# Supporting Information to

# First Total Synthesis of Dioxepine Bastadin 3†

**Santiago Pérez-Rodríguez,[a] Raquel Pereira-Cameselle,[a] and Ángel R. de Lera[a,*]**

[a]*Departamento de Química Orgánica, Facultade de Química, Universidade de Vigo, Lagoas-Marcosende, 36310 Vigo, Spain.*

*Fax: +34 986 811940; Tel: +34 986 812316; E-mail:qolera@uvigo.es*

**Index**

**1. General synthetic methods**.

Solvents were dried according to published methods and distilled before use. HPLC grade solvents were used for HPLC purification. All other reagents were commercial compounds of the highest purity available. All reactions were carried out under argon atmosphere, and those not involving aqueous reagents were carried out in oven-dried glassware. Analytical thin layer chromatography (TLC) was performed on aluminium plates with Merck Kieselgel $60F_{254}$ and visualized by UV irradiation (254 nm) or by staining with a solution of phosphomolybdic acid. Flash column chromatography was carried out using Merck Kieselgel 60 (230-400 mesh) under pressure. Infrared spectra were obtained on a JASCO FTIR 4200 spectrophotometer, from a thin film deposited onto a NaCl glass plate. $^{1}$H-NMR spectra were recorded in $CDCl_3$, $CD_3OD$, DMSO-$d_6$ and $(CD_3)_2CO$ at ambient temperature on a Bruker AMX-400 spectrometer at 400 MHz with residual protic solvent as the internal reference ($CDCl_3$, $\delta_H$ = 7.26 ppm; $(CD_3)_2CO$, $\delta_H$ = 2.05 ppm; $CD_3OD$, $\delta_H$ = 3.31; DMSO-$d_6$, $\delta_H$ = 2.50); chemical shifts (δ) are given in parts per million (ppm), and coupling constants (*J*) are given in Hertz (Hz). The proton spectra are reported as follows: δ (multiplicity, coupling constant *J*, number of protons, assignment). $^{13}$C-NMR spectra were recorded in $CDCl_3$ $CD_3OD$, DMSO-$d_6$ and $(CD_3)_2CO$ at ambient temperature on the same spectrometer at 100 MHz, with the central peak of $CDCl_3$ ($\delta_C$ = 77.0 ppm), $CD_3OD$ ($\delta_C$ = 49.0 ppm), DMSO-$d_6$ ($\delta_C$ = 39.4 ppm) or $(CD_3)_2CO$ ($\delta_C$ = 30.8 ppm) as the internal reference. The DEPT135 pulse sequence was used to aid in the assignment of signals in the $^{13}$C NMR spectra. Melting points were determined on a Stuart SMP10 apparatus. Elemental analyses were determined on a Carlo Erba EA 1108 analyzer. Mass Spectra were obtained on an instrument operating at 70 eV by electron ionisation. Data acquisition and data processing were performed using the XMASS software, version 6.1.2 (Bruker Daltonics). FAB experiments were performed on a VG AutoSpec instrument, using 3-nitrobenzylalcohol or glycerol as matrices. ESI experiments were performed on an microTOF (Focus) mass spectrometer (Bruker Daltonics). Ions were generated using an Apollo ll (ESI) source. Ionization was achieved by electrospray, using a voltage of 4500 V applied to the capillary. Samples were prepared by adding a spray solution of 97:3 (v/v) acetone/water or 70:30 (v/v) methanol/water with a 0.1% of formic acid to a solution of the sample in $CH_2Cl_2$ at a v/v ratio of 1 to 5% to give the best signal-to-noise ratio. Data for adquisition was performed using the microTOFControl software version 2.1, and data processing was performed using the data Analysis software, version 3.4, both from Bruker Daltonics. Irradiation with microwaves was performed using a CEM DISCOVER apparatus.

**2. Additional experiments described in the text.**

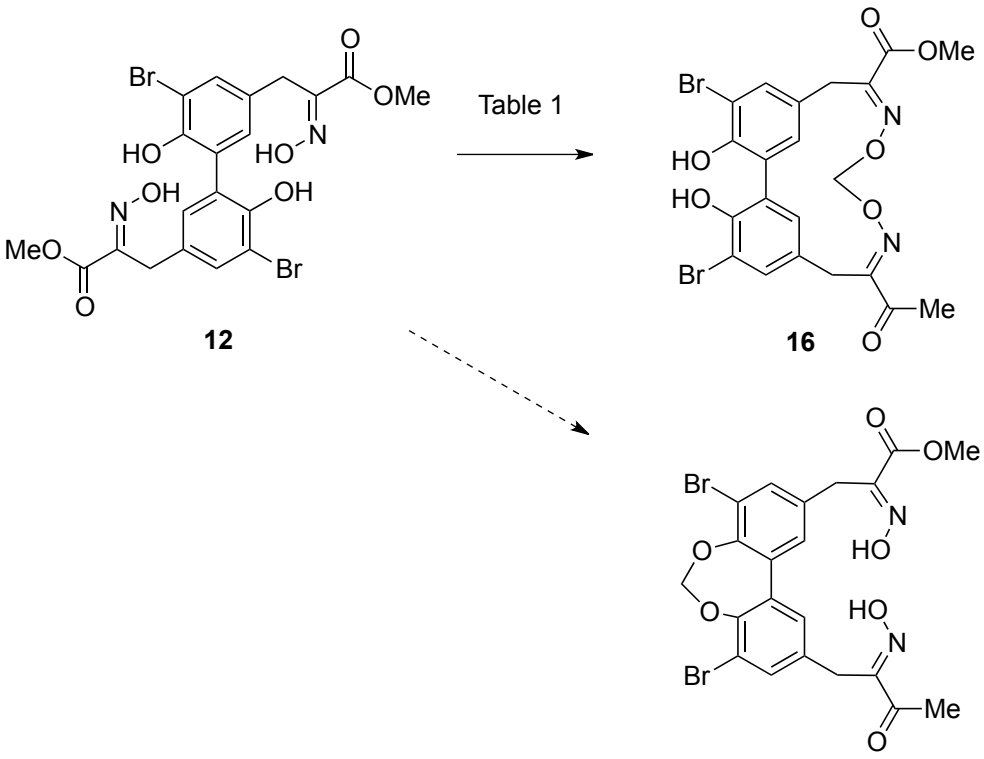



**Table 1.** Attempted formation of the dioxepine moiety in product **12**.

| Entry | Reaction conditions | T (ºC) | t (h) | yield of 16 (%) |
|---|---|---|---|---|
| **1** | $CH_2I_2$, $K_2CO_3$, DMF | 70 | 12 | 51 |
| **2** | $CH_2I_2$, $K_2CO_3$, DMF, Microwave irradiation | 90 | 0.33 | [a] |
| **3** | $CH_2I_2$, $Cs_2CO_3$, DMF | 25 | 2 | 78 |
| **4** | $CH_2I_2$, $Cs_2CO_3$, acetone | 25 | 18 | [b] |
| **5** | $CH_2I_2$, $Cs_2CO_3$, DMF | 0 | 2 | [b] |
| **6** | $ICH_2Br$, $Cs_2CO_3$, DMF | 25 | 2 | 28 |

[a] Degradation. [b] Starting material was recovered.

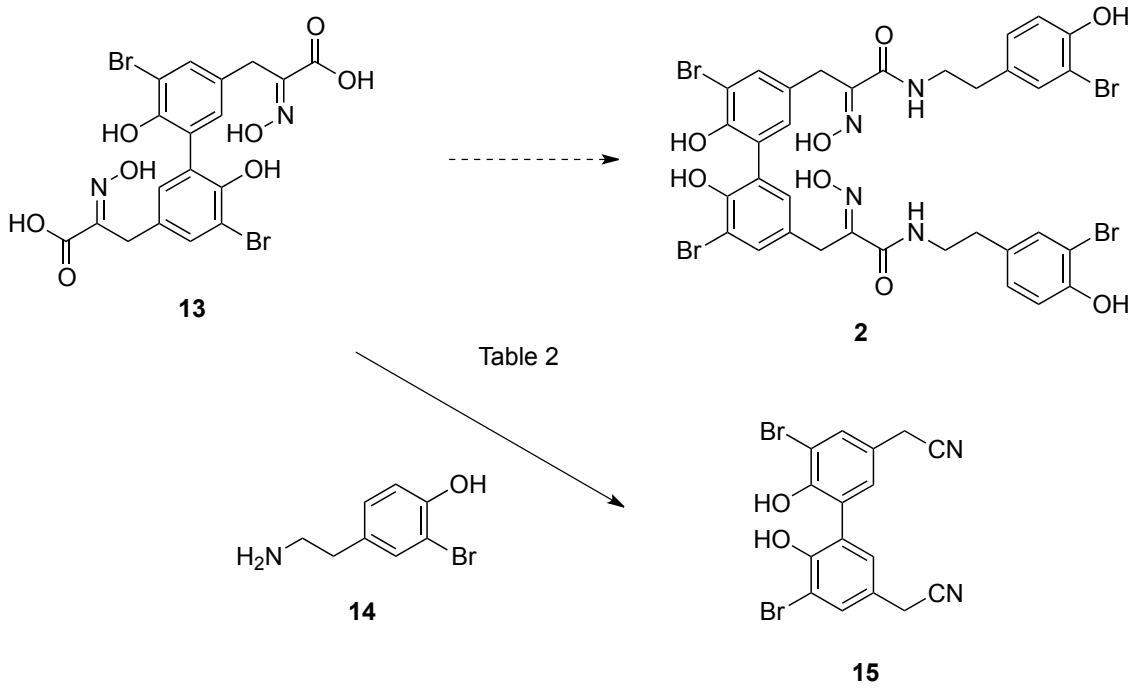



**Table 2.** Attempts at protecting group-free amidation of **13** with 3-bromotyramine **14**.

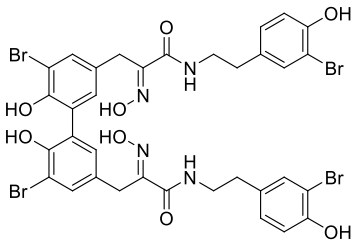
| Entry | Reaction conditions | T (ºC) | t (h) | Product |
|---|---|---|---|---|
| **1** | HOBt, DCC, DMF, $Et_3N$, **14** | 25 | 18 | Nitrile **15** |
| **2** | HOBt, EDCI, $CH_2Cl_2$, $^iPr_2NEt$, **14** | 0 | 18 | Nitrile **15** |
| **3** | 1) HOBt, DCC, DMF<br>2) **14**, $Et_3N$ | 25 | 18 | Nitrile **15** |
| **4** | 1) NHPI, DCC, dioxane<br>2) **14**, $Et_3N$ | 25 | 18 | [b] |
| **5** | HOBt, DIC, DMF, **14**, $Et_3N$ | 60, MW | 15 min | [c] |
| **6** | 1) $CH_2Cl_2$, DMF, $(COCl)_2$ (20 equiv)<br>2) **14**, $Et_3N$ | 25 | 3 | Nitrile **15** |
| **7** | HATU, $Et_3N$, **14** | 25 | 18 | [b] |
| **8** | COMU, TMP, **14** | 25 | 18 | [b] |
| **9** | PyBOP, DMF, DMAP, **14** | 0 a 25 | 16 | [b] |
| **10** | T3P, *N*-Methylmorpholine, DMF, **14** | 25 | 18 | [b] |
| **11** | 2-bromophenylboronic acid (0.01 equiv), 4 Å MS, $CH_2Cl_2$/DMF (1:1), **14** | 25 | 48 | [b] |

[a] Except where indicated otherwise, 2.0-3.0 equivalents of the activating agents were used. [b] Degradation.

[c] Complex mixture.

## 3. Comparison of NMR data of synthetic with the natural Bastadin 3 (2) and Dioxepine Bastadin ( 3)

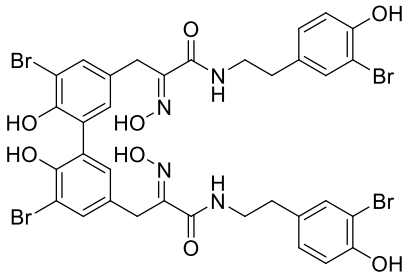
**Bastadin-3 (2)**




**2**

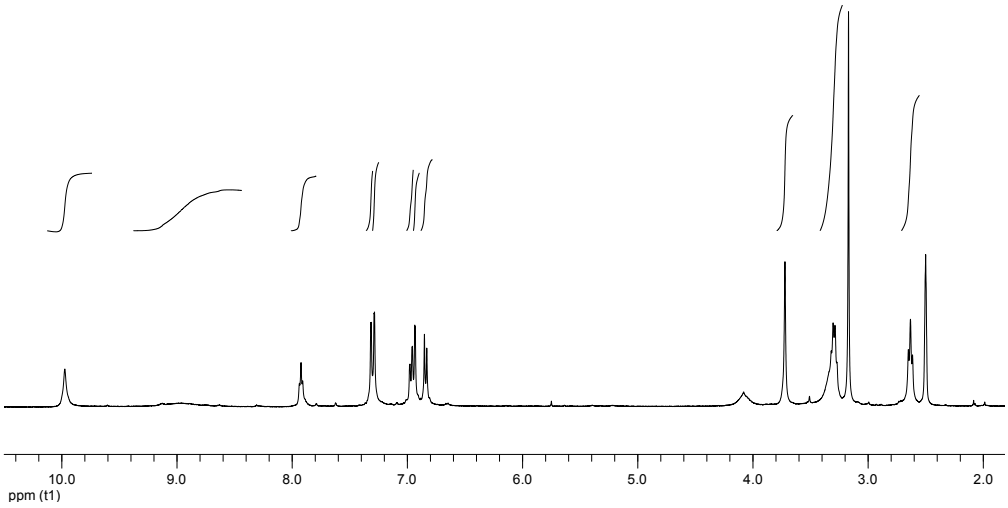
**Table 3**. Comparison of $^{1}H$ and $^{13}C$ NMR data for natural and synthetic bastadin-3

| | *Natural bastadin-3* | | *Synthetic bastadin-3* | |
|---|---|---|---|---|
| **Position** | **$^{13}C$ RMN [DMSO-d6, 67.89 MHz]** | **$^{1}H$ RMN [DMSO-d6, 100 MHz]** | **$^{13}C$ RMN [DMSO-d6, 100 MHz]** | **$^{1}H$ RMN [DMSO-d6, 400 MHz]** |
| **1, 25** | 27.7 (t) | 3.72 (s) | 27.7 (t) | 3.72 (s) |
| **2, 24** | 151.7 (s) | ----- | 151.7 (s) | ----- |
| **3, 23** | 163.0 (s) | ----- | 162.9 (s) | ----- |
| **4, 22** | ---- | 8.00 (t, 7.0) | ----- | 7.92 (t, 5.7) |
| **5, 21** | 40.4 (t) | 3.29 (q, 7.0) | 40.3 (t) | 3.30 (q, 6.4) |
| **6, 20** | 33.6 (t) | 2.62 (t, 7.0) | 33.5 (t) | 2.63 (t, 7.2) |
| **7, 18** | 131.4 (s) | ----- | 131.4 (s) | ----- |
| **8, 17** | 132.6 (d) | 7.29 (d, 1.9) | 132.5 (d) | 7.29 (d, 1.4) |
| **9, 16** | 109.1 (s) | ----- | 108.9 (s) | ----- |
| **10, 15** | 152.3 (s) | ----- | 152.2 (s) | ----- |
| **11, 14** | 116.2 (d) | 6.85 (d, 8.2) | 116.1 (d) | 6.84 (d, 8.2) |
| **12, 19** | 128.8 (d) | 6.98 (dd, 1.9, 8.2) | 128.7 (d) | 6.97 (d, 8.1) |
| **26, 37** | 129.1 (s) | ----- | 129.3 (s) | ----- |
| **27, 36** | 132.2 (d) | 7.32 (d, 1.9) | 132.0 (d) | 7.32 (d, 1.6) |
| **28, 35** | 111.3 (s) | ----- | 111.3 (s) | ----- |
| **29, 34** | 149.5 (s) | ----- | 149.7 (s) | ----- |
| **30, 33** | 127.6 (s) | ----- | 127.6 (s) | ----- |
| **31, 38** | 131.1 (d) | 6.93 (d, 1.9) | 131.0 (d) | 6.93 (d, 1.5) |
| **2/24-NOH** | ----- | 11.84 (s) | ----- | ------ |
| **10/15-OH** | ----- | 10.02 (s) | ----- | 9.97 (s, 1H) |
| **29/34-OH** | ----- | 8.94 (s) | ----- | 8.94 (s- br, 1H) |

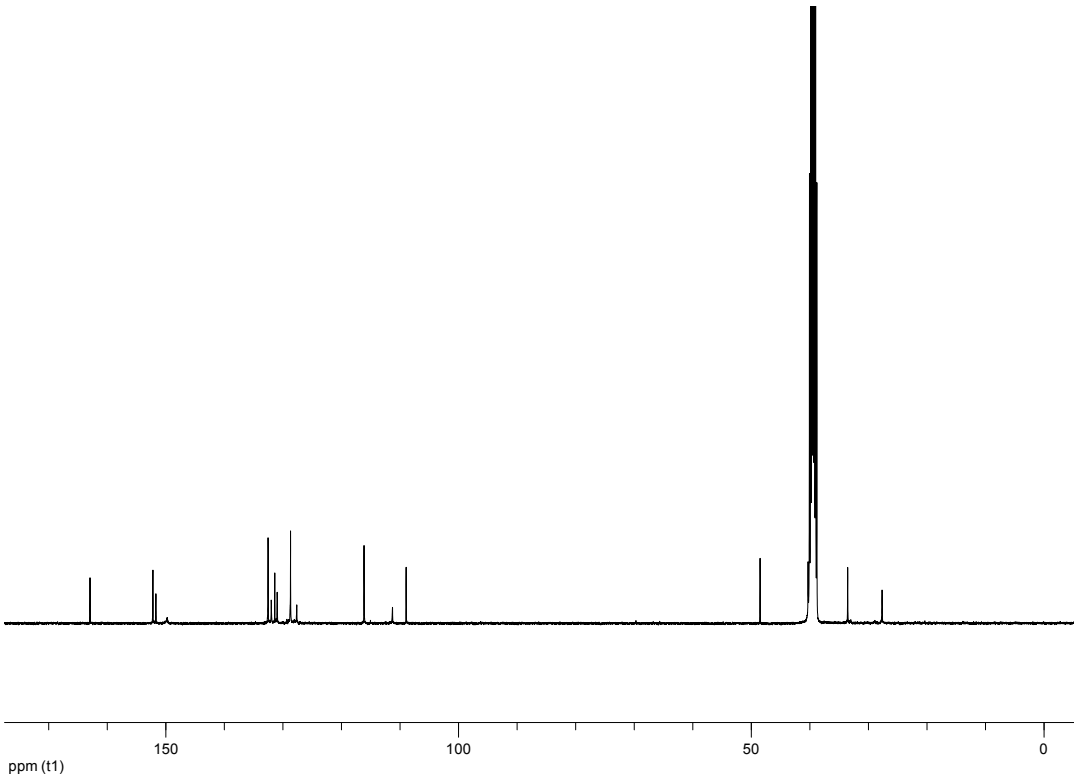



**2**

**$^{1}$H-NMR** (400.13 MHz, $(CD_3)_2SO$)




**$^{13}$C-NMR** (100.61 MHz, $(CD_3)_2SO$)



## Dioxepine Bastadin 3 (3)

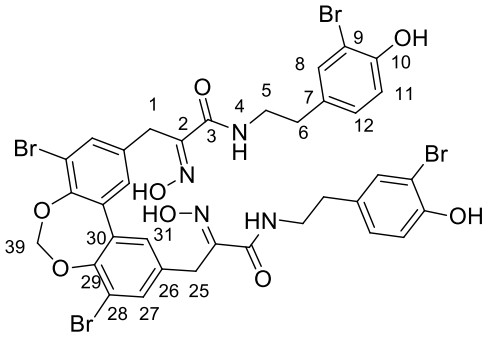
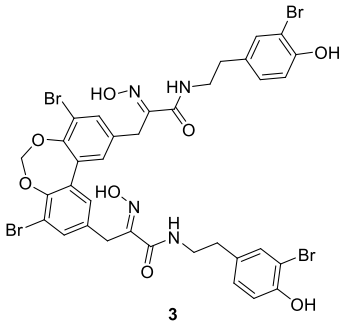


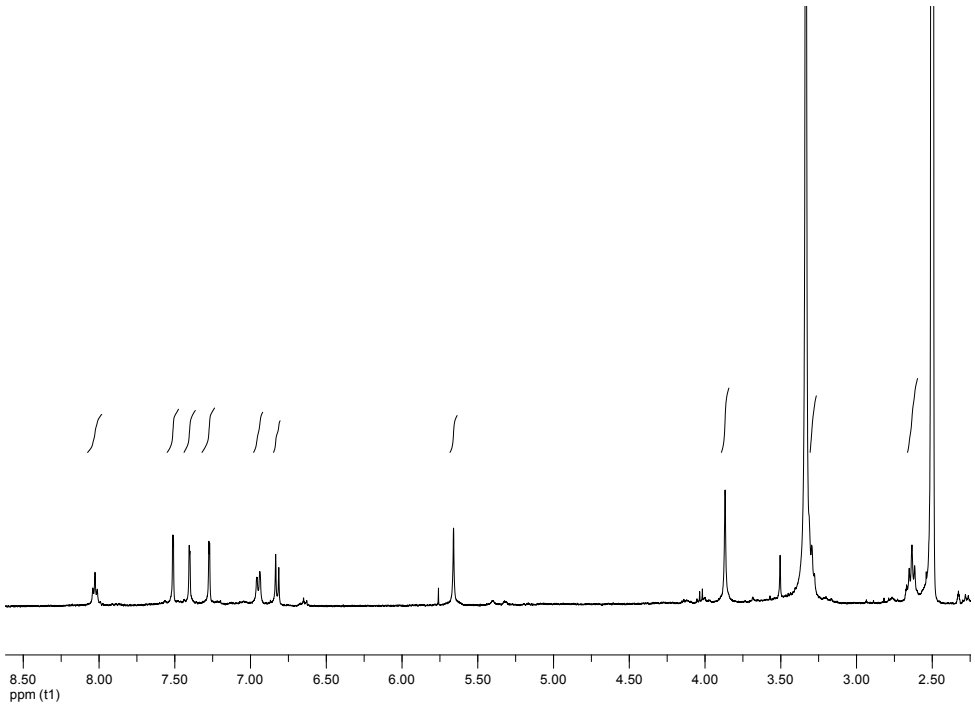

**Table 4.** Comparison of $^{1}H$ and $^{13}C$ NMR data for natural and synthetic Dioxepine bastadin-3

| | *natural dioxepine bastadin 3* | | *synthetic dioxepine bastadin 3* | |
|---|---|---|---|---|
| **Position** | **$^{13}C$ NMR [DMSO-d6, 100 MHz]** | **$^{1}H$ NMR [DMSO-d6, 400 MHz]** | **$^{13}C$ NMR [DMSO-d6, 100 MHz]** | **$^{1}H$ NMR [DMSO-d6, 400 MHz]** |
| **1, 25** | 28.3 | 3.83 (s) | 28.4 | 3.87 (s) |
| **2, 24** | 151.3 | | 151.3 | |
| **3, 23** | 163.0 | | 163.0 | |
| **4, 22** | | 8.02 (t, 6.6) | | 8.03 (t, 5.8) |
| **5, 21** | 40.3 | 3.30 (m) | 40.3 | 3.30 (s), |
| **6, 20** | 33.5 | 2.64 (t, 6.6) | 33.5 | 2.63 (t, 7.2) |
| **7, 18** | 131.5 | | 131.4 | |
| **8, 17** | 132.6 | 7.28 (d, 1.9) | 132.6 | 7.27 (d,1.9 ) |
| **9, 16** | 109.0 | | 109.0 | |
| **10, 15** | 152.3 | | 152.3 | |
| **11, 14** | 116.2 | 6.83 (d, 8.7) | 116.2 | 6.82 (d, 8.3) |
| **12, 19** | 128.8 | 6.96 (dd, 1.9, 8.7) | 128.8 | 6.95 (d, 7.3) |
| **26, 37** | 135.8 | | 135.8 | |
| **27, 36** | 132.8 | 7.51 (d, 1.9) | 132.8 | 7.51 (d, 1.8) |
| **28, 35** | 115.4 | | 115.4 | |
| **29, 34** | 147.7 | | 147.7 | |
| **30, 33** | 132.6 | | 132.6 | |
| **31, 38** | 128.5 | 7.40 (d, 1.9) | 128.5 | 7.40 (d, 1.7), |
| **39** | 101.3 | 5.66 (s) | 101.3 | 5.66 (s), |
| **2/24-NOH** | | 11.97 (brs) | | 11.99 (s) |
| **9/15-OH** | | 9.99 (brs) | | 10.03 (s) |

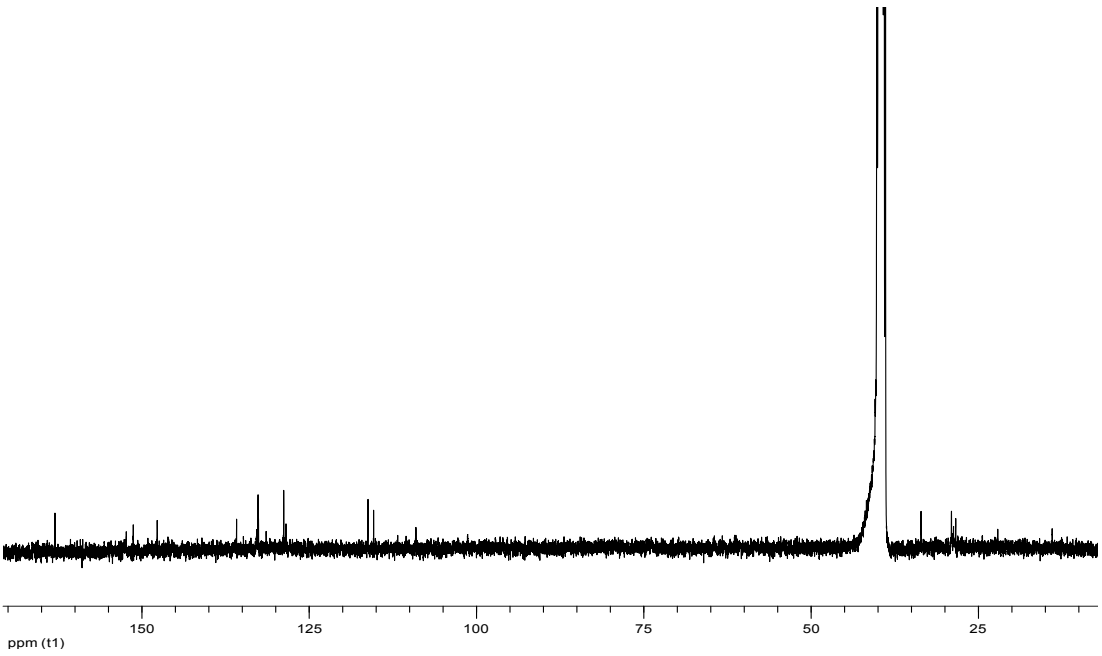



3

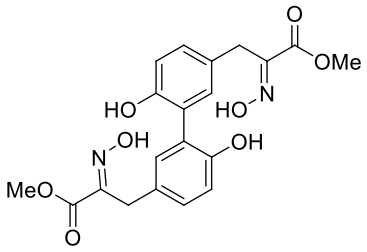
**[1]H-NMR** (400.13 MHz, (DMSO-d6)




**[13]C-NMR** (100.61 MHz, (DMSO-d6)

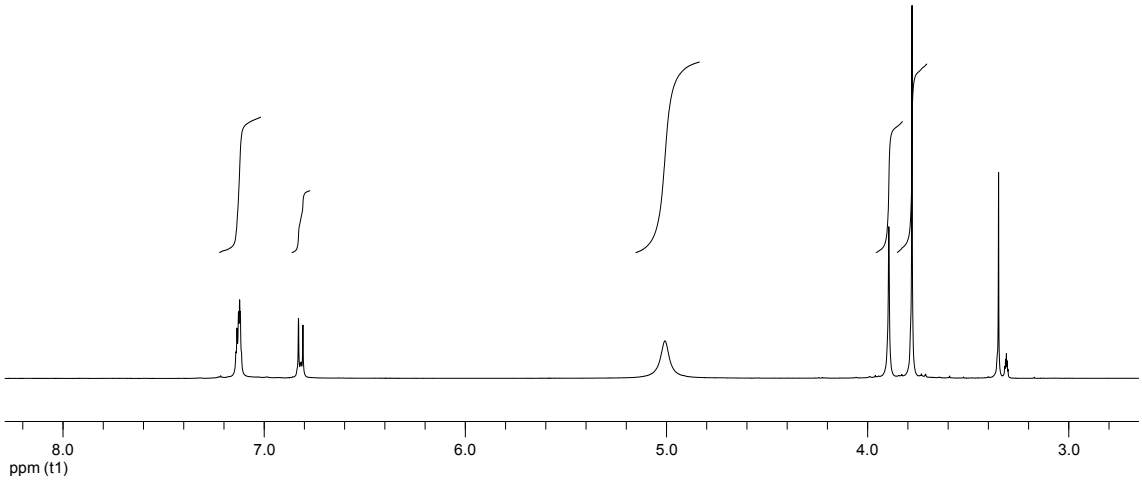


**4. $^{1}$H NMR and $^{13}$C NMR Spectral Data**

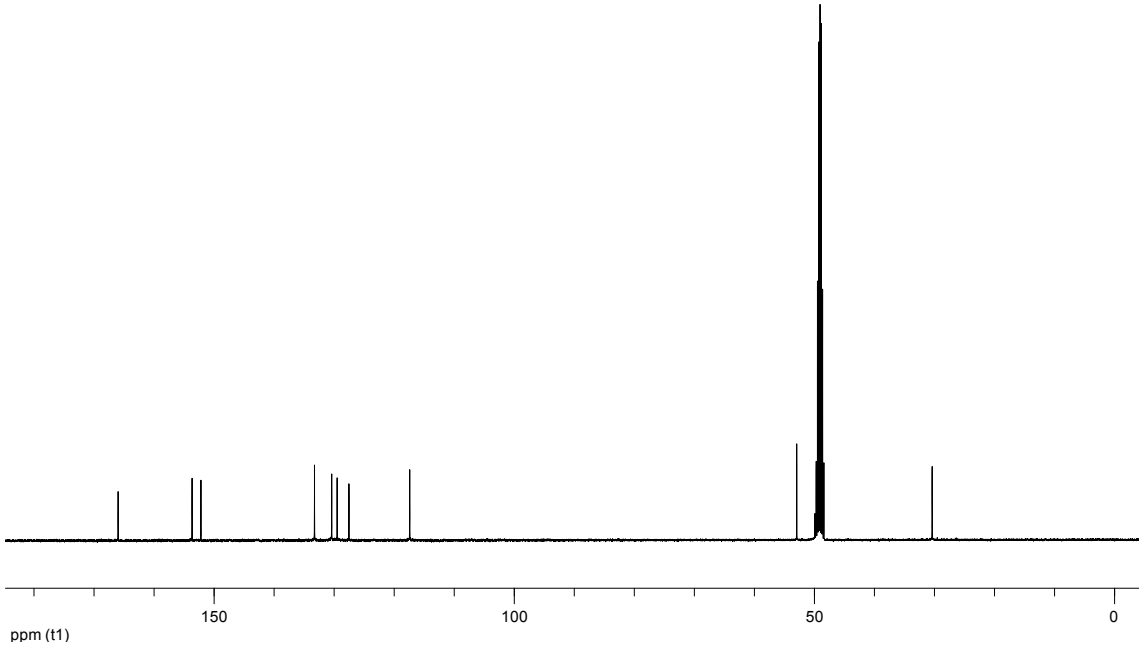



**11**

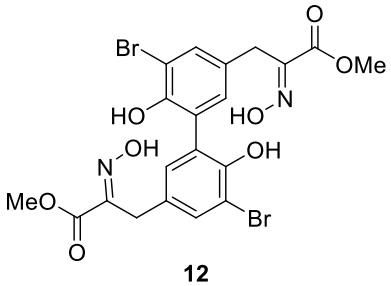
**$^{1}$H-NMR** (400.13 MHz, $CD_3OD$)



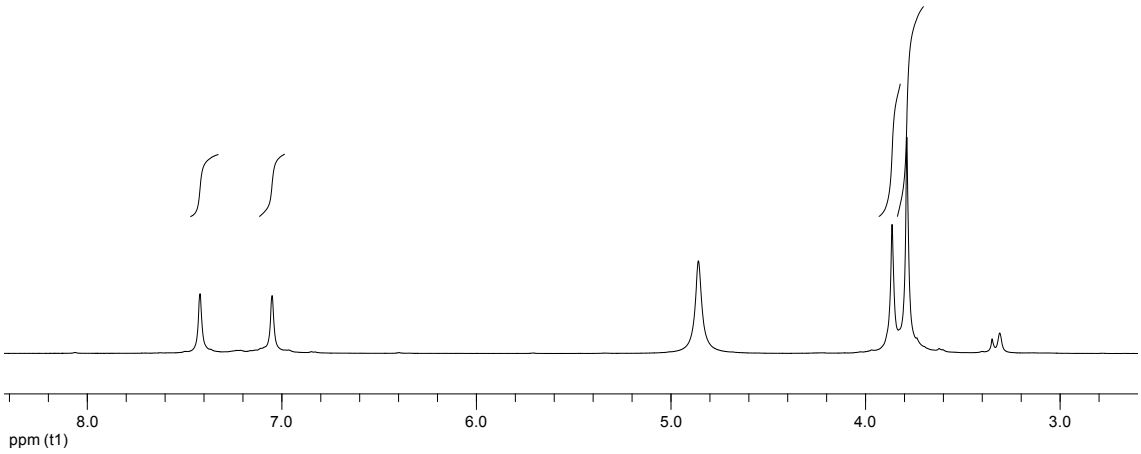

**$^{13}$C-NMR** (100.61 MHz, $CD_3OD$)



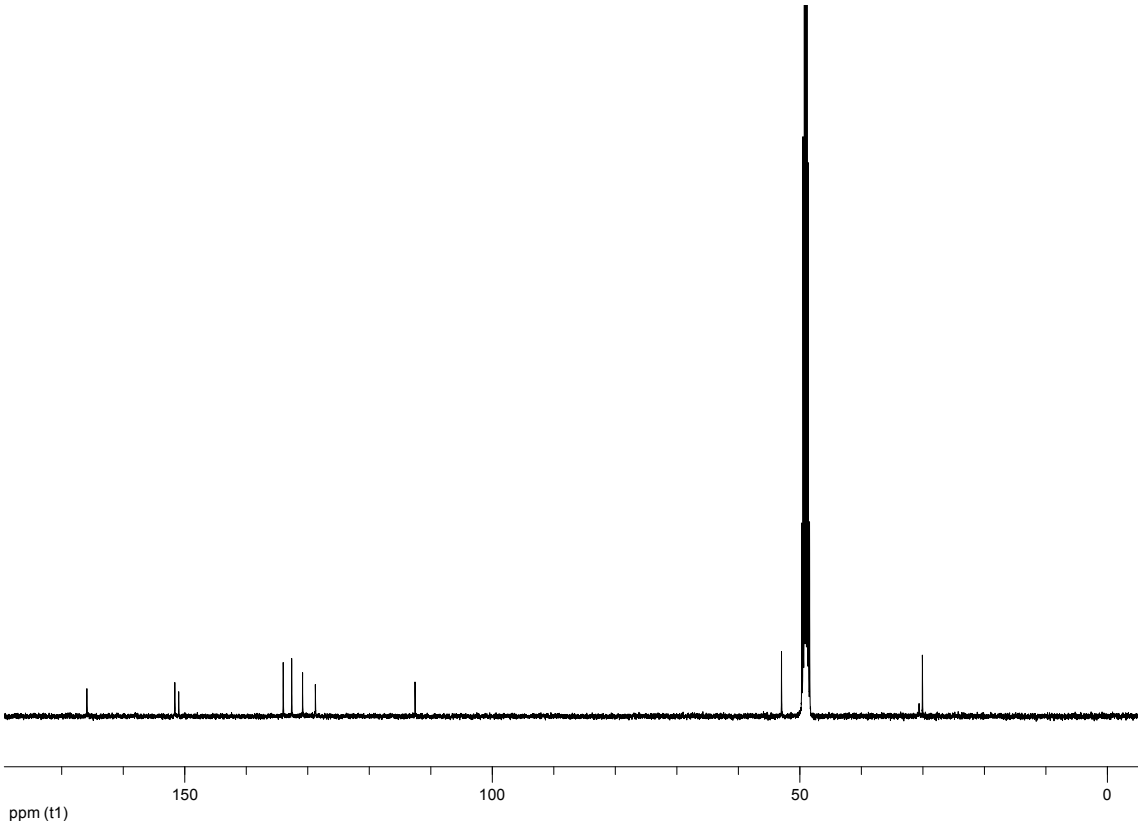
**$^{1}$H-NMR** (400.13 MHz, $CD_3OD$)



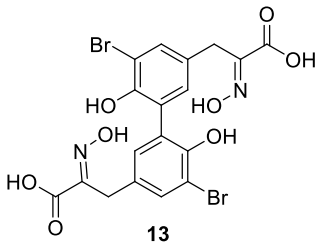

**12**



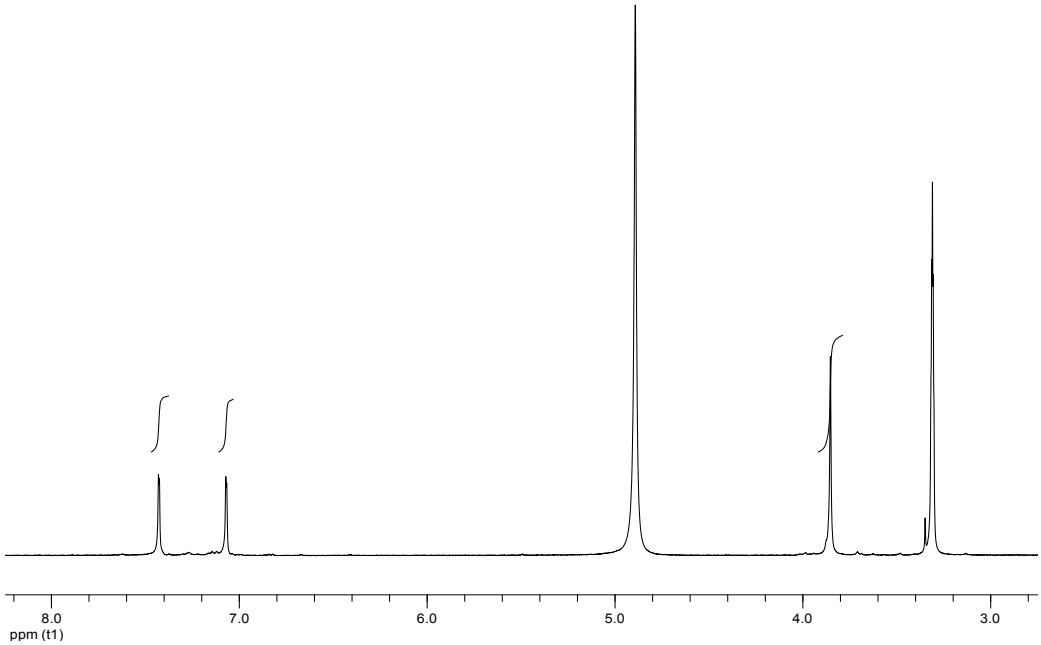

**$^{13}$C-NMR** (100.61 MHz, $CD_3OD$)



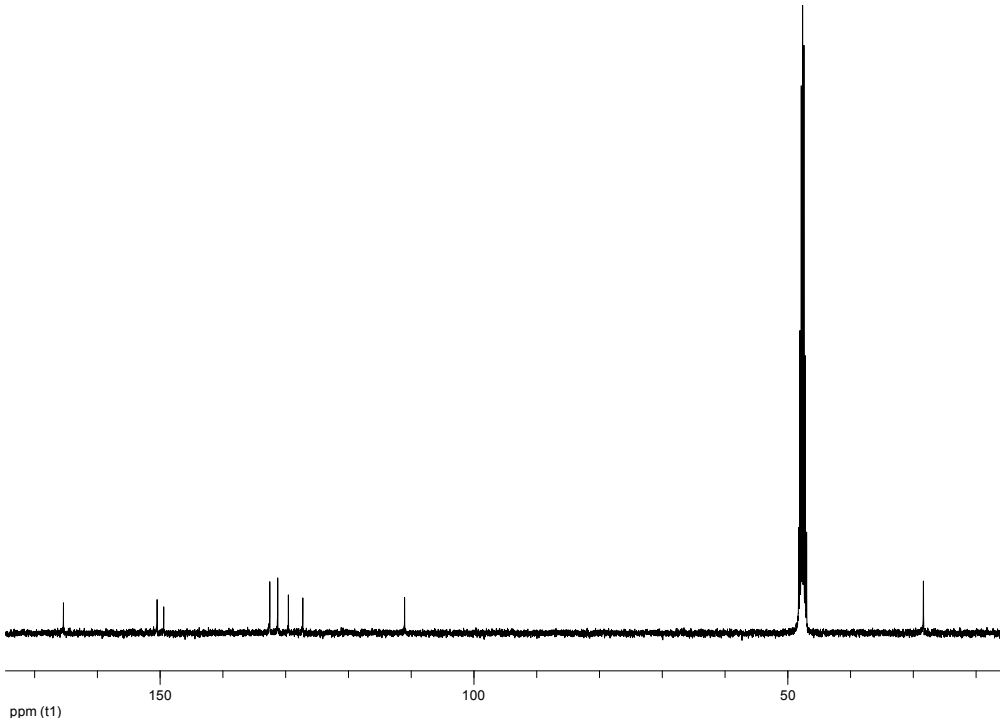
**$^{1}$H-NMR** (400.13 MHz, $CD_3OD$)

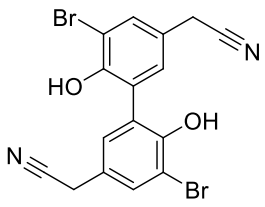



**13**



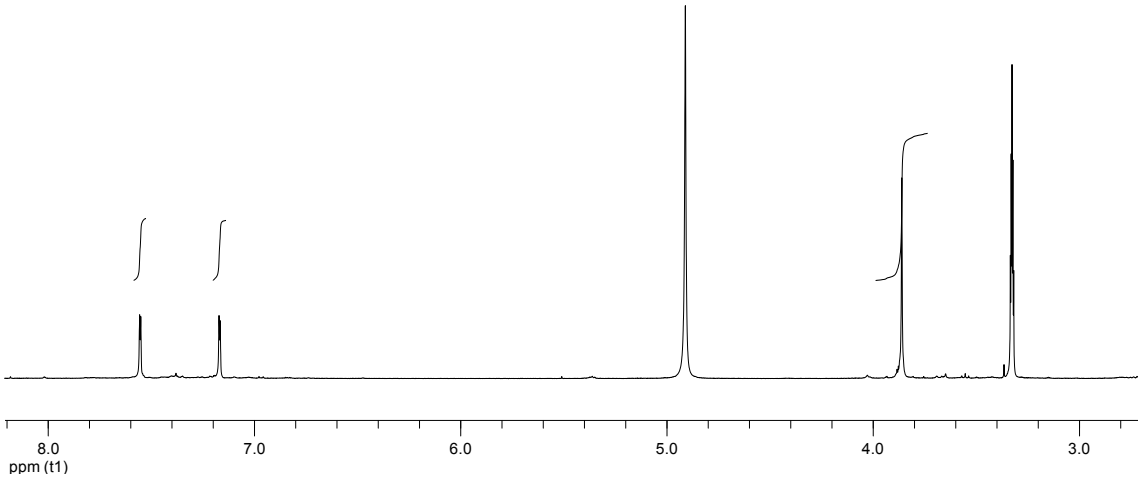

**$^{13}$C-NMR** (100.61 MHz, $CD_3OD$)



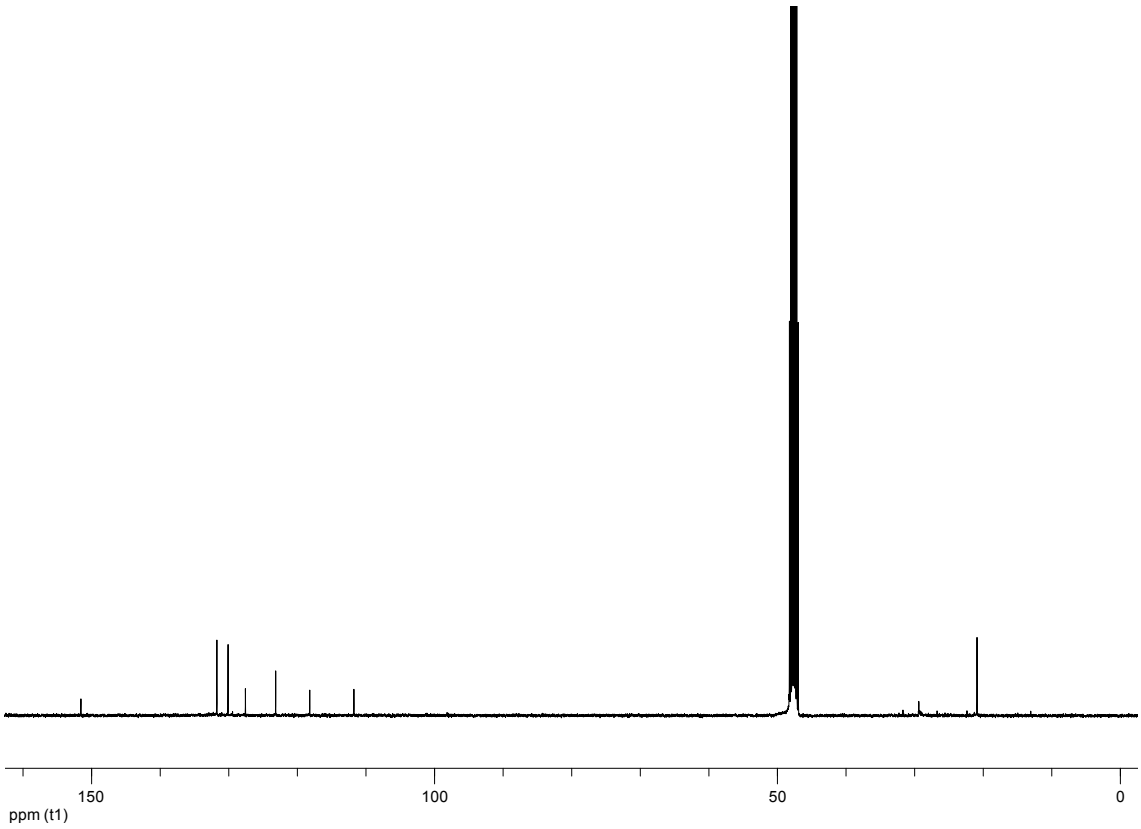


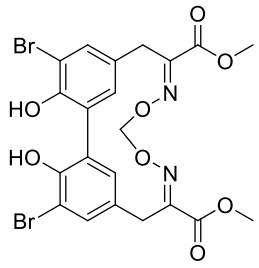

**15**

**$^{1}$H-NMR** (400.13 MHz, $CD_3OD$)



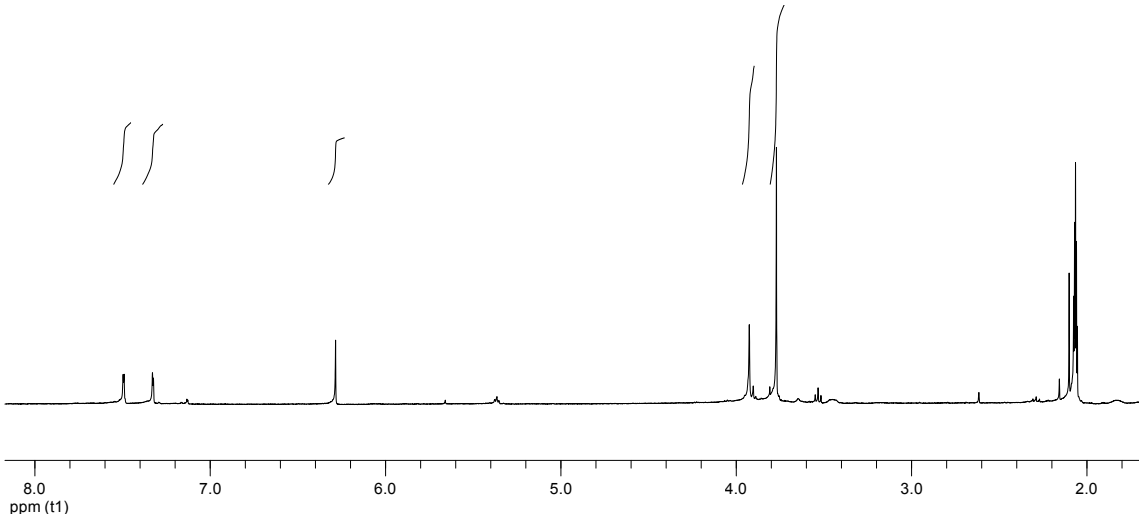

**$^{13}$C-NMR** (100.61 MHz, $CD_3OD$)



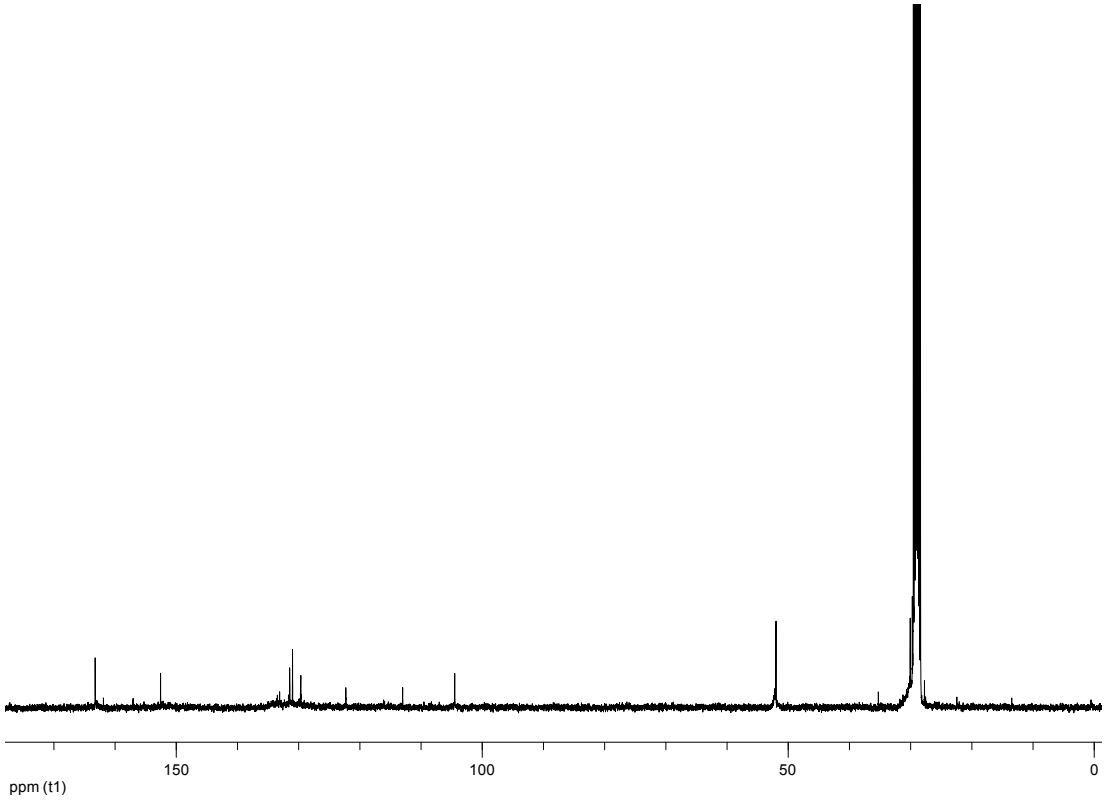


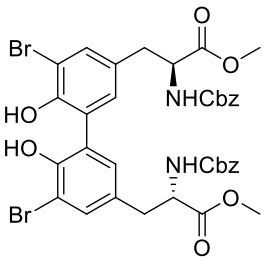

**16**

**$^{1}$H-NMR** (400.13 MHz, $CD_3OD$)



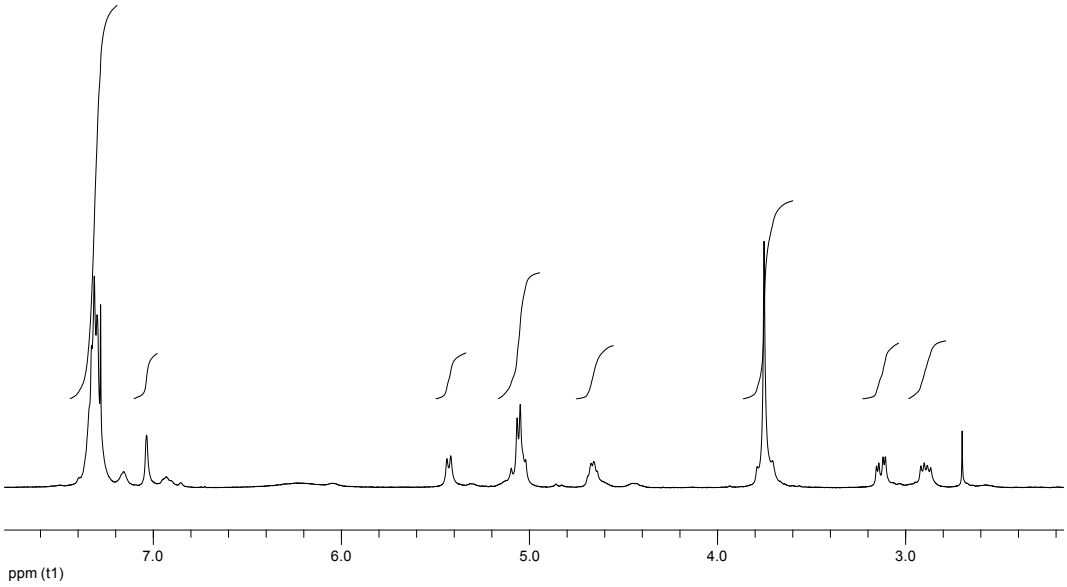

**$^{13}$C-NMR** (100.61 MHz, $CD_3COCD_3$)



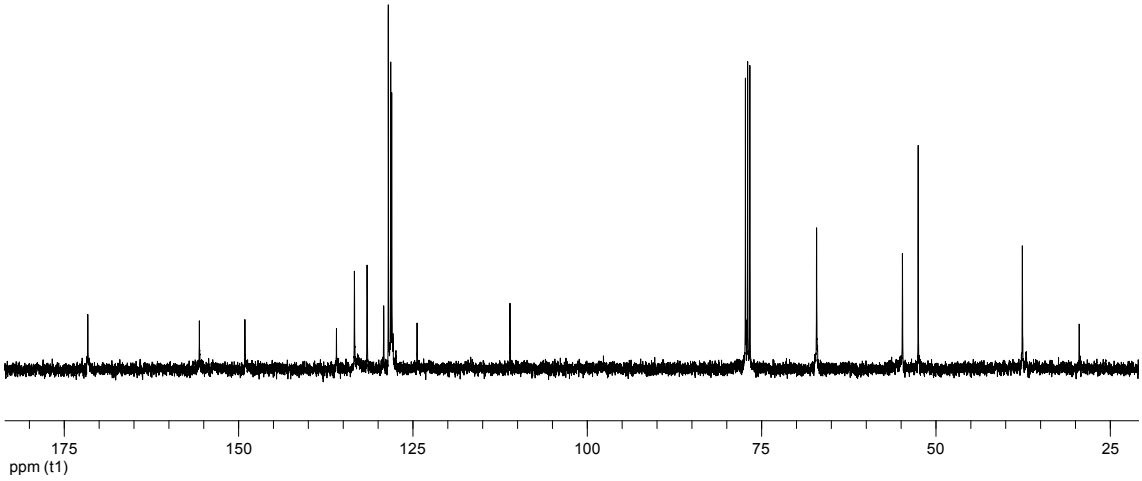


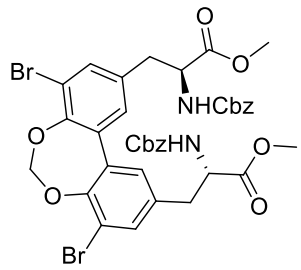

**17**

**$^{1}$H-NMR** (400.13 MHz, $CDCl_3$)



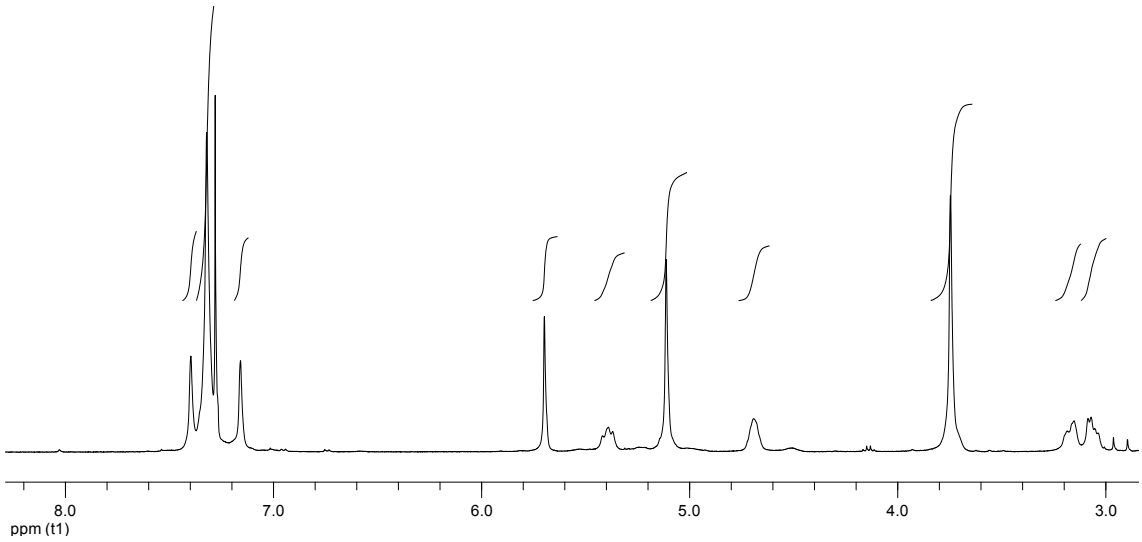

**$^{13}$C-NMR** (100.61 MHz, $CDCl_3$)



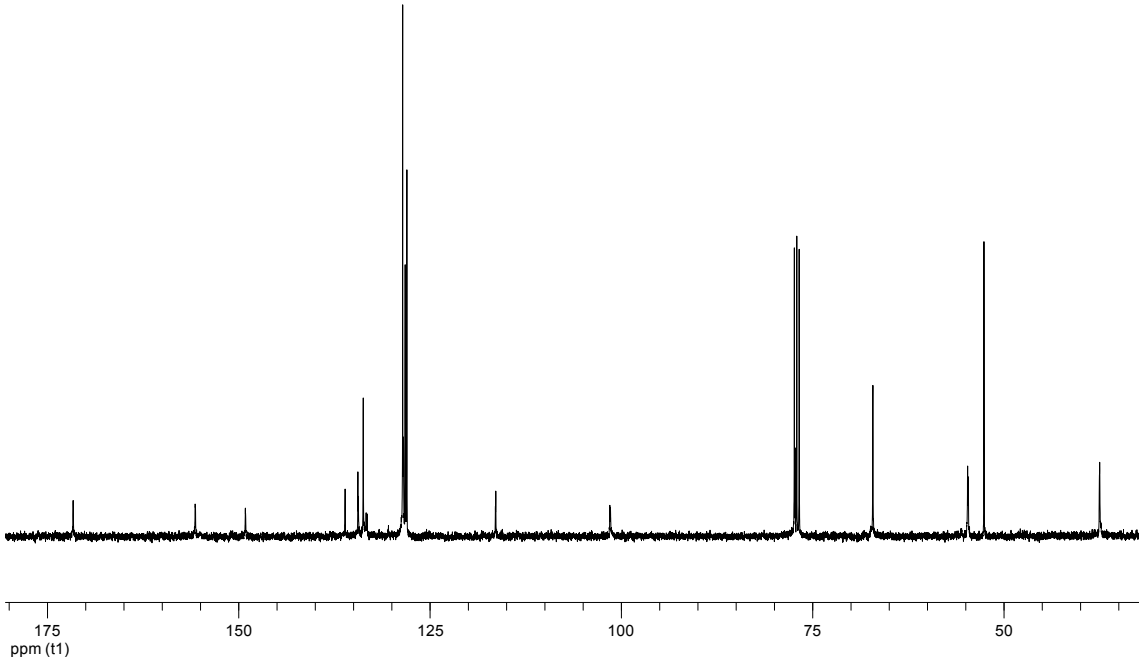


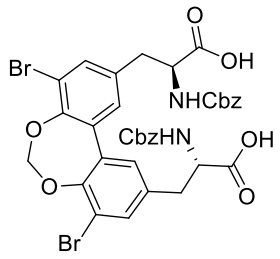

**18**

**$^{1}$H-NMR** (400.13 MHz, $CDCl_3$)



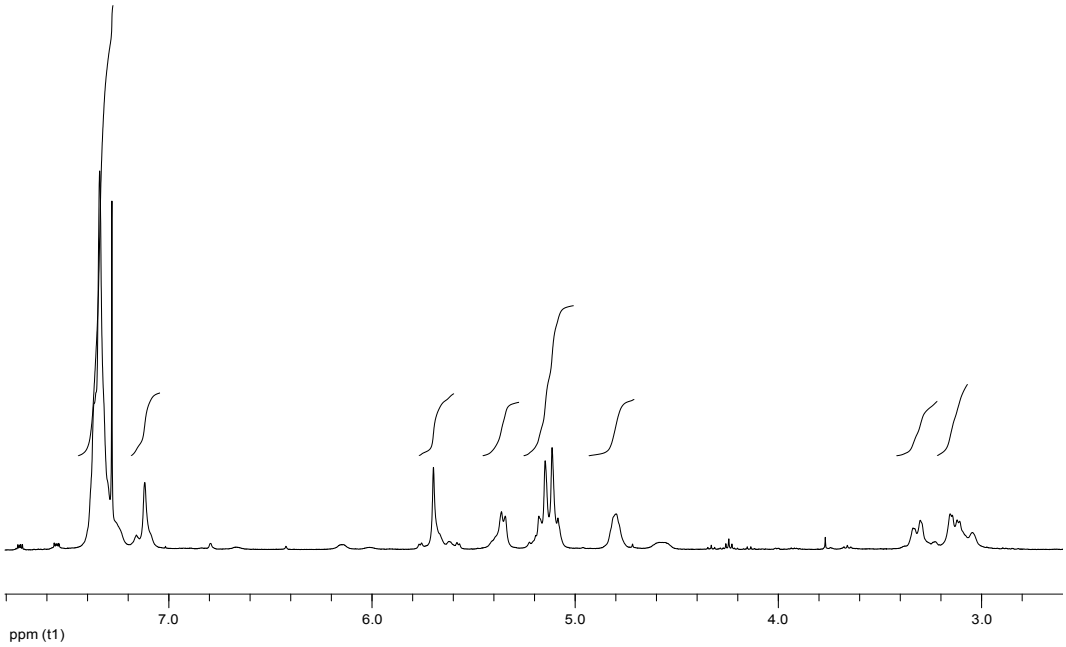

**$^{13}$C-NMR** (100.61 MHz, $CDCl_3$)



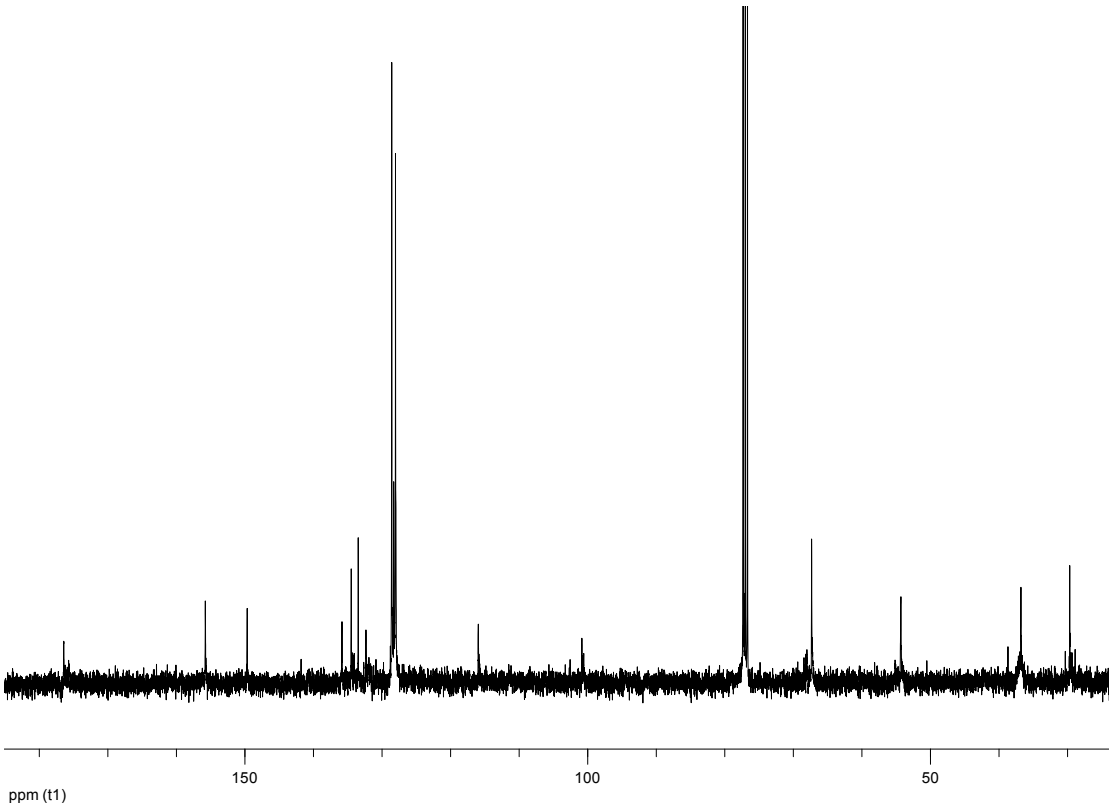



**19**

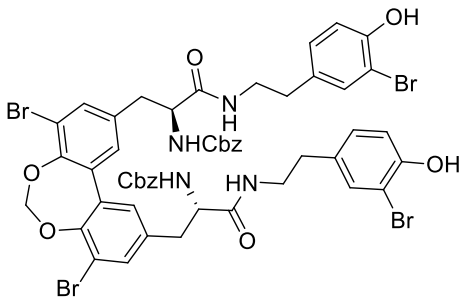
**$^{1}$H-NMR** (400.13 MHz, $CDCl_3$)



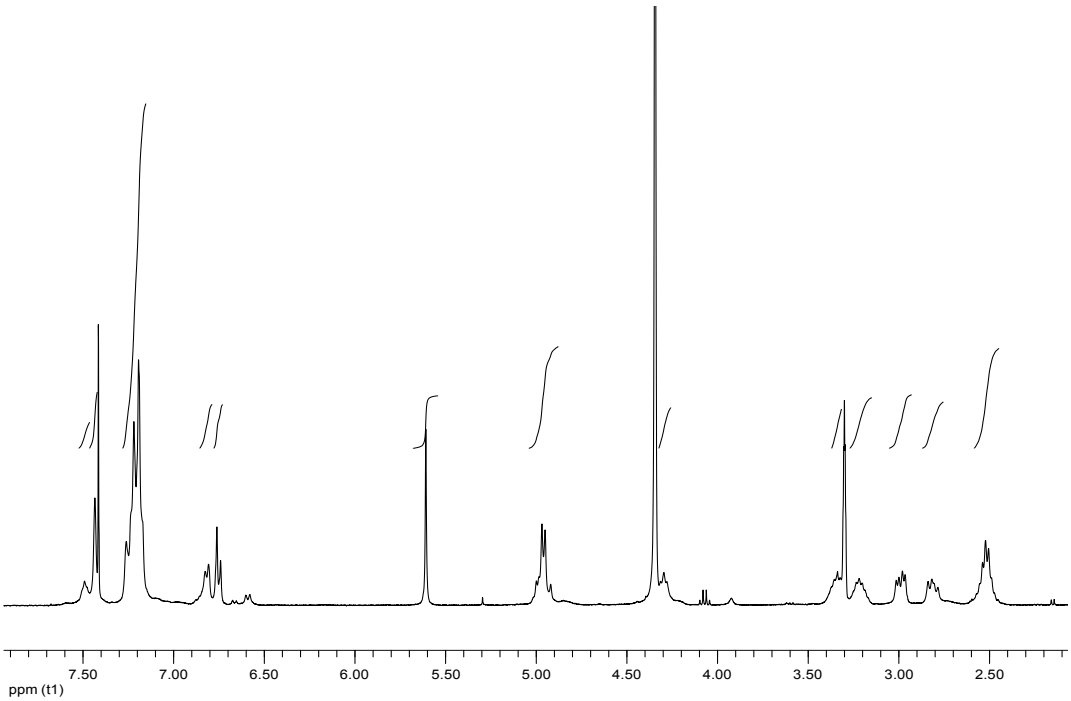

**$^{13}$C-NMR** (100.61 MHz, $CDCl_3$)



**$^{1}$H-NMR** (400.13 MHz, $CD_3OD$ + $CDCl_3$)




**20**




**$^{13}$C-NMR** (100.61 MHz, $CD_3OD$ + $CDCl_3$)