4aS,11bS)-4-(2-(4-(3-hydroxypropyl)-1H-1,2,3-triazol-1-yl)ethyl)-1,2,4a,5,6,11b-hexahydro-[1,3]dioxolo[4,5-j]phenanthridine-1,2-diyl diacetate (**32**)

In a one-dram vial equipped with a septum, under inert atmosphere **29** (60 mg, 0.095 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (1.4 mL, 0.07 M) and Me_2S (0.18 mL, 2.45 mmol, 25 equiv) was added. Next, boron trifluoride diethyl etherate (0.11 mL, 0.89 mmol, 10 equiv) was added and the resulting mixture was stirred for 2 hr before saturated sodium bicarbonate (1 mL) was added to quench the reaction stirring for 10 minutes. Next, CH_2Cl_2 and saturated sodium bicarbonate were added, the layers separated, and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The resulting crude product was then purified by preparatory HPLC (C18 20x250mm, 10–100% ACN in H_2O) to afford **32** (8.1 mg, 17%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (bs, 1H), 7.37 (s, 1H), 6.74 (s, 1H), 6.54 (s, 1H), 5.93 (d, *J* = 1.8 Hz, 2H), 5.64 (s, 1H), 5.56 (s, 1H), 4.98 (s, 1H), 4.65–4.49 (m, 2H), 4.22 (d, *J* = 16.5 Hz, 1H), 4.14 (d, *J* = 16.8 Hz, 1H), 3.66 (d, *J* = 10.1 Hz, 3H), 3.21–2.97 (m, 2H), 2.82 (t, *J* = 7.1 Hz, 2H), 2.71 (dt, *J* = 15.1, 7.5 Hz, 1H), 2.07 (s, 3H), 1.98 (s, 3H), 1.91 (t, *J* = 6.5 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.0, 169.7, 147.5, 146.9, 146.7, 141.1, 127.7, 126.0, 122.2, 120.9, 106.1, 104.9, 101.1, 68.4, 67.1, 61.6, 52.9, 48.6, 48.5, 39.5, 34.1, 31.7, 22.0, 21.0, 20.8.

HRMS (*m*/*z*) [M + H]+ calcd for $C_{25}H_{31}N_4O_7$, 499.2187; found, 499.2195.



(1S,2S,4aS,11bS)-4-(2-aminoethyl)-5-((benzyloxy)carbonyl)-1,2,4a,5,6,11b-hexahydro-[1,3]dioxolo[4,5-j]phenanthridine-1,2-diyl diacetate (**34**)

In a 50 mL flask under N_2, **27** (167 mg, 0.30 mmol, 1.0 equiv) was dissolved in a 1M solution of trimethyl phosphine in THF (6.1 mL, 6.1 mmol, 10 equiv) and stirred for one hour at room temperature. Deionized water (55 µL, 3.1 mmol, 10 equiv) was added, and the reaction mixture was stirred for 16 hr at room temperature, before being concentrated under a stream of air (caution: stench). Purification by preparatory HPLC (C18 10x250mm, 10–100% [ACN with 0.1% formic acid] in [H_2O with 0.1% formic acid]) afforded **34** as a yellow oil (37 mg, 23%).

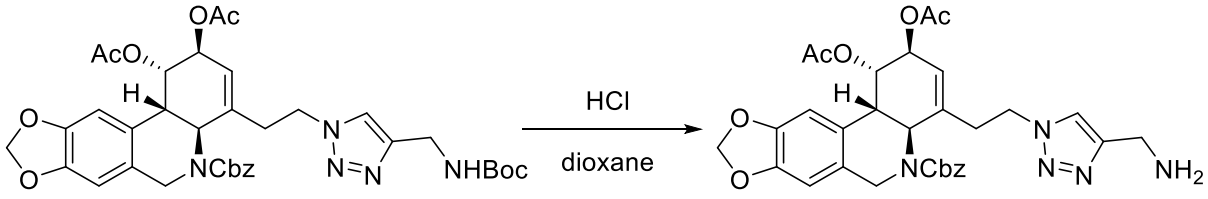
Note: The carbamate protecting group results in rotamers, which coalesce at 100 °C, but not sufficiently to resolve all of the ^{13}C signals. Therefore, the cooled spectrum of the same sample at –30 °C (resulting in rotameric products) is reported below. Poor solubility of **34** in toluene at lower temperatures necessitated the change in solvents.

^{1}H NMR (600 MHz, Toluene-d_8, 100 °C) δ 7.19–6.90 (m, 5H), 6.78 (s, 1H), 6.31 (s, 1H), 5.85 (s, 1H), 5.69 (s, 1H), 5.45–5.24 (m, 3H), 4.99 (dp, *J* = 23.4, 12.5 Hz, 2H), 4.20 (broad s, 5H), 3.58 (s, 1H), 2.82 (s, 2H), 2.46 (s, 1H), 2.31 (s, 1H), 1.71 (s, 3H), 1.53 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$, –30 °C) δ 170.7, 170.52, 170.46, 170.41, 170.35, 170.1, 169.7, 158.4, 157.0, 156.1, 147.2, 147.0, 146.94, 146.87, 146.4, 146.32, 146.30, 146.0, 141.4, 137.7, 135.83, 135.77, 135.3, 131.4, 128.75, 128.72, 128.69, 128.67, 128.64, 128.56, 128.52, 128.47, 128.44, 128.39, 128.35, 128.32, 128.27, 128.1, 128.04, 128.00, 127.96, 127.92, 127.91, 127.88, 127.85, 127.81, 127.76, 127.7, 126.6, 126.4, 117.4, 117.0, 106.8, 106.6, 106.3, 105.6, 105.3, 101.30, 101.26, 101.2, 69.1, 68.8, 68.4, 67.5,

67.4, 66.73, 66.69, 66.5, 56.4, 56.0, 51.2, 50.9, 36.3, 35.4, 23.5, 21.59, 21.55, 21.42, 21.39, 21.20, 21.18, 21.17.

HRMS (*m*/*z*) [M + H]+ calcd for $C_{28}H_{31}N_2O_8$, 523.2075; found, 523.2073.



30 39% **35**

(1S,2S,4aS,11bS)-4-(2-(4-(aminomethyl)-1H-1,2,3-triazol-1-yl)ethyl)-5-((benzyloxy)carbonyl)-1,2,4a,5,6,11b-hexahydro-[1,3]dioxolo[4,5-j]phenanthridine-1,2-diyl diacetate (**35**)

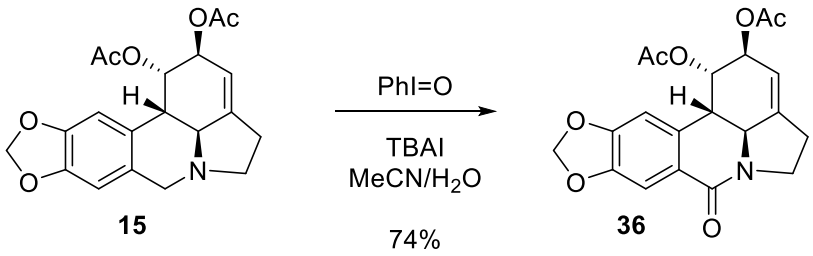
In a 1 dram vial, dissolved **30** (30.2 mg, 0.043 mmol) in a solution of 4N HCl in dioxane (0.4 mL, 0.1 M) and stirred at room temperature for 1.5 hr. Saturated aqueous $NaHCO_3$ was added until the mixture was basified, then $CHCl_3$ was added and the layers were separated. The aqueous layer was extracted twice with $CHCl_3$, and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification by preparatory HPLC (C18 20x250mm, 10–100% ACN in H_2O) afforded **35** as a yellow oil (10.1 mg, 39%).

Note: The carbamate protecting group results in rotamers, which coalesce at 100 °C, but not sufficiently to resolve all of the ^{13}C signals. Therefore, the cooled spectrum of the same sample at –30 °C (resulting in rotameric products) is reported below. Poor solubility of **35** in toluene at lower temperatures necessitated the change in solvents.

^1H NMR (600 MHz, Toluene-d_8, 100 °C) δ 7.11–6.99 (m, 6H), 6.95 (s, 1H), 6.76 (s, 1H), 6.27 (s, 1H), 5.79 (s, 1H), 5.41 (s, 1H), 5.33 (dd, *J* = 16.0, 1.6 Hz, 2H), 5.14 (s, 1H), 4.94 (dd, *J* = 23.8, 12.6 Hz, 2H), 4.20–4.06 (m, 2H), 4.06–3.89 (m, 2H), 3.71 (s, 2H), 3.50 (s, 1H), 2.62 (s, 1H), 2.41 (s, 1H), 1.68 (s, 3H), 1.63 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$ –30 °C) δ 170.55, 170.49, 170.4, 170.1, 169.9, 157.1, 156.1, 149.4, 146.98, 146.92, 146.5, 146.3, 143.8, 141.0, 140.9, 137.8, 135.9, 135.2, 128.8, 128.7, 128.5, 128.4, 128.1, 127.80, 127.77, 126.6, 126.3, 120.5, 120.3, 106.7, 106.3, 105.5, 105.3, 101.31, 101.29, 69.1, 68.7, 68.5, 67.5, 66.5, 66.4, 55.8, 55.4, 51.3, 50.9, 48.5, 48.1, 37.6, 36.3, 35.2, 34.4, 21.6, 21.15, 21.12.

HRMS (*m*/*z*) [M + H]+ calcd for $C_{31}H_{34}N_5O_8$, 604.2402; found, 604.2424.



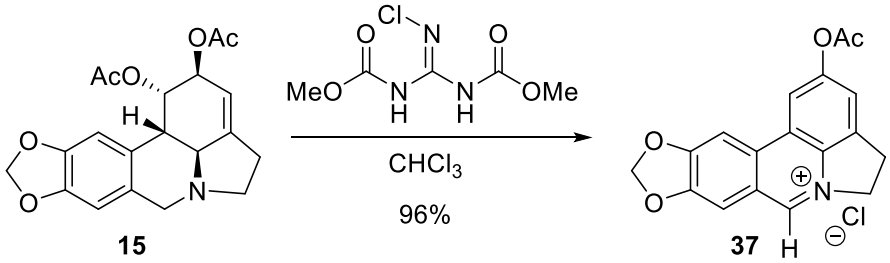
(1S,2S,3a1S,12bS)-7-oxo-2,3a1,4,5,7,12b-hexahydro-1H-[1,3]dioxolo[4,5-j]pyrrolo[3,2,1-de]phenanthridine-1,2-diyl diacetate (**36**)[5]

In a 50 mL round bottom flask, **15** (209 mg, 0.56 mmol, 1.0 equiv) was dissolved in a 9:1 mixture of MeCN/H_2O (11.3 mL, 0.05 M). Freshly prepared iodosobenzene[6] (346 mg, 1.57 mmol, 2.8 equiv) and tetrabutylammonium iodide (42 mg, 0.11 mmol, 0.2 equiv) were added, and the reaction mixture was stirred at room temperature for 3 h. It was then concentrated under vacuum, and redissolved in $CHCl_3$ and saturated aqueous $Na_2S_2O_3$. The layers were separated, and the aqueous layer was extracted three times with $CHCl_3$. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification by silica gel column chromatography (2–5% MeOH in $CHCl_3$) afforded **36** as a light yellow solid (161 mg, 74%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (s, 1H), 6.65 (s, 1H), 5.98 (s, 2H), 5.72 (s, 1H), 5.59 (dt, *J* = 2.3, 1.1 Hz, 1H), 5.26 (dd, *J* = 3.0, 1.5 Hz, 1H), 4.21 (d, *J* = 13.1 Hz, 1H), 3.79 (ddt, *J* = 16.5, 11.9, 7.9 Hz, 2H), 3.02 (ddd, *J* = 12.6, 2.2, 1.1 Hz, 1H), 2.87–2.69 (m, 2H), 2.07 (s, 3H), 2.01 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.9, 169.5, 162.6, 150.8, 147.1, 143.7, 131.9, 126.4, 115.5, 109.0, 103.6, 101.8, 70.3, 67.4, 55.2, 43.6, 40.5, 28.7, 21.1, 20.9.

HRMS (*m*/*z*) [M + H]+ calcd for $C_{20}H_{20}NO_7$, 386.1234; found, 386.1251.



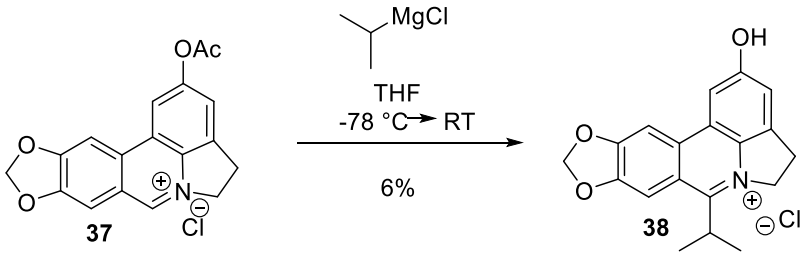
2-(carbamimidoyloxy)-4,5-dihydro-[1,3]dioxolo[4,5-j]pyrrolo[3,2,1-de]phenanthridin-6-ium acetate (**37**)

In a 20 mL screw top vial under air, diacetyl lycorine, **15**, (123 mg, 0.33 mmol, 1.0 equiv) was dissolved in $CHCl_3$ (3.3 mL, 0.1M). 2-Chloro-1,3-bis(methoxycarbonyl)guanidine (Palau'Chlor)[7] (130 mg, 0.62 mmol, 1.8 equiv) was then added, and the reaction was stirred at room temperature for 20 h. It was then concentrated, and the resulting residue was loaded directly onto a silica gel column. Chromatography (10–20% MeOH/$CHCl_3$) afforded **37** as a light yellow solid (109 mg, 96% yield).

^{1}H NMR (500 MHz, 3:1 $CDCl_3/CD_3OD$) δ 9.82 (s, 1H), 7.94 (s, 1H), 7.82 (s, 1H), 7.73 (s, 1H), 7.43 (dd, *J* = 1.5, 1.5 Hz, 1H), 6.23 (s, 2H), 5.25 (t, *J* = 7.0 Hz, 2H), 3.71 (t, 5.4 Hz 2H), 2.27 (s, 3H).

^{13}C NMR (126 MHz, 3:1 $CDCl_3/CD_3OD$) δ 169.4, 157.1, 153.1, 151.1, 145.0, 138.0, 134.3, 132.9, 124.2, 123.1, 121.6, 113.0, 108.4, 104.2, 101.2, 56.2, 27.7, 20.8.

HRMS (*m*/*z*) [M]+ calcd for $C_{18}H_{14}NO_4$, 308.917; found, 308.0915.



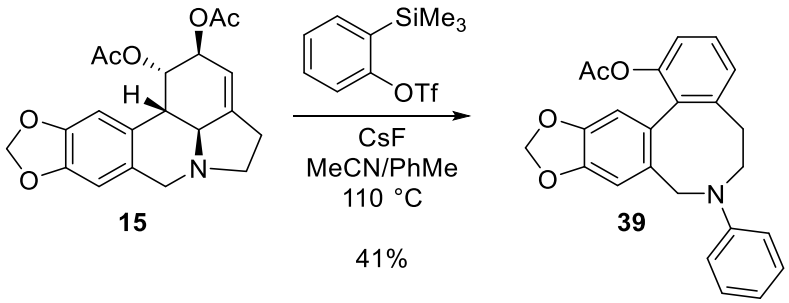
7-isopropyl-4,5-dihydro-7H-[1,3]dioxolo[4,5-j]pyrrolo[3,2,1-de]phenanthridin-2-yl carbamimidate (**38**)

In a 20 mL vial under N_2 **37** (102 mg, 0.297 mmol, 1.0 equiv) was dissolved in tetrahydrofuran (9.9 mL, 0.03 M) and stirred 5 minutes before cooling to –78 °C and adding isopropylmagnesium chloride (1.3 M in THF, 0.9 mL, 4.5 equiv). The solution was stirred 30 minutes at –78 °C before warming to room temperature and stirring 16 hr. The reaction was quenched by the addition of methanol, concentrated under vacuum, and the crude mixture was purified by HPLC to yield **38** (6.2 mg, 6%) as a yellow solid.

^{1}H NMR (500 MHz, 3:1 $CDCl_3/CD_3OD$) δ 7.93 (s, 1H), 7.83 (s, 1H), 7.54 (s, 1H), 7.28 (d, *J* = 1.8 Hz, 1H), 6.29 (s, 2H), 5.18 (s, 2H), 3.89 (s, 1H), 3.70 (t, *J* = 7.1 Hz, 2H), 1.71 (d, *J* = 4.8 Hz, 6H).

^{13}C NMR (151 MHz, 3:1 $CDCl_3/CD_3OD$) δ 160.8, 157.7, 154.9, 150.0, 138.0, 133.3, 130.4, 124.7, 120.8, 117.3, 105.5, 103.9, 103.4, 101.8, 55.9, 32.7, 26.8, 20.9.

HRMS (*m*/*z*) [M]+ calcd for $C_{19}H_{18}NO_3$, 308.1281; found, 308.1288.



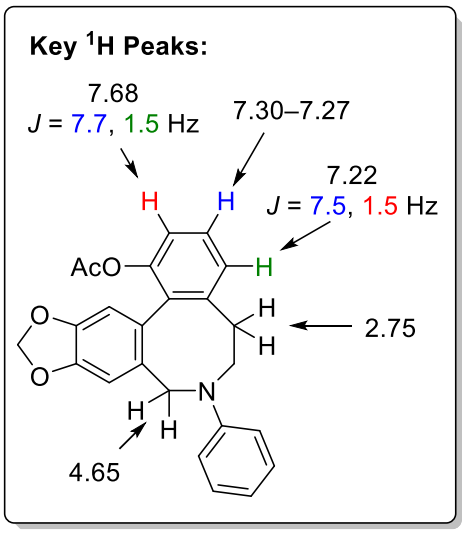
7-phenyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4',5':4,5]benzo[1,2-c]benzo[e]azocin-1-yl acetate (**39**)

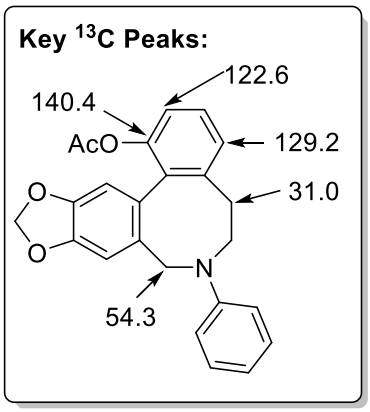
In a sealed test tube, diacetyl lycorine (104 mg, 0.28 mmol, 1.0 equiv) was dissolved in a 3:1 mixture of toluene/acetonitrile (1.35 mL, 0.2 M). 2-(Trimethylsilyl)phenyl trifluoromethanesulfonate (75 µL, 0.31 mmol, 1.1 equiv) was added, followed by CsF (140 mg, 0.92 mmol, 3.3 equiv), and the reaction mixture was heated to 110 °C for 48 h. The reaction was filtered, washing with additional toluene, and concentrated under vacuum. Silica gel column chromatography ($CHCl_3$) afforded **39** (45 mg, 41%) as a yellow oil.

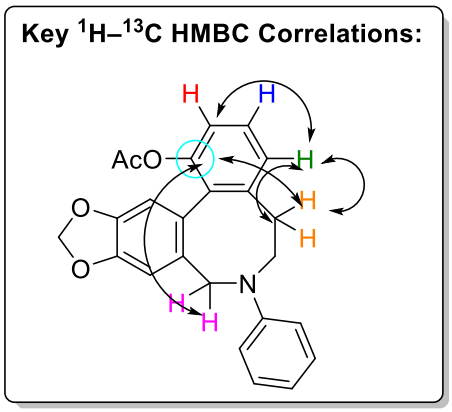
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.30–7.27 (m, 2H), 7.22 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.16 (dd, *J* = 8.5, 7.2 Hz, 2H), 6.90–6.82 (m, 1H), 6.79 (d, *J* = 7.4 Hz, 2H), 6.65 (s, 1H), 5.95 (s, 2H), 4.65 (s, 2H), 4.29 (t, *J* = 7.0 Hz, 2H), 2.75 (t, *J* = 7.0 Hz, 2H), 2.02 (s, 3H).

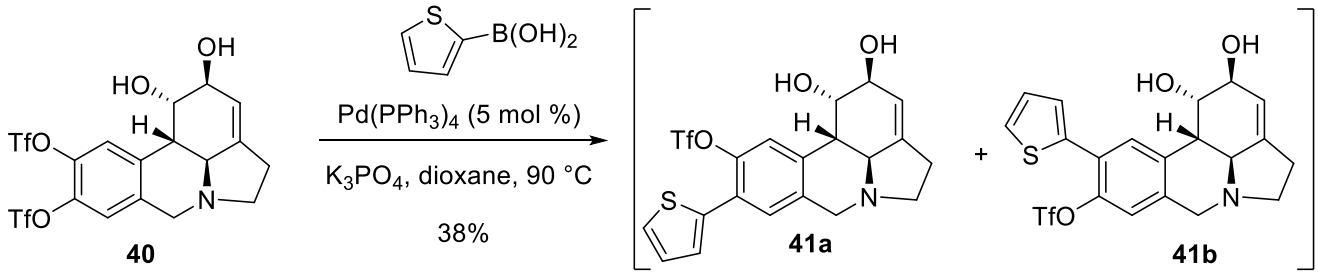
^{13}C NMR (126 MHz, $CDCl_3$) δ 171.0, 148.4, 147.5, 147.2, 140.4, 133.8, 131.4, 129.2, 129.0, 127.9, 126.5, 125.2, 122.6, 120.9, 119.2, 106.4, 103.9, 101.0, 63.7, 54.3, 31.0, 21.0.

HRMS (*m*/*z*) [M + H]+ calcd for $C_{24}H_{22}NO_4$, 388.1543; found, 388.1540.









(1S,2S,3a1S,11bS)-1,2-dihydroxy-9-(thiophen-2-yl)-2,3a1,4,5,7,11b-hexahydro-1H-pyrrolo[3,2,1-de]phenanthridin-10-yl trifluoromethanesulfonate (**41a**)

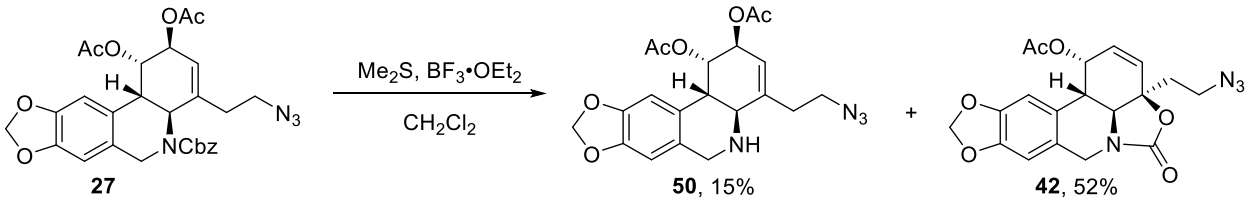
(1S,2S,3a1S,11bS)-1,2-dihydroxy-10-(thiophen-2-yl)-2,3a1,4,5,7,11b-hexahydro-1H-pyrrolo[3,2,1-de]phenanthridin-9-yl trifluoromethanesulfonate (**41b**)

In a dry 20 mL vial equipped with a septum, ditriflate **40** (80.7 mg, 0.15 mmol, 1.0 equiv), 2-thienylboronic acid (50 mg, 0.39 mmol, 2.6 equiv), $Pd(PPh_3)_4$ (8.6 mg, 0.007 mmol, 0.05 equiv), and K_3PO_4 (127 mg, 0.60 mmol, 4.0 equiv) were dissolved in dry and degassed 1,4-dioxane (4 mL, 0.6 M) under N_2. The reaction mixture was heated to 90 °C for 16 h. After cooling to room temperature, sat. aqueous $NaHCO_3$ and $CHCl_3$ were added, and the layers were separated. The aqueous layer was extracted three times with $CHCl_3$, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. Purification by preparatory HPLC (C18 10x250mm, 10–100% ACN in H_2O) afforded **41a** and **41b** in a 2.5:1 ratio (23.1 mg, 38%) as a yellow solid.

^{1}H NMR (500 MHz, 3:1 $CDCl_3$/CD_3OD) δ 7.58 (s, 0.2 H [b]), 7.48 (s, 0.3H [b]), 7.43–7.38 (m, 0.9H [a]), 7.37 (s, 0.6H [a]), 7.32 (s, 0.7H [a]), 7.28 (dd, *J* = 3.7, 1.2 Hz, 0.4H [b]), 7.25–7.19 (m, 0.6 [a]), 7.09 (ddd, *J* = 5.2, 3.6, 1.8 Hz, 0.8H [a]), 6.91 (ddd, *J* = 5.1, 3.5 Hz, 0.4H [b]), 6.83 (ddd, *J* = 22.4, 3.5, 1.2 Hz, 0.3H [b]), 5.58 (s, 1H), 4.59–4.40 (m, 1H), 4.27 (d, *J* = 14.8 Hz, 1H), 4.16–4.11 (m, 1H), 3.64 (ddt, *J* = 14.5, 8.5, 1.6 Hz, 1H), 3.36 (ddd, *J* = 9.3, 7.5, 1.8 Hz, 1H), 2.96–2.86 (m, 1H), 2.82–2.72 (m, 1H), 2.69–2.54 (m, 2H), 2.42 (dd, *J* = 18.1, 9.4 Hz, 1H).

^{13}C NMR (126 MHz, 3:1 $CDCl_3$/CD_3OD, *major isomer*) δ 145.3, 142.0, 137.4, 136.9, 136.3, 130.2, 128.7 (q, *J* =316.7 Hz), 128.0, 127.9, 127.0, 126.0, 119.0, 118.4, 72.1, 70.6, 60.7, 56.3, 53.9, 40.4, 28.4.

HRMS (*m*/*z*) [M + H]+ calcd for $C_{20}H_{19}F_3NO_5S_2$, 474.0651; found, 474.0676.



In a one-dram vial equipped with a septum, under inert atmosphere **27** (123 mg, 0.21 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (3.0 mL, 0.07 M) and Me_2S (0.38 mL, 5.2 mmol, 25 equiv) was added. Next, boron trifluoride diethyl etherate (0.26 mL, 2.11 mmol, 10 equiv) was added and the resulting mixture was stirred for 2 hr before saturated sodium bicarbonate (1 mL) was added to quench the reaction stirring for 10 minutes. Next, CH_2Cl_2 and saturated sodium bicarbonate were added, the layers separated, and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The resulting crude product was then purified by preparatory HPLC (C18 20x250mm, 10–100% ACN in H_2O) to afford **50** (12.6 mg, 15%) as a colorless oil and **42** (42.6 mg, 52%) as a yellow oil.

(1S,2S,4aS,11bS)-4-(2-azidoethyl)-1,2,4a,5,6,11b-hexahydro-[1,3]dioxolo[4,5-j]phenanthridine-1,2-diyl diacetate (**50**)

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.77 (s, 1H), 6.51 (s, 1H), 5.90 (dd, *J* = 1.5 Hz, 2H), 5.77–5.71 (m, 1H), 5.67 (dd, *J* = 1.8, 1.8 Hz, 1H), 5.21–5.06 (m, 1H), 4.12 (dd, *J* = 17.0, 1.3 Hz, 1H), 4.03 (d, *J* = 16.9 Hz, 1H), 3.52–3.40 (m, 3H), 2.95 (d, *J* = 10.2 Hz, 1H), 2.79 (dtd, *J* = 14.5, 6.1, 1.3 Hz, 1H), 2.43 (dt, *J* = 14.5, 7.5 Hz, 1H), 2.09 (s, 3H), 1.93 (s, 3H), 1.44 (bs, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.1, 169.6, 146.5, 146.3, 143.8, 129.8, 126.7, 120.8, 106.0, 105.0, 100.8, 68.9, 67.6, 52.9, 49.7, 49.5, 40.5, 32.9, 21.1, 20.8.

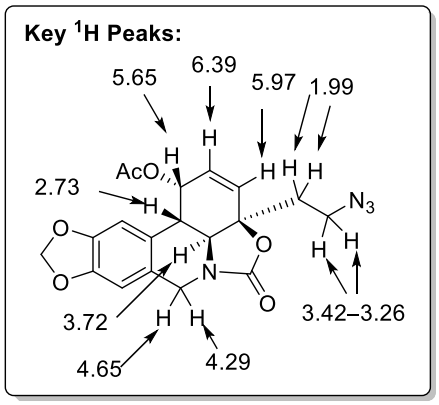
HRMS (*m*/*z*) [M + H]+ calcd for $C_{20}H_{23}N_4O_6$, 415.1612; found, 415.1609.

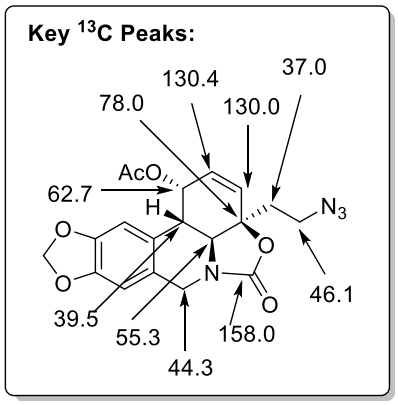
(1R,3aR,3a1S,12bS)-3a-(2-azidoethyl)-5-oxo-3a,3a1,7,12b-tetrahydro-1H,5H-[1,3]dioxolo[4,5-j]oxazolo[5,4,3-de]phenanthridin-1-yl acetate (**42**)

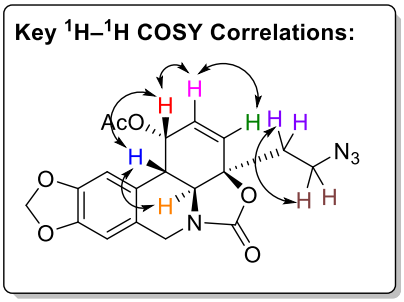
^{1}H NMR (500 MHz, 3:1 $CDCl_3$/CD_3OD) δ 6.53 (s, 1H), 6.42 (s, 1H), 6.39 (dd, *J* = 9.9, 6.2 Hz, 1H), 5.97 (d, *J* = 9.9 Hz, 1H), 5.82 (dd, *J* = 9.7, 1.3 Hz, 2H), 5.65 (dd, *J* = 6.3, 2.5 Hz, 1H), 4.65 (d, *J* = 16.6 Hz, 1H), 4.29 (d, *J* = 16.5 Hz, 1H), 3.72 (d, *J* = 10.7 Hz, 1H), 3.42–3.26 (m, 2H), 2.73 (ddd, *J* = 10.7, 2.5, 1.2 Hz, 1H), 1.99 (td, *J* = 6.9, 1.5 Hz, 2H), 1.87 (s, 3H).

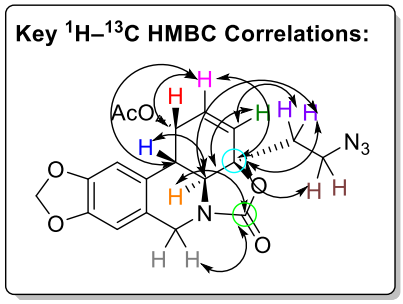
^{13}C NMR (126 MHz, 3:1 $CDCl_3$/CD_3OD) δ 170.9, 158.0, 147.112, 147.110, 130.4, 130.0, 125.6, 124.9, 106.8, 104.7, 101.3, 78.0, 62.7, 55.3, 46.1, 44.3, 39.5, 37.0, 20.6.

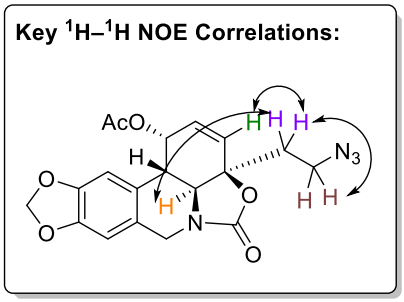
HRMS (*m*/*z*) [M + H]+ calcd for $C_{19}H_{19}N_4O_6$, 399.1299; found, 399.1287.

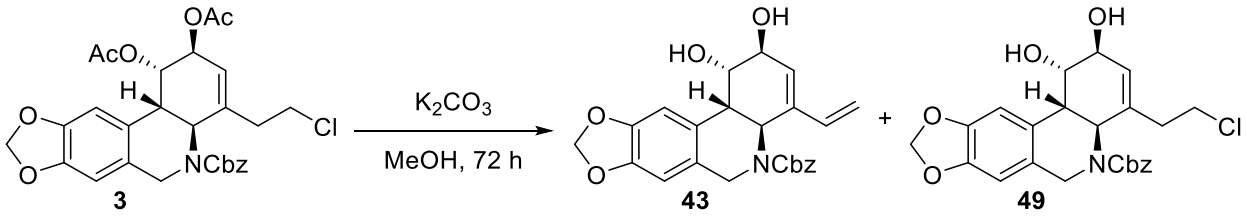












In a 20 mL vial, **3** (210 mg, 0.39 mmol, 1.0 equiv) was dissolved in MeOH (9 mL, 0.04 M), and K_2CO_3 (185 mg, 3.4 mmol, 9.0 equiv) was added. The reaction mixture was stirred at room temperature for 72 h, before being concentrated under vacuum and passed through a plug of silica gel, eluting with 5% MeOH in $CHCl_3$. Purification by preparatory HPLC (C18 20x250mm, 10–100% ACN in H_2O) provided major product **43** (79 mg, 48%) as a white solid, and minor product **49** (38 mg, 21%) as a white solid.

Note: The carbamate protecting group results in rotamers, which coalesce at 100 °C, but not sufficiently to resolve all of the ^{13}C signals. Therefore, the cooled spectrum of the same sample at –30 °C (resulting in rotameric products) is reported below. Poor solubility of **43** and **49** in toluene at lower temperatures necessitated the change in solvents.

Benzyl (1S,2S,4aS,11bS)-1,2-dihydroxy-4-vinyl-2,4a,6,11b-tetrahydro-[1,3]dioxolo[4,5-j]phenanthridine-5(1H)-carboxylate (**43**)

^{1}H NMR (600 MHz, Toluene-d_8, 100 °C) δ 7.06–7.01 (m, 4H), 6.97 (t, *J* = 1.3 Hz, 1H), 6.61 (s, 1H), 6.31–6.20 (m, 2H), 5.56 (s, 1H), 5.39 (dd, *J* = 8.2, 1.5 Hz, 2H), 5.33 (dd, *J*

= 17.6, 1.5 Hz, 1H), 4.99 (d, *J* = 12.3 Hz, 1H), 4.94 (dd, *J* = 11.2, 1.5 Hz, 1H), 4.80 (m, 2H), 4.12 (s, 1H), 4.02 (s, 2H), 3.84 (s, 1H), 3.30 (s, 1H).

^{13}C NMR (151 MHz, 2:1 $CD_3OD/CDCl_3$, –30 °C) δ 156.9, 155.1, 147.0, 146.8, 146.3, 146.1, 139.4, 139.0, 136.0, 135.92, 135.89, 135.6, 128.43, 128.40, 128.1, 128.0, 127.9, 127.8, 127.7, 127.3, 123.8, 123.4, 114.4, 114.1, 106.2, 106.0, 105.6, 105.5, 101.1, 101.0, 69.9, 69.7, 68.4, 67.9, 67.3, 67.1, 54.4, 50.4, 50.3, 37.5, 36.7.

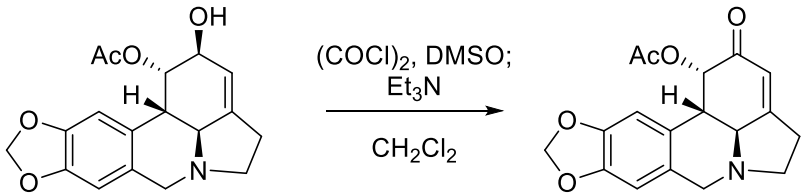
HRMS (*m*/*z*) [M+Na]+ calcd for $C_{24}H_{23}NO_6Na$, 444.1418; found, 444.1434.

Benzyl (1S,2S,4aS,11bS)-4-(2-chloroethyl)-1,2-dihydroxy-2,4a,6,11b-tetrahydro-[1,3]dioxolo[4,5-j]phenanthridine-5(1H)-carboxylate (**49**)

^{1}H NMR (600 MHz, Toluene-d_8, 100 °C) δ 7.07–6.96 (m, 5H), 6.62 (s, 1H), 6.26 (s, 1H), 5.39 (dd, *J* = 7.5, 1.7 Hz, 2H), 5.29 (s, 1H), 4.94 (d, *J* = 12.3 Hz, 1H), 4.82 (d, *J* = 12.4 Hz, 1H), 4.61 (s, 1H), 4.12 (s, 1H), 4.10–3.86 (m, 2H), 3.77 (s, 1H), 3.34 (dt, *J* = 7.4, 4.4 Hz, 2H), 3.18 (s, 1H), 2.56 (dt, *J* = 14.4, 7.0 Hz, 1H), 2.47–2.33 (m, 1H).

^{13}C NMR (151 MHz, $CDCl_3$, –30 °C) δ 157.1, 156.3, 147.0, 146.9, 146.3, 146.2, 140.4, 139.2, 135.6, 135.1, 129.0, 128.93, 128.90, 128.71, 128.68, 128.6, 128.4, 128.33, 128.28, 128.0, 127.9, 121.4, 120.7, 106.9, 106.4, 105.8, 105.3, 101.2, 71.0, 70.2, 68.3, 68.1, 67.7, 67.5, 56.1, 55.8, 51.3, 51.0, 43.5, 42.9, 36.8, 36.2, 36.1, 36.0.

HRMS (*m*/*z*) [M+Na]+ calcd for $C_{24}H_{24}NO_6NaCl$, 480.1184; found, 480.1172.



19 **44**

(1S,3a1S,12bS)-2-oxo-2,3a1,4,5,7,12b-hexahydro-1H-[1,3]dioxolo[4,5-j]pyrrolo[3,2,1-de]phenanthridin-1-yl acetate (**44**)[4]

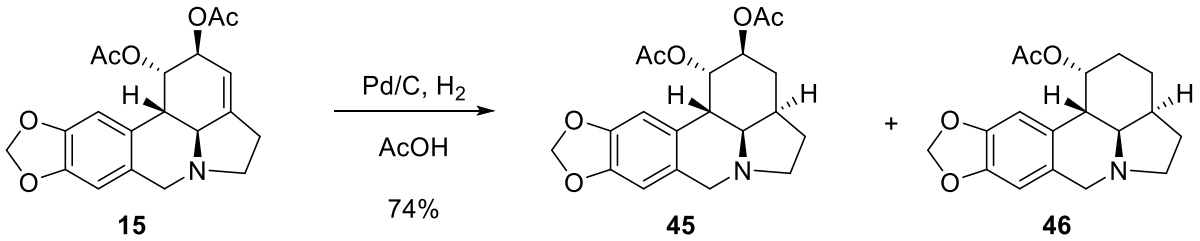
In a dry 300 mL round bottom flask under N_2 a solution of oxalyl chloride (0.9 mL, 10.6 mmol, 2.5 equiv) and CH_2Cl_2 (6 mL) was cooled to –78 °C. Next, a solution of DMSO (1 mL, 14.1 mmol, 3.1 equiv) and CH_2Cl_2 (20 mL) was added to the flask dropwise washing the syringe with additional CH_2Cl_2 (1 mL). The mixture was then stirred for 30 minutes and then **19** (1.33 g, 3.75 mmol, 1.0 equiv) in CH_2Cl_2 (24 mL), was added to the flask. The reaction was stirred at –78 °C for 2 h, and then Et_3N (3.5 mL, 25.1 mmol, 3.2 equiv) was added. The reaction was stirred at –78 °C for an additional 10 minutes before being allowed to warm to room temperature. Brine (40 mL) was added to quench the reaction and excess solvent was removed by vacuum. Water and CH_2Cl_2 were added, and the layers were separated. The aqueous layer was extracted twice with CH_2Cl_2, and the resulting combined organic layers were washed with brine. The organic layer was then dried over $MgSO_4$, filtered and, concentrated. The resulting residue was purified by

column chromatography (EtOAc to 10:1 EtOAc/MeOH) to yield **44** as an off-white solid (1.53 g, 93% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.74 (s, 1H), 6.59 (s, 1H), 6.01 (d, *J* = 3.8 Hz, 2H), 5.94 (dd, 2H), 4.19 (d, *J* = 14.0 Hz, 1H), 3.62 (d, *J* = 13.9 Hz, 1H), 3.47 (dt, *J* = 9.0, 4.3 Hz, 1H), 3.28 (ddt, *J* = 10.0, 2.4, 1.2 Hz, 1H), 3.19 (dd, *J* = 9.9, 1.3 Hz, 1H), 2.88 (ddt, *J* = 9.0, 5.1, 1.9 Hz, 2H), 2.54 (dd, *J* = 8.7 Hz, 1H), 1.97 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 193.0, 169.5, 169.0, 146.7, 146.7, 128.8, 125.2, 120.4, 107.3, 105.4, 101.1, 69.0, 62.3, 56.3, 53.2, 45.5, 30.0, 20.8.

HRMS (*m*/*z*) [M + H]+ calcd for $C_{18}H_{18}NO_5$, 328.1179; found, 328.1194.



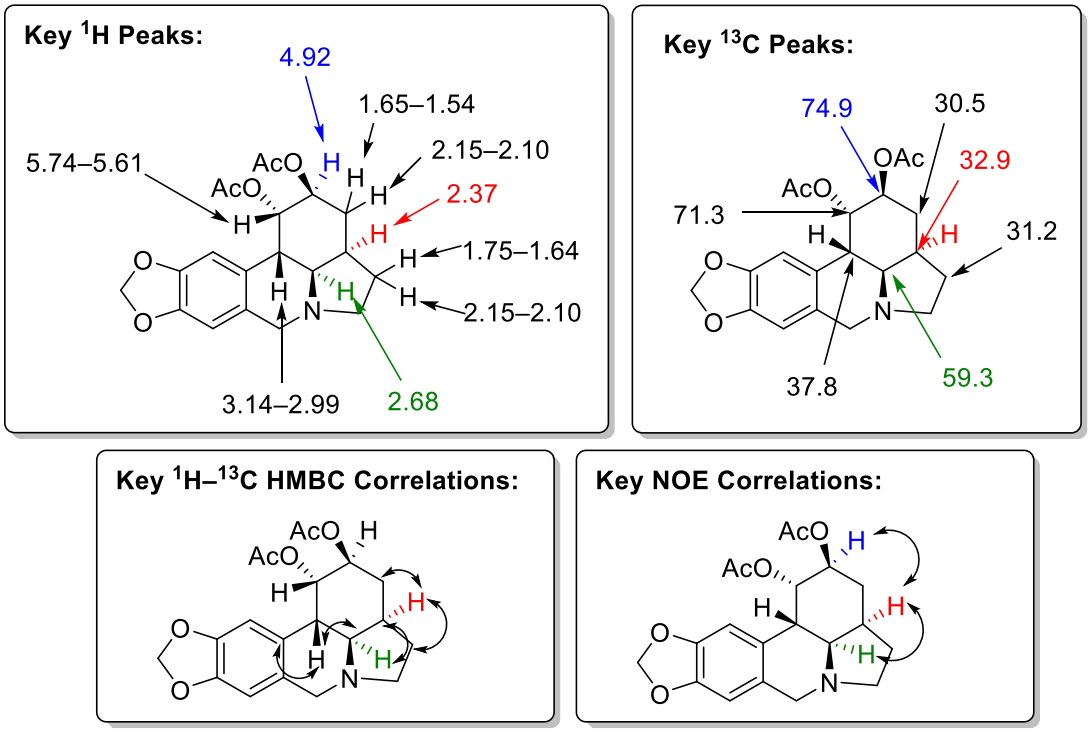
In a high-pressure reactor, diacetyl lycorine (645 mg, 1.74 mmol, 1.0 equiv) was dissolved in acetic acid (8 mL, 0.2 M). Pd/C (5% by weight, 100 mg) was added, the reactor was flushed with N_2, and then charged with H_2 (300 psi). The reaction was stirred at room temperature for 20 h, flushed with N_2 again, and filtered through a pad of celite, washing with MeOH. The filtrate was concentrated under vacuum, then dissolved in $CHCl_3$. Saturated aqueous $NaHCO_3$ was then added, and the layers were separated. The aqueous layer was extracted with $CHCl_3$ four times, dried over $MgSO_4$, filtered and concentrated. Silica gel column chromatography (2–10% MeOH in $CHCl_3$) afforded major product **45** (365 mg, 56%) as a light yellow solid and minor product **46** (100 mg, 18%) as an orange solid.

(1S,2S,3aS,3a1R,12bS)-2,3,3a,3a1,4,5,7,12b-octahydro-1H-[1,3]dioxolo[4,5-j]pyrrolo[3,2,1-de]phenanthridine-1,2-diyl diacetate (**45**)[3]

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.63 (s, 1H), 6.56 (s, 1H), 5.89 (s, 2H), 5.74–5.61 (m, 1H), 4.92 (ddd, *J* = 9.6, 5.4, 2.0 Hz, 1H), 4.00 (d, *J* = 14.7 Hz, 1H), 3.80 (dd, *J* = 14.8, 1.0 Hz, 1H), 3.14–2.99 (m, 2H), 2.68 (dd, *J* = 10.9, 9.3 Hz, 1H), 2.59 (td, *J* = 9.4, 6.2 Hz, 1H), 2.37 (ddt, *J* = 14.5, 10.8, 7.2 Hz, 1H), 2.15–2.10 (m, 2H), 2.09 (s, 3H), 1.95 (s, 3H), 1.75–1.64 (m, 1H), 1.65–1.54 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 169.9, 146.3, 146.1, 129.1, 128.2, 107.1, 105.1, 100.9, 74.9, 71.3, 59.3, 55.2, 53.3, 37.8, 32.9, 31.2, 30.5, 21.2, 21.0.

HRMS (*m*/*z*) [M + H]+ calcd for $C_{20}H_{24}NO_6$, 374.1598; found, 374.1601.

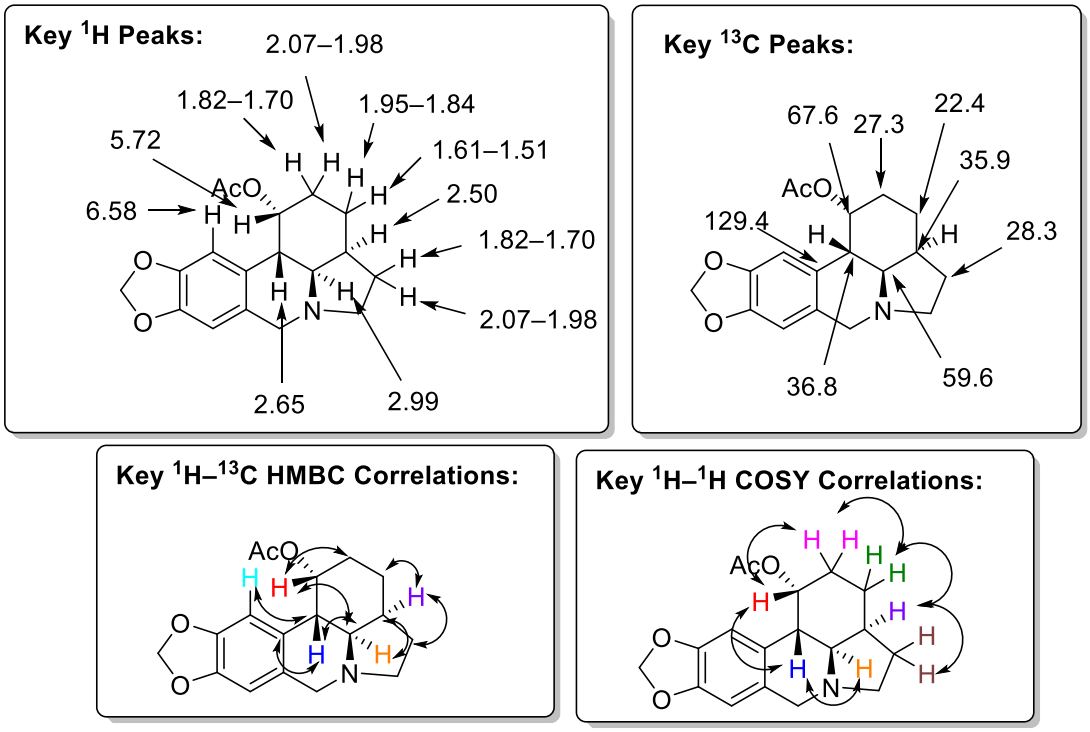


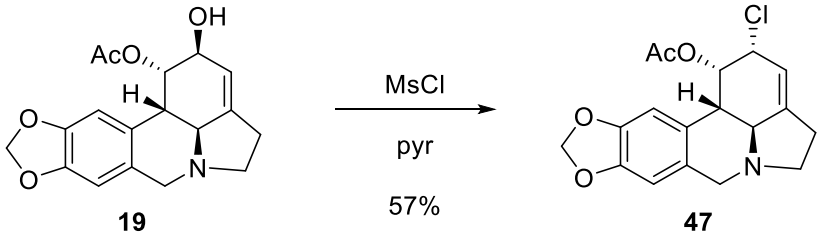
(1R,3aS,3a1R,12bS)-2,3,3a,3a1,4,5,7,12b-octahydro-1H-[1,3]dioxolo[4,5-j]pyrrolo[3,2,1-de]phenanthridin-1-yl acetate (**46**):

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.60 (s, 1H), 6.58 (s, 1H), 5.89 (dd, *J* = 4.6, 1.4 Hz, 2H), 5.72 (dt, *J* = 5.0, 2.7 Hz, 1H), 4.10 (d, *J* = 15.4 Hz, 1H), 3.85 (d, *J* = 15.4 Hz, 1H), 3.08 (dd, *J* = 8.6, 8.3 Hz, 1H), 2.99 (dd, *J* = 10.4, 7.9 Hz, 1H), 2.94 (td, *J* = 9.4, 3.2 Hz, 1H), 2.65 (d, *J* = 10.4 Hz, 1H), 2.50 (ddd, *J* = 10.5, 7.9, 4.7 Hz, 1H), 2.07–1.98 (m, 2H), 1.97 (s, 3H) 1.95–1.84 (m, 1H), 1.82–1.70 (m, 2H), 1.61–1.51 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 146.5, 146.0, 129.4, 127.9, 107.0, 104.5, 100.8, 67.6, 59.6, 53.7, 53.4, 36.8, 35.9, 28.3, 27.3, 22.4, 21.2.

HRMS (*m*/*z*) [M + H]+ calcd for $C_{18}H_{22}NO_4$, 316.1543; found, 316.1557.





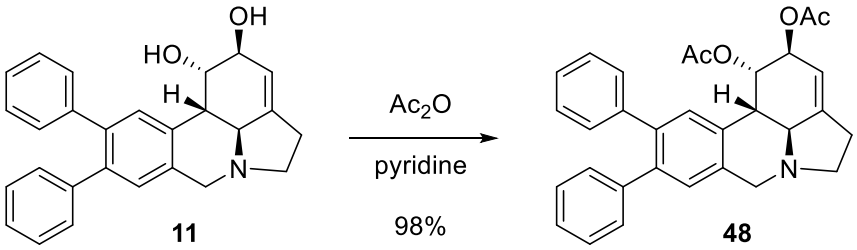
(3a1S,12bS)-3a1,4,5,12b-tetrahydro-7H-[1,3]dioxolo[4,5-j]pyrrolo[3,2,1-de]phenanthridin-2-yl methanesulfonate (**47**)

In a 1 dram vial, **19** (73 mg, 0.22 mmol, 1.0 equiv) was dissolved in pyridine (0.9 mL, 0.25 M) and cooled to 0 °C. Methanesulfonyl chloride (23 µL, 0.23 mmol, 1.05 equiv) was added and the reaction mixture was stirred at 0 °C for 30 min before being warmed to room temperature for 2 hr. Saturated aqueous $NaHCO_3$ and $CHCl_3$ were then added, and the layers were separated. The aqueous layer was extracted three times with $CHCl_3$, dried over $MgSO_4$, filtered, and concentrated. Silica gel column chromatography (0–2% MeOH in $CHCl_3$) afforded **47** as a tan solid (44.2 mg, 57%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.72 (s, 1H), 6.59 (s, 1H), 5.93 (d, *J* = 1.1 Hz, 2H), 5.90 (s, 1H), 5.57 (d, *J* = 2.8 Hz, 1H), 4.61 (dd, *J* = 3.6, 1.8 Hz, 1H), 4.15 (d, *J* = 14.0 Hz, 1H), 3.58 (d, *J* = 14.1 Hz, 1H), 3.37 (ddd, *J* = 9.7, 6.7, 3.3 Hz, 1H), 3.15 (d, *J* = 10.6 Hz, 1H), 2.92 (s, 1H), 2.74–2.60 (m, 2H), 2.48 (s, 1H), 1.97 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 146.7, 146.4, 143.5, 129.0, 126.6, 116.5, 107.5, 104.8, 101.1, 71.7, 61.1, 56.5, 56.4, 53.7, 38.2, 28.9, 20.9.

HRMS (*m*/*z*) [M + H]+ calcd for $C_{18}H_{19}NO_4Cl$, 348.0997; found, 348.0996.



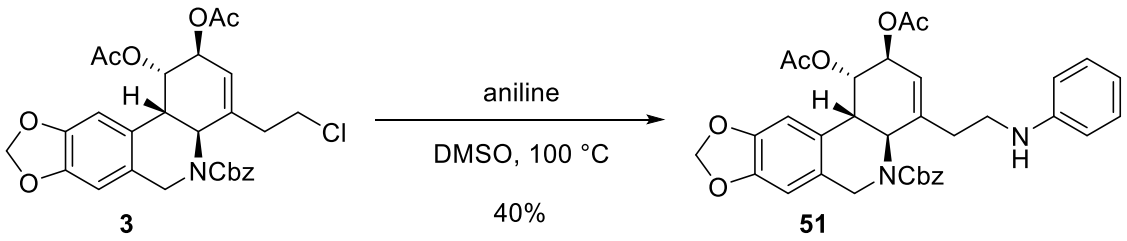
(1S,2S,3a1S,11bS)-9,10-diphenyl-2,3a1,4,5,7,11b-hexahydro-1H-pyrrolo[3,2,1-de]phenanthridine-1,2-diyl diacetate (**48**)

In a 20 mL vial, **11** (90 mg, 0.23 mmol, 1.0 equiv) was dissolved in pyridine (2.3 mL, 0.1 M), acetic anhydride (0.22 mL, 2.3 mmol, 10.0 equiv) was added, and the reaction mixture was heated to 50 °C for 24 h. The reaction mixture was cooled to room temperature, methanol (1.0 mL) was added to quench the reaction, and it was stirred for 3.5 h. The solvents were then removed under vacuum, and the resulting crude material was purified by silica gel column chromatography (1–2% MeOH in $CHCl_3$) afforded **48** as a yellow solid (107 mg, 98%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.11 (m, 12H), 5.97 (s, 1H), 5.63 (t, *J* = 2.6 Hz, 1H), 5.39–5.32 (m, 1H), 4.42 (d, *J* = 14.5 Hz, 1H), 3.77 (d, *J* = 14.7 Hz, 1H), 3.53 (dt, *J* = 9.4, 4.9 Hz, 1H), 3.14 (d, *J* = 10.7 Hz, 1H), 3.04 (d, *J* = 10.7 Hz, 1H), 2.75 (ddt, *J* = 8.9, 4.0, 1.9 Hz, 2H), 2.57 (dd, *J* = 17.3, 8.8 Hz, 1H), 2.12 (s, 3H), 2.04 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 170.1, 146.0, 141.4, 141.2, 139.2, 139.2, 135.3, 132.8, 130.1, 130.0, 129.8, 128.20, 128.17, 127.4, 126.8, 114.6, 71.0, 69.3, 61.3, 56.4, 53.9, 40.5, 28.9, 21.4, 21.3.

HRMS (*m*/*z*) [M + H]+ calcd for $C_{31}H_{30}NO_4$, 480.2169; found, 480.2153.



(1S,2S,4aS,11bS)-5-((benzyloxy)carbonyl)-4-(2-(phenylamino)ethyl)-1,2,4a,5,6,11b-hexahydro-[1,3]dioxolo[4,5-j]phenanthridine-1,2-diyl diacetate (**51**)

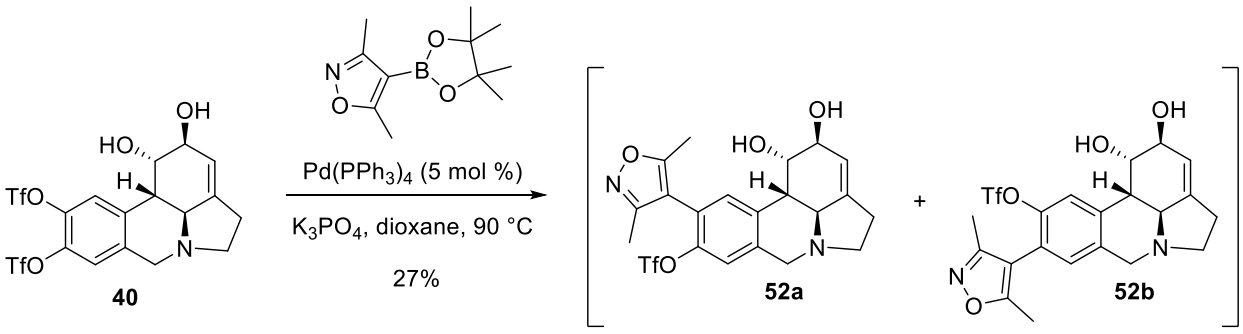
In a 20 mL vial **3** (160 mg, 0.30mmol, 1.0 equiv) was dissolved in DMSO (6.0 mL, 0.05 M), and aniline (0.40 mL, 300 mmol, 10 equiv) was then added. The solution was heated to 100 °C for 16 hr. After cooling to room temperature, saturated sodium bicarbonate, water, and $CHCl_3$ were added, and the layers separated. The aqueous layer was extracted with $CHCl_3$ five times, and the combined organic layers were dried over $MgSO_4$, filtered and concentrated. Purification by silica gel column chromatography (0–2% MeOH in $CHCl_3$) afforded **51** (50 mg, 40%) as a yellow solid.

Note: The carbamate protecting group results in rotamers, which coalesce at 100 °C, but not sufficiently to resolve all of the ^{13}C signals. Therefore, the cooled spectrum of the same sample at –30 °C (resulting in rotameric products) is reported below. Poor solubility of **51** in toluene at lower temperatures necessitated the change in solvents.

^1H NMR (600 MHz, Toluene-d_8, 100 °C) δ 7.12–6.92 (m, 7H), 6.78 (s, 1H), 6.61 (td, *J* = 7.3, 1.1 Hz, 1H), 6.43 (d, *J* = 8.0 Hz, 2H), 6.24 (s, 1H), 5.86 (s, 1H), 5.68 (s, 1H), 5.39–5.25 (m, 3H), 4.95 (dd, *J* = 12.5, 12.5 Hz, 2H), 4.11 (bs, 2H), 3.59 (bs, 1H), 3.08 (t, *J* = 6.9 Hz, 2H), 2.48 (dt, *J* = 13.7, 6.5 Hz, 1H), 2.29 (s, 1H), 2.15–2.02 (m, 2H), 1.68 (s, 3H), 1.44 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$, –30 °C) δ 170.5, 170.29, 170.26, 170.2, 157.0, 155.8, 148.1, 147.8, 146.93, 146.87, 146.4, 146.3, 143.1, 143.0, 135.9, 135.3, 129.49, 129.45, 128.7, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.7, 126.8, 126.5, 118.0, 117.5, 117.29, 117.26, 112.5, 112.4, 106.7, 106.3, 105.6, 105.2, 101.29, 101.26, 69.2, 68.9, 68.5, 67.4, 66.8, 66.6, 55.8, 55.6, 51.2, 50.8, 41.3, 41.1, 36.3, 35.2, 33.2, 33.0, 21.6, 21.5, 21.2, 21.1.

HRMS (*m*/*z*) [M + H]+ calcd for $C_{34}H_{35}N_2O_8$, 599.2388; found, 599.2393.



(1S,2S,3a1S,11bS)-10-(3,5-dimethylisoxazol-4-yl)-1,2-dihydroxy-2,3a1,4,5,7,11b-hexahydro-1H-pyrrolo[3,2,1-de]phenanthridin-9-yl trifluoromethanesulfonate (**52a**)

(1S,2S,3a1S,11bS)-9-(3,5-dimethylisoxazol-4-yl)-1,2-dihydroxy-2,3a1,4,5,7,11b-hexahydro-1H-pyrrolo[3,2,1-de]phenanthridin-10-yl trifluoromethanesulfonate (**52b**)

In a dry 20 mL vial equipped with a septum, ditriflate **40** (116 mg, 0.22 mmol, 1.0 equiv), 3,5-dimethylisoxazole-4-boronic acid pinacol ester (125 mg, 0.54 mmol, 2.5 equiv), $Pd(PPh_3)_4$ (13 mg, 0.011 mmol, 0.05 equiv), and K_3PO_4 (183 mg, 0.86mmol, 4.0 equiv) were dissolved in dry and degassed 1,4-dioxane (5 mL, 0.04 M) under N_2. The reaction mixture was heated to 90 °C for 27 h. After cooling to room temperature, sat. aqueous $NaHCO_3$ and $CHCl_3$ were added, and the layers were separated. The aqueous layer was extracted three times with $CHCl_3$, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. Silica gel column chromatography (5–20% MeOH/$CHCl_3$) afforded a 4:1 mixture of **52a** and **52b** as a tan solid (28.1 mg, 27%).

^{1}H NMR (500 MHz, 3:1 $CDCl_3$/CD_3OD) δ 7.37/7.32 (4:1) (s, 1H), 7.11/7.05 (1:4) (s, 1H), 5.60–5.57 (m, 1H), 4.51–4.45 (m, 1H), 4.27 (d, *J* = 14.7 Hz, 1H), 4.18–4.09 (m, 1H), 3.65 (d, *J* = 15.0 Hz, 1H), 3.37 (ddd, *J* = 9.4, 5.9, 1.9 Hz, 1H), 2.92 (d, *J* = 10.5 Hz, 1H), 2.78 (d, *J* = 11.6 Hz, 1H), 2.64 (ddddd, *J* = 20.6, 19.0, 17.0, 8.0, 2.0 Hz, 2H), 2.44 (dd, *J* = 17.8, 9.0 Hz, 1H), 2.30/2.28 (1:4) (s, 3H), 2.15/2.13 (1:4) (s, 3H).

^{13}C NMR (126 MHz, 3:1 $CDCl_3$/CD_3OD, *major isomer*) δ 167.7, 159.4, 146.6, 142.1, 139.1, 137.4, 131.0, 122.1, 119.0, 118.6 (q, *J* =319.5 Hz), 118.4, 111.1, 72.1, 70.5, 60.6, 56.3, 53.9, 40.5, 28.4, 11.4, 10.2.

HRMS (*m*/*z*) [M + H]+ calcd for $C_{21}H_{22}F_3N_2O_6S$, 487.1145; found, 487.1143.

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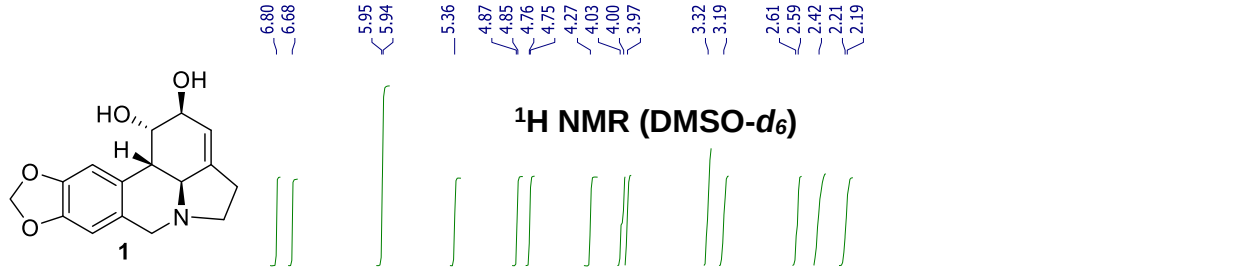
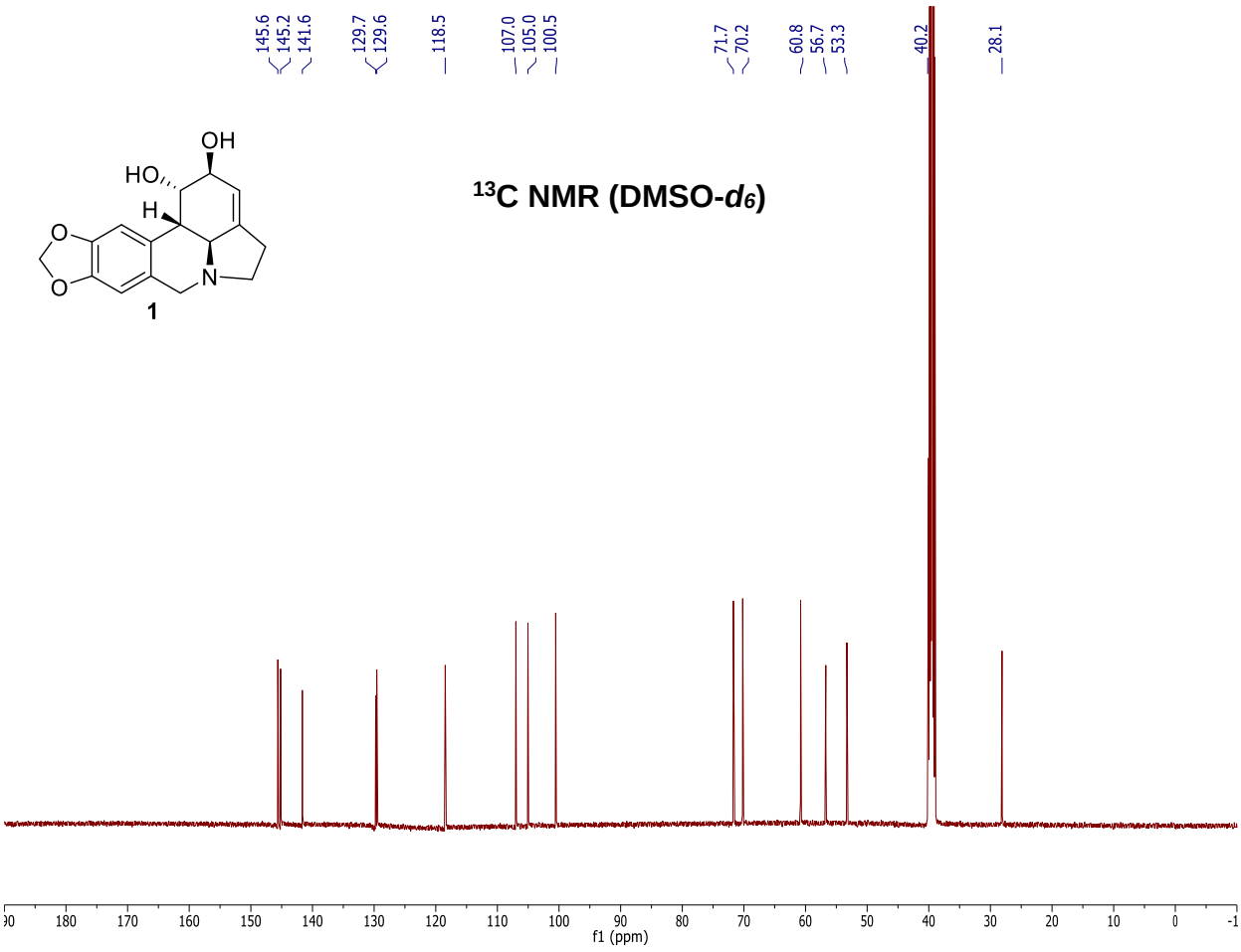
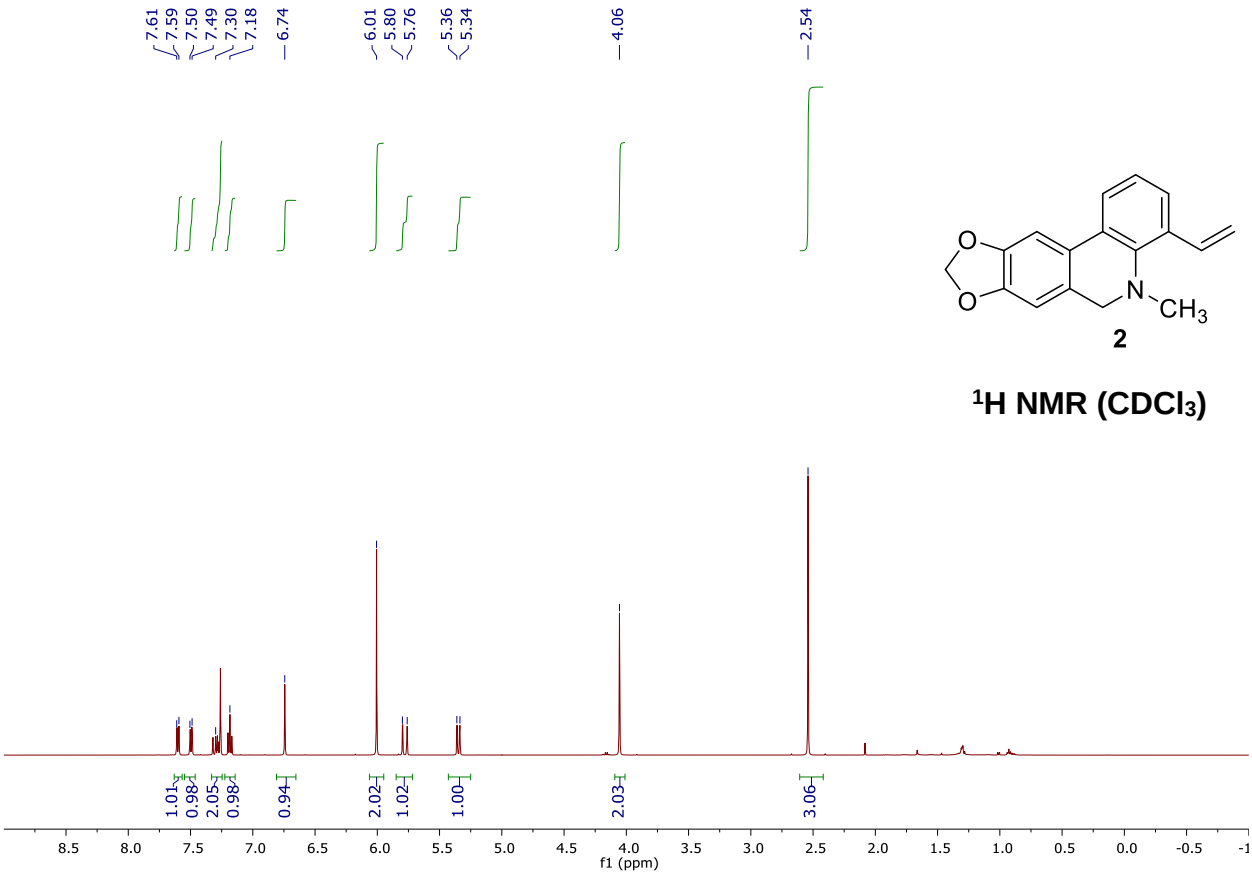
[7] Rodriguez, R. A.; Pan, C.-M.; Yabe, Y.; Kawamata, Y.; Eastgate, M. D.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 6908–6911.



^{1}H NMR (DMSO-*d*$_6$)

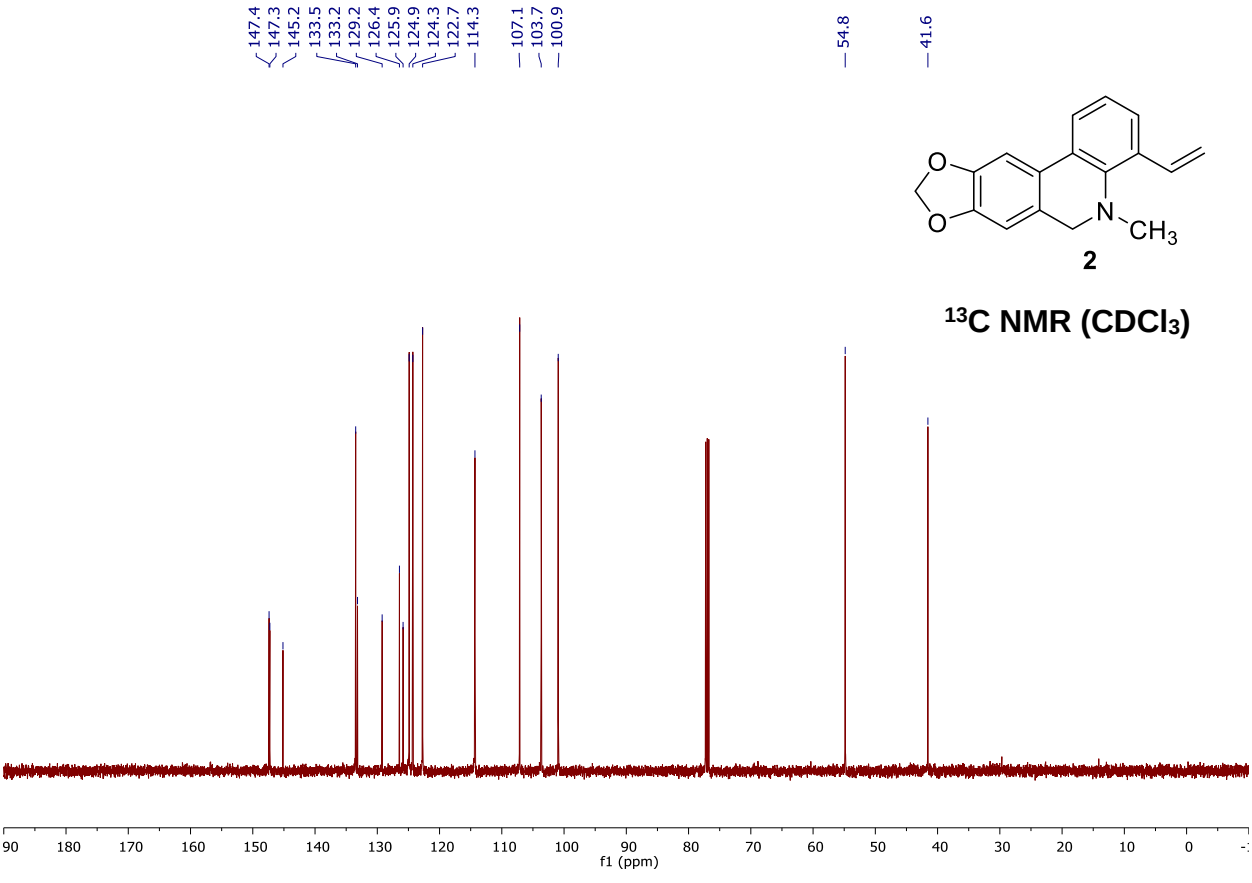


^{13}C NMR (DMSO-*d*$_6$)



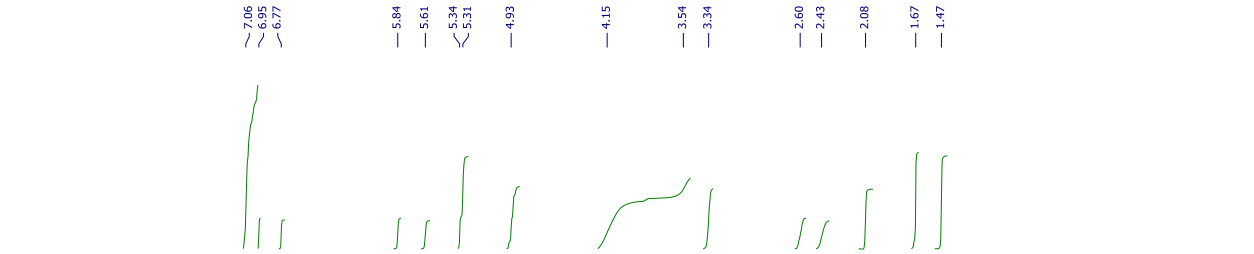
2

^{1}H NMR ($CDCl_3$)

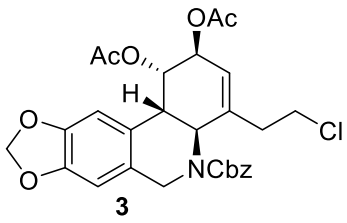


2

^{13}C NMR ($CDCl_3$)



^{1}H NMR (Toluene-*d*$_8$, 100 °C)



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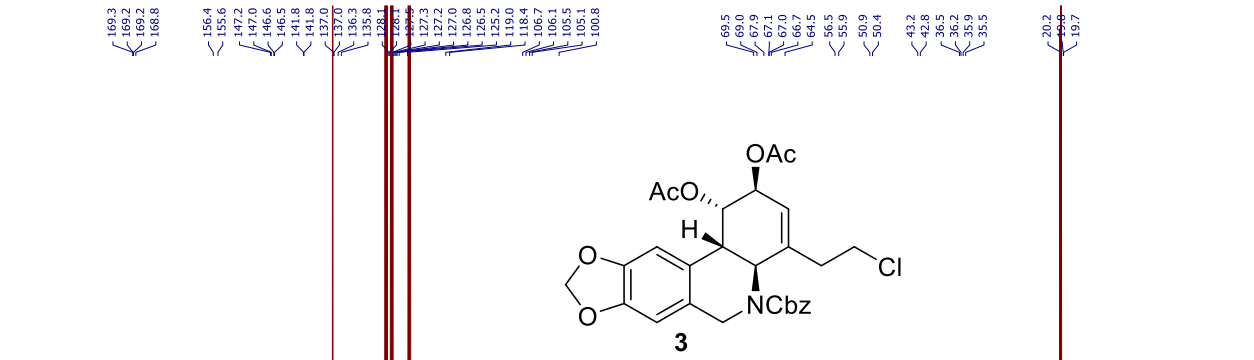
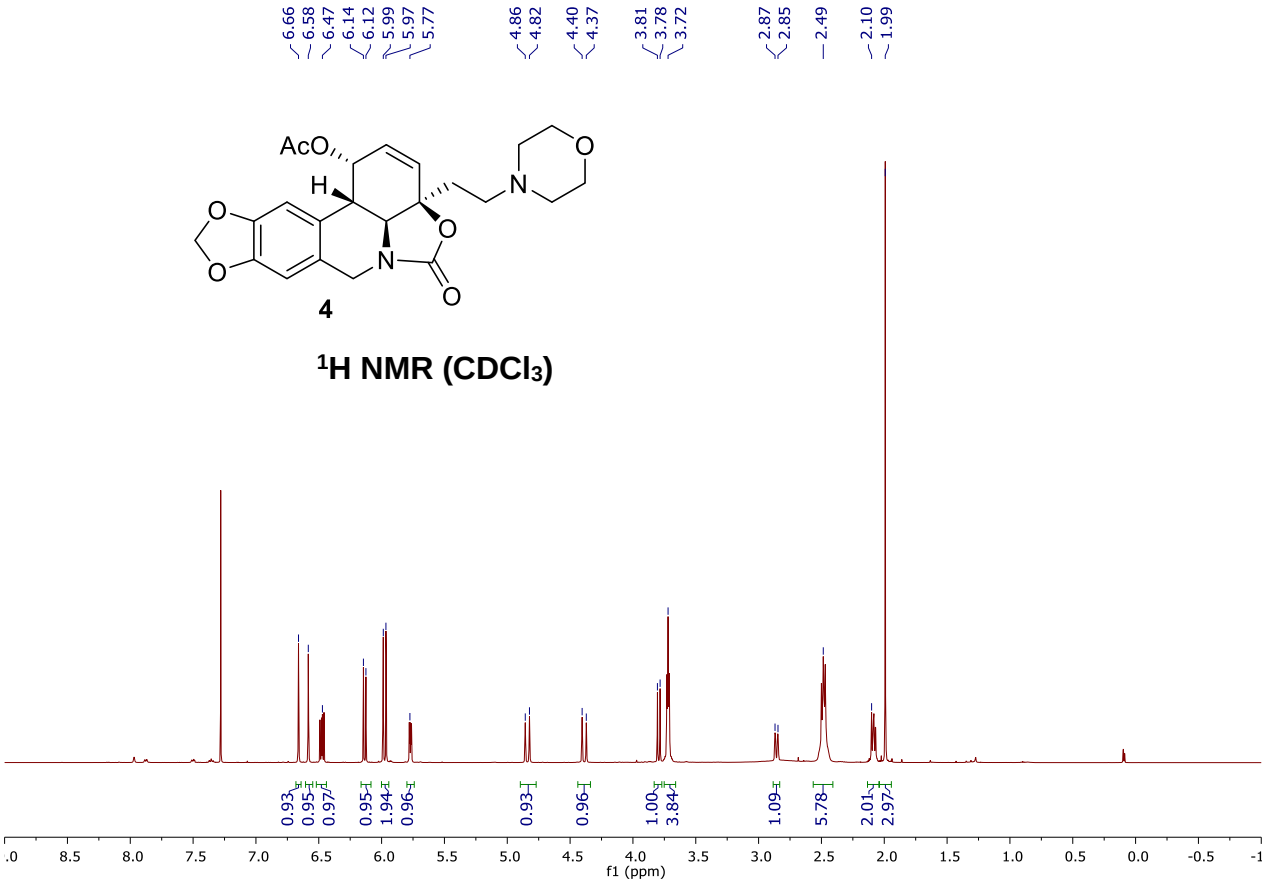


3

^{13}C NMR (Toluene-*d*$_8$, –40 °C)



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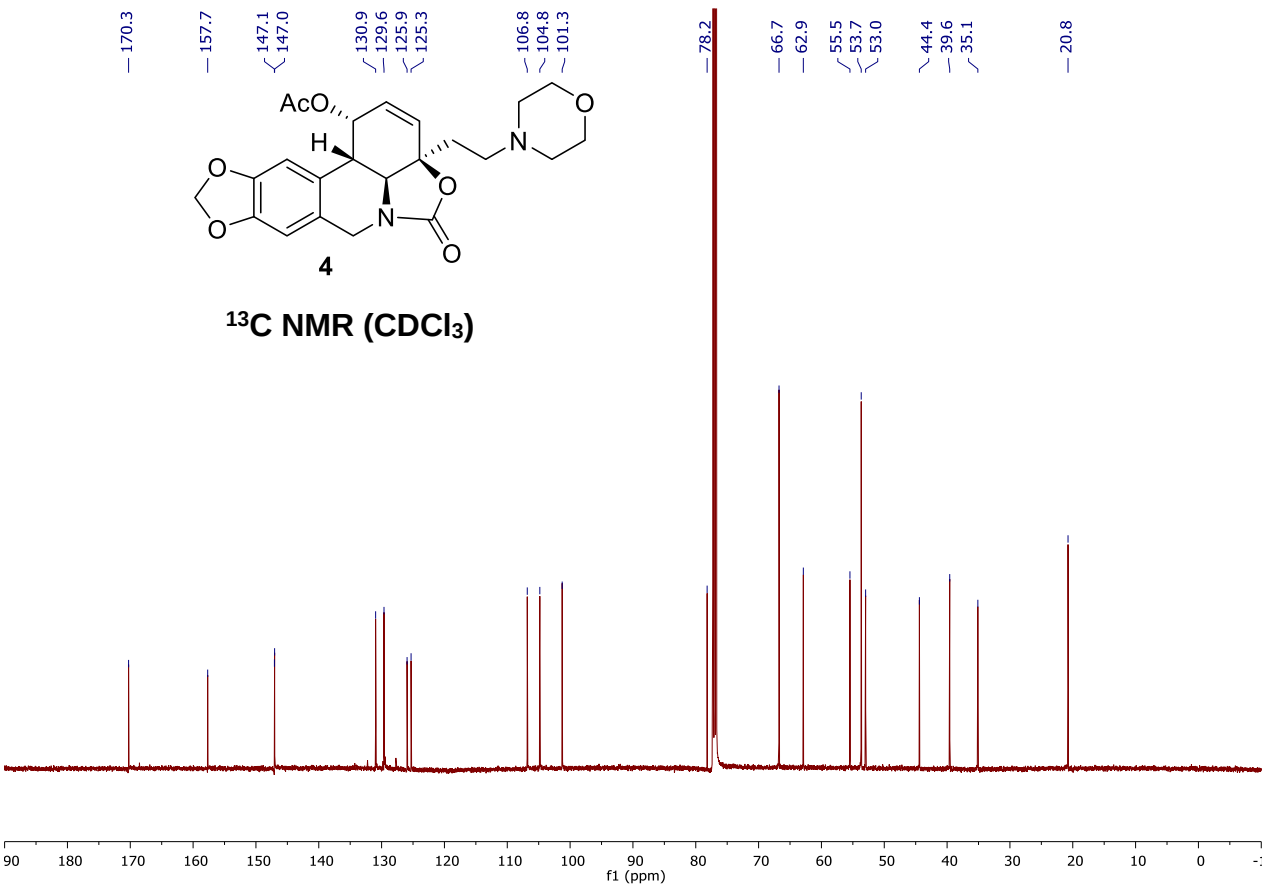
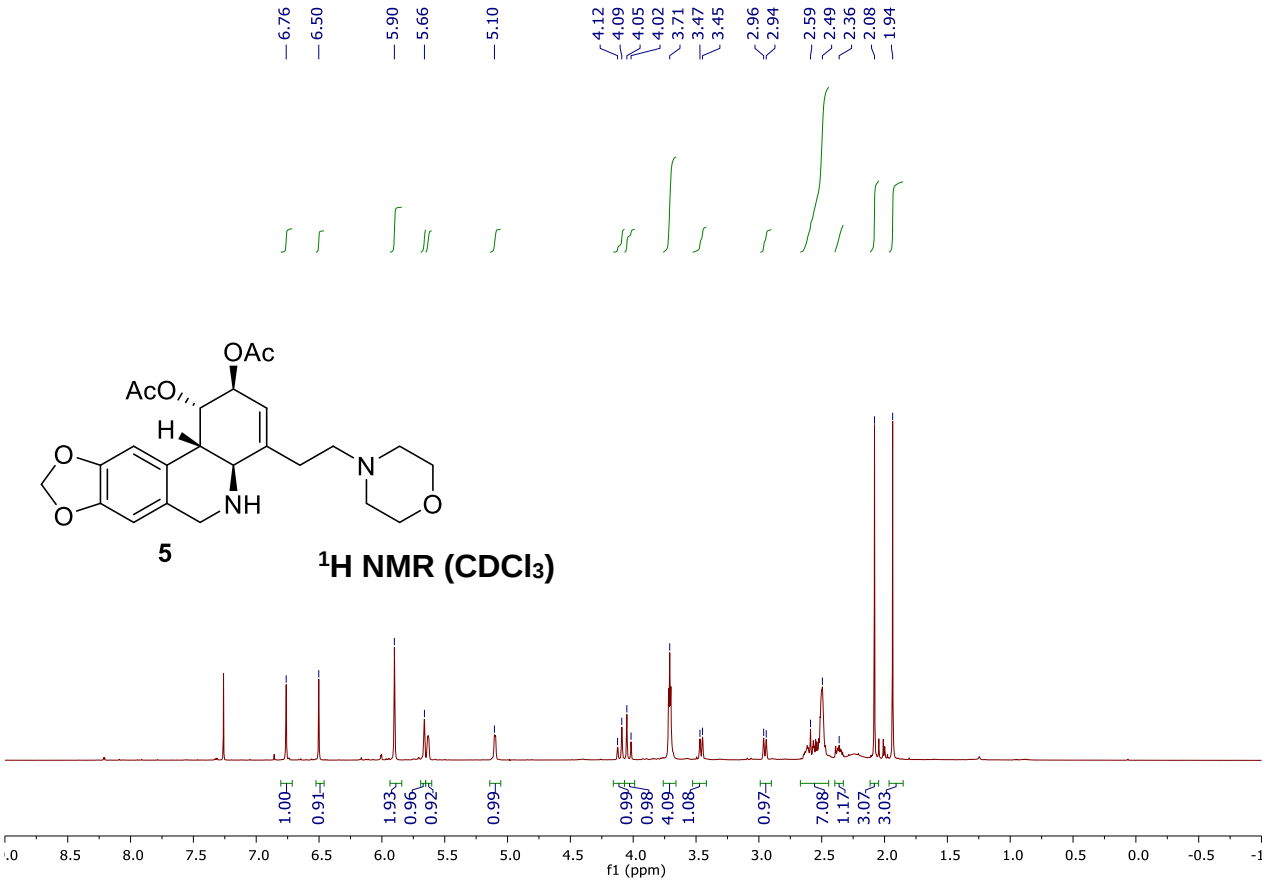
^{1}H NMR ($CDCl_3$)



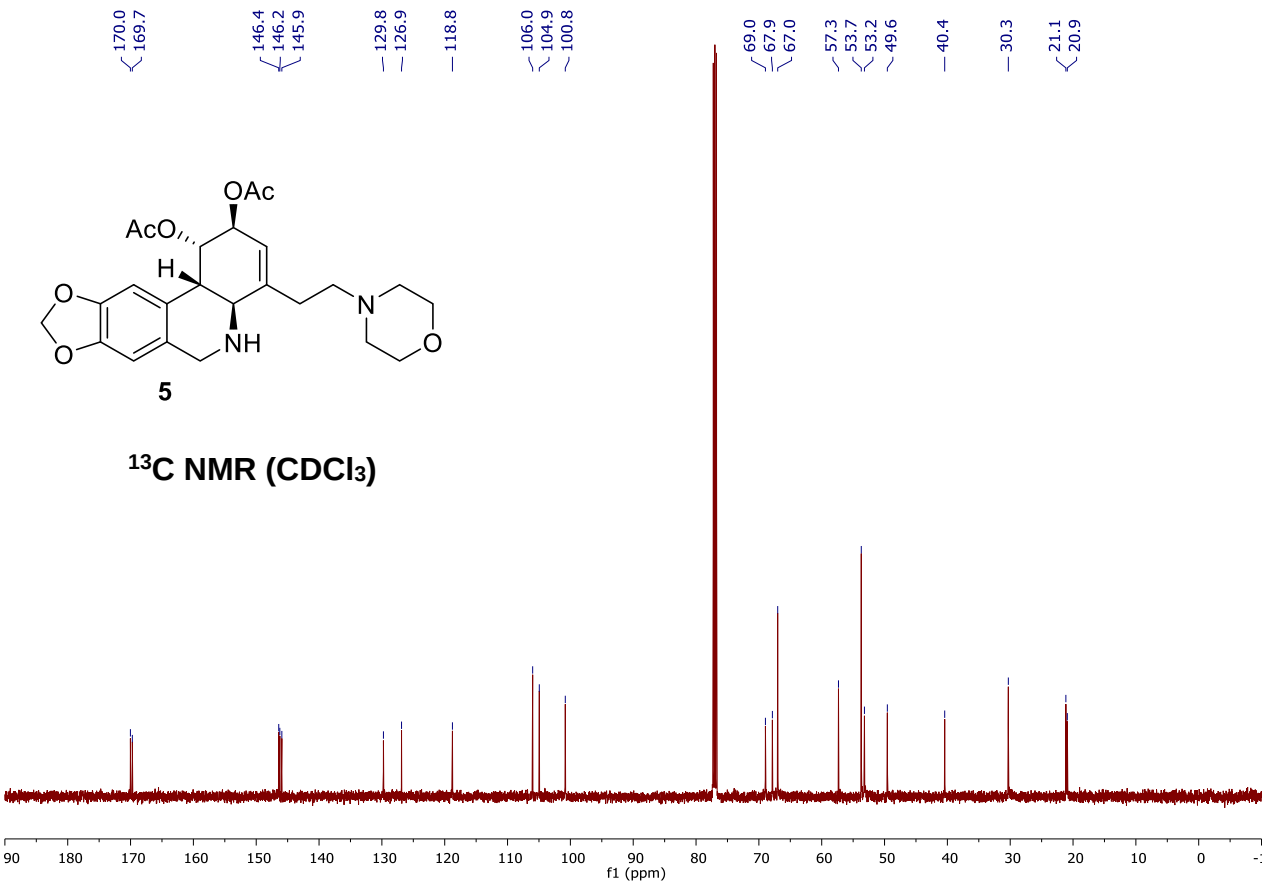
4

^{13}C NMR ($CDCl_3$)



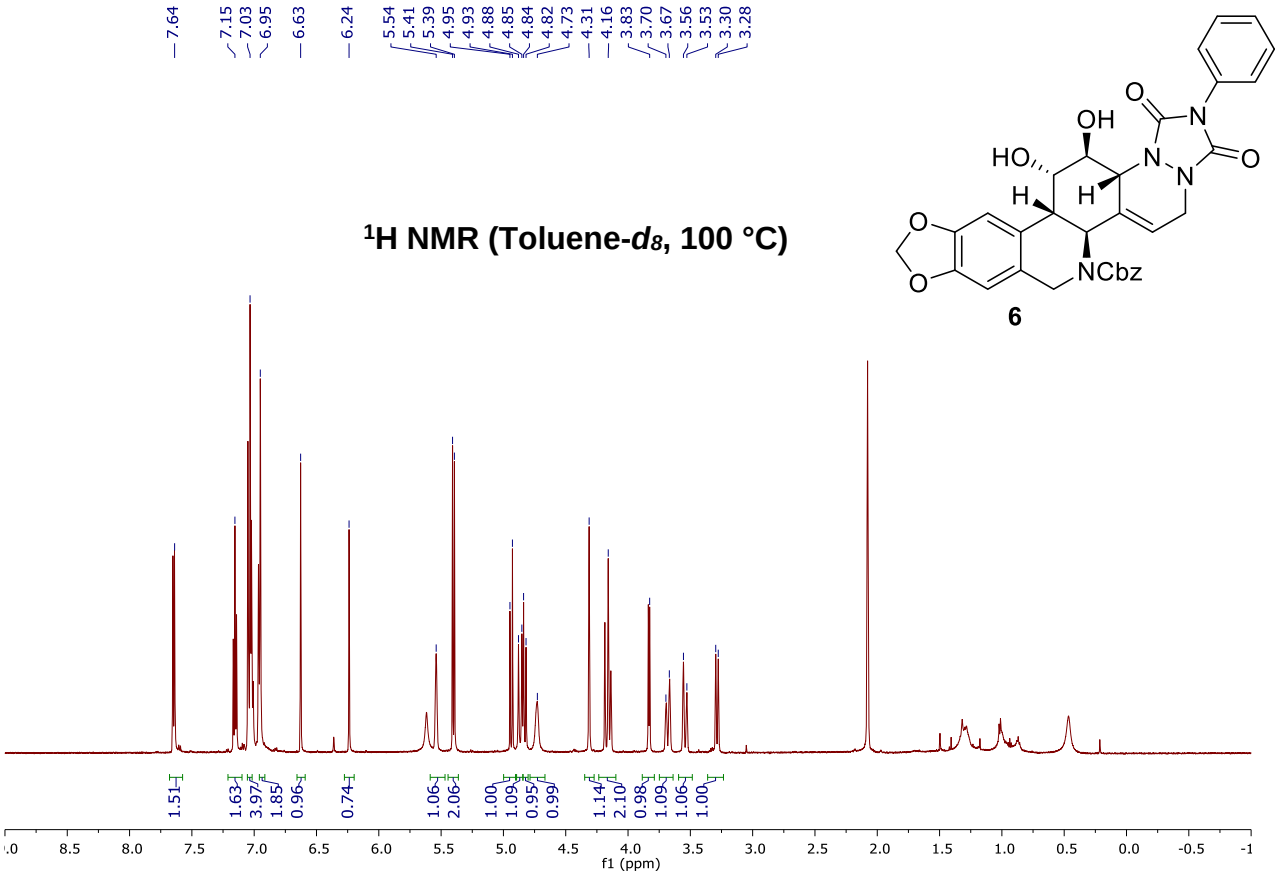
5

^{1}H NMR ($CDCl_3$)



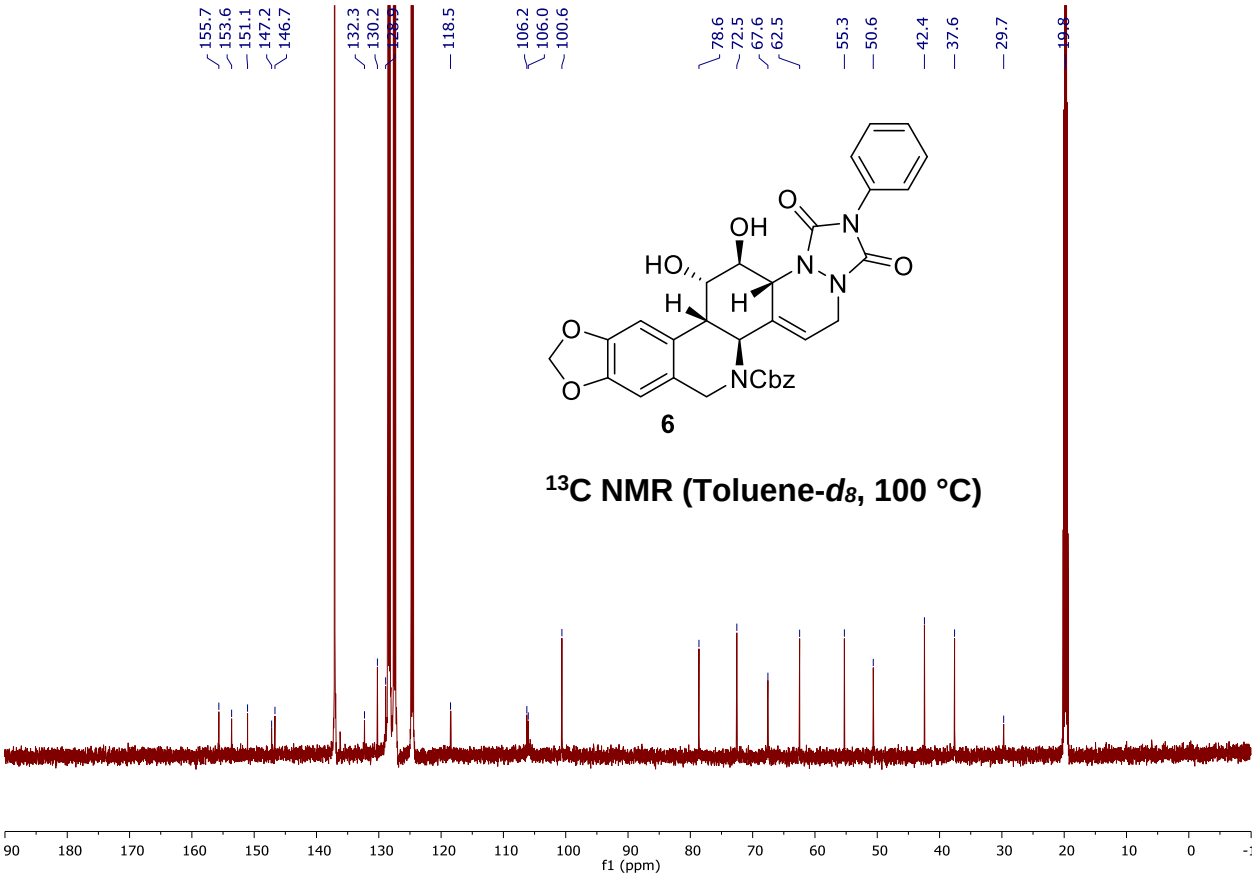
5

^{13}C NMR ($CDCl_3$)



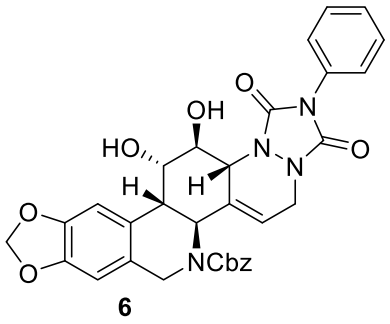
^{1}H NMR (Toluene-*d*$_8$, 100 °C)

6



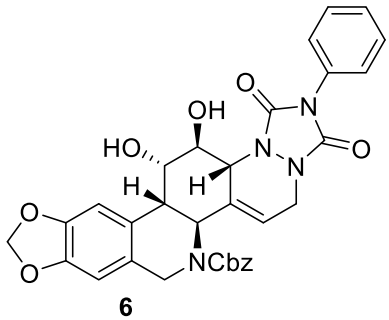
6

^{13}C NMR (Toluene-*d*$_8$, 100 °C)



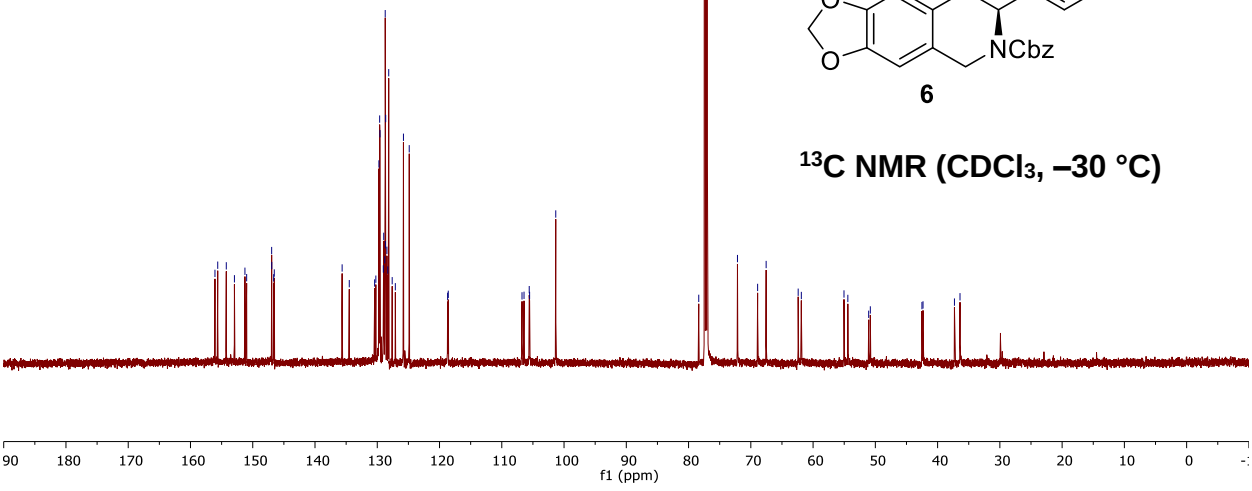
6

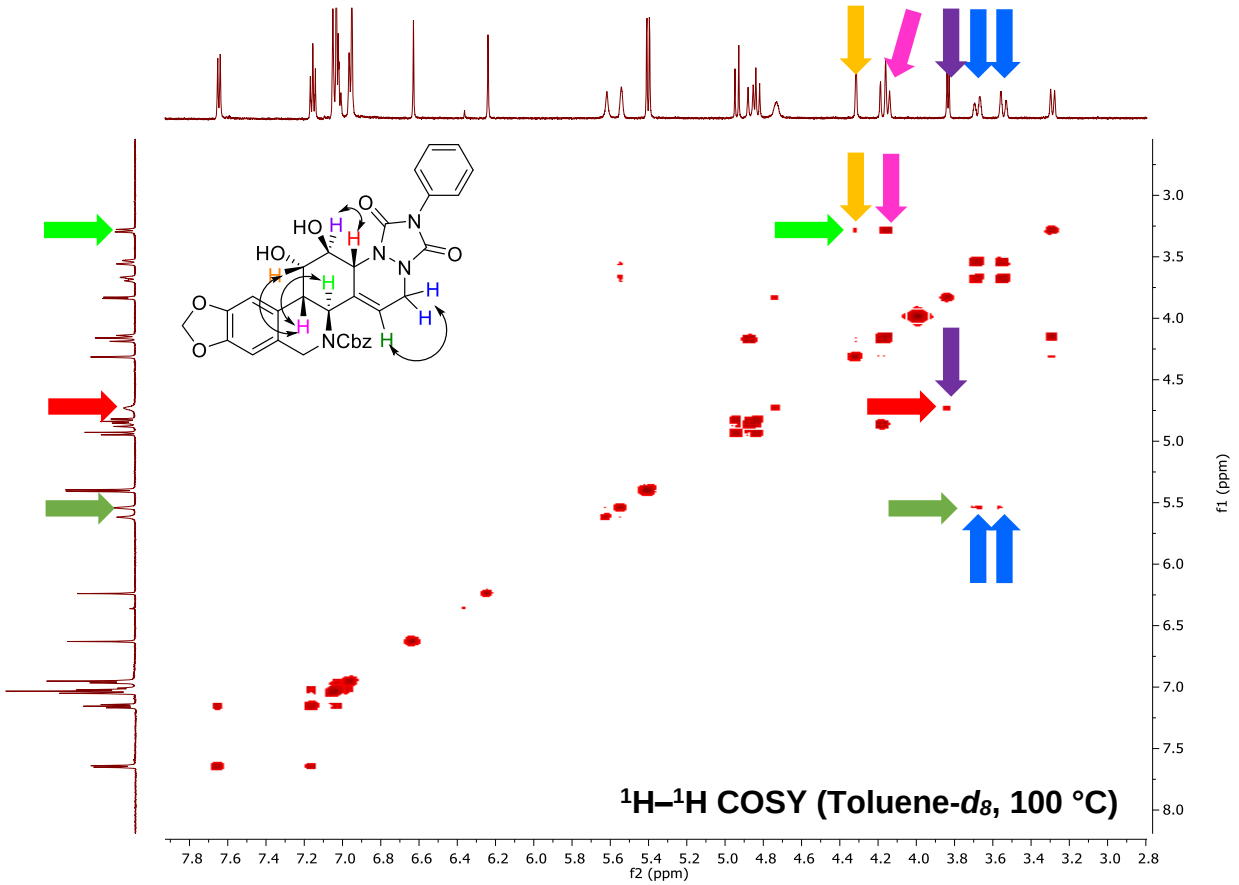
^{1}H NMR ($CDCl_3$, –30 °C)



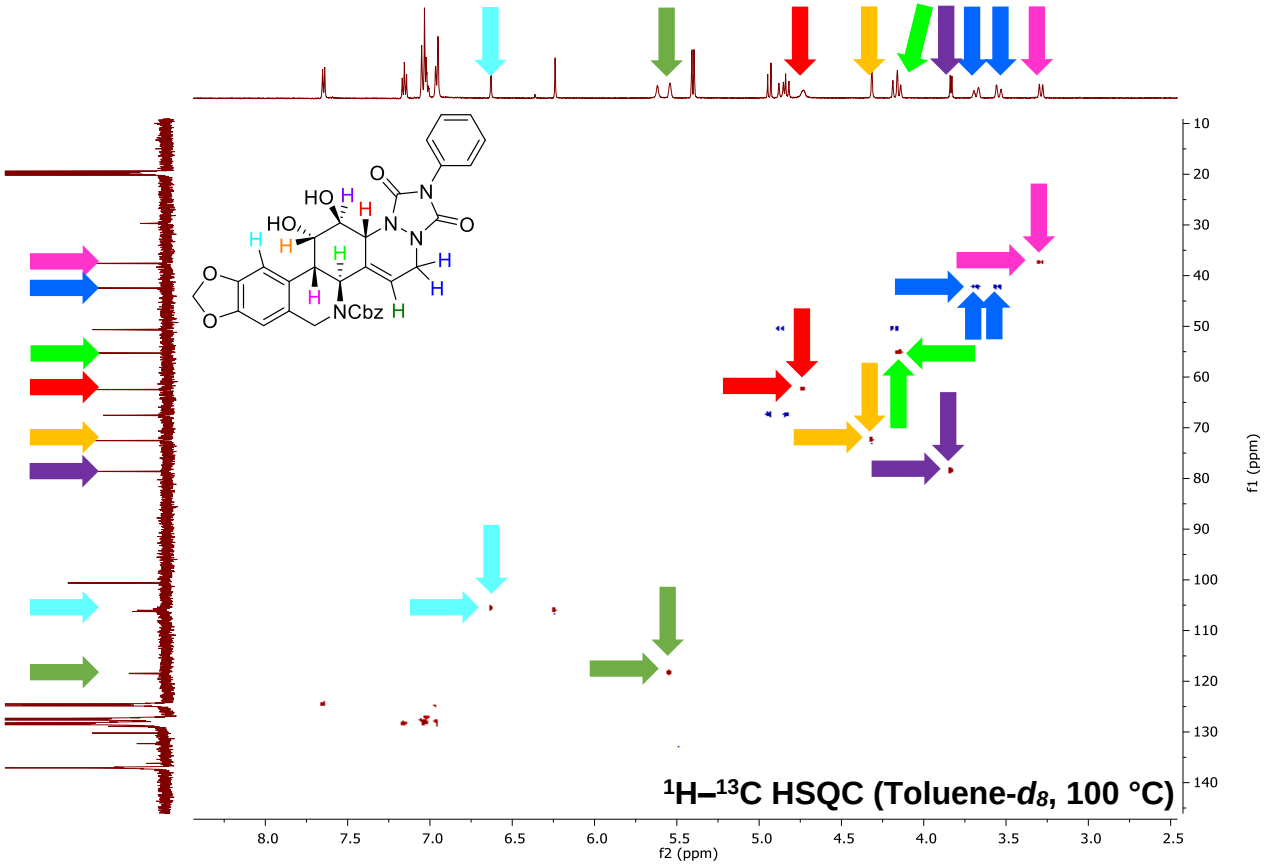
6

^{13}C NMR ($CDCl_3$, –30 °C)

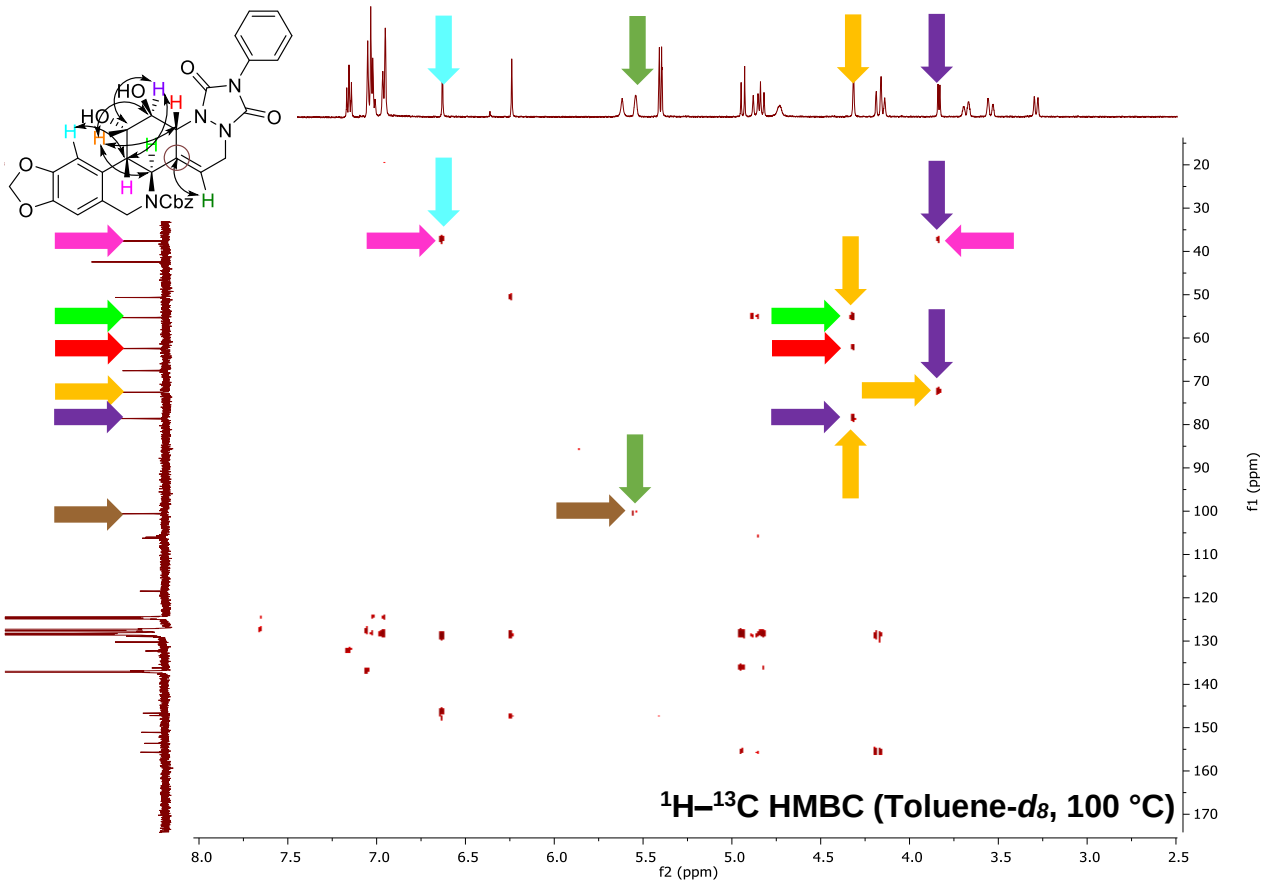




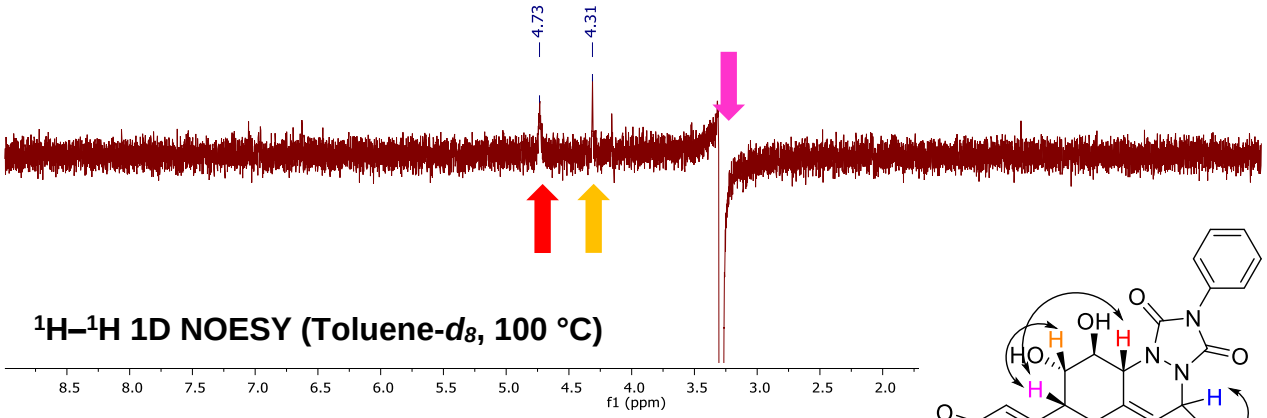
^{1}H–^{1}H COSY (Toluene-*d*$_8$, 100 °C)



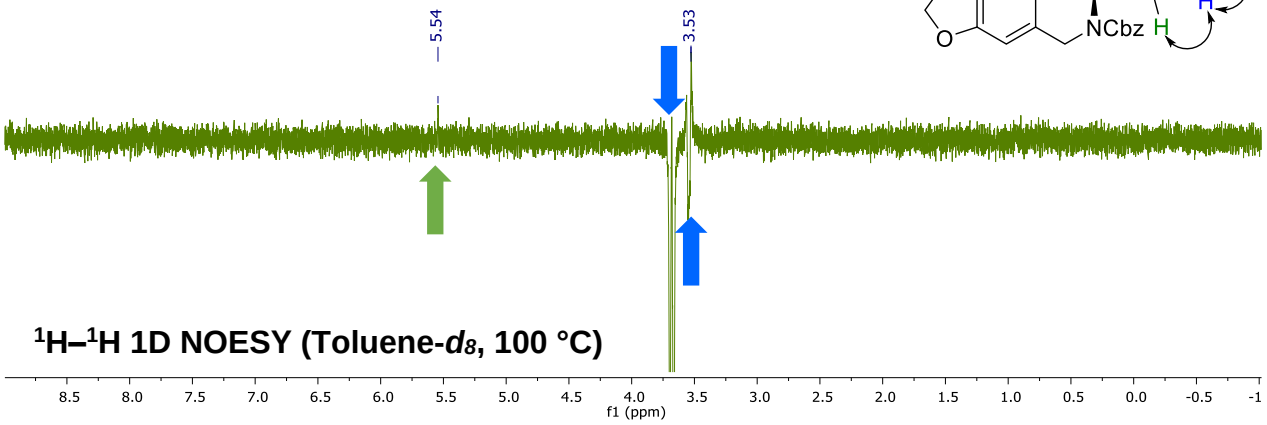
^{1}H–^{13}C HSQC (Toluene-*d*$_8$, 100 °C)



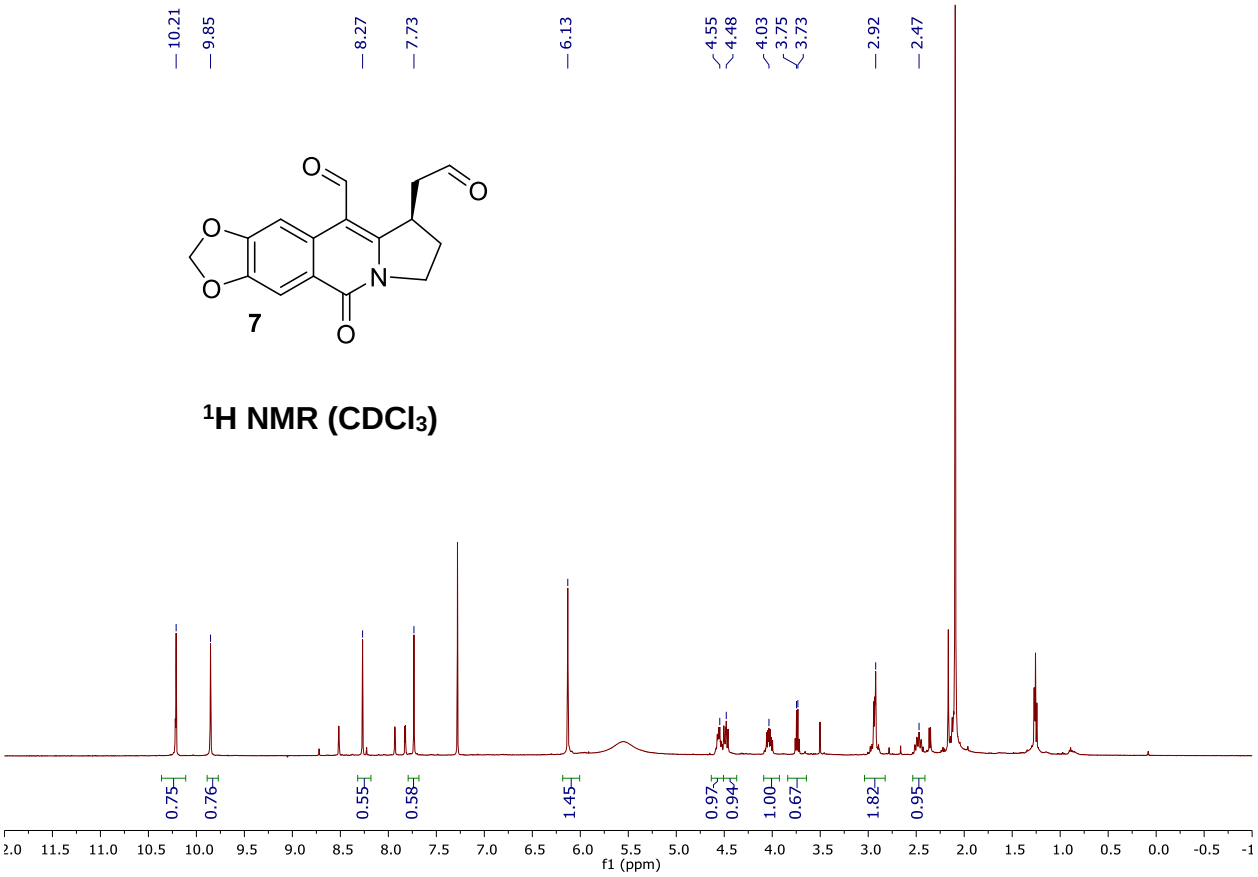
^{1}H–^{13}C HMBC (Toluene-*d*$_8$, 100 °C)



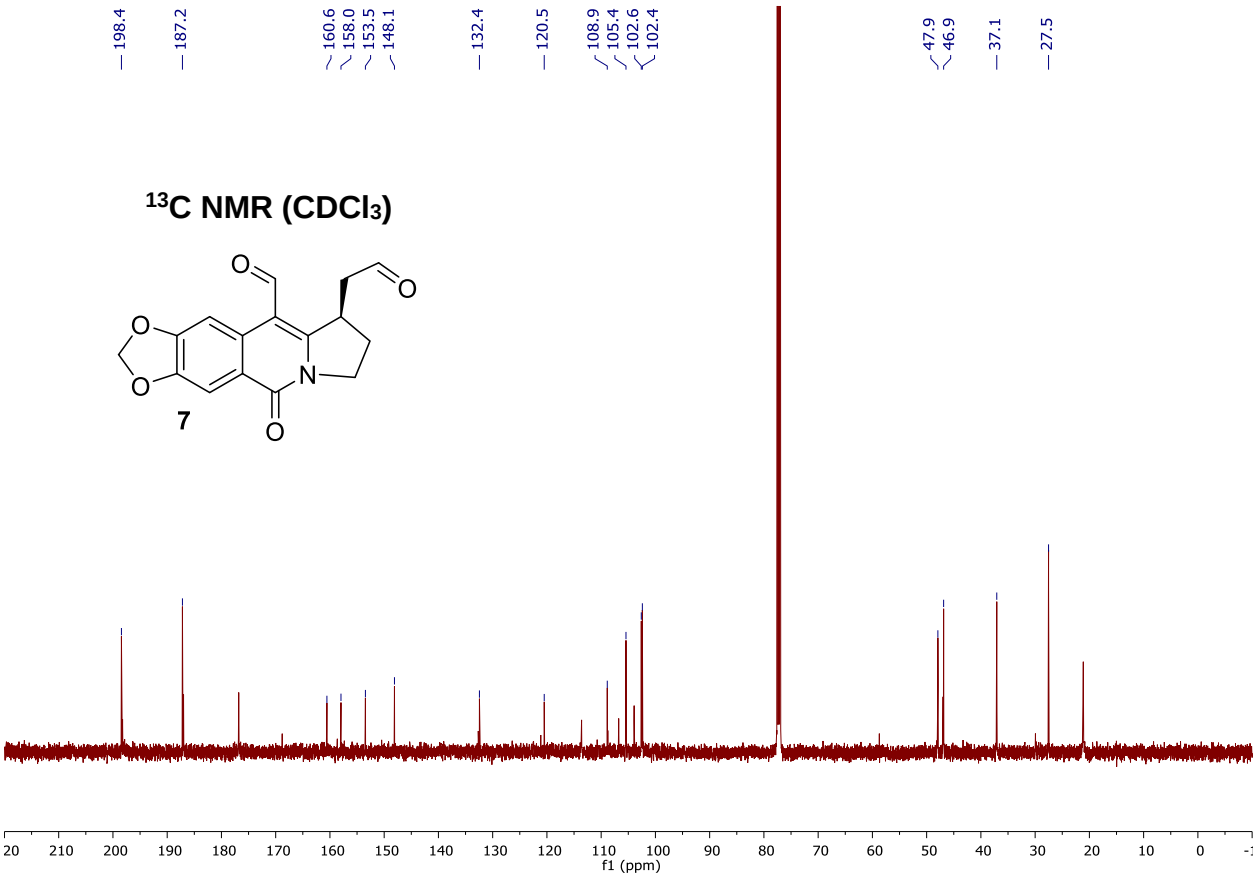
^{1}H–^{1}H 1D NOESY (Toluene-*d*$_8$, 100 °C)



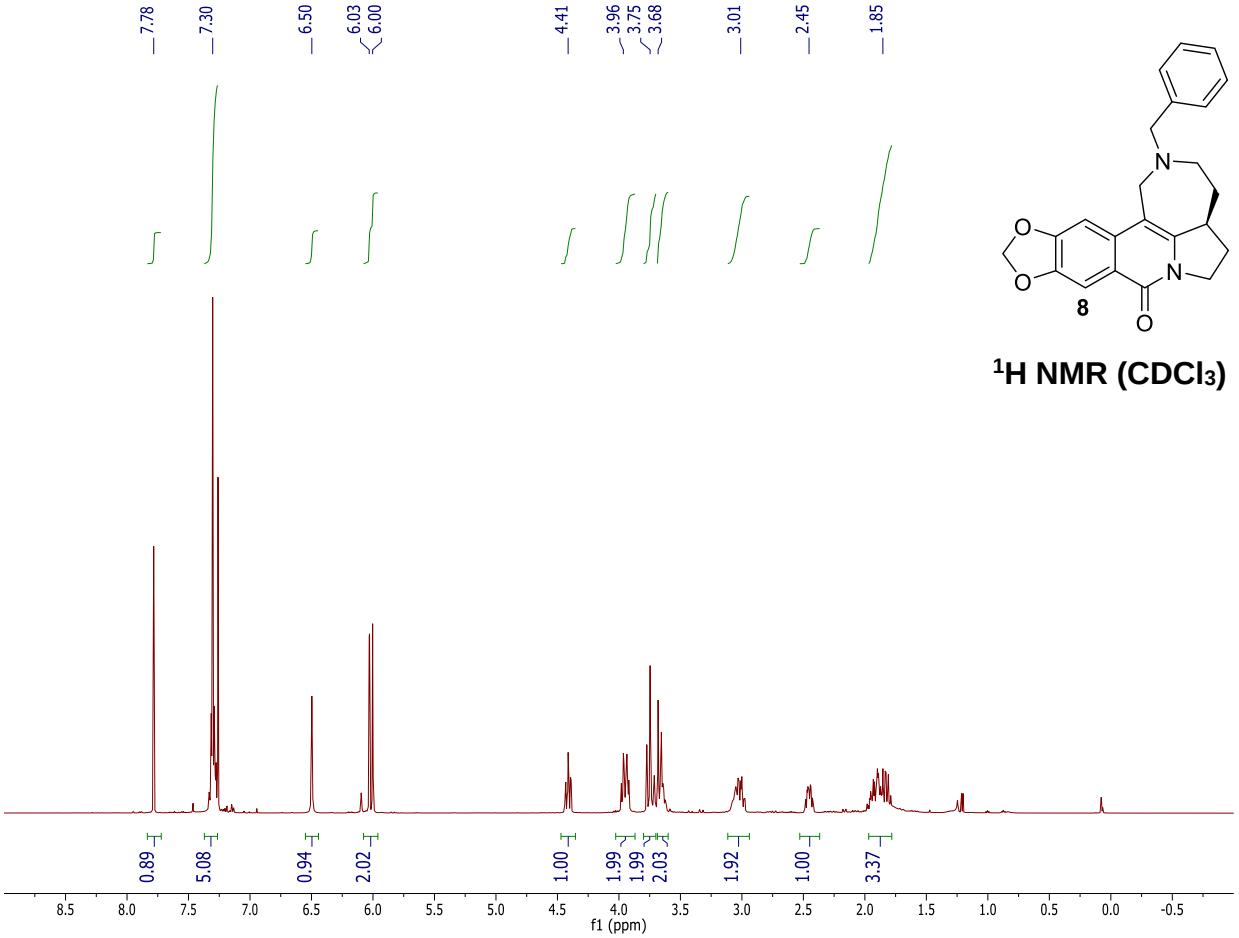
^{1}H–^{1}H 1D NOESY (Toluene-*d*$_8$, 100 °C)



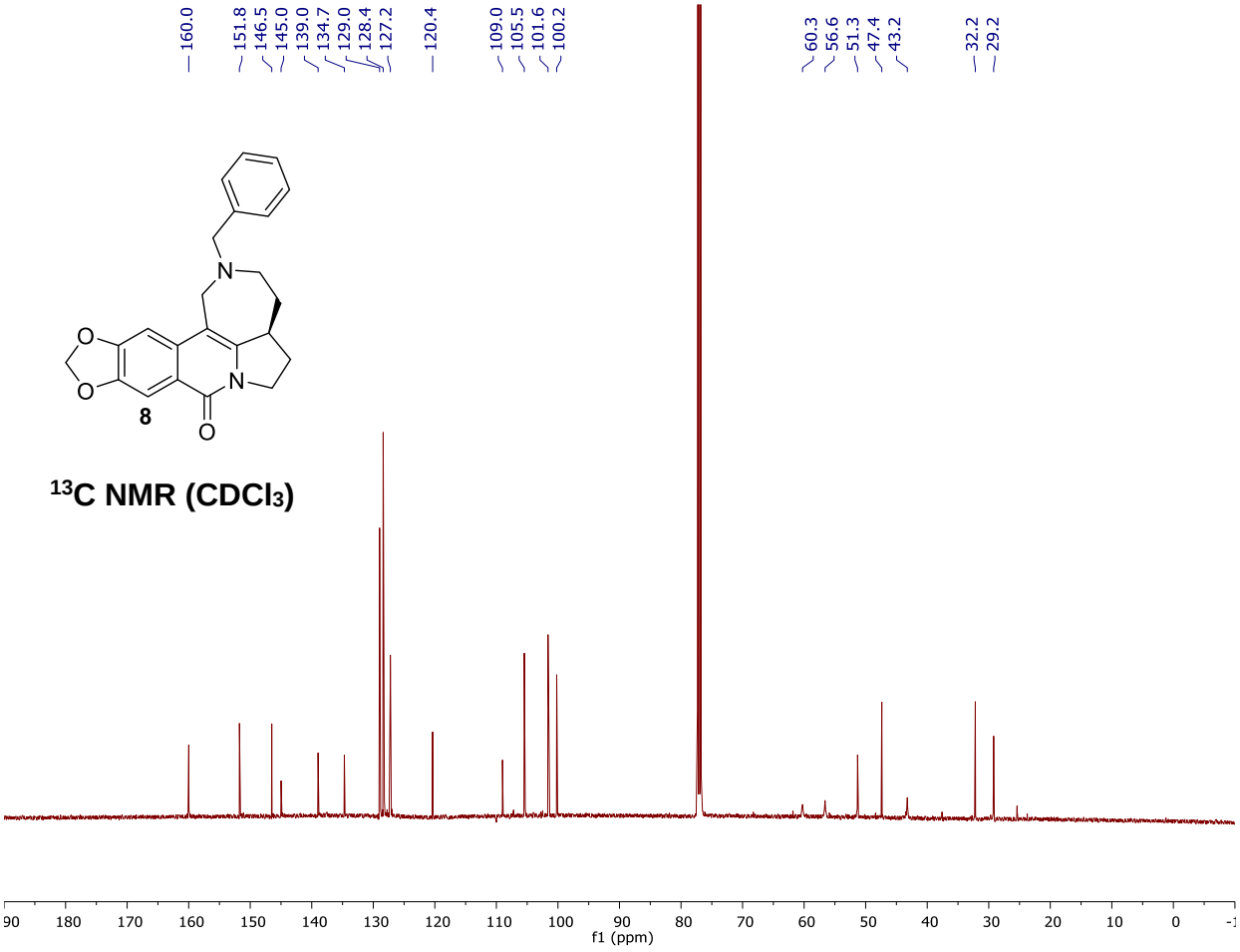
^{1}H NMR ($CDCl_3$)



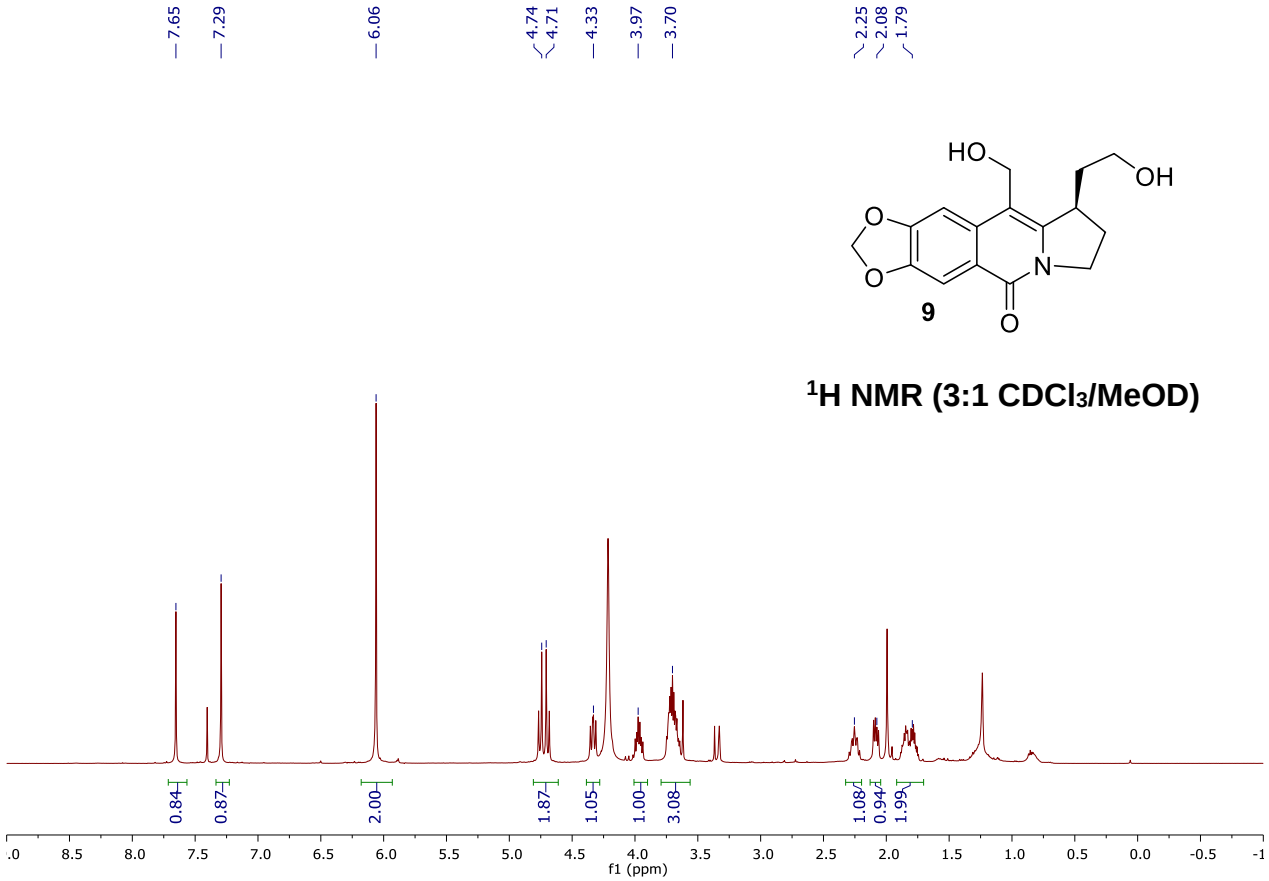
^{13}C NMR ($CDCl_3$)



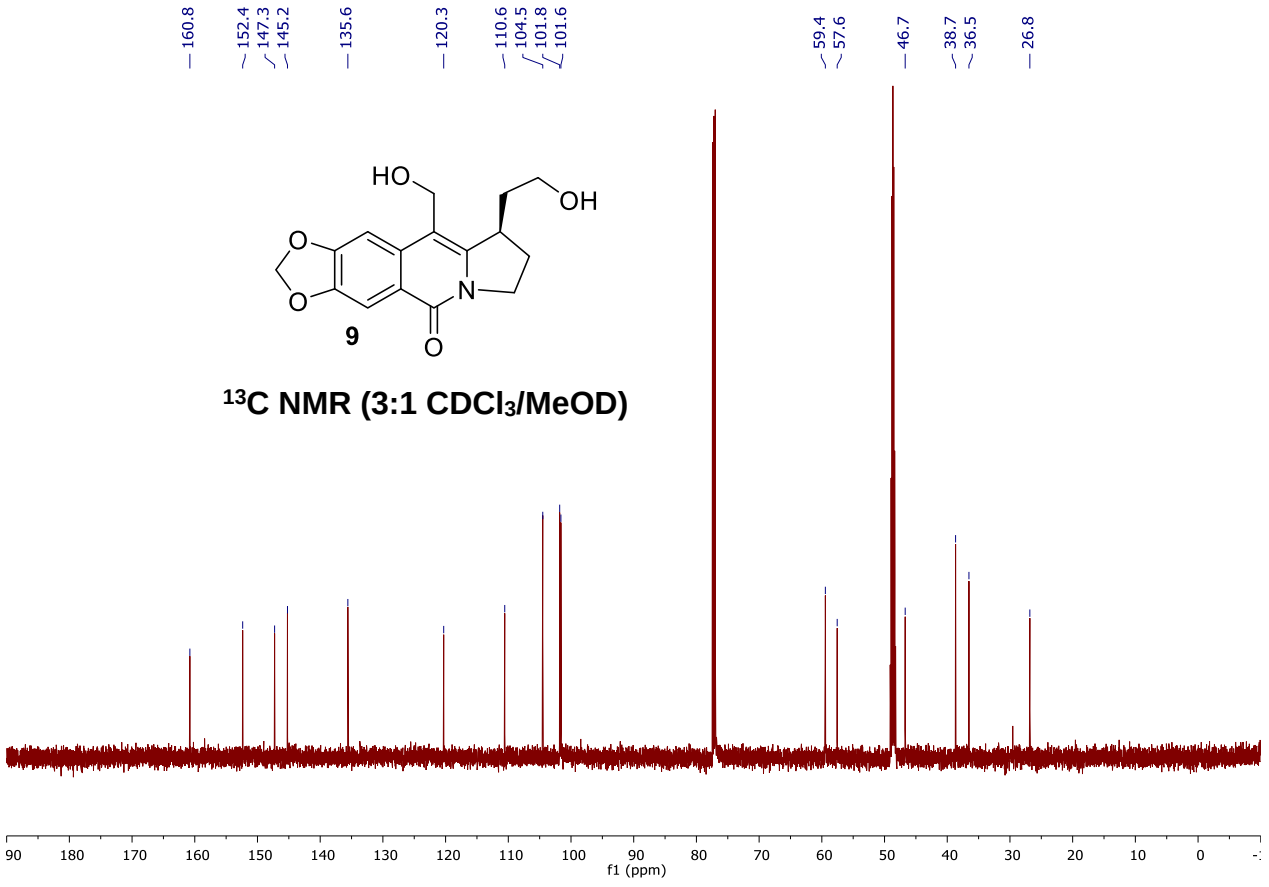
^{1}H NMR ($CDCl_3$)



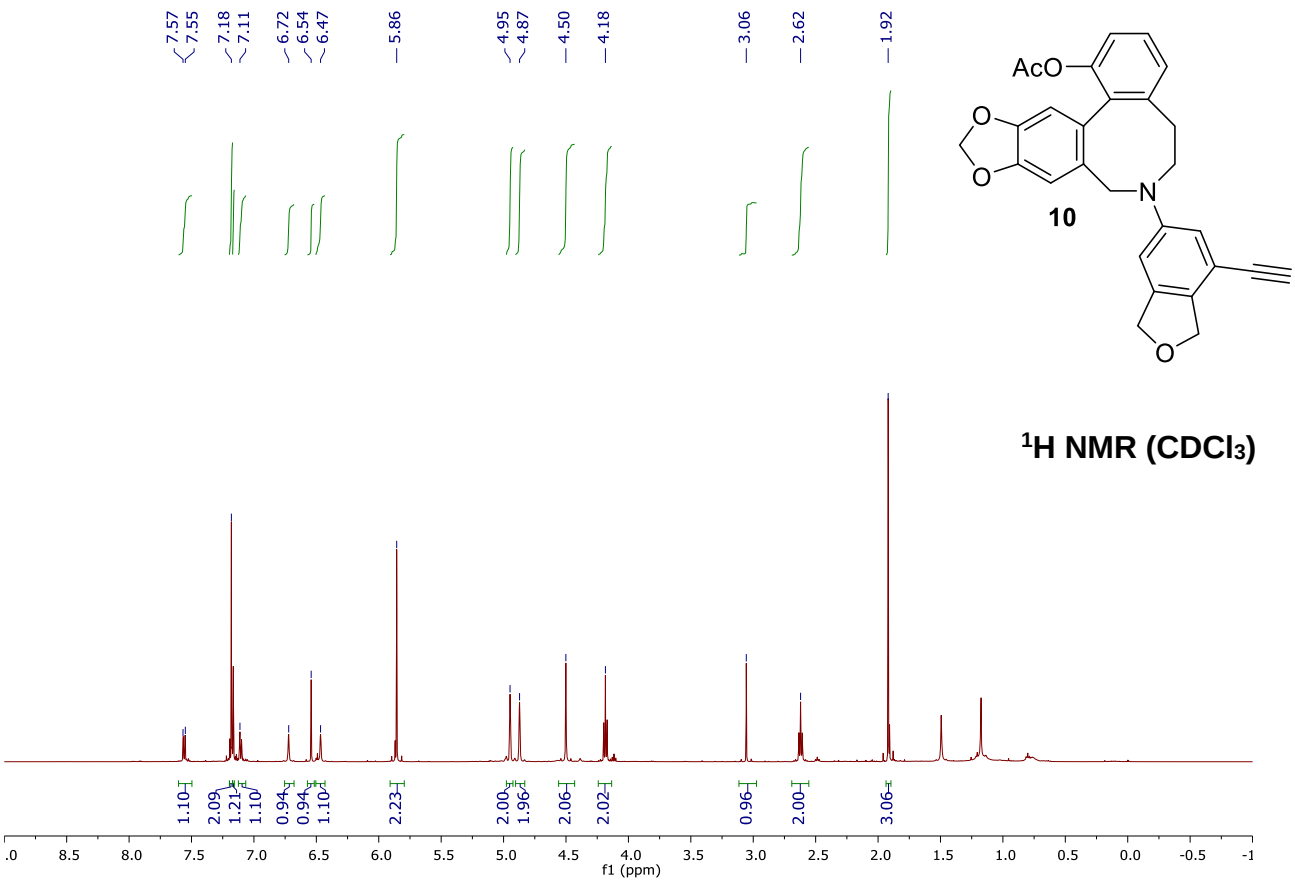
^{13}C NMR ($CDCl_3$)



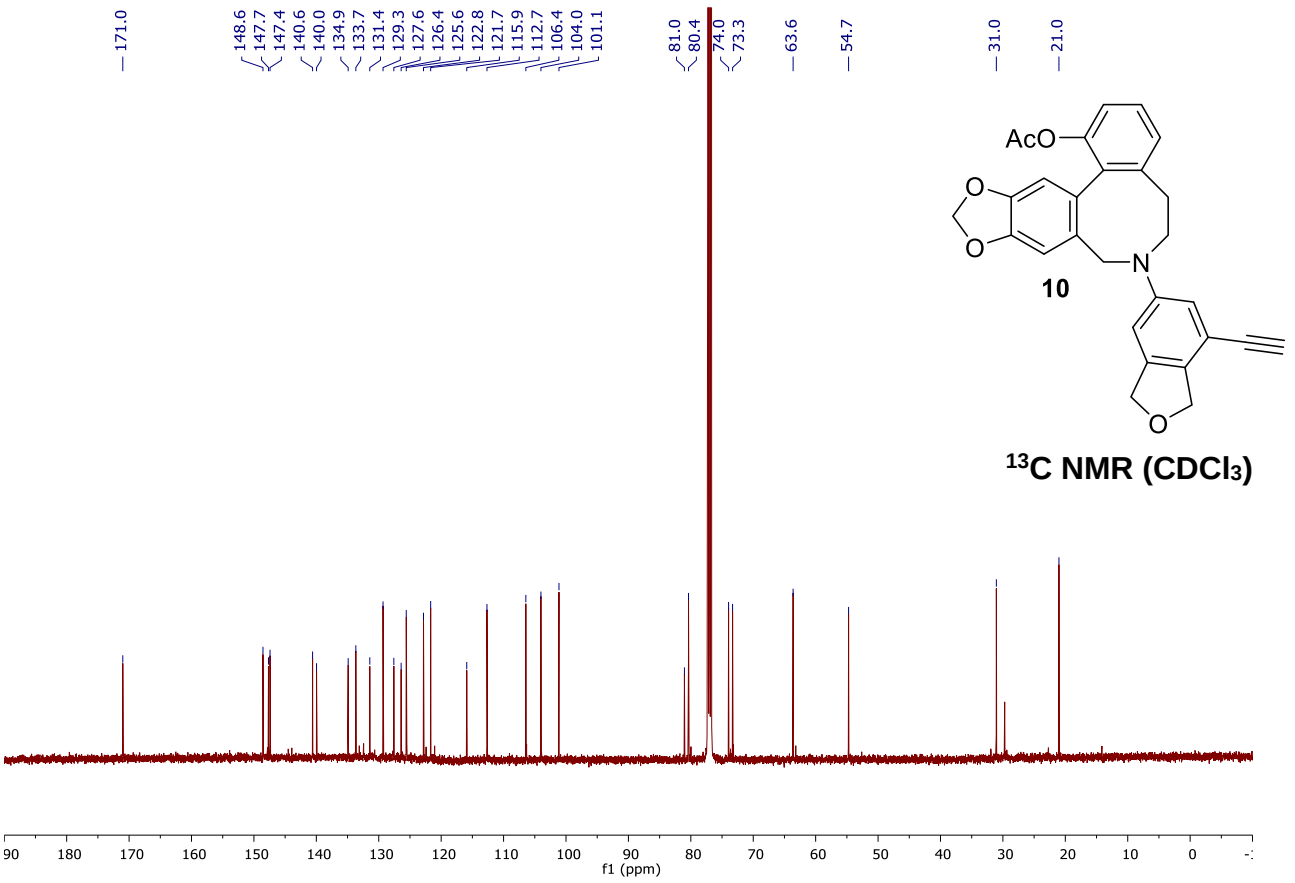
^{1}H NMR (3:1 $CDCl_3$/MeOD)



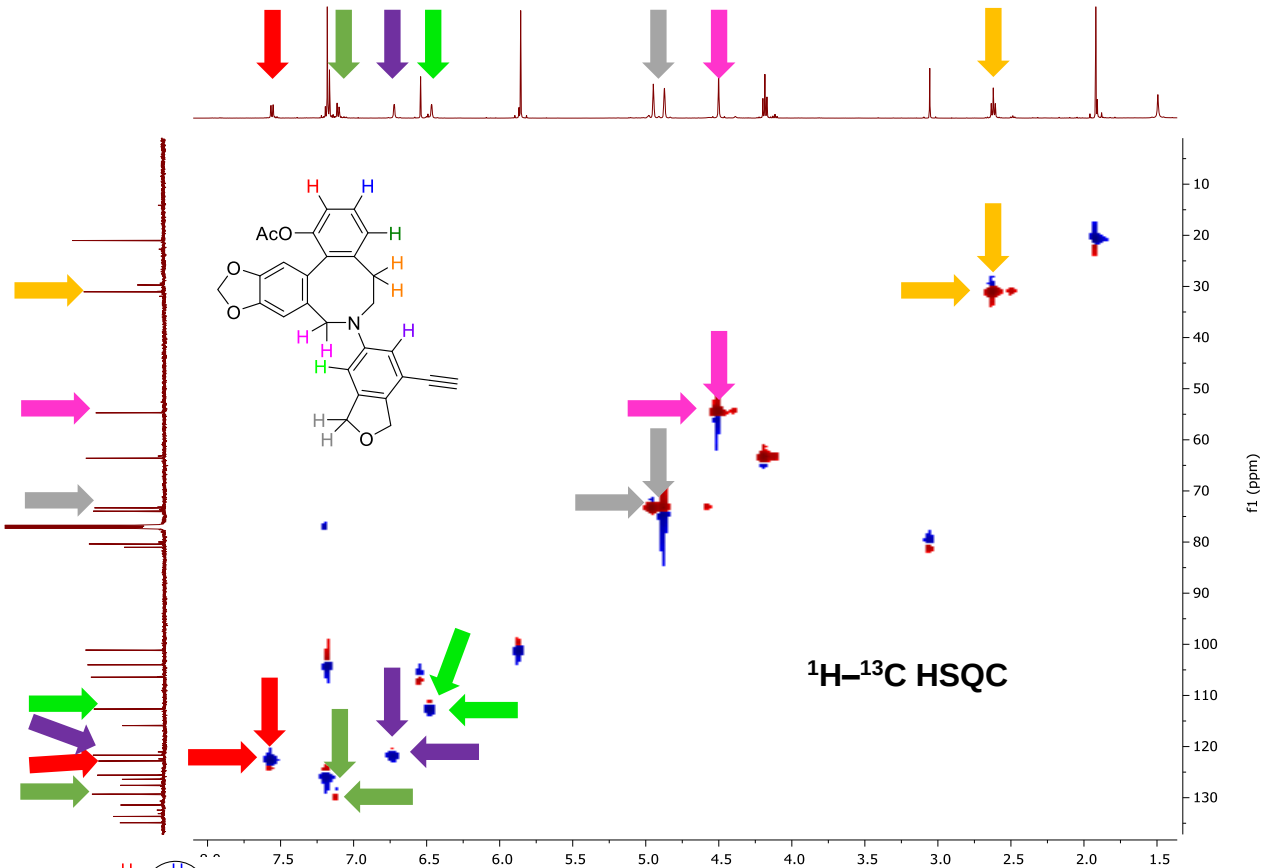
^{13}C NMR (3:1 $CDCl_3$/MeOD)

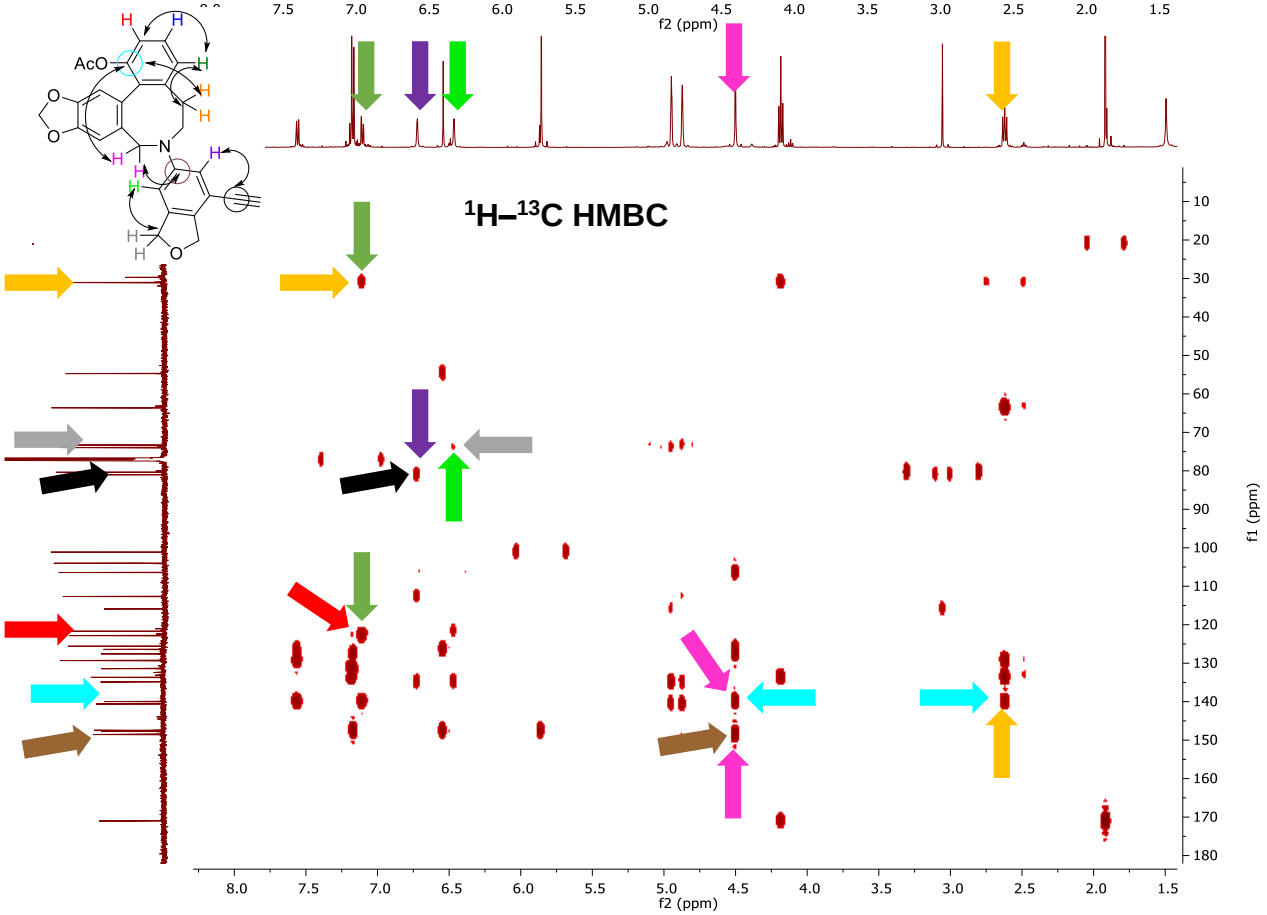


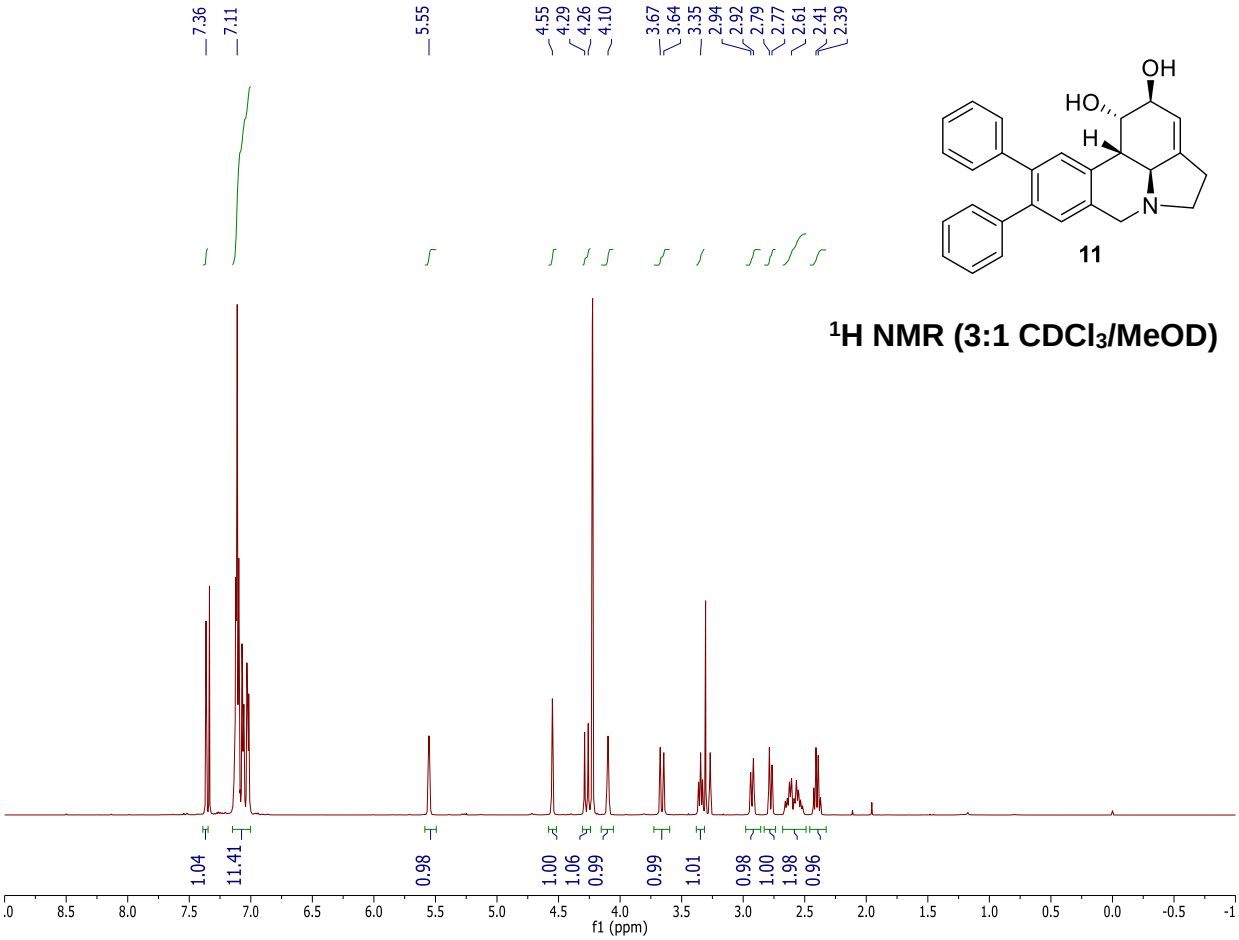
^{1}H NMR ($CDCl_3$)



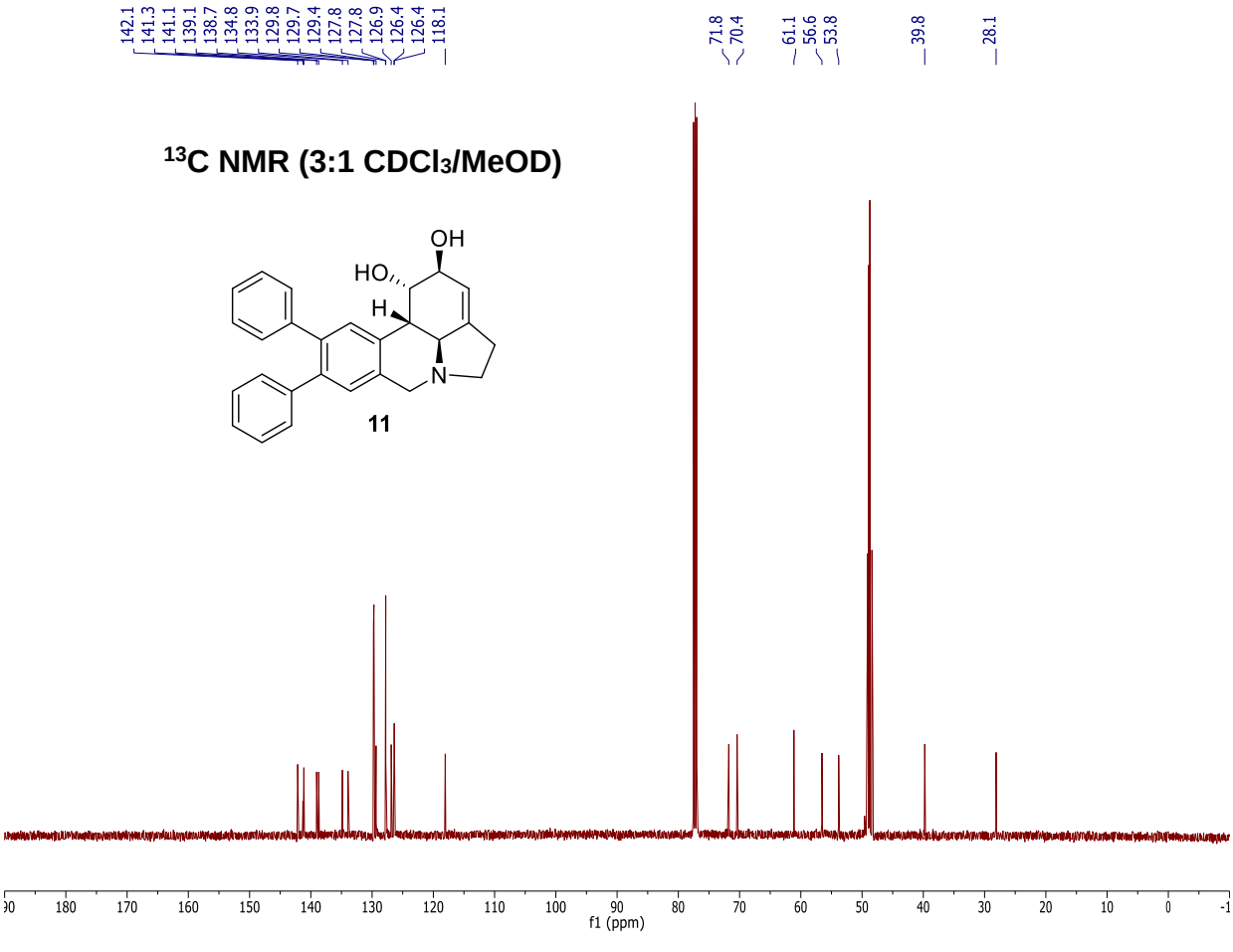
^{13}C NMR ($CDCl_3$)


AcO
O
O
N
O
^{1}H–^{13}C HSQC
f2 (ppm)
f1 (ppm)

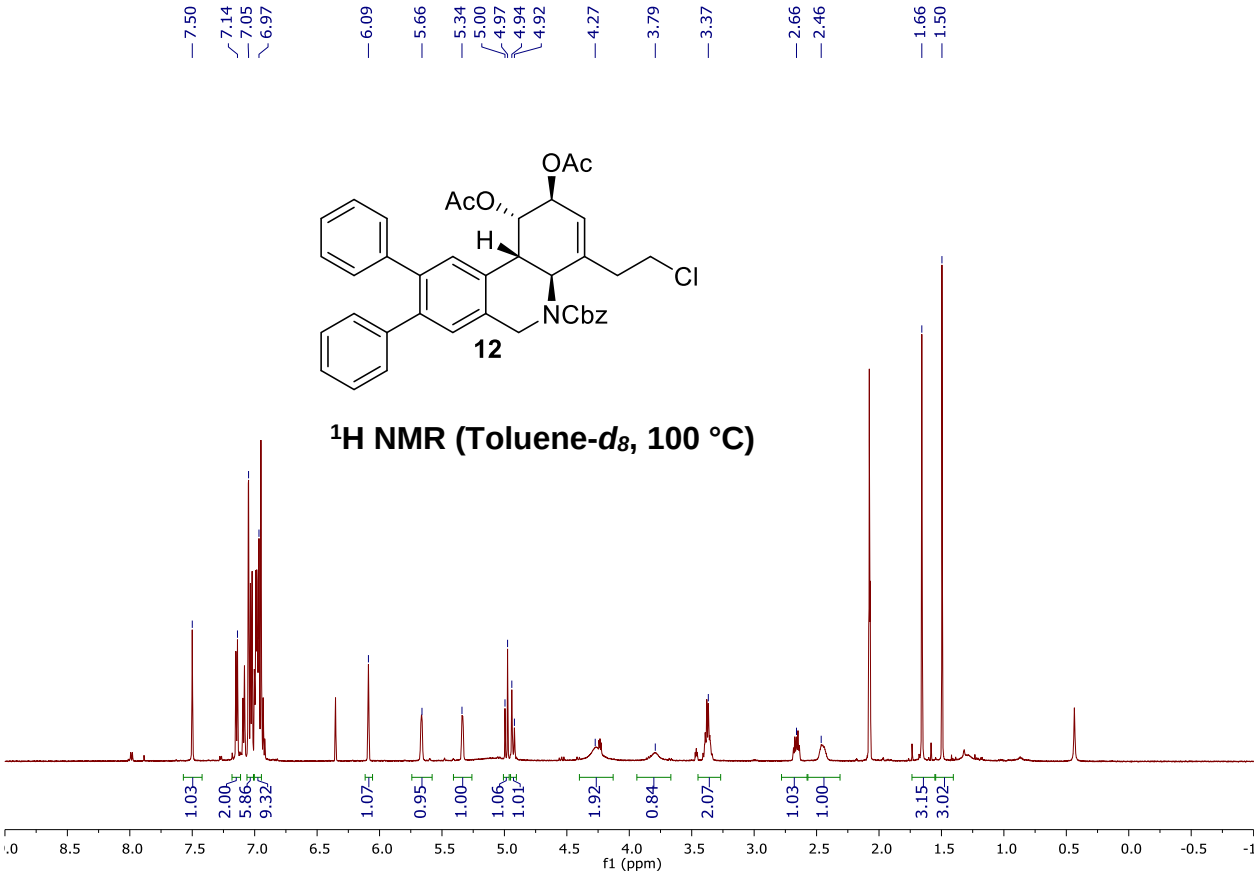

AcO
O
O
N
O
^{1}H–^{13}C HMBC
f2 (ppm)
f1 (ppm)



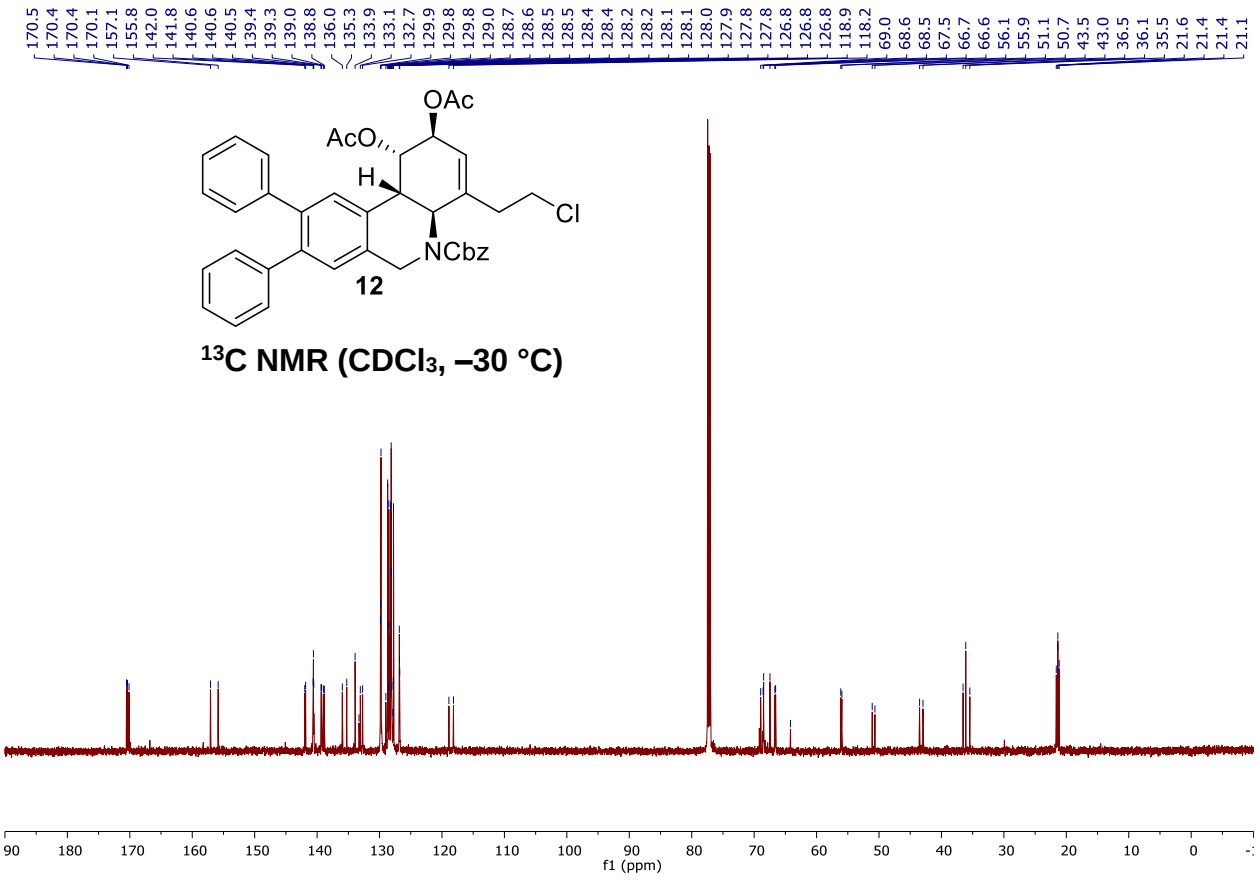
^{1}H NMR (3:1 $CDCl_3$/MeOD)



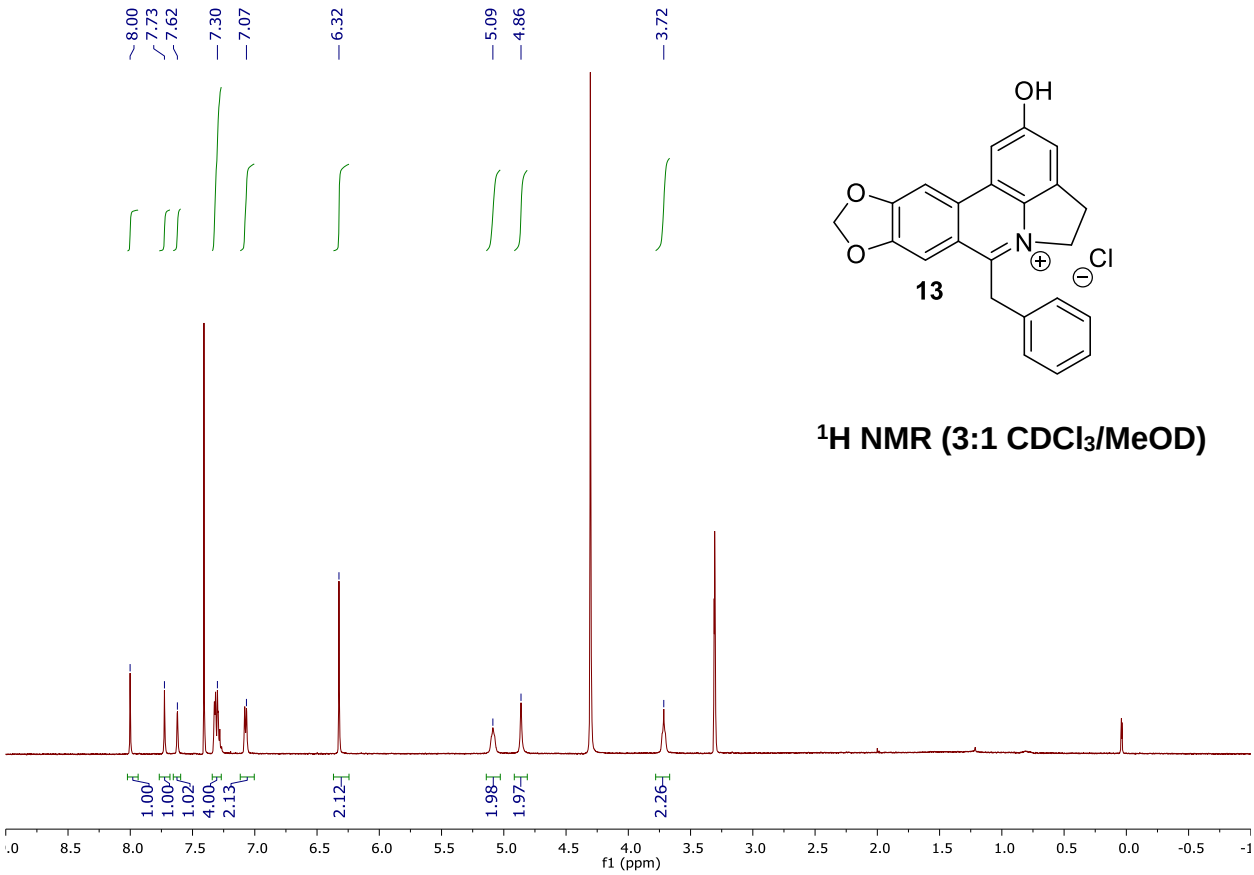
^{13}C NMR (3:1 $CDCl_3$/MeOD)



^{1}H NMR (Toluene-*d*$_8$, 100 °C)



^{13}C NMR ($CDCl_3$, –30 °C)



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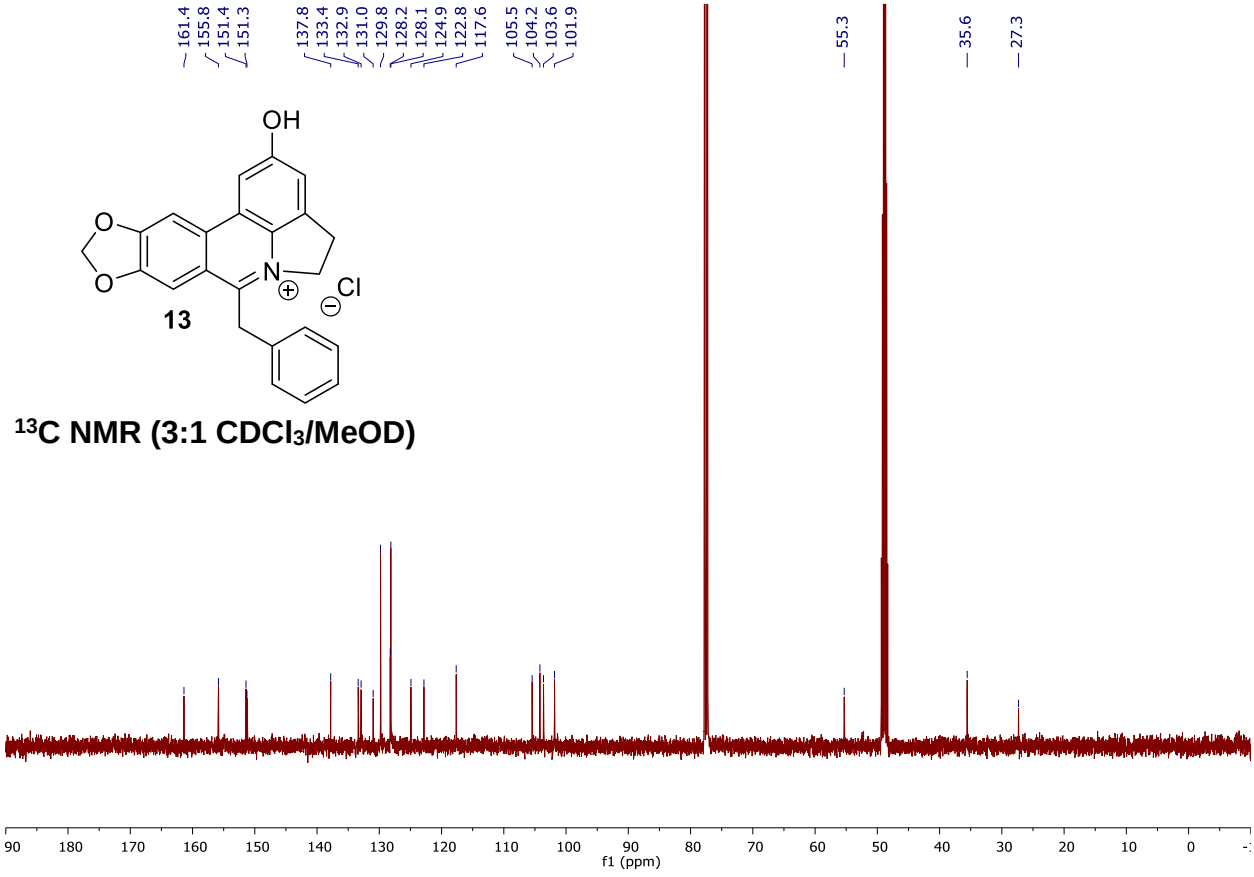
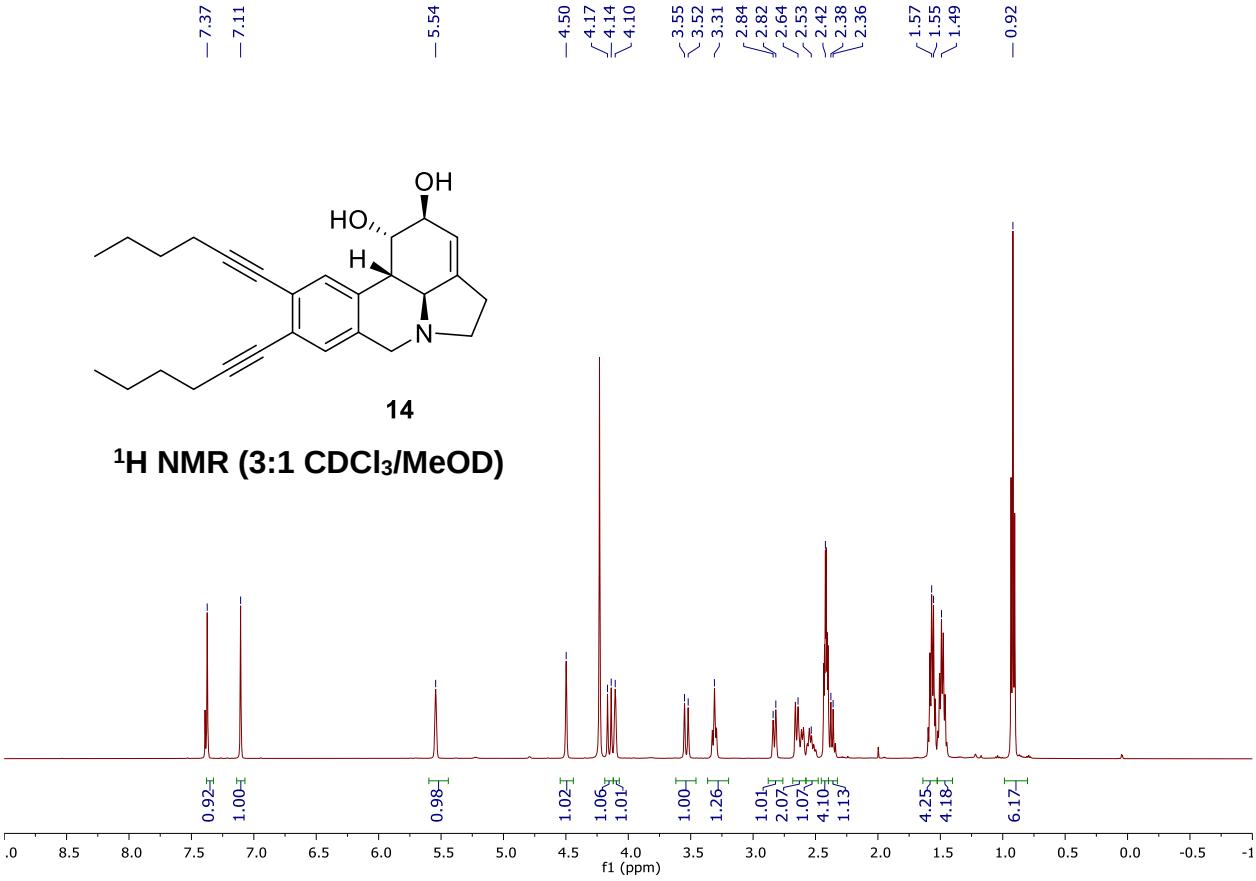
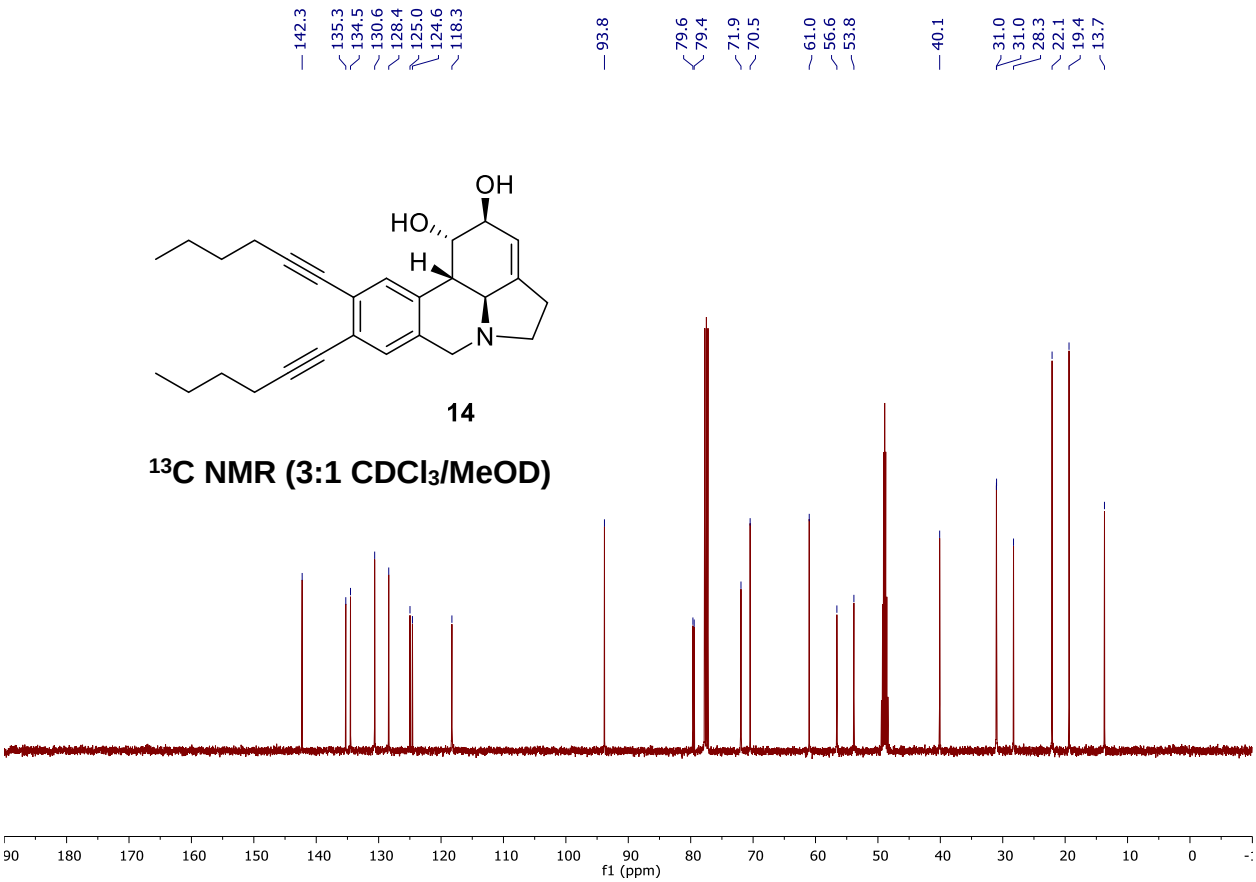


^{13}C NMR (3:1 $CDCl_3$/MeOD)



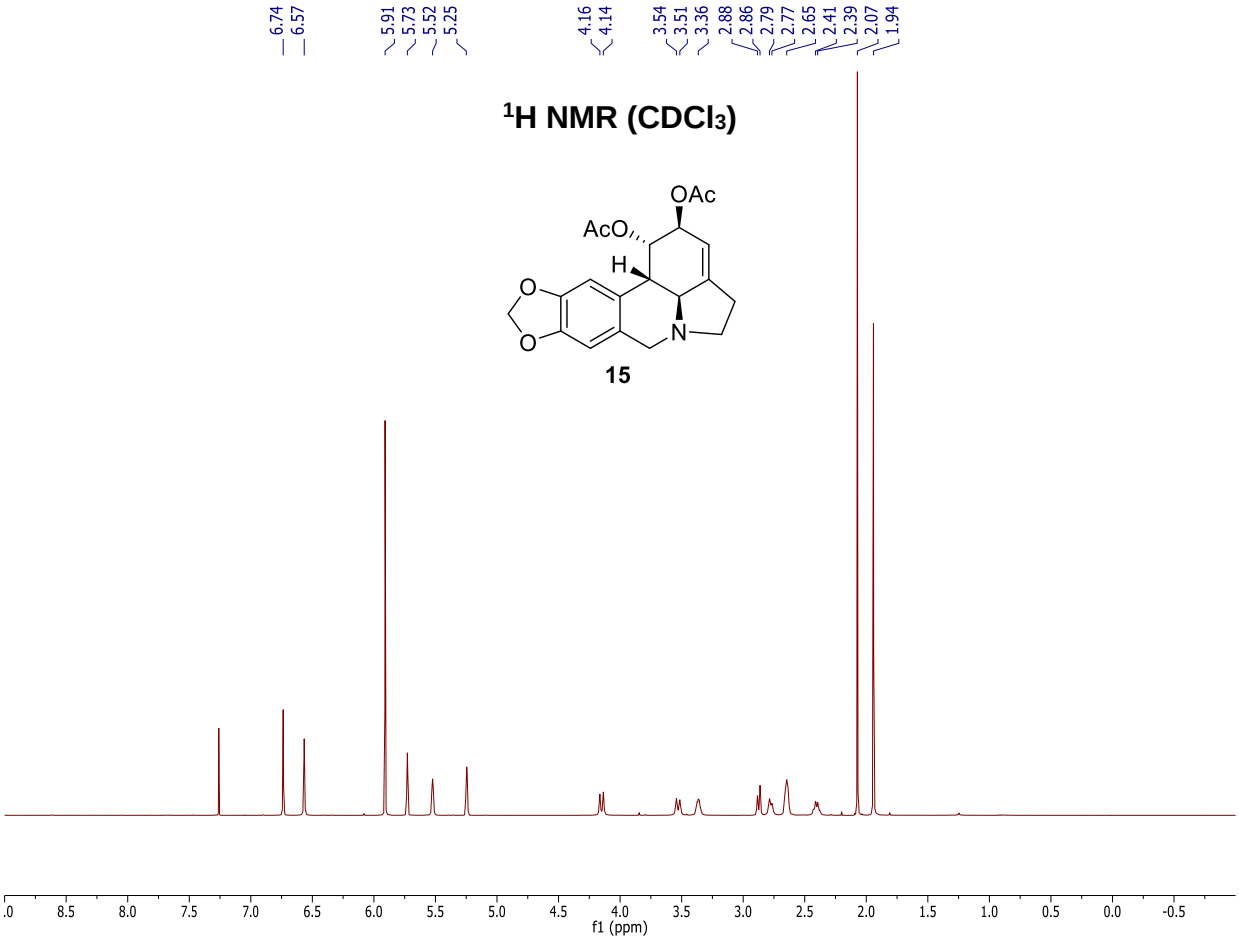
14

^{1}H NMR (3:1 $CDCl_3$/MeOD)



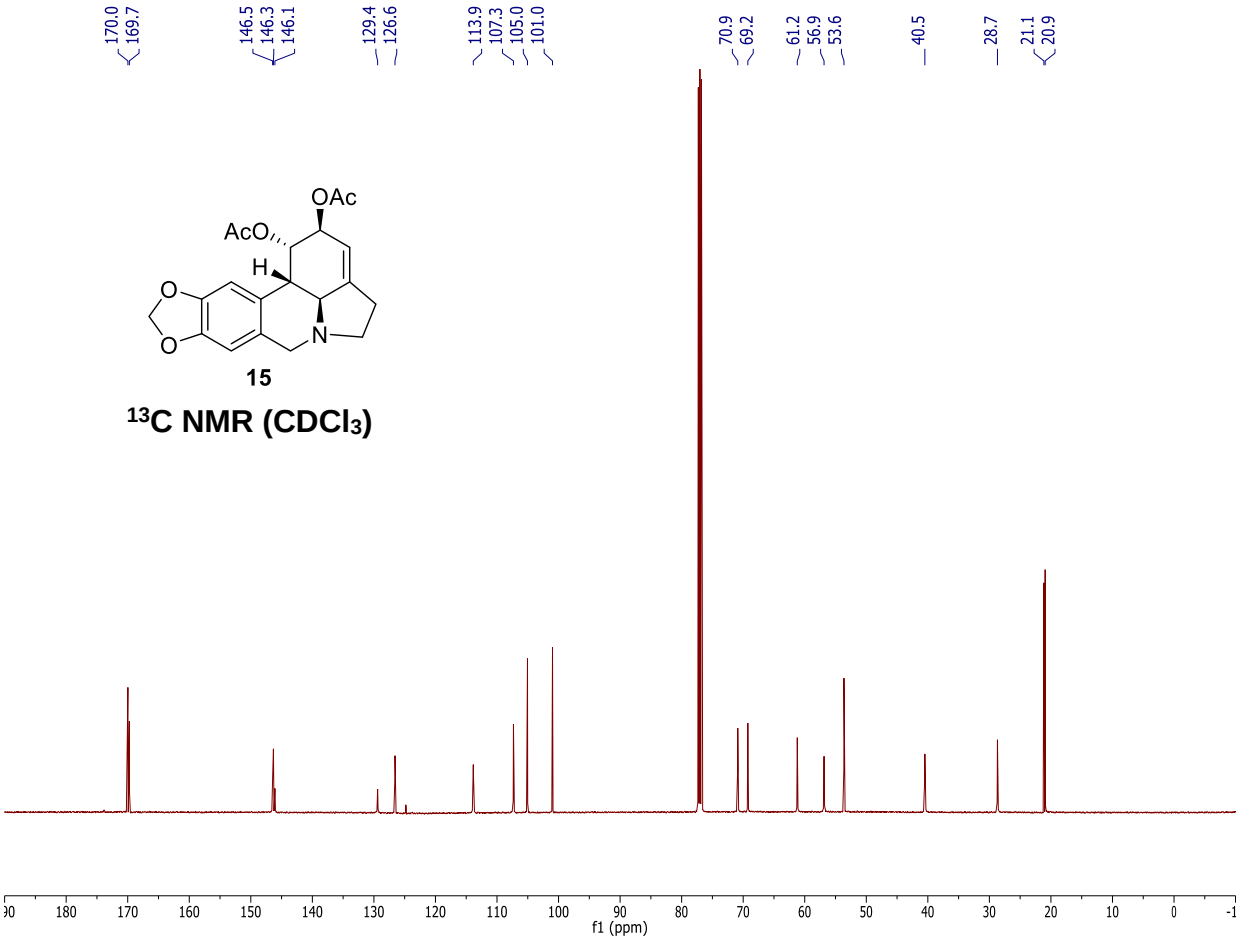
14

^{13}C NMR (3:1 $CDCl_3$/MeOD)



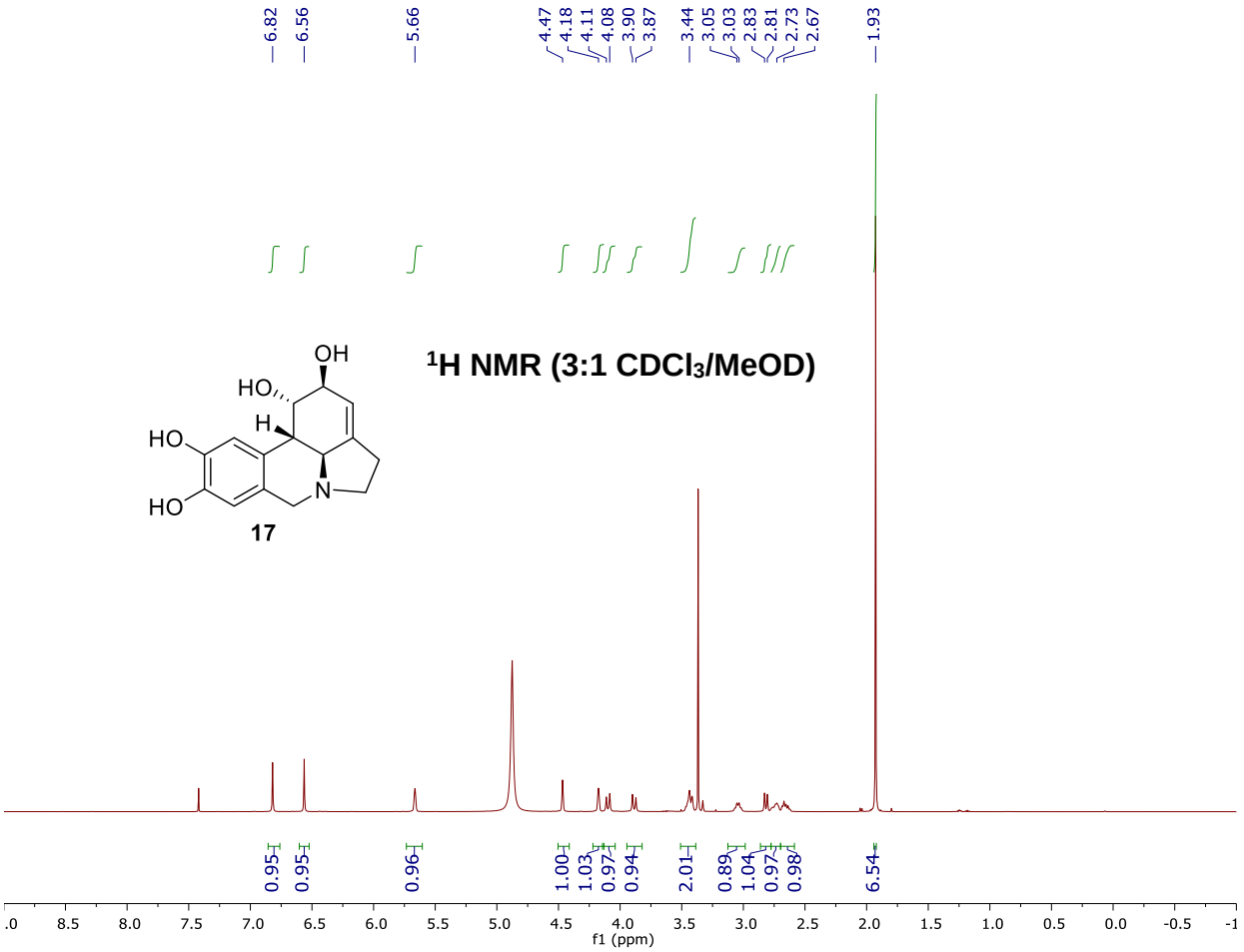
^{1}H NMR ($CDCl_3$)

15



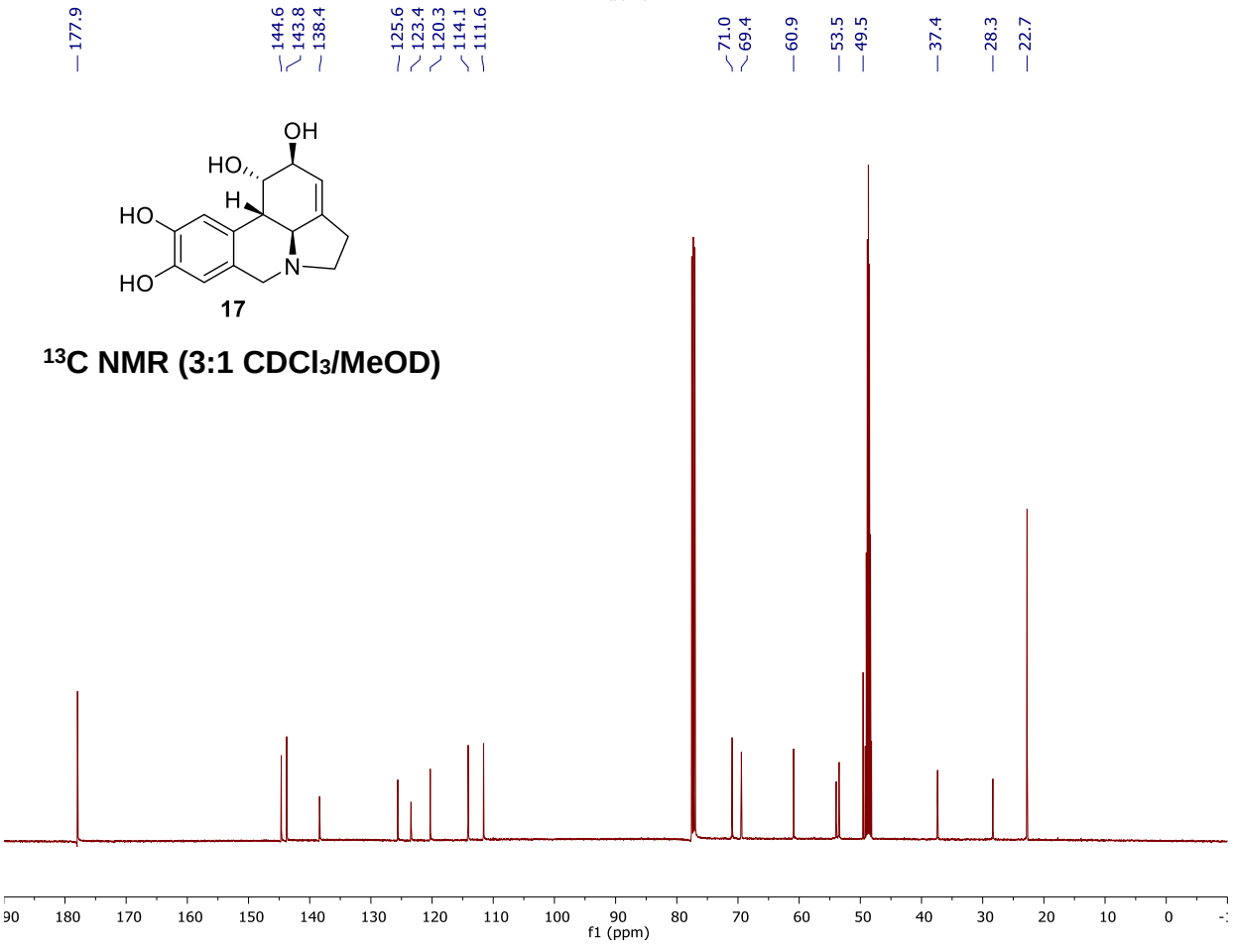
15

^{13}C NMR ($CDCl_3$)



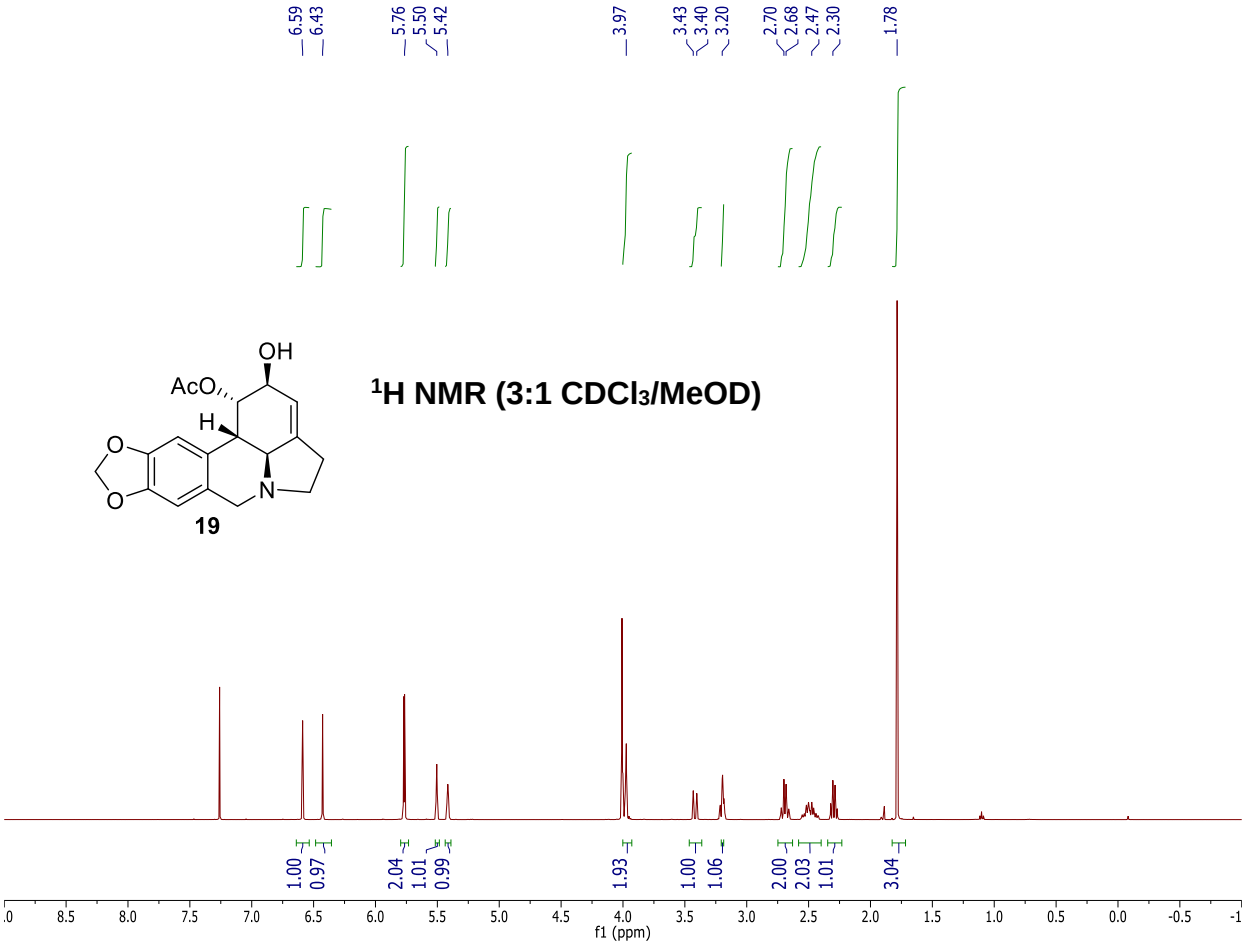
17

^{1}H NMR (3:1 $CDCl_3$/MeOD)



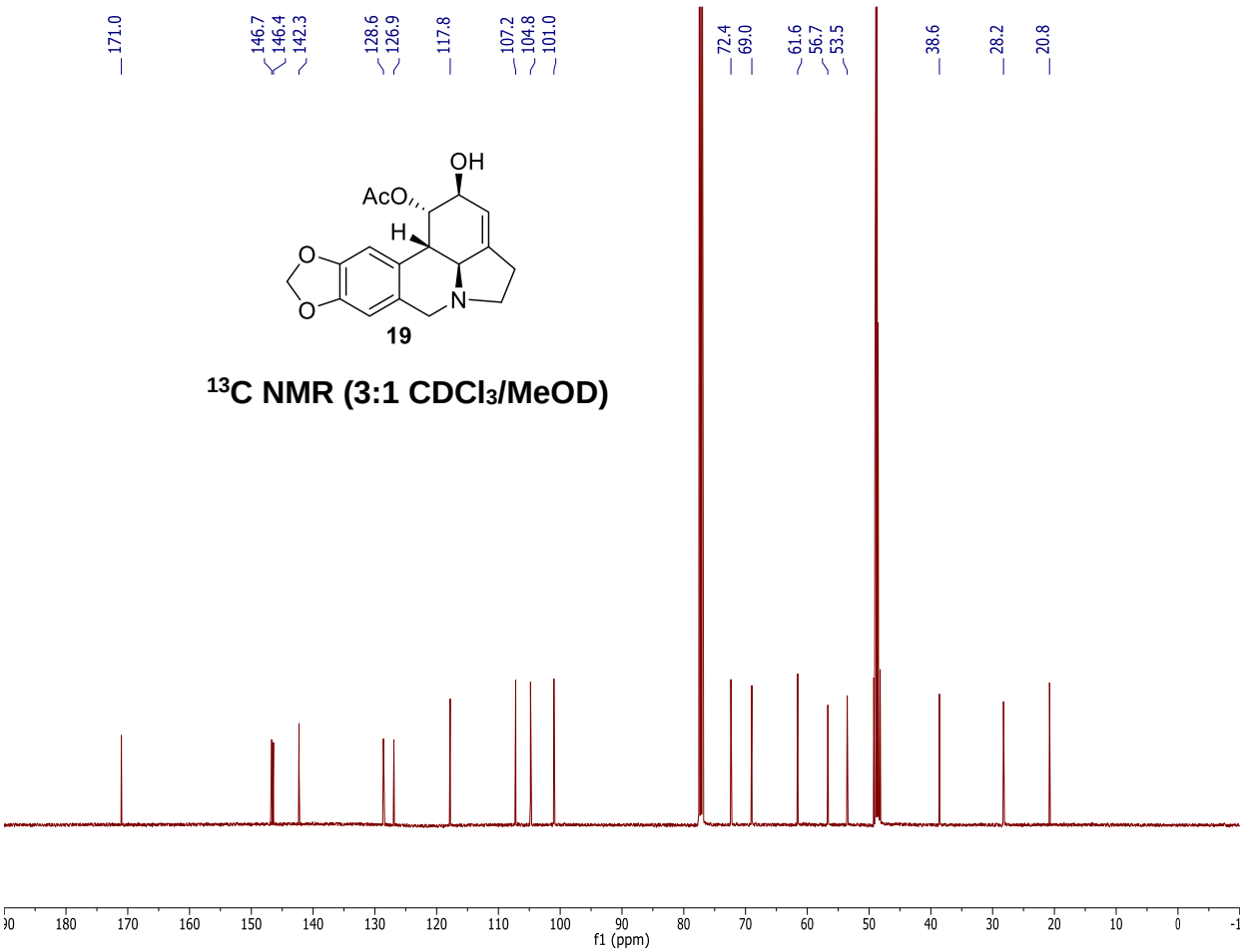
17

^{13}C NMR (3:1 $CDCl_3$/MeOD)



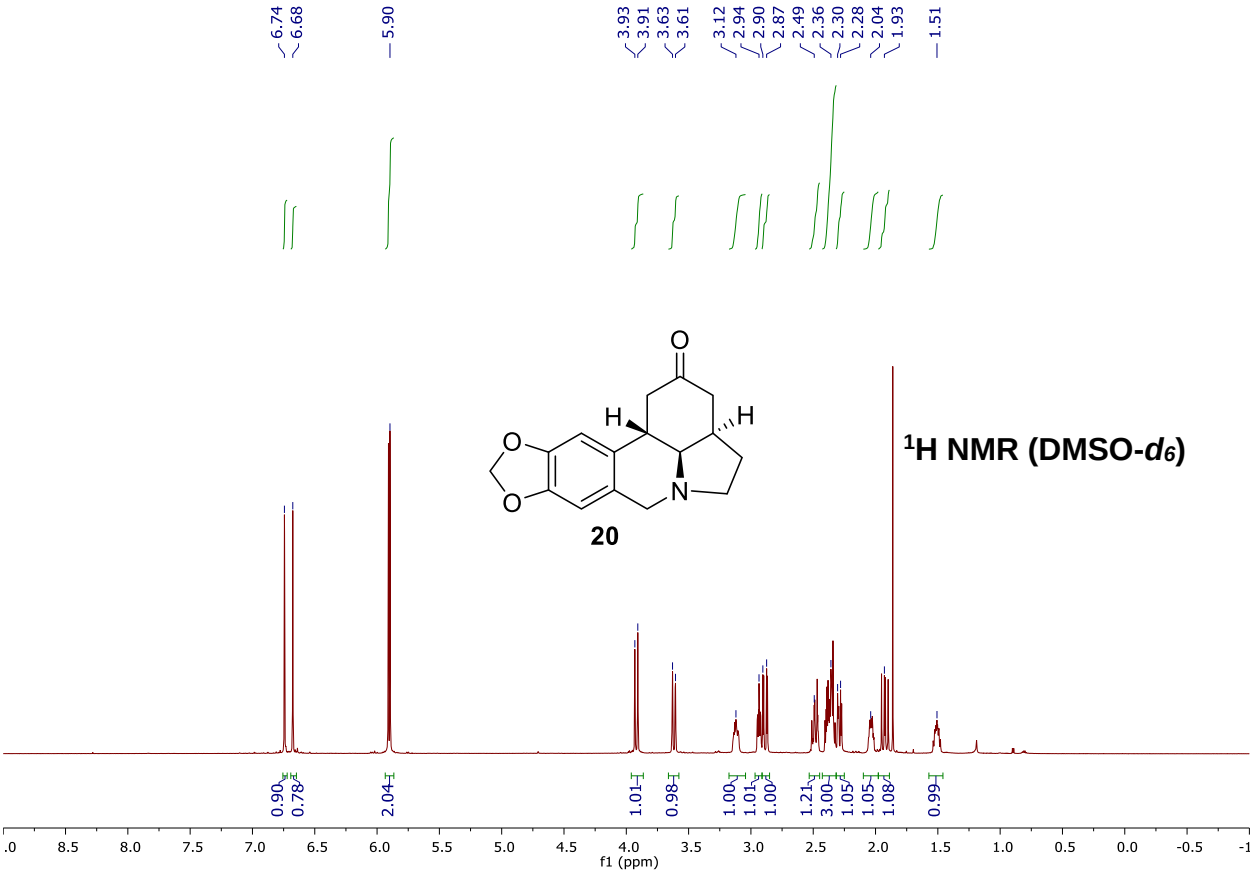
19

^{1}H NMR (3:1 $CDCl_3$/MeOD)



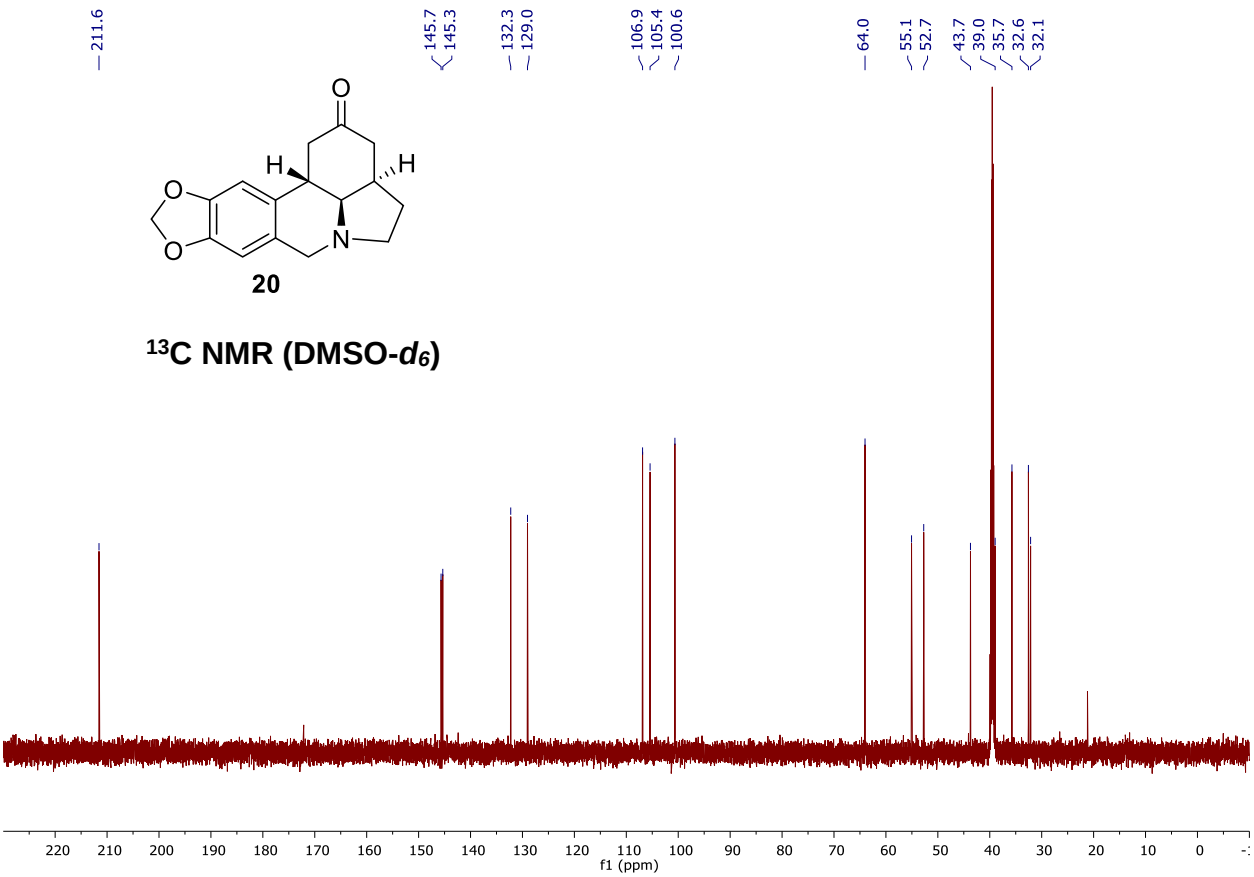
19

^{13}C NMR (3:1 $CDCl_3$/MeOD)



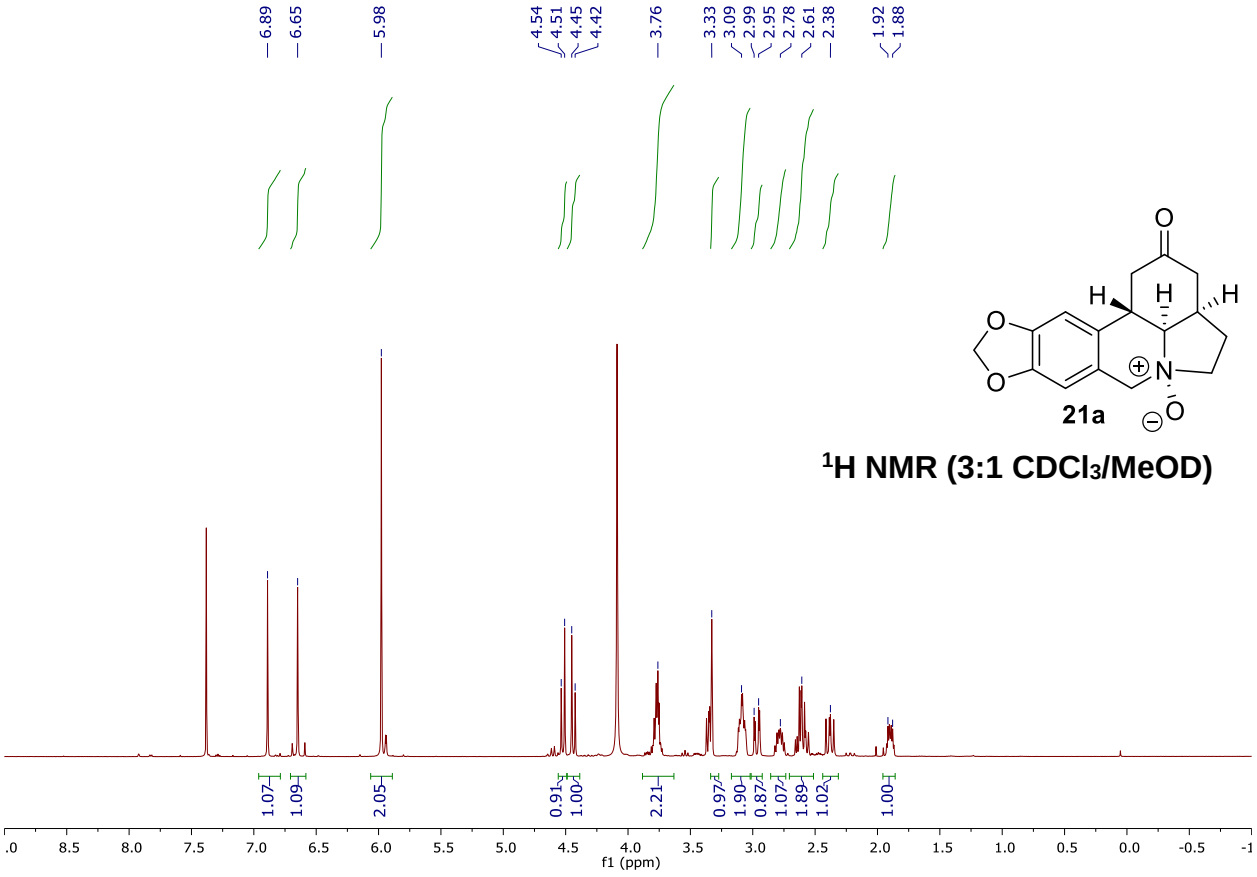
20

^{1}H NMR (DMSO-*d*$_6$)



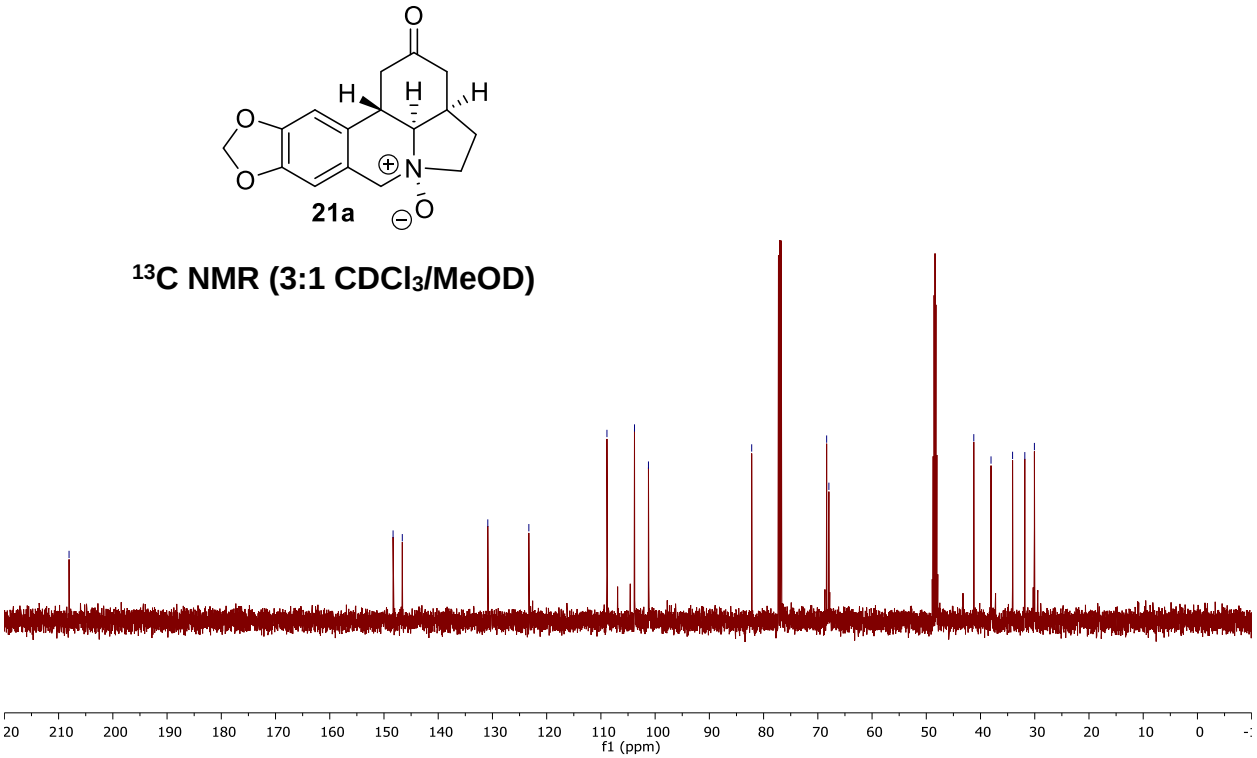
20

^{13}C NMR (DMSO-*d*$_6$)



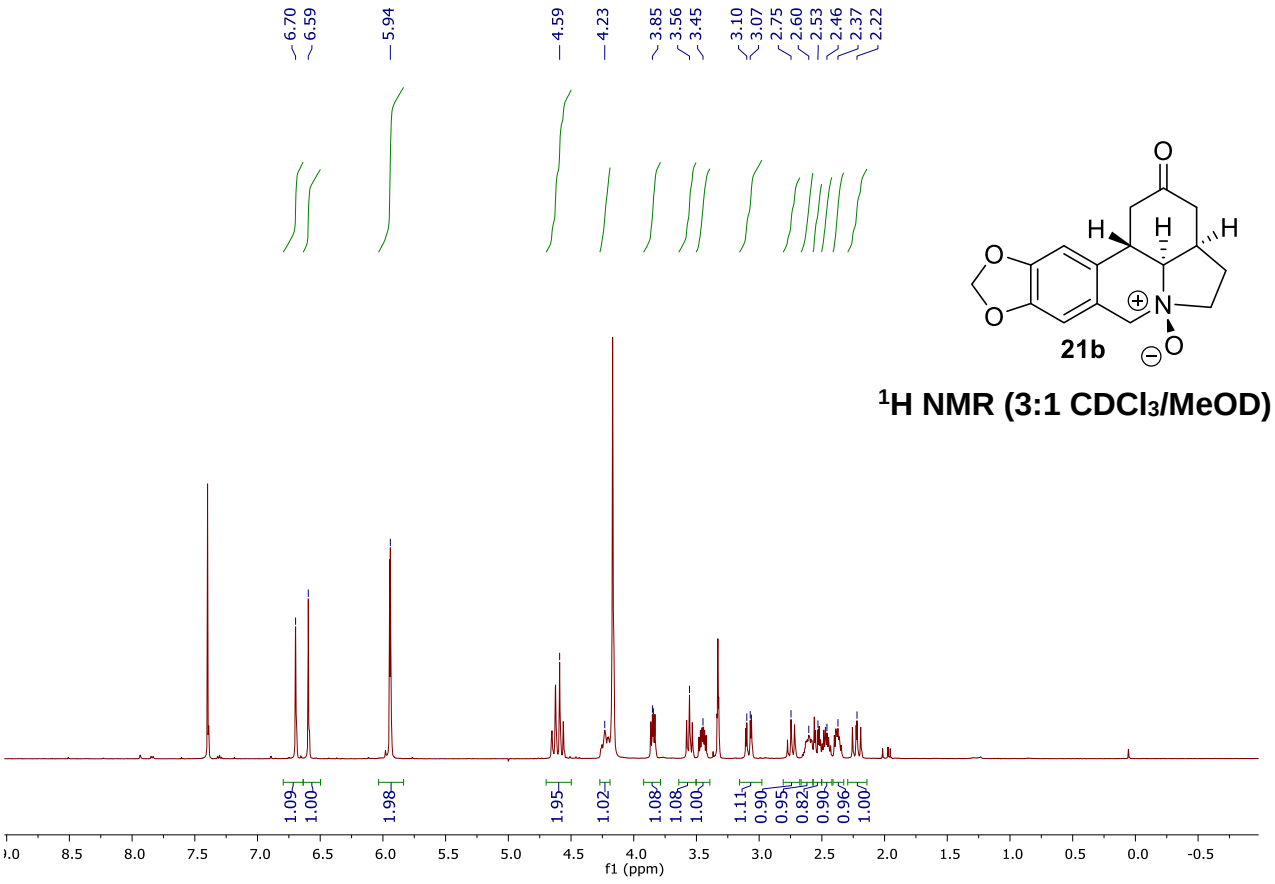
21a

^{1}H NMR (3:1 CDCl$_3$/MeOD)

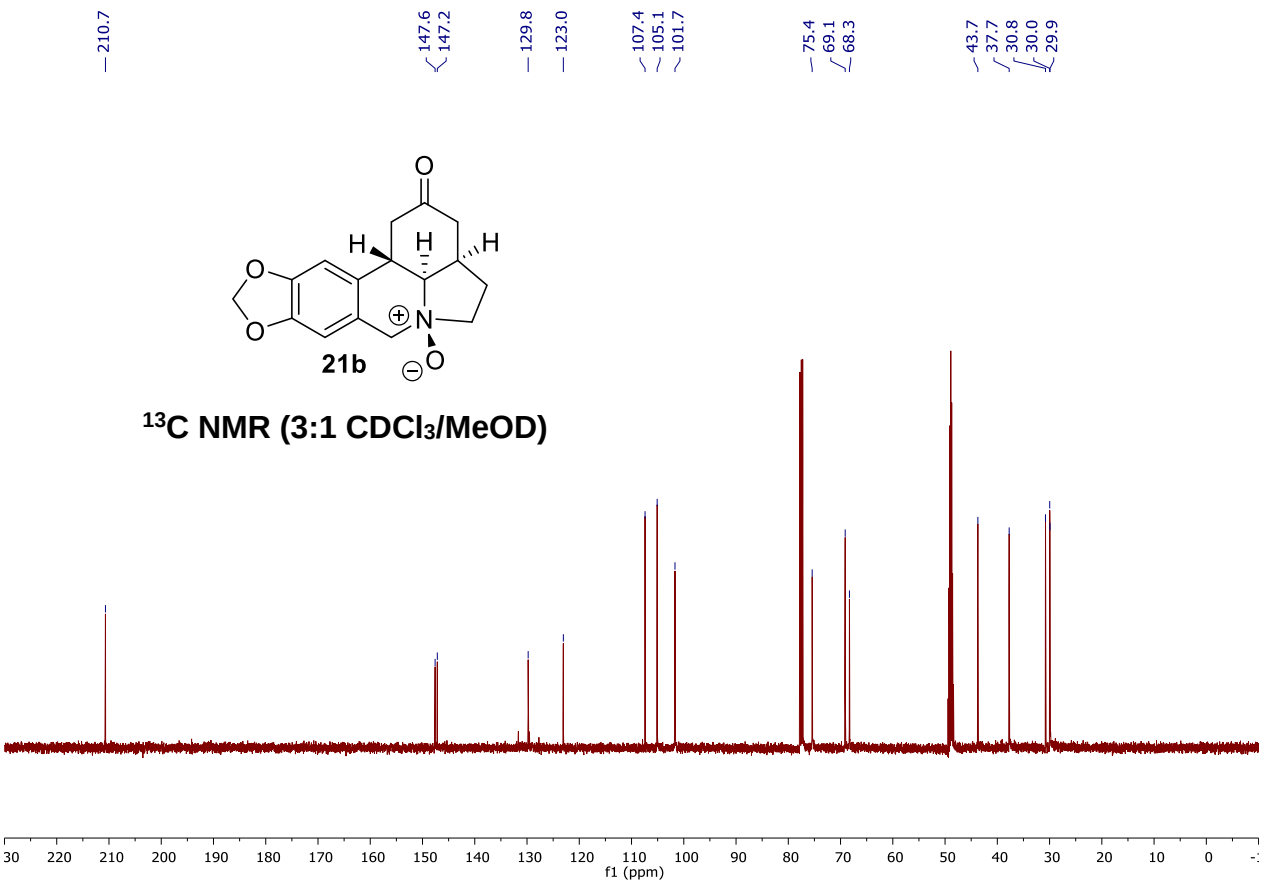


21a

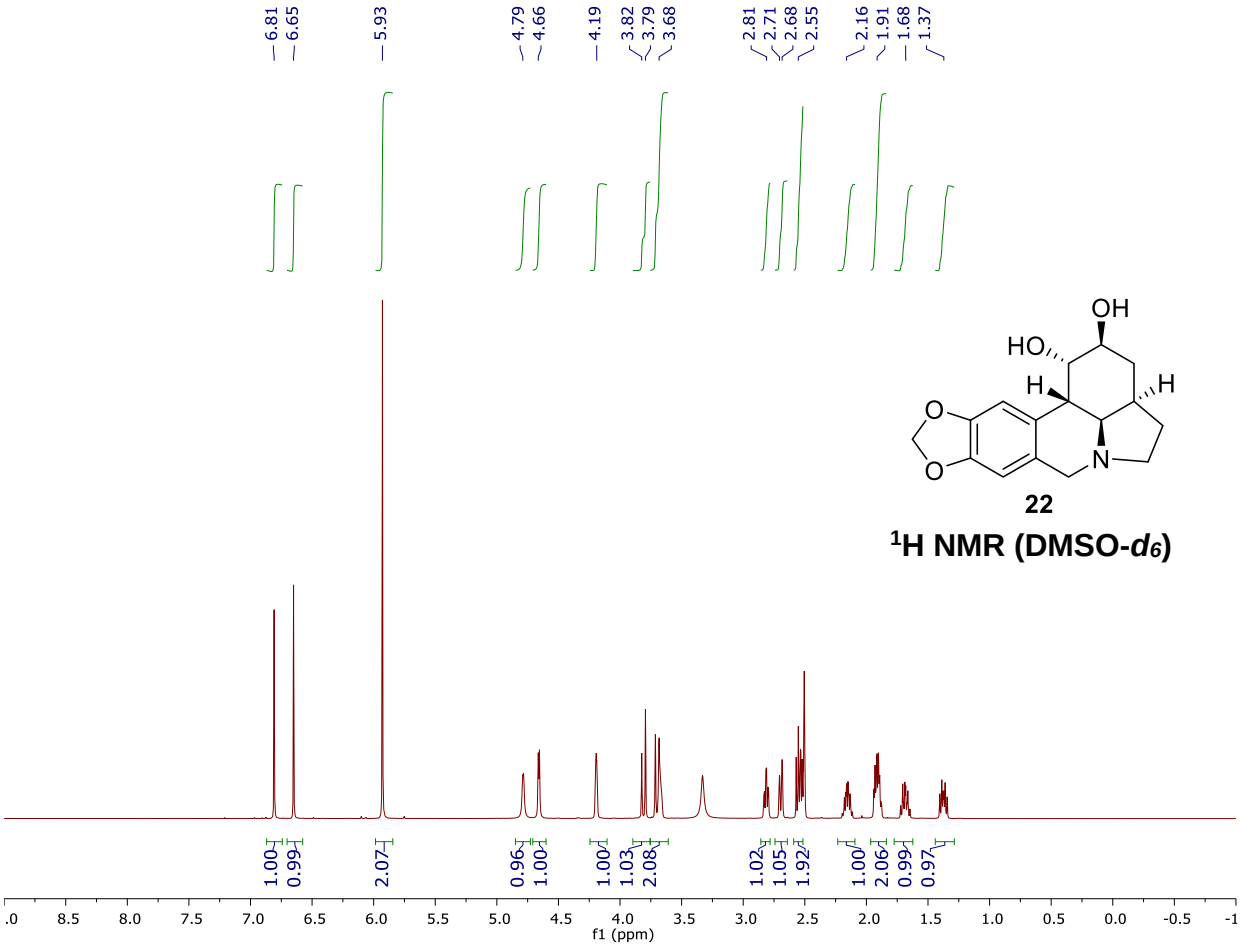
^{13}C NMR (3:1 CDCl$_3$/MeOD)



^{1}H NMR (3:1 $CDCl_3$/MeOD)

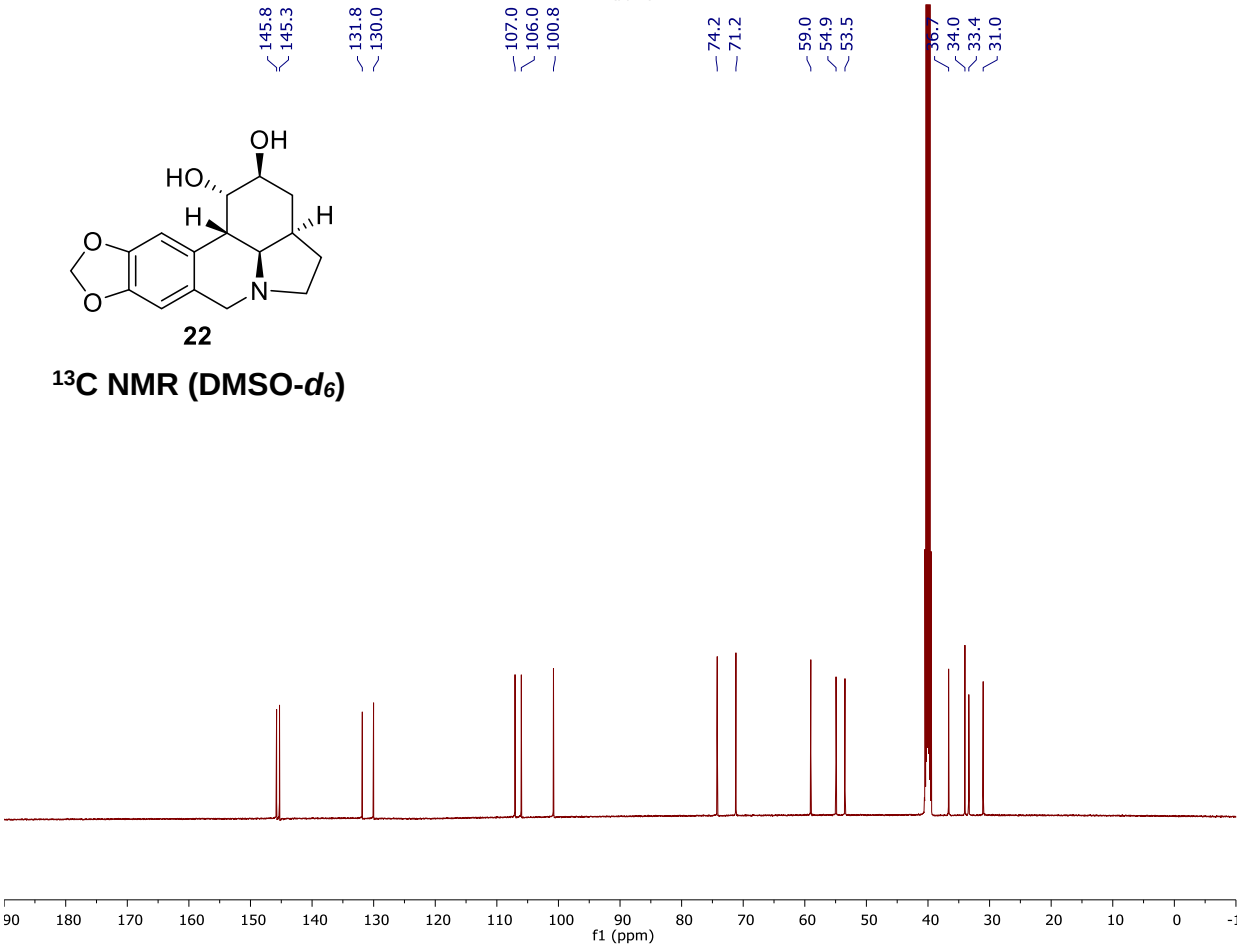


^{13}C NMR (3:1 $CDCl_3$/MeOD)



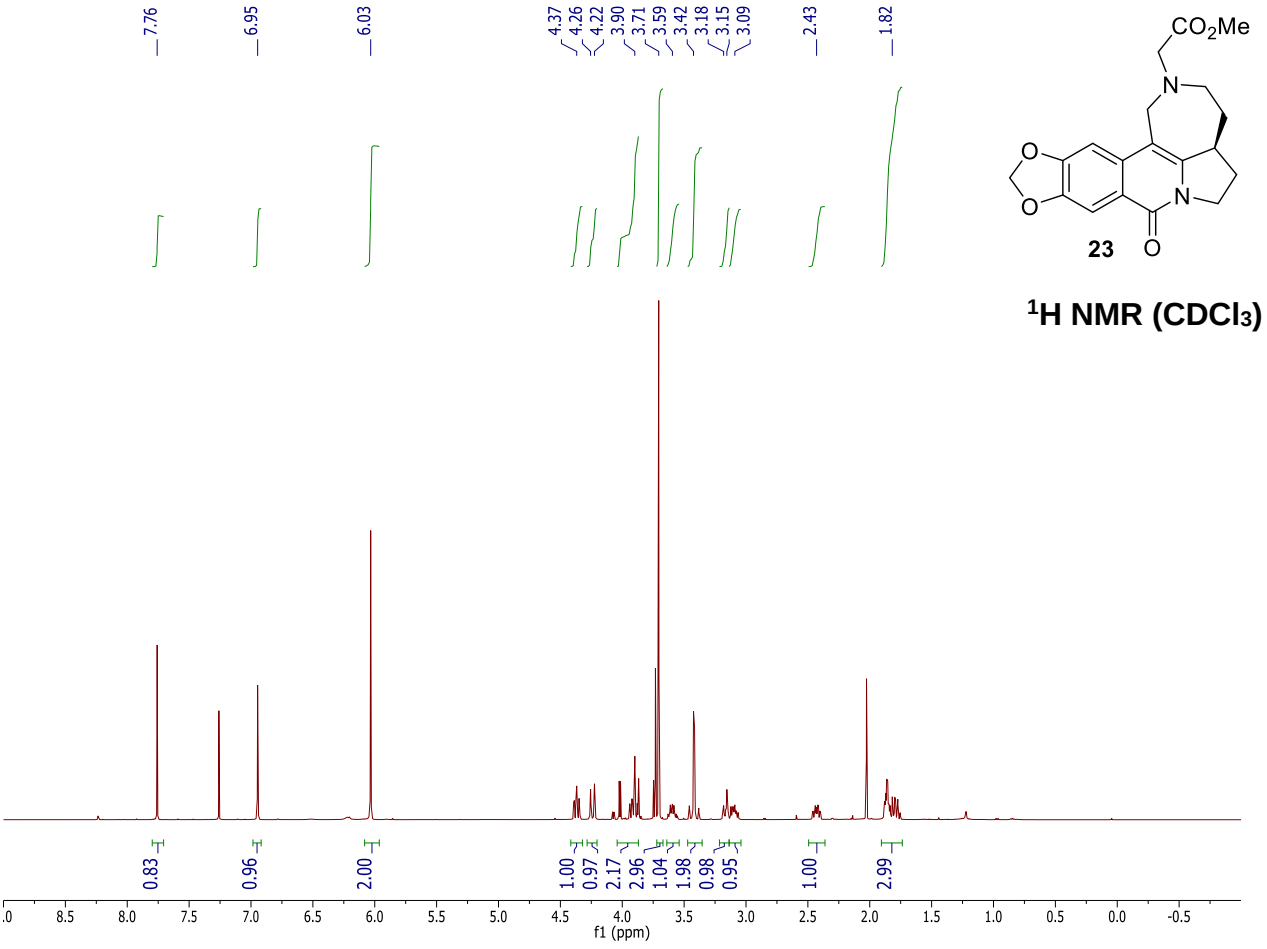
22

^{1}H NMR (DMSO-*d*$_6$)

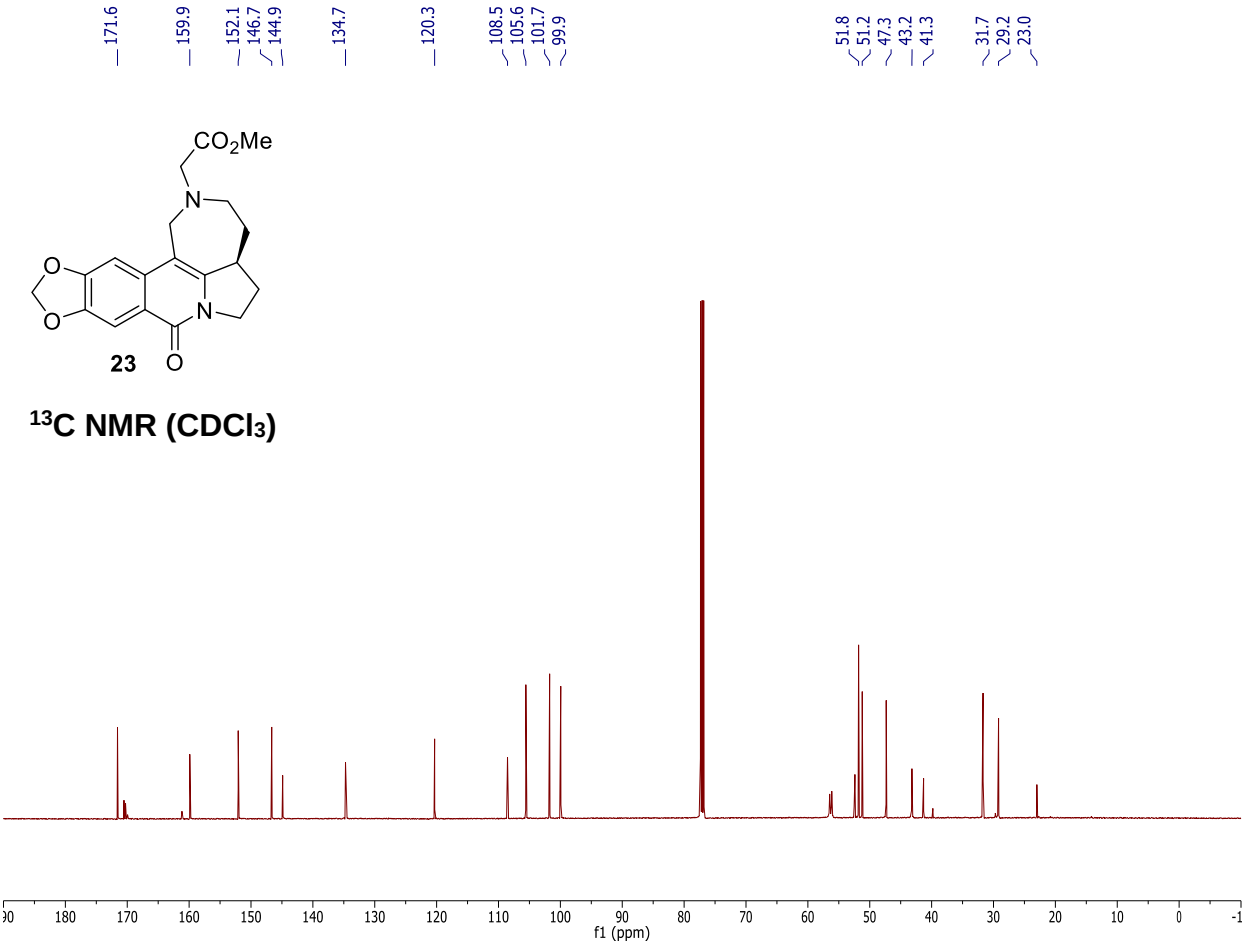


22

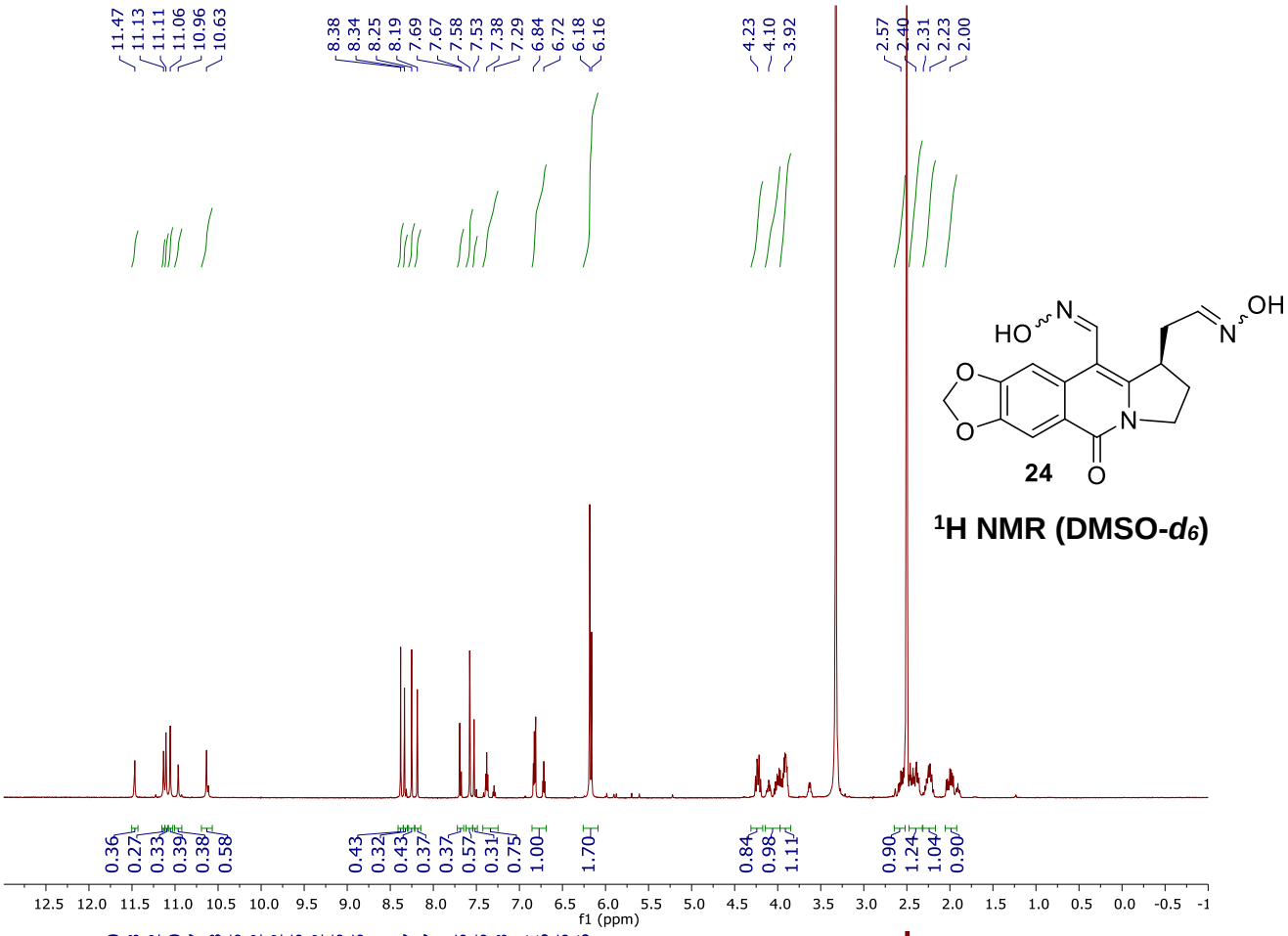
^{13}C NMR (DMSO-*d*$_6$)



^{1}H NMR ($CDCl_3$)

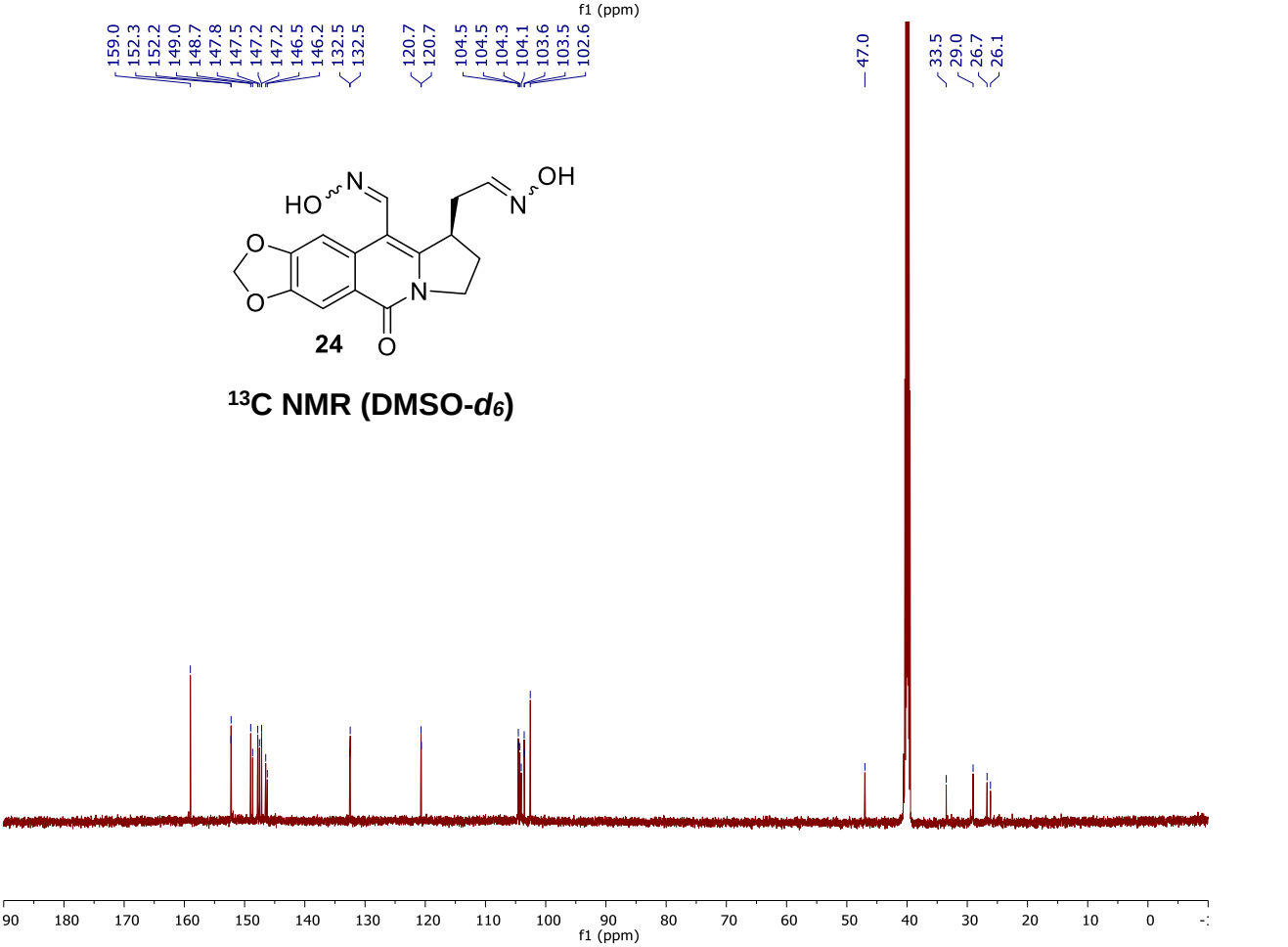


^{13}C NMR ($CDCl_3$)



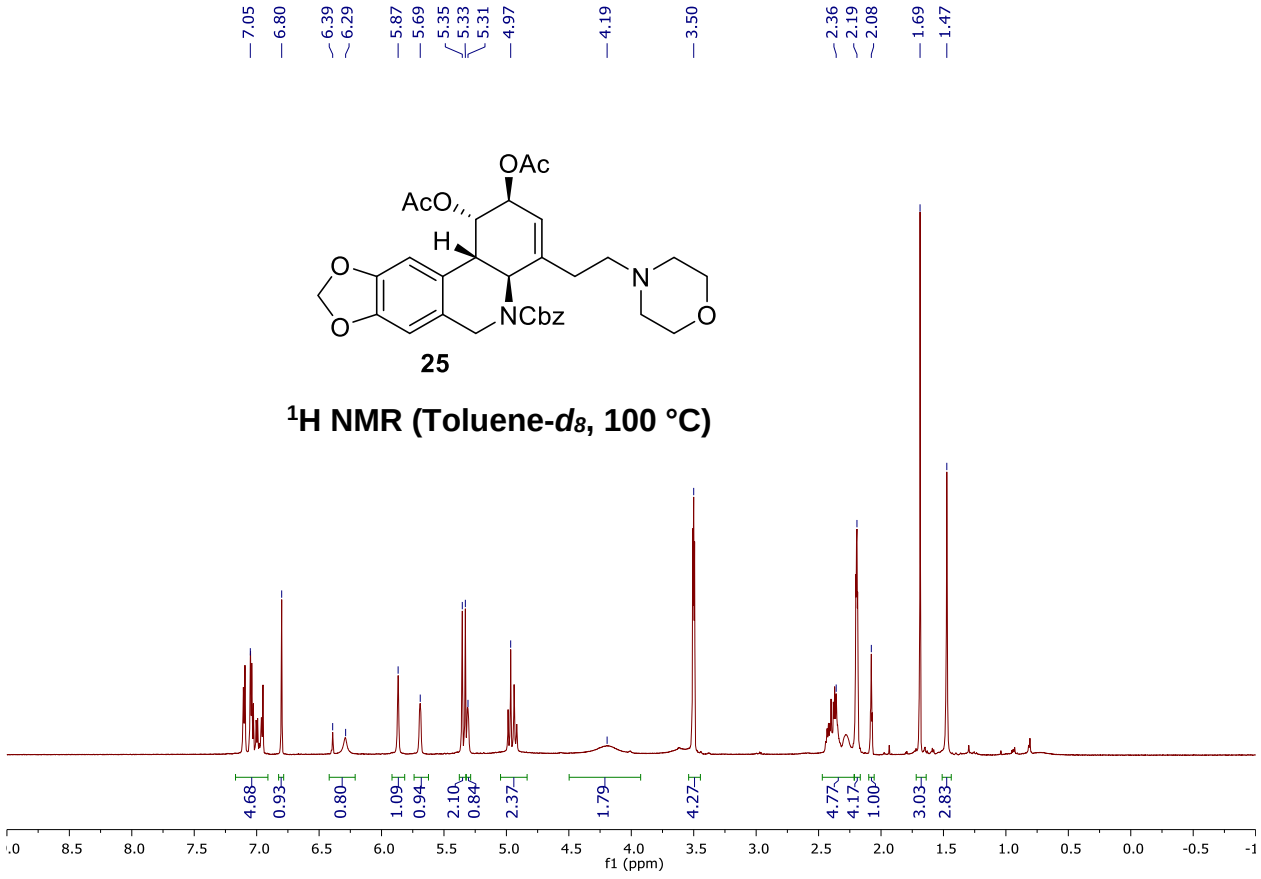
24

^{1}H NMR (DMSO-*d*$_6$)



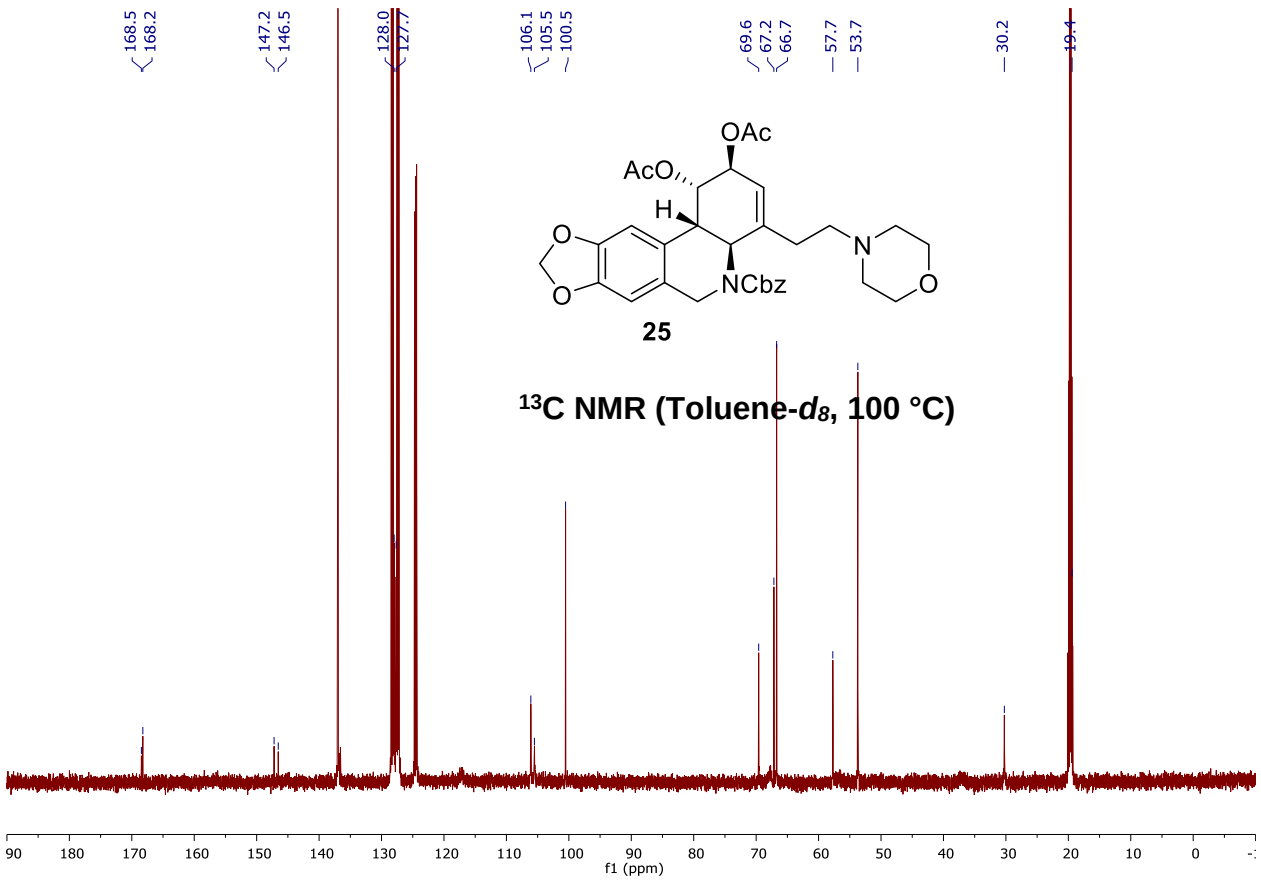
24

^{13}C NMR (DMSO-*d*$_6$)



25

^{1}H NMR (Toluene-*d*$_8$, 100 °C)



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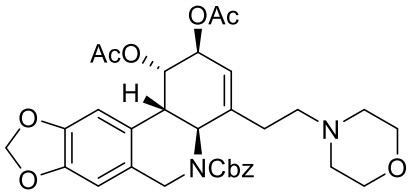
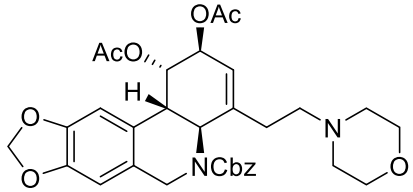
^{13}C NMR (Toluene-*d*$_8$, 100 °C)



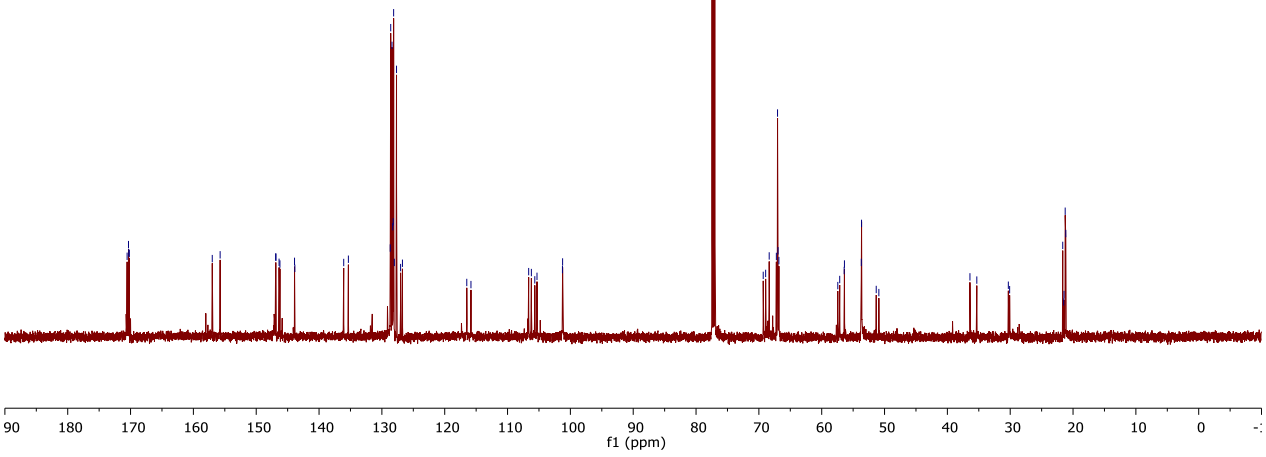
25

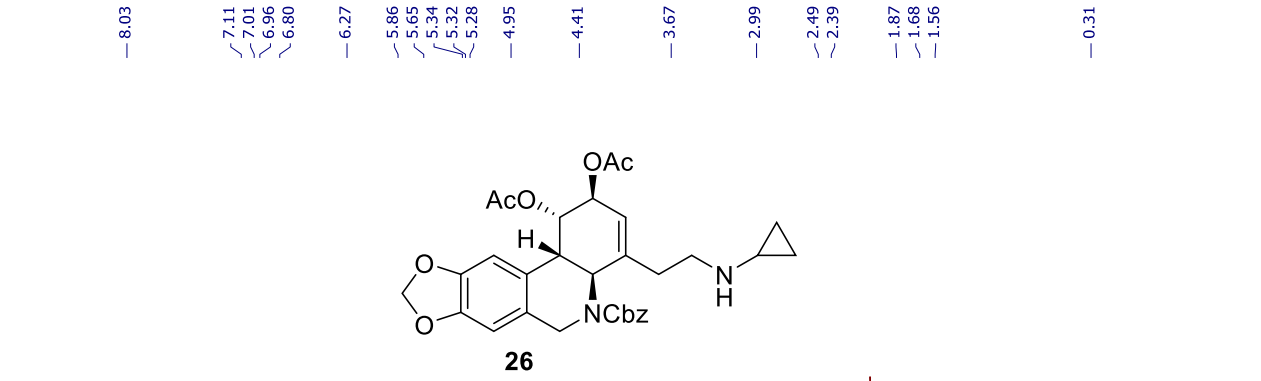
^{1}H NMR ($CDCl_3$ –30 °C)



25

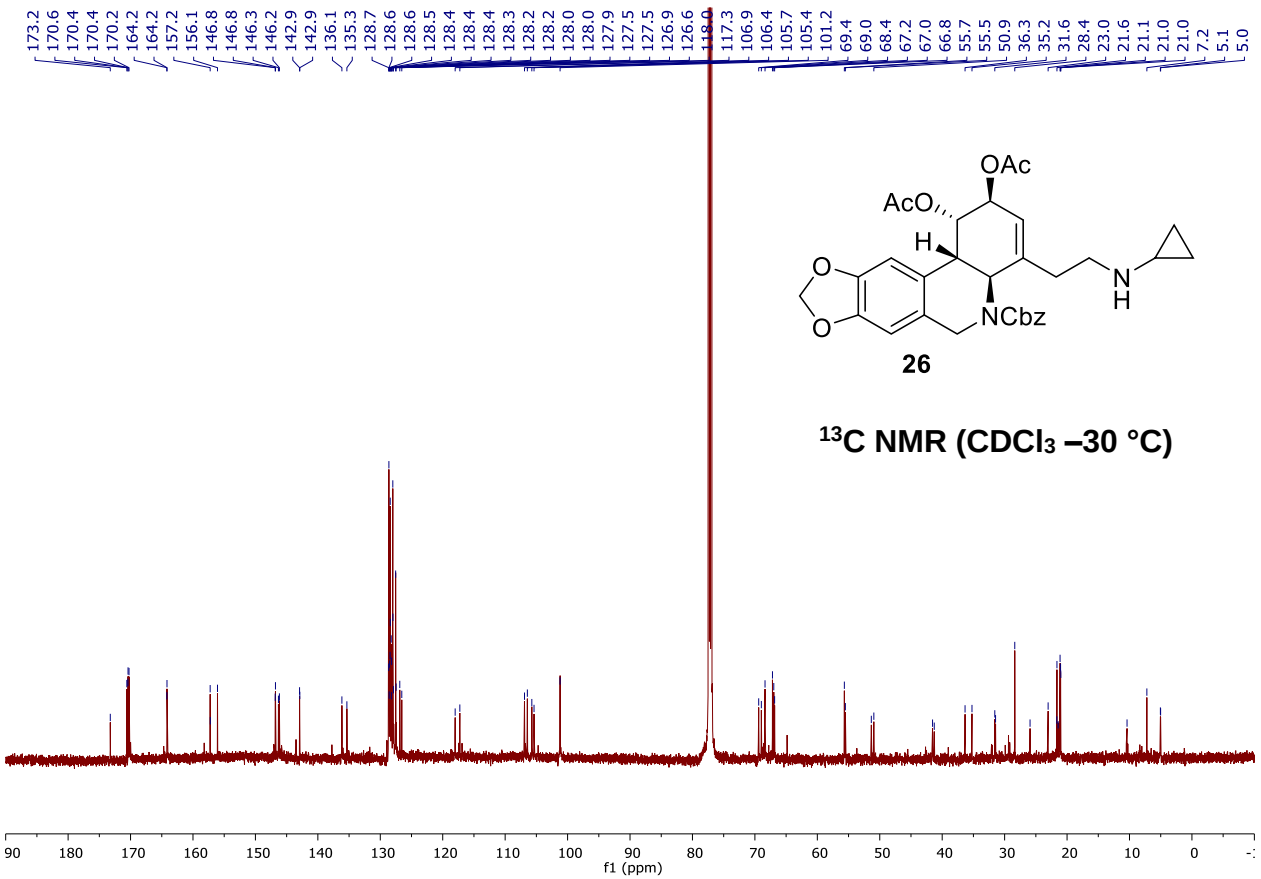
^{13}C NMR ($CDCl_3$ –30 °C)





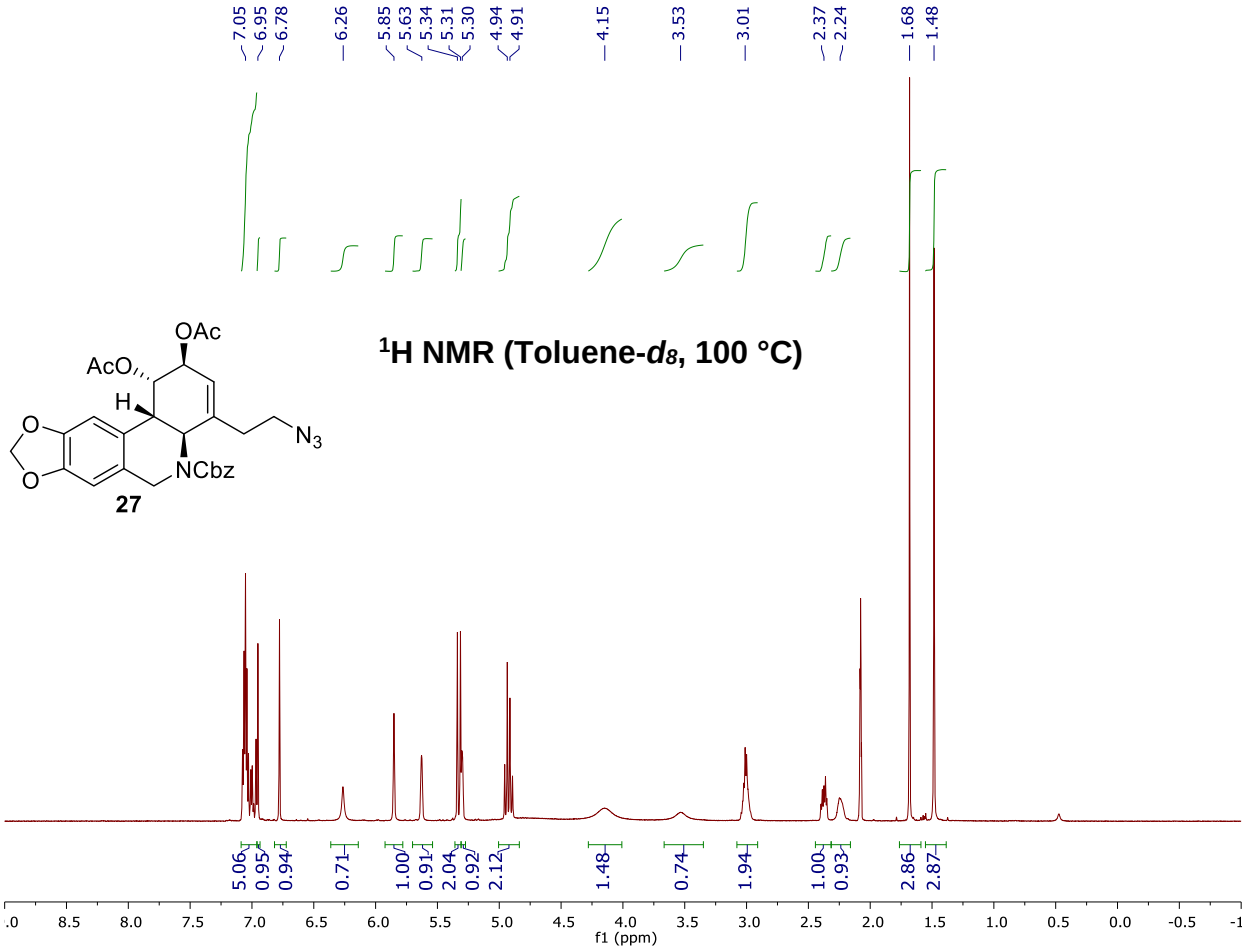
26

^{1}H NMR (Toluene-*d*$_8$, 100 °C)

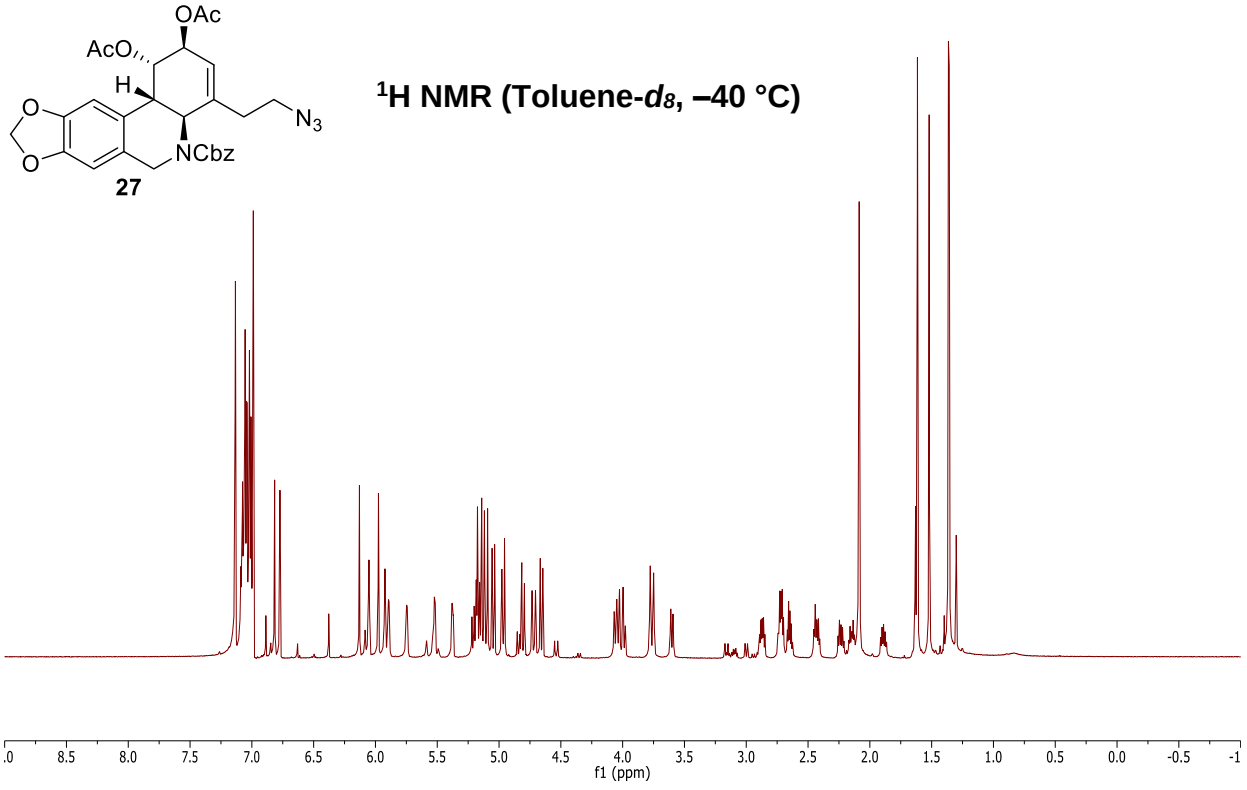


26

^{13}C NMR ($CDCl_3$ –30 °C)

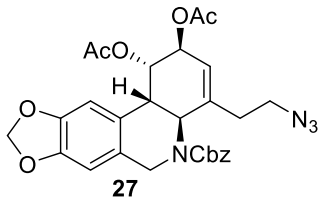


^{1}H NMR (Toluene-*d*$_8$, 100 °C)



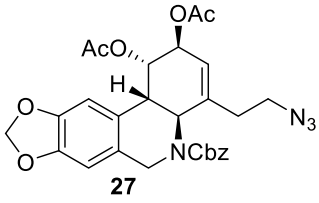
^{1}H NMR (Toluene-*d*$_8$, –40 °C)

^{13}C NMR (Toluene-*d*$_8$, 100 °C)

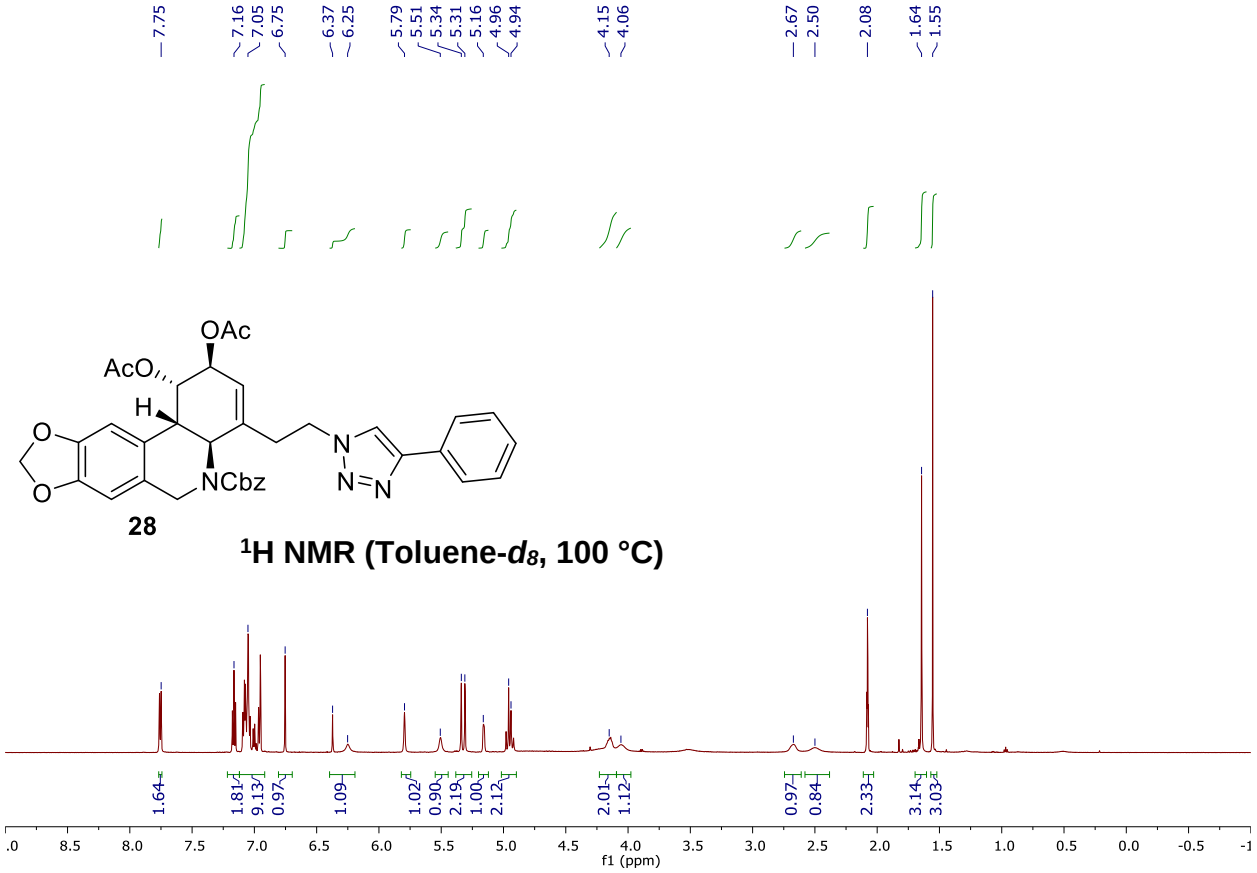


27

^{13}C NMR (Toluene-*d*$_8$, –40 °C)

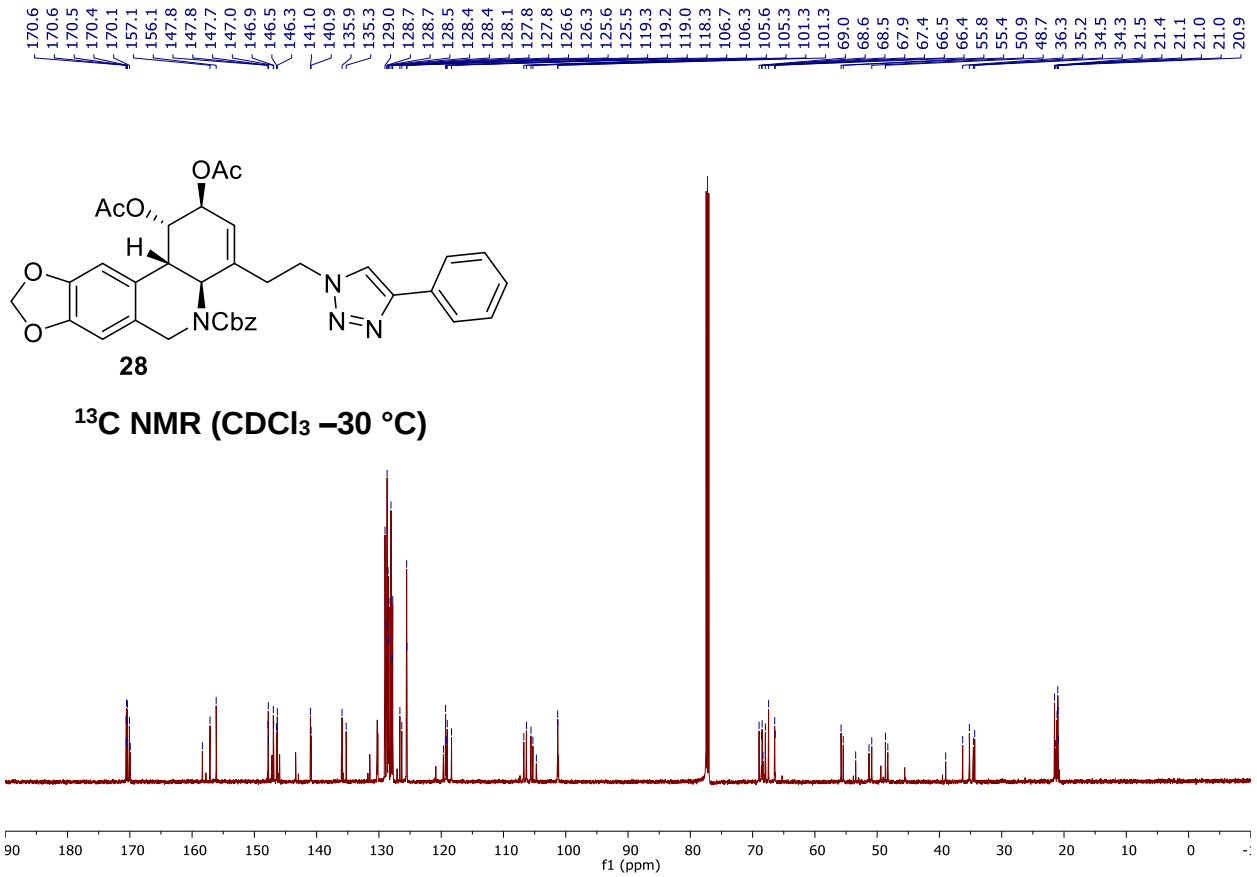


27



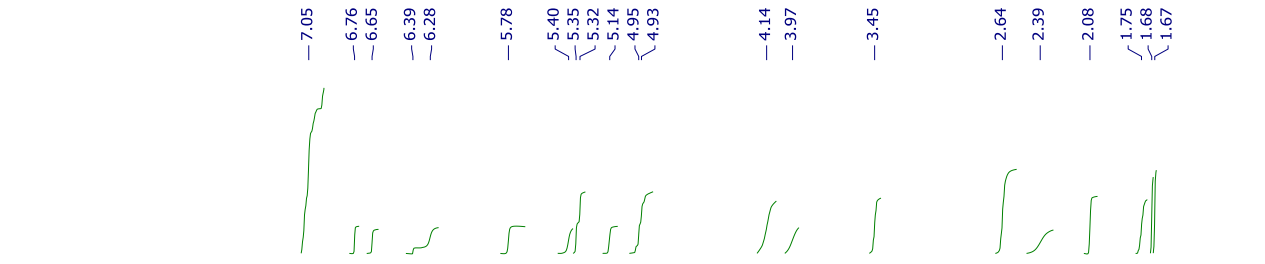
28

^{1}H NMR (Toluene-*d*$_8$, 100 °C)

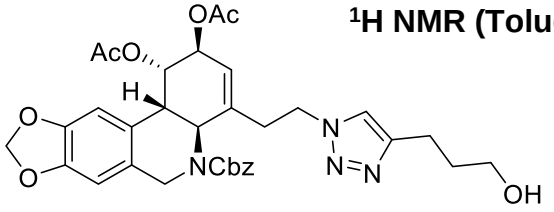


28

^{13}C NMR ($CDCl_3$ –30 °C)



^{1}H NMR (Toluene-d_8, 100 °C)



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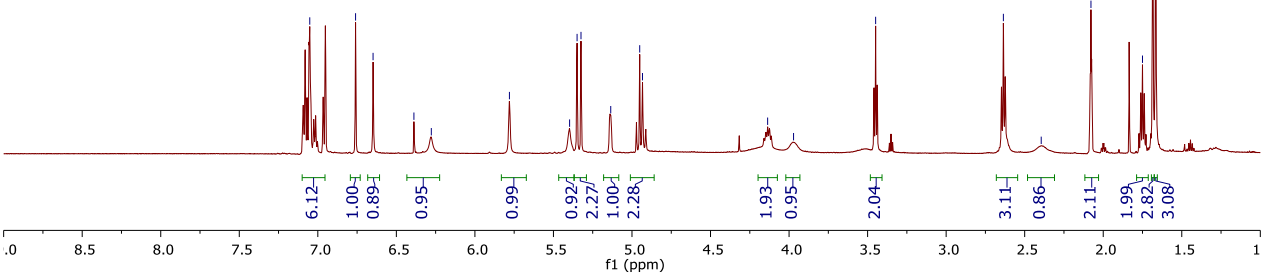
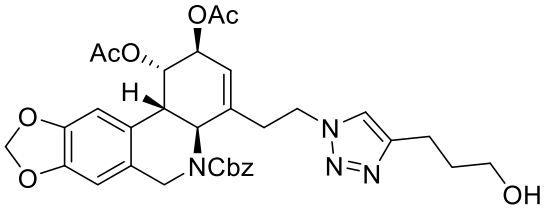
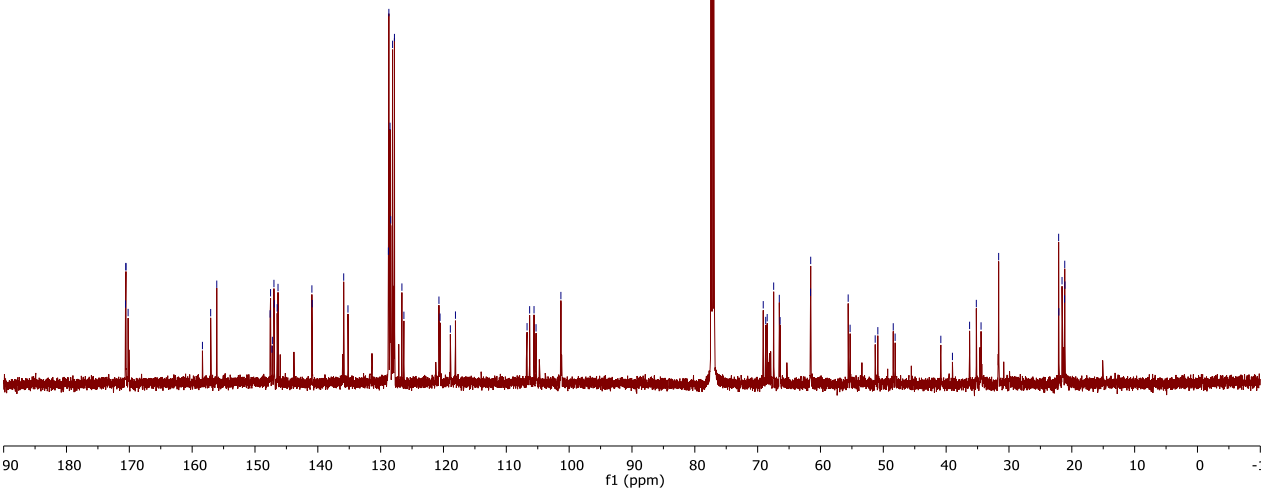
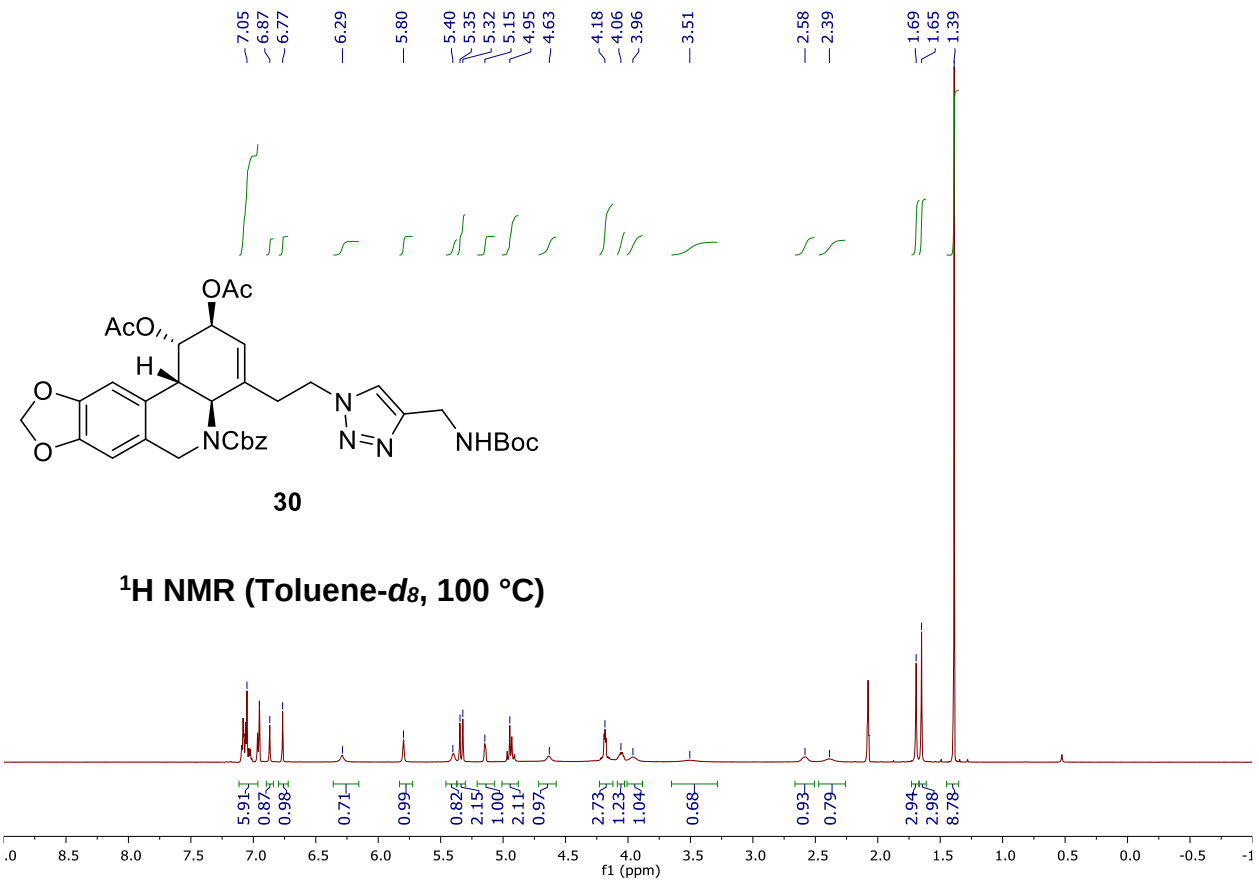




29

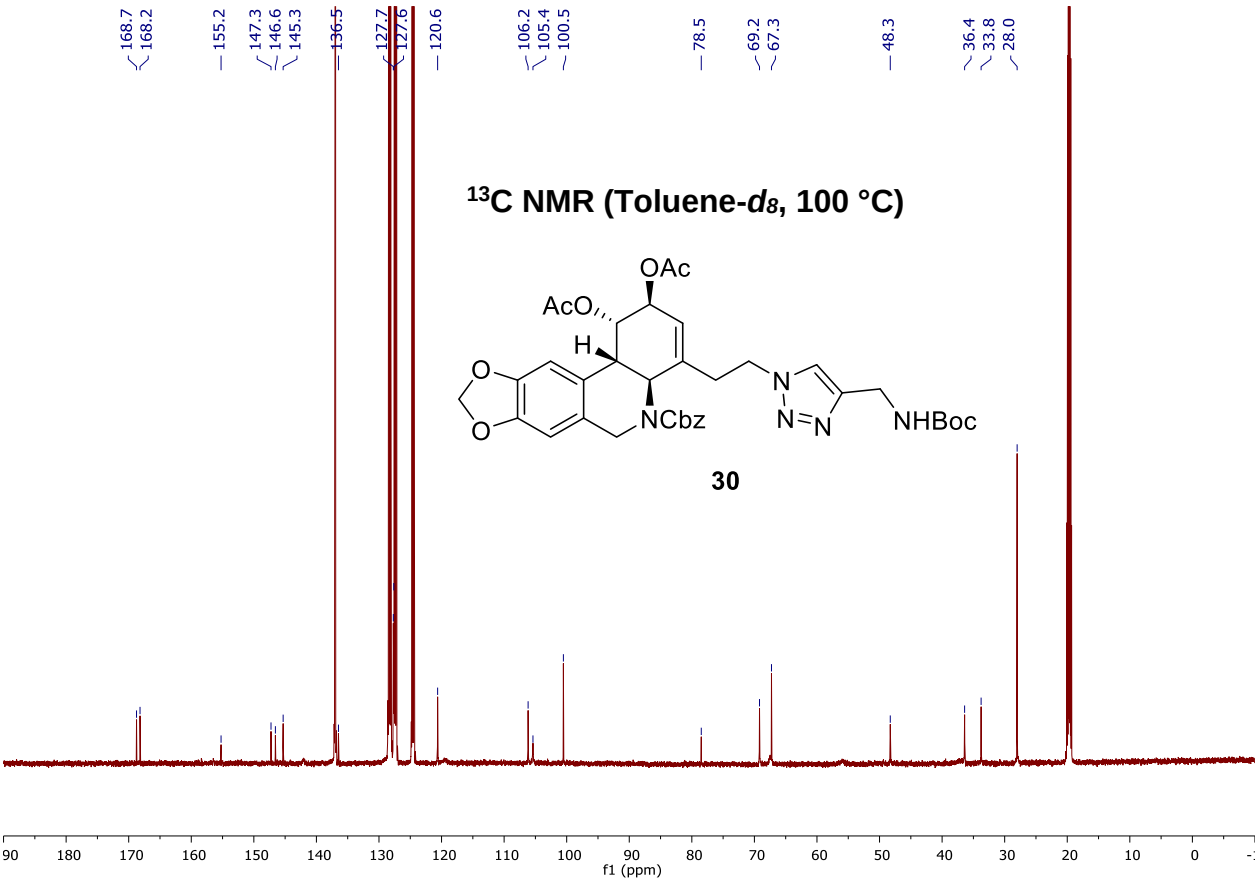
^{13}C NMR ($CDCl_3$ –30 °C)





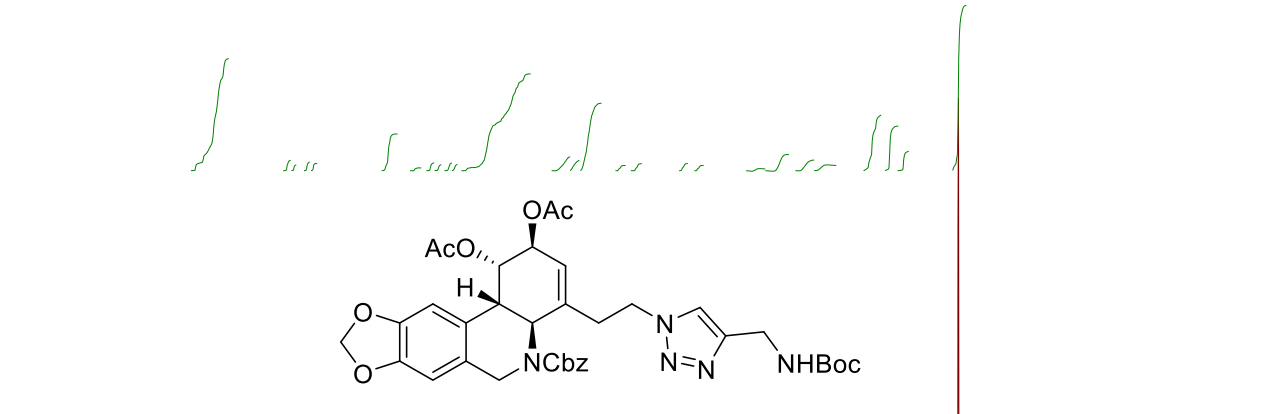
30

^{1}H NMR (Toluene-*d*$_8$, 100 °C)



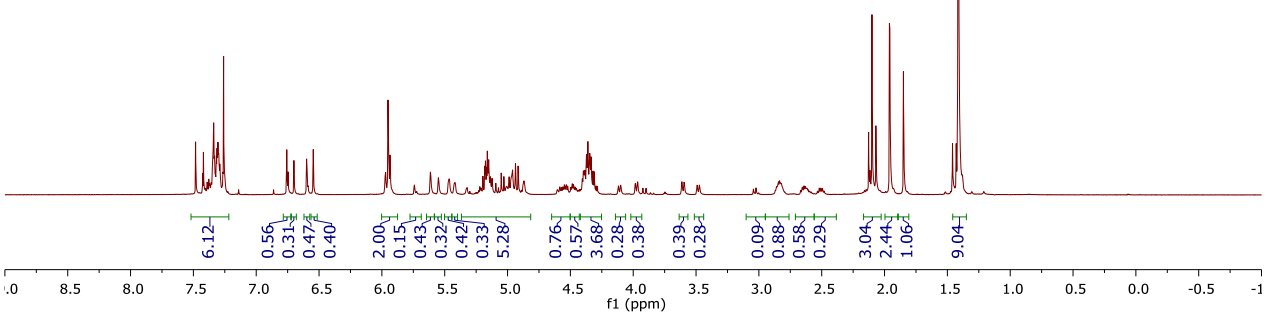
30

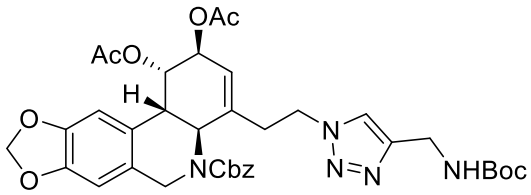
^{13}C NMR (Toluene-*d*$_8$, 100 °C)



30

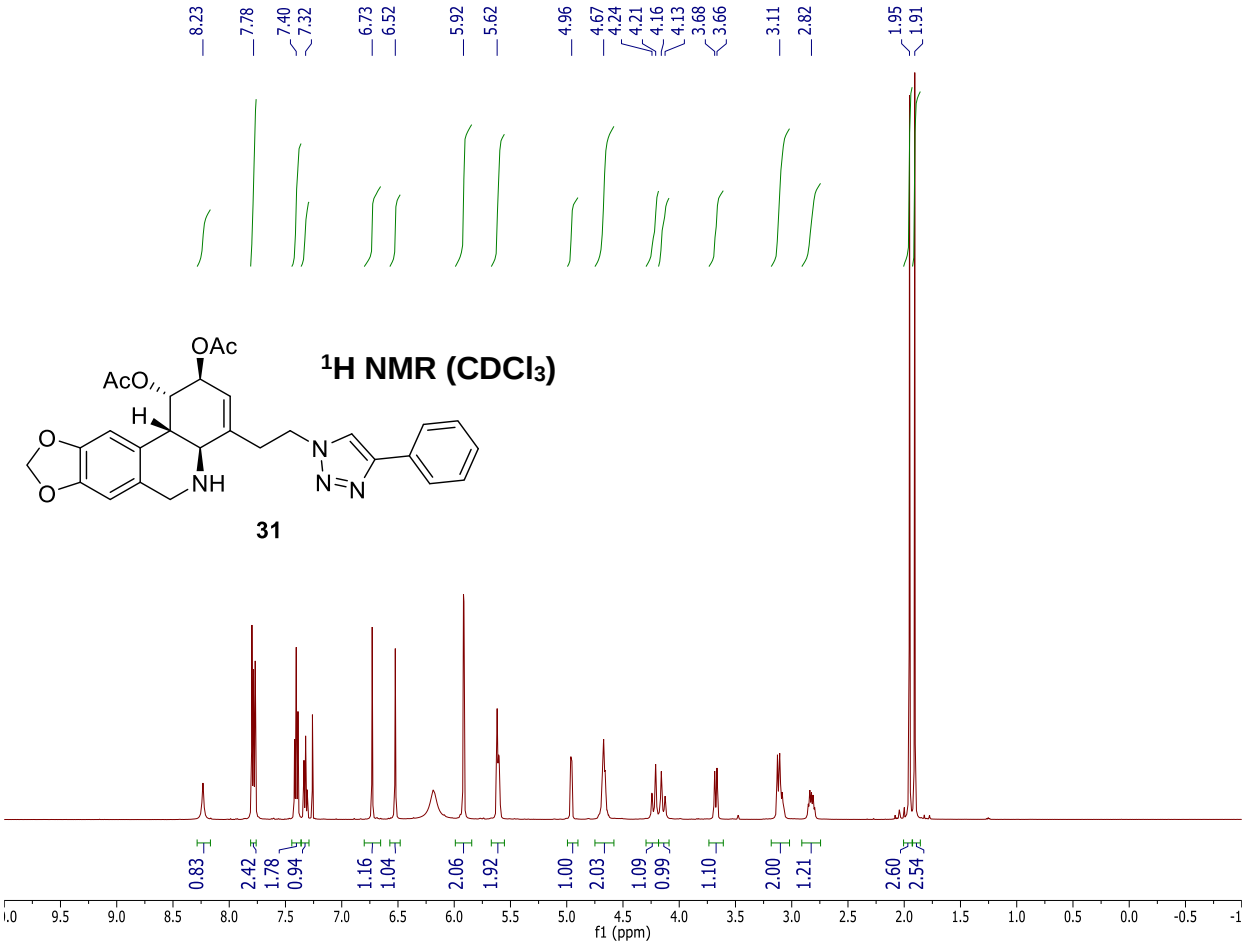
^{1}H NMR ($CDCl_3$, –30 °C)





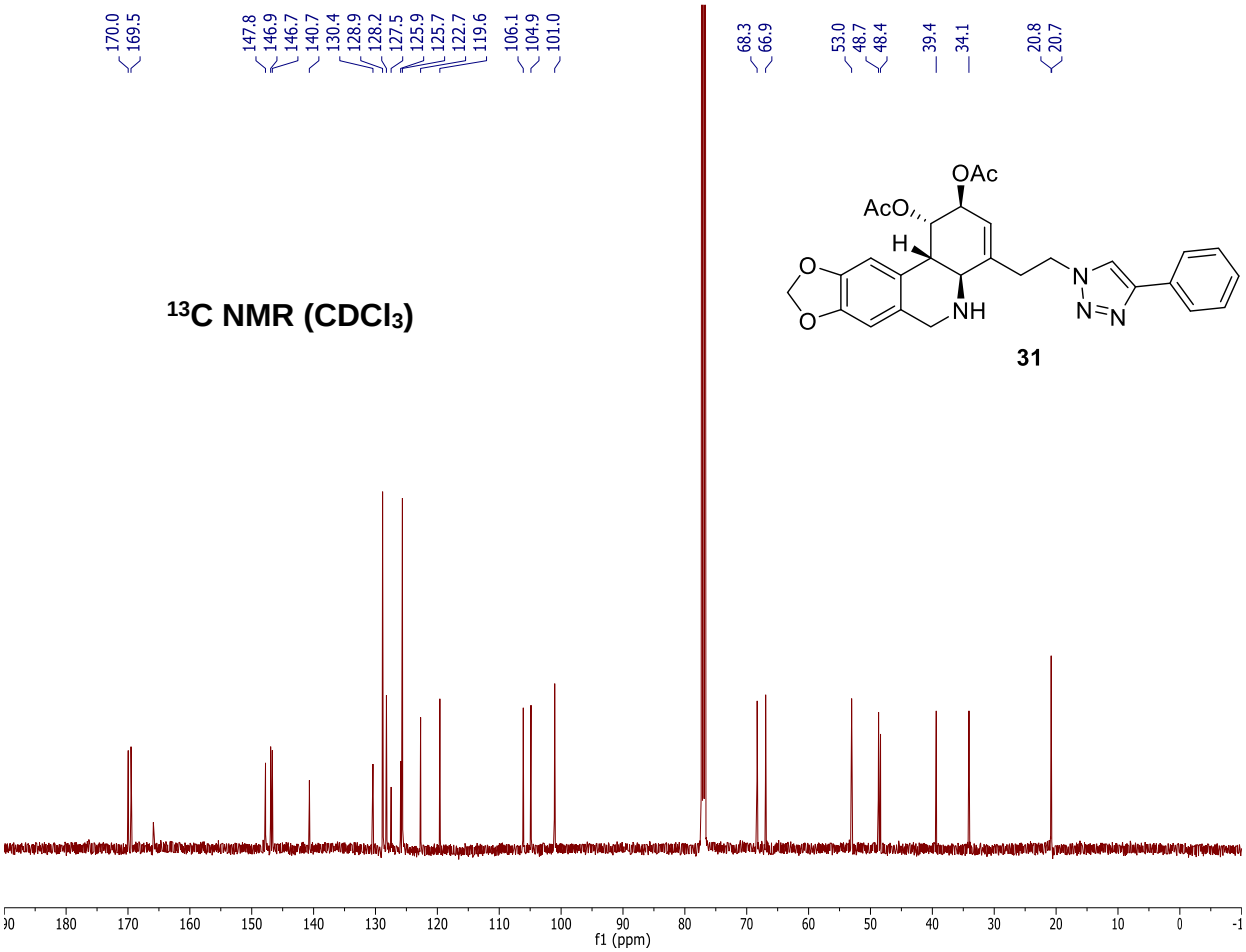
30

^{13}C NMR ($CDCl_3$, –30 °C)



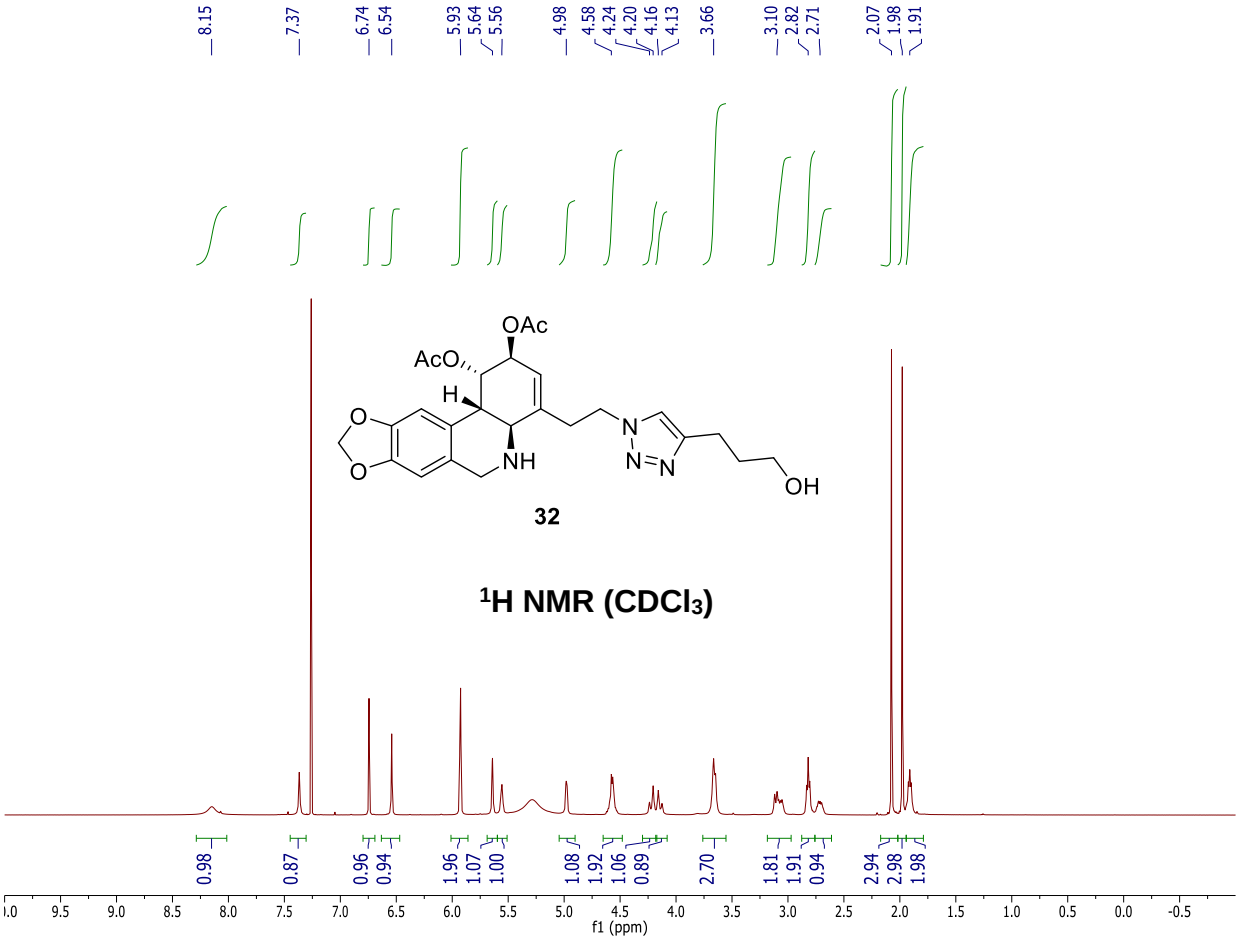
^{1}H NMR ($CDCl_3$)

31



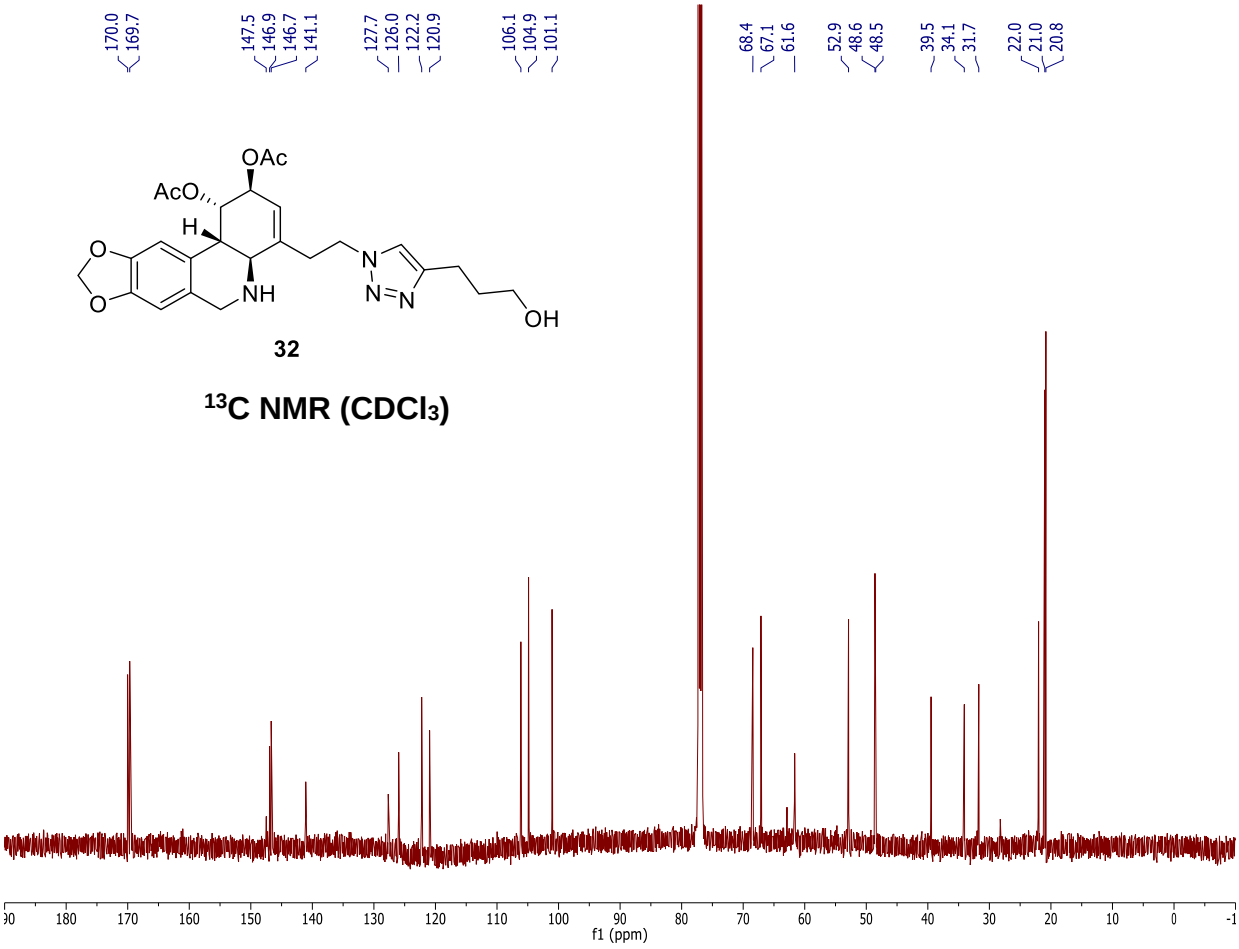
^{13}C NMR ($CDCl_3$)

31



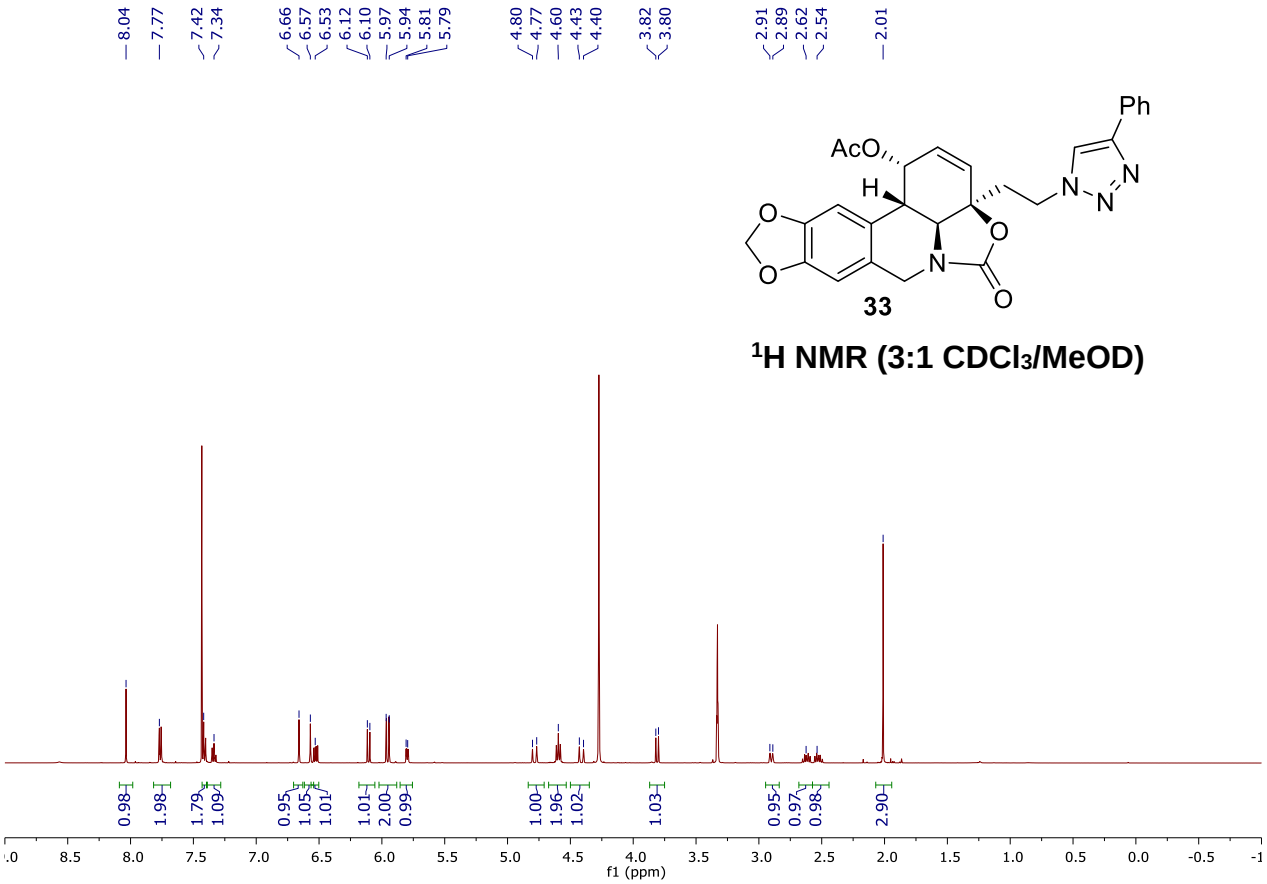
32

^{1}H NMR ($CDCl_3$)

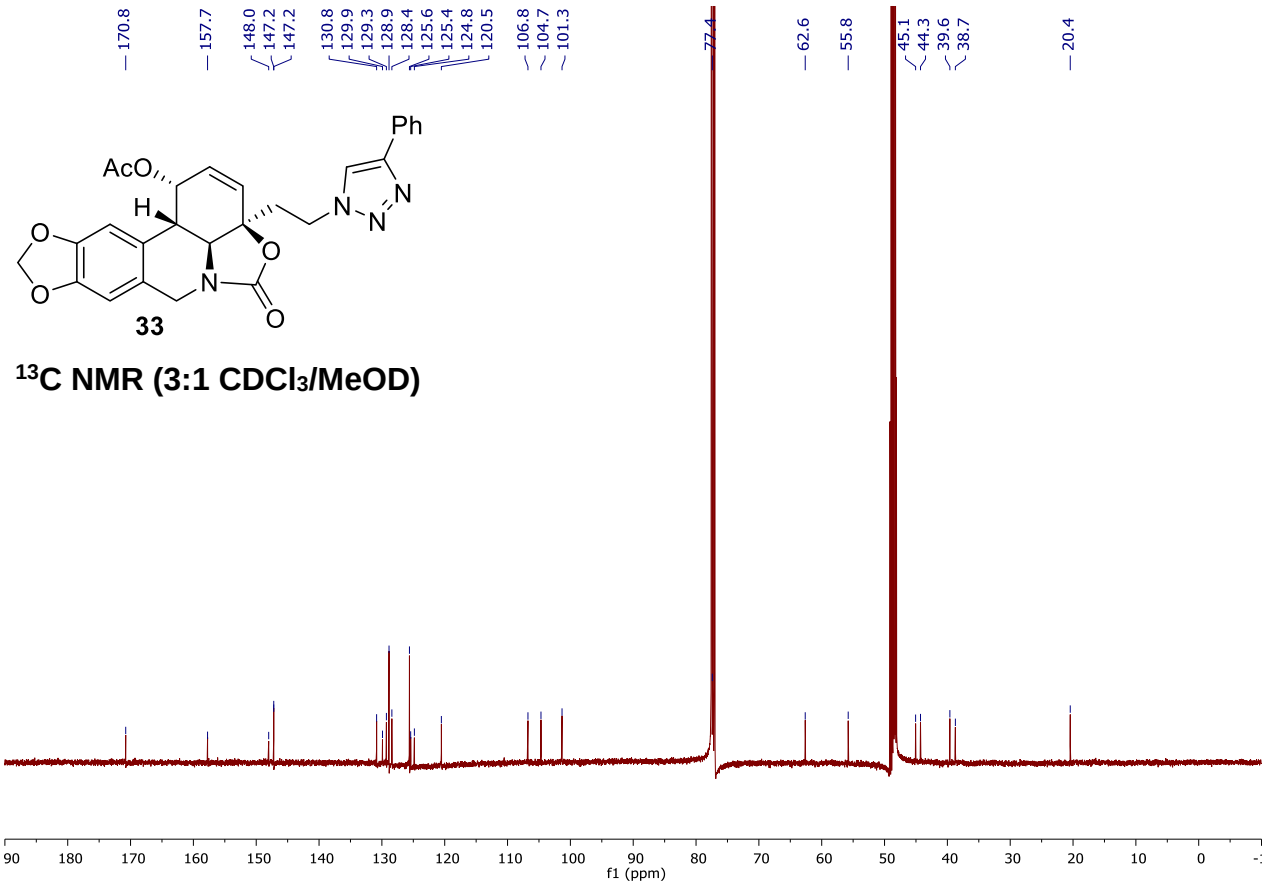


32

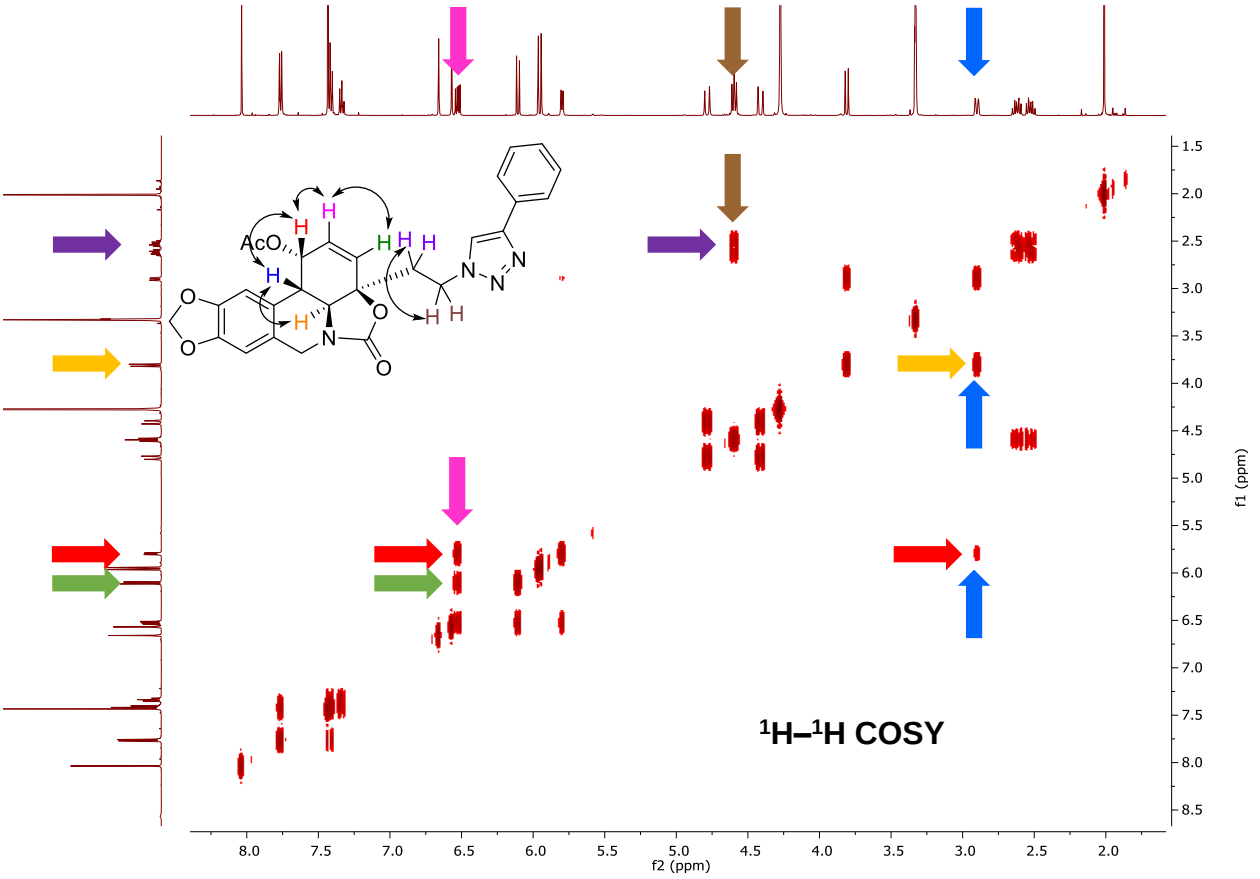
^{13}C NMR ($CDCl_3$)

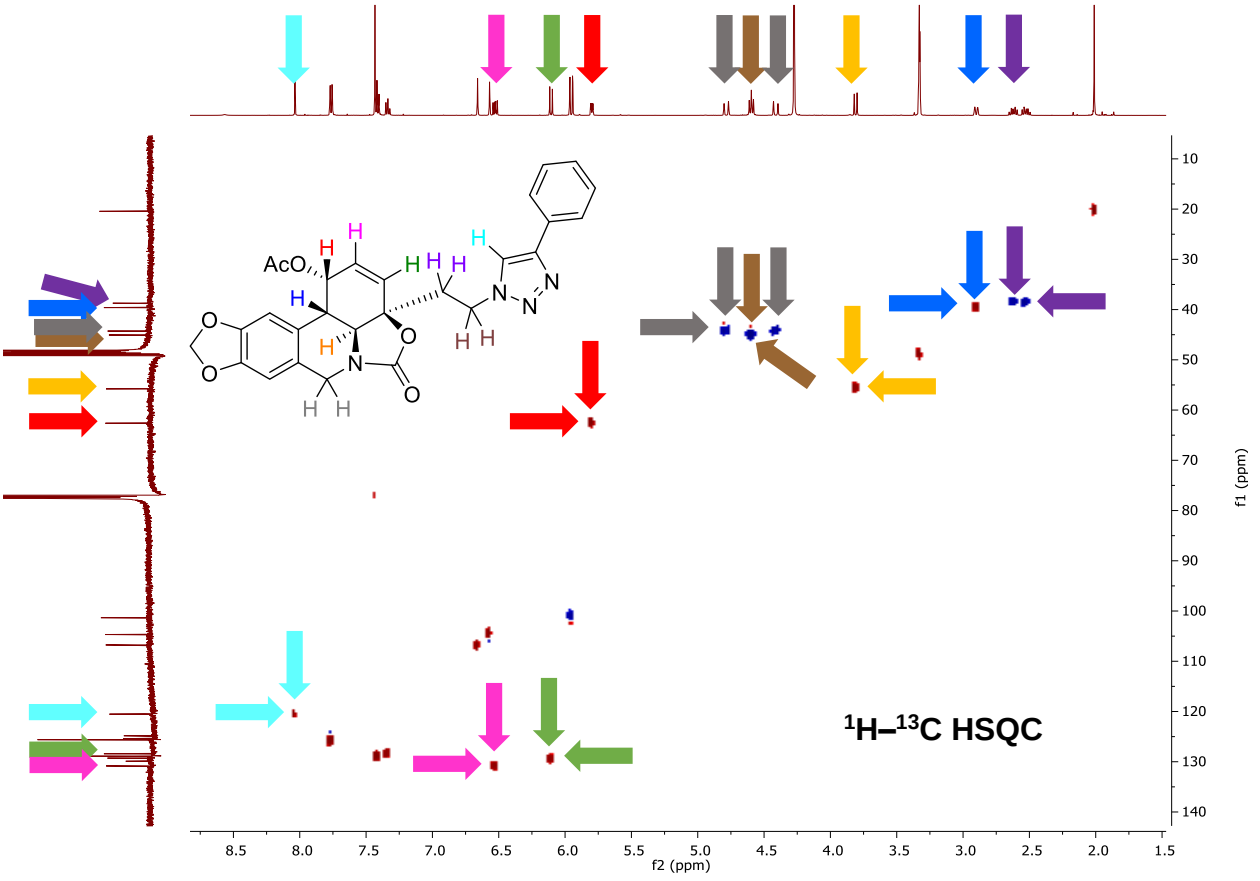


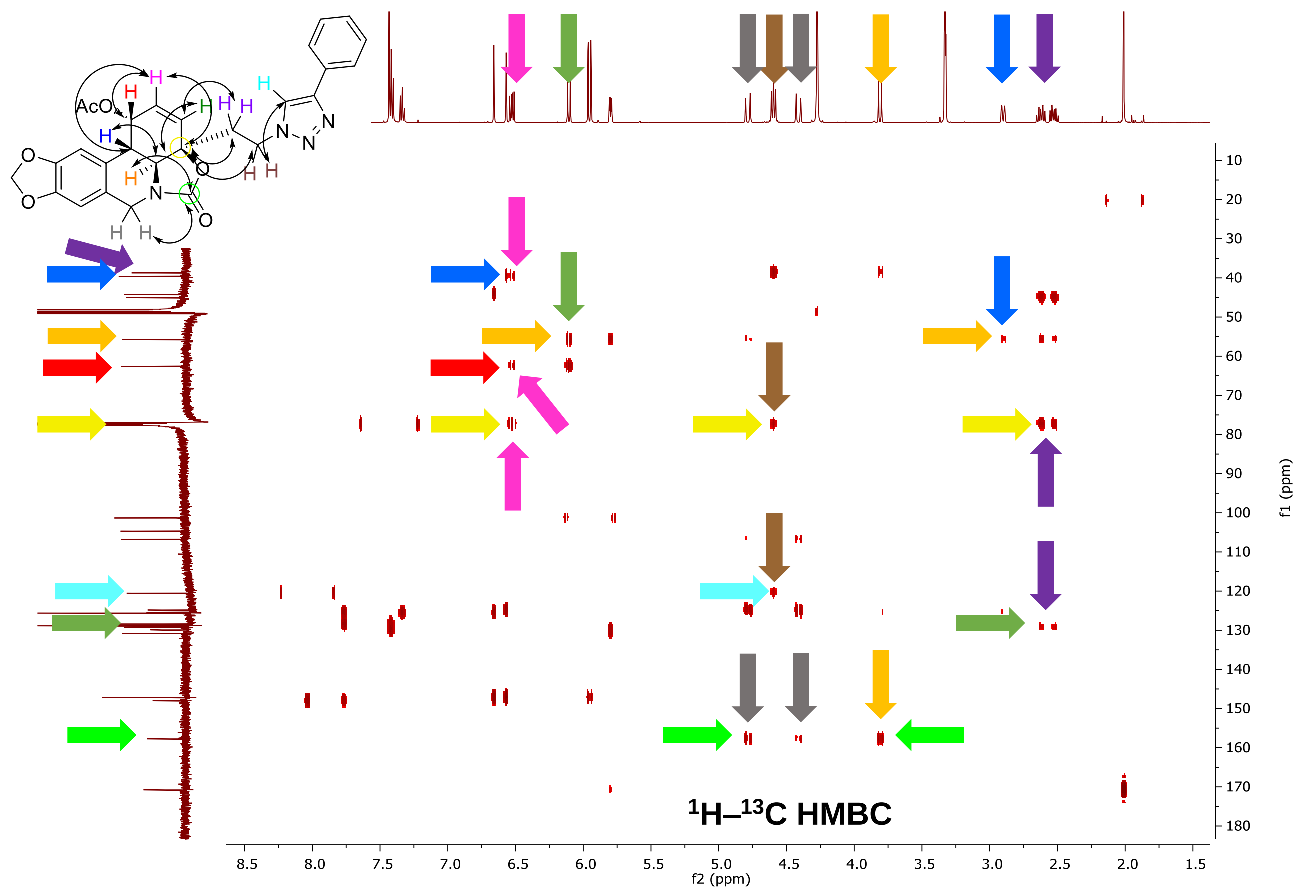
^{1}H NMR (3:1 CDCl$_3$/MeOD)

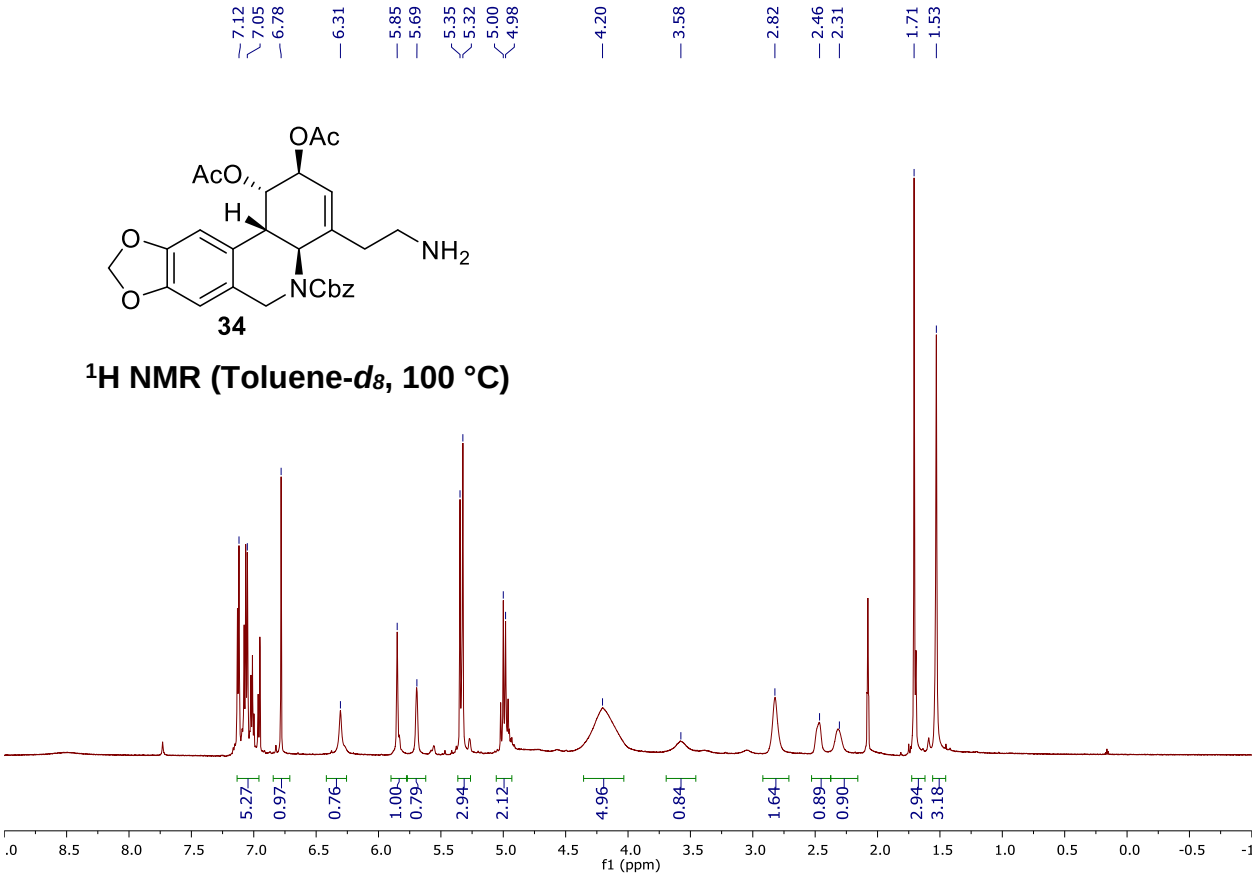


^{13}C NMR (3:1 CDCl$_3$/MeOD)


AcO
O
O
N
N
N
O
O
H
H H H
H H
H
H
H
H H
f2 (ppm)
f1 (ppm)
1H–1H COSY

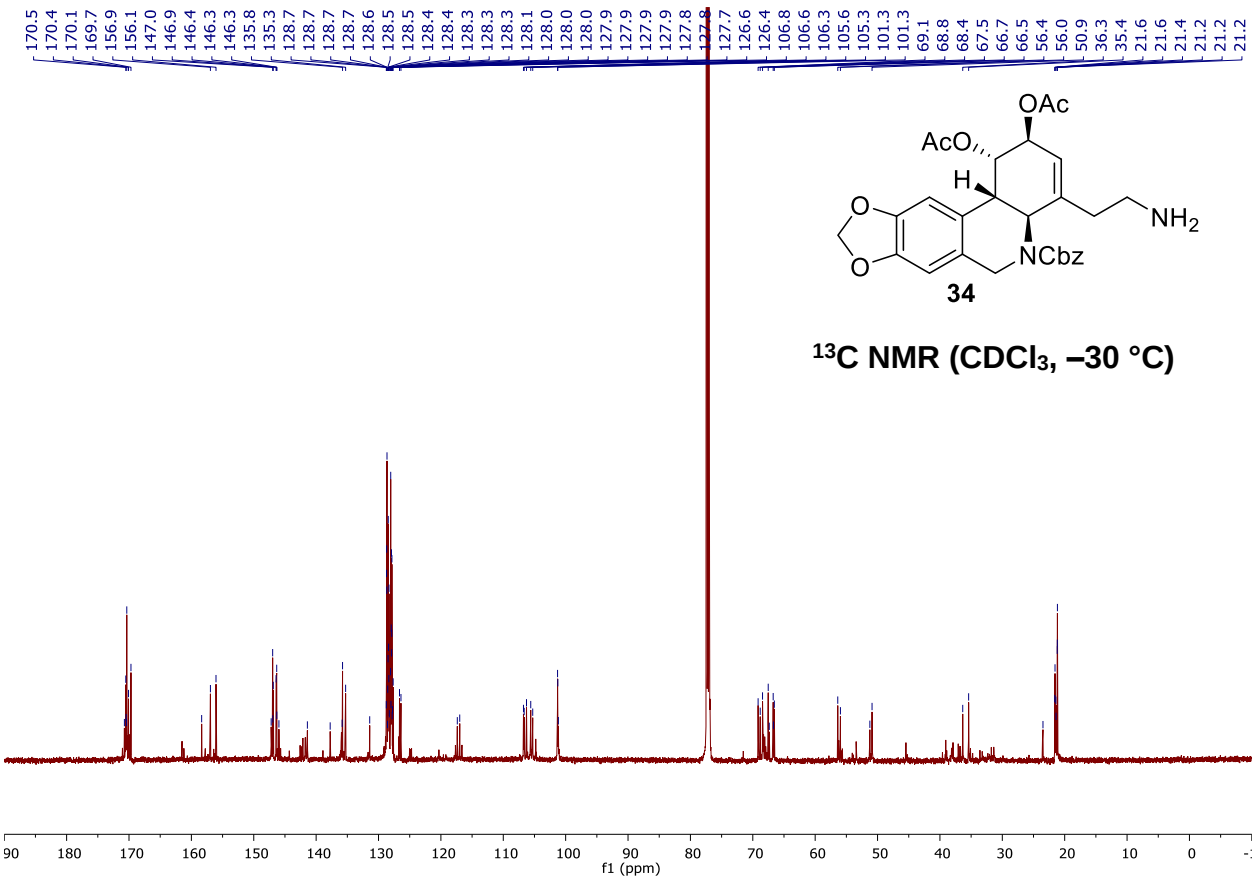

AcO
O
O
N
N
N
O
O
H
H H H
H H
H
H
H
H H
f2 (ppm)
f1 (ppm)
1H–13C HSQC


AcO
N
O
O
O
N
N
N
f1 (ppm)
f2 (ppm)
¹H–¹³C HMBC



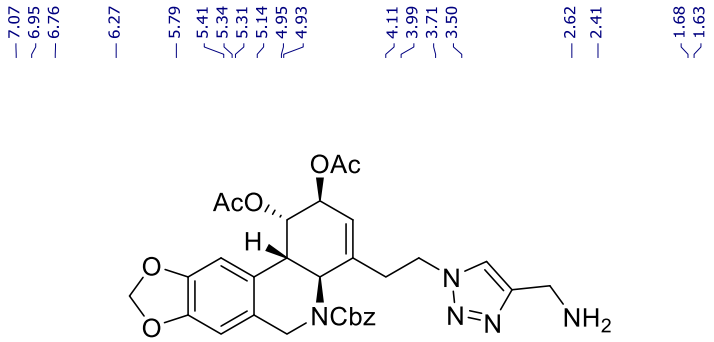
34

^{1}H NMR (Toluene-*d*$_8$, 100 °C)



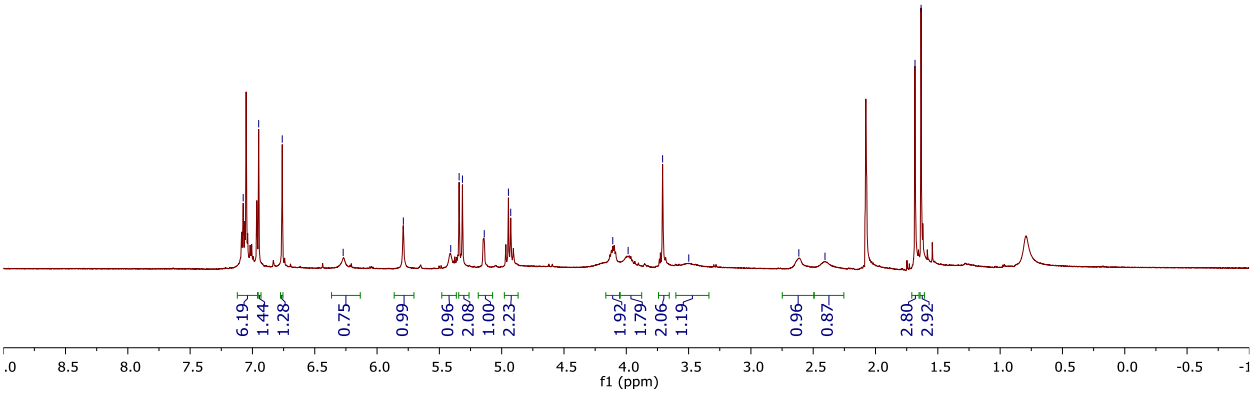
34

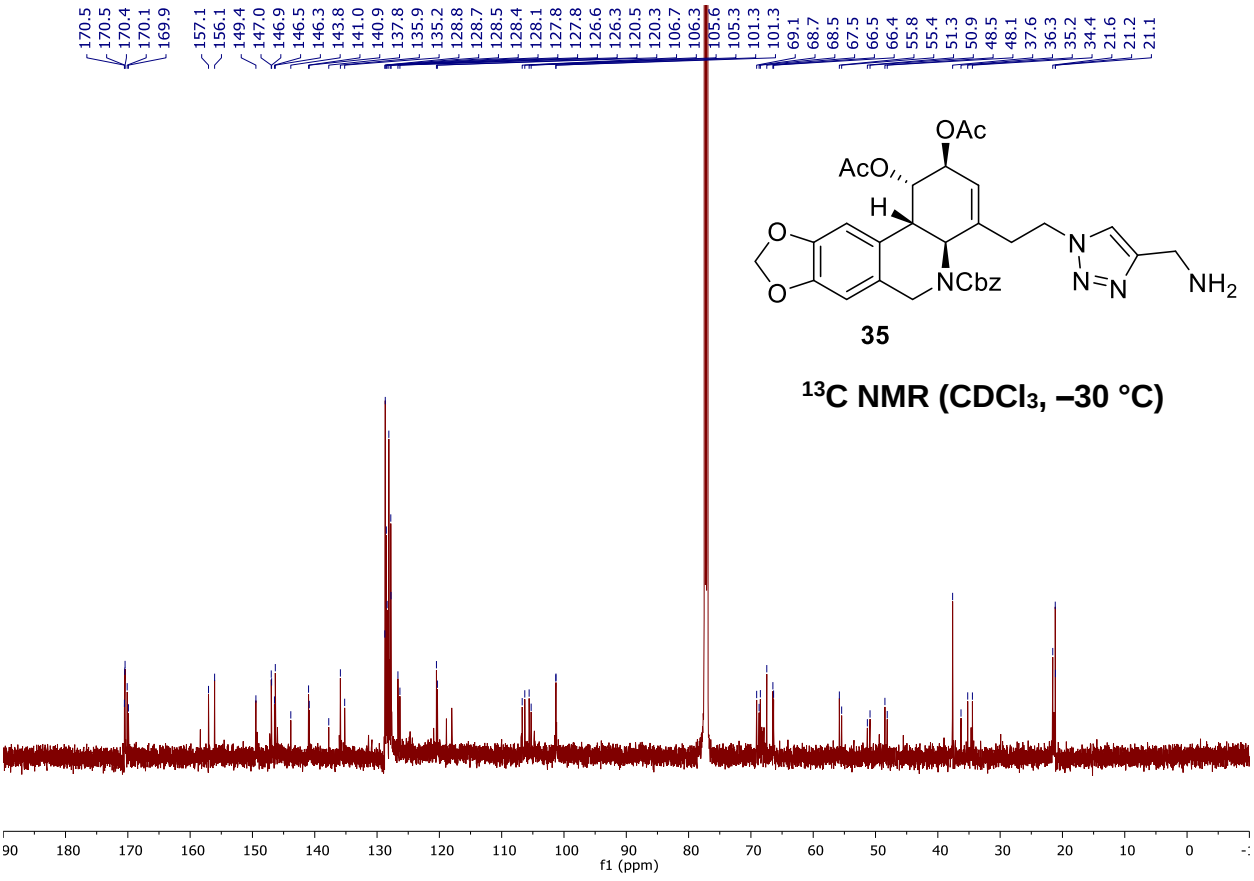
^{13}C NMR ($CDCl_3$, –30 °C)



35

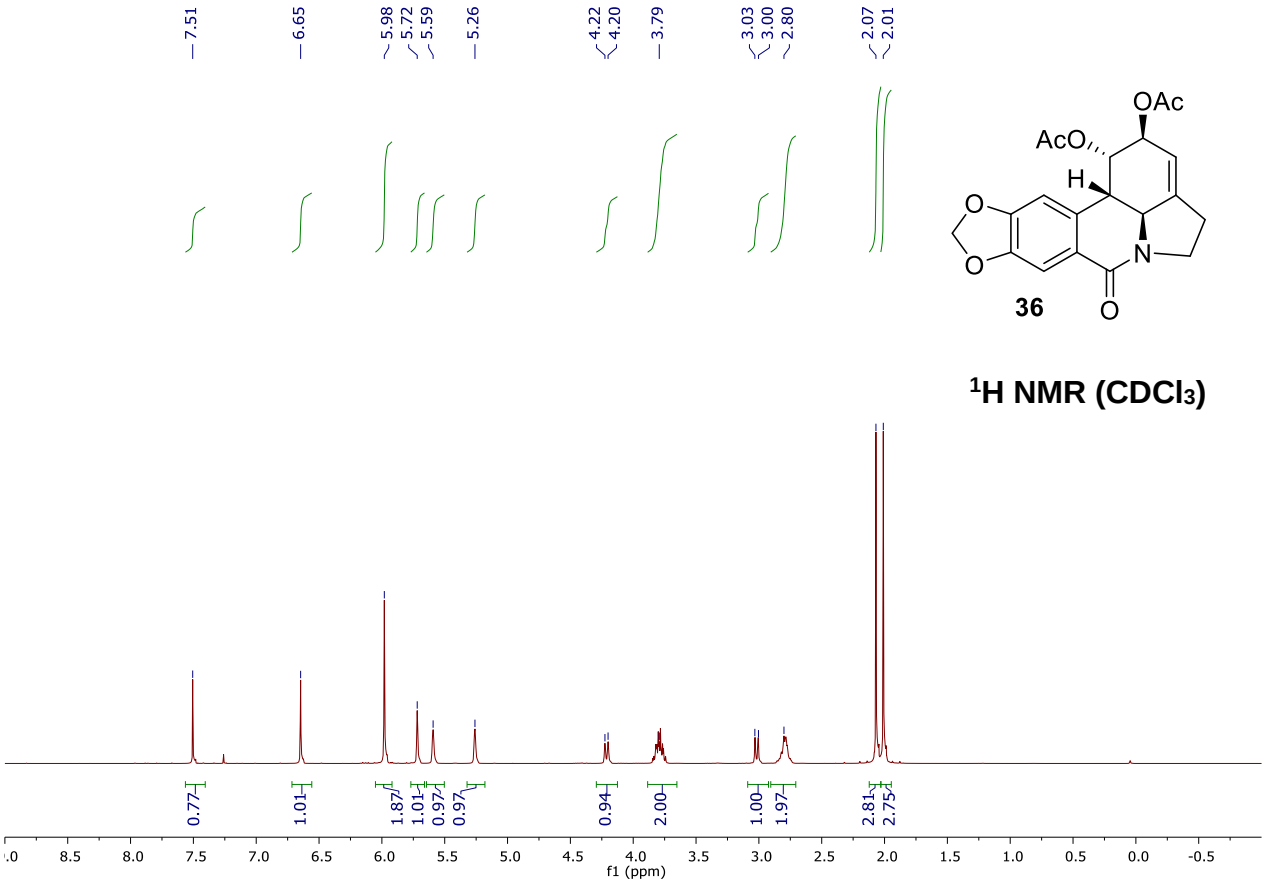
^{1}H NMR (Toluene-d_8, 100 °C)



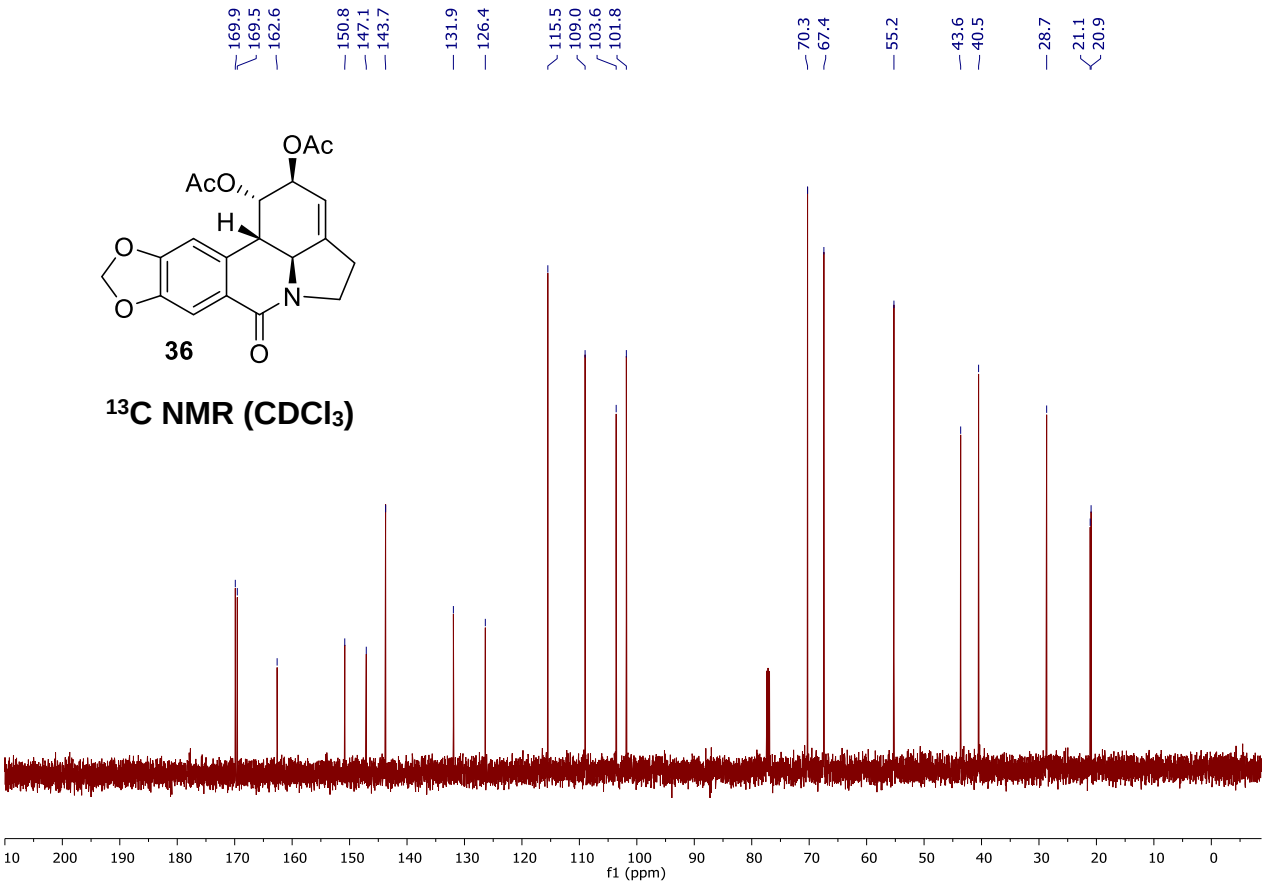


35

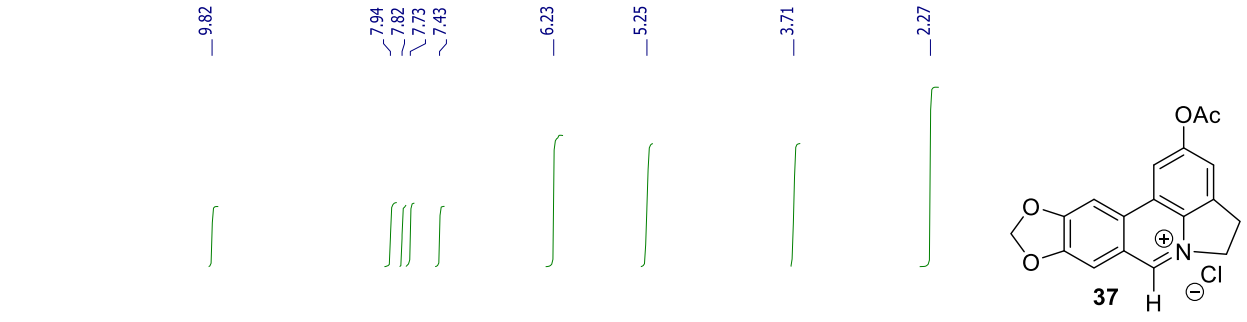
^{13}C NMR ($CDCl_3$, –30 °C)



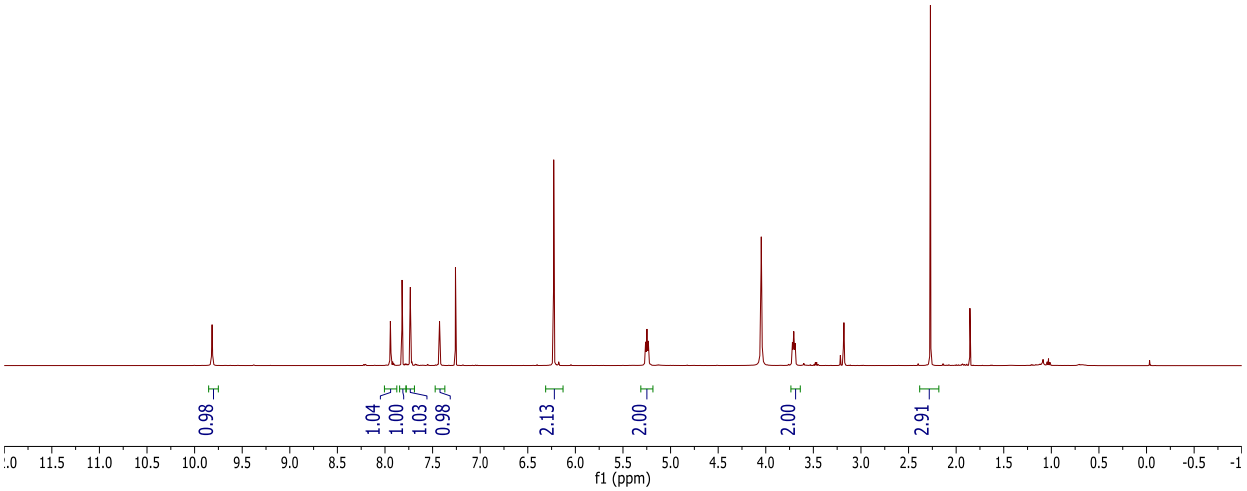
^{1}H NMR ($CDCl_3$)



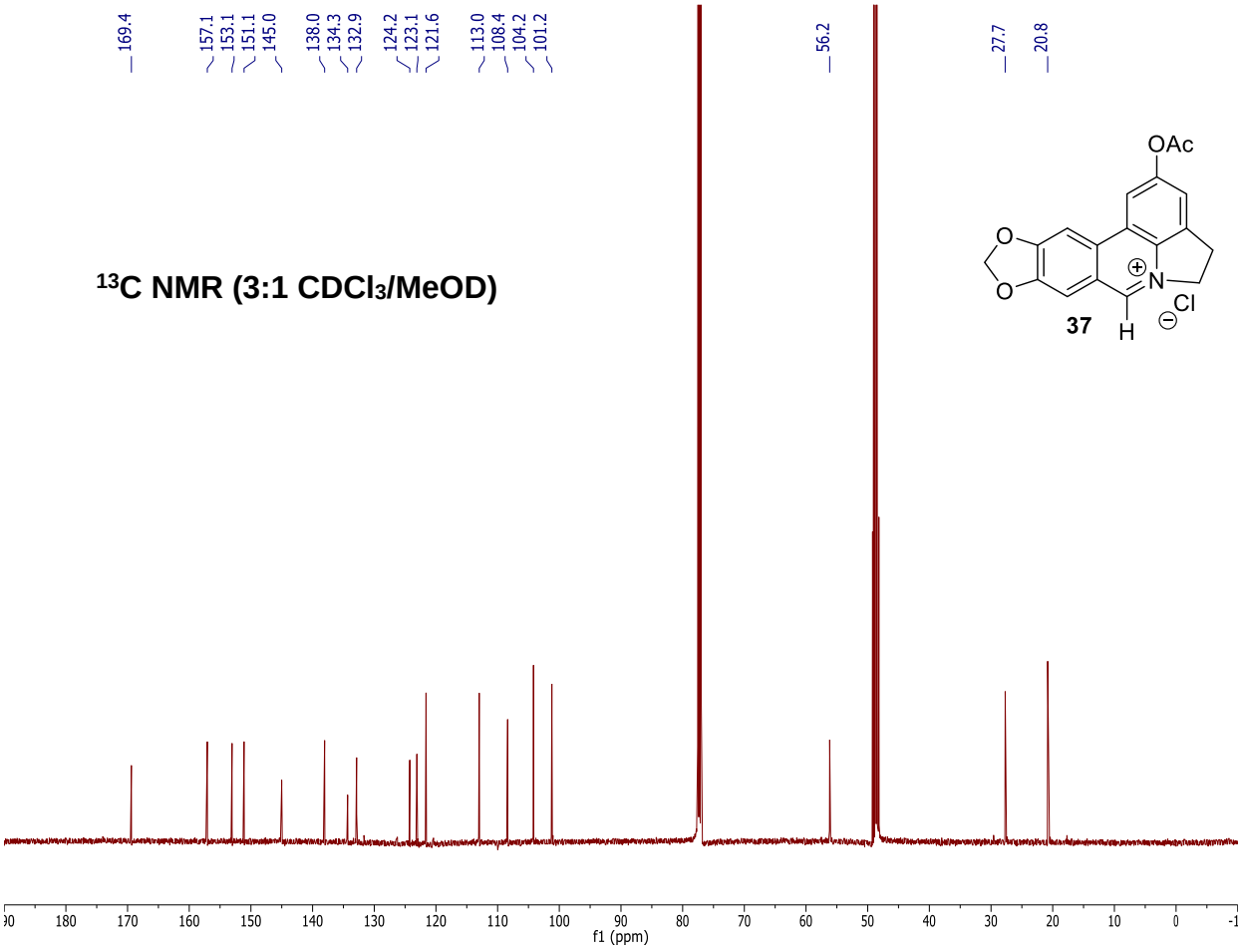
^{13}C NMR ($CDCl_3$)

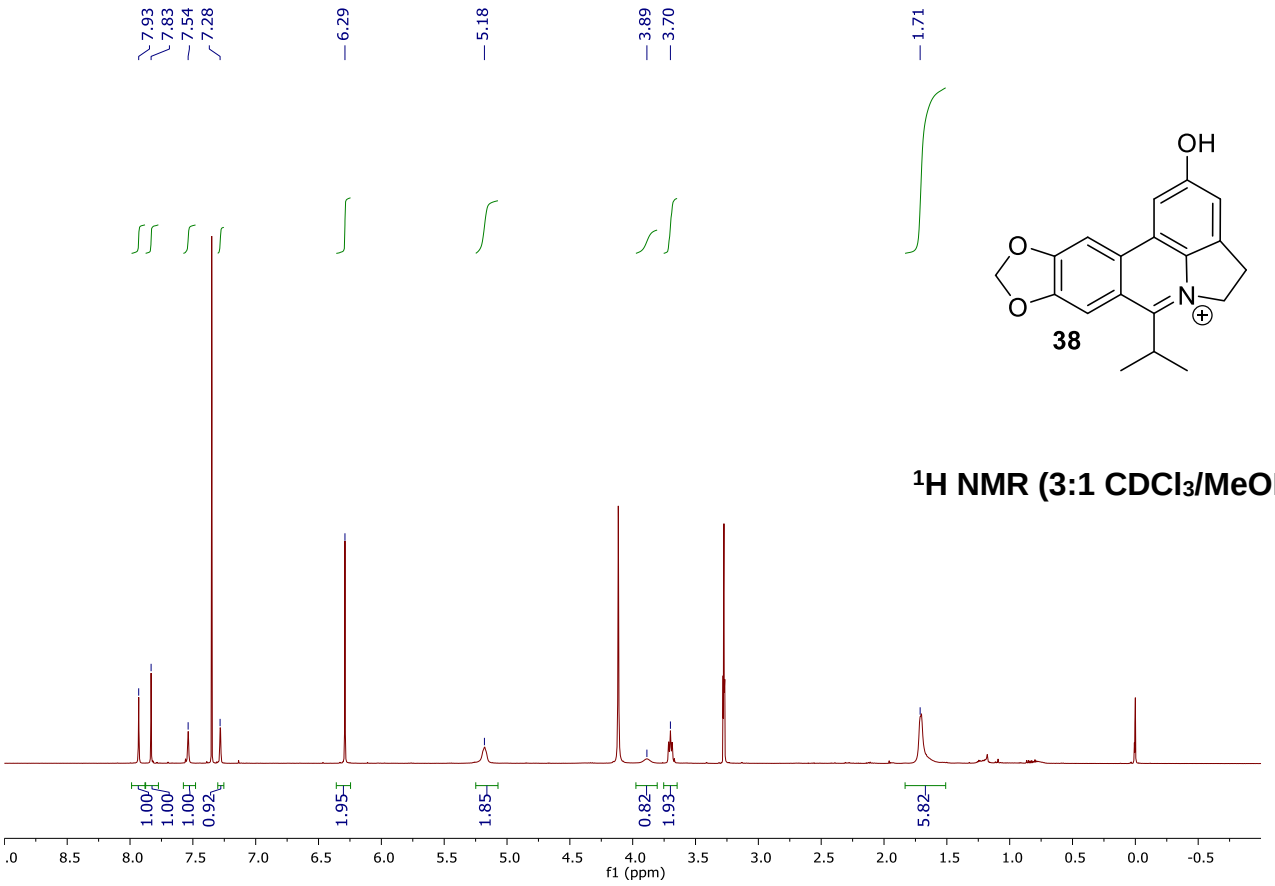


^{1}H NMR (3:1 $CDCl_3$/MeOD)

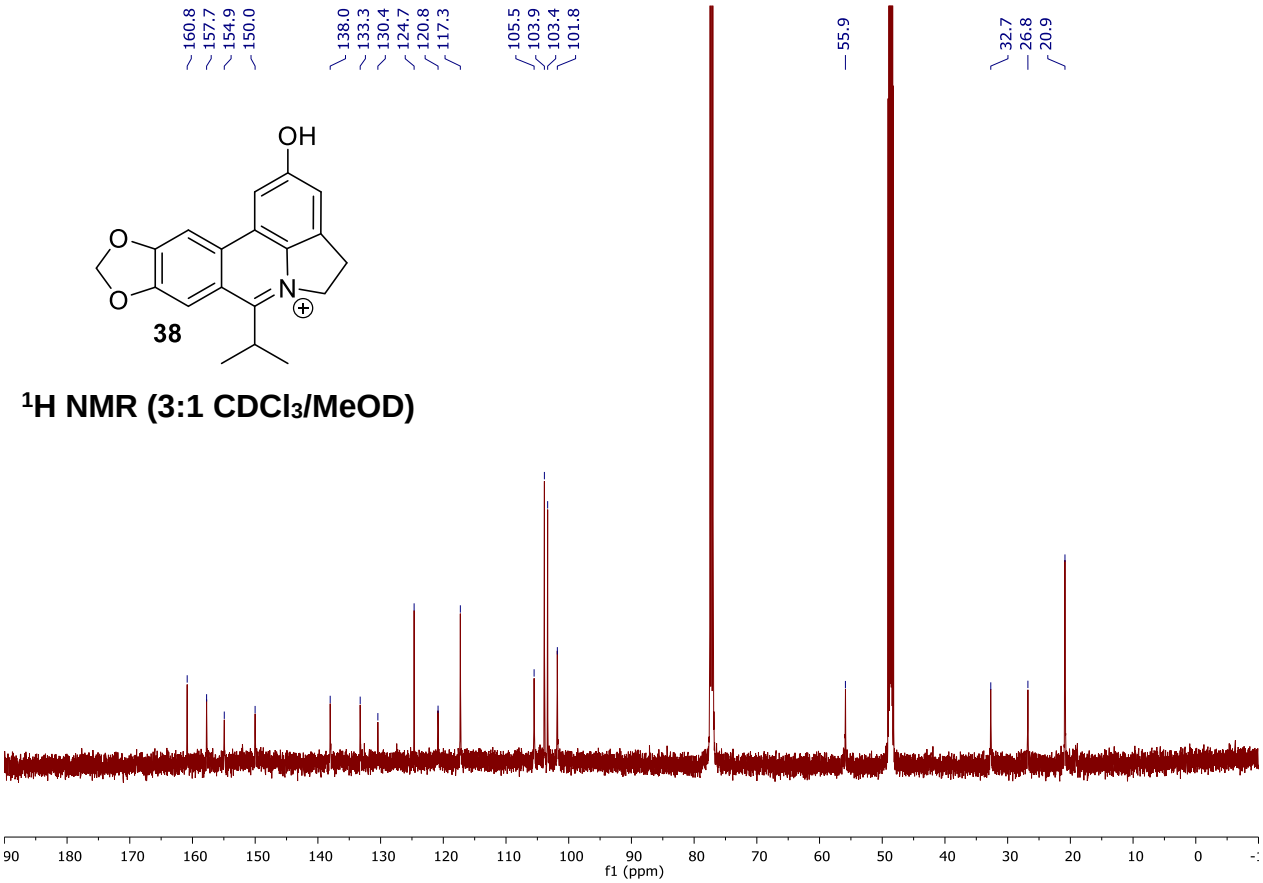


^{13}C NMR (3:1 $CDCl_3$/MeOD)

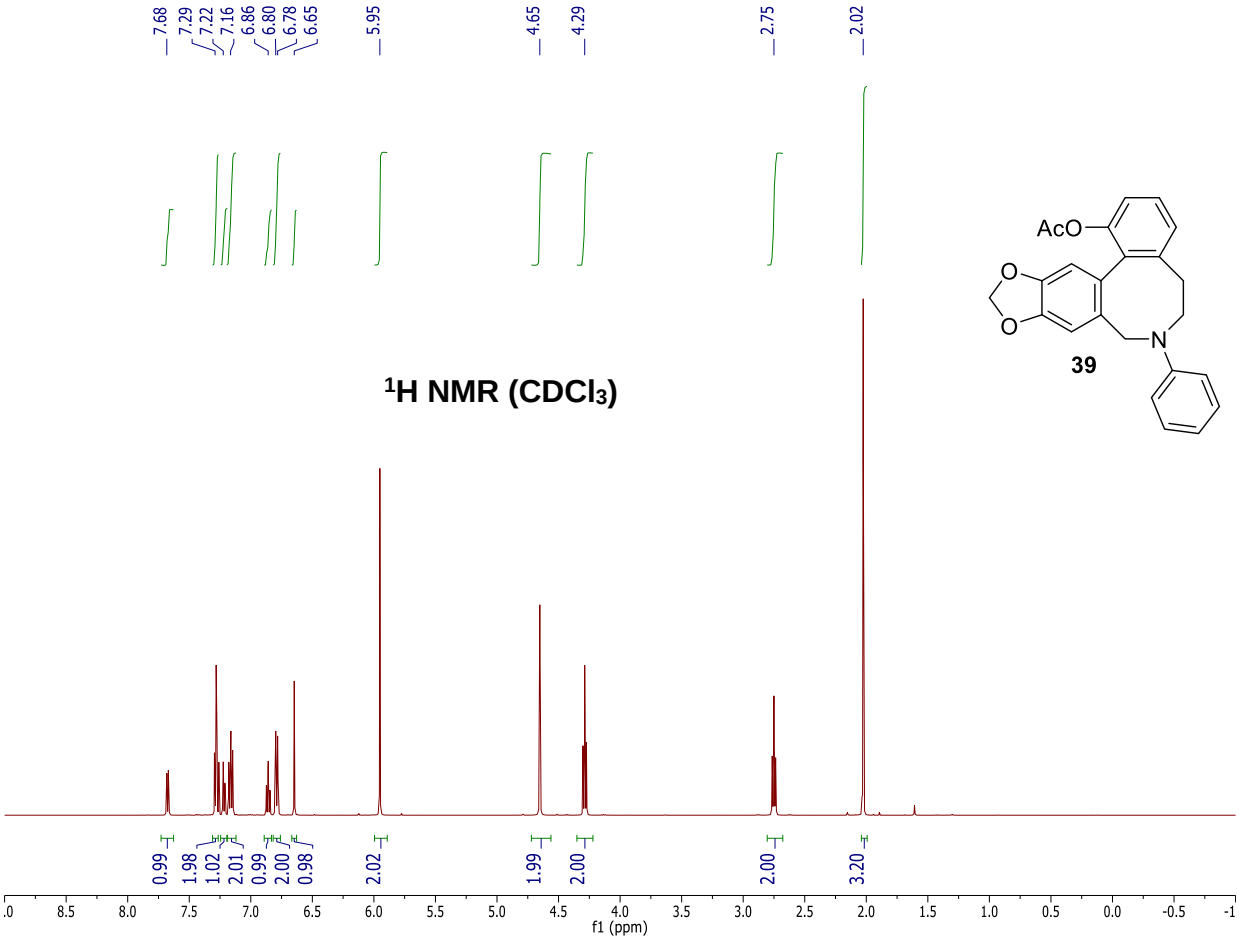




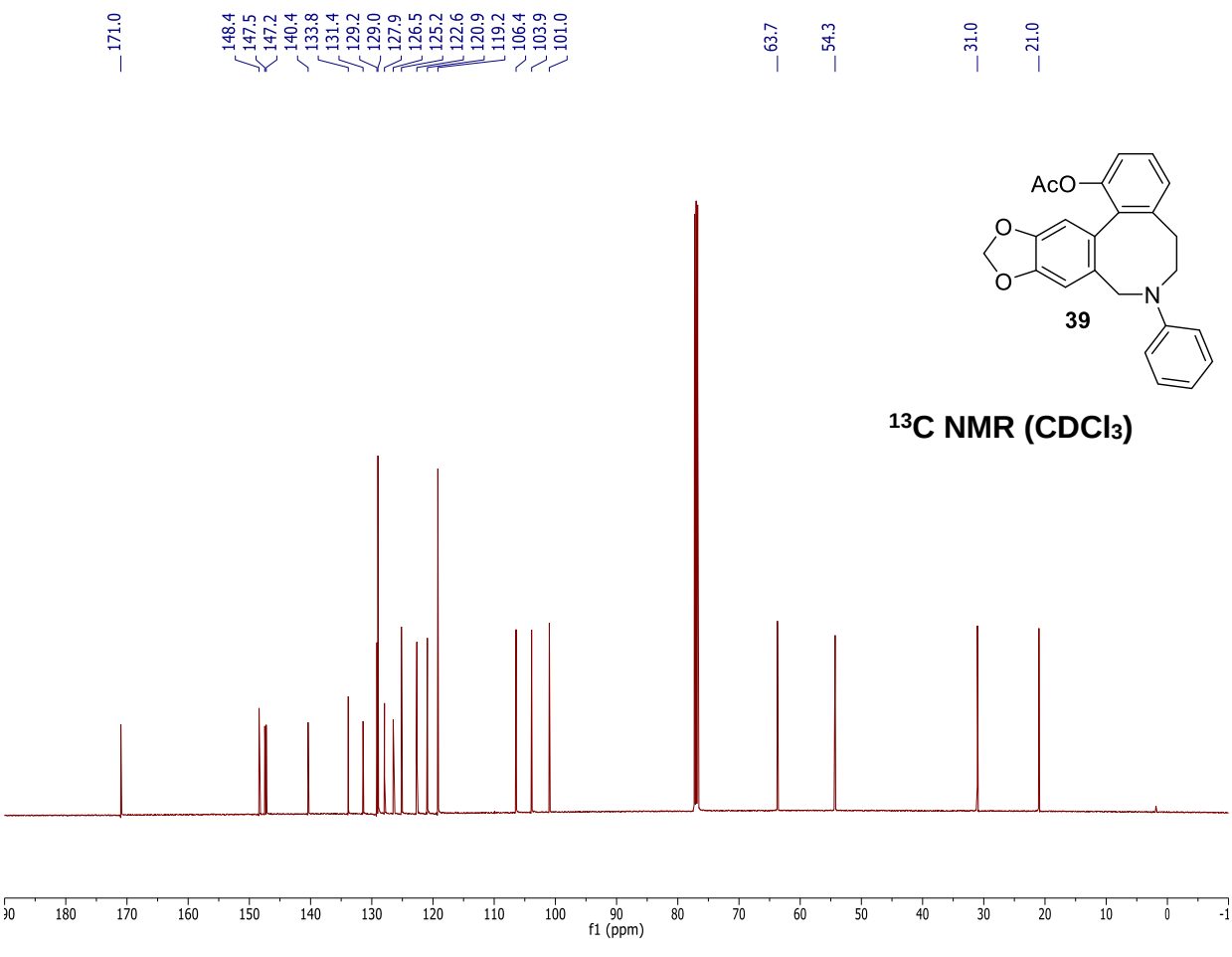
^{1}H NMR (3:1 $CDCl_3$/MeOD)



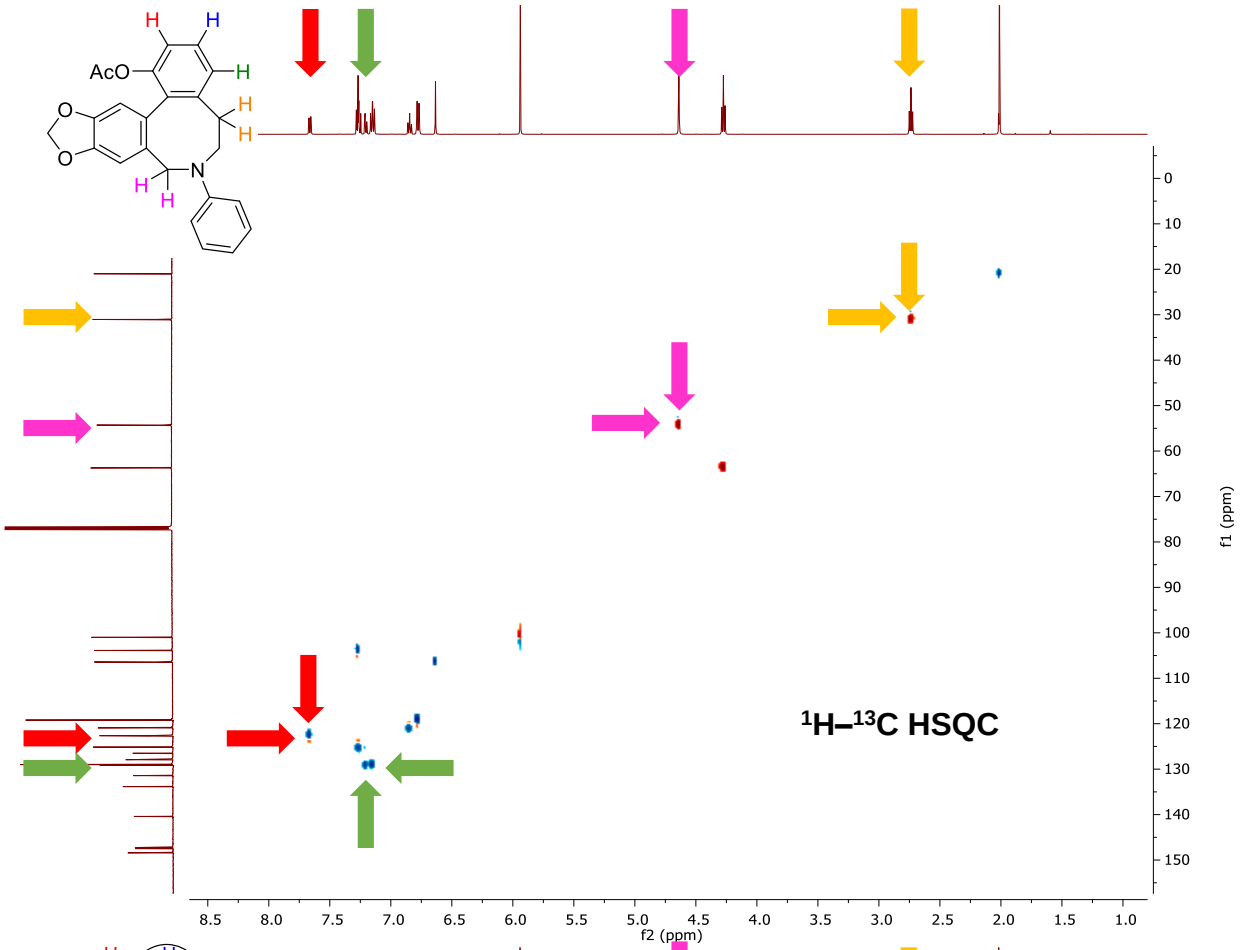
^{1}H NMR (3:1 $CDCl_3$/MeOD)



^{1}H NMR ($CDCl_3$)



^{13}C NMR ($CDCl_3$)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O
O
N
H
H
H
H
H
H
H
^{1}H–^{13}C HSQC
f1 (ppm)
f2 (ppm)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
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0
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80
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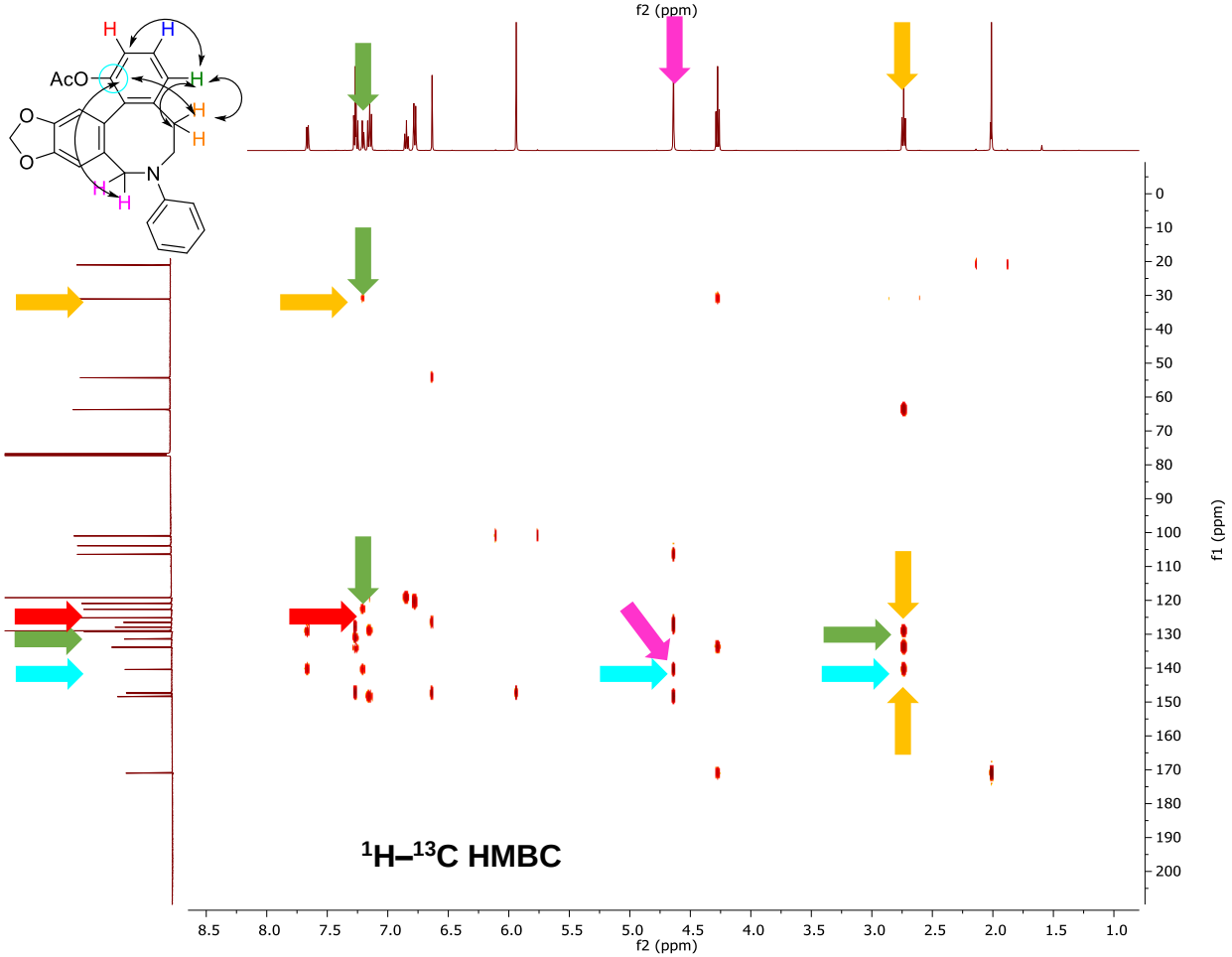
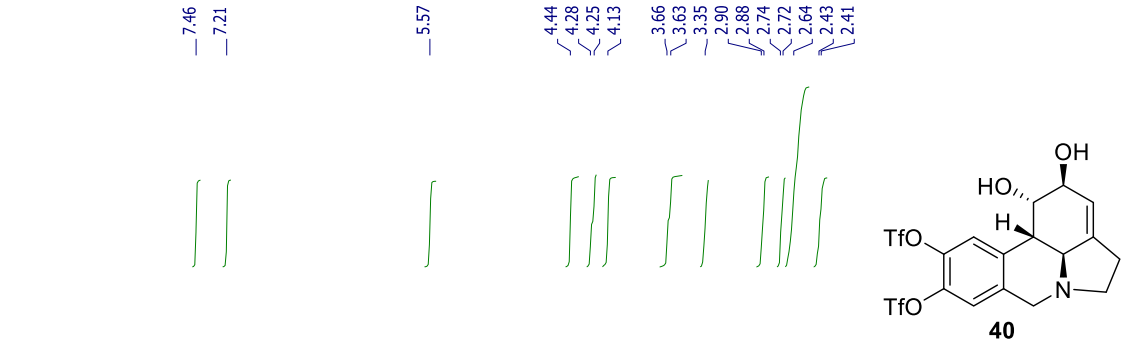
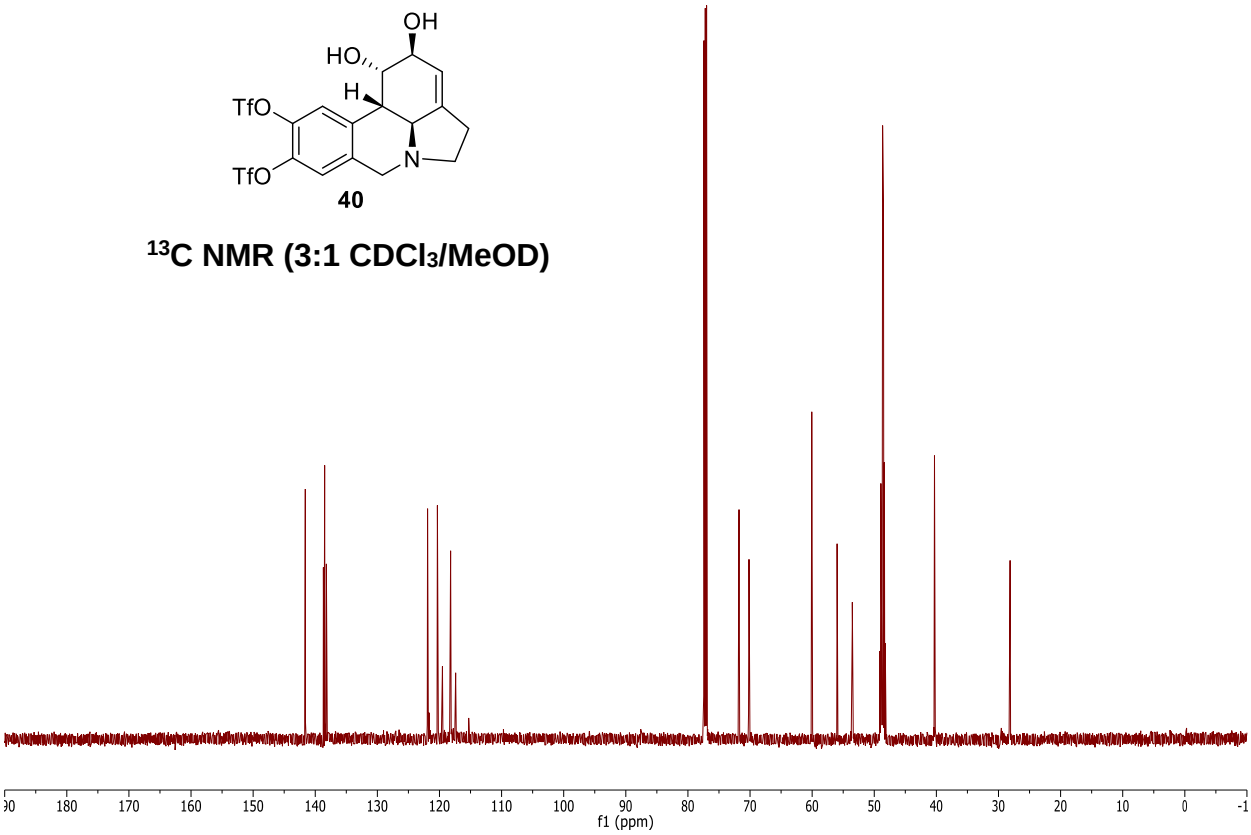
140
150


AcO
O
O
N
H
H
H
H
H
H
H
^{1}H–^{13}C HMBC
f1 (ppm)
f2 (ppm)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200



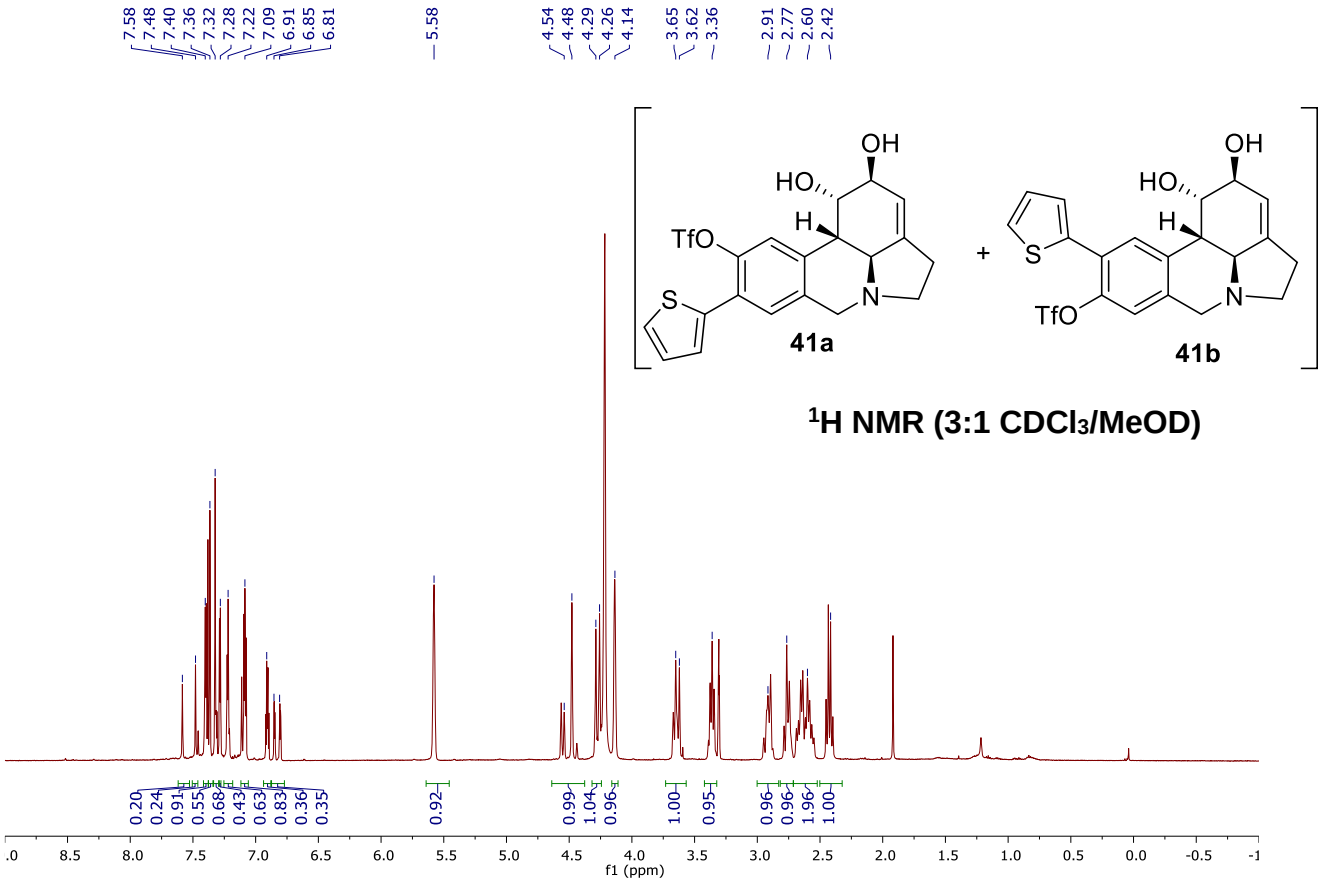
40

^{1}H NMR (3:1 CDCl$_3$/MeOD)

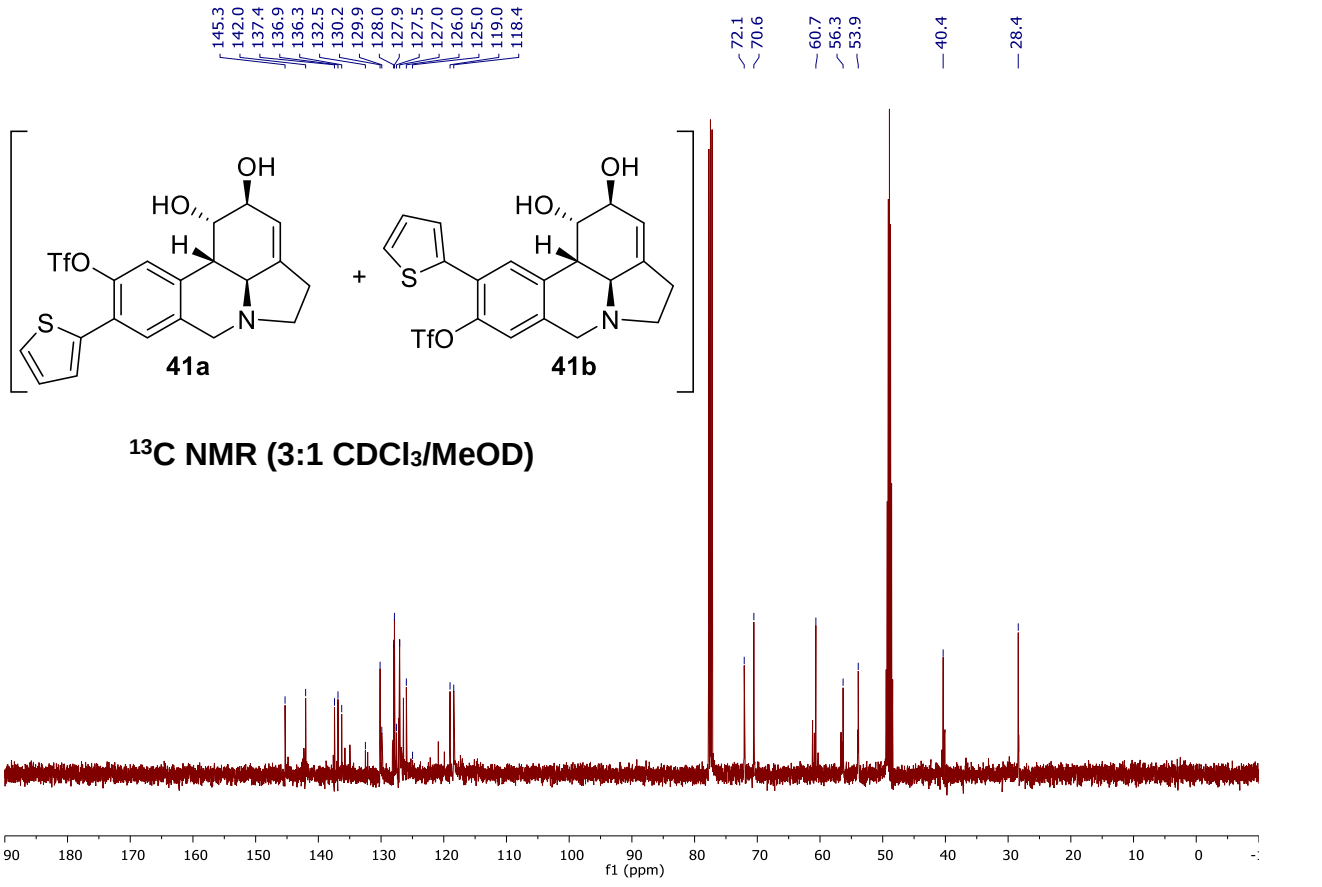


40

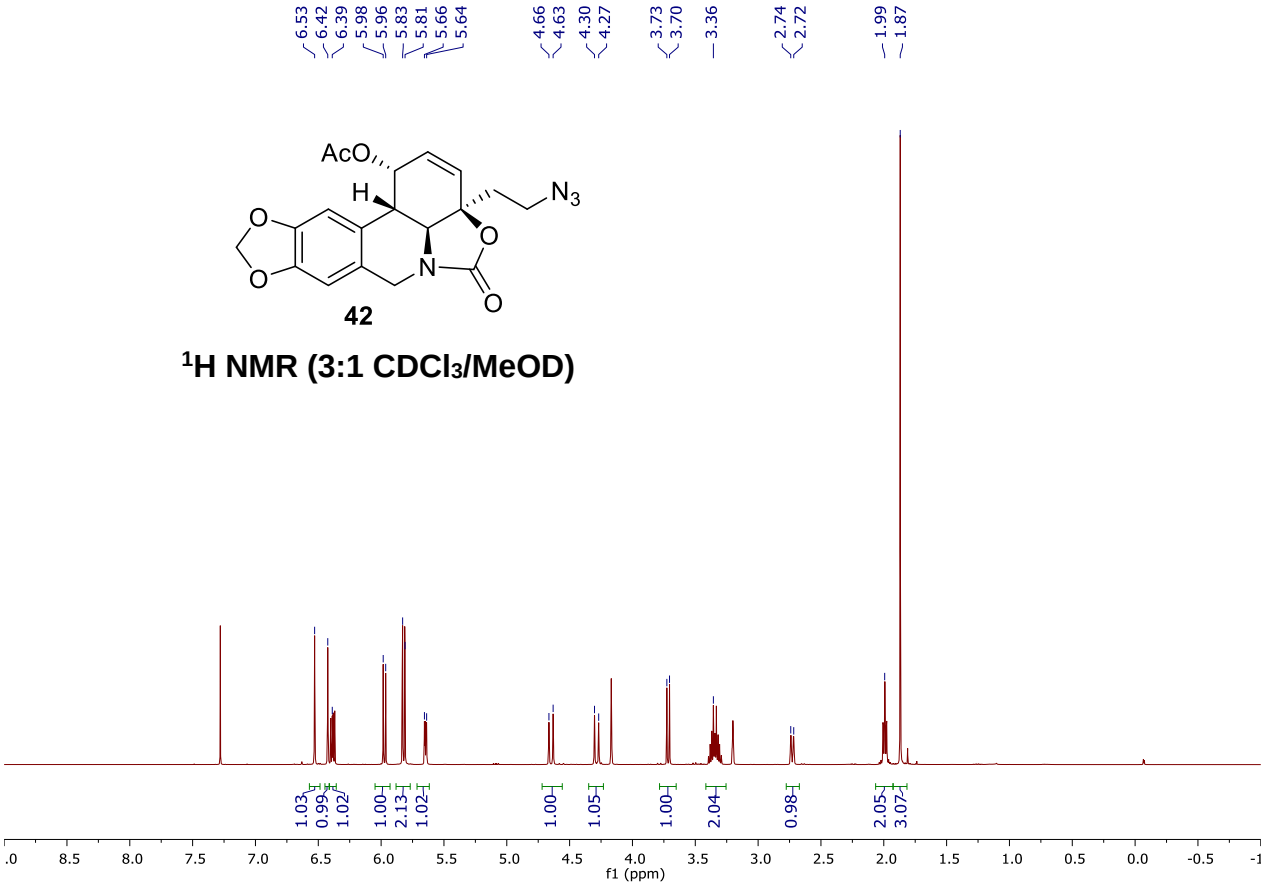
^{13}C NMR (3:1 CDCl$_3$/MeOD)



^{1}H NMR (3:1 $CDCl_3$/MeOD)

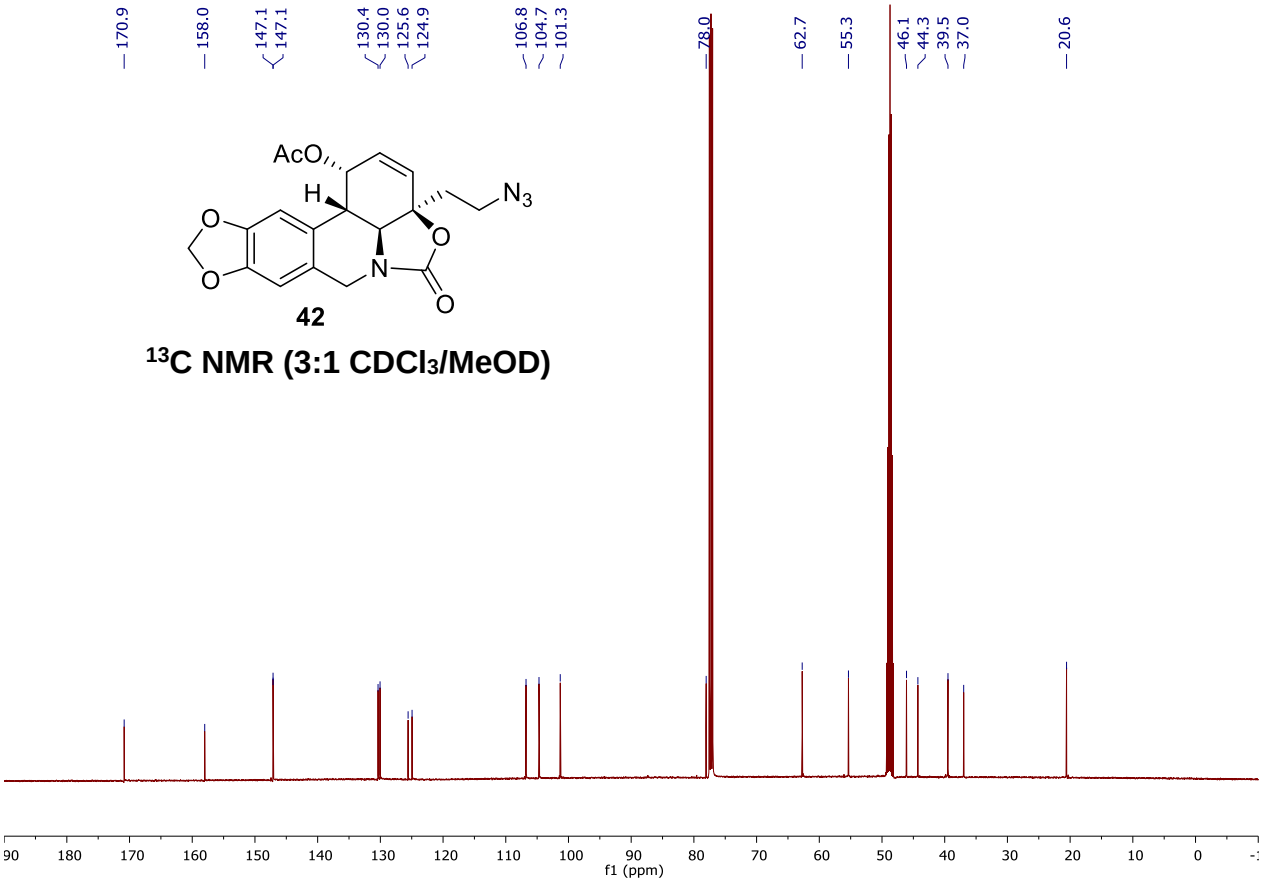


^{13}C NMR (3:1 $CDCl_3$/MeOD)



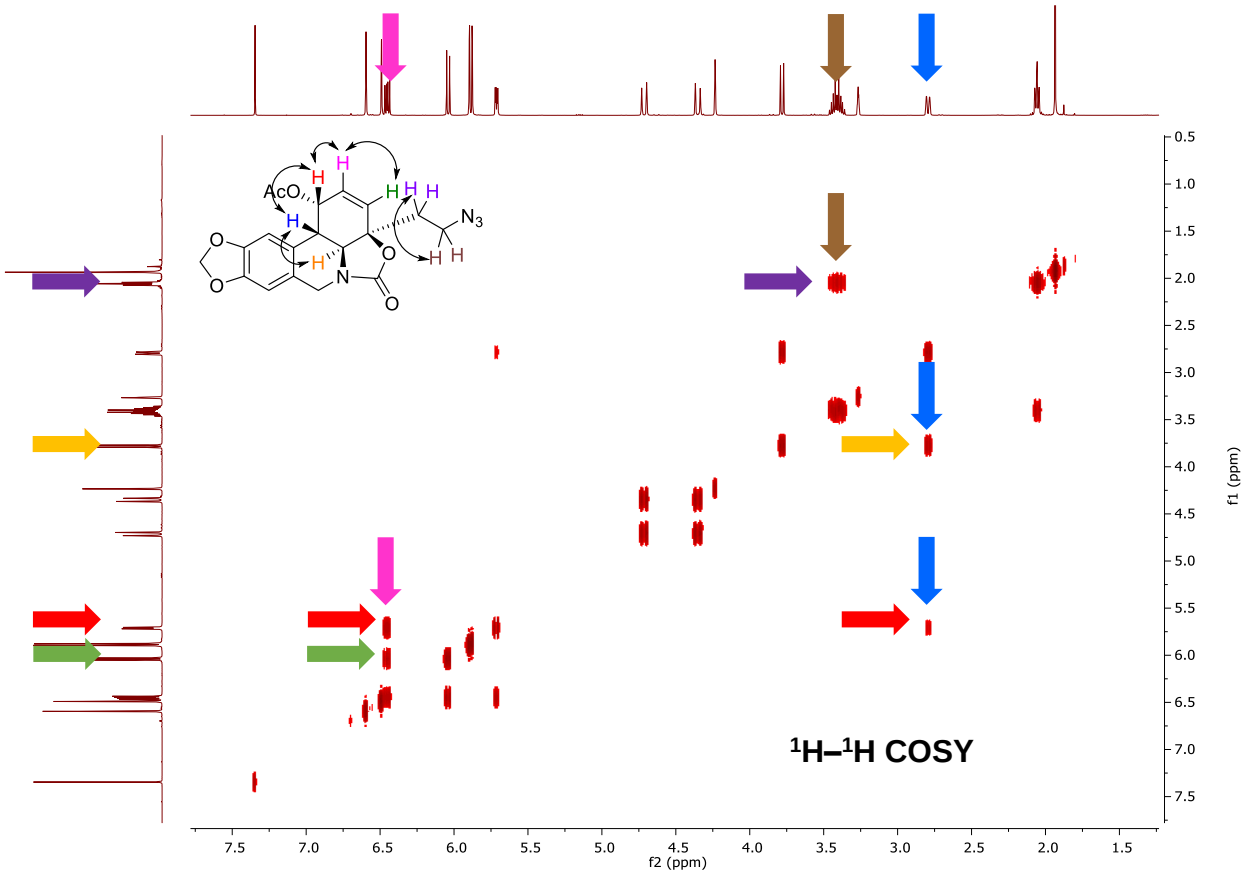
42

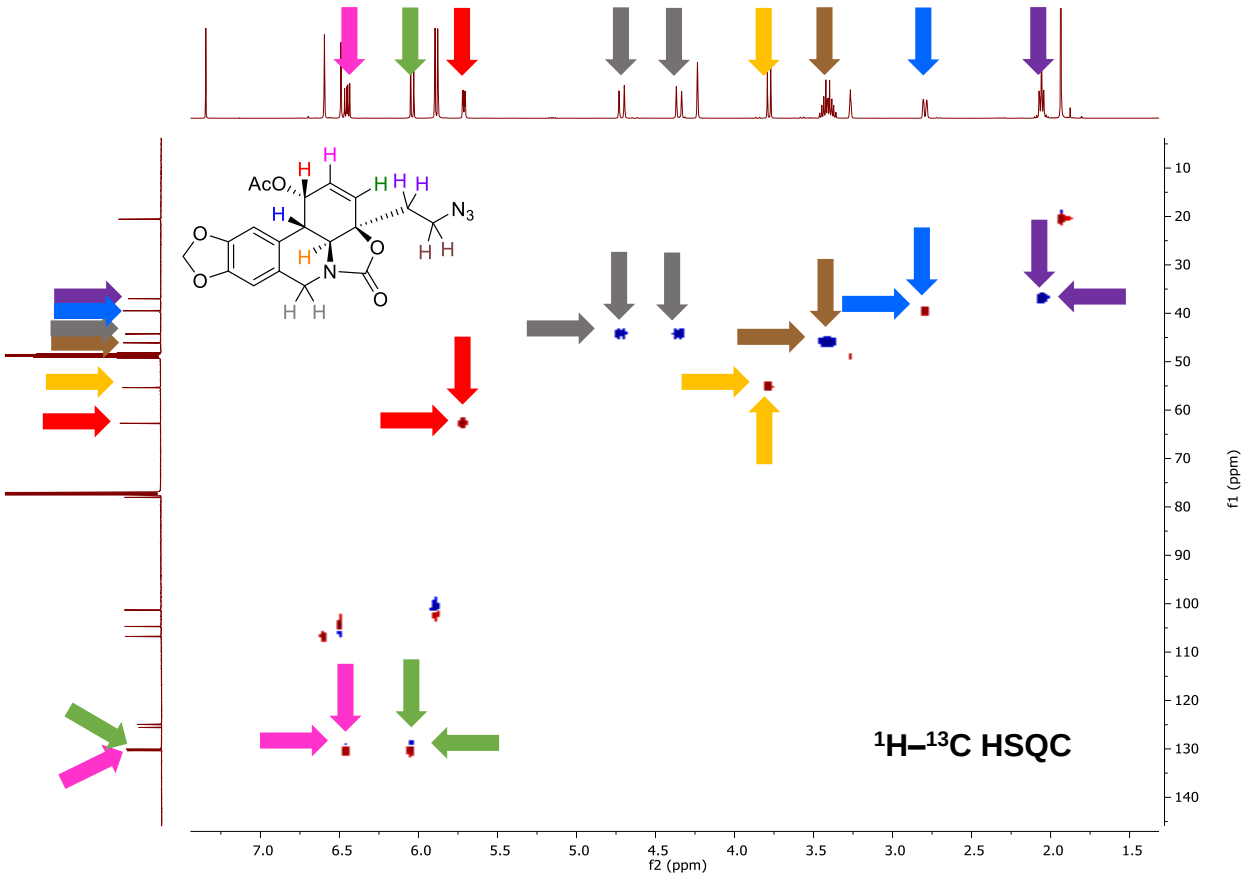
^{1}H NMR (3:1 $CDCl_3$/MeOD)

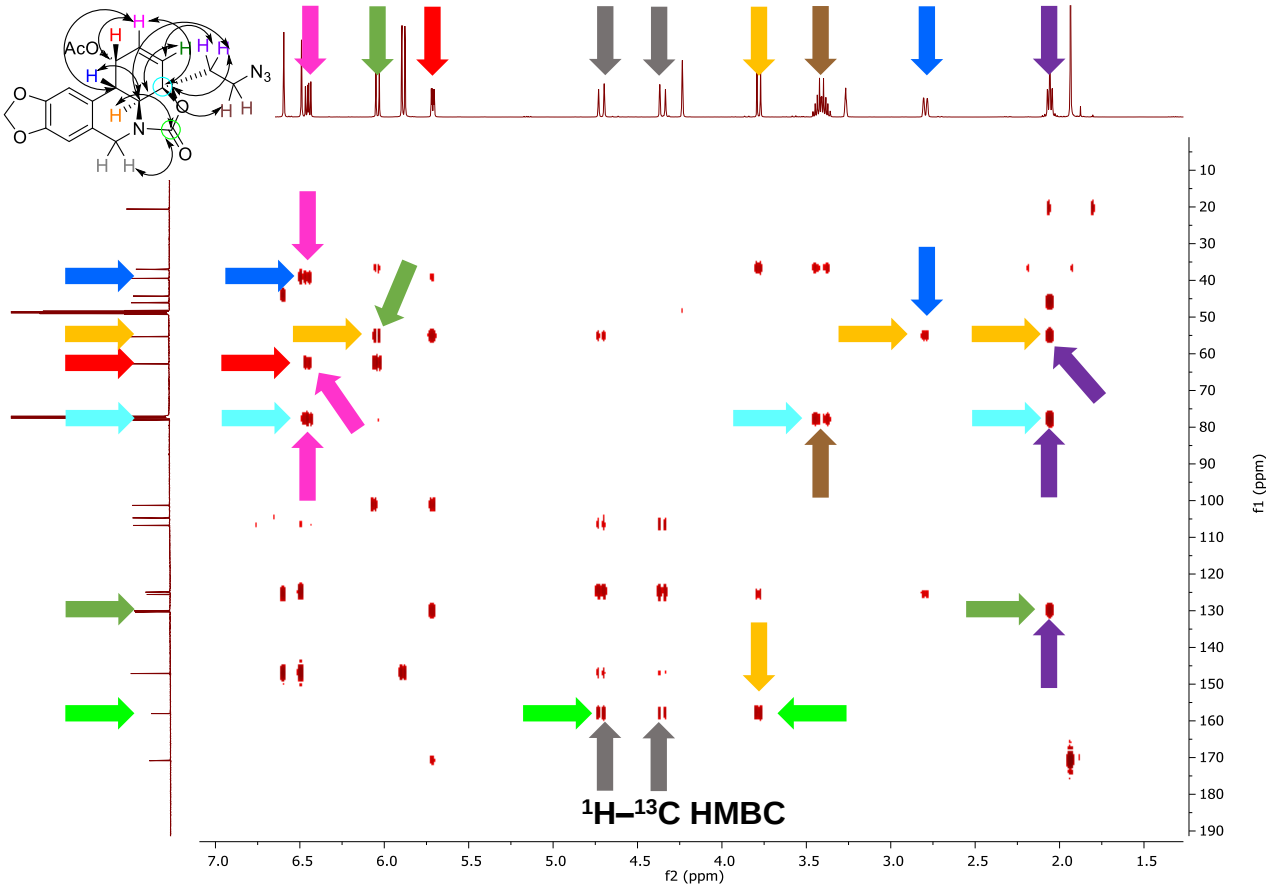


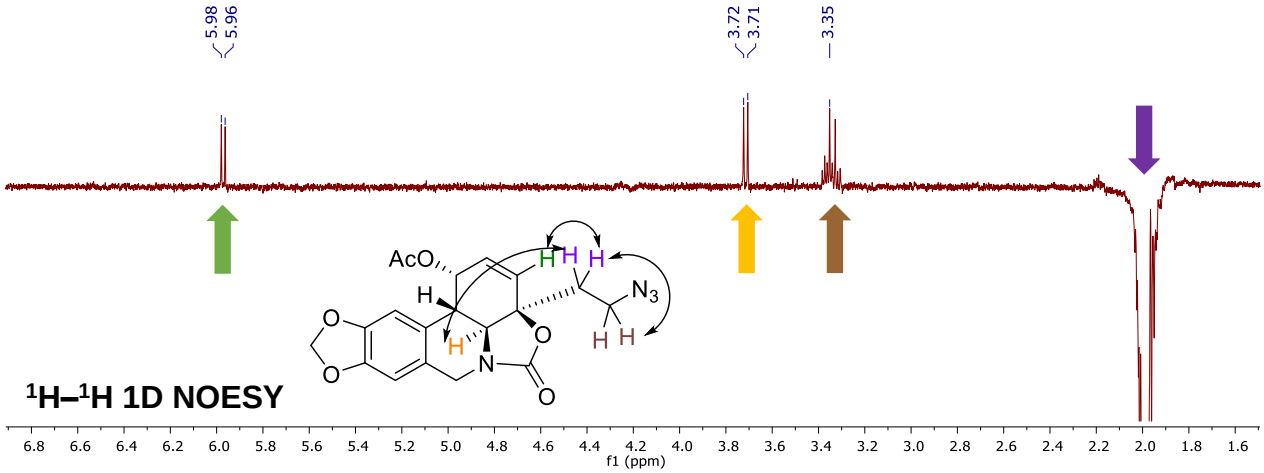
42

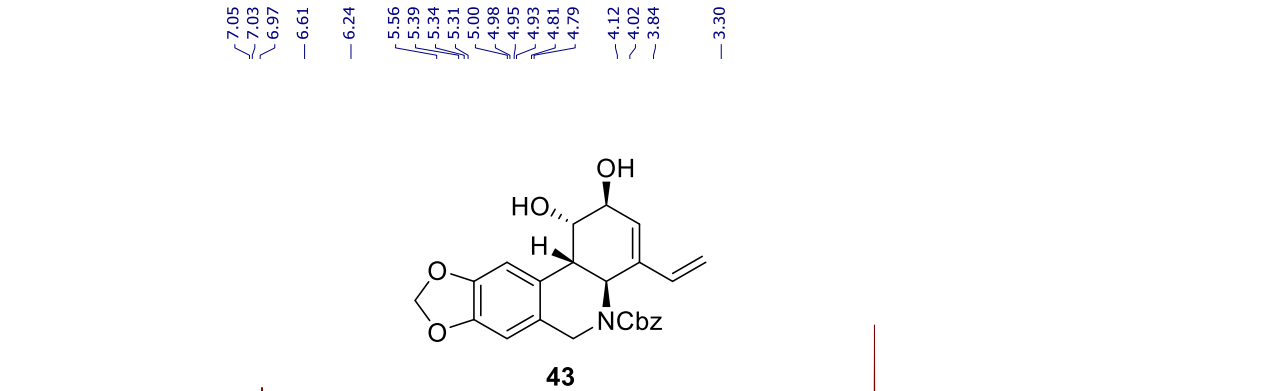
^{13}C NMR (3:1 $CDCl_3$/MeOD)


AcO
N3
^{1}H–^{1}H COSY
f2 (ppm)
f1 (ppm)


AcO
N3
^{1}H–^{13}C HSQC
f2 (ppm)
f1 (ppm)

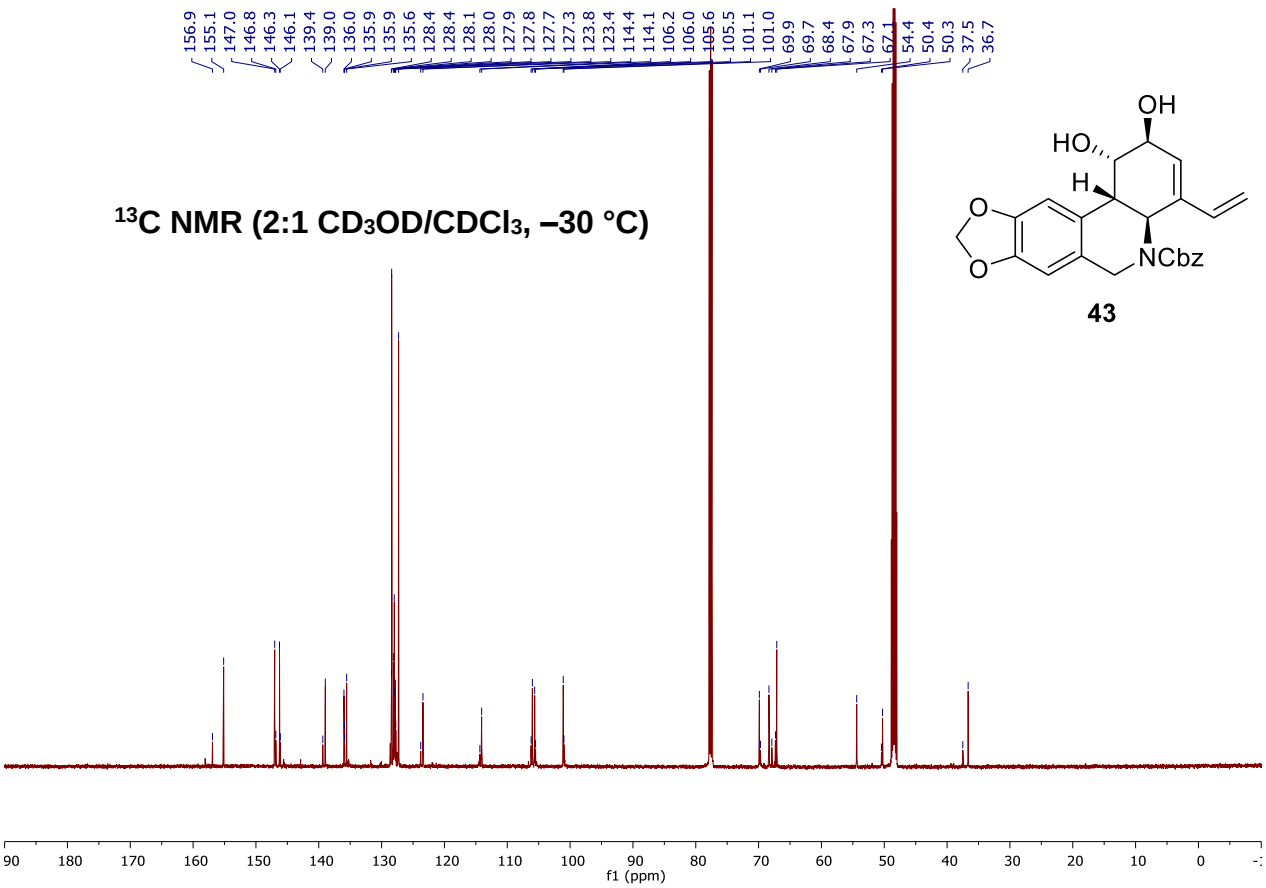

AcO
N3
O
N
H
1H–13C HMBC
f2 (ppm)
f1 (ppm)


5.98
5.96
3.72
3.71
3.35
AcO
N3
1H–1H 1D NOESY
f1 (ppm)



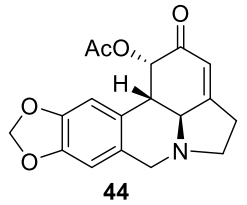
43

^{1}H NMR (Toluene-*d*$_8$, 100 °C)



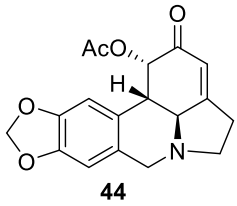
^{13}C NMR (2:1 CD$_3$OD/CDCl$_3$, –30 °C)

43



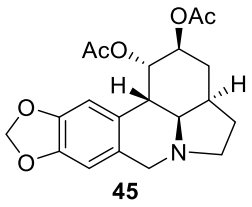
44

^{1}H NMR ($CDCl_3$)



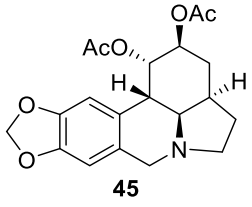
44

^{13}C NMR ($CDCl_3$)



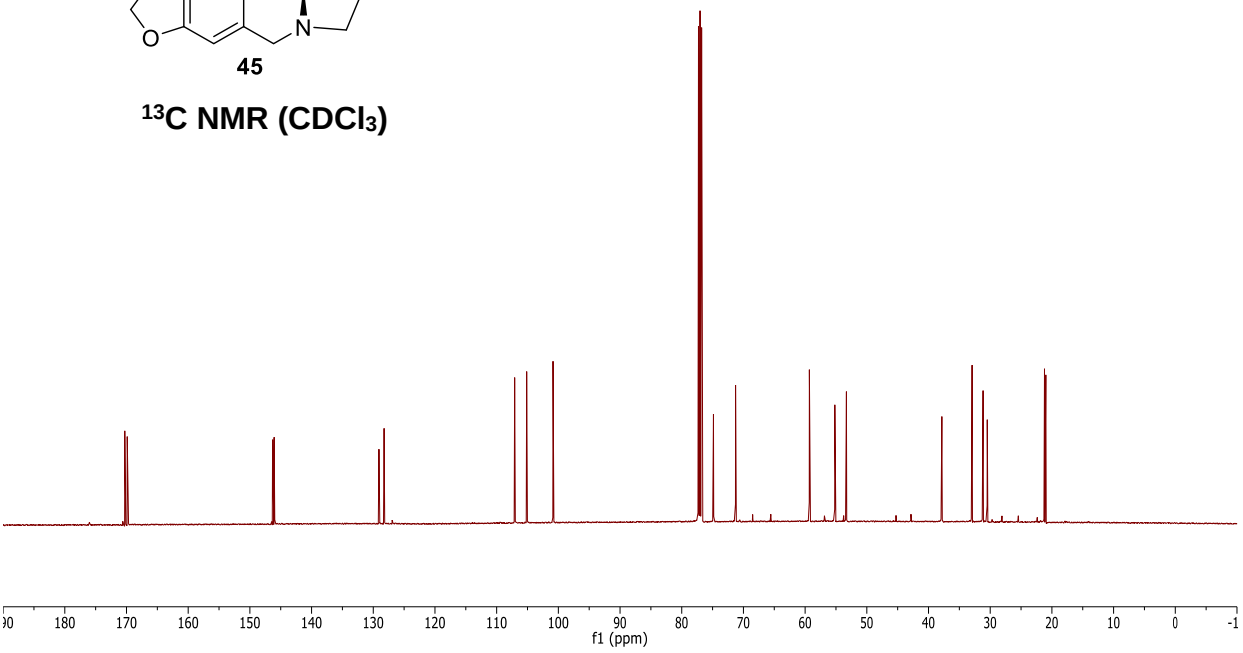
45

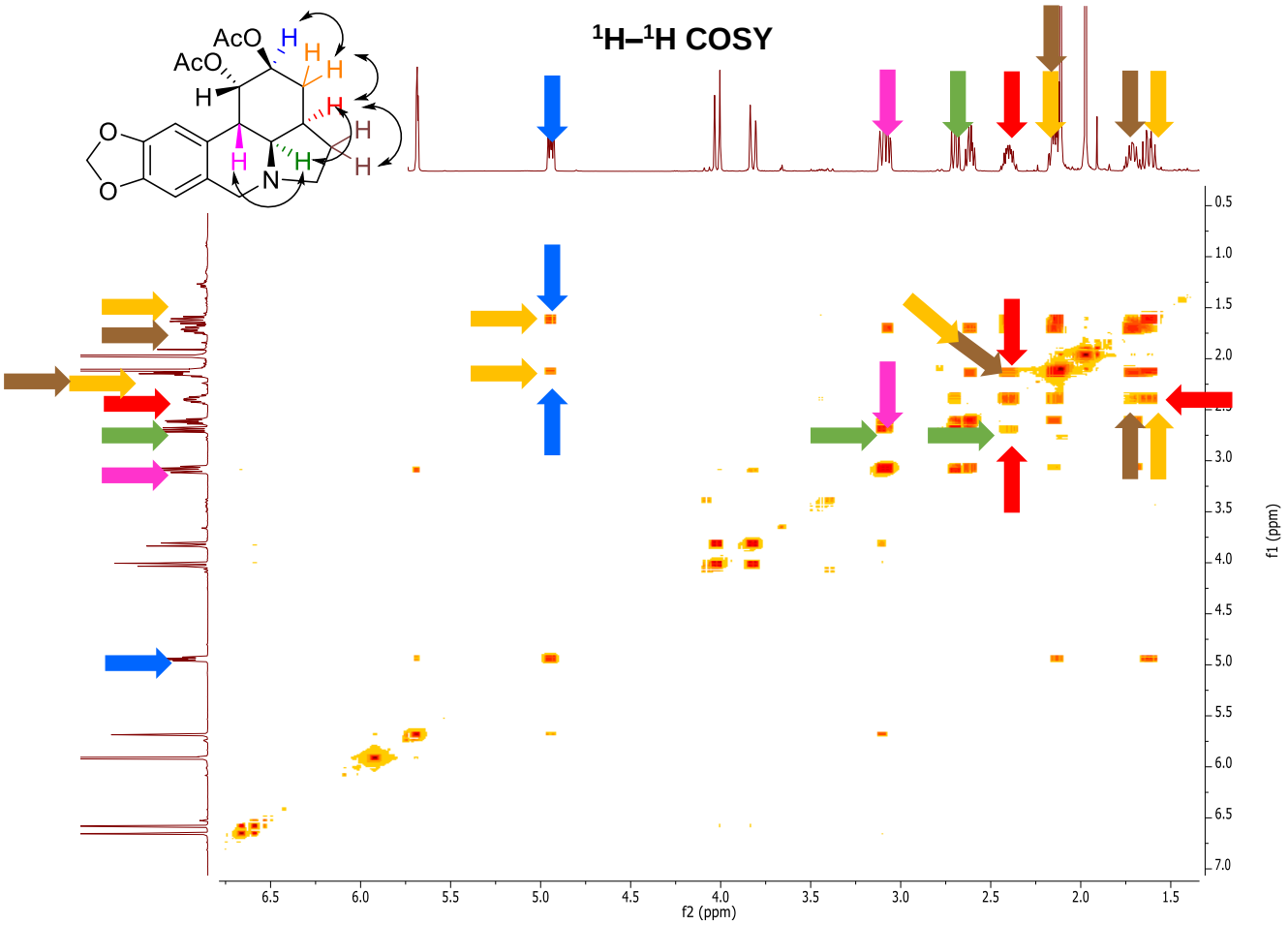
^{1}H NMR ($CDCl_3$)

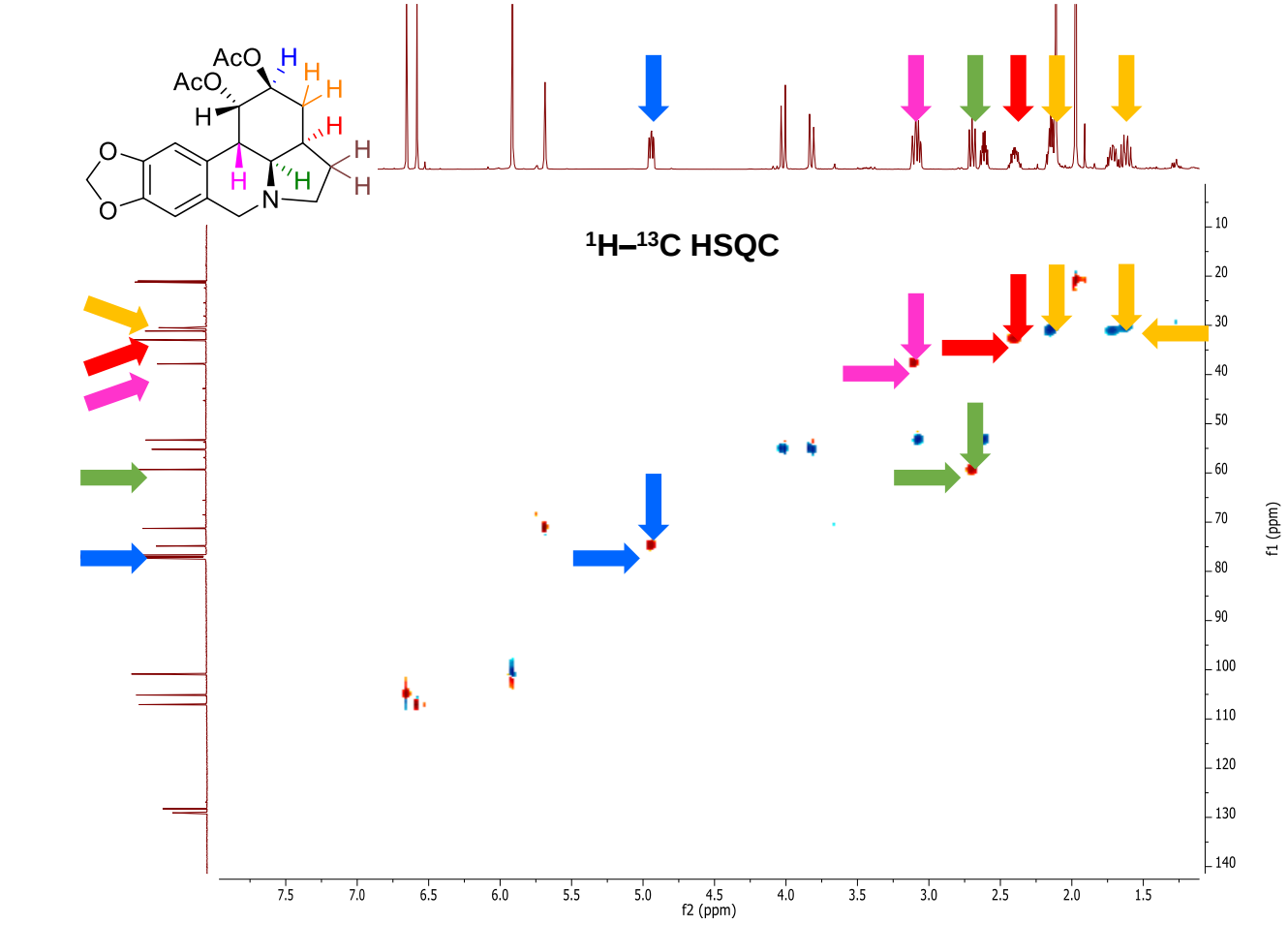


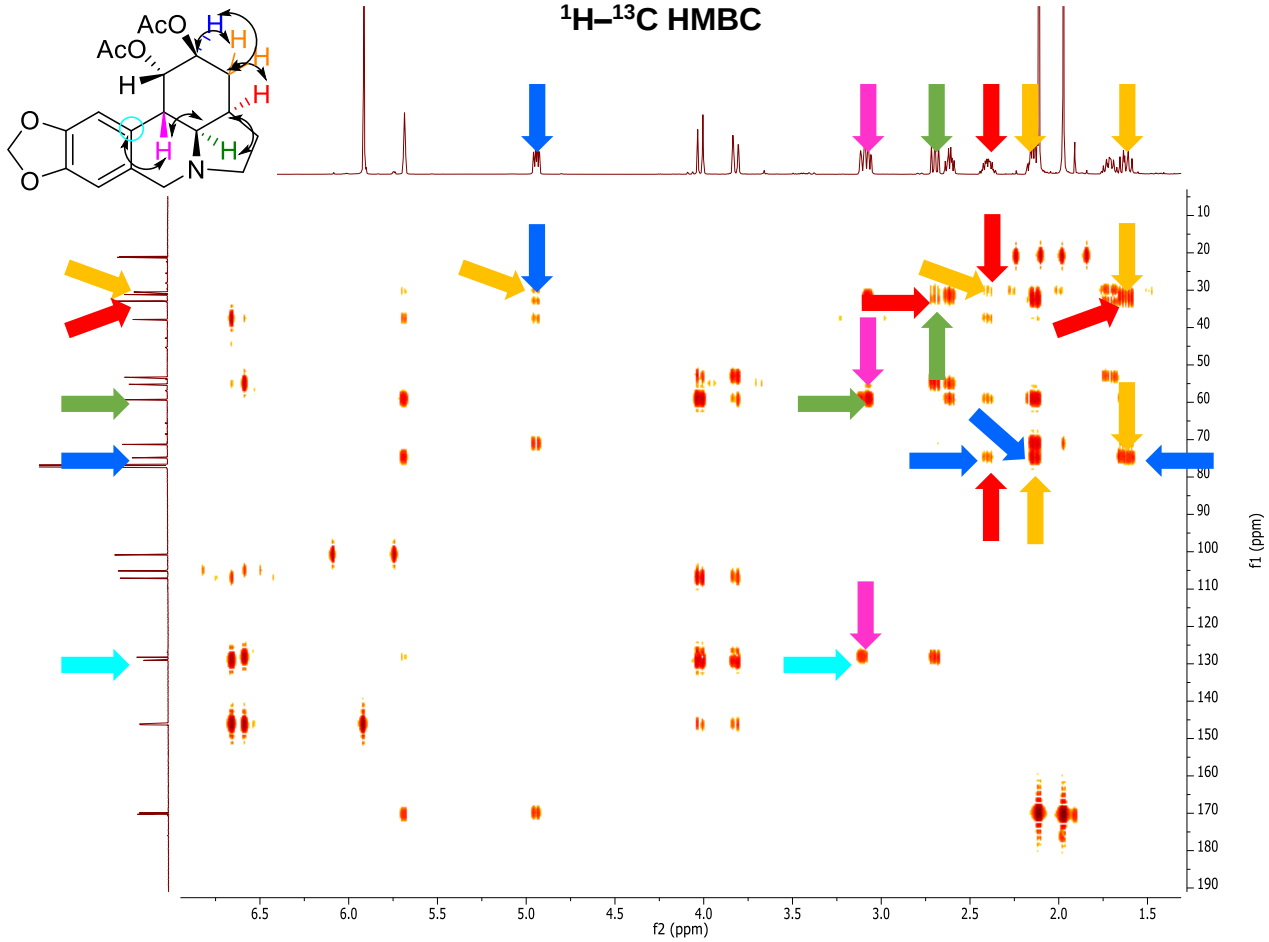
45

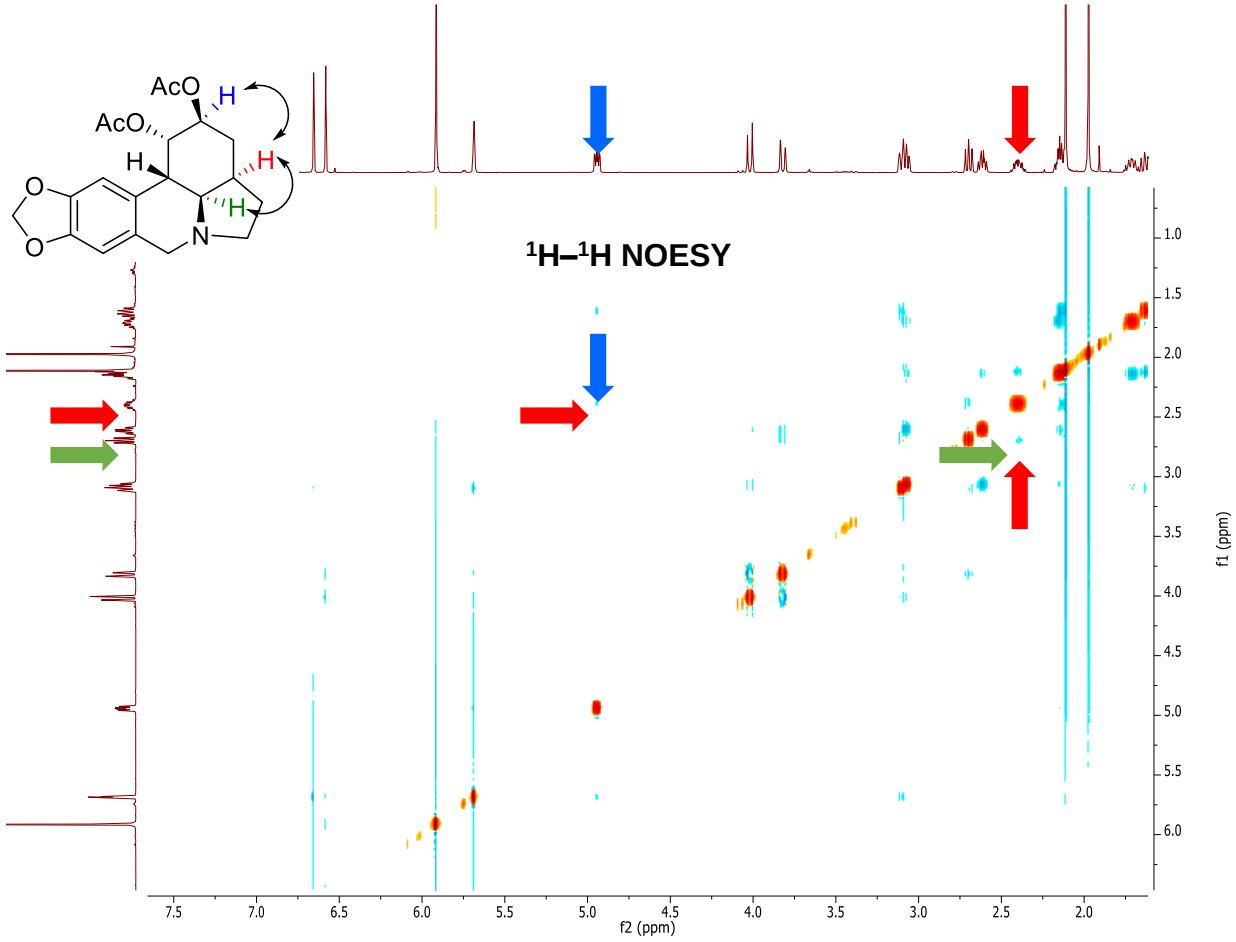
^{13}C NMR ($CDCl_3$)

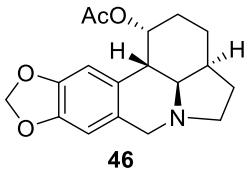



AcO
AcO
H
H
H
H
H
H
H
H
H
H
O
O
N
^{1}H–^{1}H COSY
f2 (ppm)
f1 (ppm)


AcO
AcO
H
H
H
H
H
H
H
H
H
H
O
O
N
^{1}H–^{13}C HSQC
f2 (ppm)
f1 (ppm)

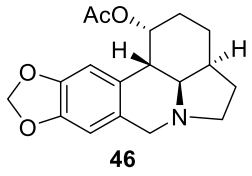

^{1}H–^{13}C HMBC
AcO
AcO
H
H
H
H
H
H
O
O
N
f2 (ppm)
f1 (ppm)


^{1}H–^{1}H NOESY
AcO
AcO
H
H
H
H
O
O
N
f2 (ppm)
f1 (ppm)



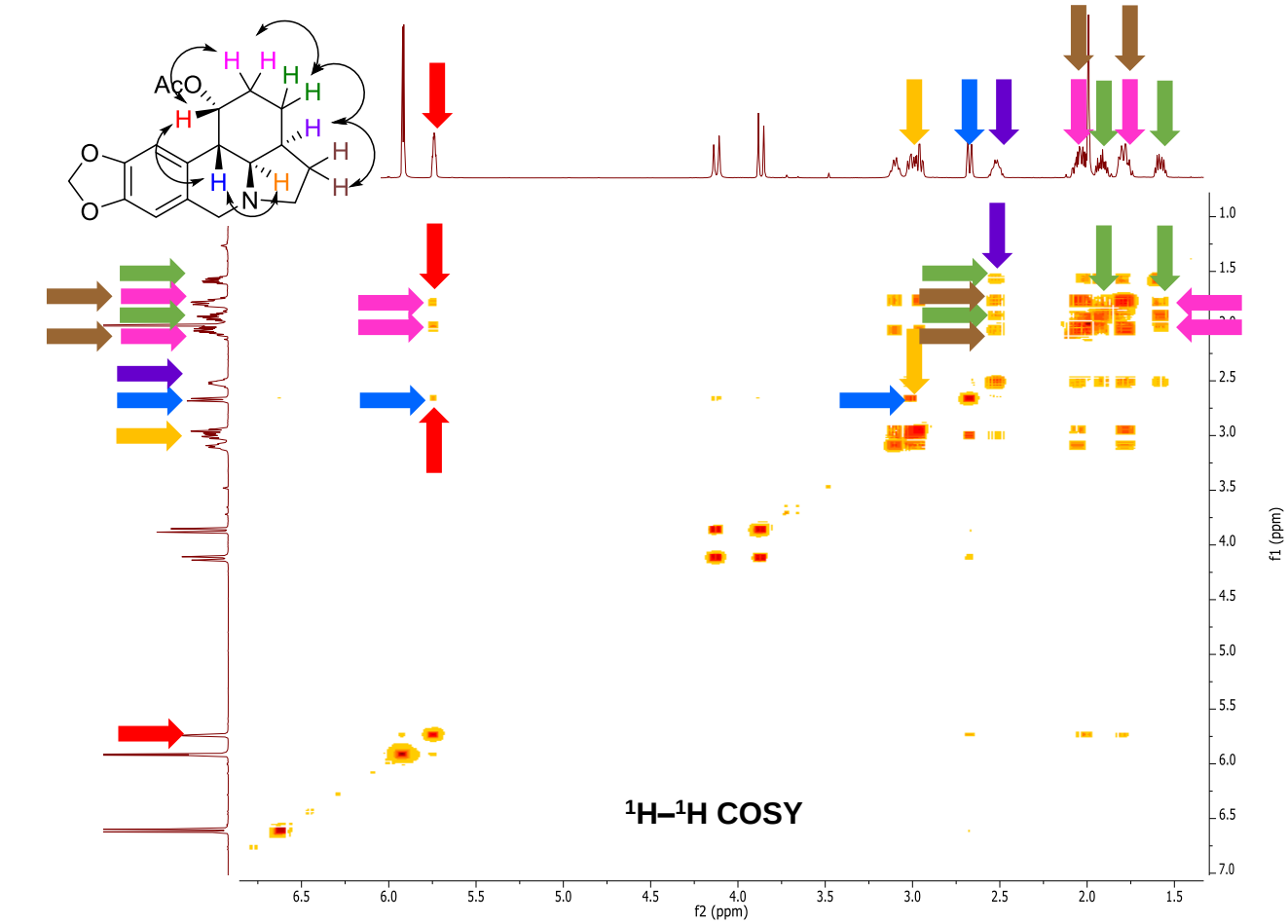
46

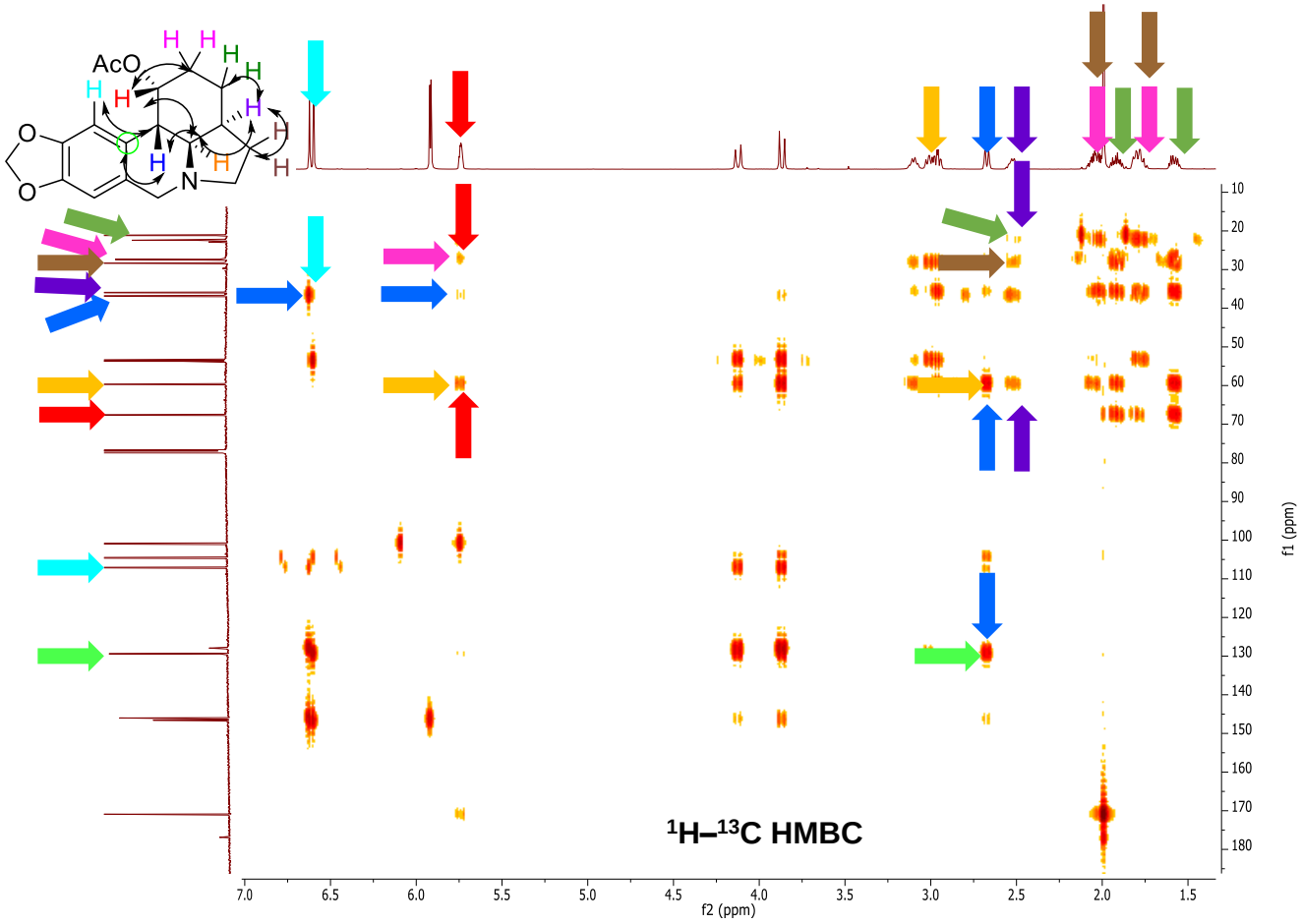
^{1}H NMR ($CDCl_3$)

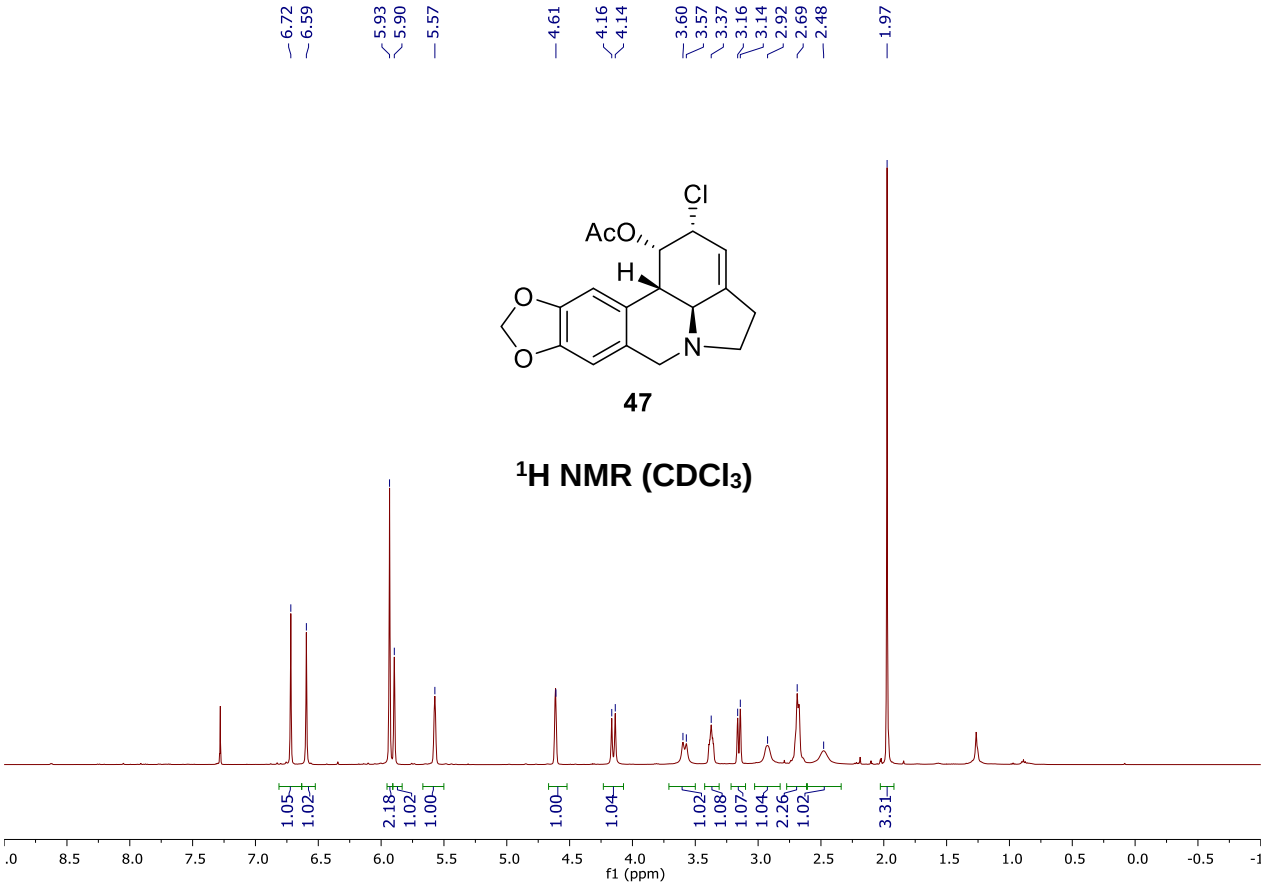


46

^{13}C NMR ($CDCl_3$)

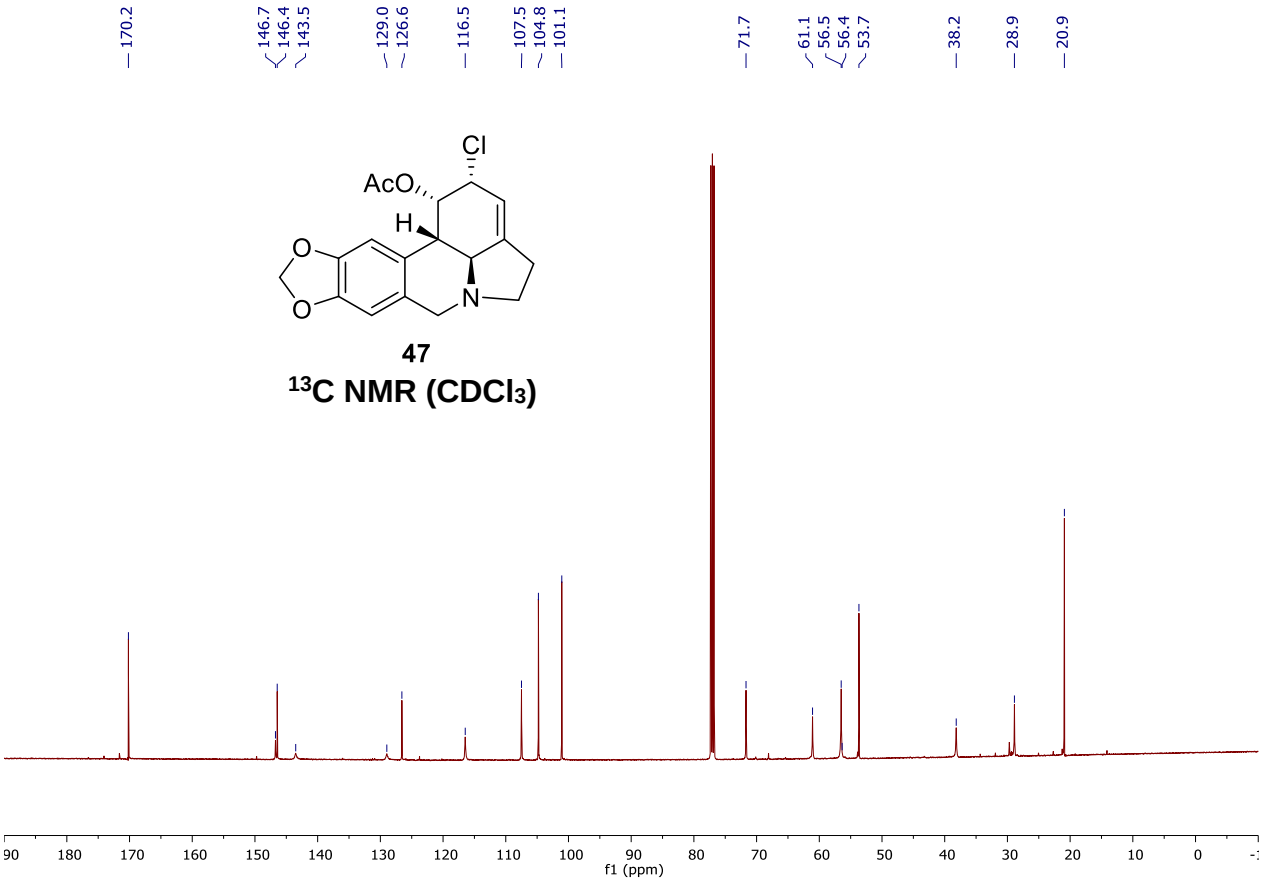

AcO
O
O
N
^{1}H–^{1}H COSY
f2 (ppm)
f1 (ppm)


AcO
O
O
N
^{1}H–^{13}C HMBC
f2 (ppm)
f1 (ppm)



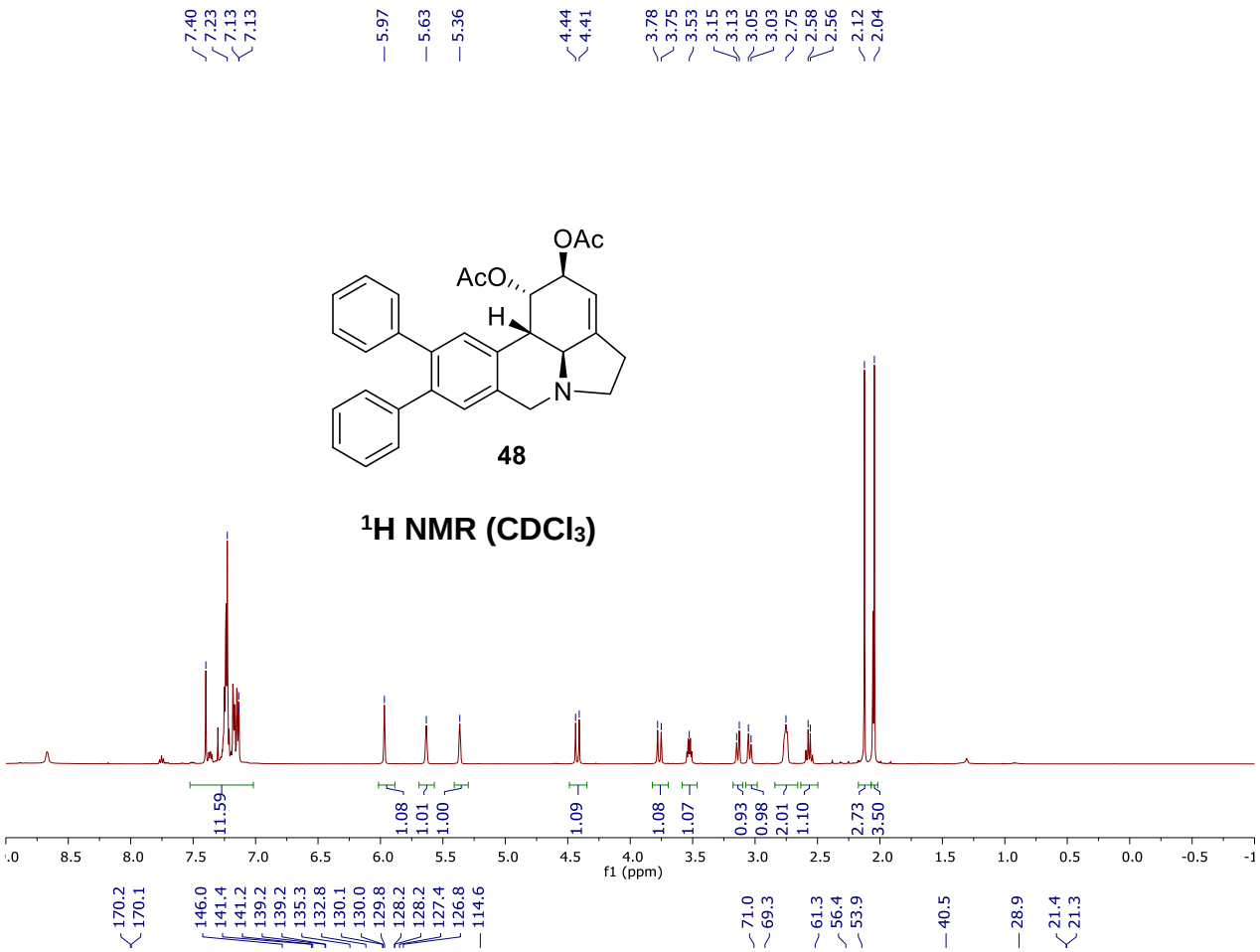
47

^{1}H NMR ($CDCl_3$)

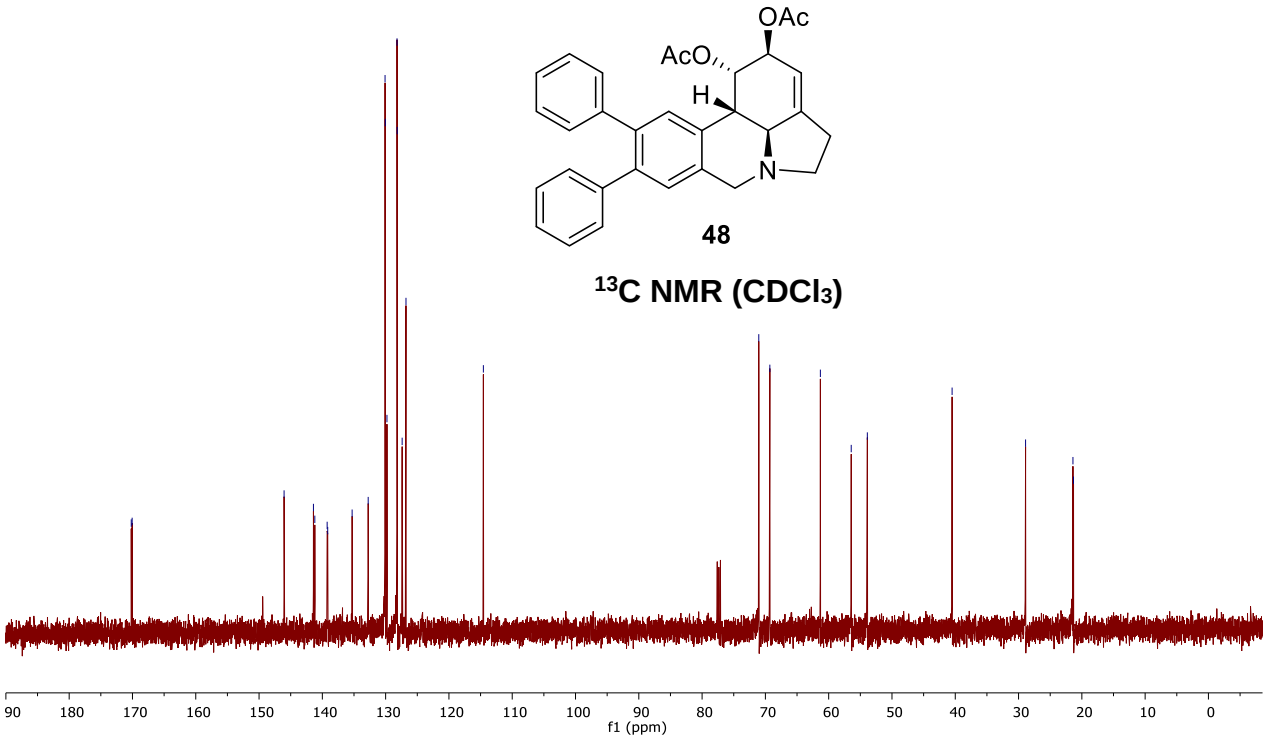


47

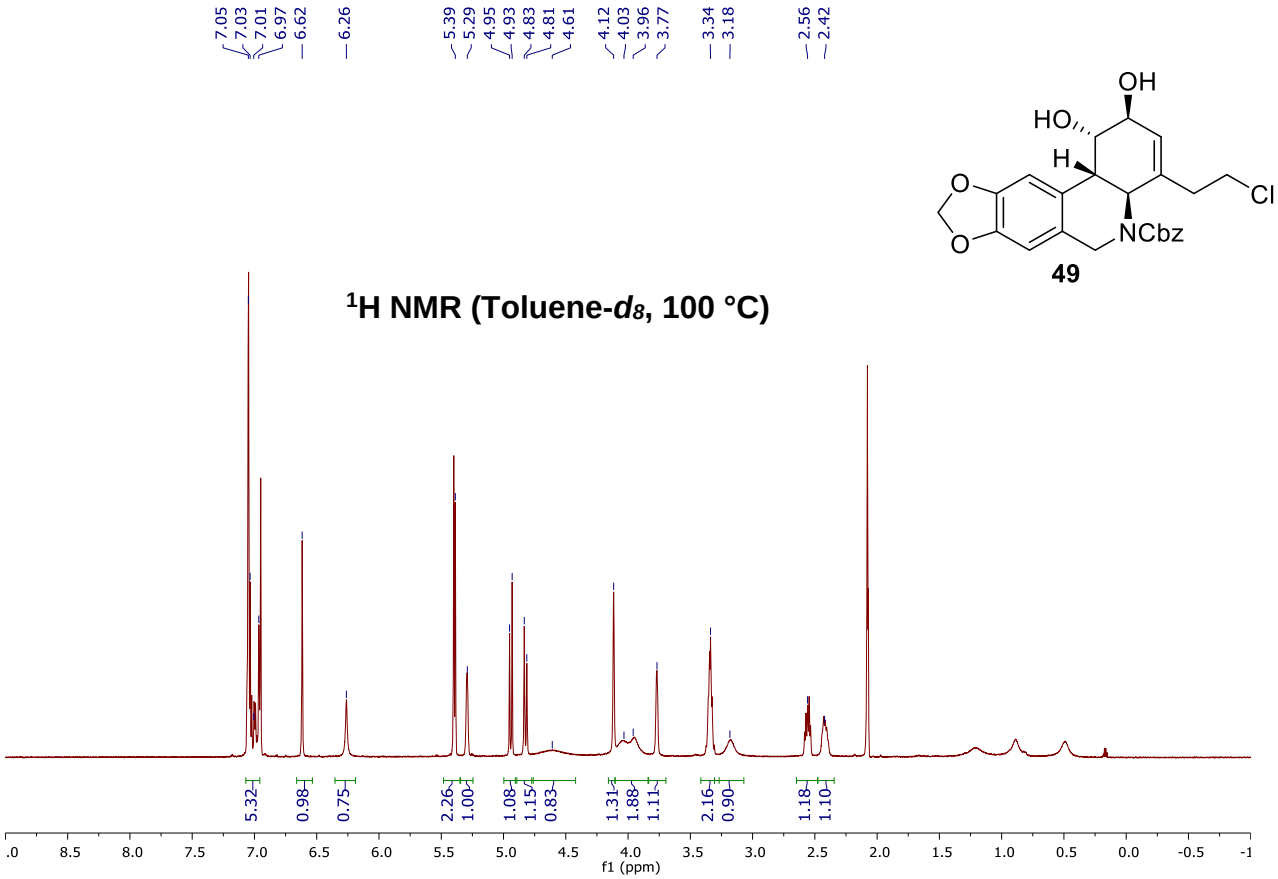
^{13}C NMR ($CDCl_3$)



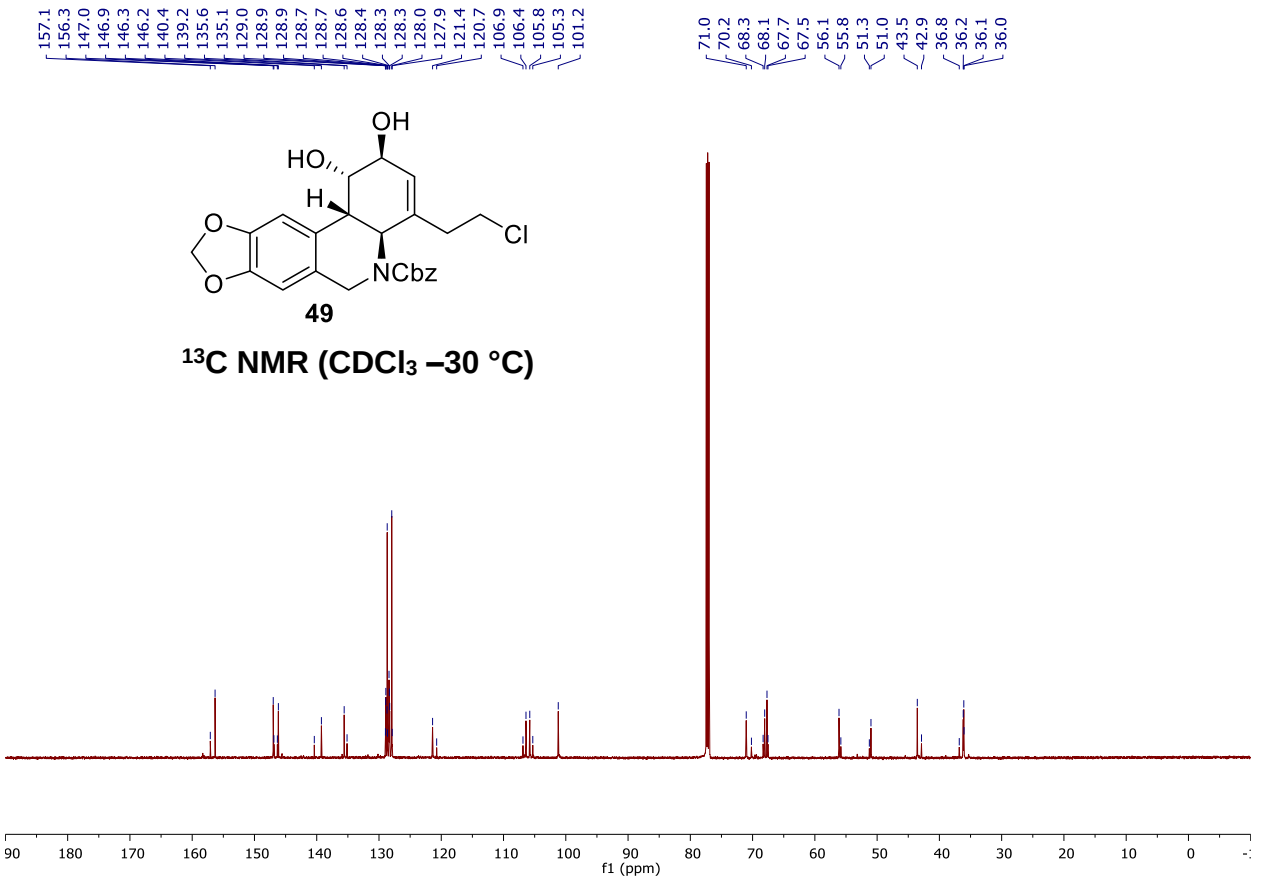
^{1}H NMR ($CDCl_3$)



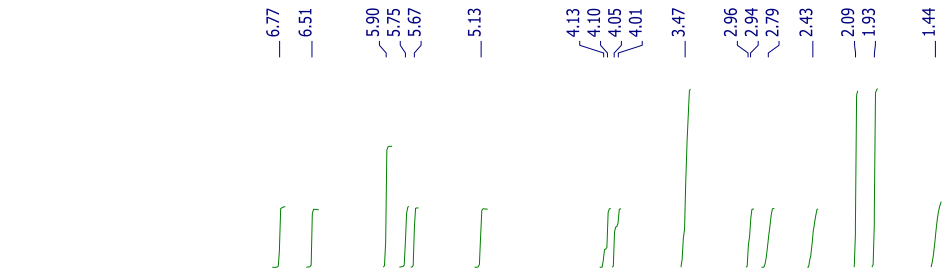
^{13}C NMR ($CDCl_3$)

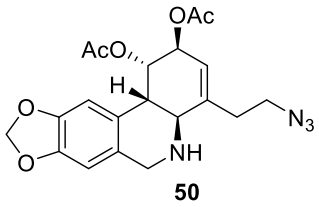


^{1}H NMR (Toluene-d_8, 100 °C)



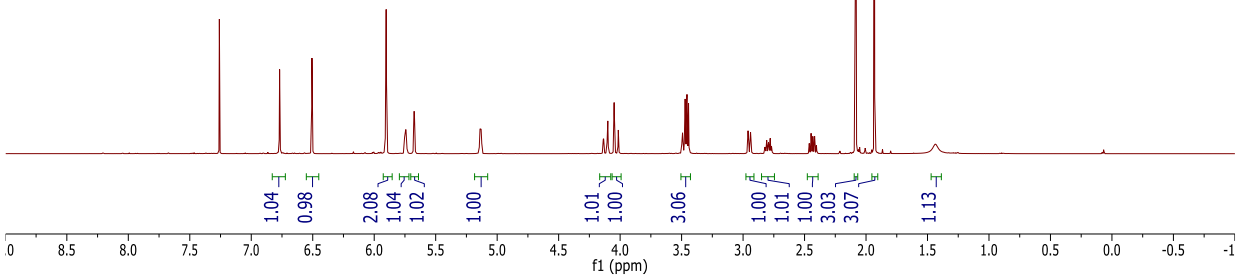
^{13}C NMR ($CDCl_3$ –30 °C)

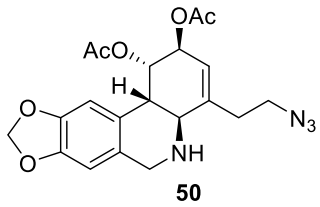




50

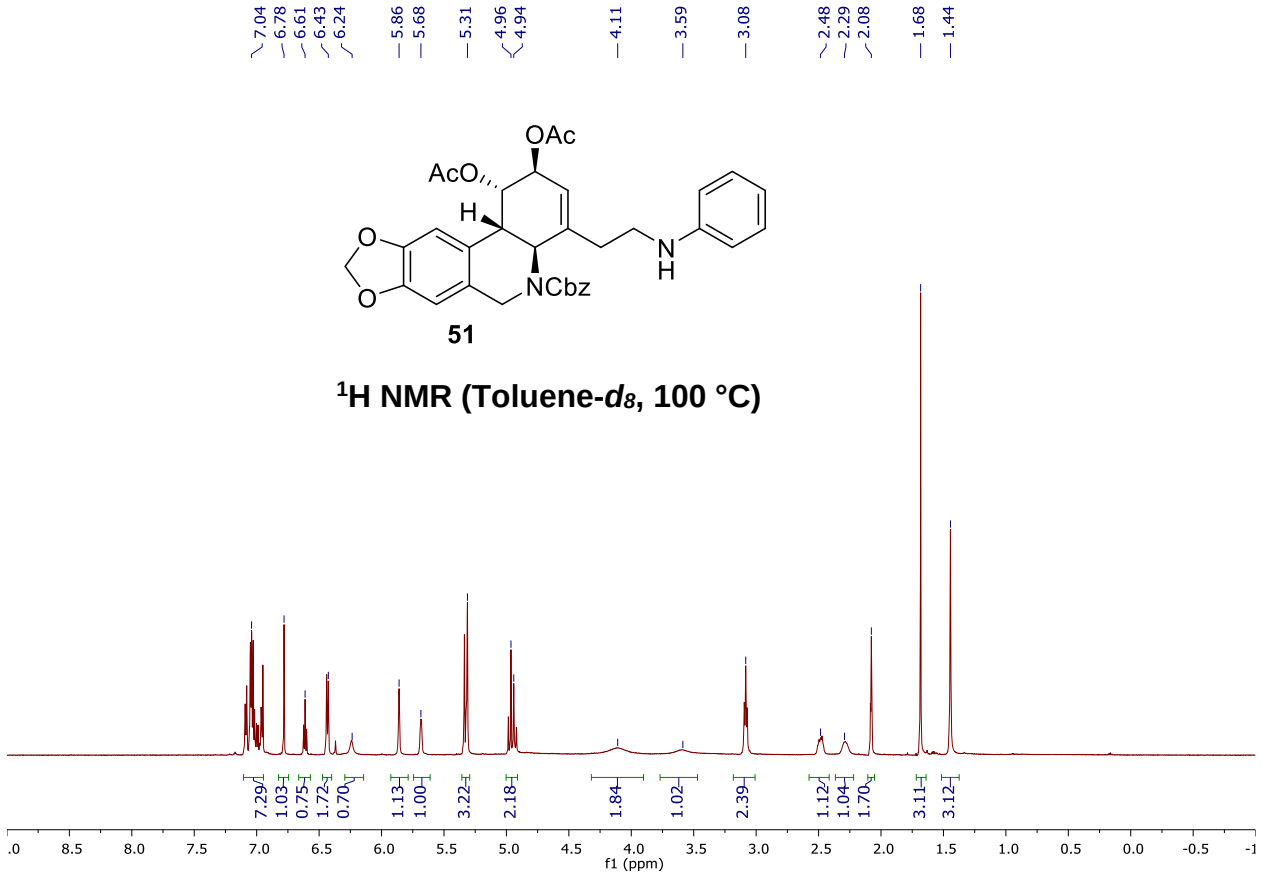
^{1}H NMR ($CDCl_3$)





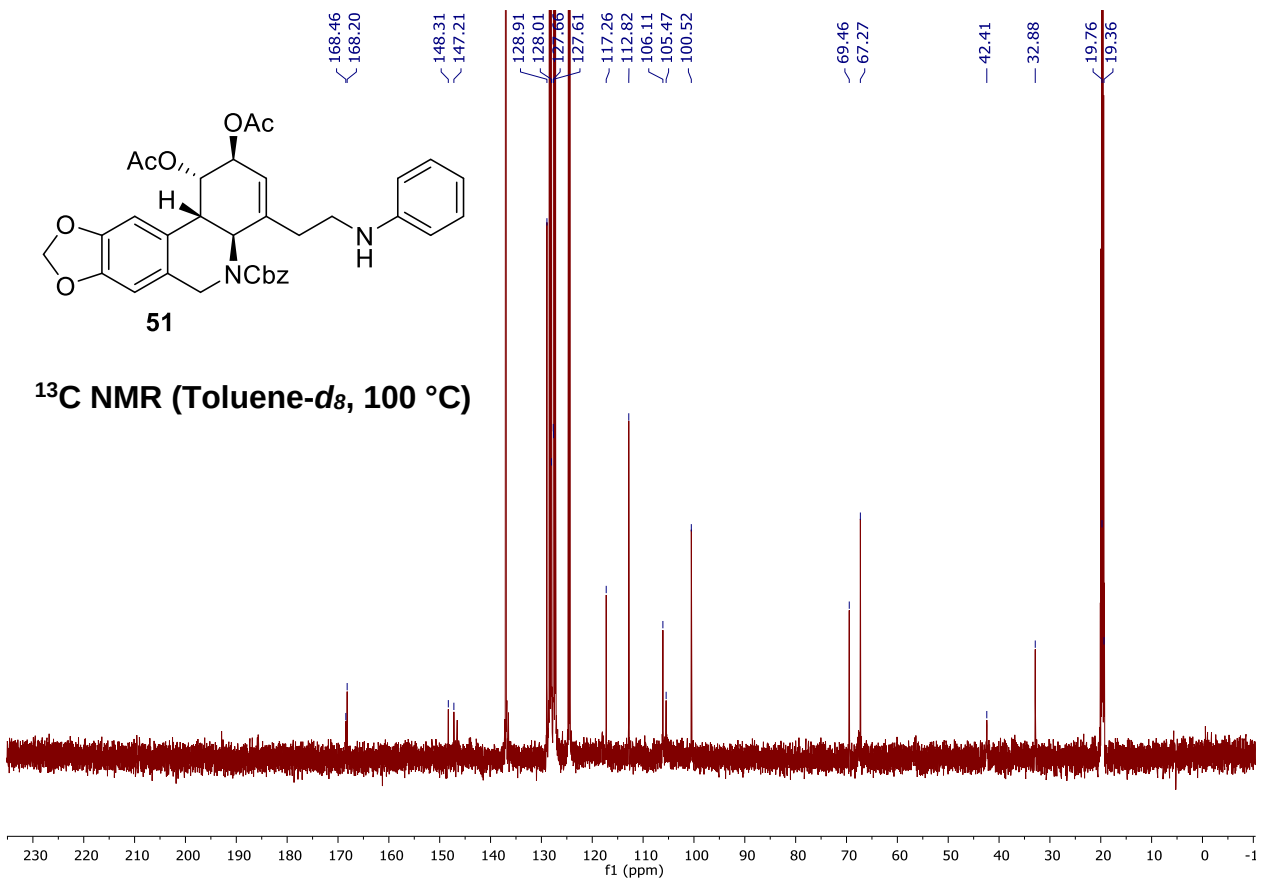
50

^{13}C NMR ($CDCl_3$)



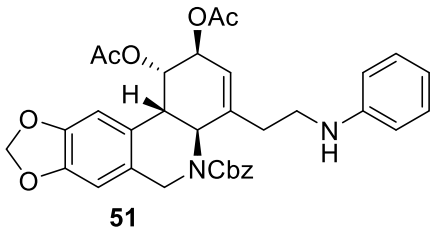
51

^{1}H NMR (Toluene-*d*$_8$, 100 °C)



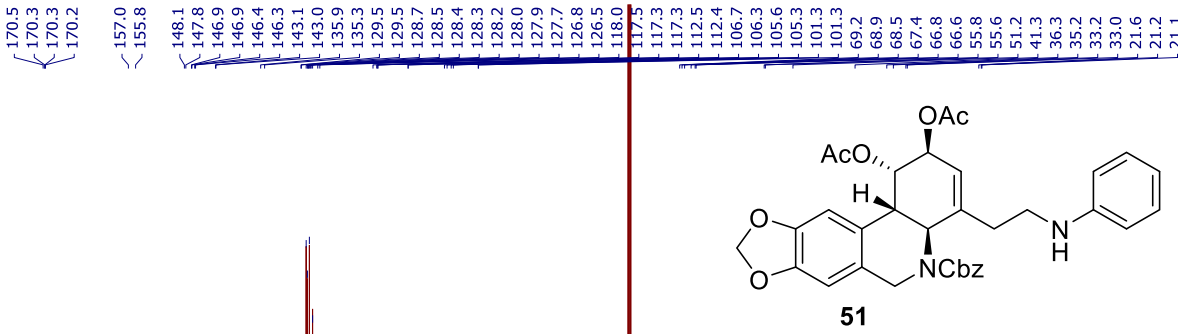
51

^{13}C NMR (Toluene-*d*$_8$, 100 °C)



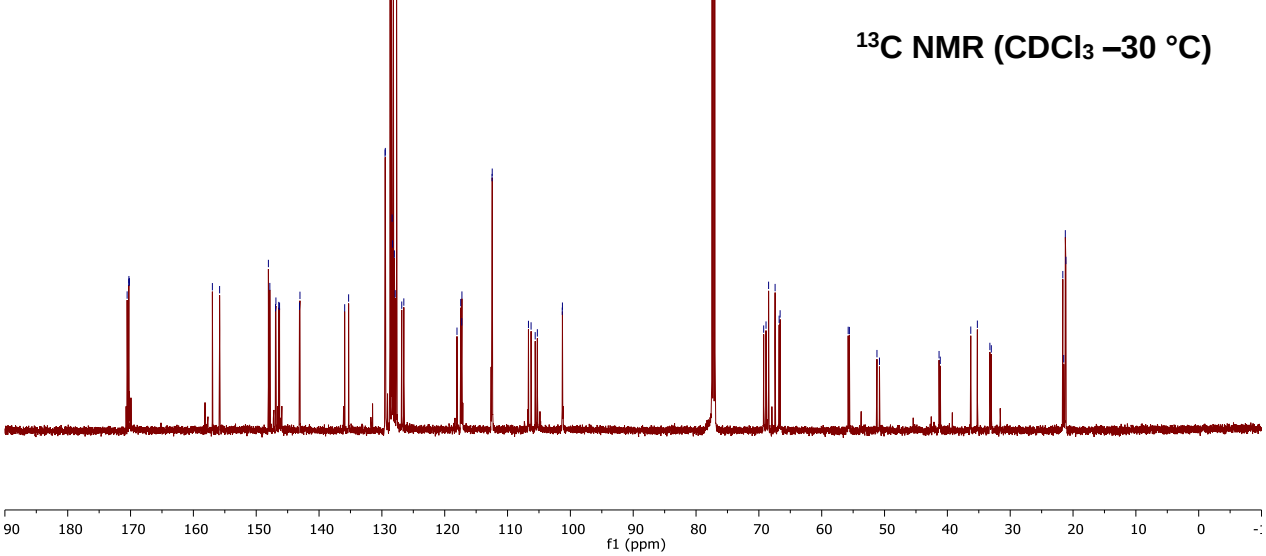
51

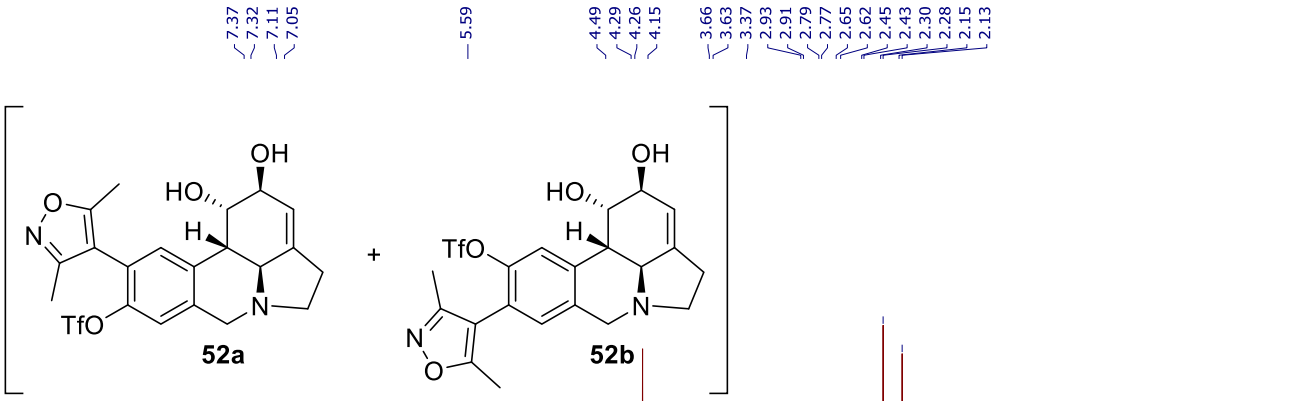
^{1}H NMR ($CDCl_3$ –30 °C)



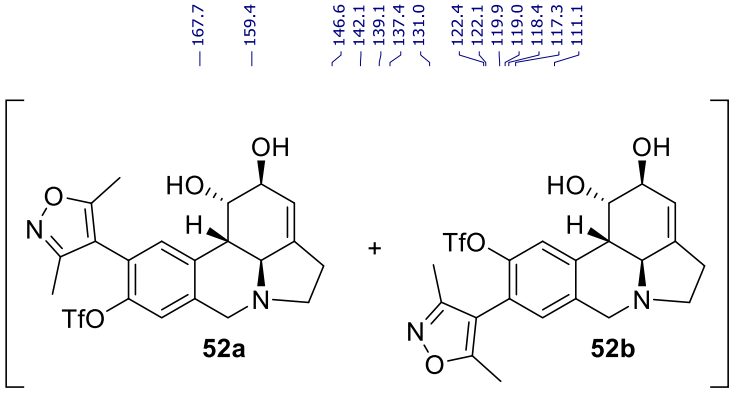
51

^{13}C NMR ($CDCl_3$ –30 °C)





^{1}H NMR (3:1 $CDCl_3$/MeOD)



^{13}C NMR (3:1 $CDCl_3$/MeOD)