

# Supporting information

## Sphaerococcenol A Derivatives: Design, Synthesis, and Cytotoxicity

Dídia Sousa<sup>1,†</sup>, Milene A. G. Fortunato<sup>2,†</sup>, Joana Silva<sup>1</sup>, Mónica Pingo<sup>1</sup>, Alice Martins<sup>1</sup>, Carlos A. M. Afonso<sup>2</sup>, Rui Pedrosa<sup>1</sup>, Filipa Siopa<sup>2,\*</sup>, Celso Alves<sup>1,\*</sup>

<sup>1</sup> MARE—Marine and Environmental Sciences Centre/ARNET - Aquatic Research Network, ESTM, Politécnico de Leiria, 2520-614 Peniche, Portugal;

<sup>2</sup> Research Institute for Medicines (iMed.Ulisboa), Faculty of Pharmacy, Universidade de Lisboa, Av. Prof. Gama Pinto, 1649-003, Lisboa, Portugal;

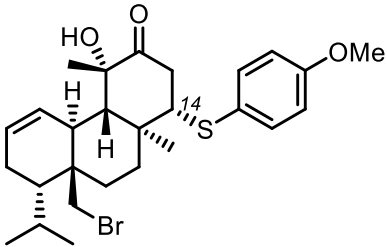
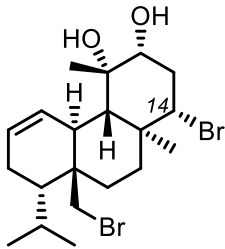
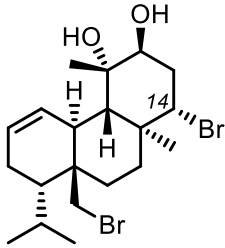
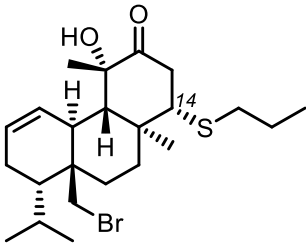
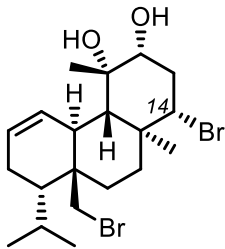
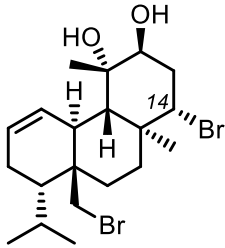
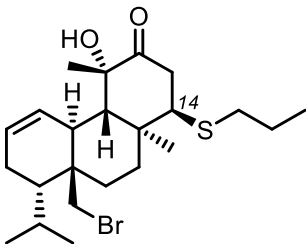
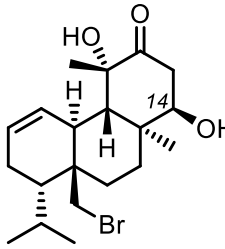
<sup>†</sup>These authors contributed equally to this work

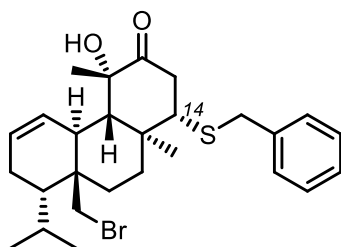
\* Correspondence: filipasiopa@ff.ulisboa.pt (F.S.), Tel.: +351-217-946-400; celso.alves@ipleiria.pt (C.A.); Tel.: +351-262-783-607

### Table of contents

Table S1.	1
Characterization - NMR spectra and HRMS	4

**Table S1.** Relevant  $^1\text{H}$  NMR spectral data of compounds **1-6**, and similar structures isolated from *Spaherooccus coronopifolius*.

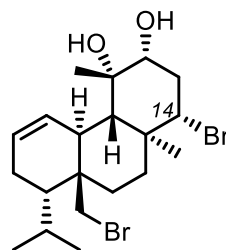
Compound	$^1\text{H}$ NMR (400 MHz, $\text{CDCl}_3$ )	Reported compound structure <sup>[a]</sup>	$^1\text{H}$ NMR (400 MHz, $\text{CDCl}_3$ )
 Compound <b>1</b>	H-14 ( $\delta_{\text{H}}$ 3.25, dd, $J = 7.3, 3.2$ Hz)	 H-14 ( $\delta_{\text{H}}$ 3.88, dd, $J = 12.8, 3.3$ Hz)	
		 H-14 ( $\delta_{\text{H}}$ 4.46, dd, $J = 12.8, 3.7$ Hz)	
 Compound <b>2</b>	H-14 ( $\delta_{\text{H}}$ 3.02, dd, $J = 10.4, 7.3$ Hz)	 H-14 ( $\delta_{\text{H}}$ 3.88, dd, $J = 12.8, 3.3$ Hz)	
		 H-14 ( $\delta_{\text{H}}$ 4.46, dd, $J = 12.8, 3.7$ Hz)	
 Compound <b>3</b>	H-14 ( $\delta_{\text{H}}$ 2.79, dd, $J = 9.0, 1.9$ Hz)	 H-14 ( $\delta_{\text{H}}$ 3.74, dd, $J = 7.9, 1.2$ Hz)	



Compound 4

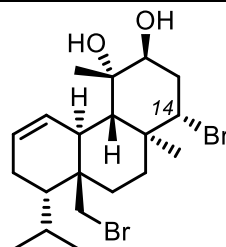
H-13 ( $\delta_H$  3.09, dd,  $J = 17.7, 10.2$  Hz)

H-14 ( $\delta_H$  2.87, dd,  $J = 10.2, 6.8$  Hz)



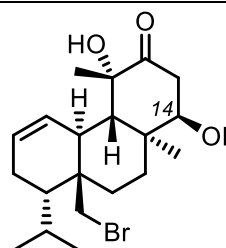
H-13 $\alpha$  ( $\delta_H$  2.33, ddd,  $J = 12.8, 12.4, 11.6$  Hz)

H-14 ( $\delta_H$  3.88, dd,  $J = 12.8, 3.3$  Hz)



H-13 $\alpha$  ( $\delta_H$  2.70, ddd,  $J = 13.7, 12.8, 12.4, 2.9$  Hz)

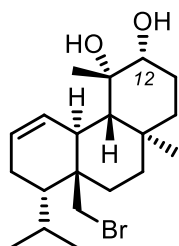
H-14 ( $\delta_H$  4.46, dd,  $J = 12.8, 3.7$  Hz)



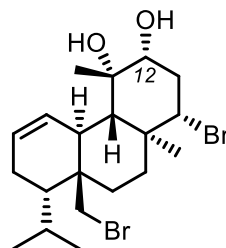
H-13 $\alpha$  ( $\delta_H$  2.63, dd,  $J = 18.2, 1.2$  Hz)

H-13 $\beta$  ( $\delta_H$  2.99, dd,  $J = 18.2, 7.9$  Hz)

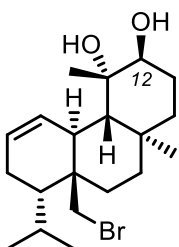
H-14 ( $\delta_H$  3.74, dd,  $J = 7.9, 1.2$  Hz)



H-12 ( $\delta_H$  3.30 d,  $J = 11.4$  Hz)

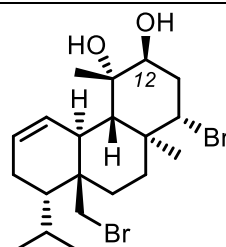


H-12 ( $\delta_H$  3.34, dt,  $J = 11.6, 5.4$  Hz)

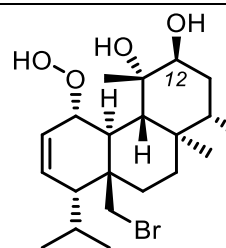


Compound 6

H-12 ( $\delta_H$  3.61 dd,  $J = 5.6, 3.0$  Hz)<sup>[b]</sup>



H-12 ( $\delta_H$  3.45, br s)



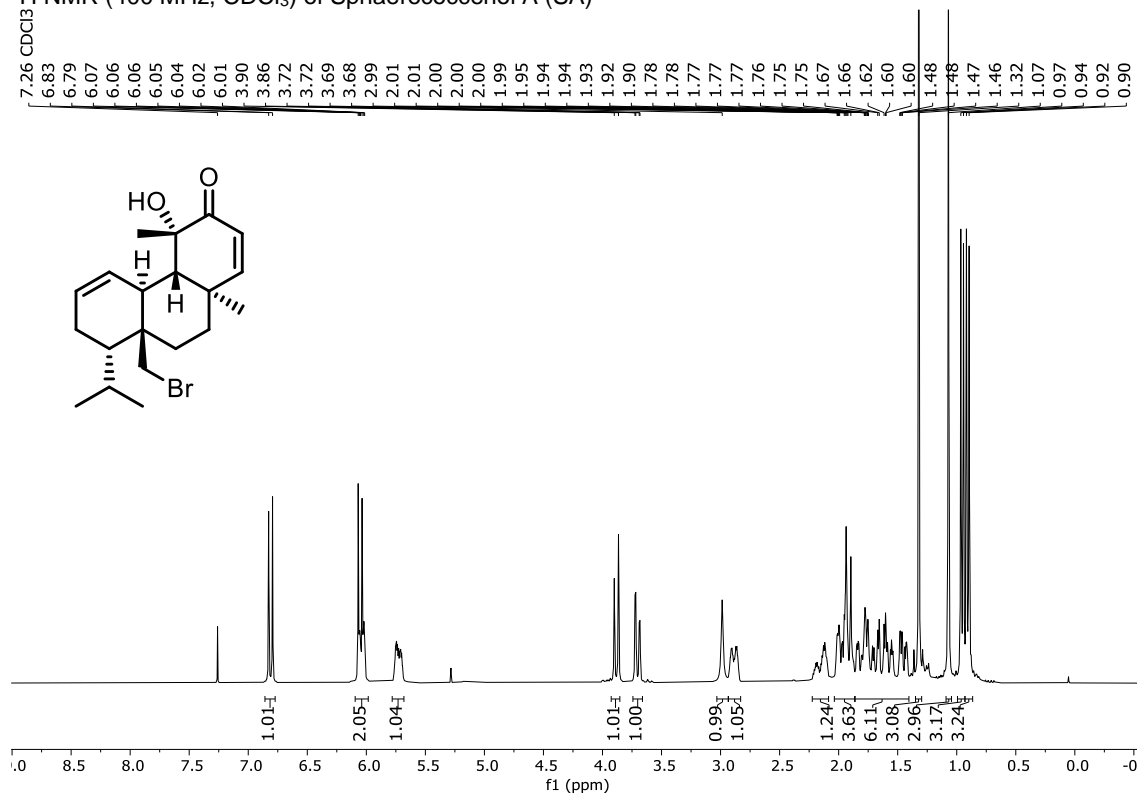
H-12 ( $\delta_H$  3.50, dd  $J = 3.4, 2.4$  Hz)

<sup>[a]</sup> Smyrniotopoulos, V.; Quesada, A.; Vagias, C.; Moreau, D.; Roussakis, C.; Roussis, V., Cytotoxic bromoditerpenes from the red alga *Sphaerococcus coronopifolius*. *Tetrahedron* **2008**, 64, (22), 5184-5190.

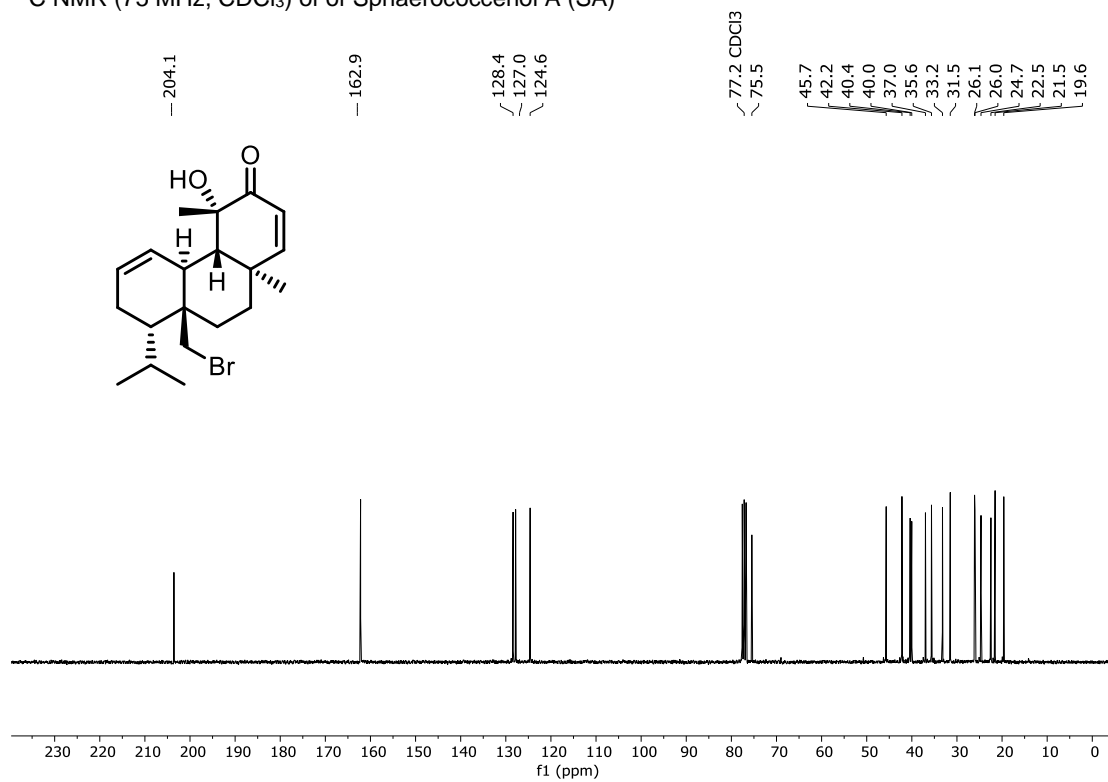
<sup>[b]</sup> <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)

# Characterization

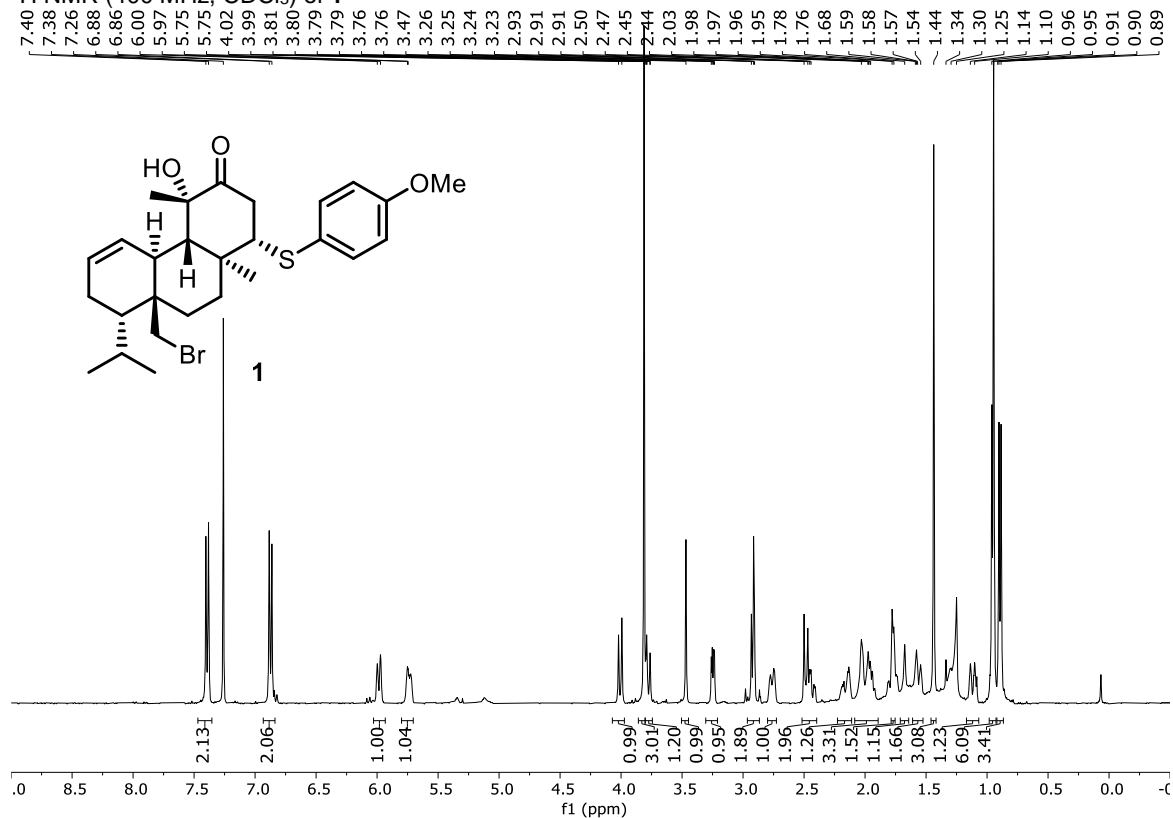
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of Sphaerococcenol A (SA)



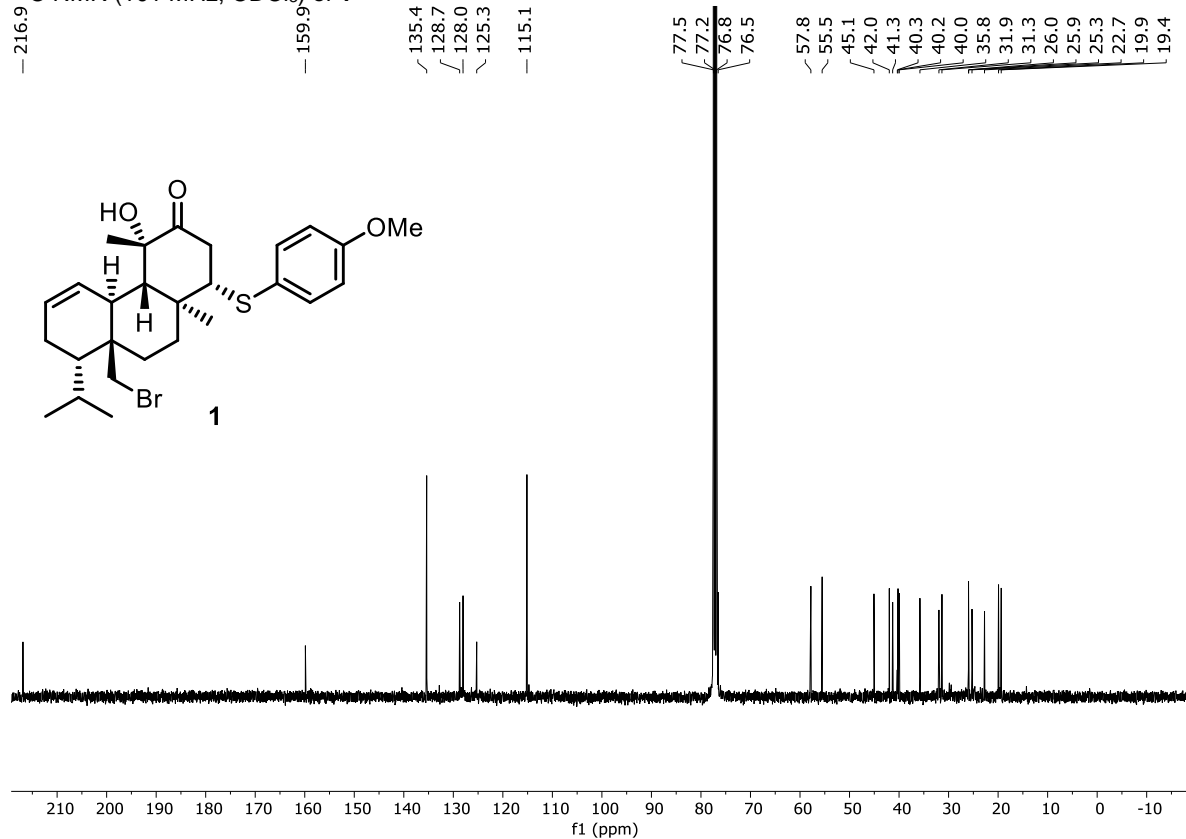
<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) of Sphaerococcenol A (SA)



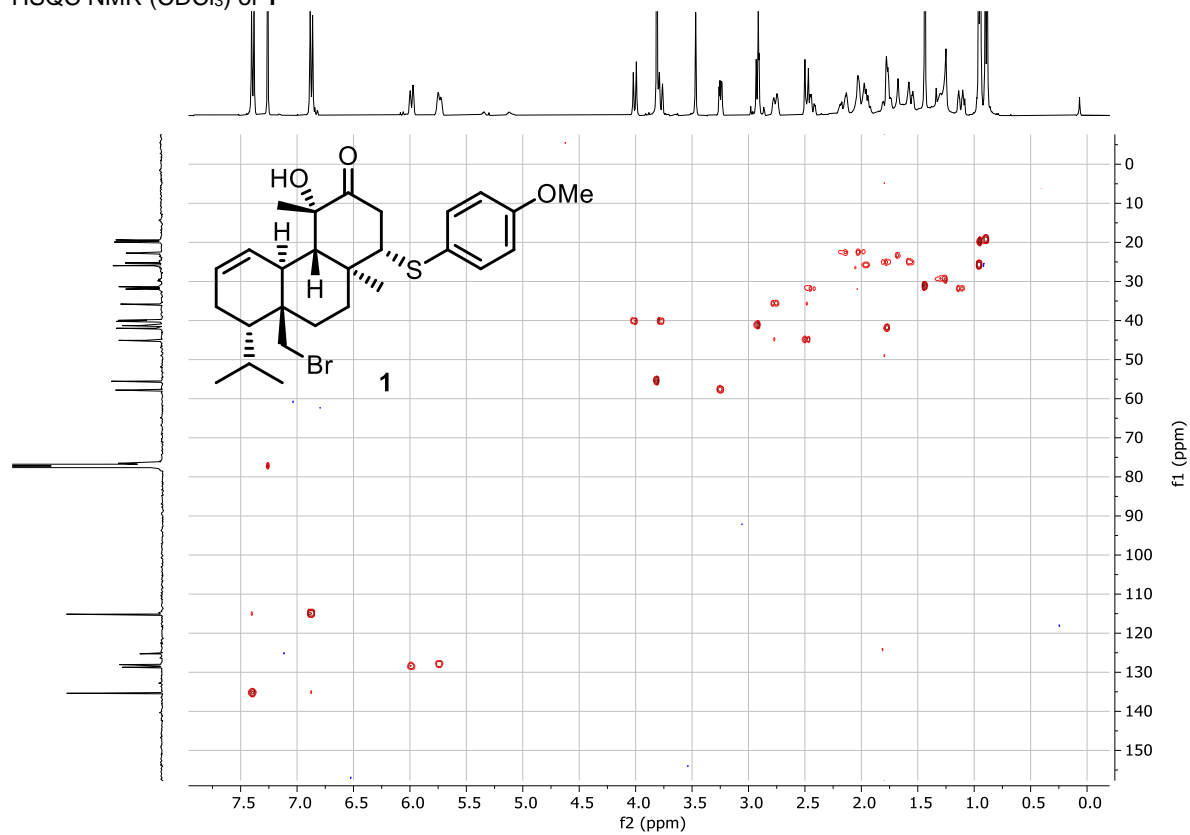
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of **1**



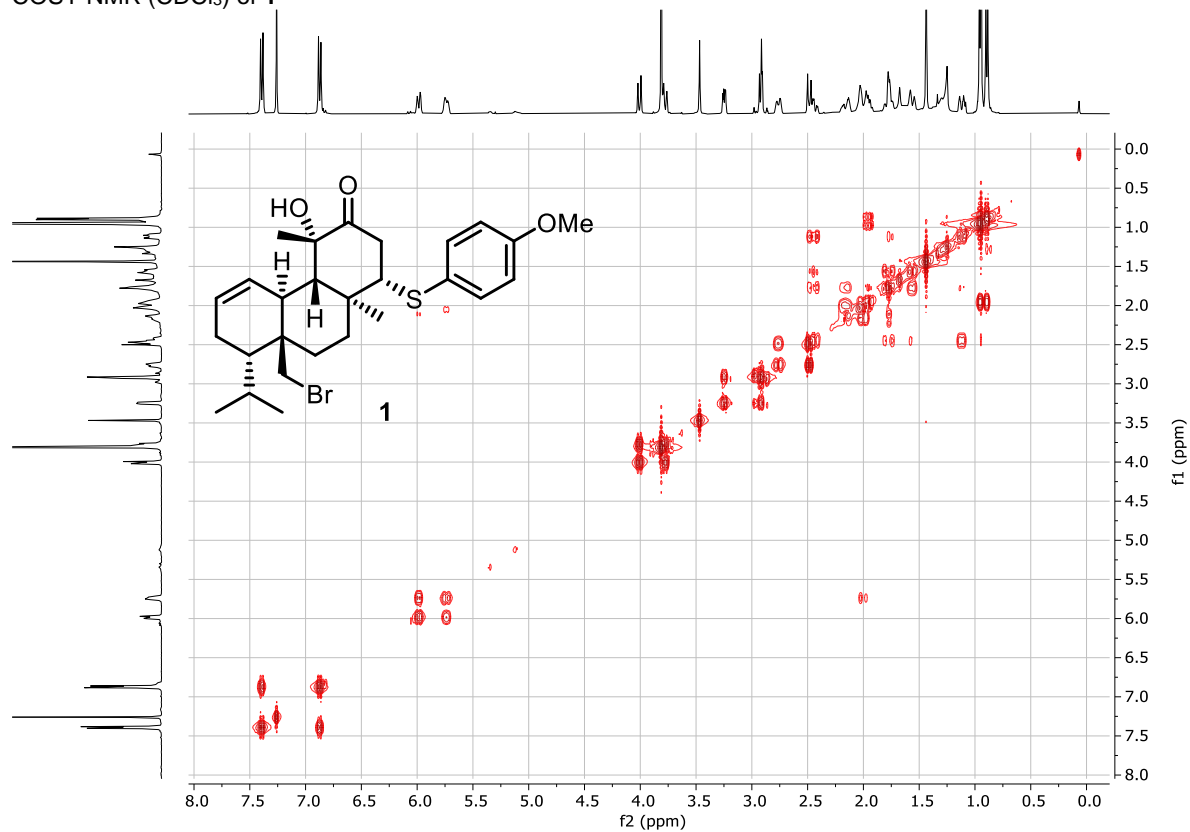
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) of **1**



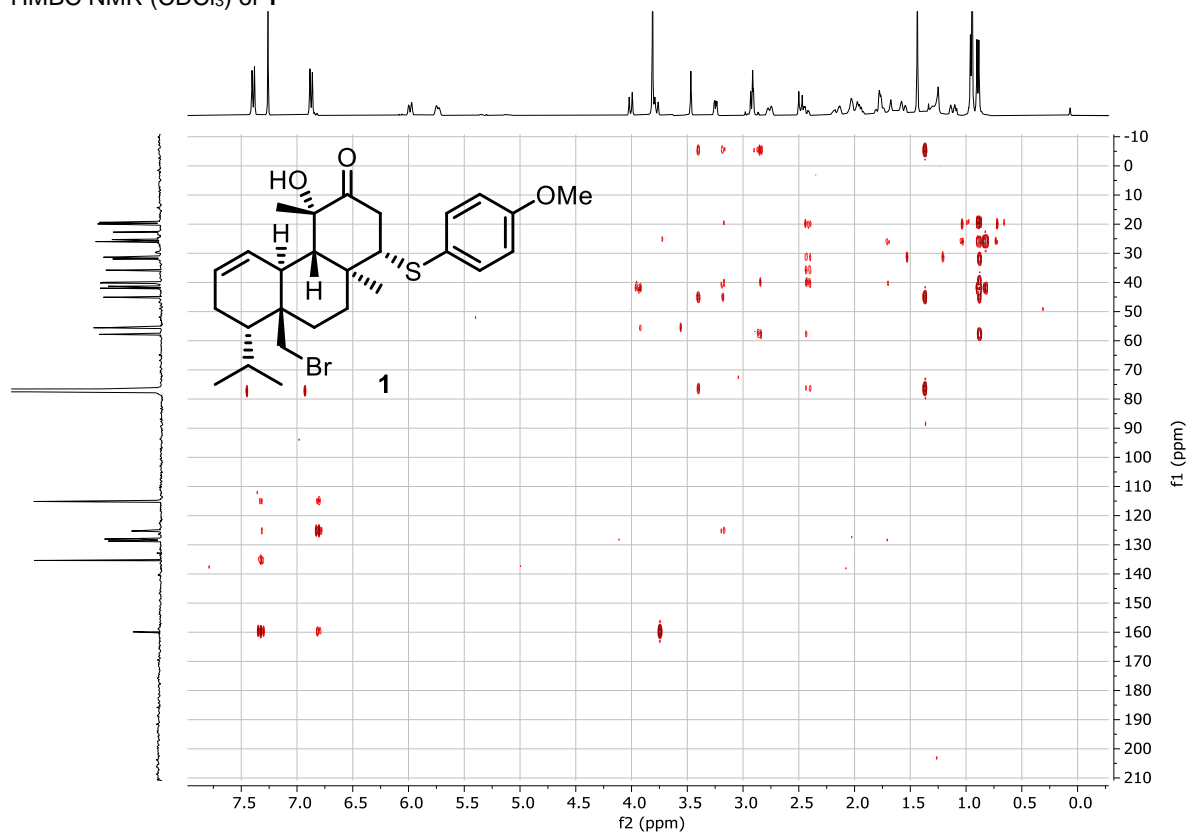
HSQC NMR (CDCl<sub>3</sub>) of **1**



COSY NMR (CDCl<sub>3</sub>) of **1**



# HMBC NMR (CDCl<sub>3</sub>) of **1**

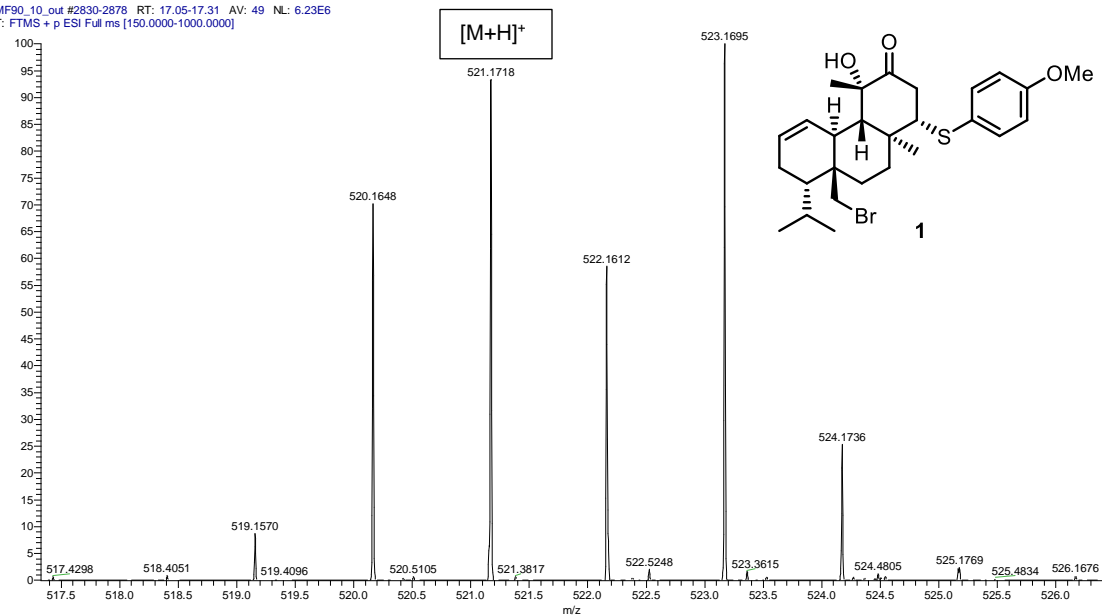


## HRMS spectra of **1**

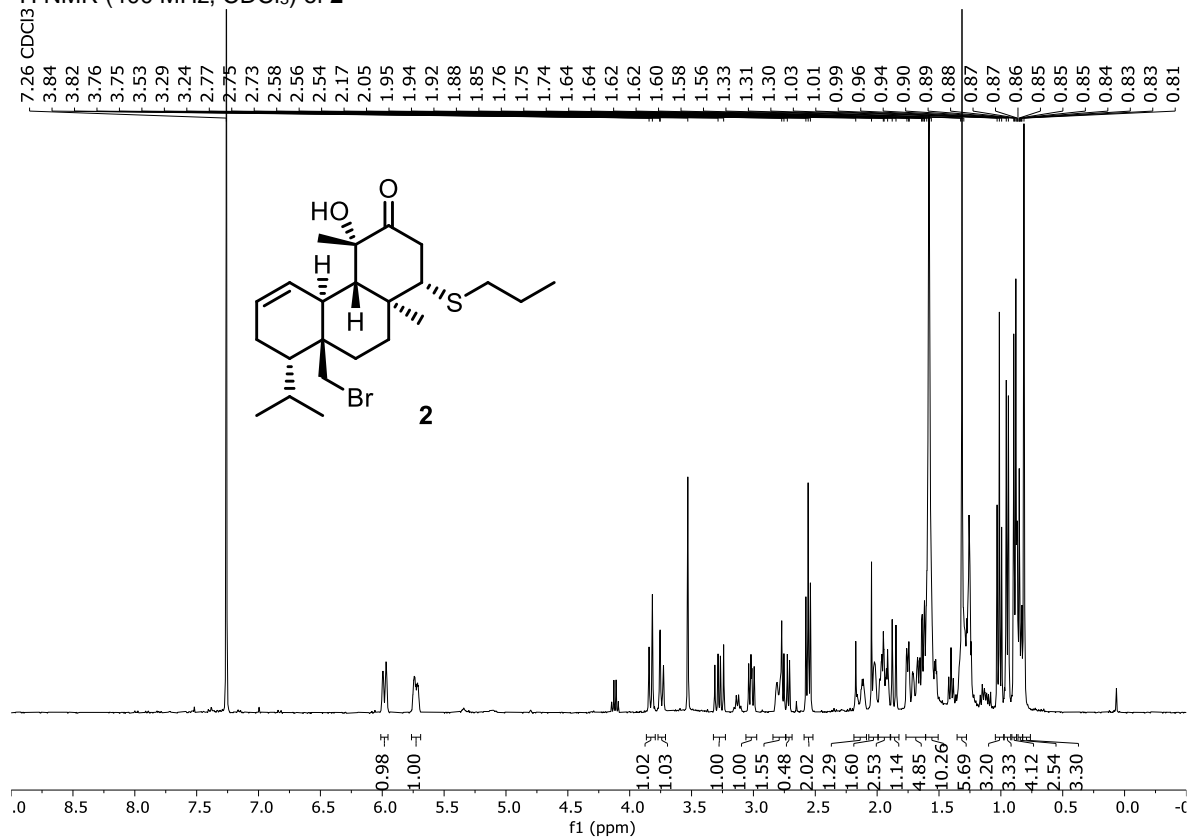
E:\Massa\MF90\_10\_out

11/10/21 15:33:58

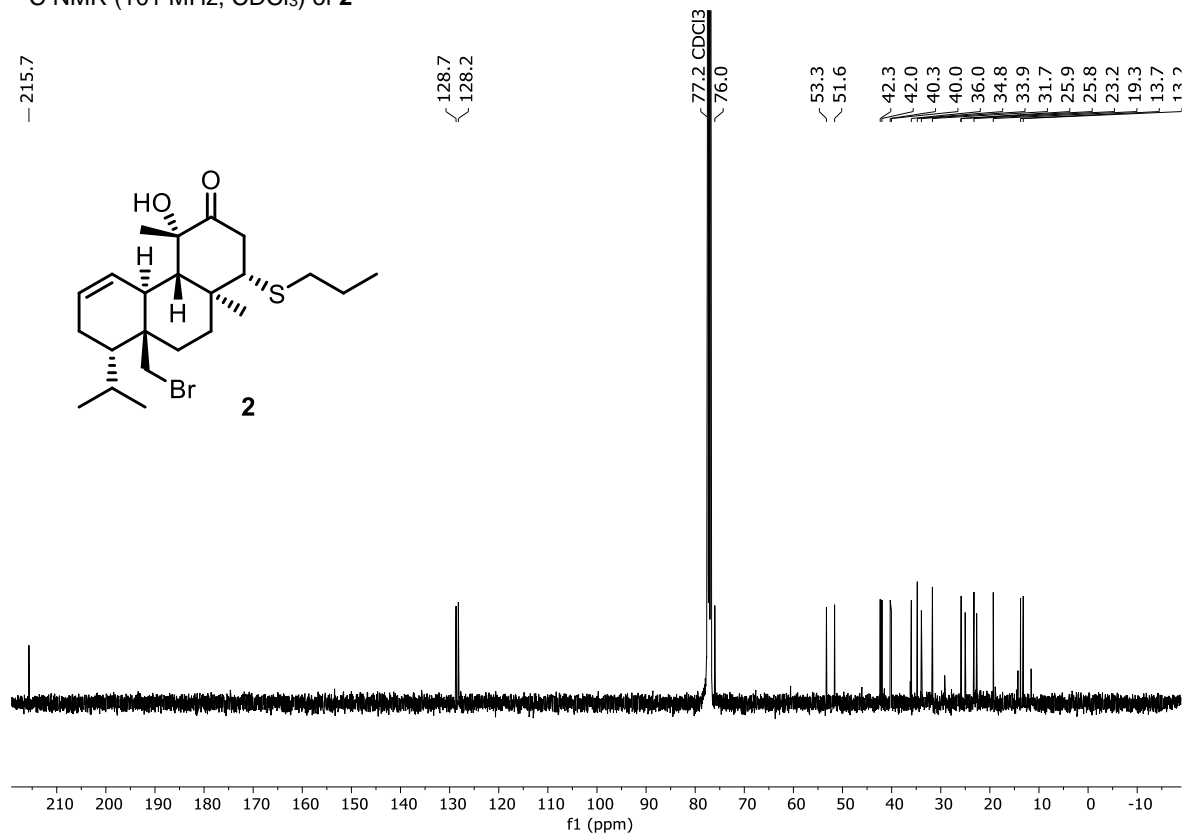
MF90\_10\_out #2830-2878 RT: 17.05-17.31 AV: 49 NL: 6.23E6  
T: FTMS + p ESI Full ms [150.0000-1000.0000]



<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of **2**

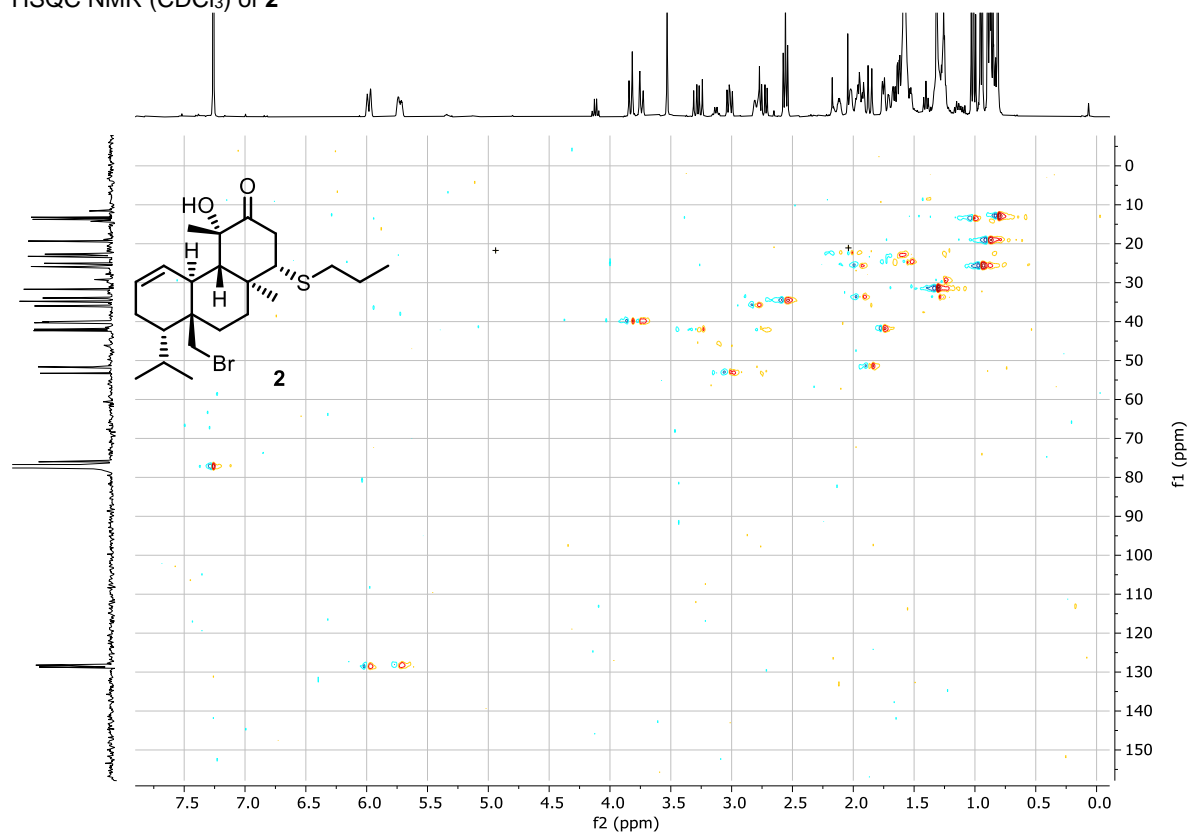


<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) of **2**

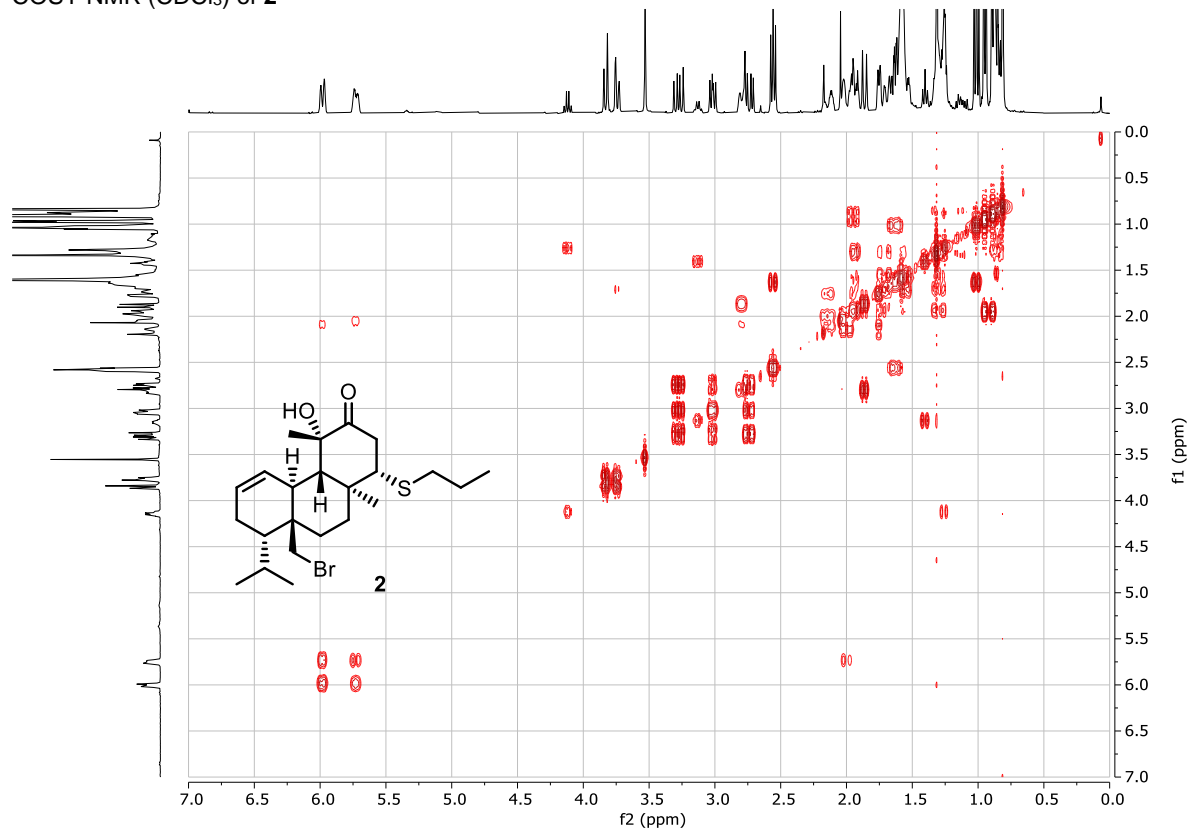




HSQC NMR (CDCl<sub>3</sub>) of **2**



COSY NMR (CDCl<sub>3</sub>) of **2**

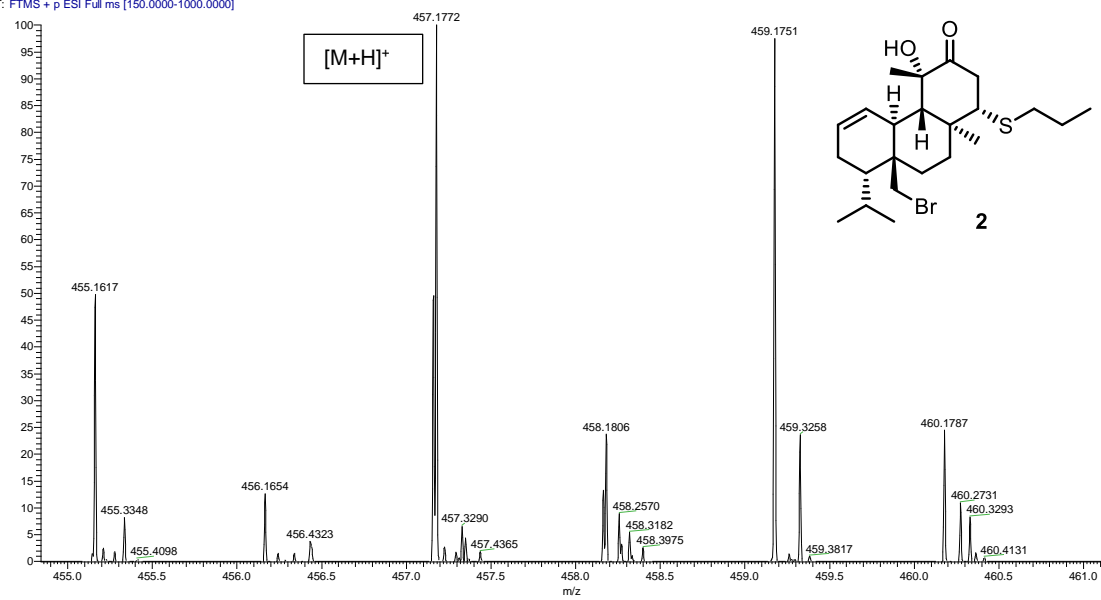


## HRMS spectra of **2**

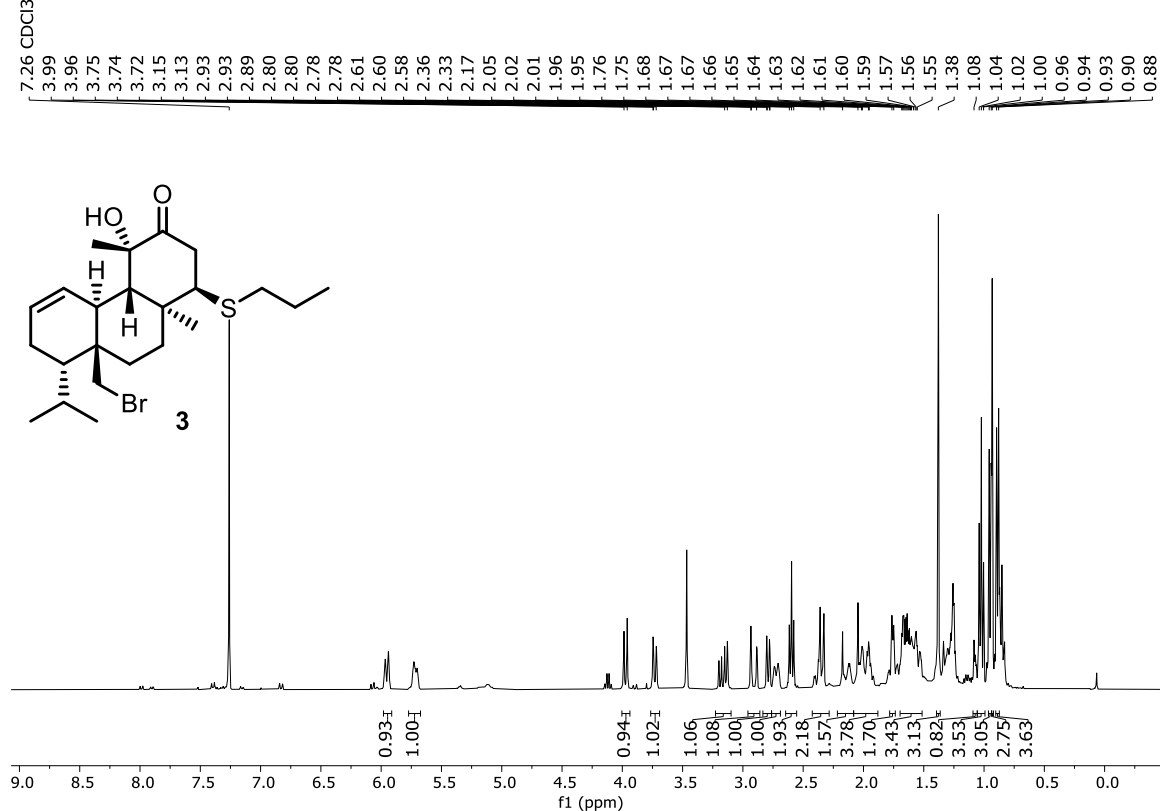
E:\Massa\MF91\_RT28\_10\_out

11/10/21 15:59:26

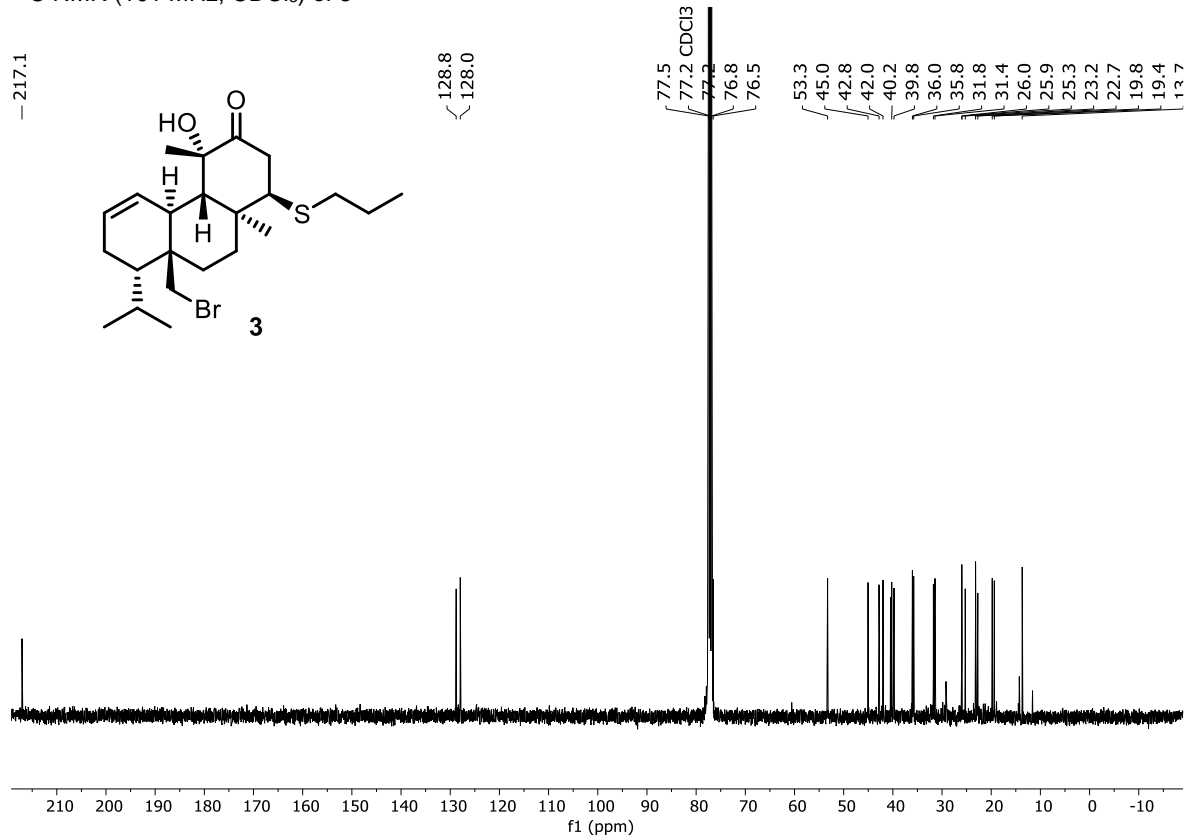
MF91\_RT28\_10\_out #2655-2755 RT: 16.18-16.70 AV: 101 NL: 1.04E6  
T: FTMS + p ESI Full ms [150.0000-1000.0000]



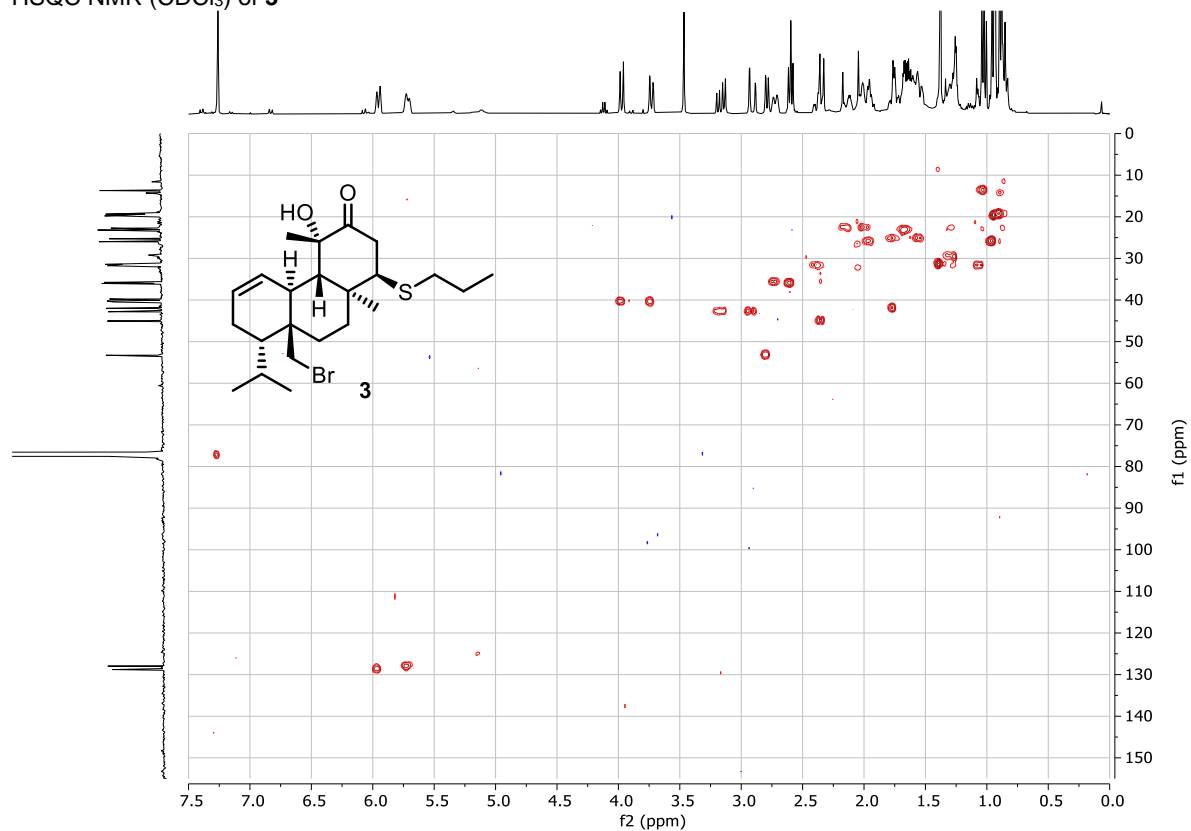
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of **3**



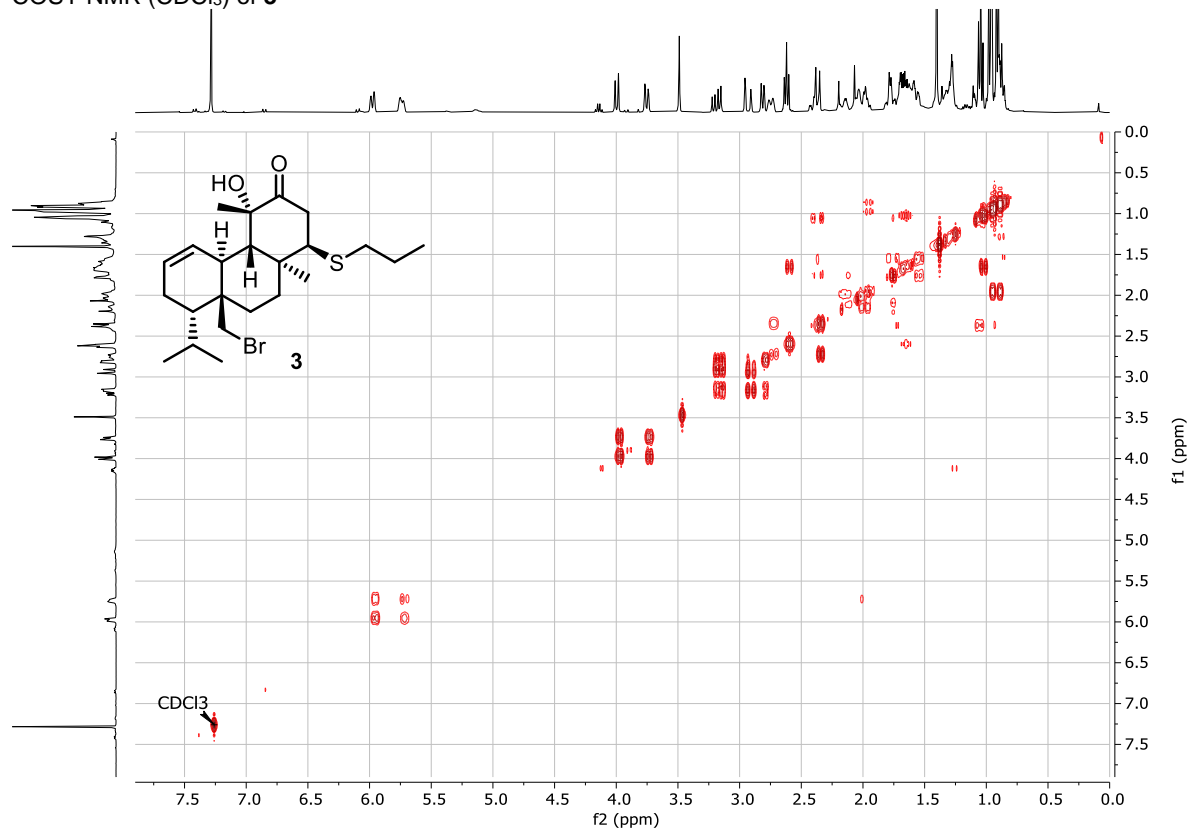
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) of **3**



HSQC NMR (CDCl<sub>3</sub>) of **3**



COSY NMR (CDCl<sub>3</sub>) of **3**

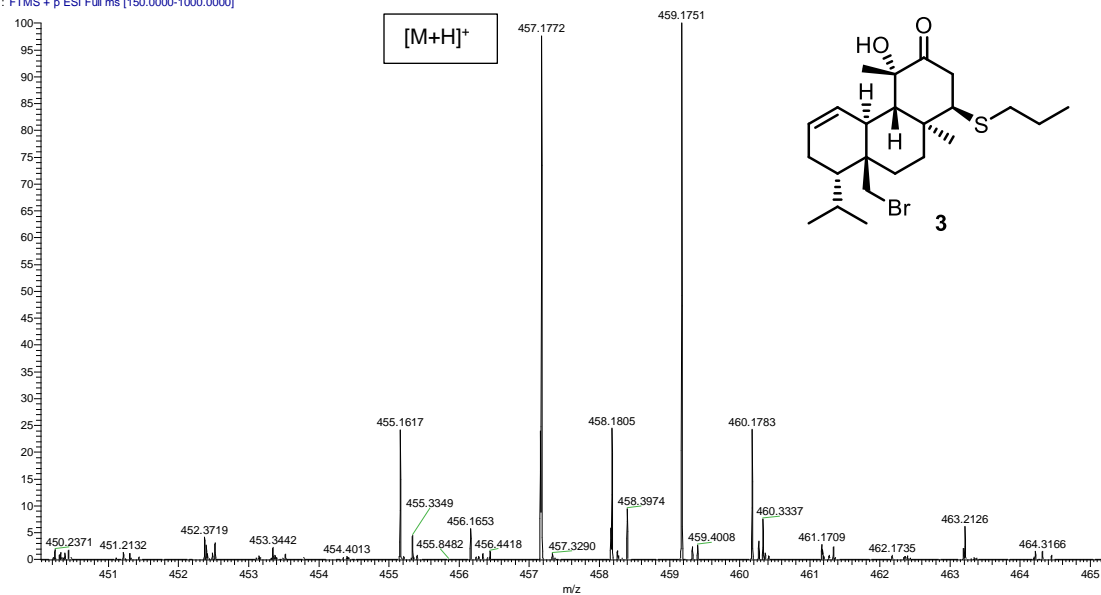


# HRMS spectra of **3**

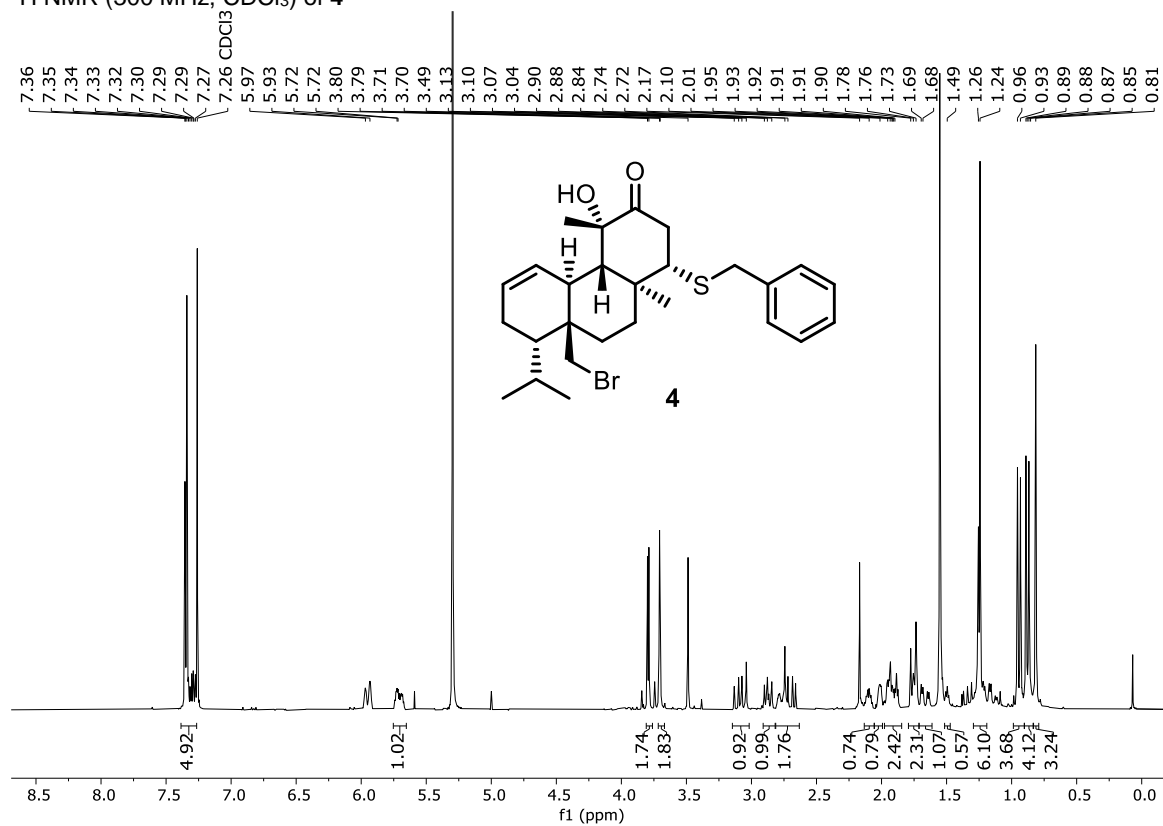
E:\Massa\MF91\_RT30\_10\_out

11/10/21 16:24:54

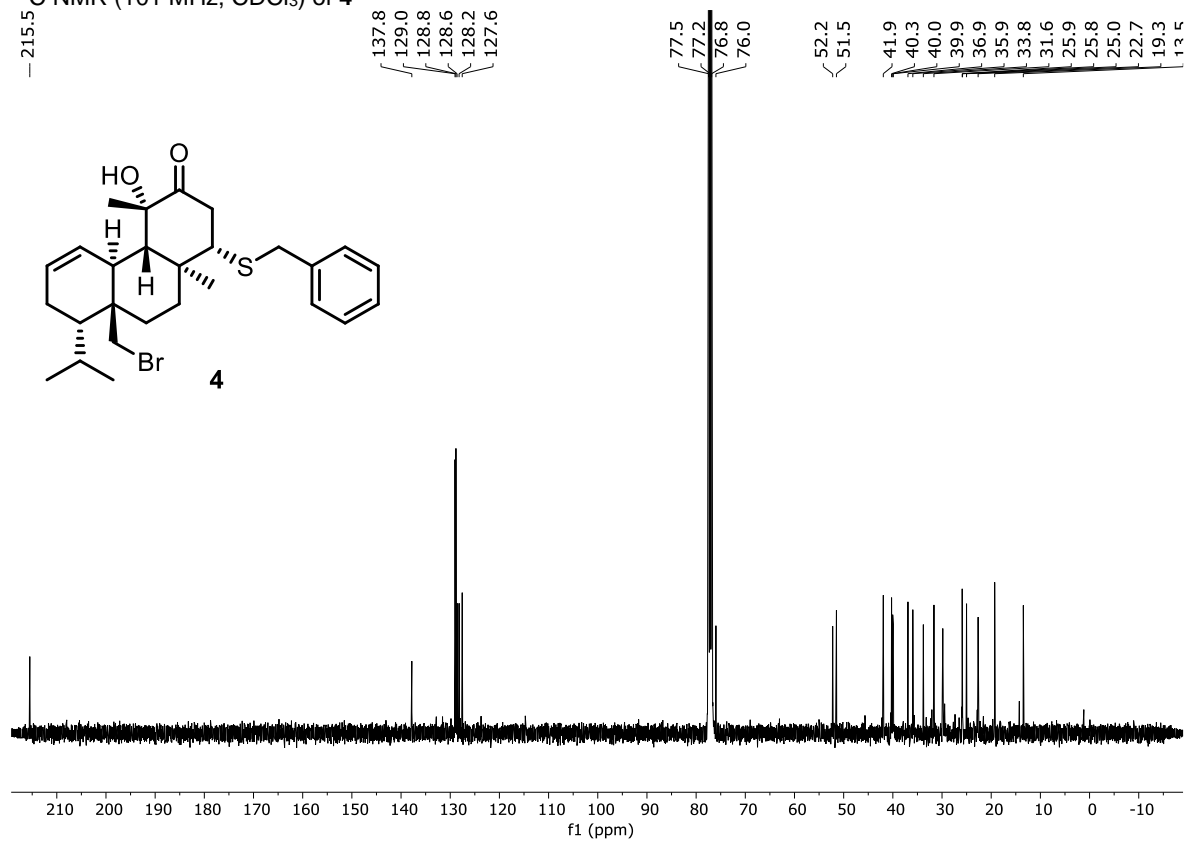
MF91\_RT30\_10\_out #2757-2855 RT: 16.71-17.24 AV: 99 NL: 3.03E6  
T: FTMS + p ESI Full ms [150.0000-1000.0000]



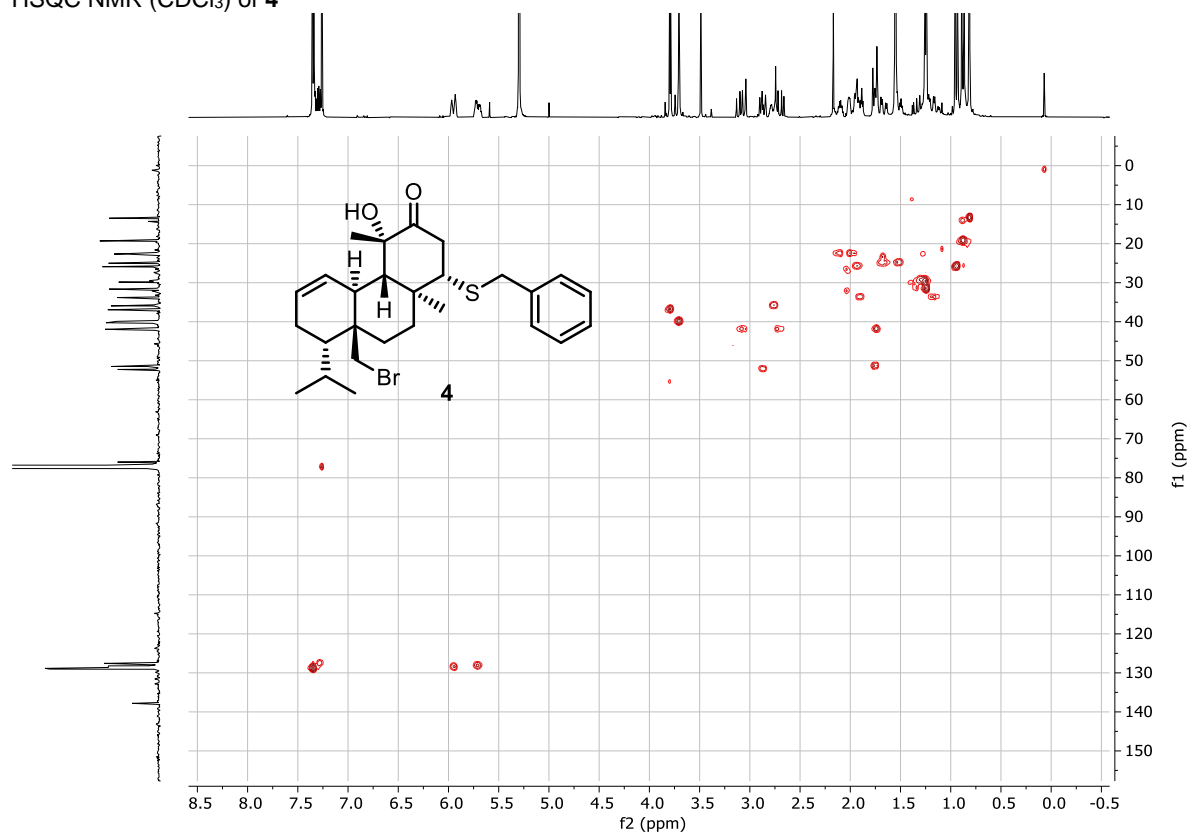
$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) of **4**



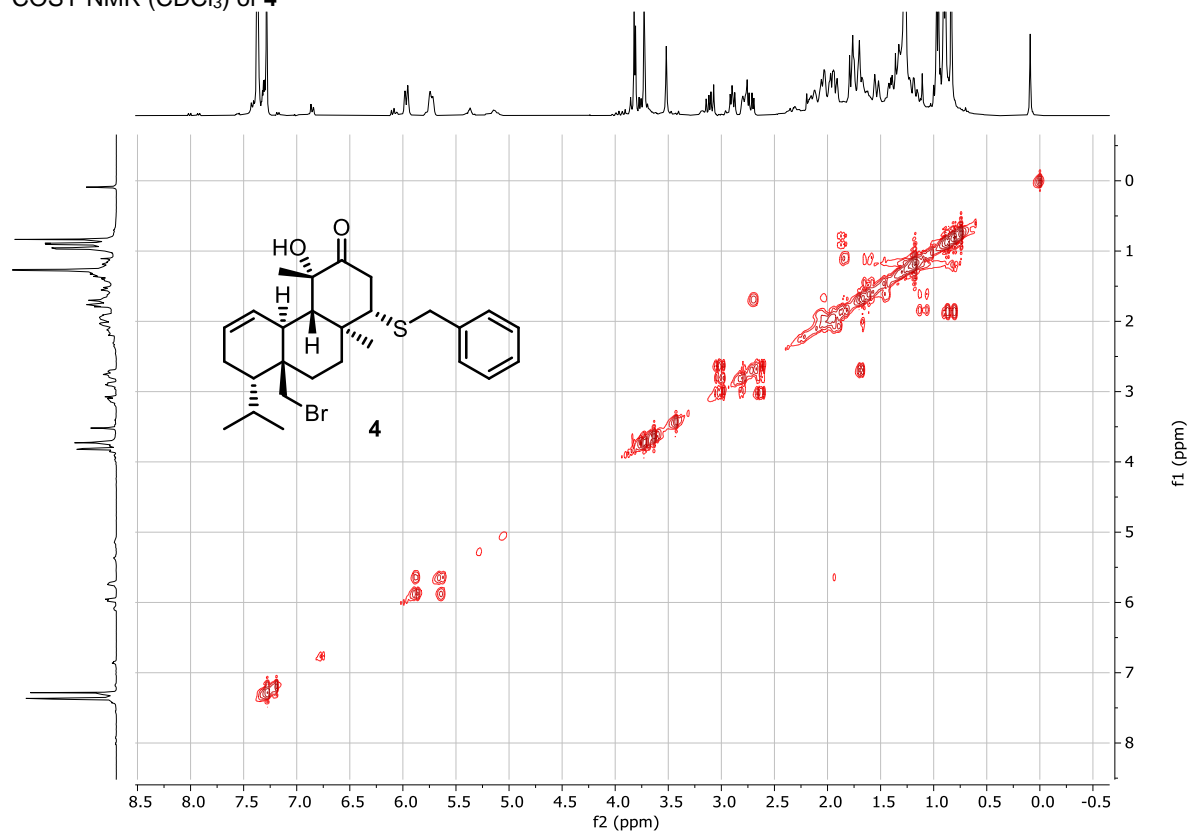
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ) of **4**



HSQC NMR (CDCl<sub>3</sub>) of **4**



COSY NMR (CDCl<sub>3</sub>) of **4**

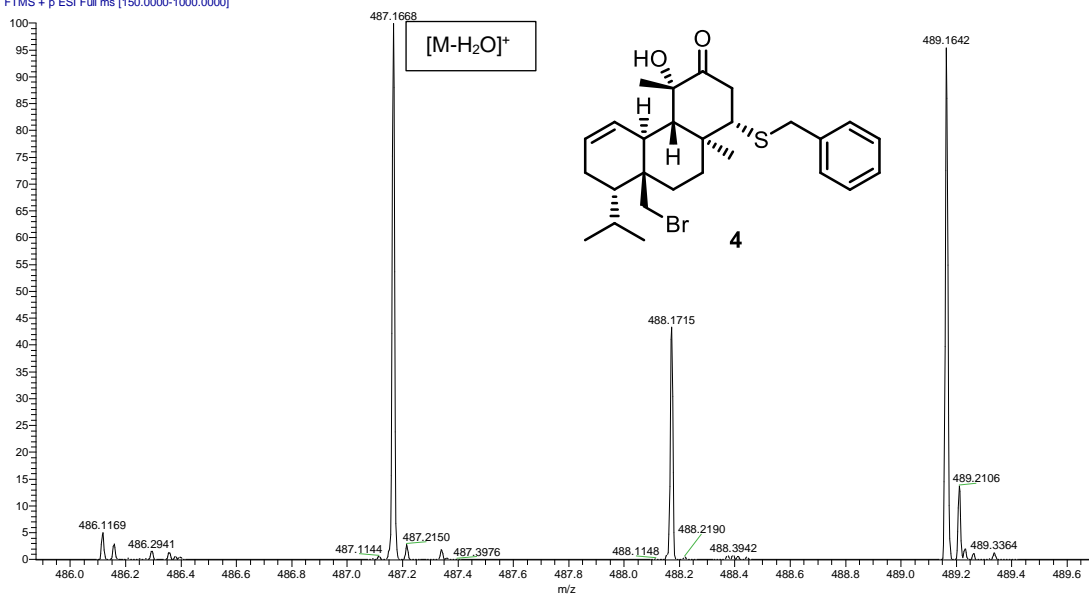


# HRMS spectra of **4**

E:\Massa\MF88\_10\_out2

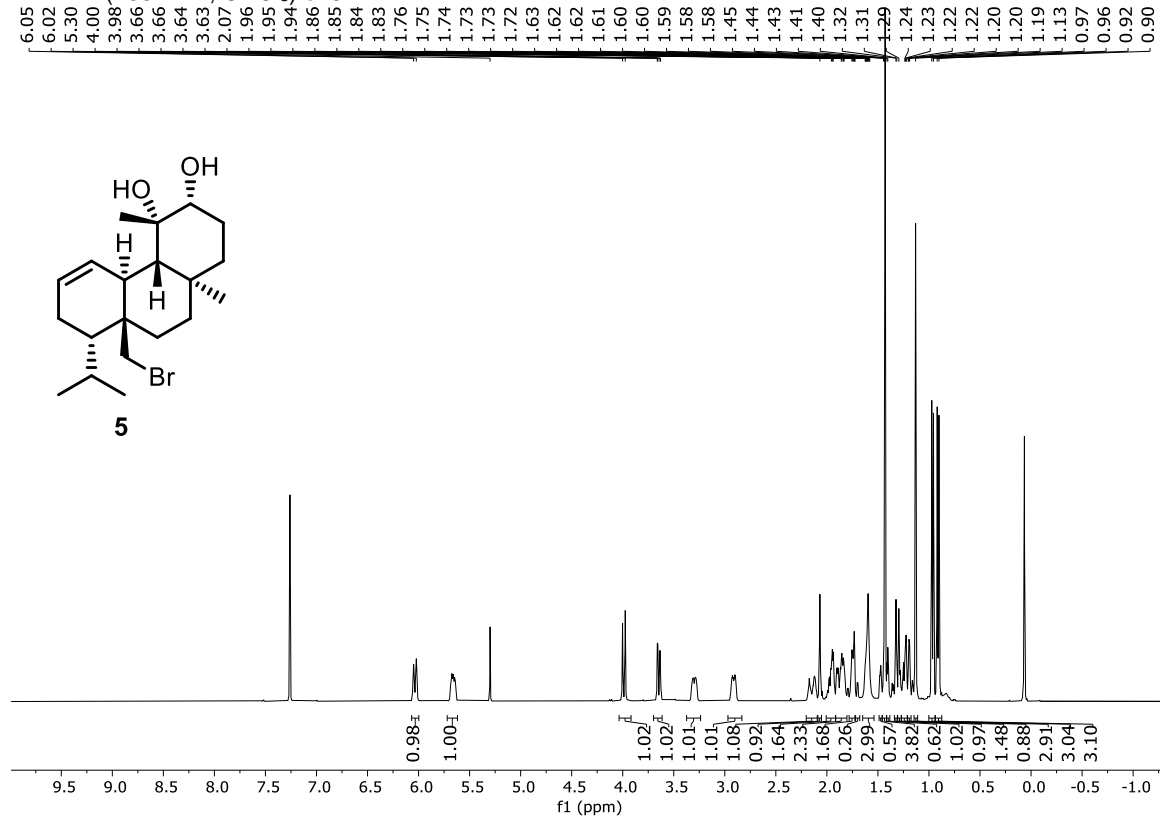
11/10/21 17:41:18

MF88\_10\_out2 #2650-2740 RT: 16.06-16.54 AV: 91 NL: 7.06E5  
T: FTMS + p ESI Full ms [150.0000-1000.0000]

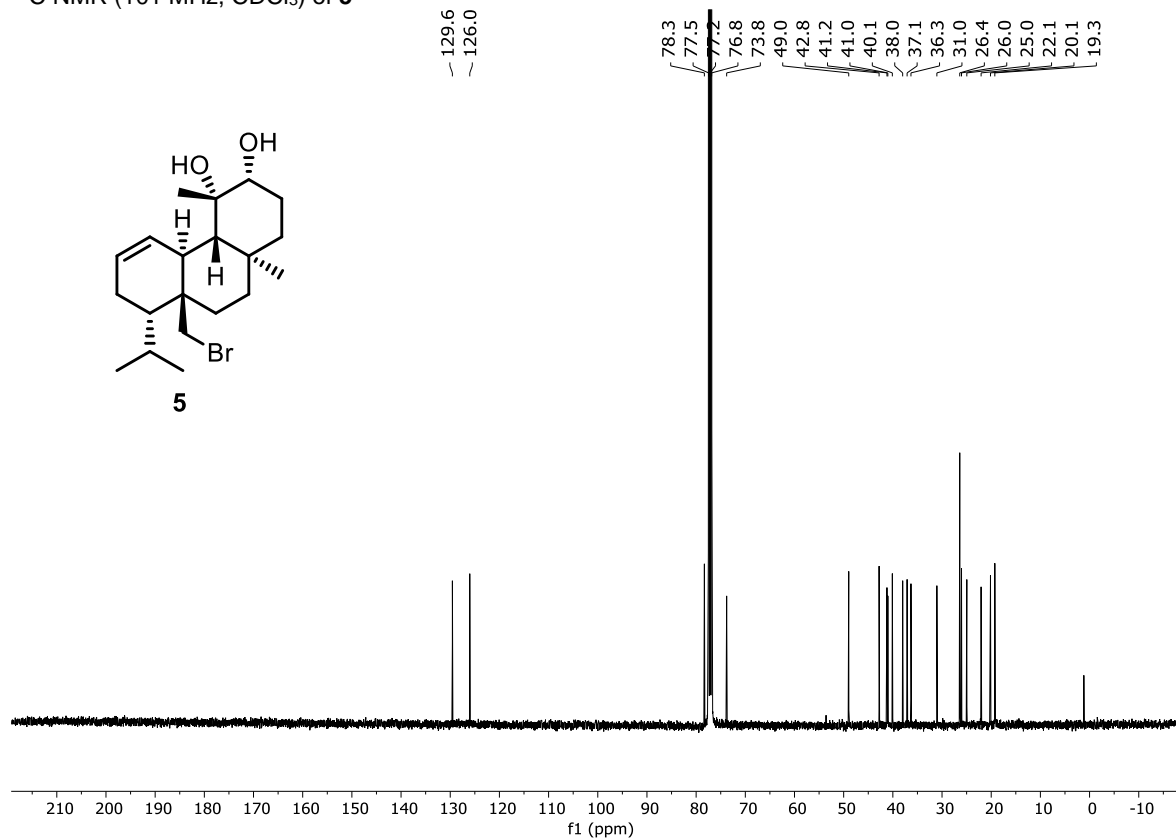




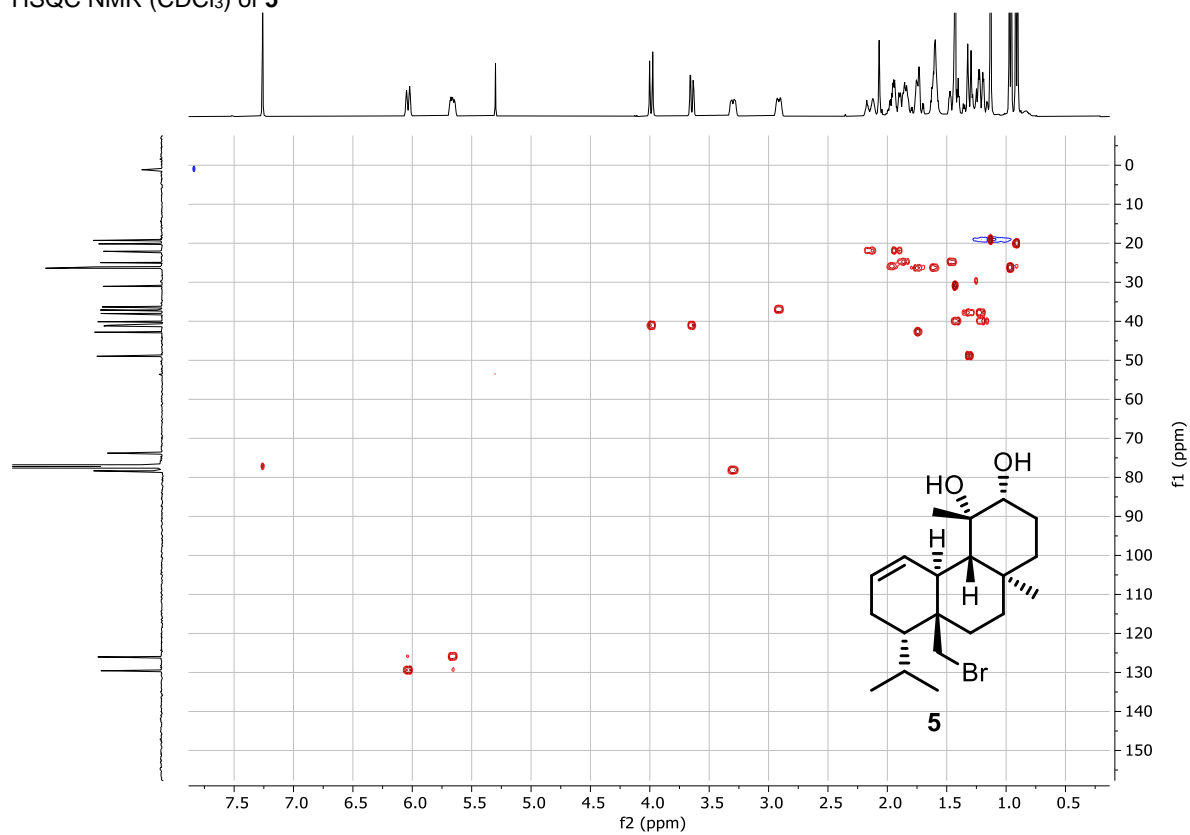
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of **5**



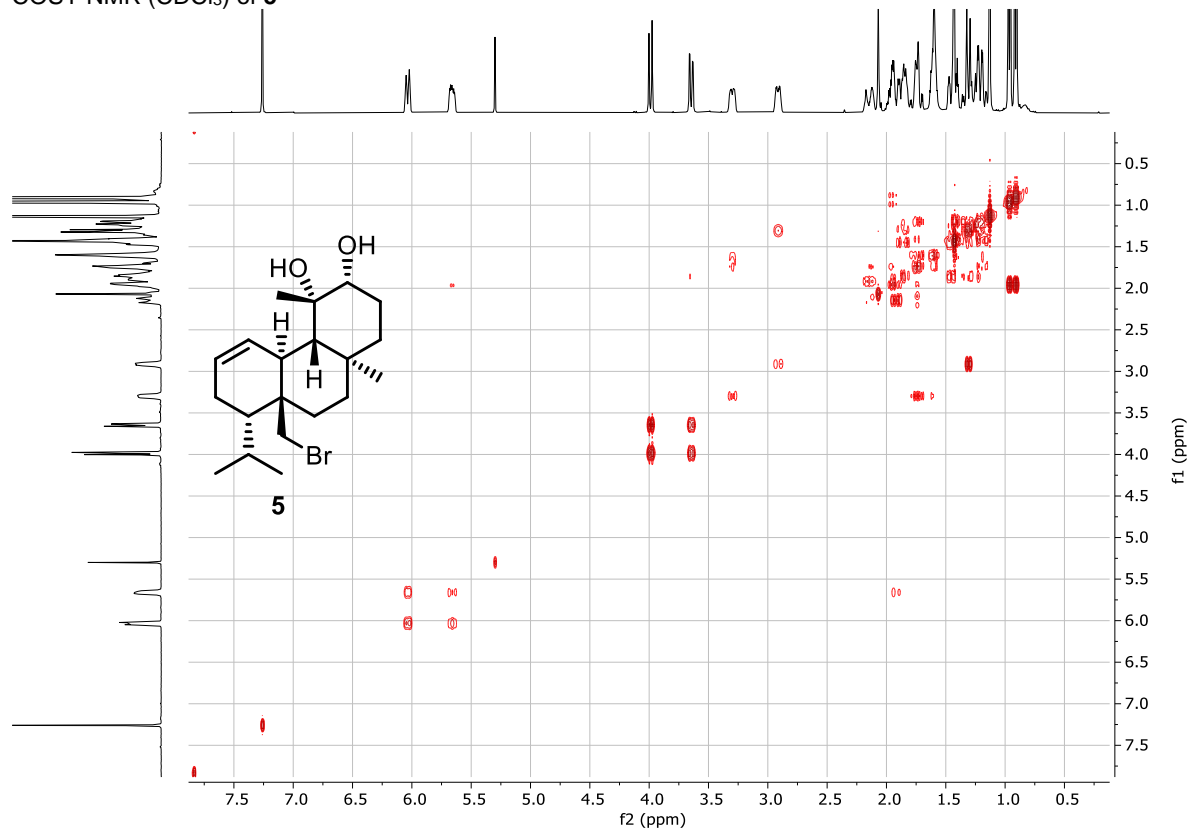
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) of **5**



HSQC NMR (CDCl<sub>3</sub>) of **5**



COSY NMR (CDCl<sub>3</sub>) of **5**

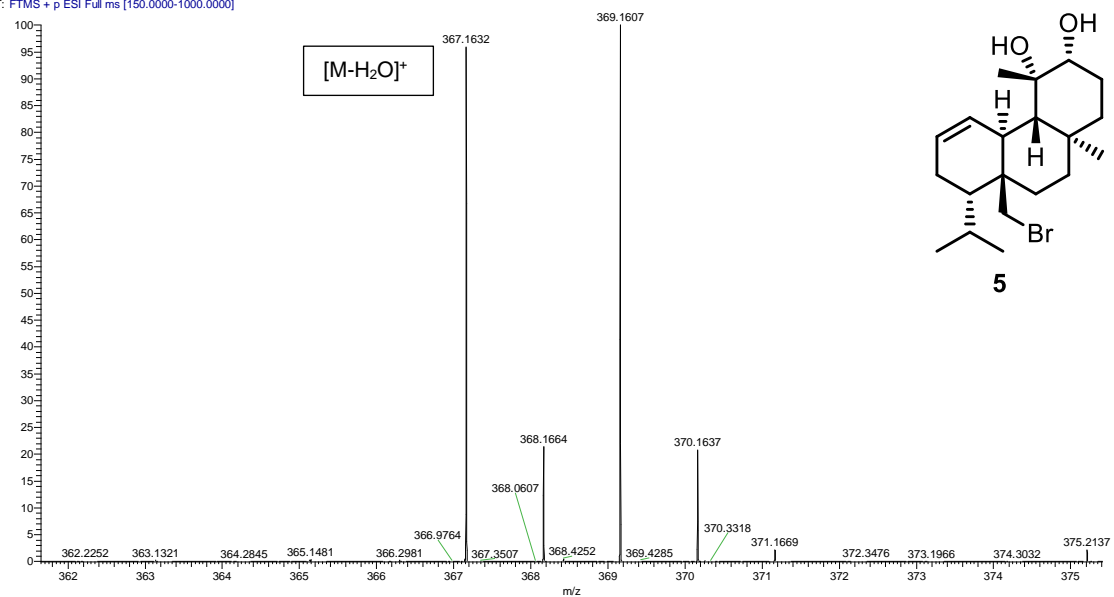


# HRMS spectra of **5**

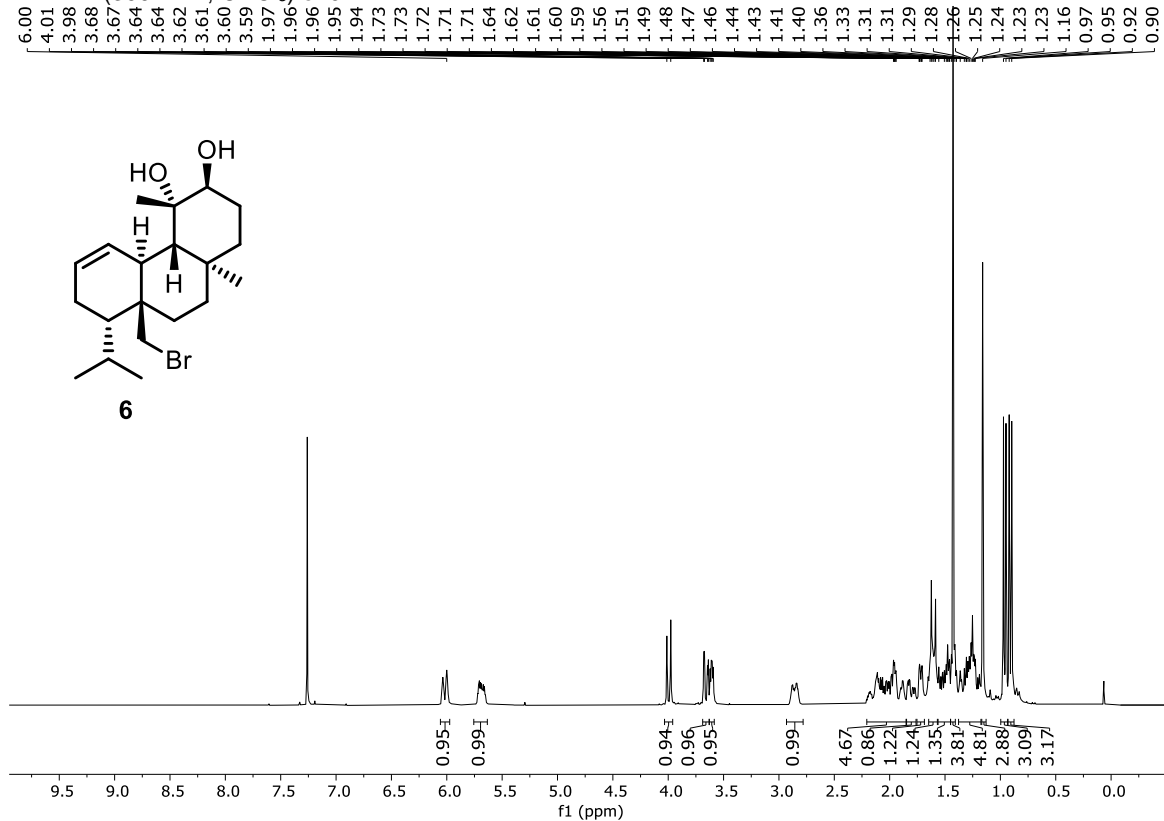
E:\Massa\MF93F11-23\_10\_out2

11/10/21 16:50:21

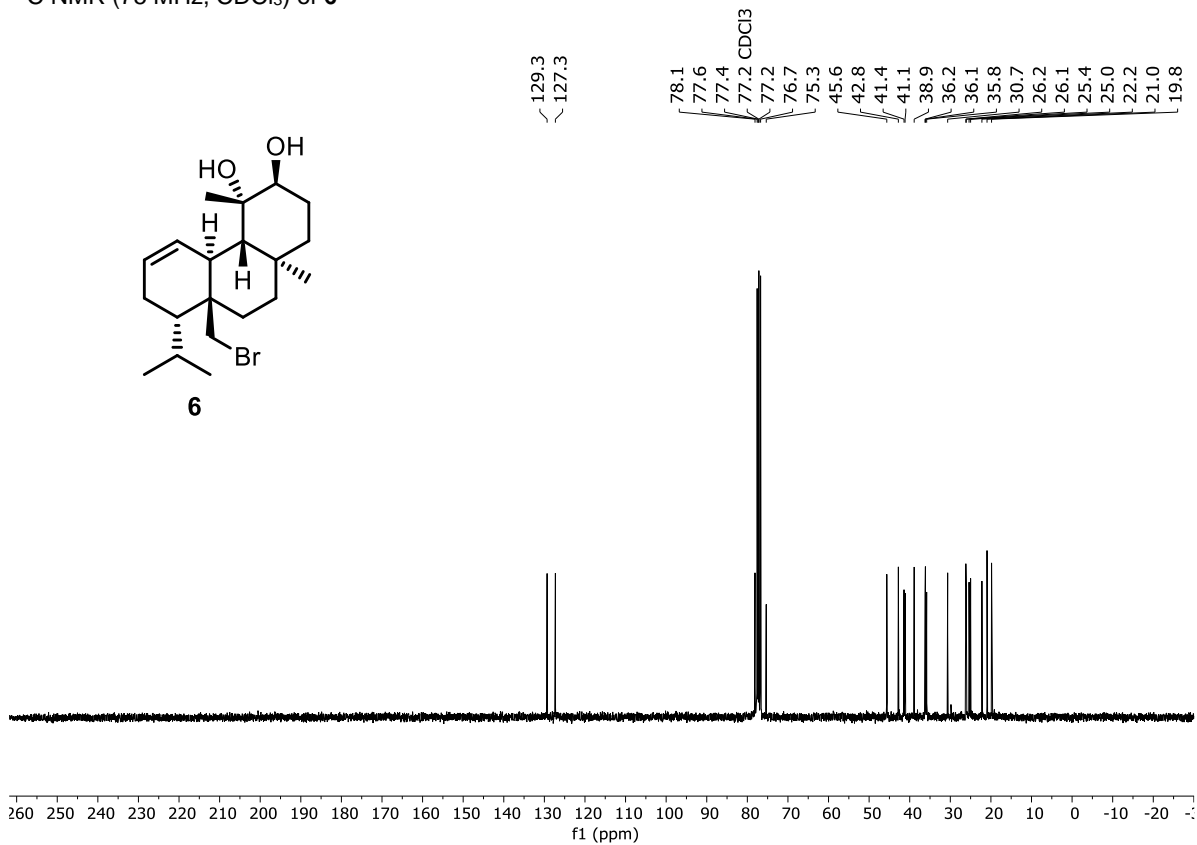
MF93F11-23\_10\_out2 #2145-2341 RT: 13.47-14.51 AV: 197 NL: 1.09E  
T: FTMS + p ESI Full ms [150.0000-1000.0000]



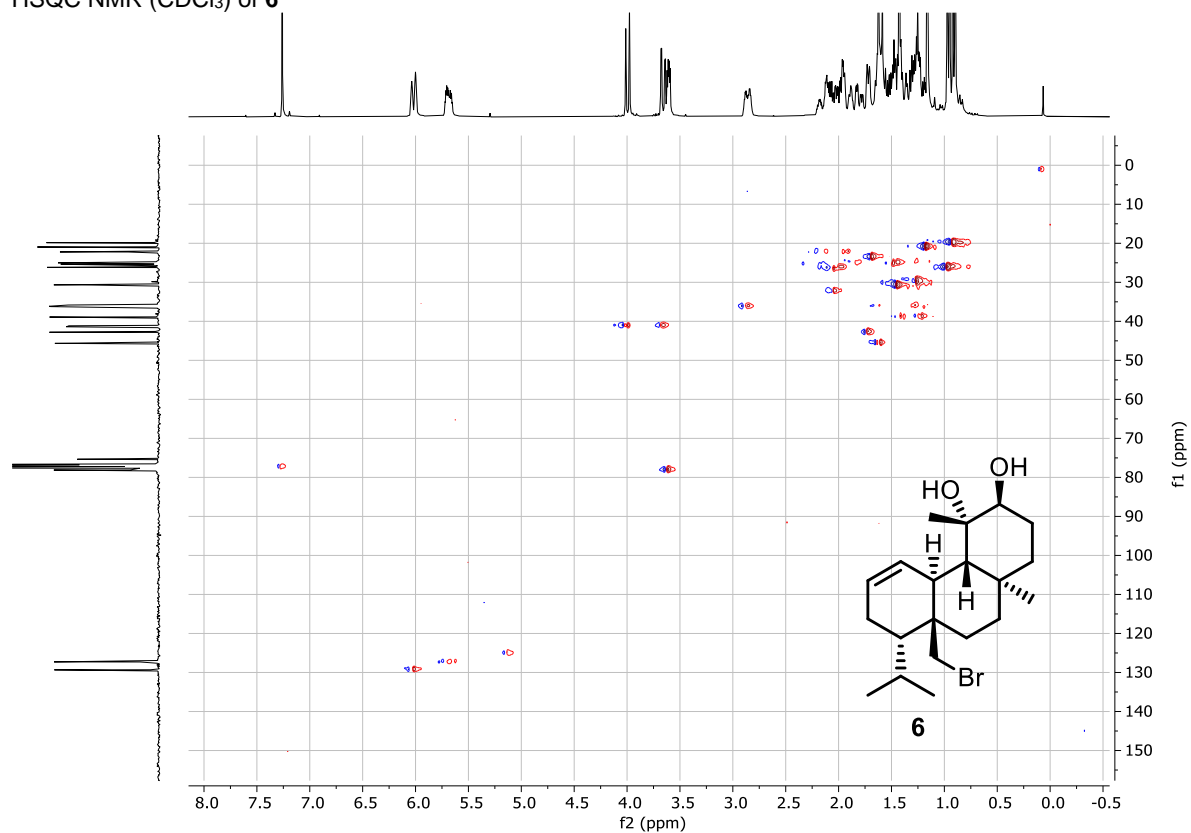
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) of **6**



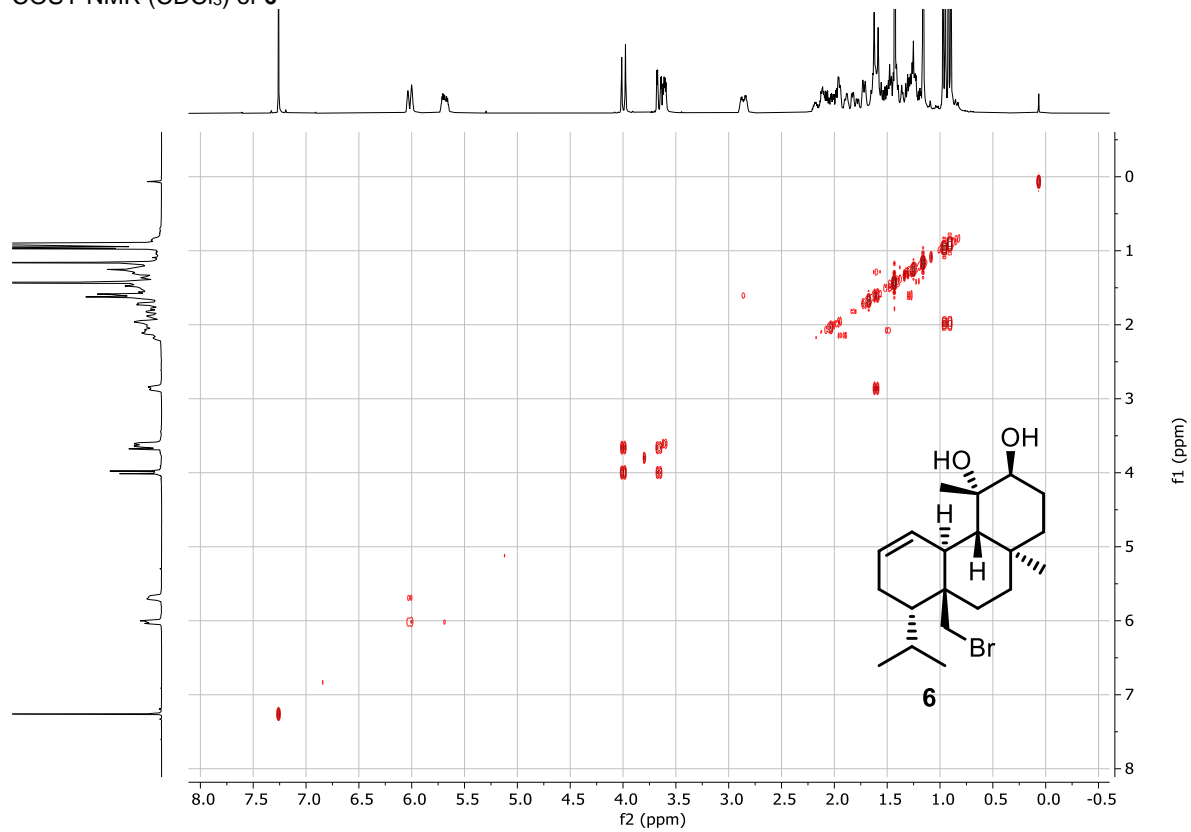
<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) of **6**



HSQC NMR (CDCl<sub>3</sub>) of **6**



COSY NMR (CDCl<sub>3</sub>) of **6**



# HRMS spectra of 6

E:\Massa\MF93F28-38\_10\_out2

11/10/21 17:15:51

MF93F28-38\_10\_out2 #1713-1918 RT: 10.94-12.04 AV: 206 NL: 5.26E  
T: FTMS + p ESI Full ms [150.0000-1000.0000]

