

# Sesquiterpene Coumarin Ethers with Selective Cytotoxic Activities from the Roots of *Ferula huber-morathii* Peşmen (Apiaceae) and Unequivocal Determination of the Absolute Stereochemistry of Samarcandin

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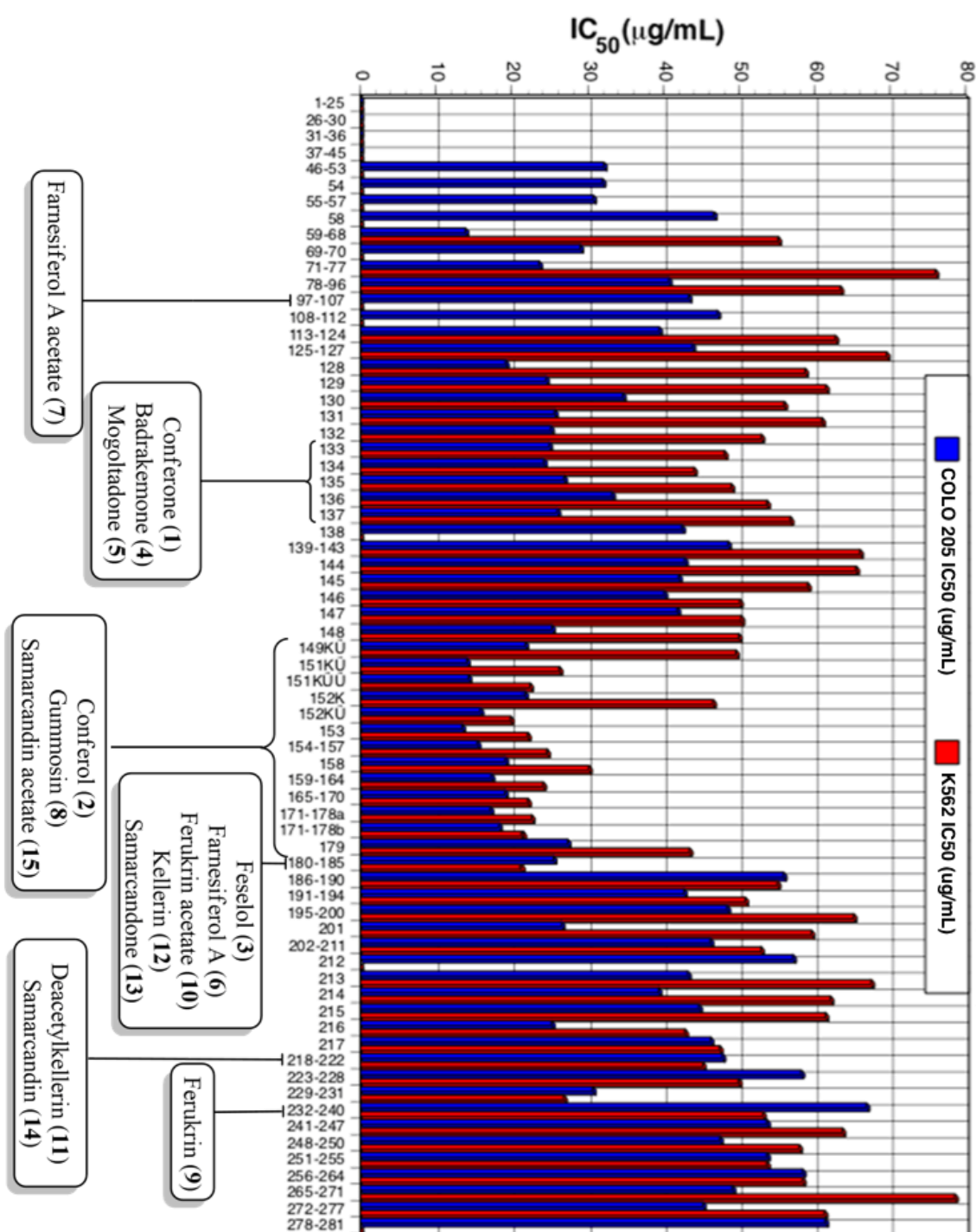
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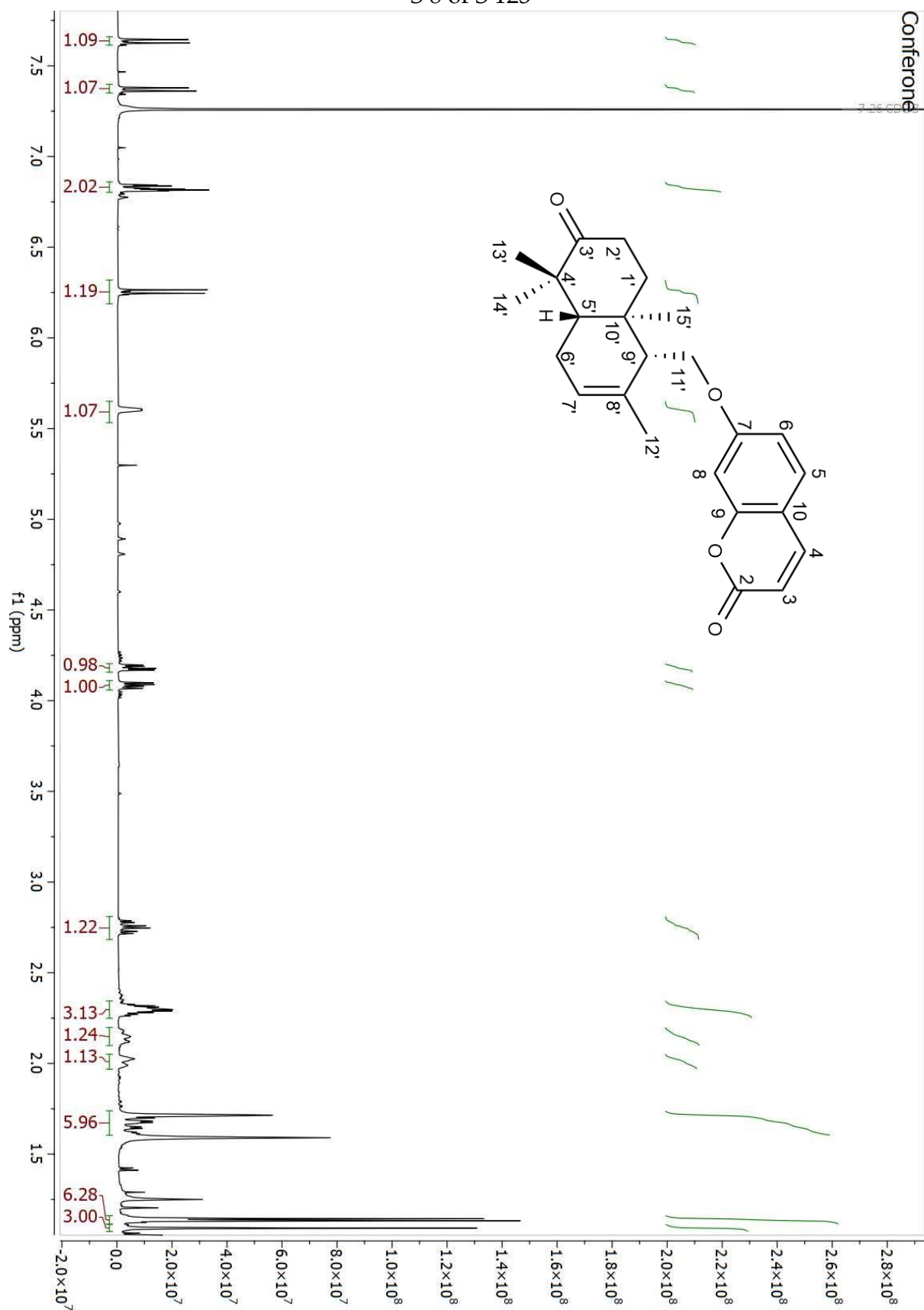
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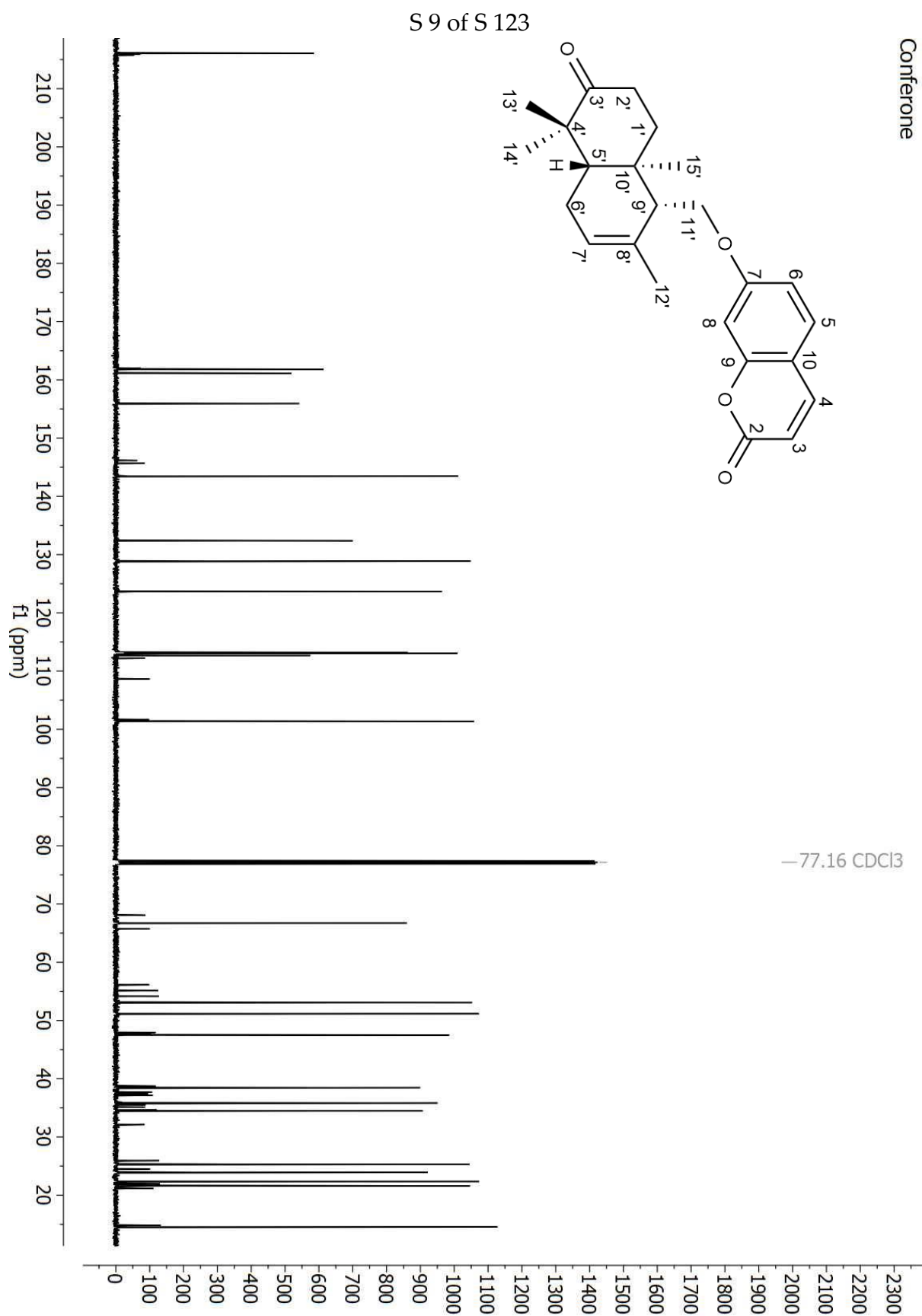
**Figure S1.** Bioactivity-guided isolation scheme for the cytotoxic sesquiterpene coumarins of the dichloromethane root extract of *Ferula huber-morathii*

**Table S1.** Physical appearance and comparison of optical rotation values of isolated terpenoid coumarins with literature data

Compound	Physical appearance	Isolated Comp.	Lit. Reference	
		$[\alpha]_{\text{D}}^{\text{temp.}}$ (Solv.)	$[\alpha]_{\text{D}}^{\text{temp.}}$ (Solv.)	Ref.
Conferone (1)	White powder	-55.0 <sup>°24</sup> (CH <sub>2</sub> Cl <sub>2</sub> )	-51.0 <sup>°20</sup> (EtOH)	[1]
Conferol (2)	White powder	-55.1 <sup>°24</sup> (CH <sub>2</sub> Cl <sub>2</sub> )	-84.2 <sup>°20</sup> (CHCl <sub>3</sub> )	[1]
Feselol (3)	Gum	-60.9 <sup>°24</sup> (CH <sub>2</sub> Cl <sub>2</sub> )	-98.5 <sup>°20</sup> (EtOH)	[1]
Badrekemone (4)	White powder	-39.7 <sup>°24</sup> (CH <sub>2</sub> Cl <sub>2</sub> )	-42.0 <sup>°22</sup> (CHCl <sub>3</sub> )	[1]
Mogoltadone (5)	White powder	-19.4 <sup>°25</sup> (CH <sub>2</sub> Cl <sub>2</sub> )	-41.7 <sup>°21</sup> (CHCl <sub>3</sub> )	[1]
Farnesiferol A (6)	Gum	-50.1 <sup>°24</sup> (CH <sub>2</sub> Cl <sub>2</sub> )	-55.0 <sup>°25</sup> (CHCl <sub>3</sub> )	[1]
Farnesiferol A acetate (7)	Gum	-27.3 <sup>°24</sup> (CH <sub>2</sub> Cl <sub>2</sub> )	-55.0 <sup>°22</sup> (CHCl <sub>3</sub> )	[2]
Gummosin (8)	Gum	-37.0 <sup>°24</sup> (CH <sub>2</sub> Cl <sub>2</sub> )	-54.0 <sup>°25</sup> (CHCl <sub>3</sub> )	[1]
Ferukrin (9)	White powder	+25.3 <sup>°24</sup> (CH <sub>2</sub> Cl <sub>2</sub> )	+30.0 <sup>°22</sup> (EtOH)	[1]
Ferukrin acetate (10)	White powder	+7.6 <sup>°24</sup> (CH <sub>2</sub> Cl <sub>2</sub> )	+20.0 <sup>°22</sup> (EtOH)	[1]
Deacetylkellerin (11)	White powder	+25.3 <sup>°24</sup> (CH <sub>2</sub> Cl <sub>2</sub> )	+52.0 <sup>°22</sup> (EtOH)	[1]
Kellerin (12)	White powder	+63.6 <sup>°24</sup> (CH <sub>2</sub> Cl <sub>2</sub> )	+66.4 <sup>°20</sup> (EtOH)	[1]
Samarcandone (13)	White powder	+10.0 <sup>°24</sup> (CH <sub>2</sub> Cl <sub>2</sub> )	+25.0 <sup>°25</sup> (EtOH)	[1]
Samarcandin (14)	Gum	+6.8 <sup>°24</sup> (CH <sub>2</sub> Cl <sub>2</sub> )	+30.0 <sup>°25</sup> (EtOH)	[1]
Samarcandin acetate (15)	Gum	-4.3 <sup>°24</sup> (CH <sub>2</sub> Cl <sub>2</sub> ) +23.9 <sup>°23</sup> (EtOH)	+29.4 <sup>°25</sup> (EtOH)	[1]

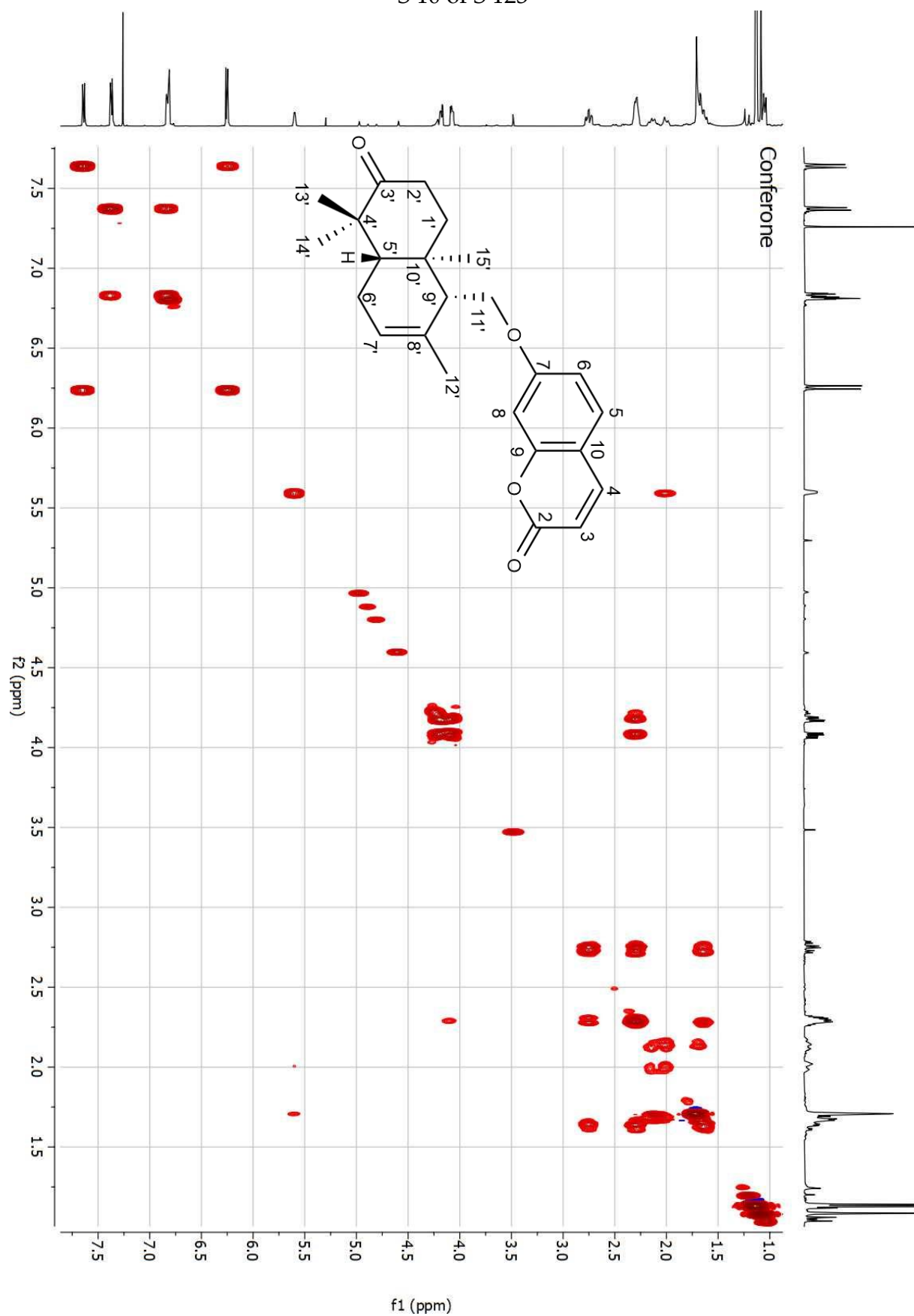


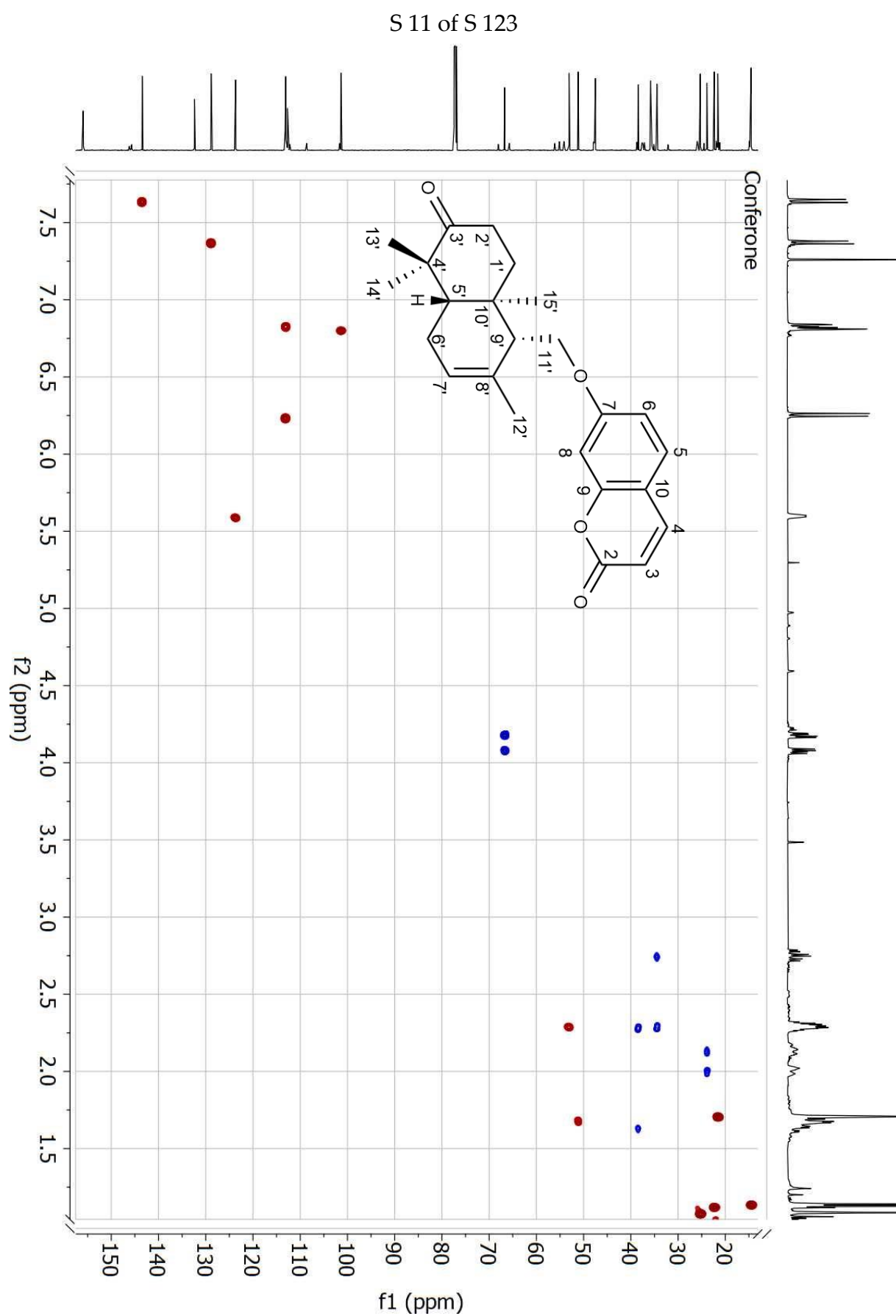
**Figure S2.** <sup>1</sup>H-NMR spectrum (500 MHz, CDCl<sub>3</sub>) of conferone (1)



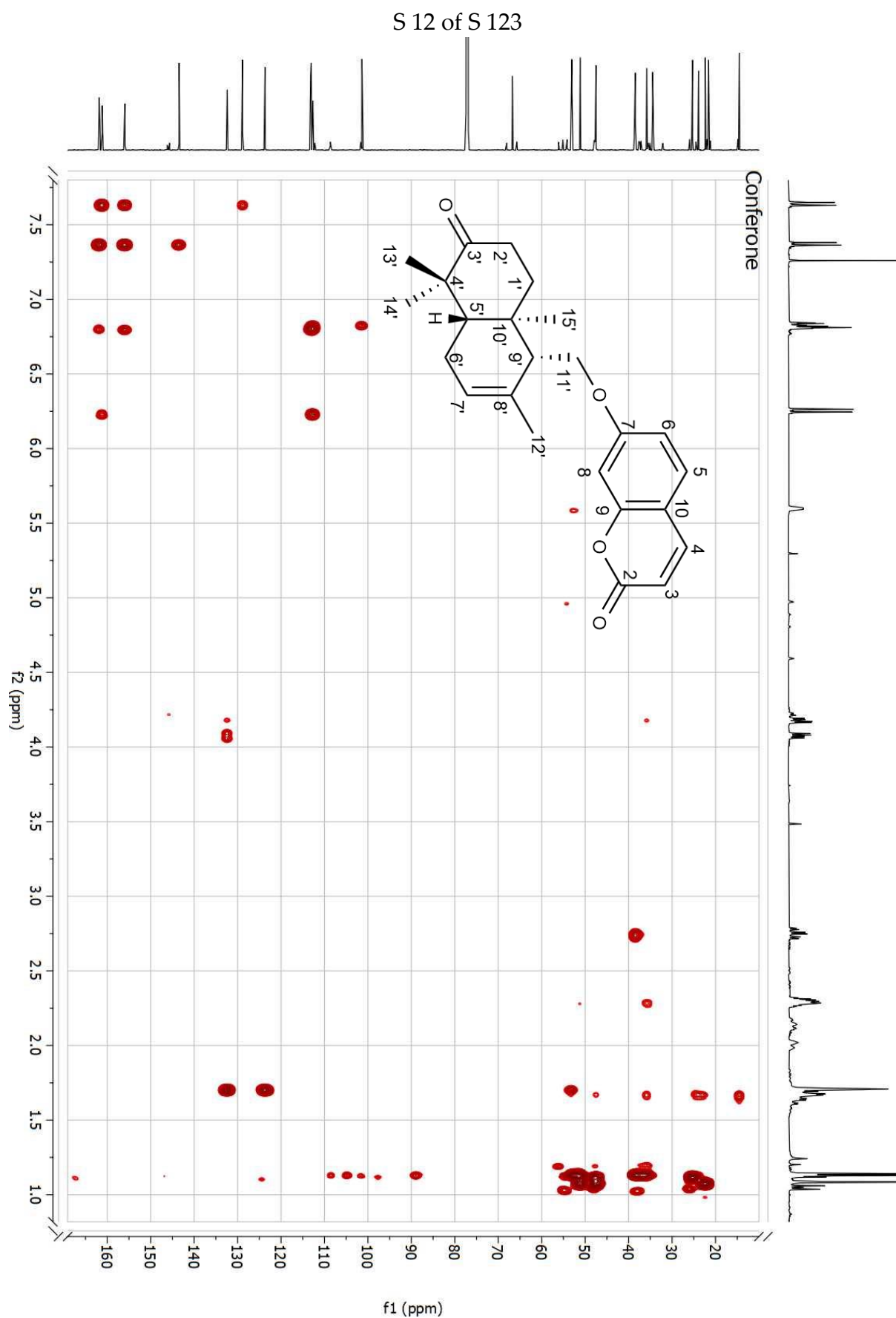
**Figure S3.**  $^{13}\text{C}$ -NMR spectrum (125 MHz,  $\text{CDCl}_3$ ) of conferone (1)

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**Figure S4.**  $^1\text{H}$ - $^1\text{H}$  COSY spectrum ( $\text{CDCl}_3$ ) of conferone (1)



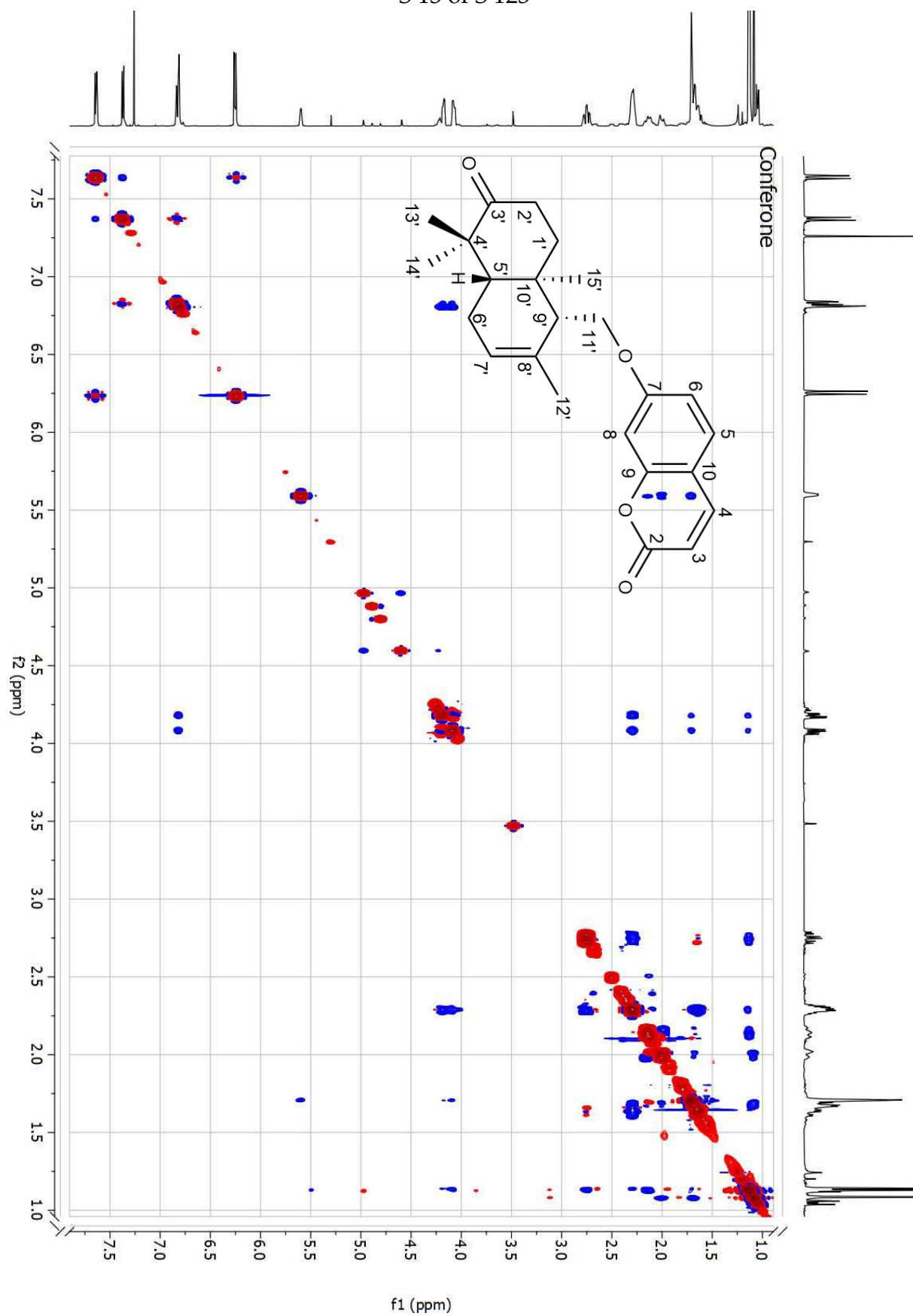
**Figure S5.** HSQC spectrum (CDCl<sub>3</sub>) of conferone (1)

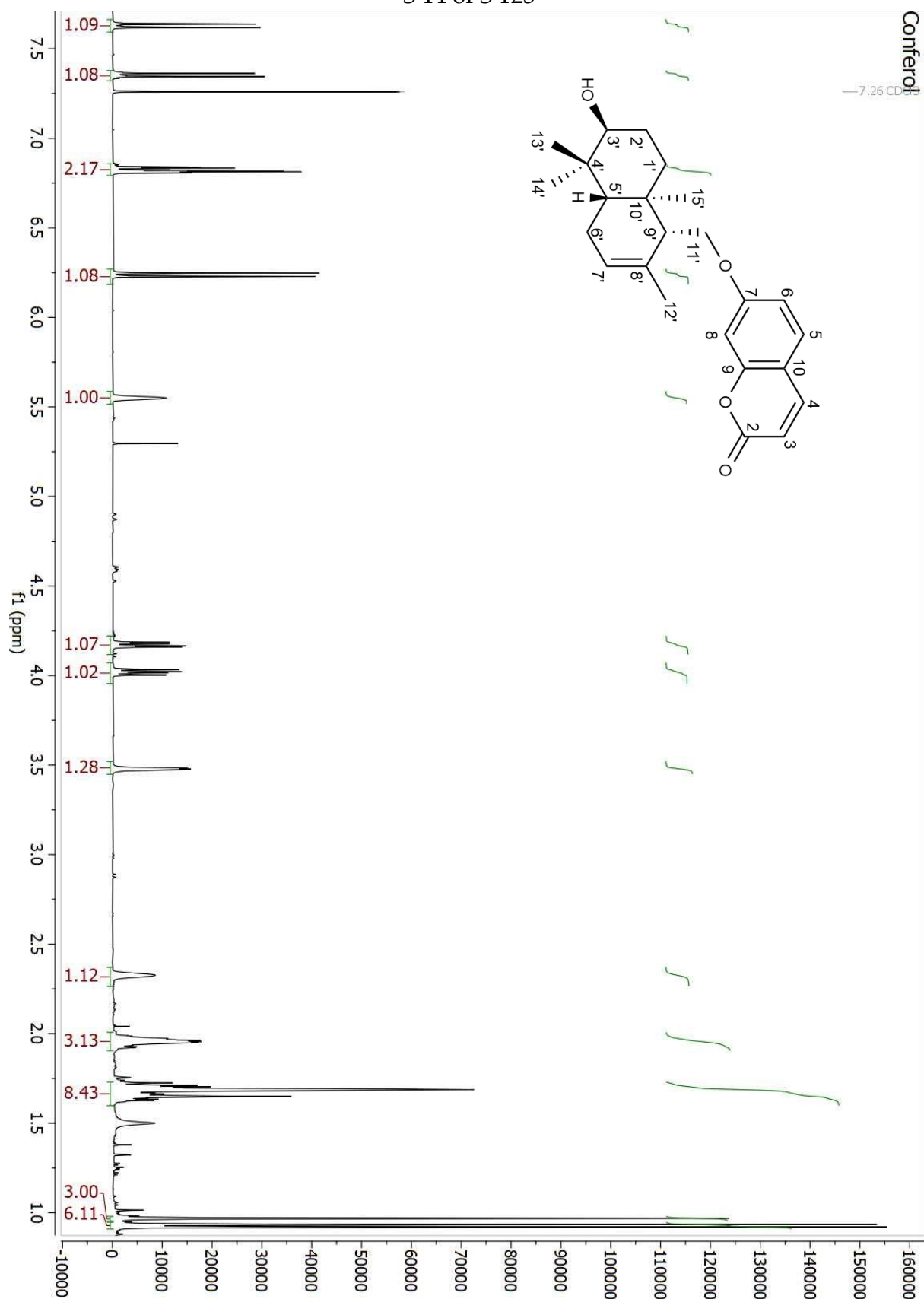


**Figure S6.** HMBC spectrum (CDCl<sub>3</sub>) of conferone (1)

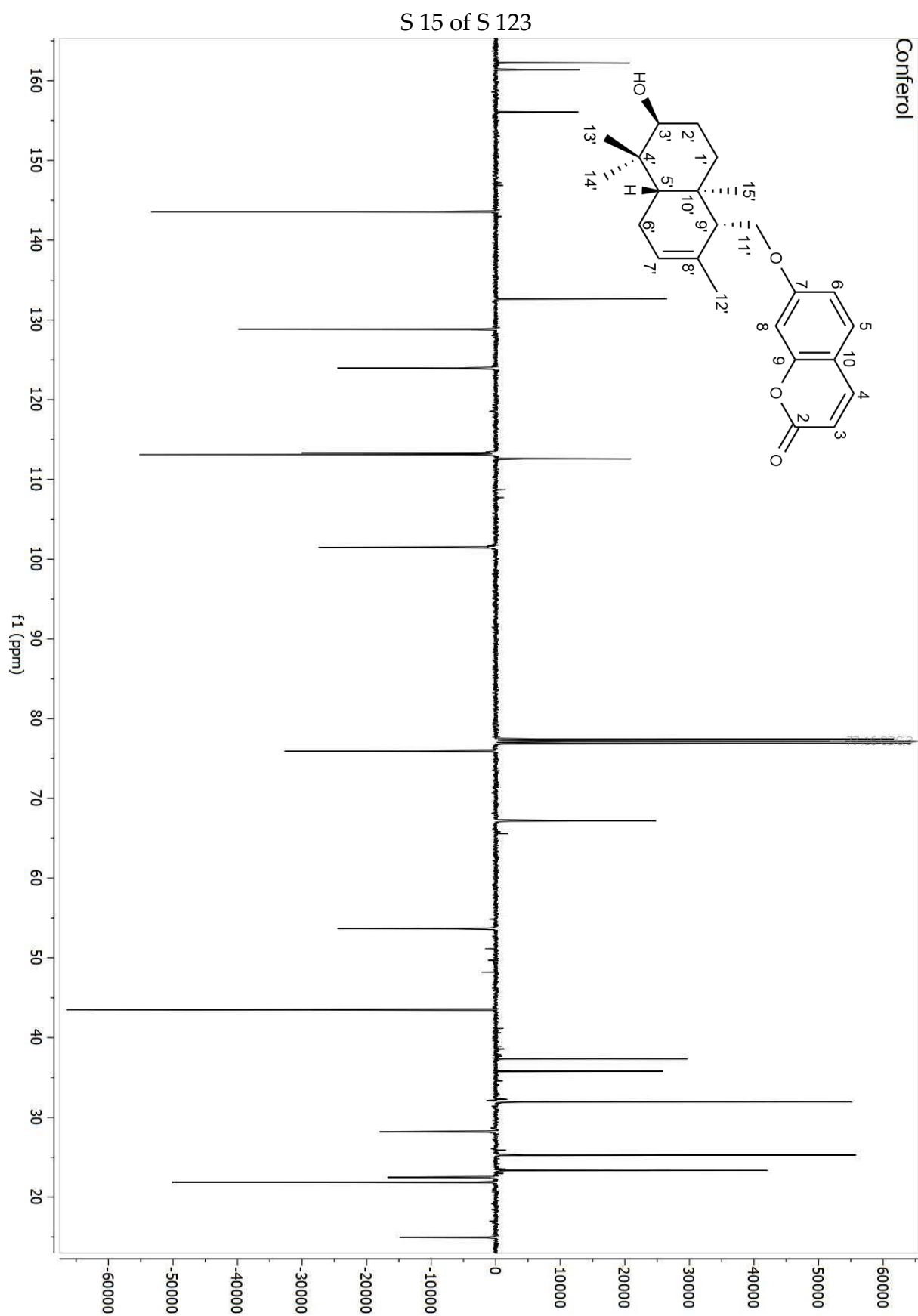


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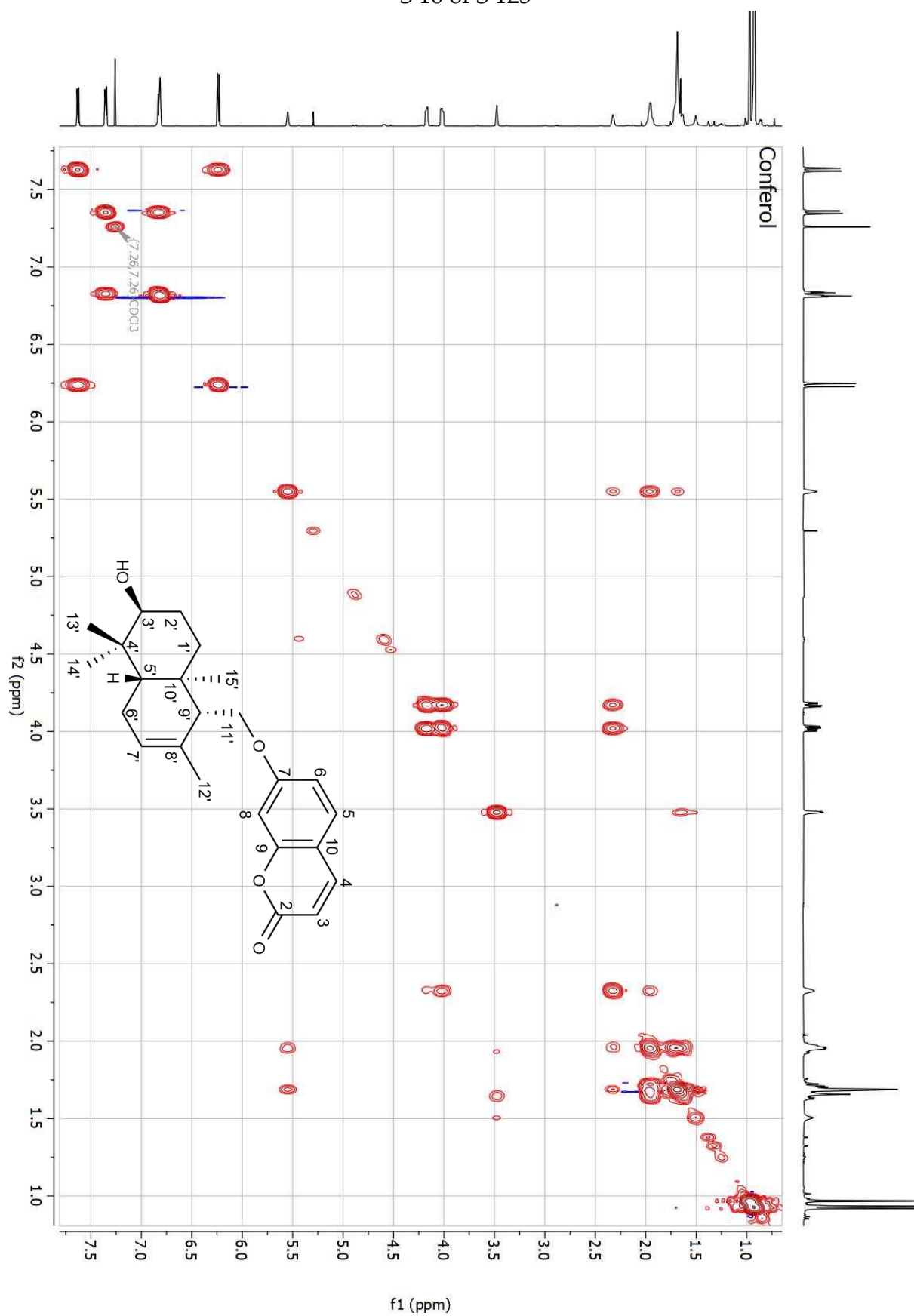
**Figure S7.** NOESY spectrum (CDCl<sub>3</sub>) of conferone (**1**)

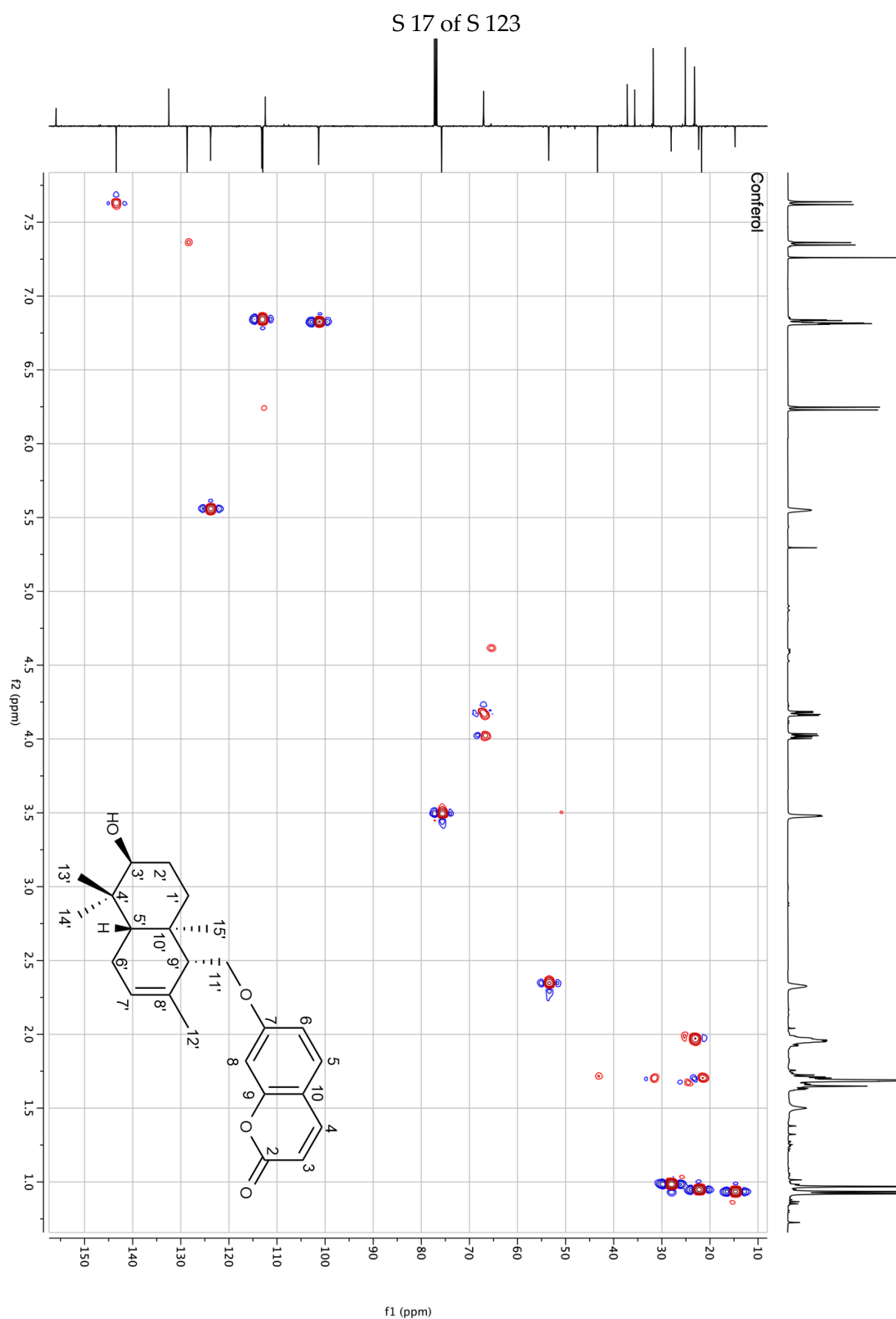


**Figure S8.** <sup>1</sup>H-NMR spectrum (500 MHz, CDCl<sub>3</sub>) of conferral (2)

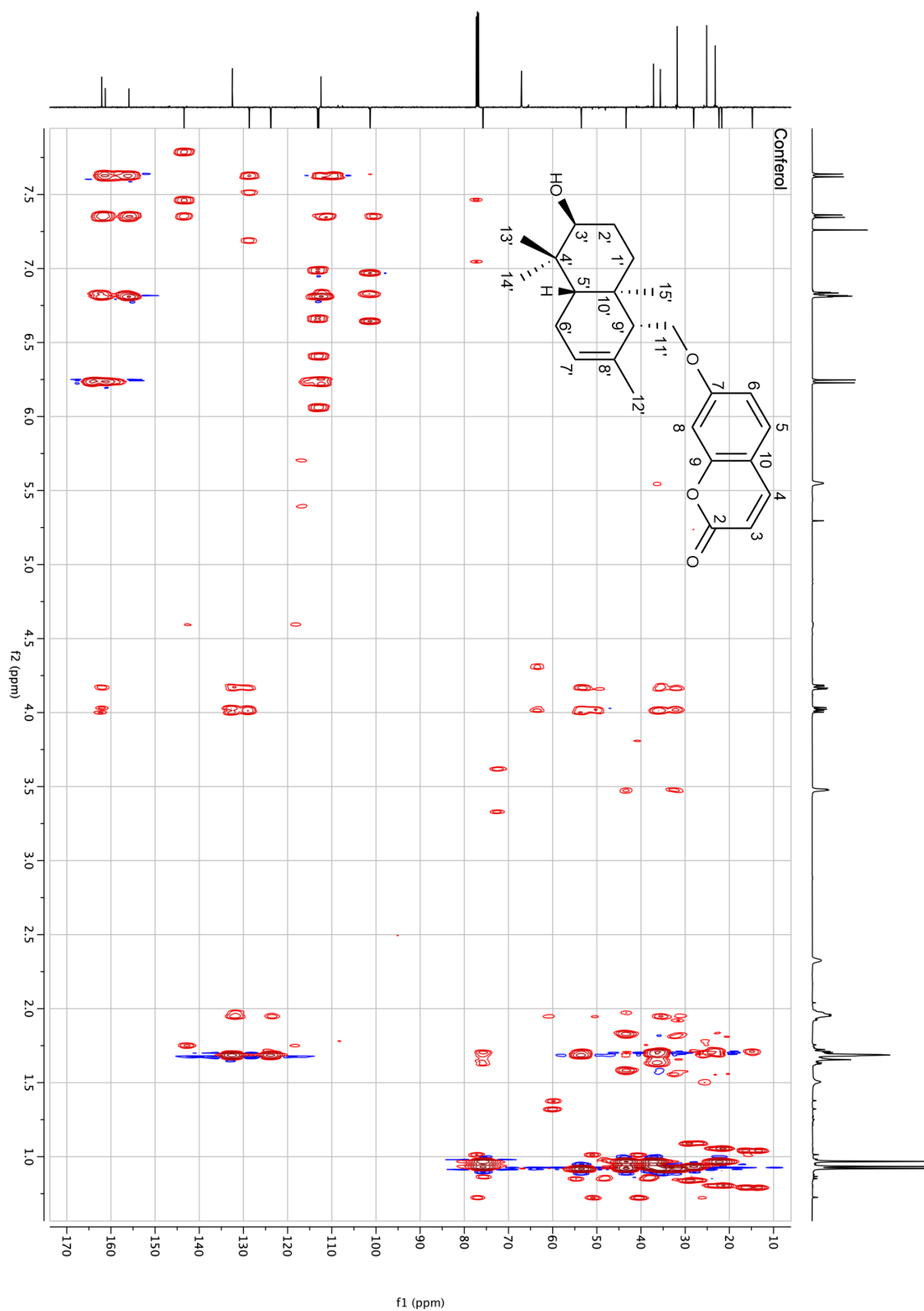


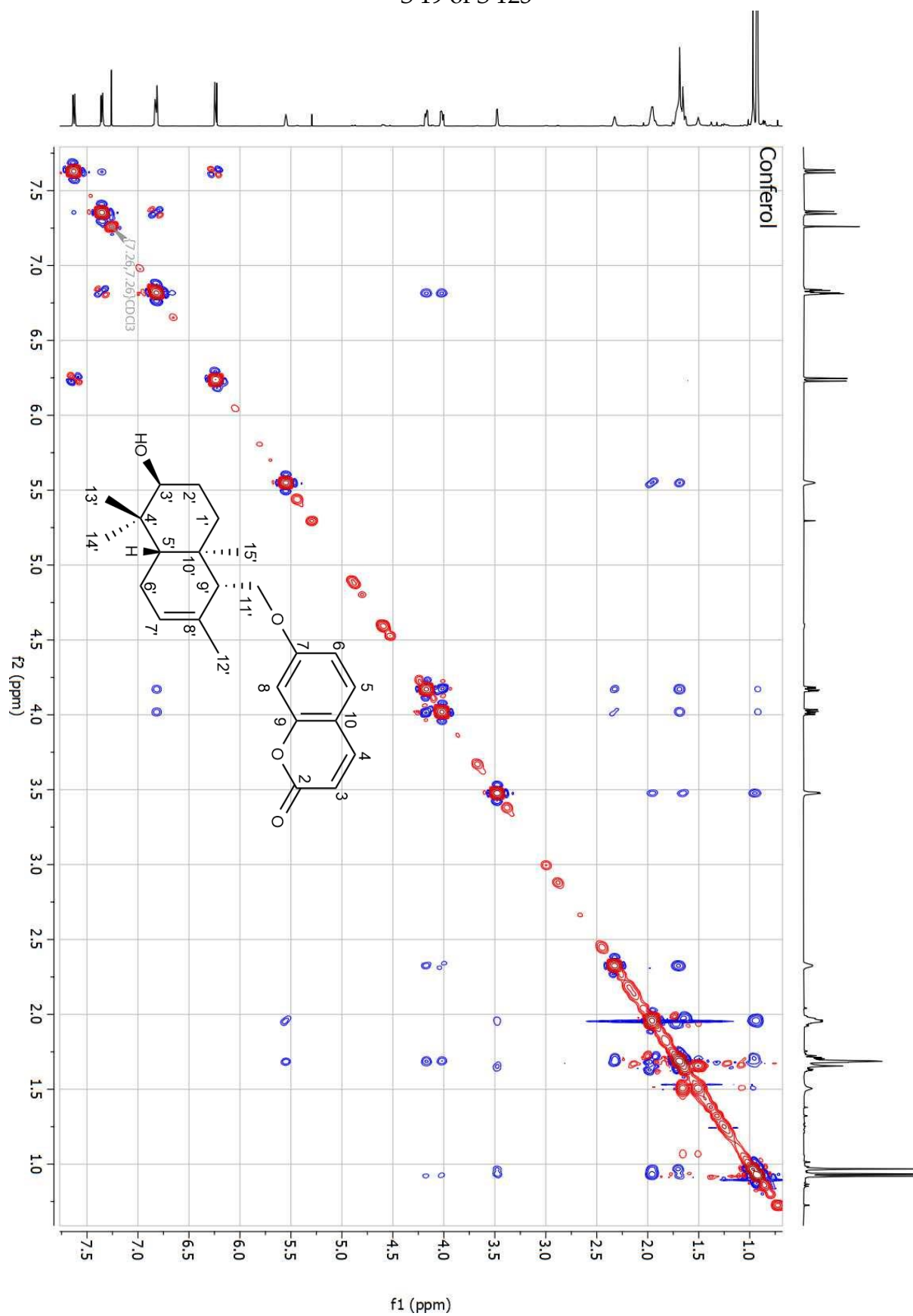
**Figure S9.**  $^{13}\text{C}$ -NMR (APT) spectrum (125 MHz,  $\text{CDCl}_3$ ) of conferol (2)

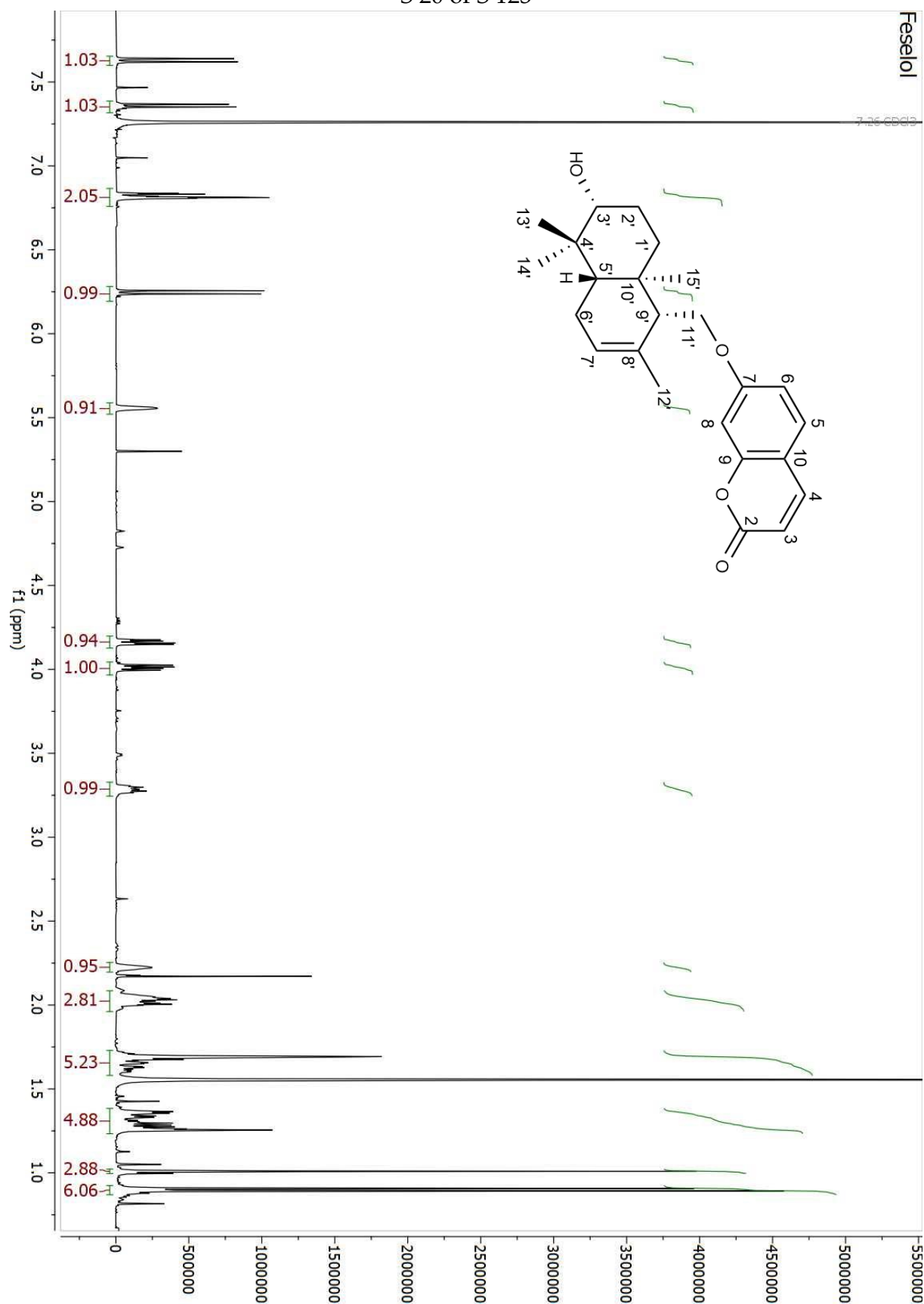
**Figure S10.**  $^1\text{H}$ - $^1\text{H}$  COSY spectrum ( $\text{CDCl}_3$ ) of conferol (2)



**Figure S11.** HSQC spectrum ( $\text{CDCl}_3$ ) of conferyl (2)

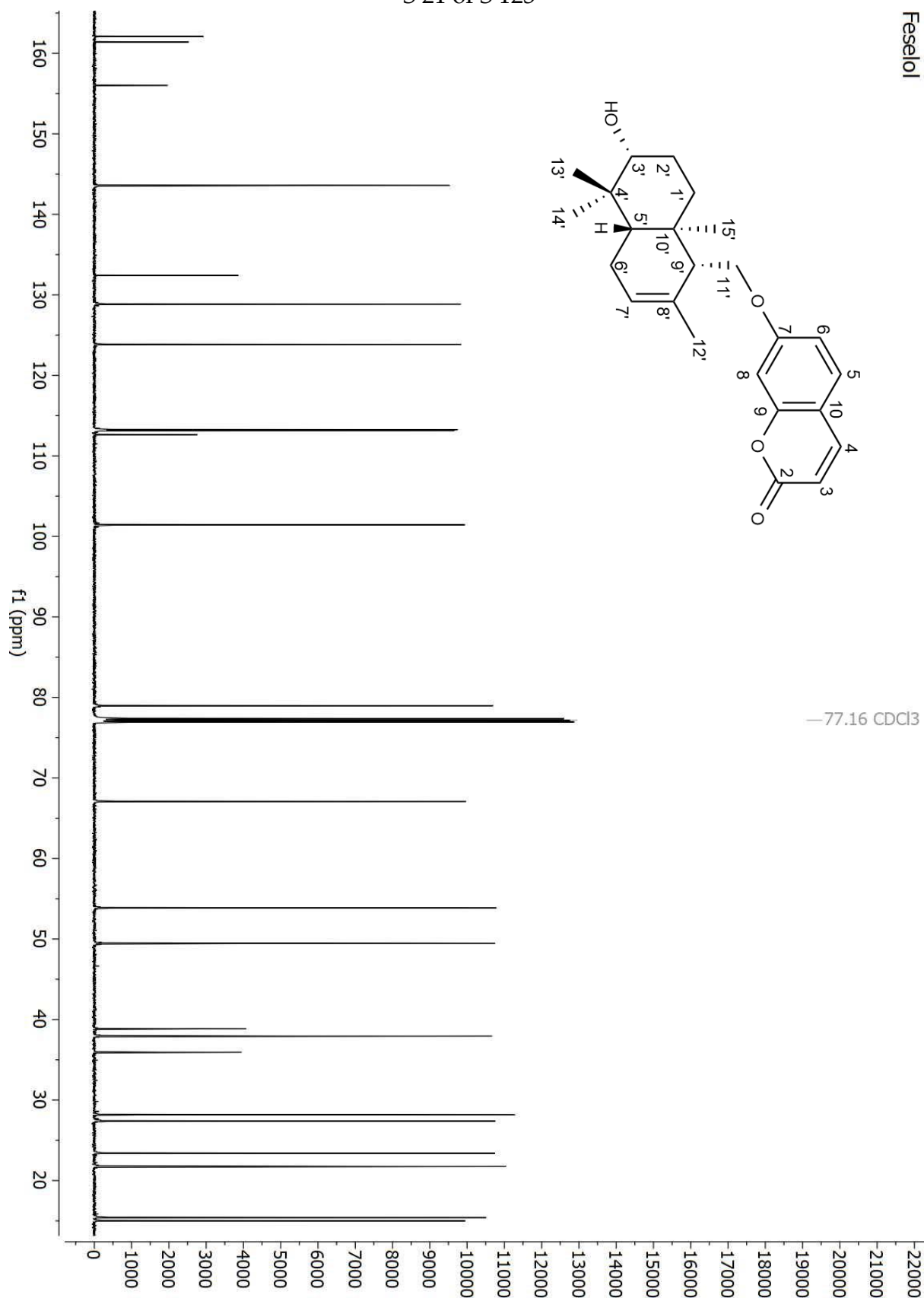
**Figure S12.** HMBC spectrum ( $\text{CDCl}_3$ ) of conferol (2)

**Figure S13.** NOESY spectrum (CDCl<sub>3</sub>) of conferol (2)



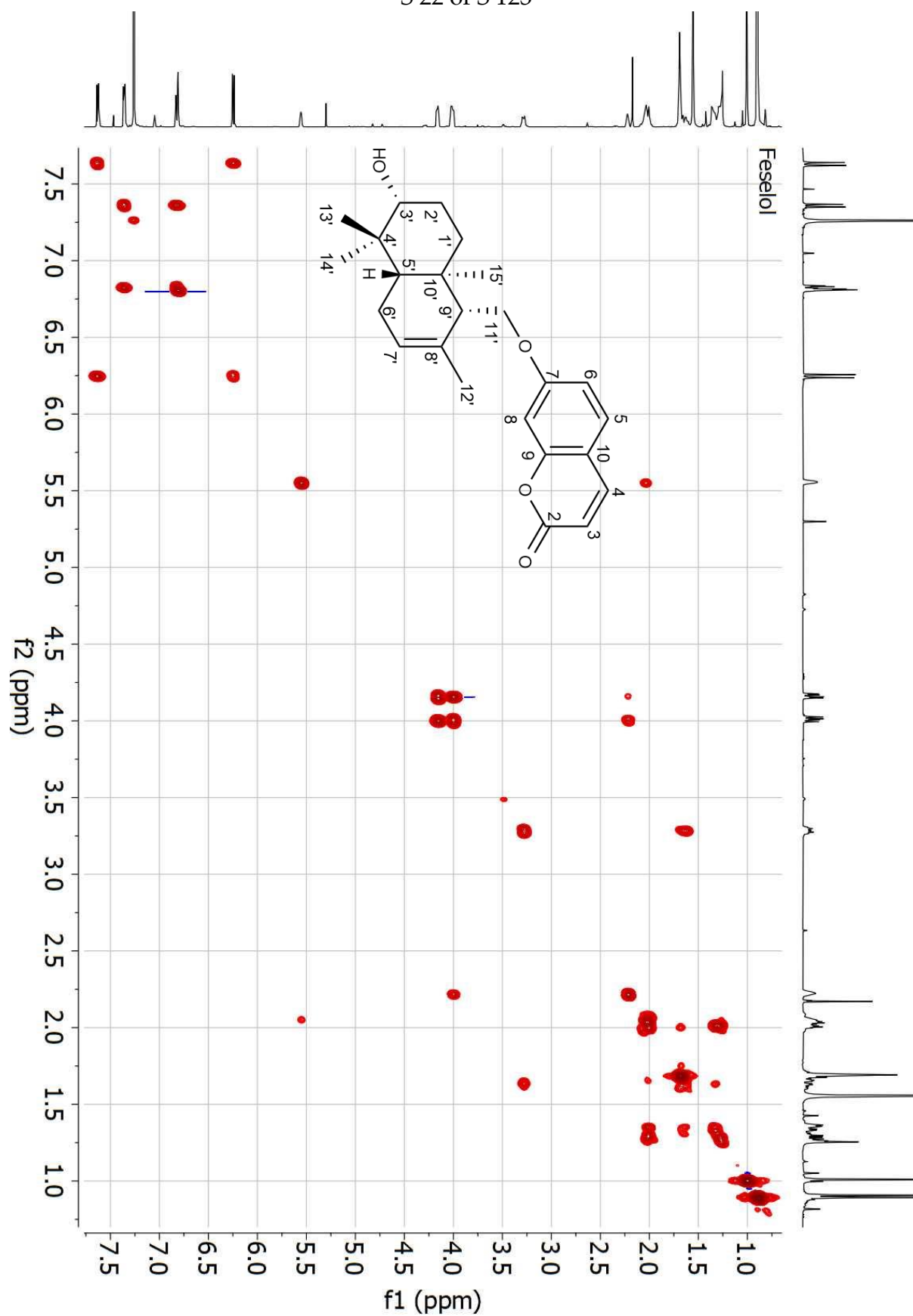
**Figure S14.** <sup>1</sup>H-NMR spectrum (500 MHz, CDCl<sub>3</sub>) of feselol (3)

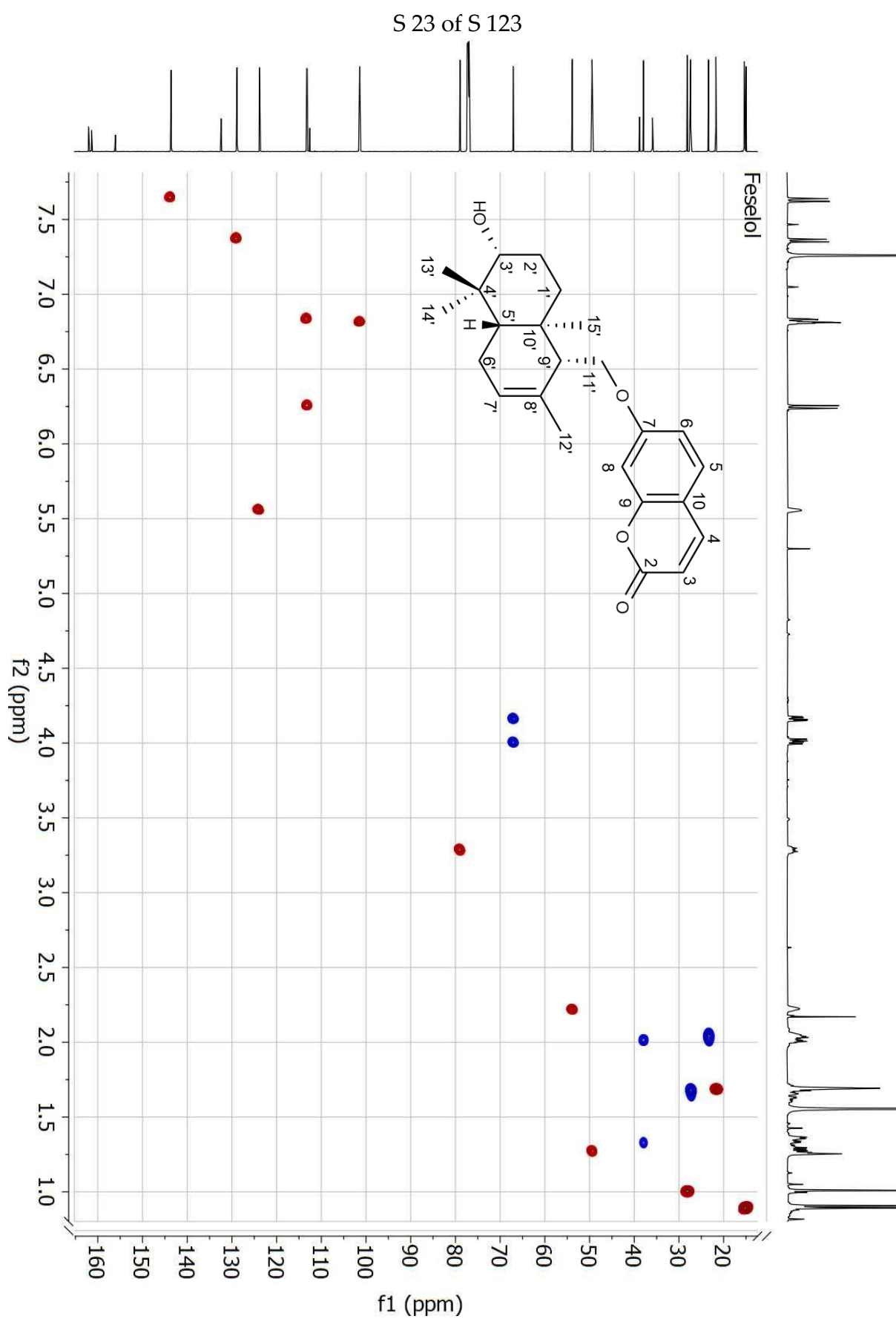




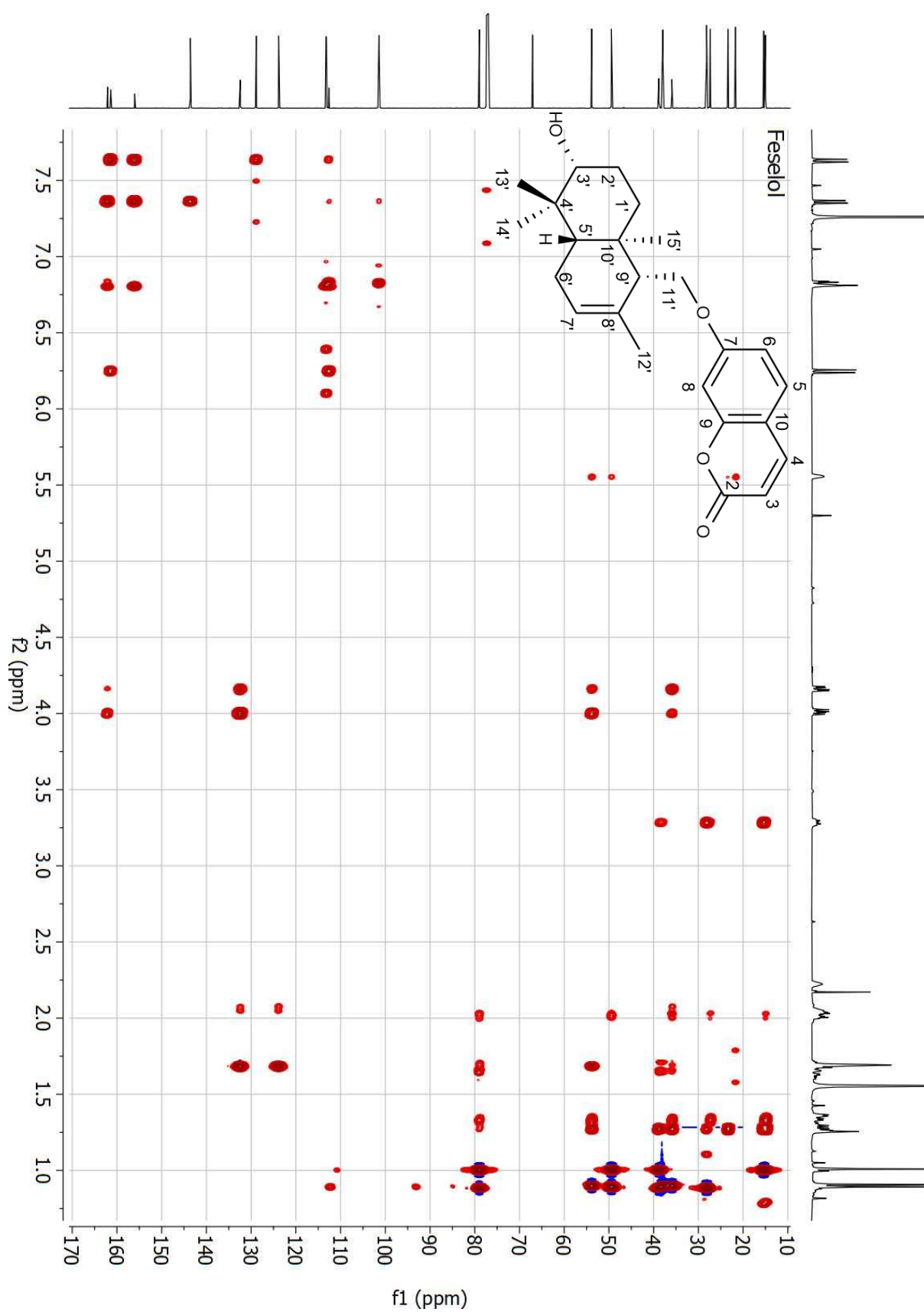
**Figure S15.** <sup>13</sup>C-NMR spectrum (125 MHz, CDCl<sub>3</sub>) of feselol (3)

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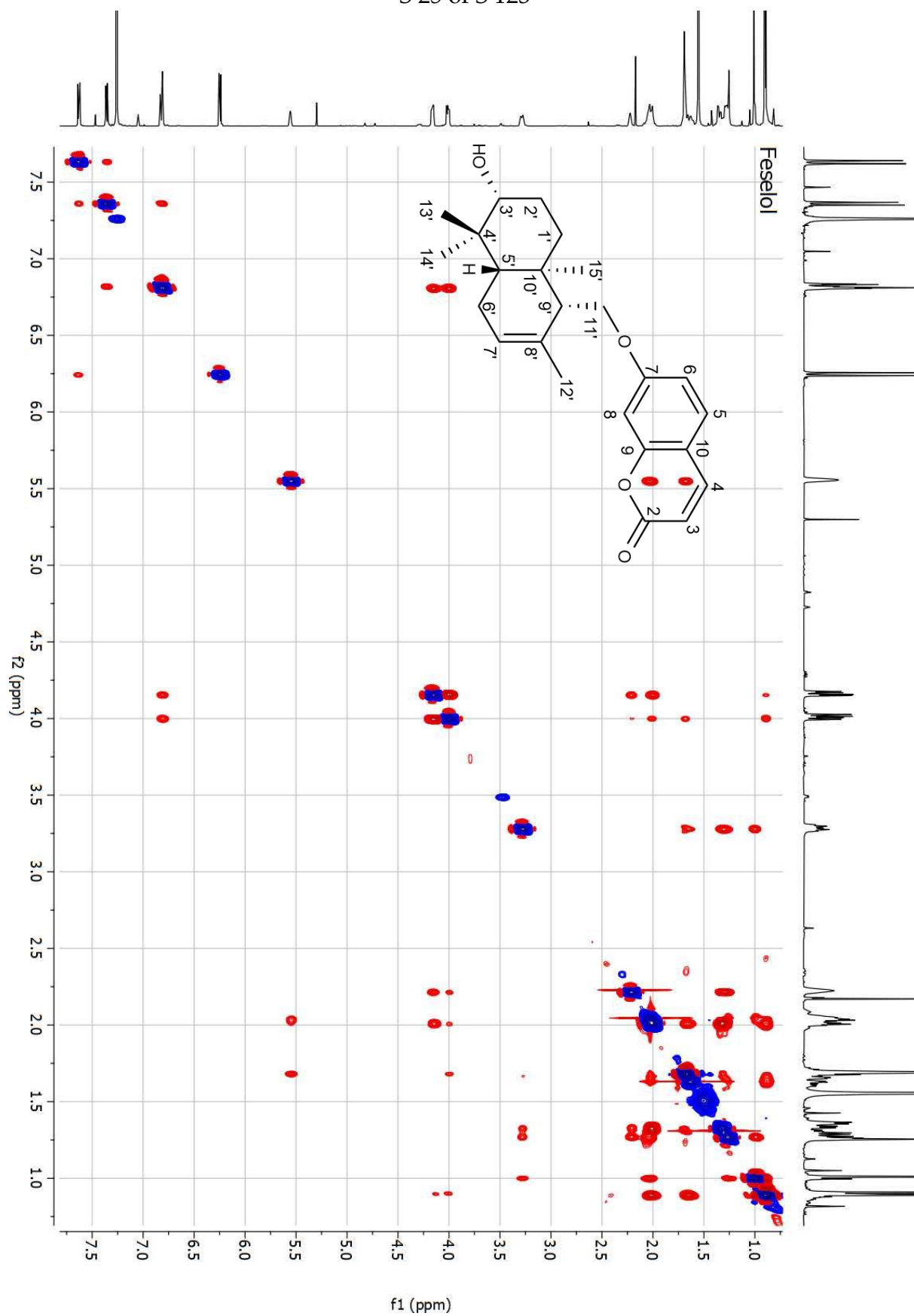
**Figure S16.**  $^1\text{H}$ - $^1\text{H}$  COSY spectrum ( $\text{CDCl}_3$ ) of fesolol (3)

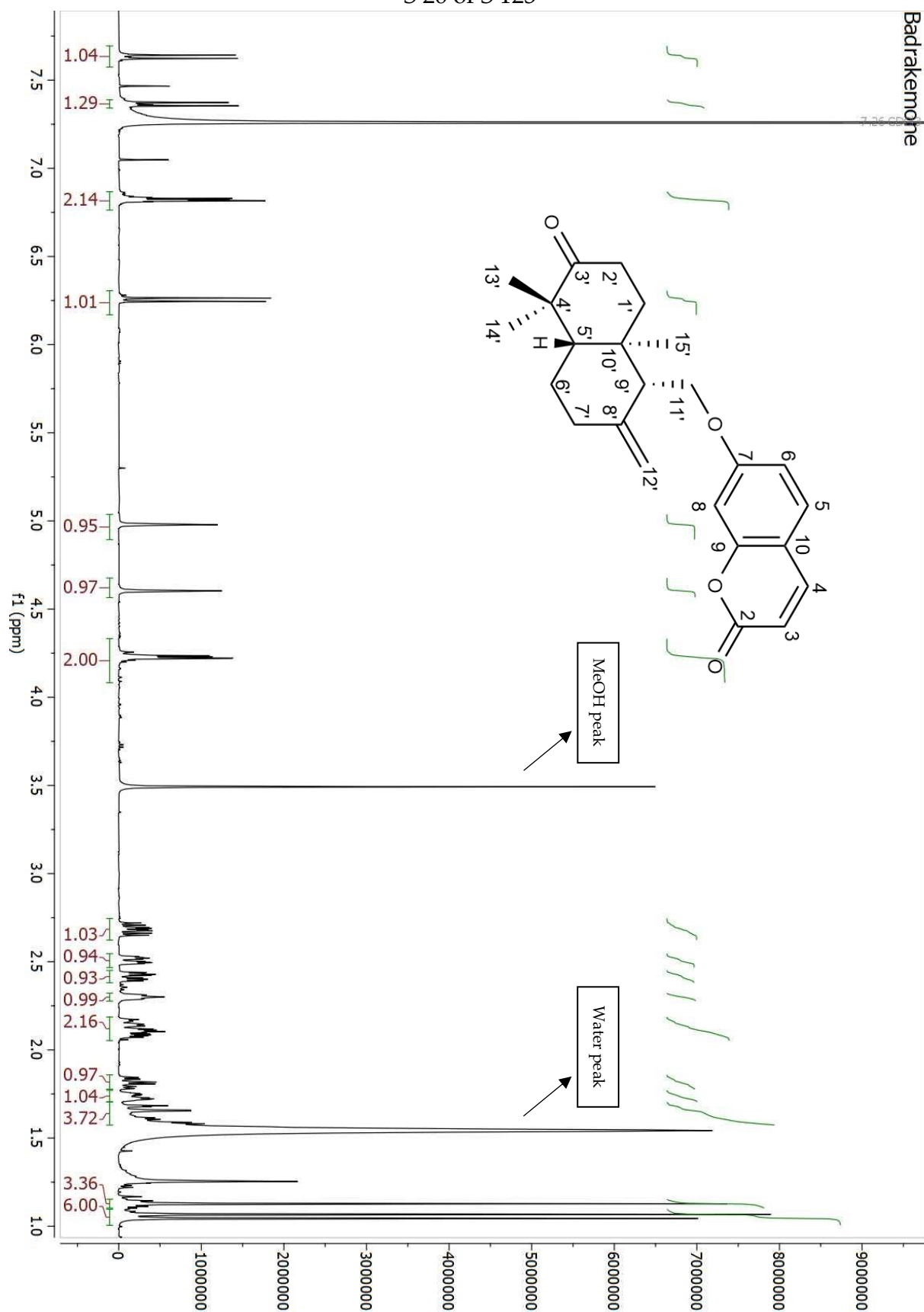


**Figure S17.** HSQC spectrum (CDCl<sub>3</sub>) of fesolol (3)

**Figure S18.** HMBC spectrum (CDCl<sub>3</sub>) of feselol (3)

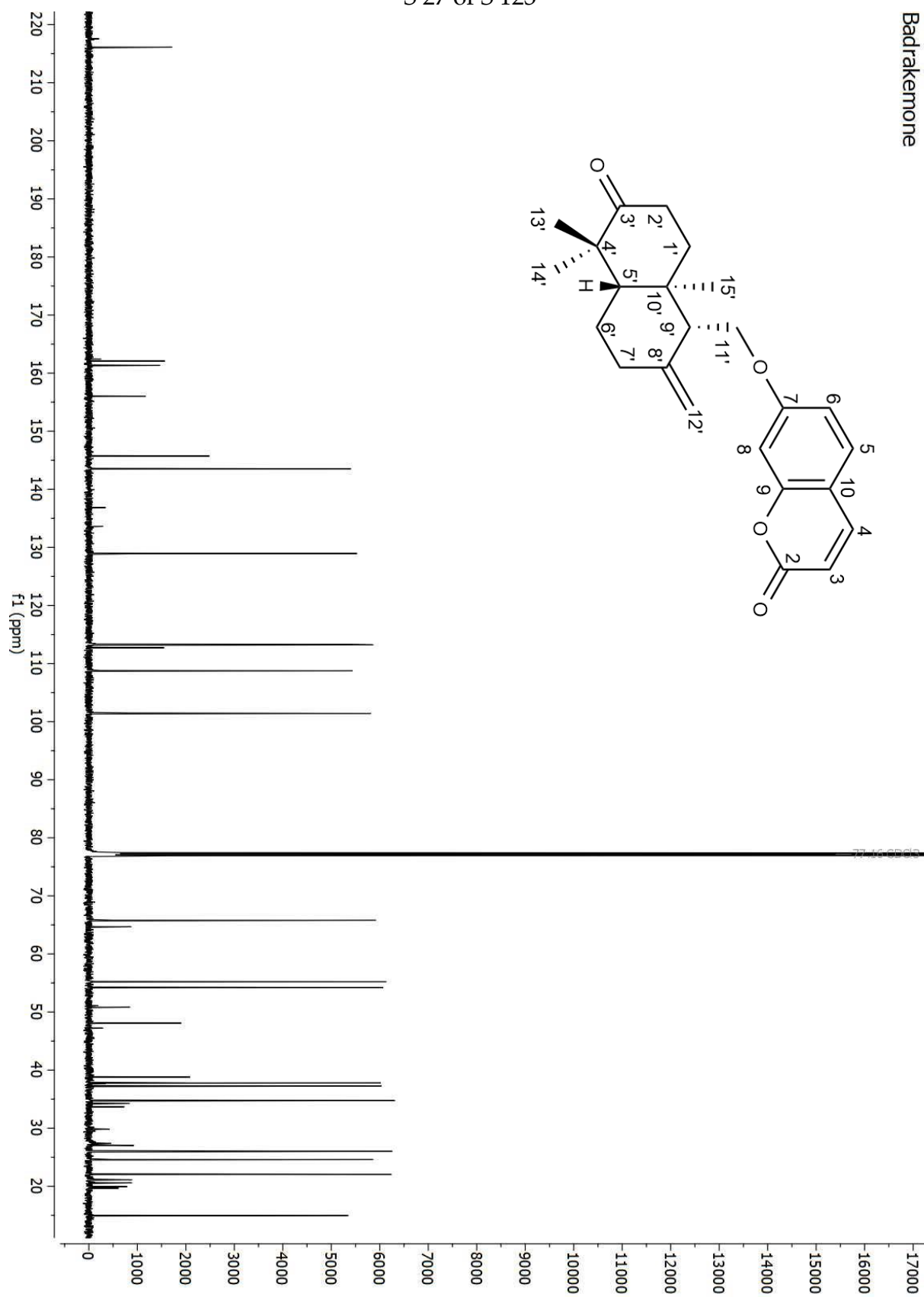
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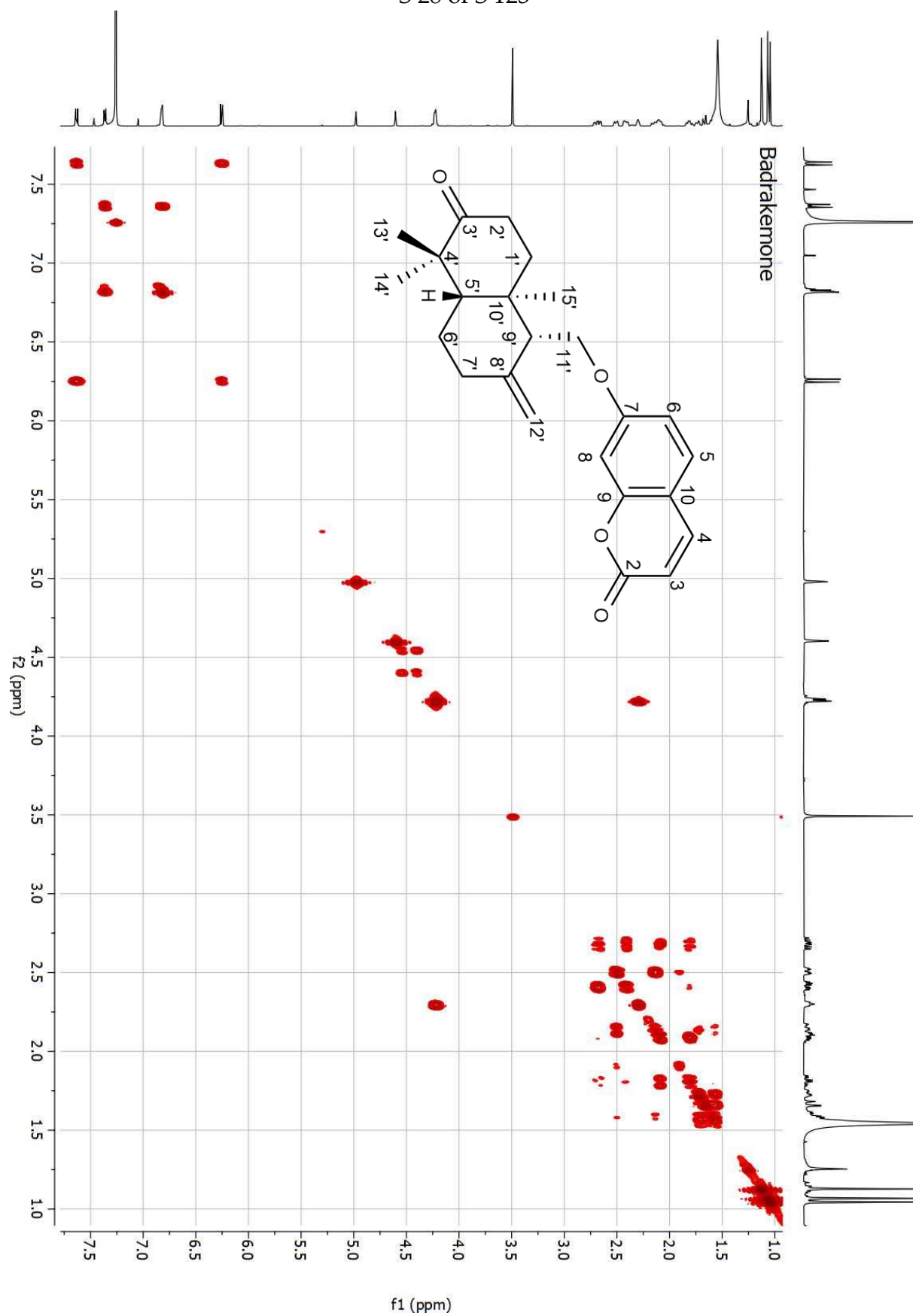
**Figure S19.** NOESY spectrum (CDCl<sub>3</sub>) of fesolol (3)



**Figure S20.**  $^1\text{H}$ -NMR spectrum (500 MHz,  $\text{CDCl}_3$ ) of badrakemone (4)

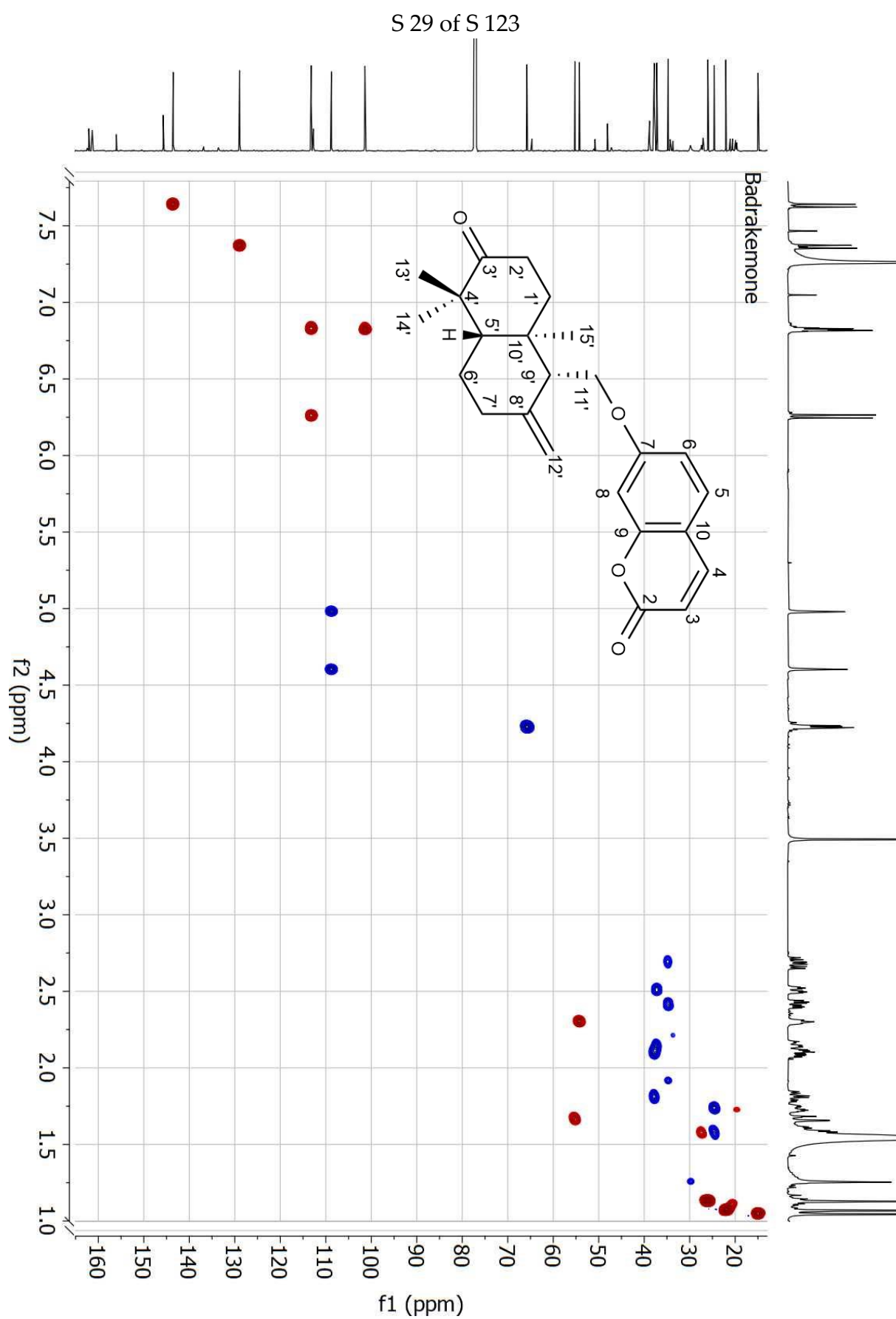
## Badrakemone

**Figure S21.**  $^{13}\text{C}$ -NMR spectrum (125 MHz,  $\text{CDCl}_3$ ) of badrakemone (4)

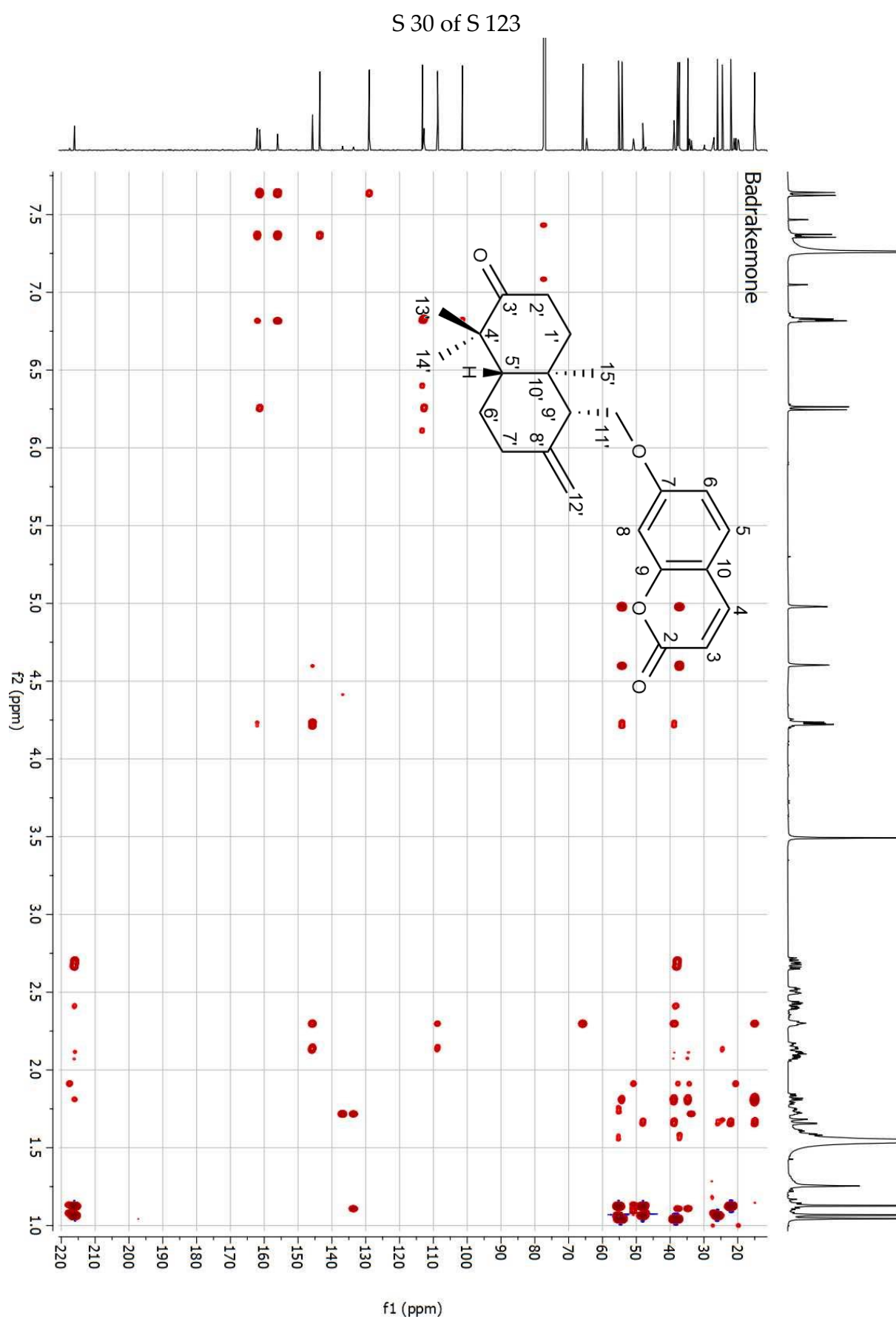


**Figure S22.** <sup>1</sup>H-<sup>1</sup>H COSY spectrum (CDCl<sub>3</sub>) of badrakemone (4)

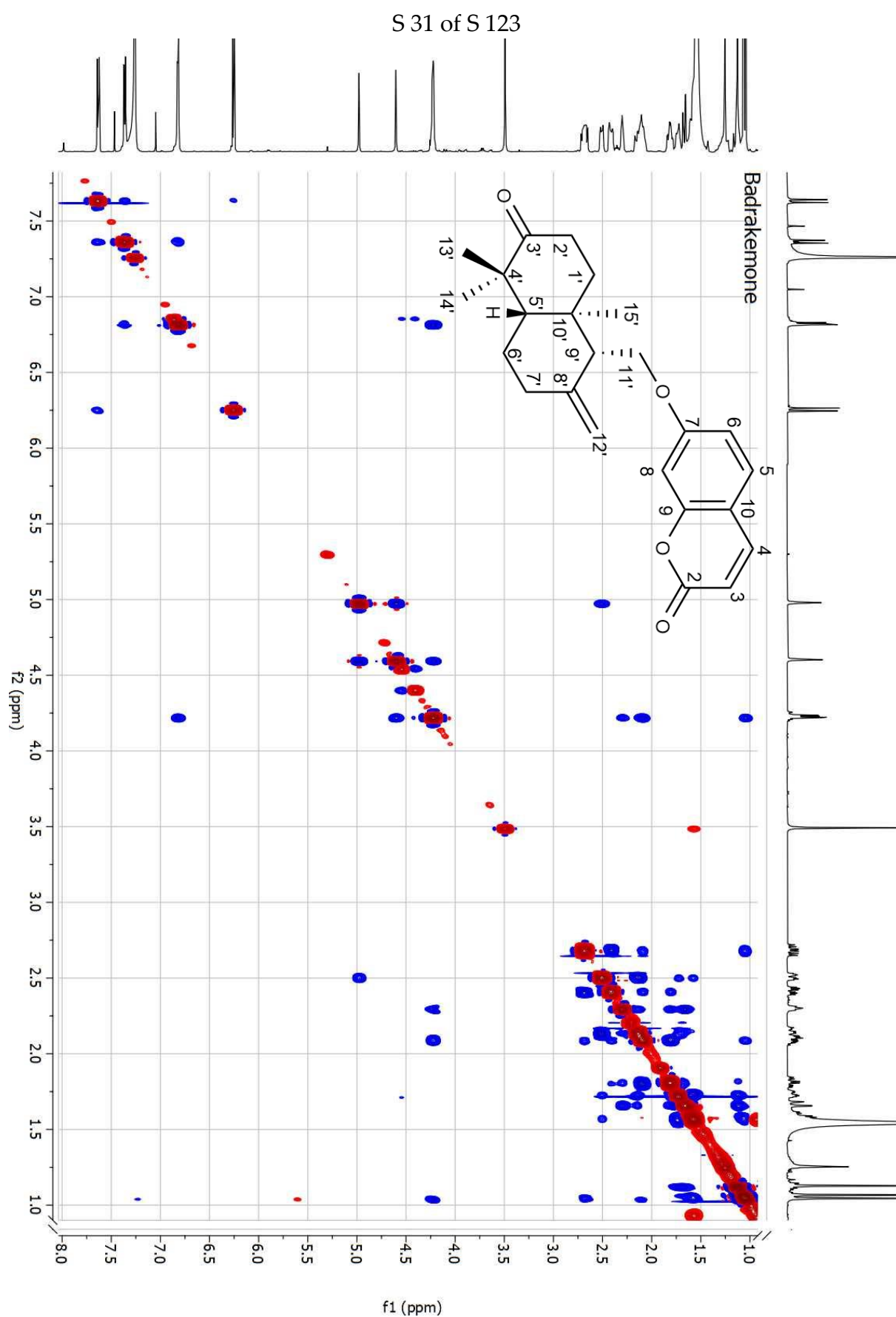




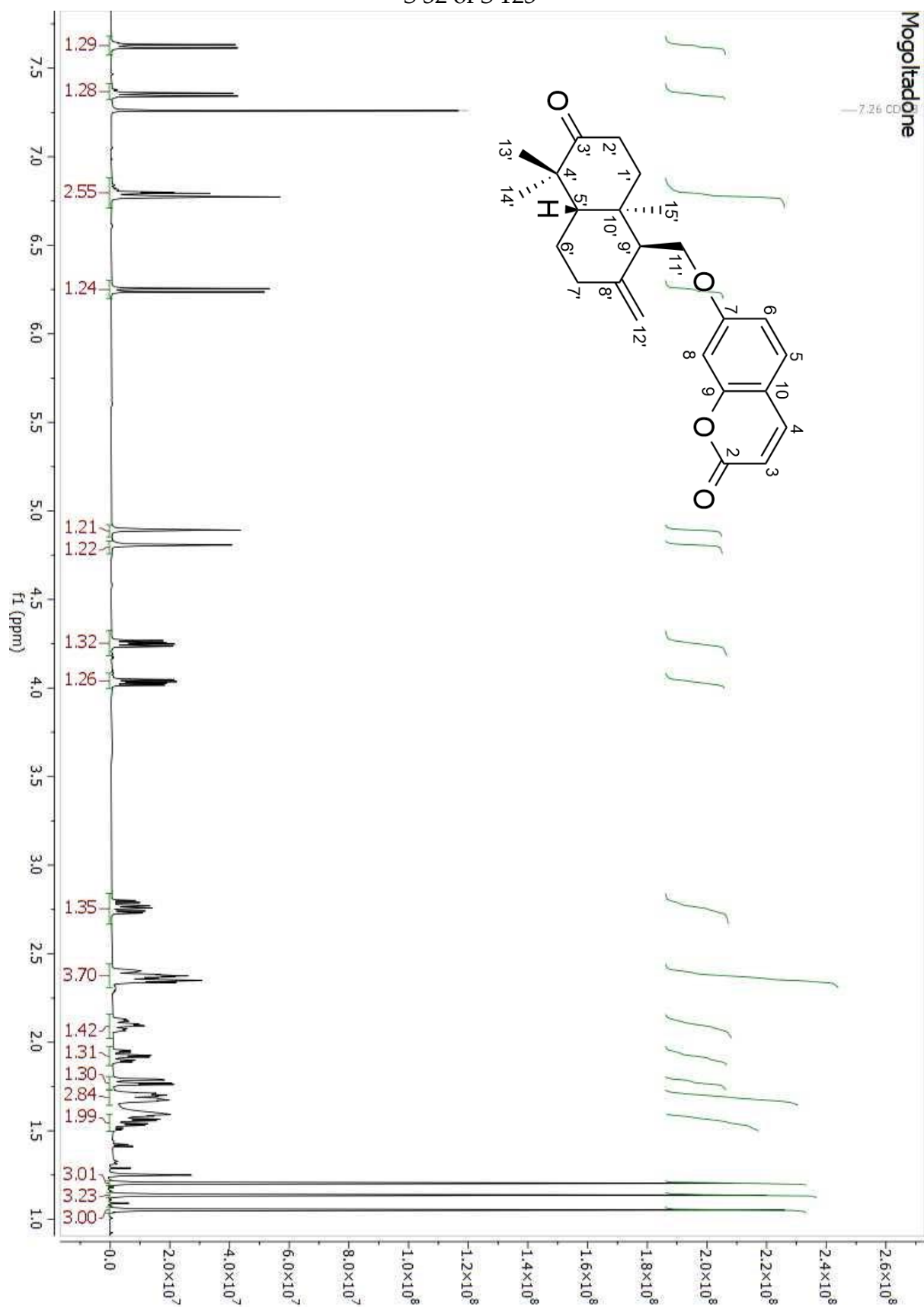
**Figure S23.** HSQC spectrum (CDCl<sub>3</sub>) of badrakemone (4)



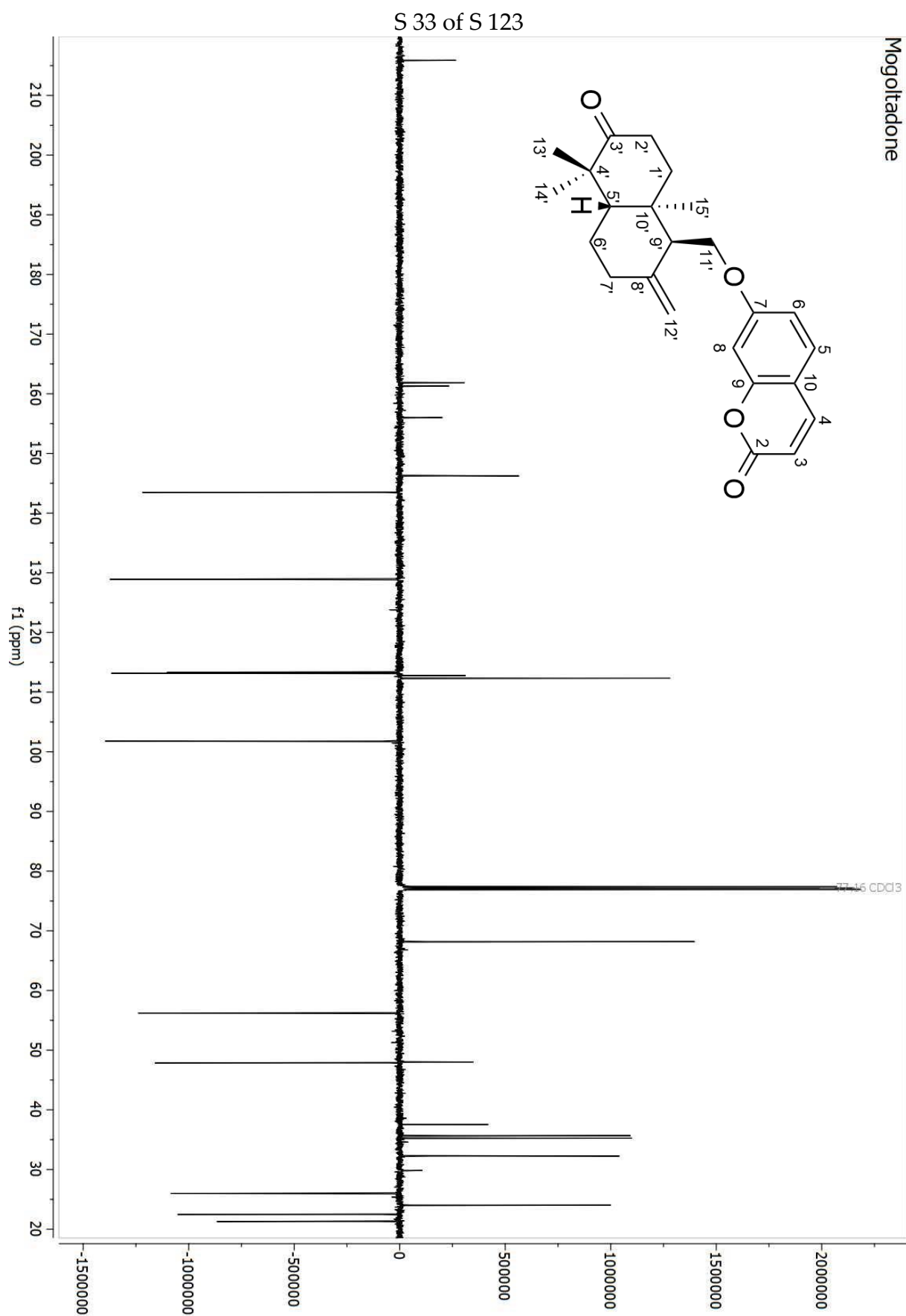
**Figure S24.** HMBC spectrum (CDCl<sub>3</sub>) of badrakemone (4)

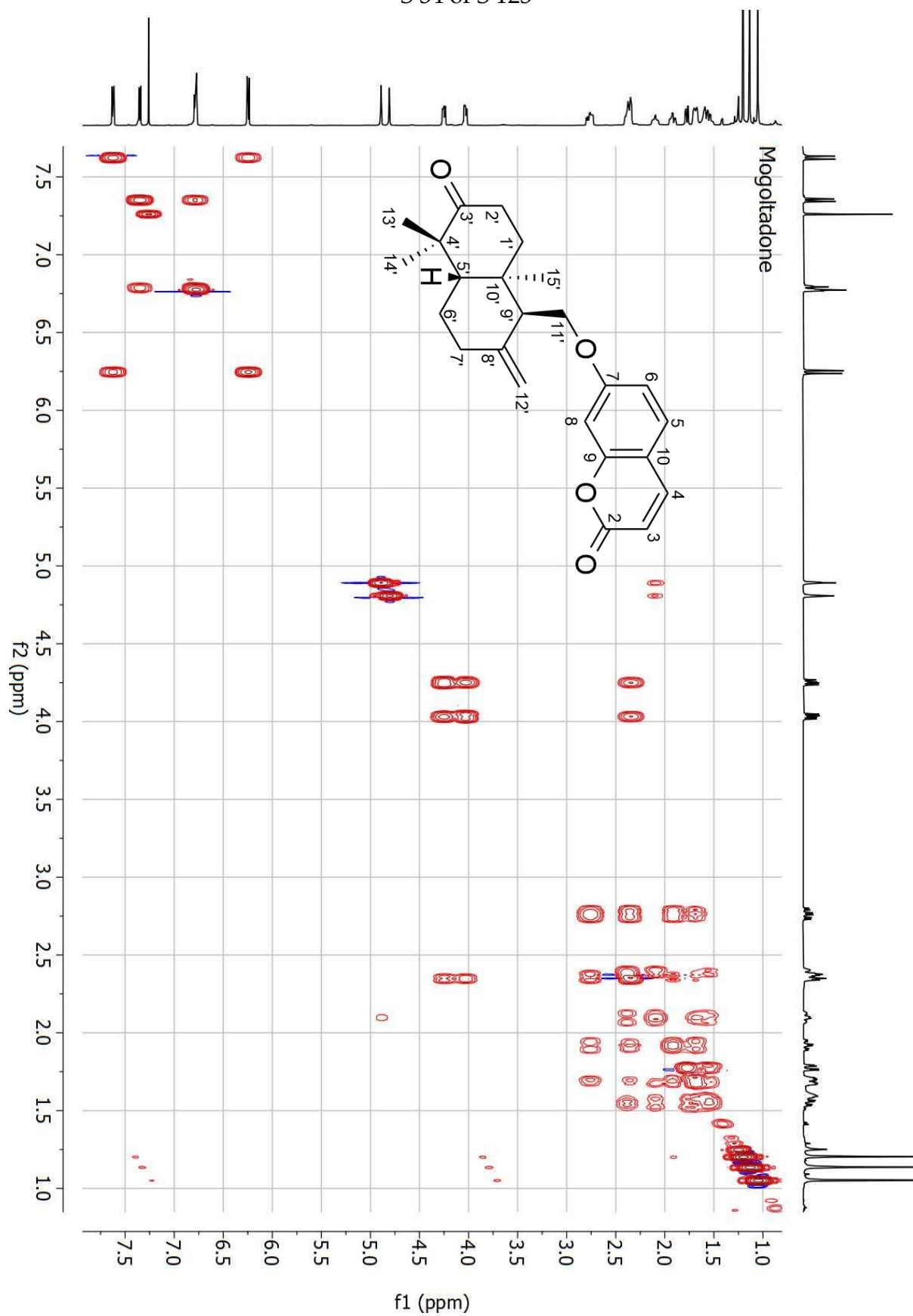


**Figure S25.** NOESY spectrum (CDCl<sub>3</sub>) of badrakemone (4)

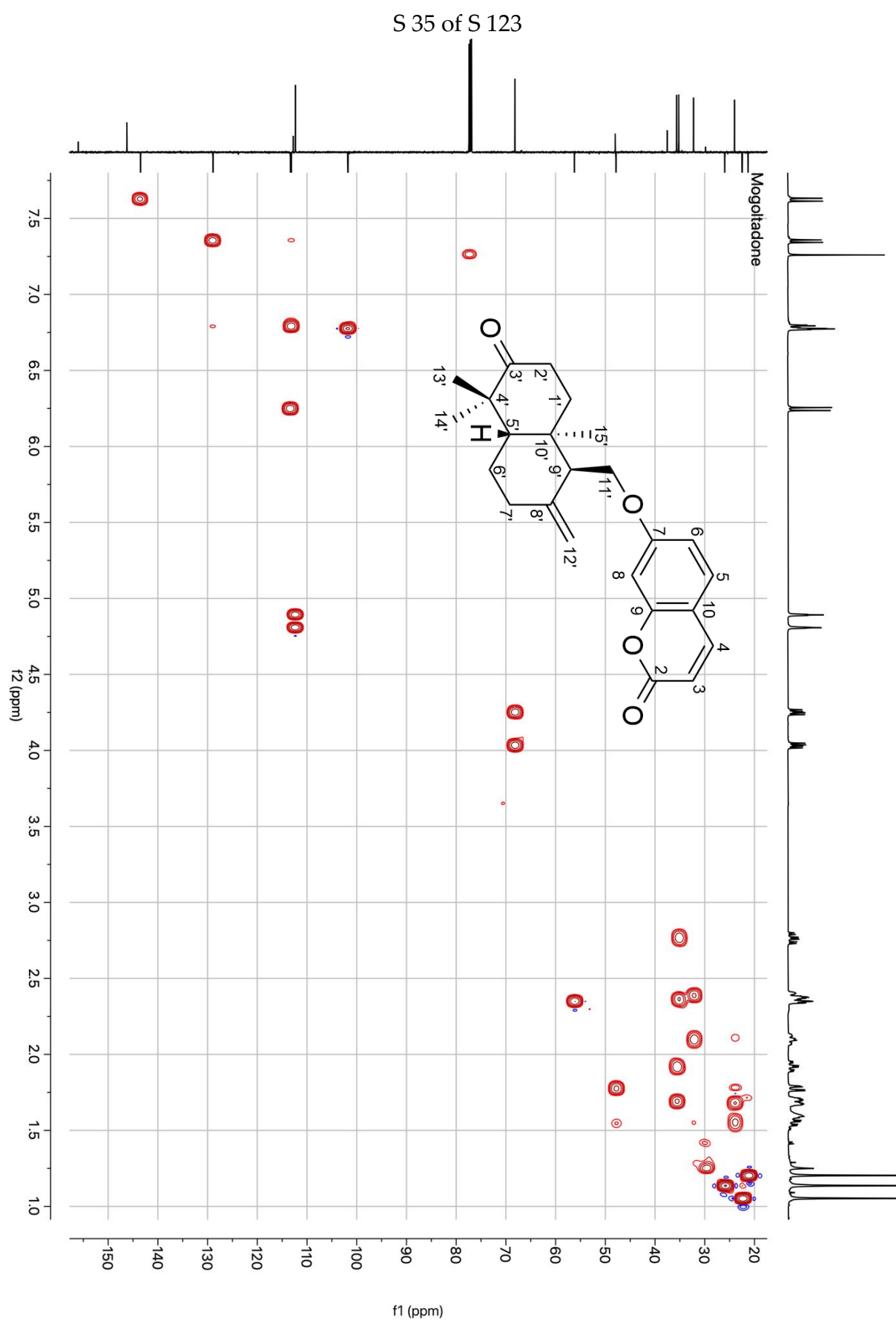


**Figure S26.** <sup>1</sup>H-NMR spectrum (500 MHz, CDCl<sub>3</sub>) of mogoltadone (5)

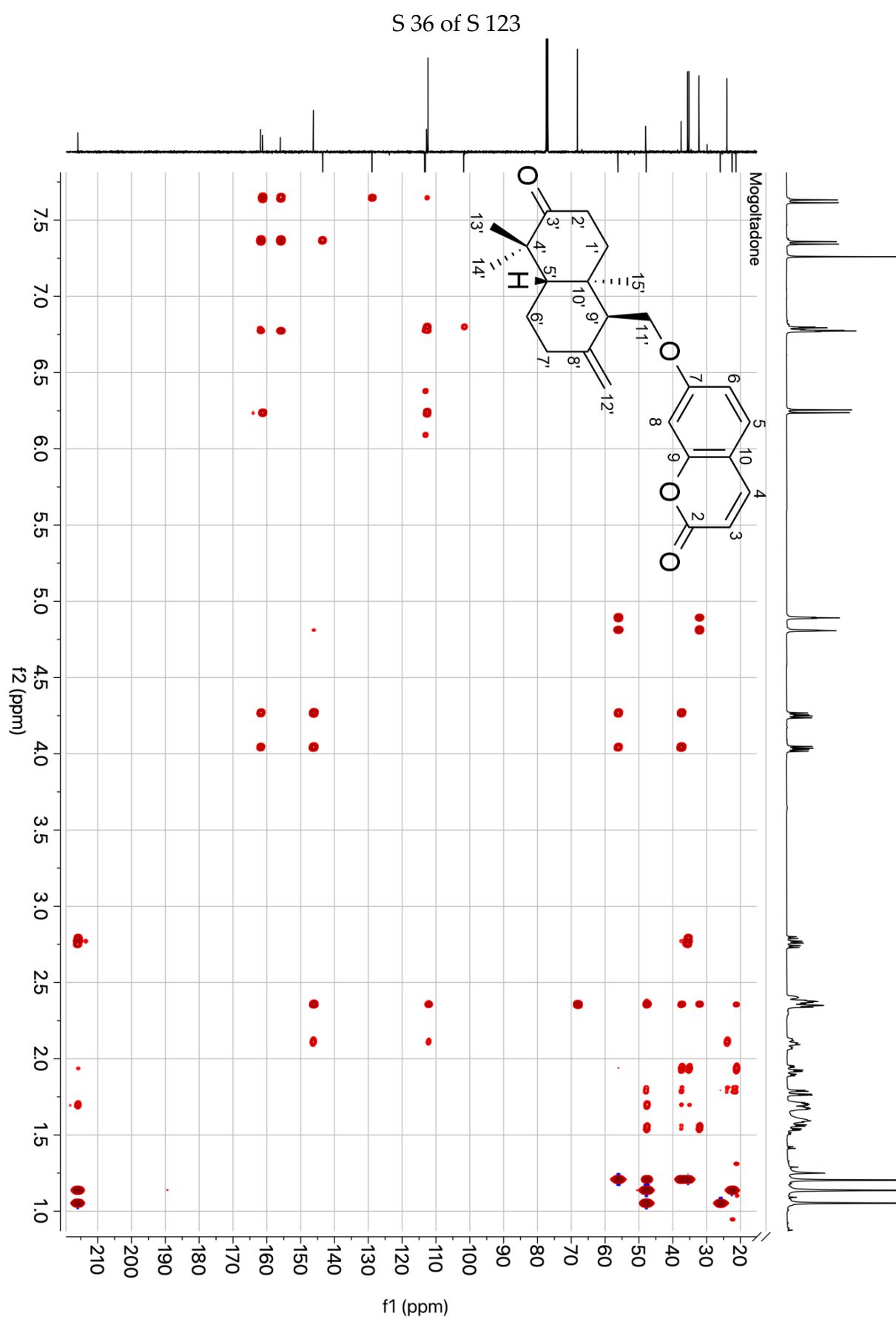




**Figure S28.**  $^1\text{H}$ - $^1\text{H}$  COSY spectrum ( $\text{CDCl}_3$ ) of mogoltadone (5)

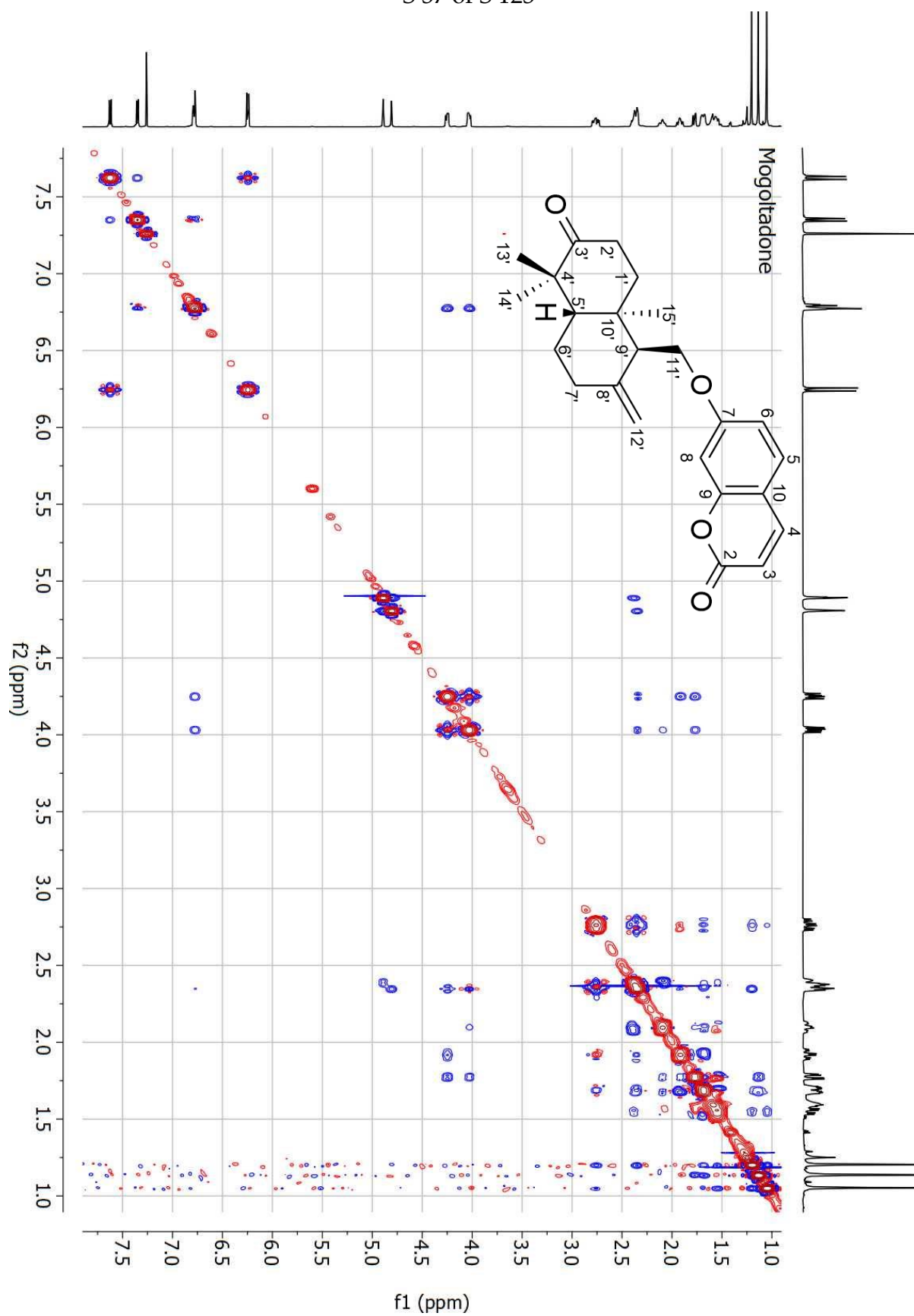


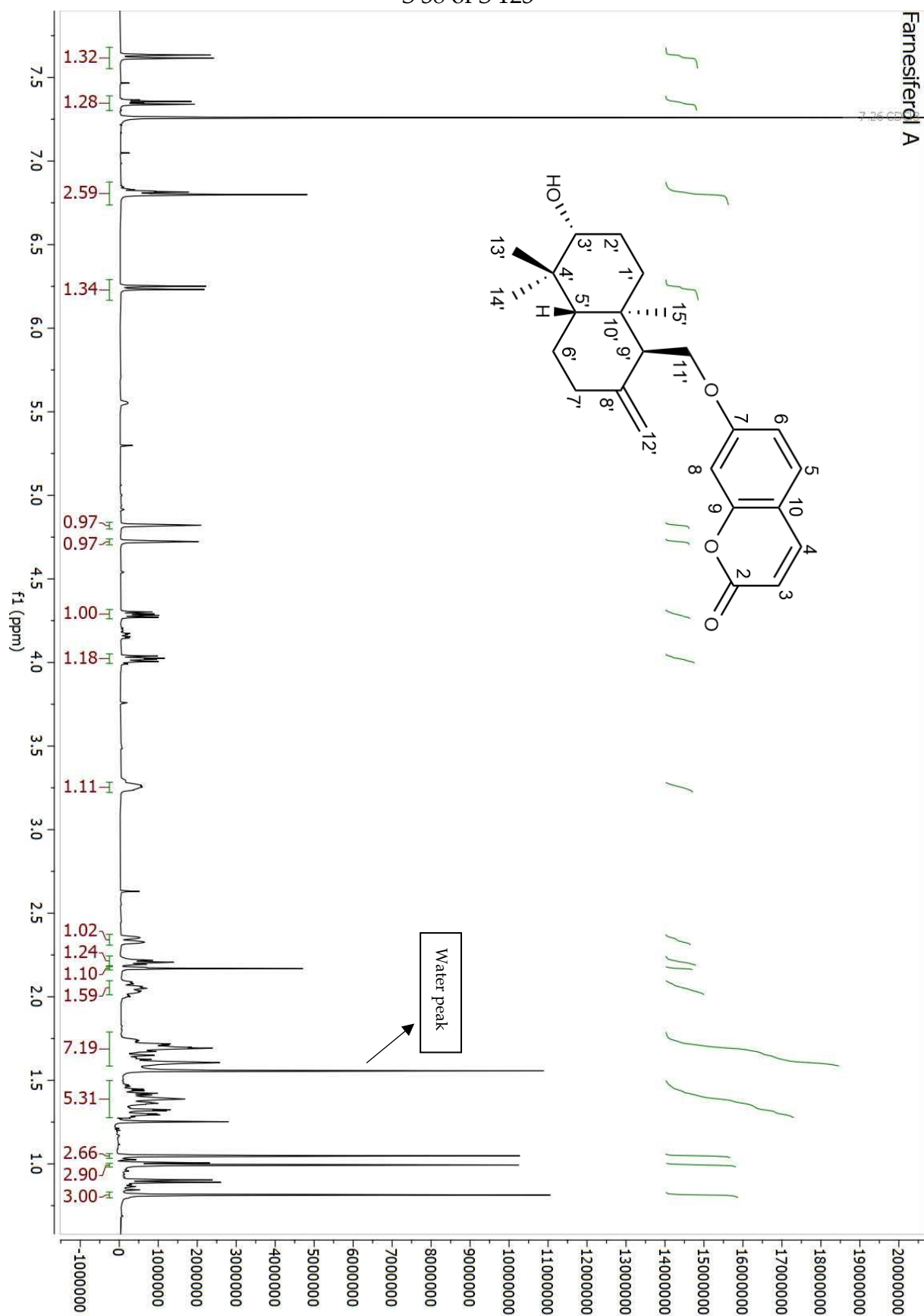
**Figure S29.** HSQC spectrum (CDCl<sub>3</sub>) of mogoltadone (5)



**Figure S30.** HMBC spectrum (CDCl<sub>3</sub>) of mogoltadone (5)

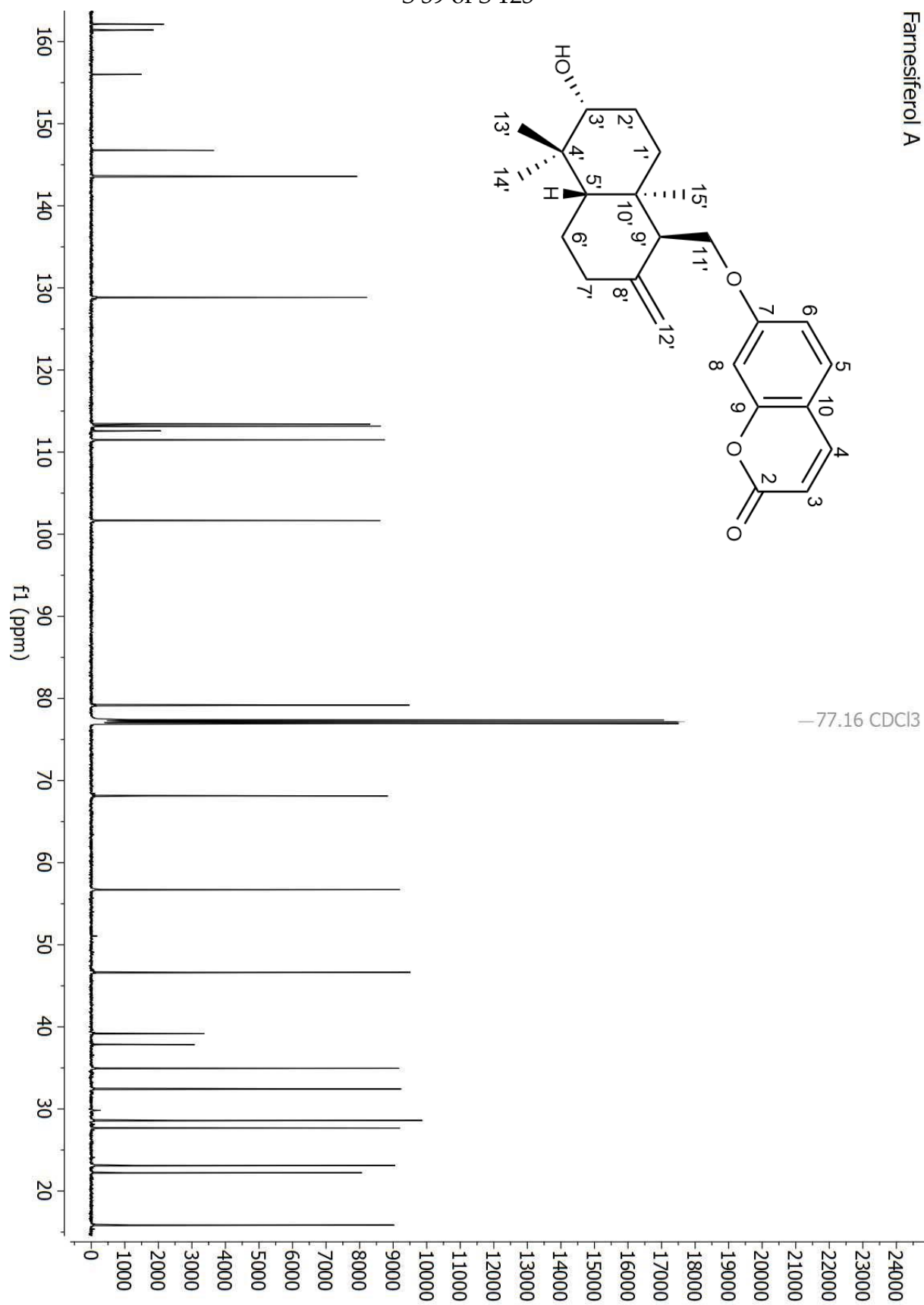


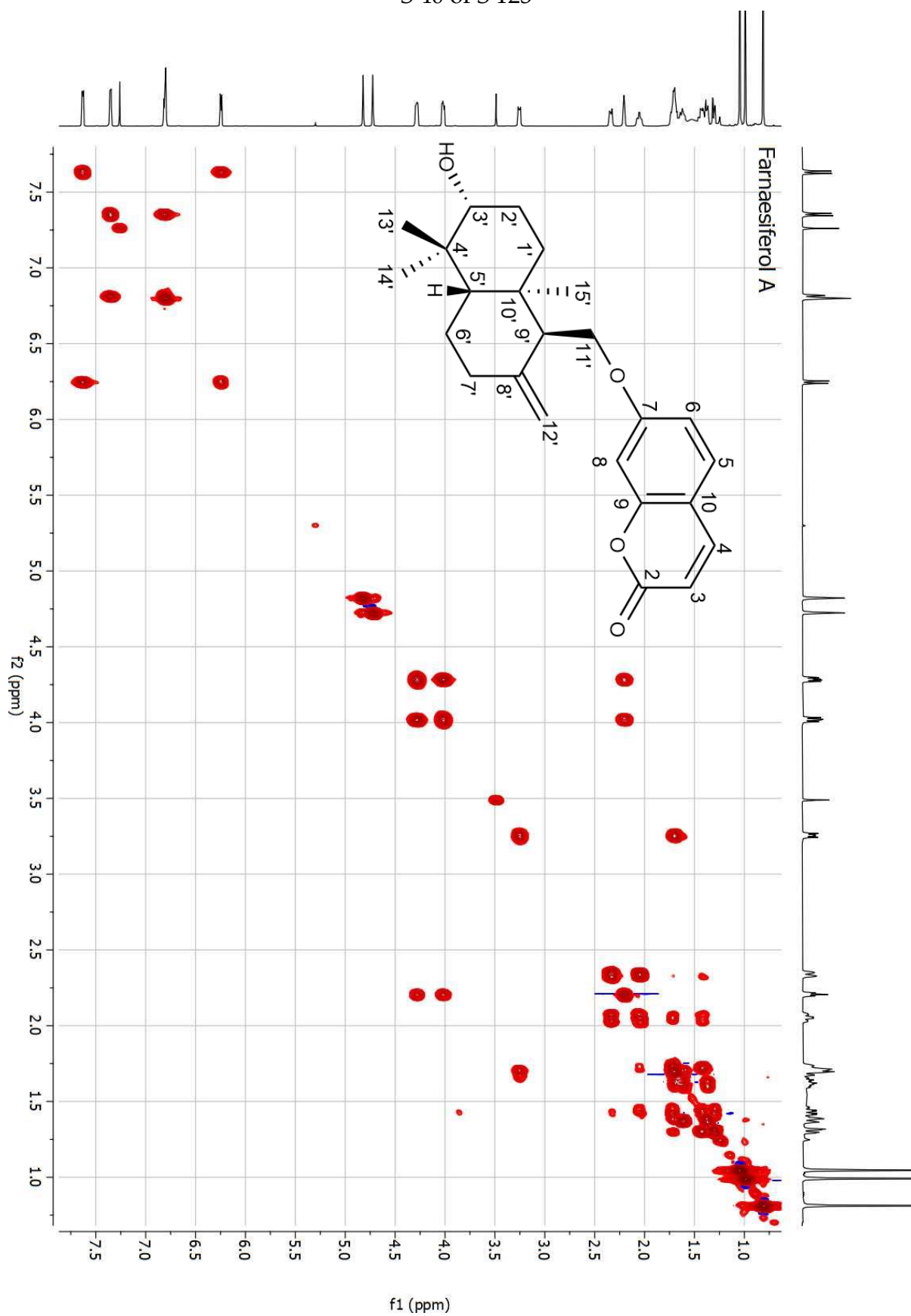
**Figure S31.** NOESY spectrum (CDCl<sub>3</sub>) of mogoltadone (5)



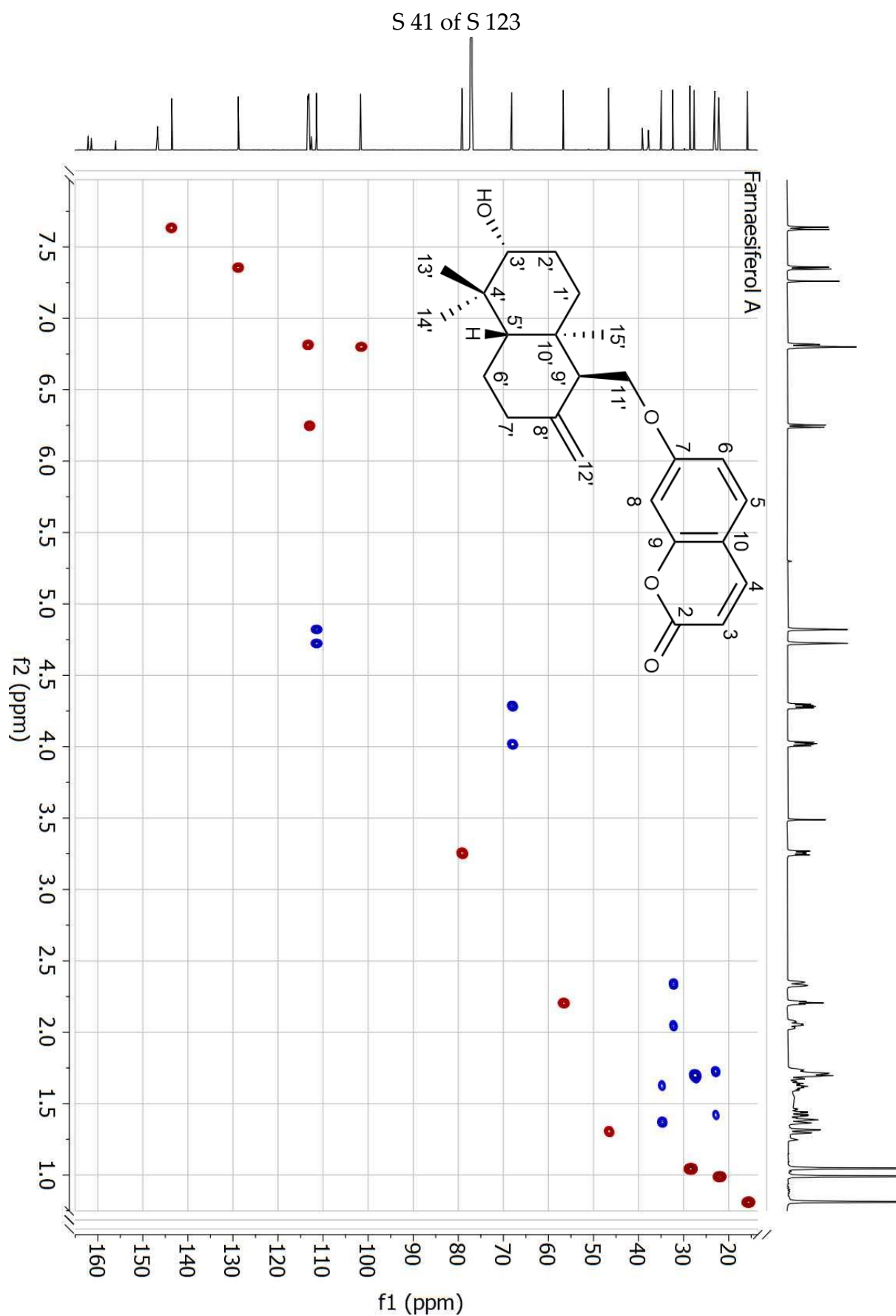
**Figure S32.**  $^1\text{H}$ -NMR spectrum (500 MHz,  $\text{CDCl}_3$ ) of farnesiferol A (6)

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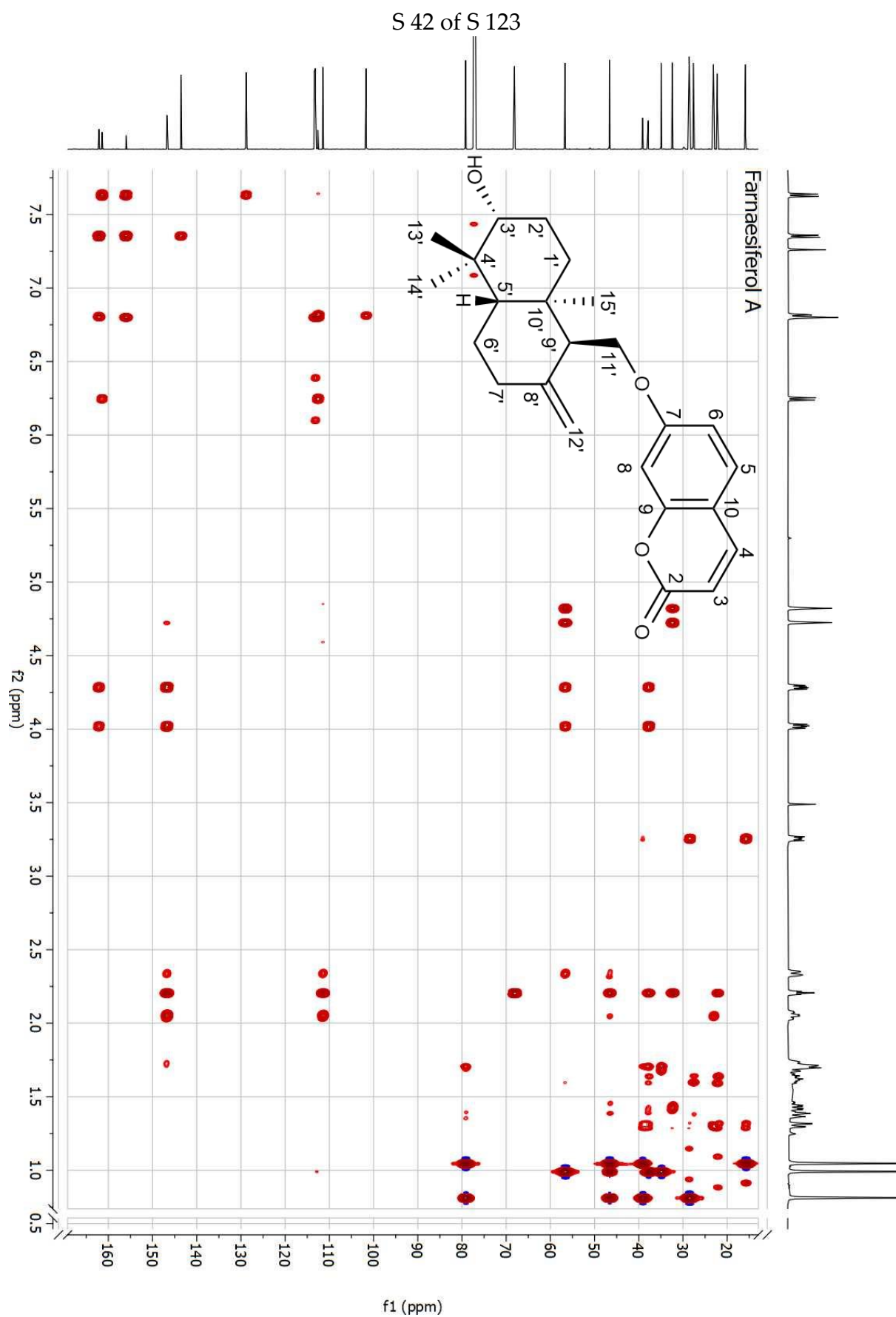
**Figure S33.**  $^{13}\text{C}$ -NMR spectrum (125 MHz,  $\text{CDCl}_3$ ) of farnesiferol A (6)



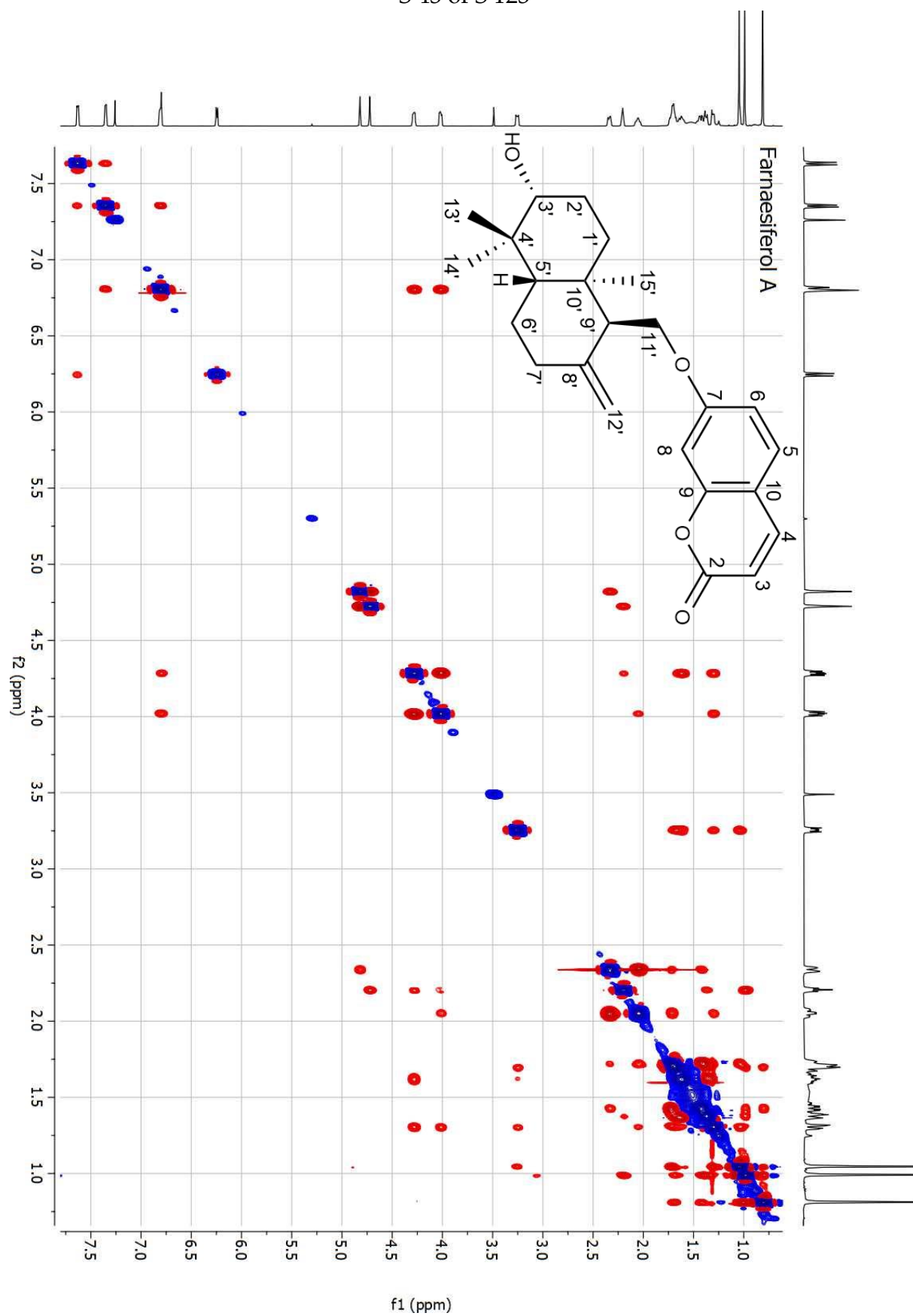
**Figure S34.**  $^1\text{H}$ - $^1\text{H}$  COSY spectrum ( $\text{CDCl}_3$ ) of farnesiferol A (6)



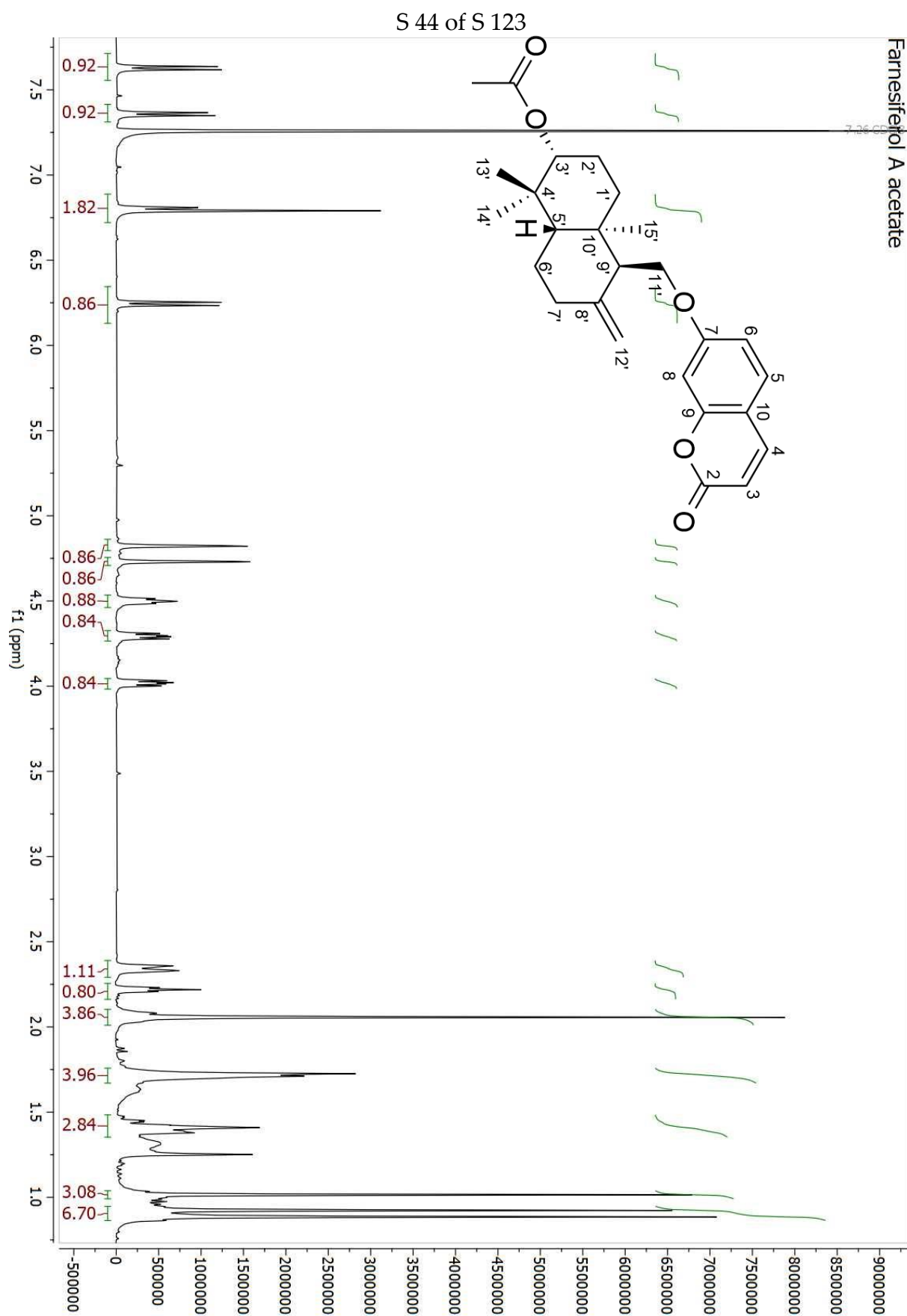
**Figure S35.** HSQC spectrum ( $\text{CDCl}_3$ ) of farnesiferol A (6)



**Figure S36.** HMBC spectrum (CDCl<sub>3</sub>) of farnesiferol A (6)

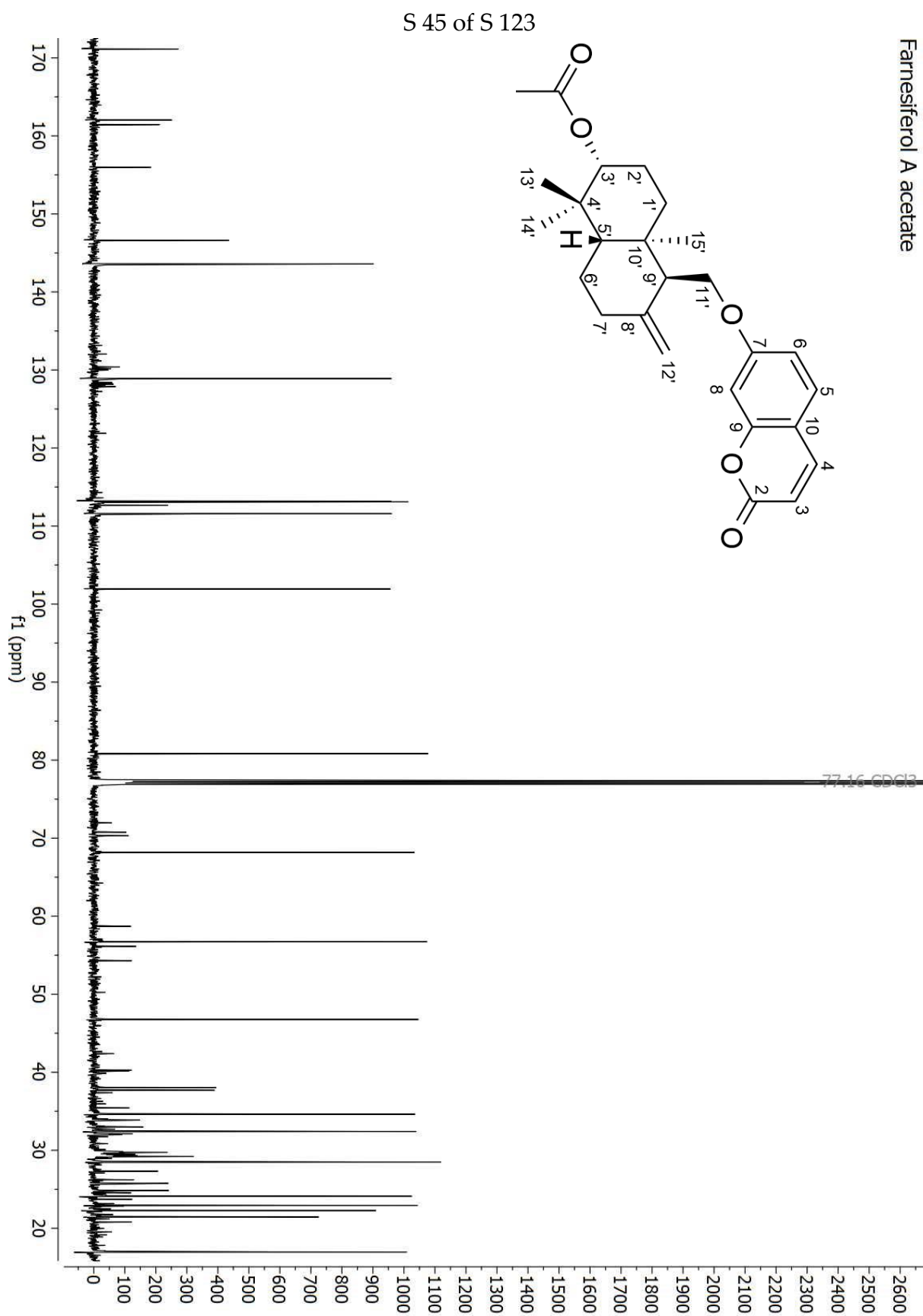


**Figure S37.** NOESY spectrum ( $\text{CDCl}_3$ ) of farnesiferol A (6)

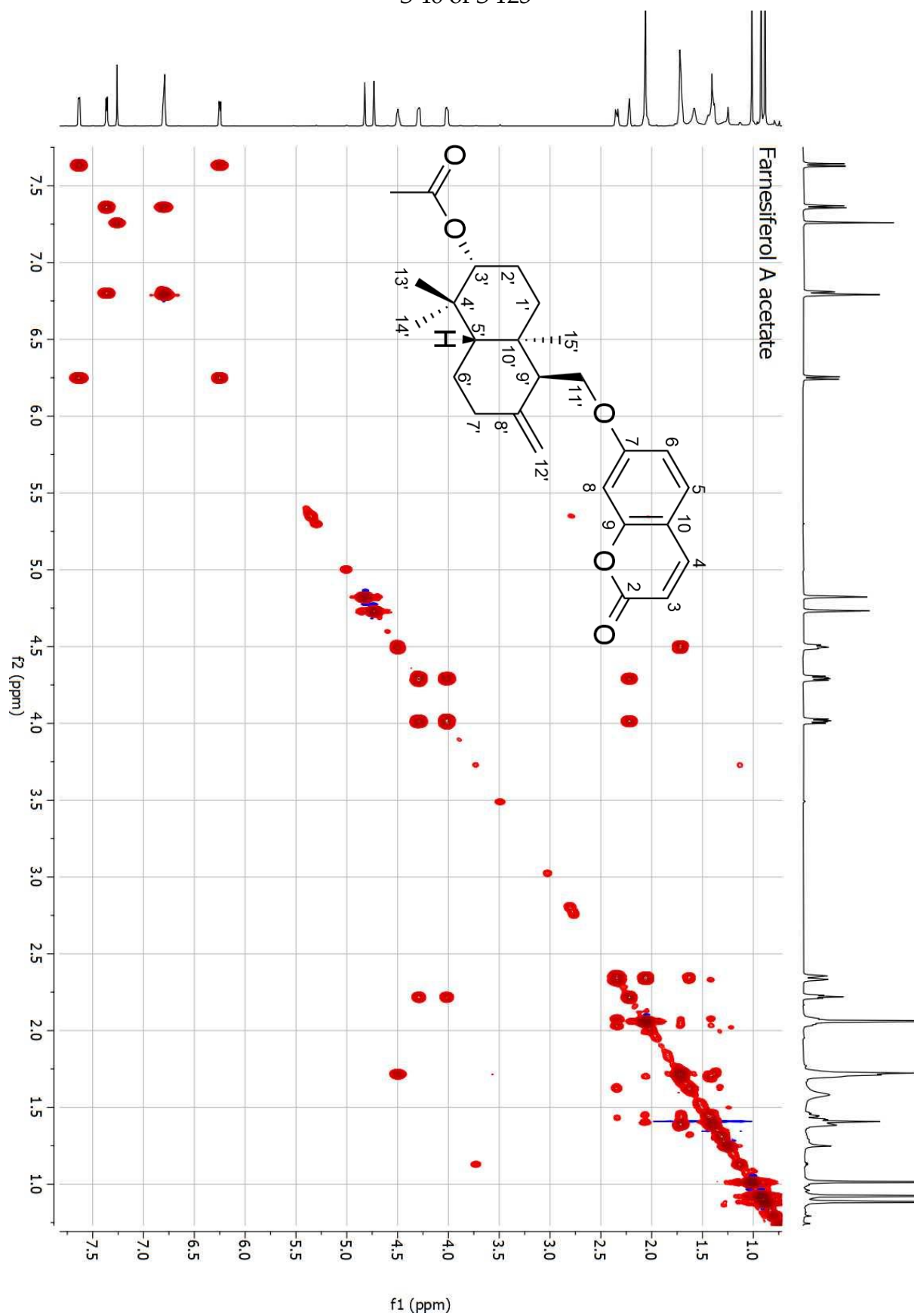


**Figure S38.**  $^1\text{H}$ -NMR spectrum (500 MHz,  $\text{CDCl}_3$ ) of farnesiferol A acetate (7)

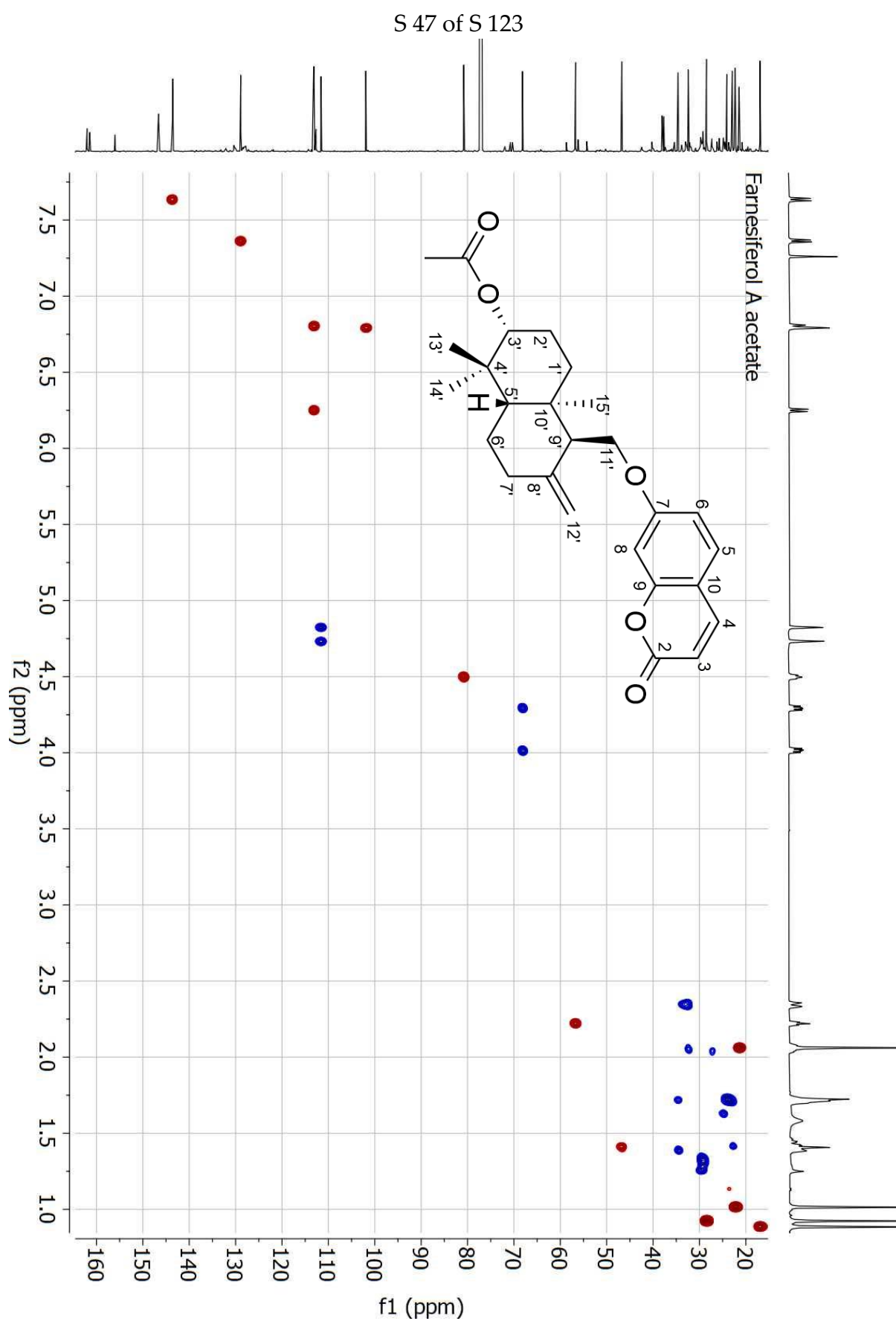




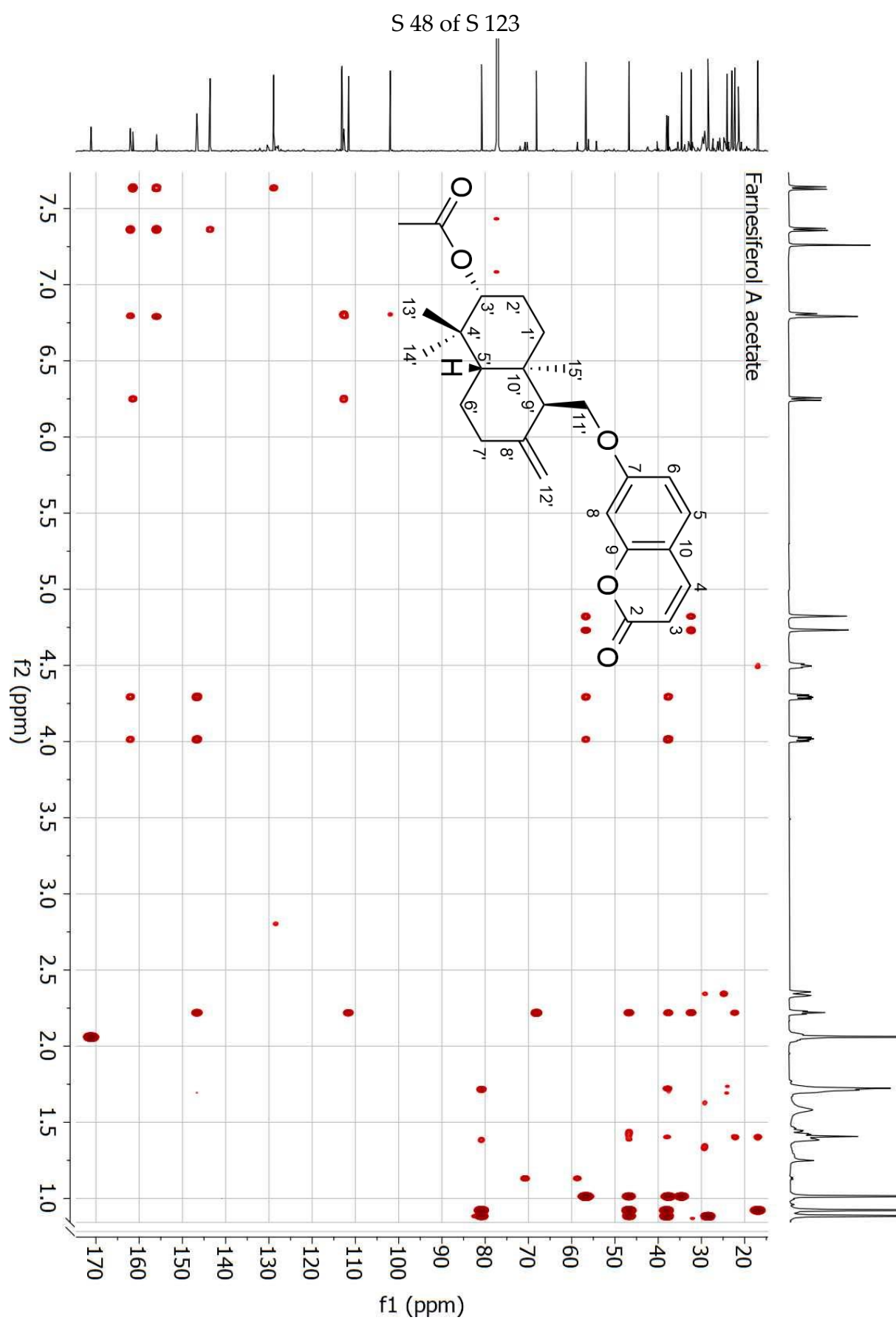
**Figure S39.**  $^{13}\text{C}$ -NMR spectrum (125 MHz,  $\text{CDCl}_3$ ) of farnesiferol A acetate (7)



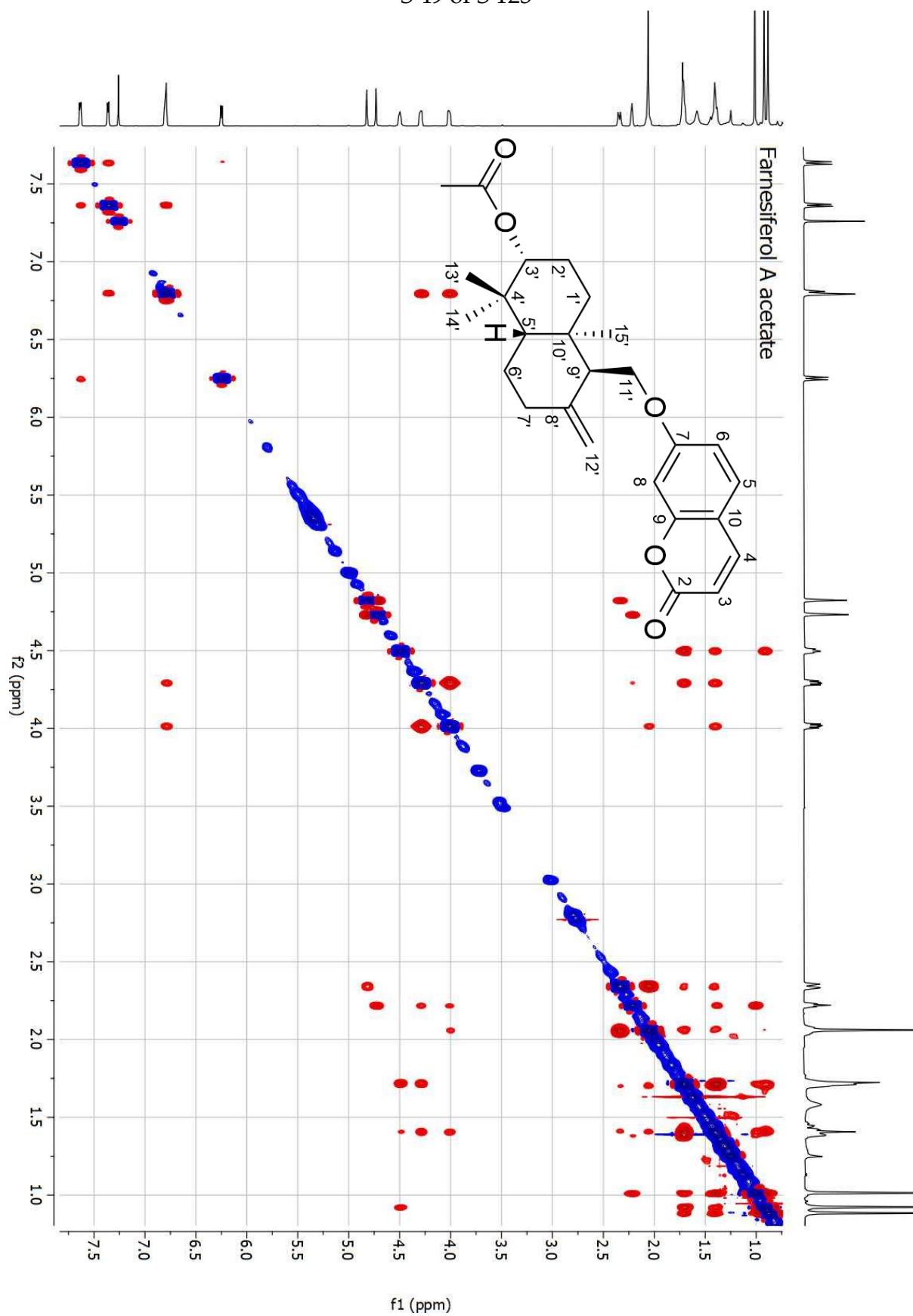
**Figure S40.**  $^1\text{H}$ - $^1\text{H}$  COSY spectrum ( $\text{CDCl}_3$ ) of farnesiferol A acetate (7)



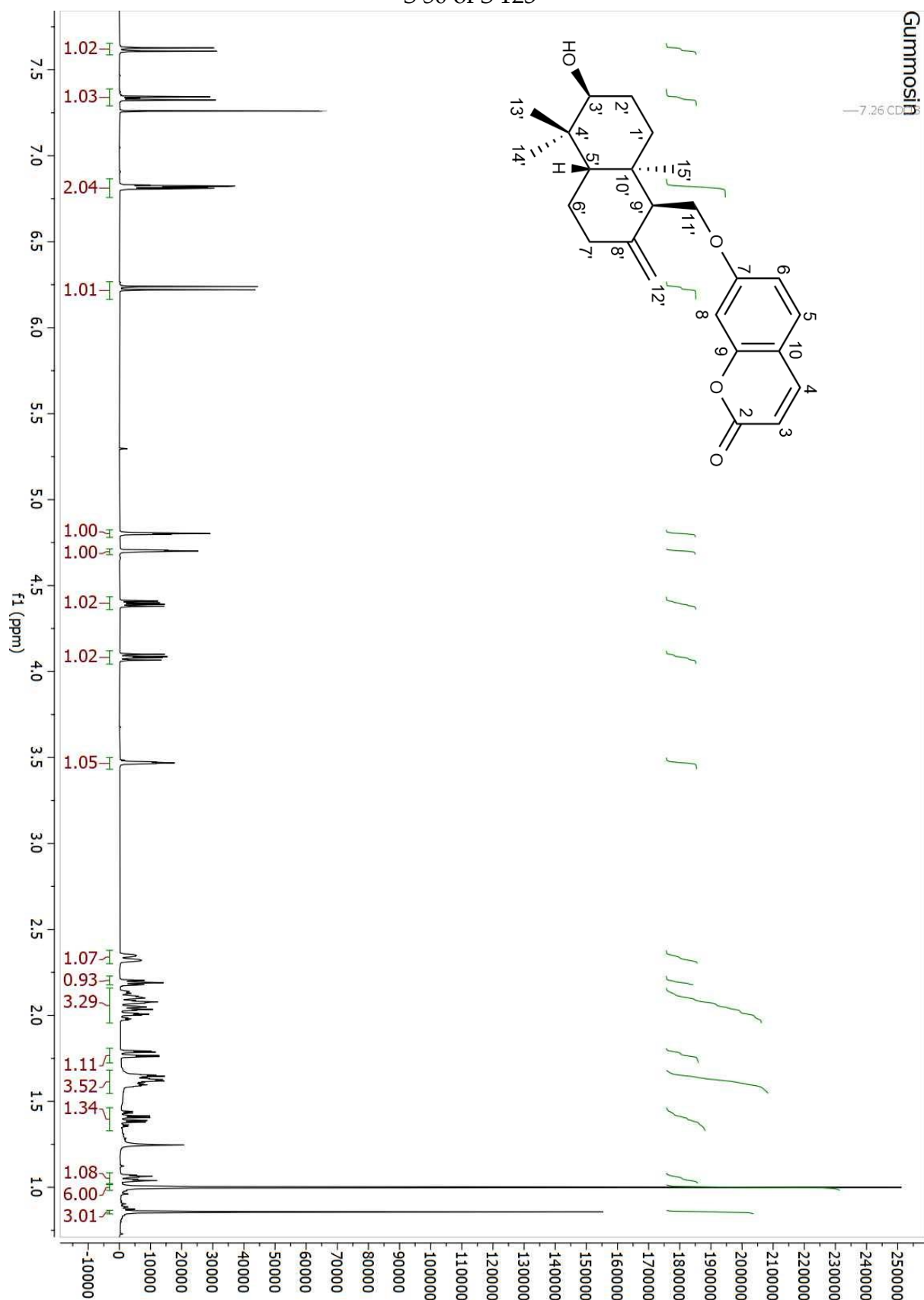
**Figure S41.** HSQC spectrum (CDCl<sub>3</sub>) of farnesiferol A acetate (7)



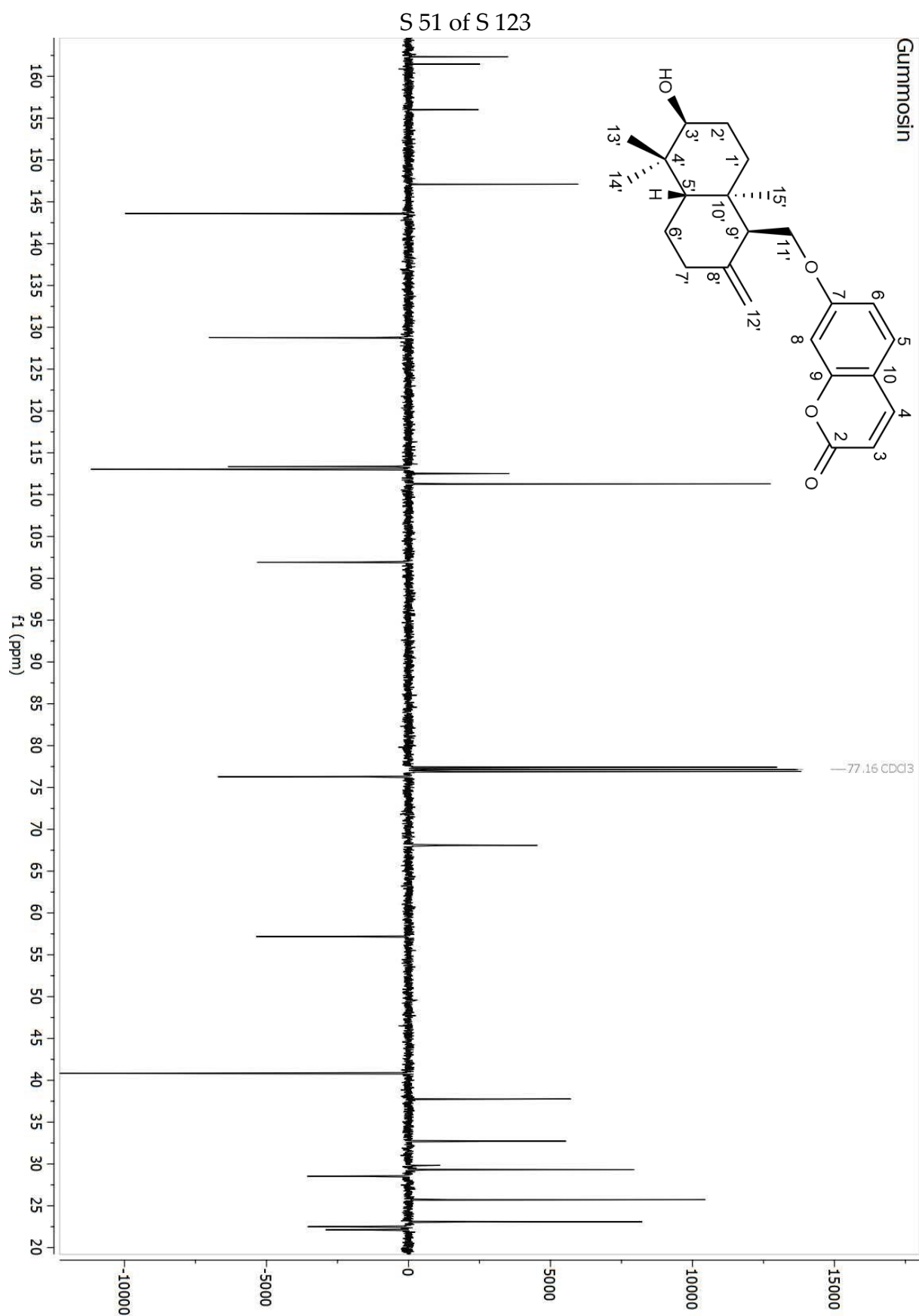
**Figure S42.** HMBC spectrum (CDCl<sub>3</sub>) of farnesiferol A acetate (7)



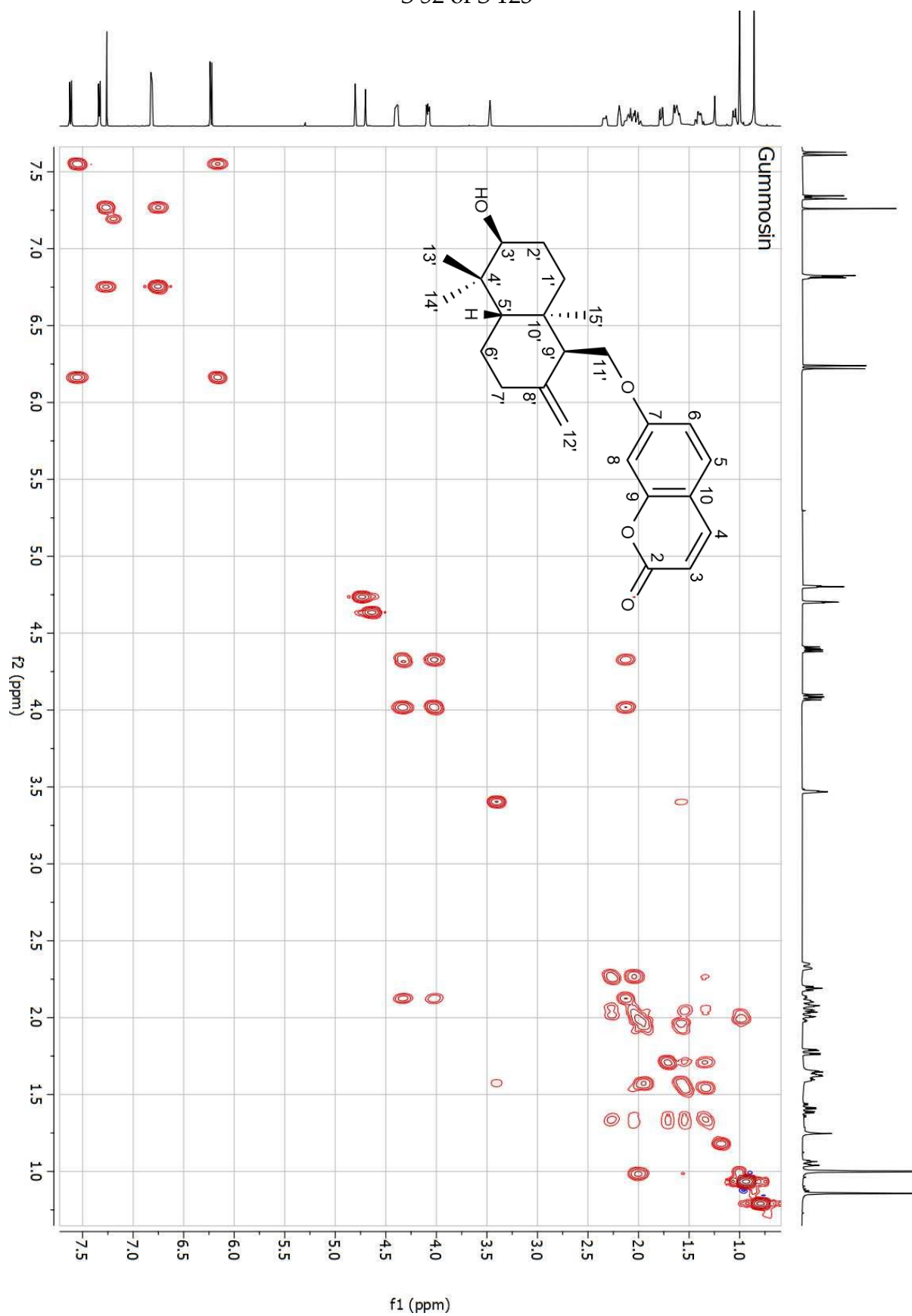
**Figure S43.** NOESY spectrum (CDCl<sub>3</sub>) of farnesiferol A acetate (7)



**Figure S44.** <sup>1</sup>H-NMR spectrum (500 MHz, CDCl<sub>3</sub>) of gummosin (8)



**Figure S45.**  $^{13}\text{C}$ -NMR (APT) spectrum (125 MHz,  $\text{CDCl}_3$ ) of gummosin (8)



**Figure S46.**  $^1\text{H}$ - $^1\text{H}$  COSY spectrum ( $\text{CDCl}_3$ ) of gummosin (8)



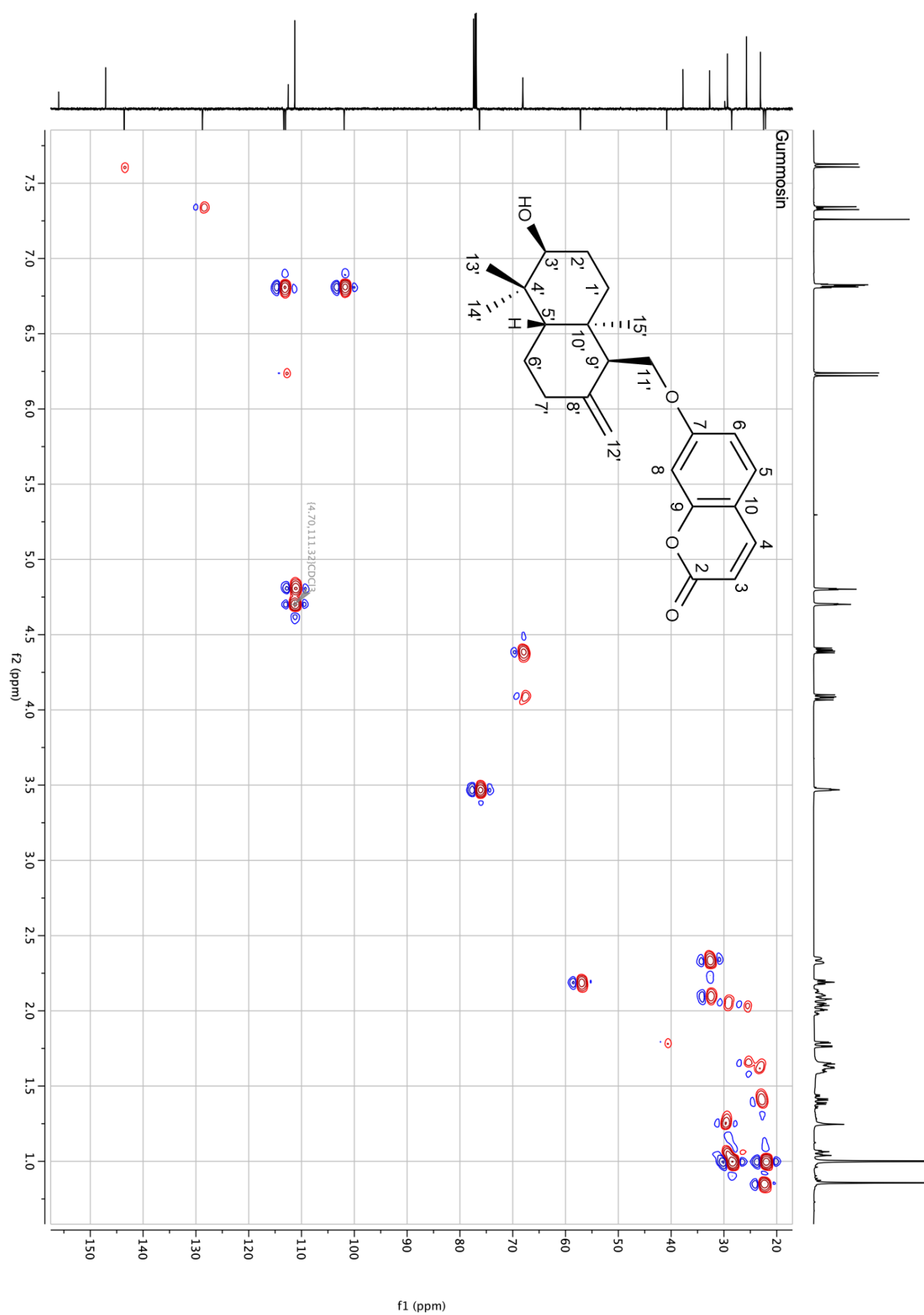
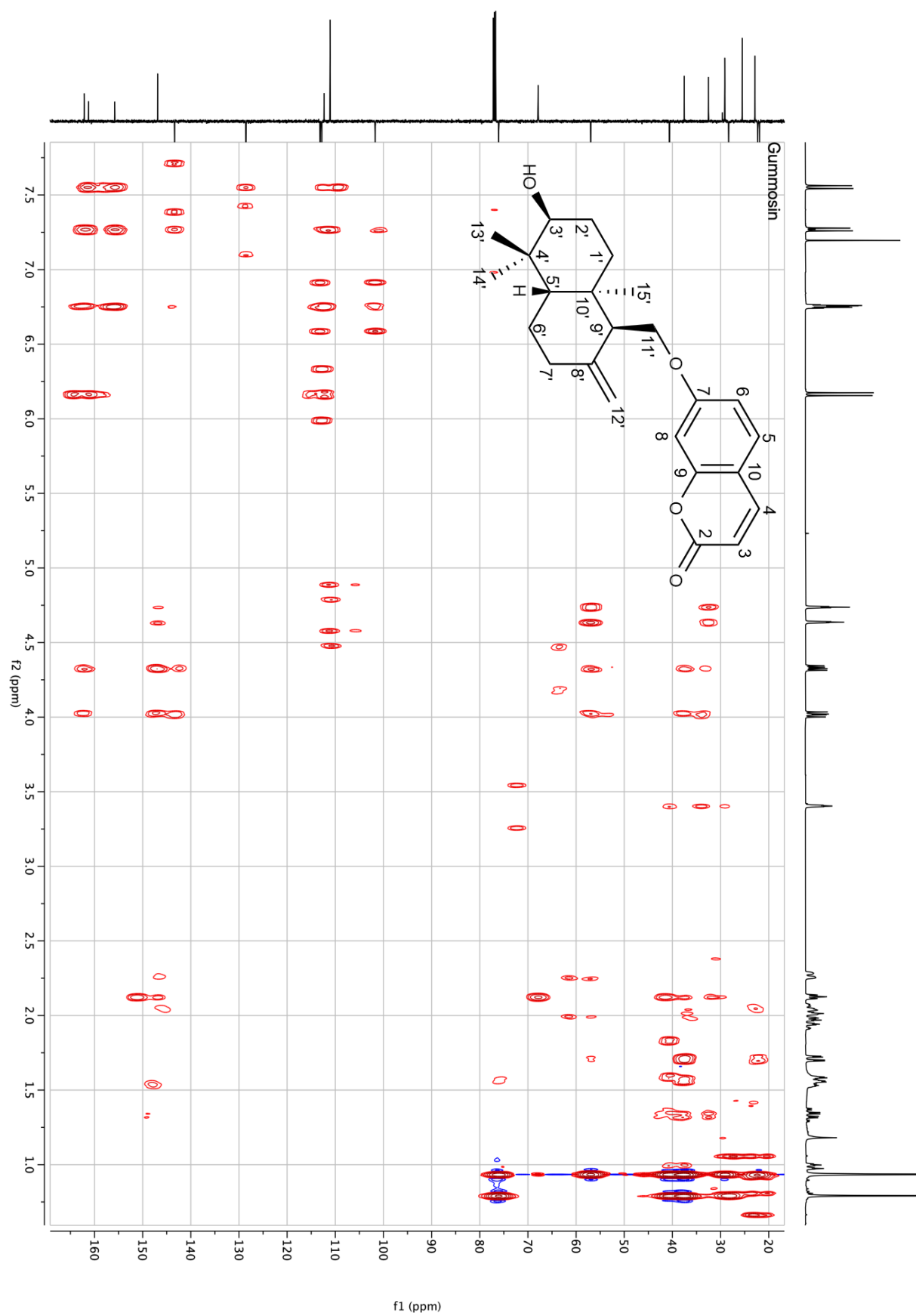
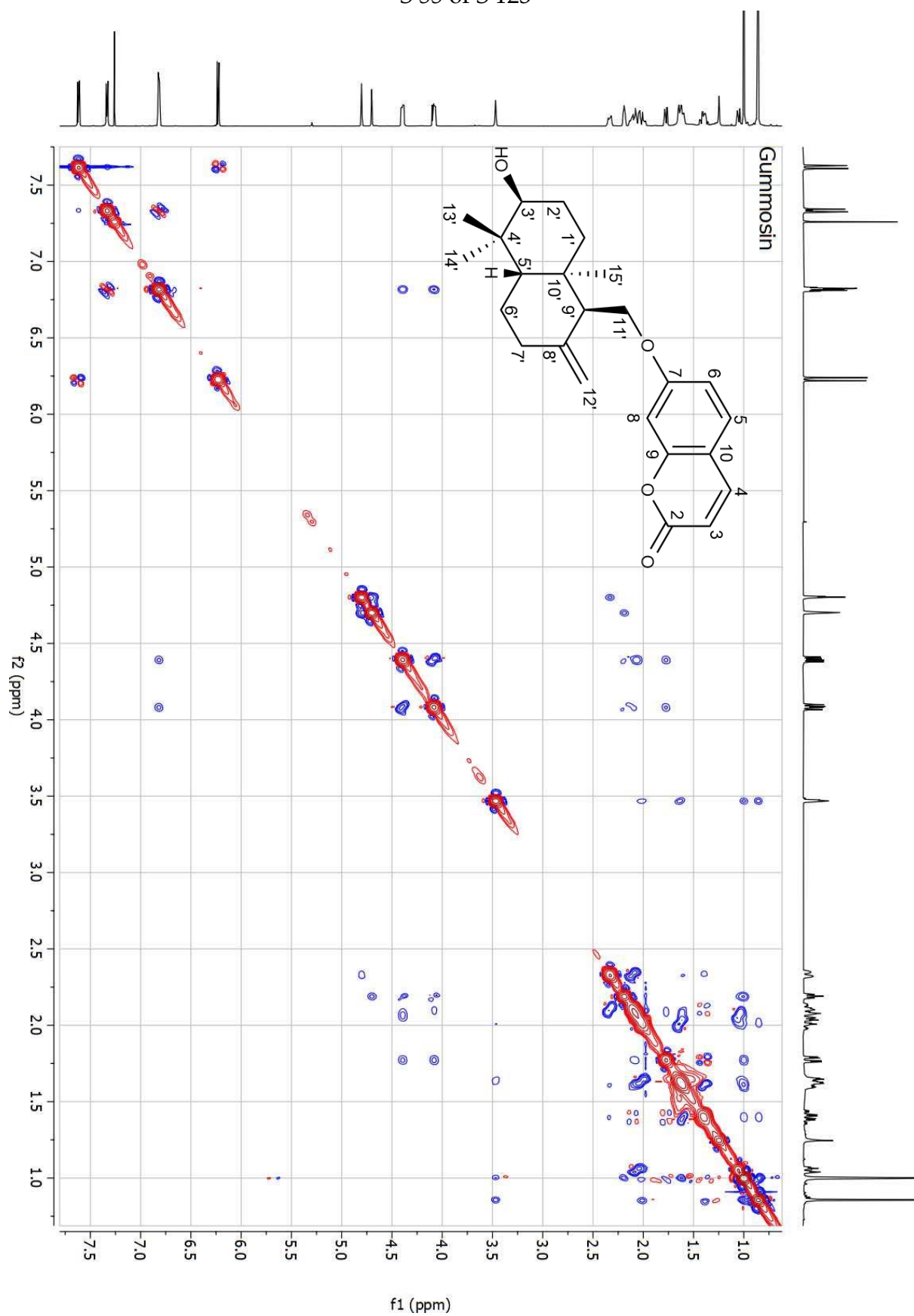
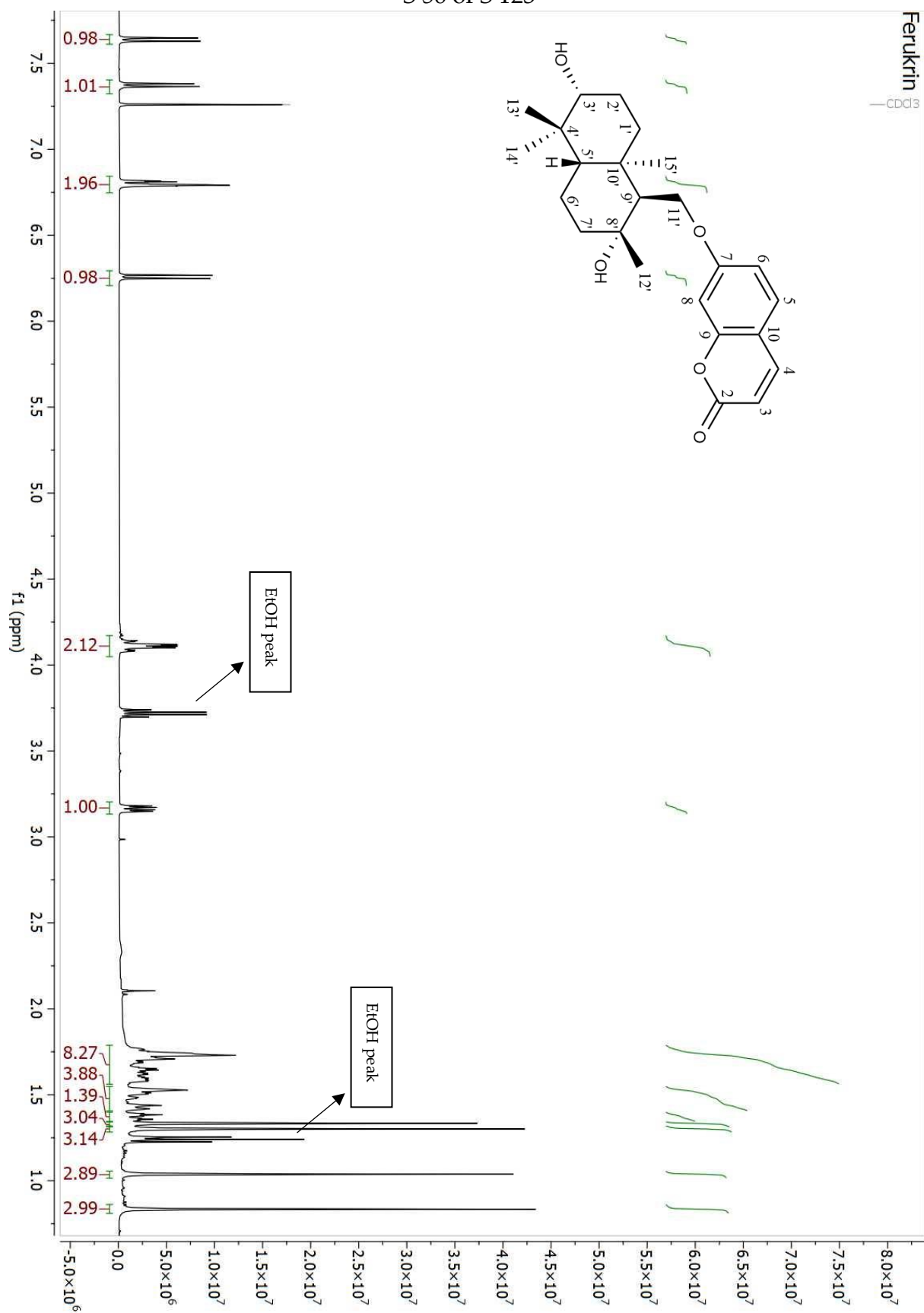


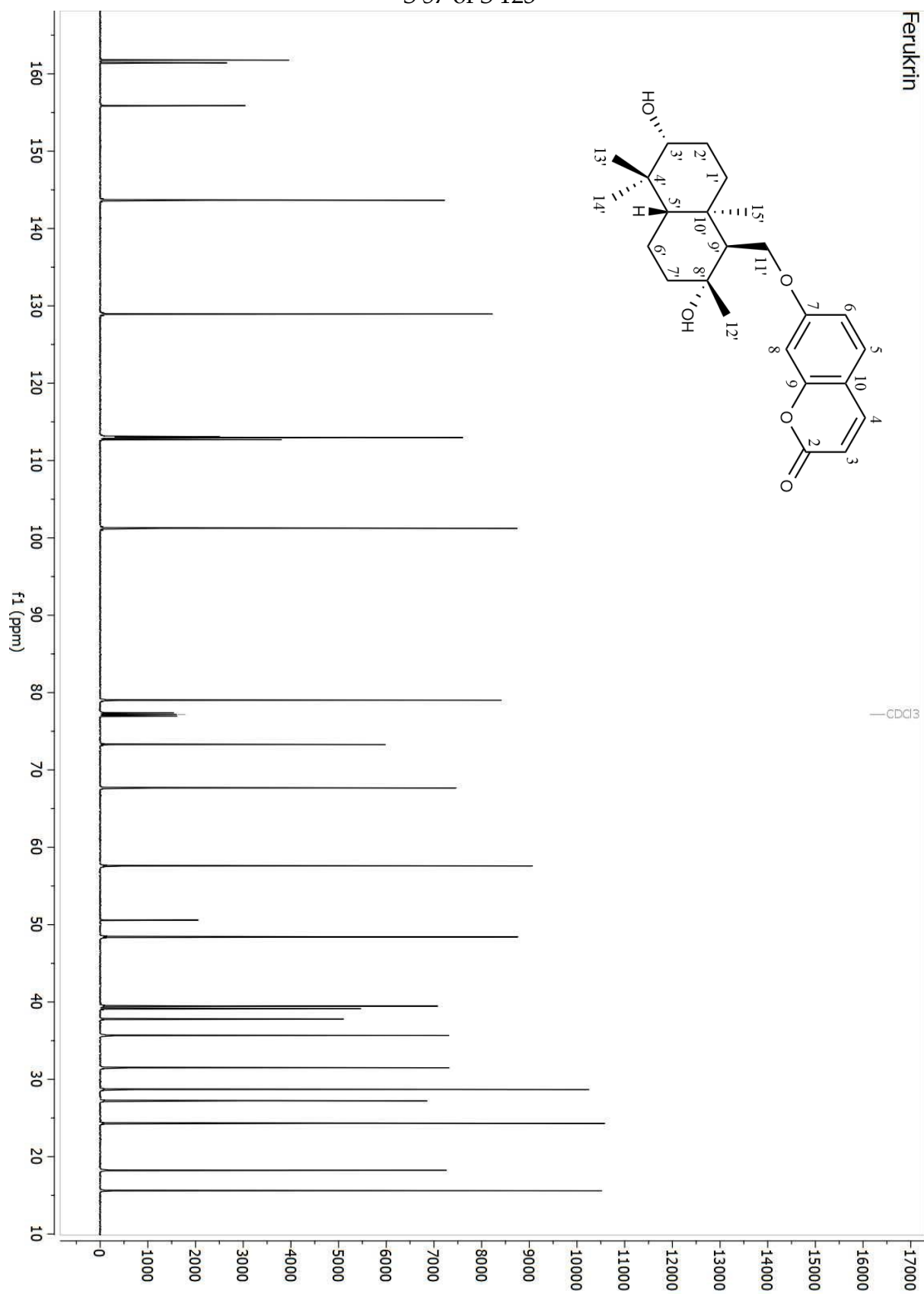
Figure S47. HSQC spectrum (CDCl<sub>3</sub>) of gummosin (8)

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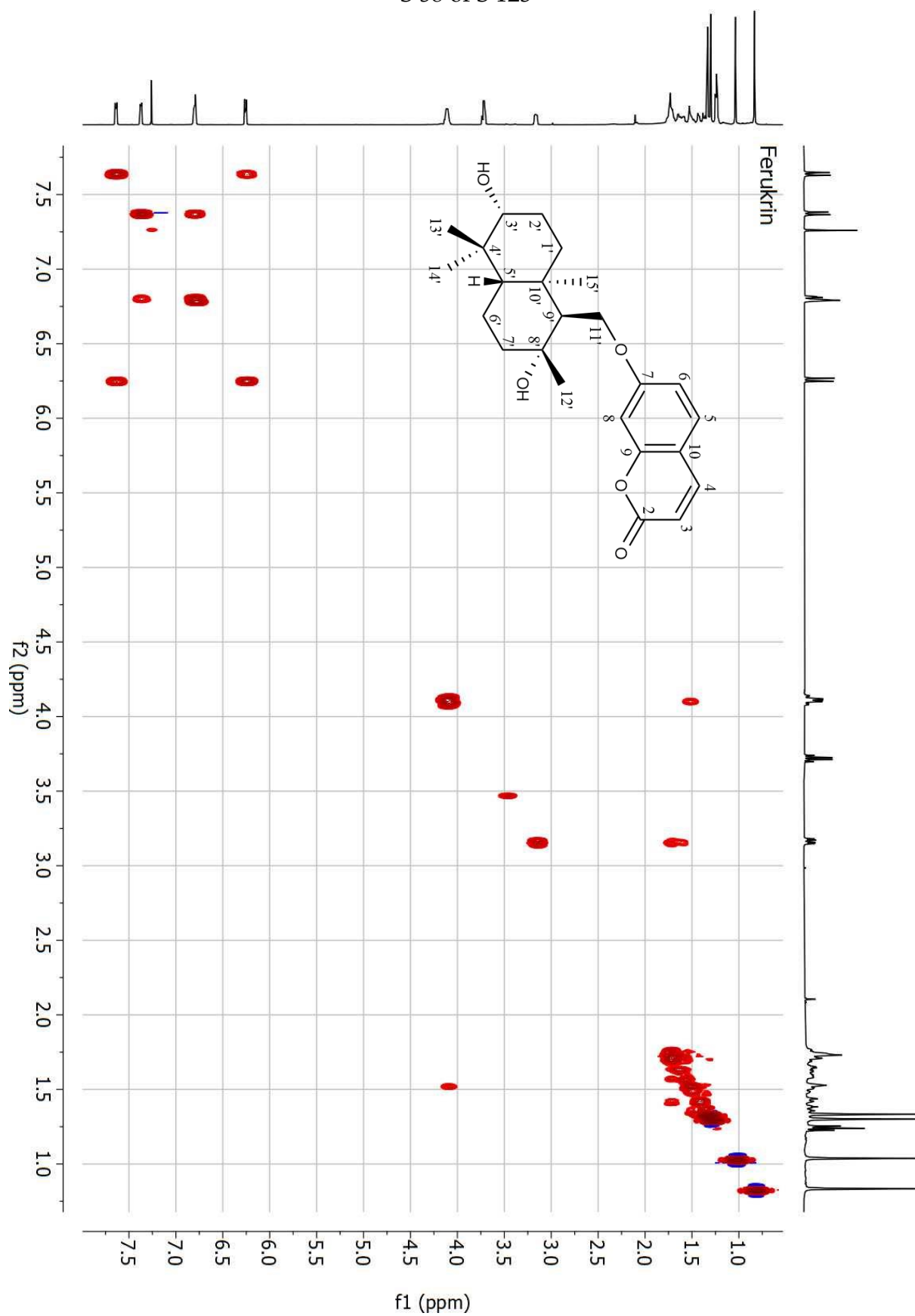
**Figure S48.** HMBC spectrum ( $\text{CDCl}_3$ ) of gummosin (8)

**Figure S49.** NOESY spectrum ( $\text{CDCl}_3$ ) of gummosin (8)

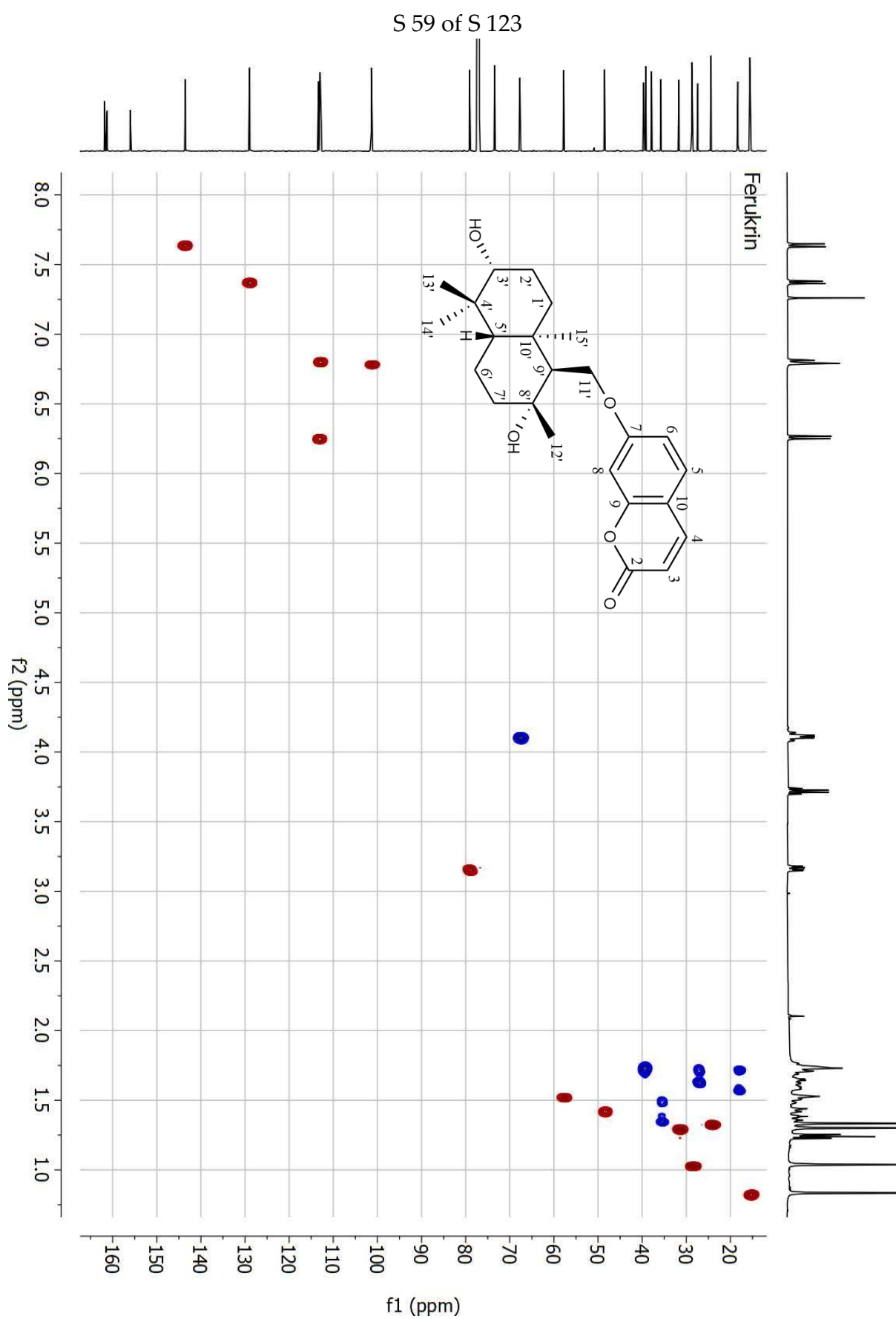
**Figure S50.**  $^1\text{H}$ -NMR spectrum (500 MHz,  $\text{CDCl}_3$ ) of ferukrin (9)



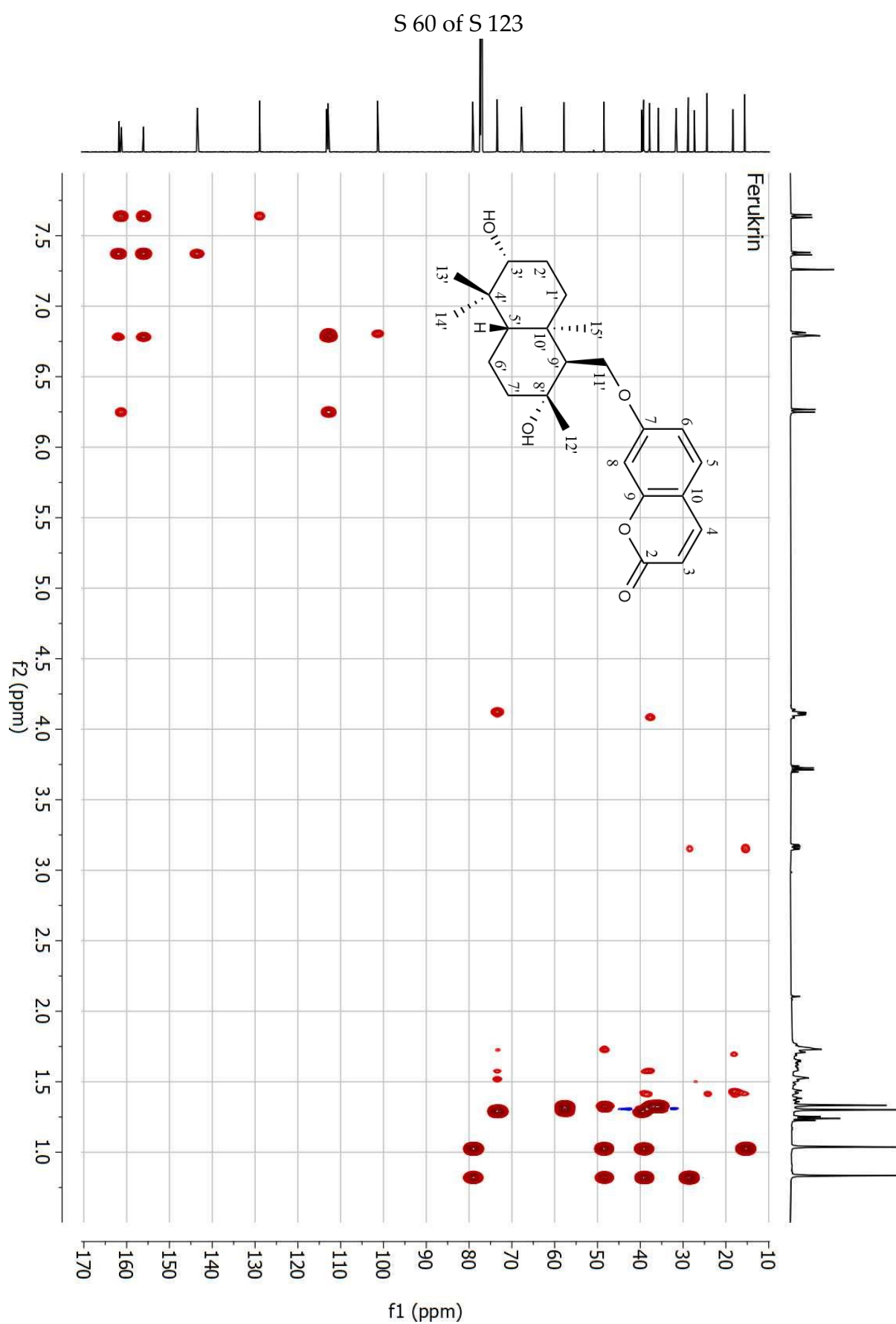
**Figure S51.**  $^{13}\text{C}$ -NMR spectrum (125 MHz,  $\text{CDCl}_3$ ) of ferukrin (9)



**Figure S52.** <sup>1</sup>H-<sup>1</sup>H COSY spectrum (CDCl<sub>3</sub>) of ferukrin (9)



**Figure S53.** HSQC spectrum (CDCl<sub>3</sub>) of ferukrin (9)



**Figure S54.** HMBC spectrum (CDCl<sub>3</sub>) of ferukrin (9)



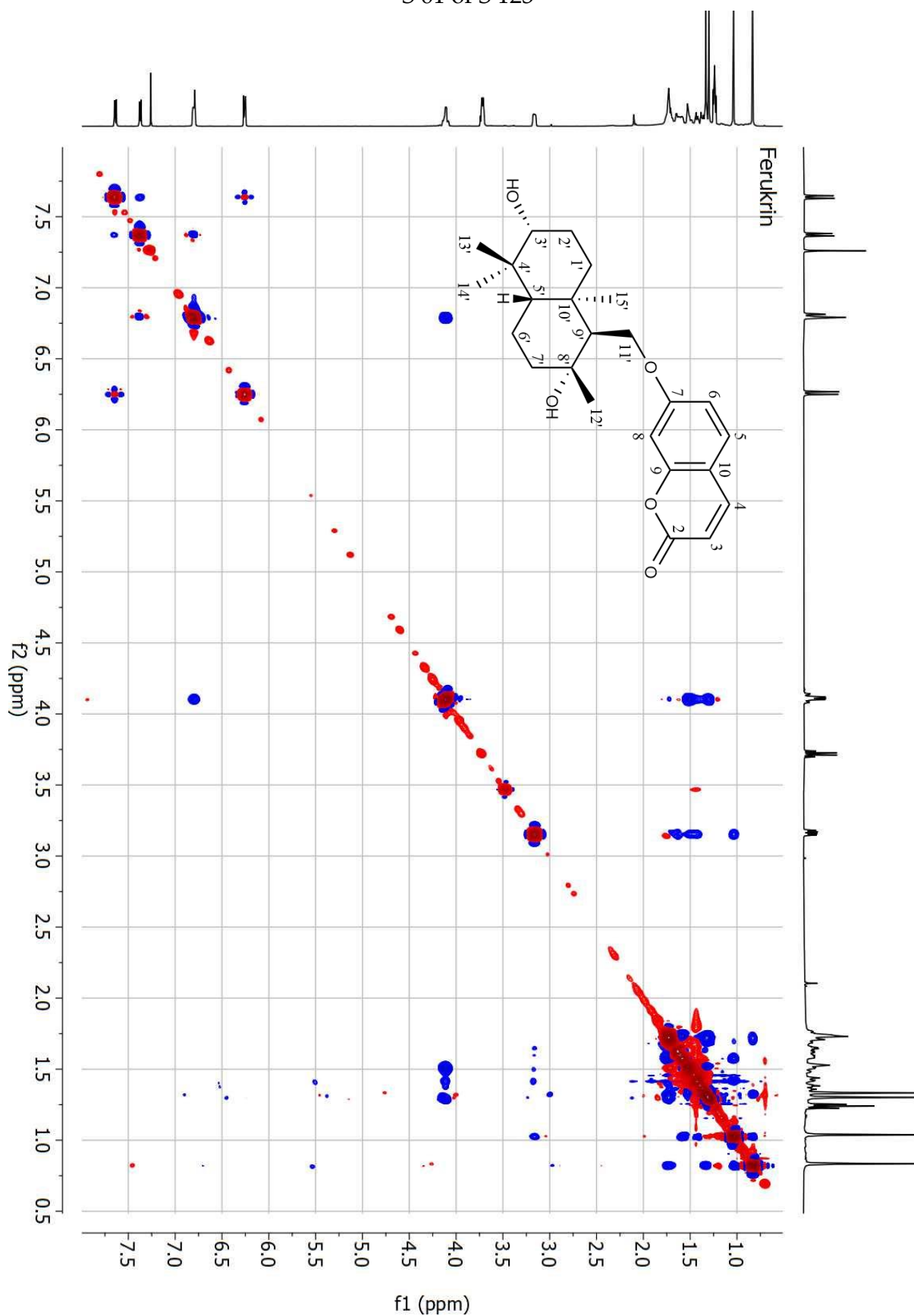
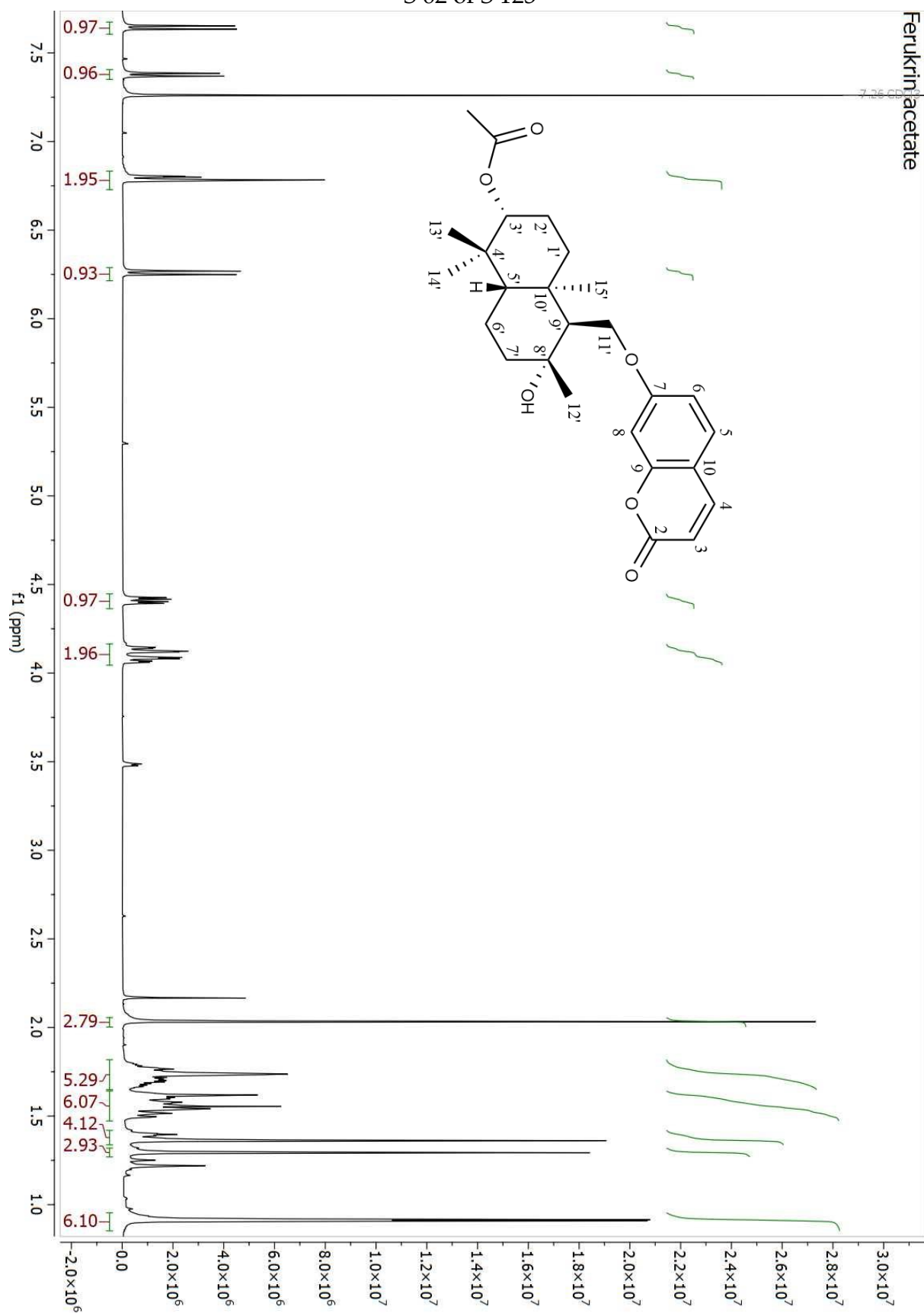


Figure S55. NOESY spectrum (CDCl<sub>3</sub>) of ferukrin (9)



**Figure S56.** <sup>1</sup>H-NMR spectrum (500 MHz, CDCl<sub>3</sub>) of ferukrin acetate (10)

## Ferukrin acetate

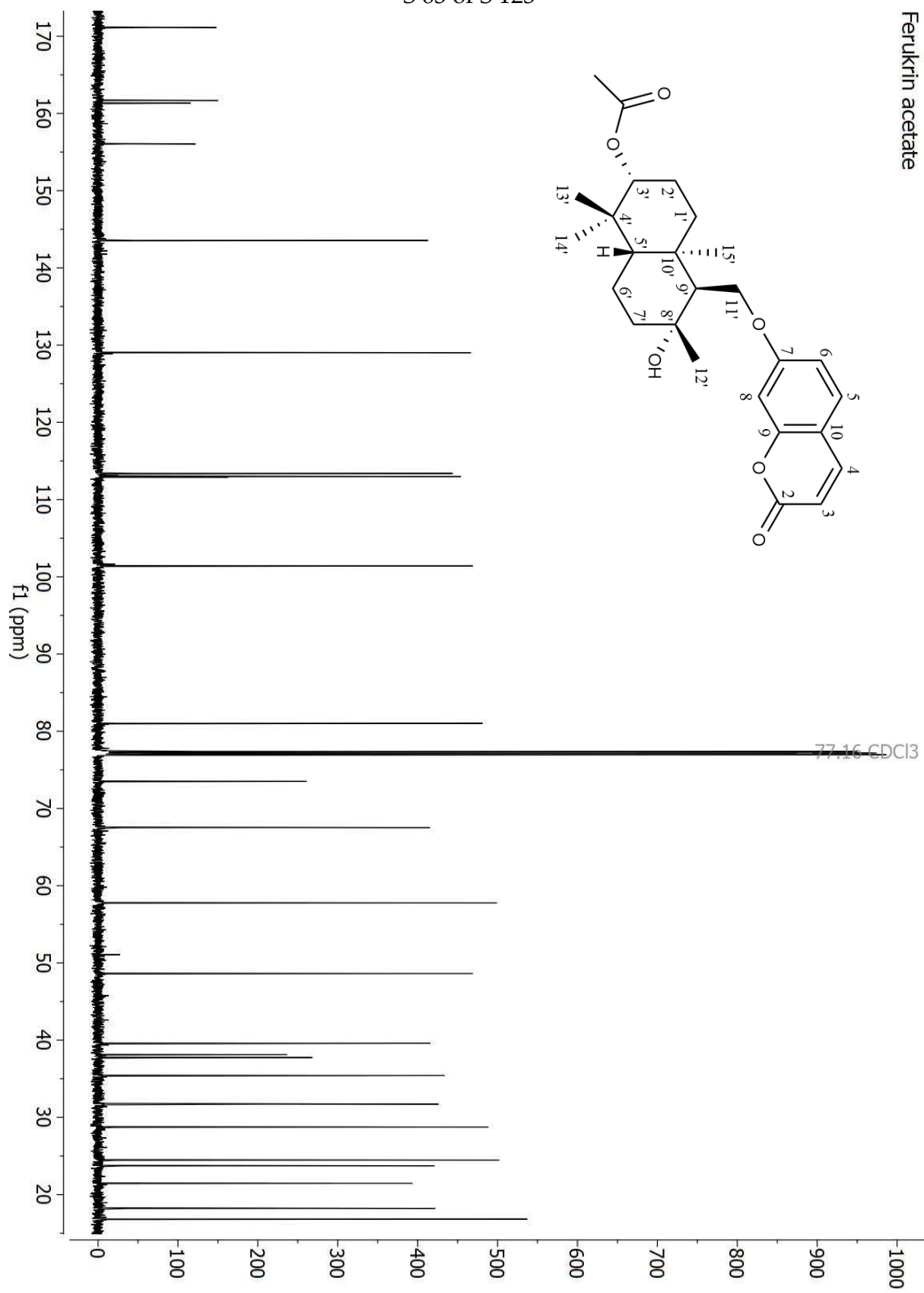
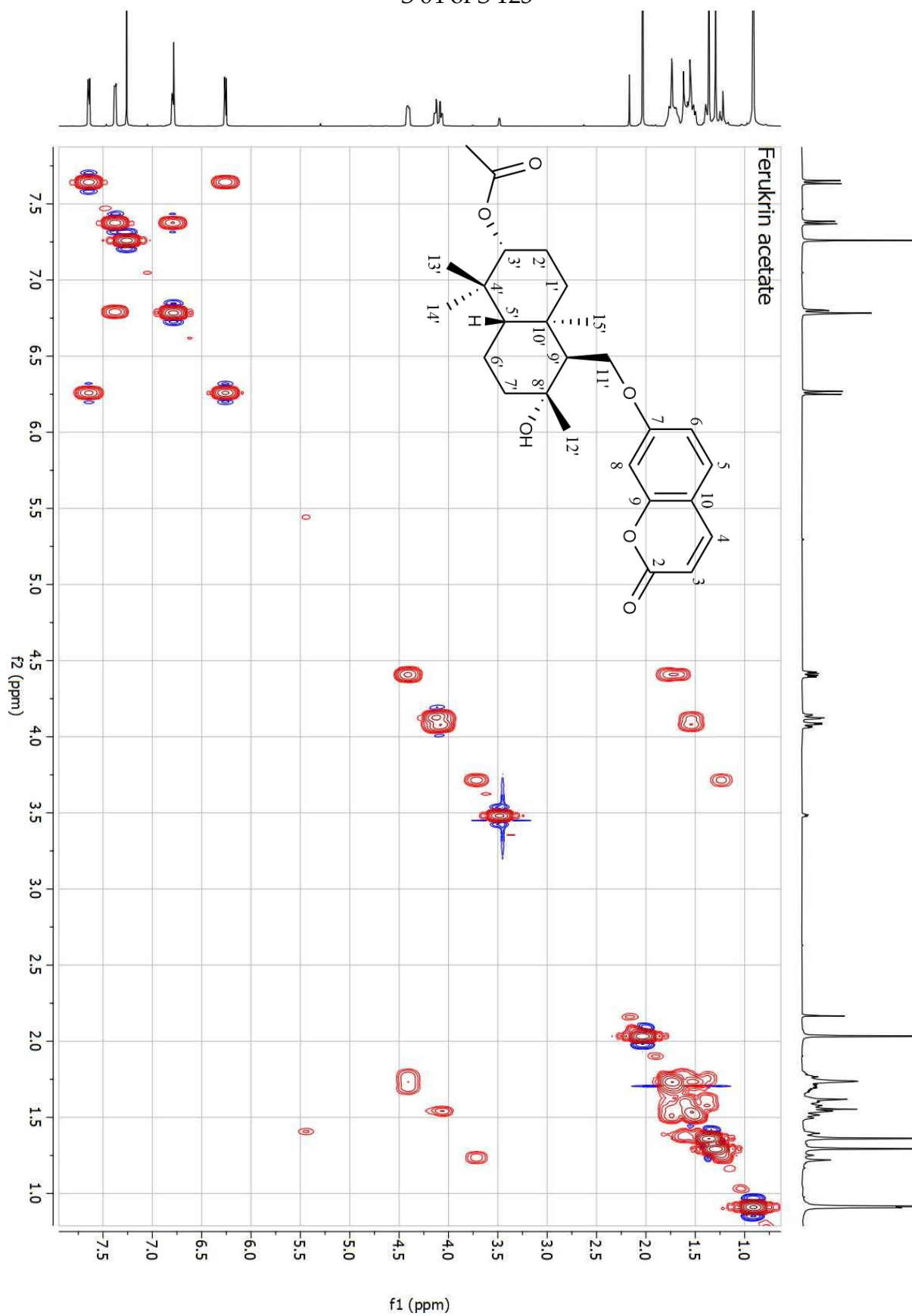
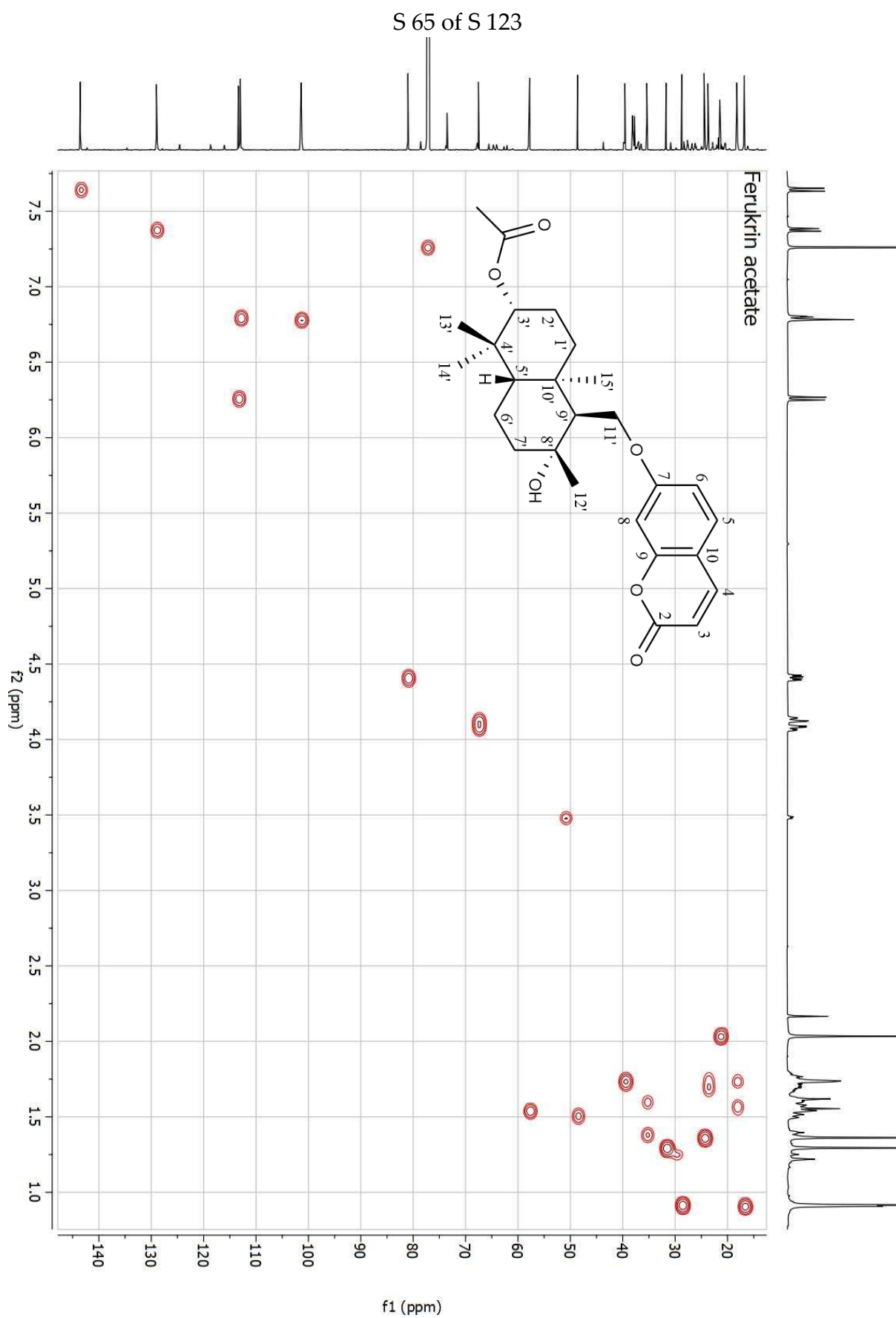


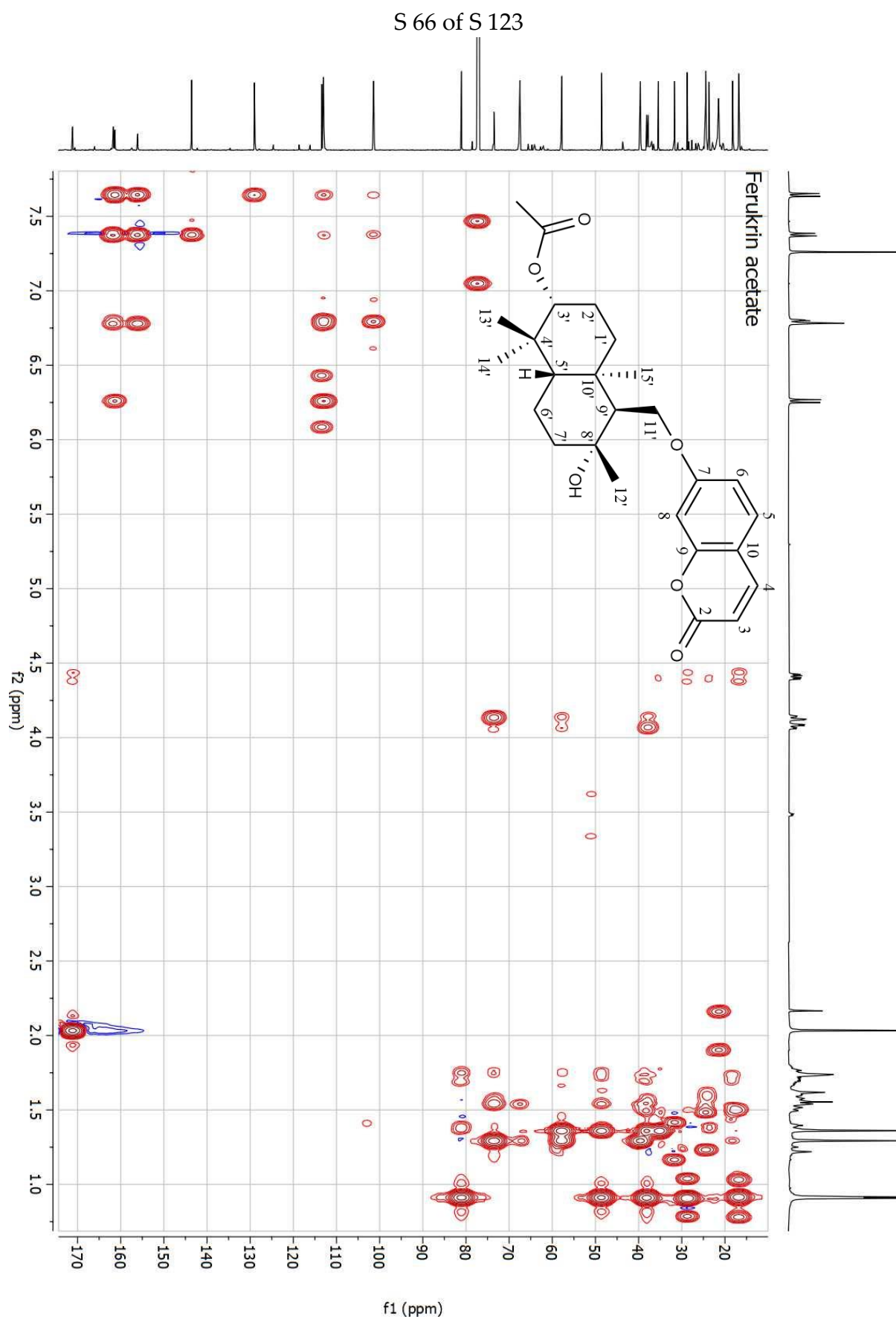
Figure S57.  $^{13}\text{C}$ -NMR spectrum (125 MHz,  $\text{CDCl}_3$ ) of ferukrin acetate (10)



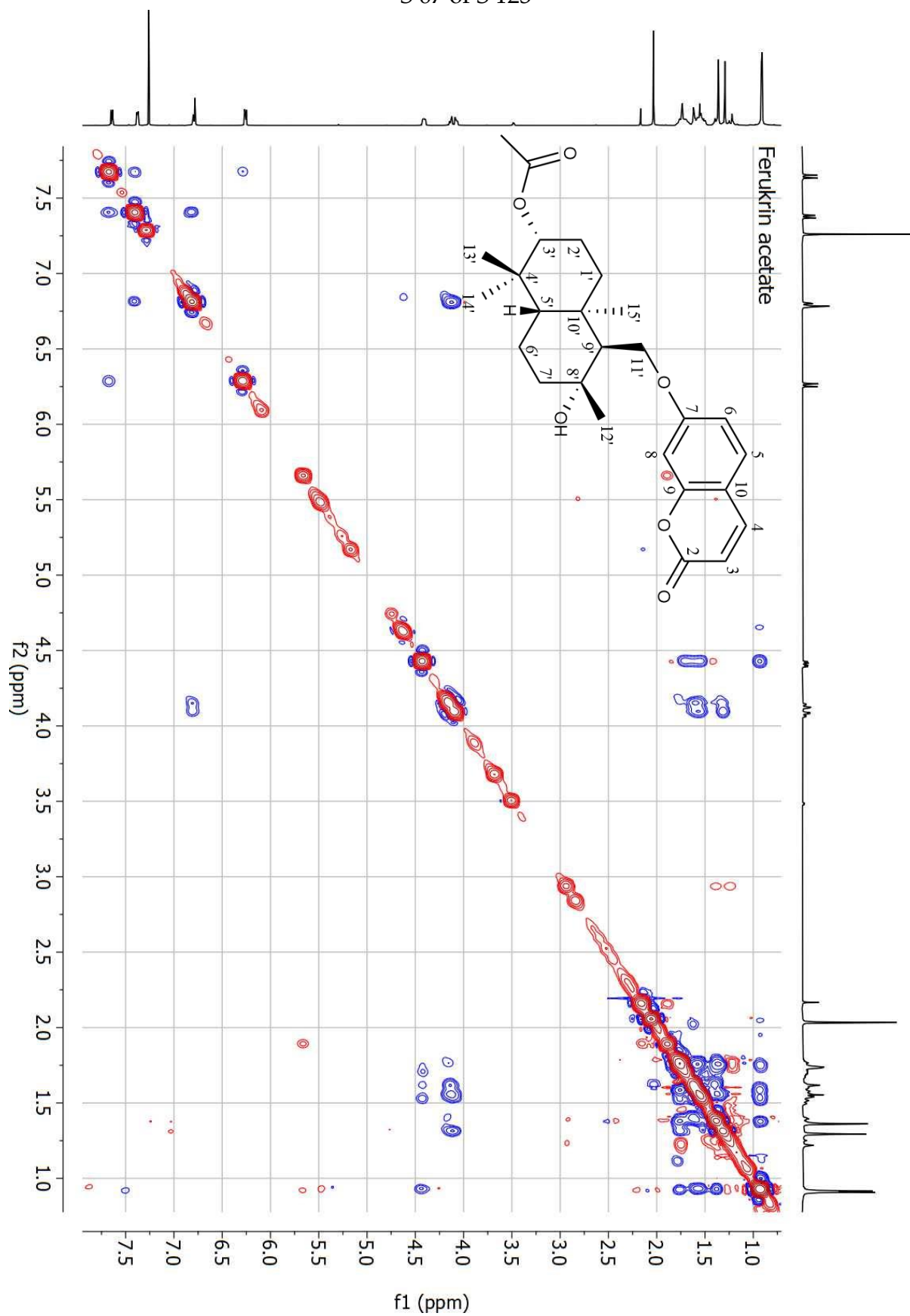
**Figure S58.**  $^1\text{H}$ - $^1\text{H}$  COSY spectrum ( $\text{CDCl}_3$ ) of ferukrin acetate (10)

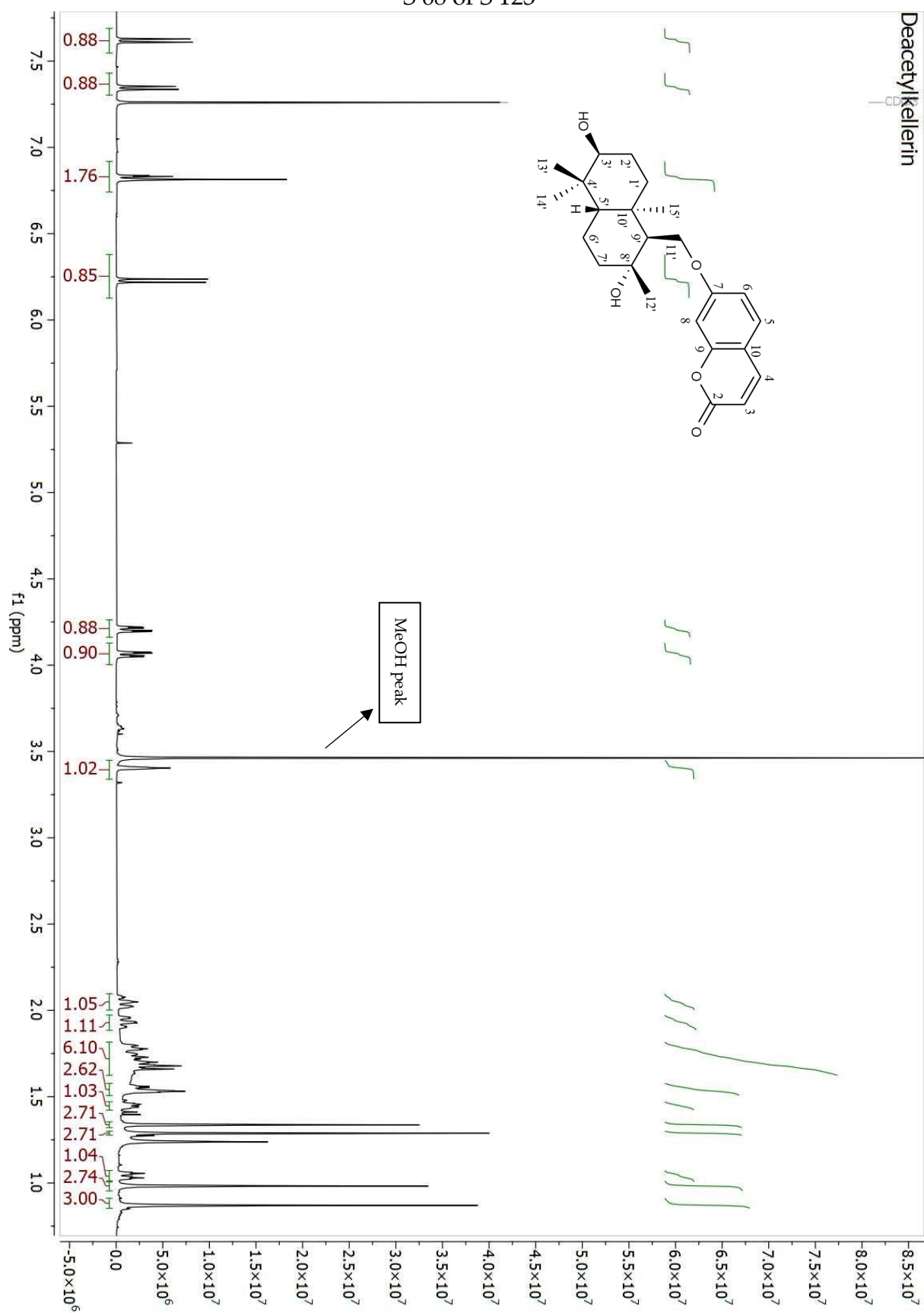


**Figure S59.** HSQC spectrum (CDCl<sub>3</sub>) of ferukrin acetate (10)



**Figure S60.** HMBC spectrum (CDCl<sub>3</sub>) of ferukrin acetate (10)

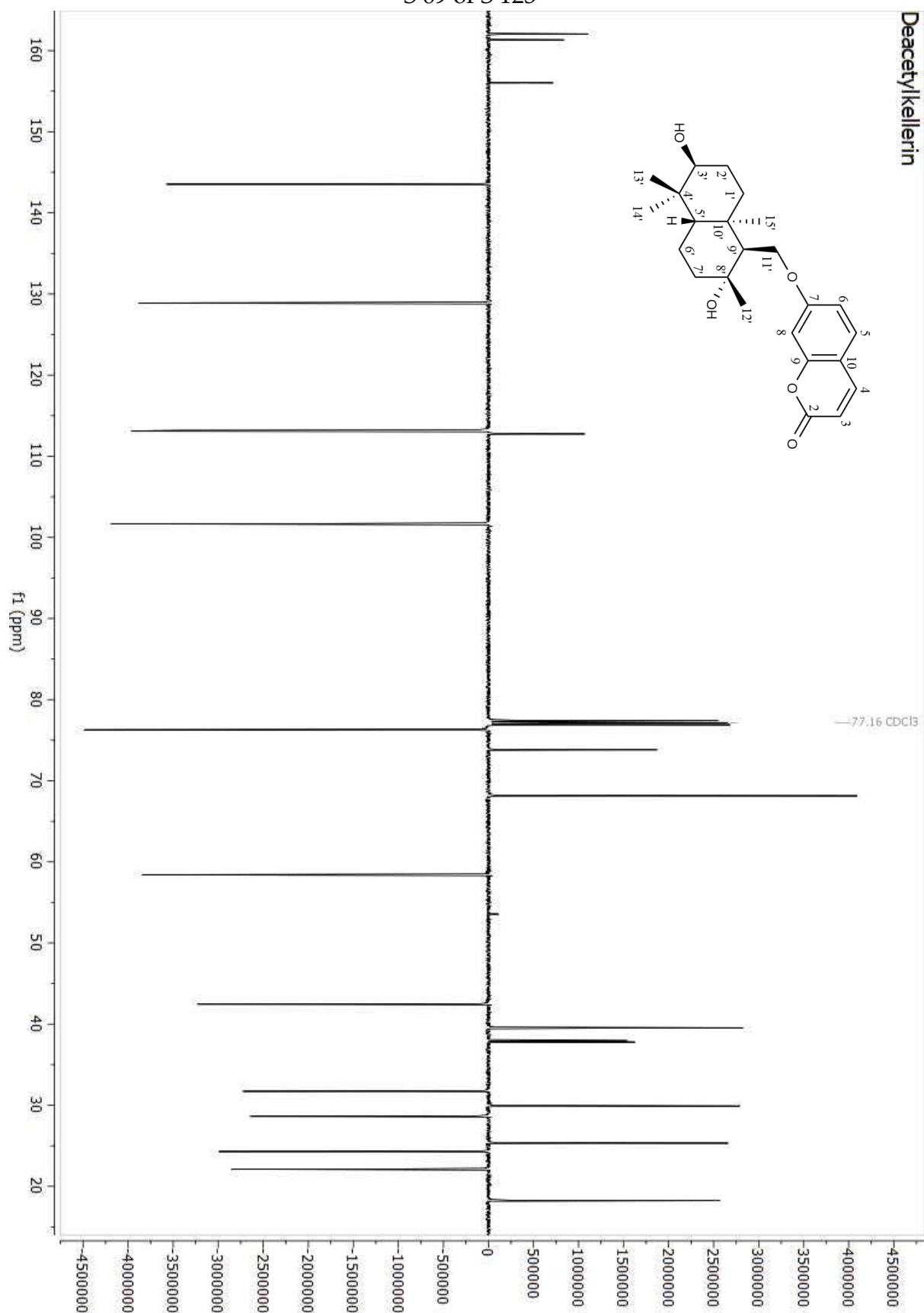
**Figure S61.** NOESY spectrum (CDCl<sub>3</sub>) of ferukrin acetate (10)

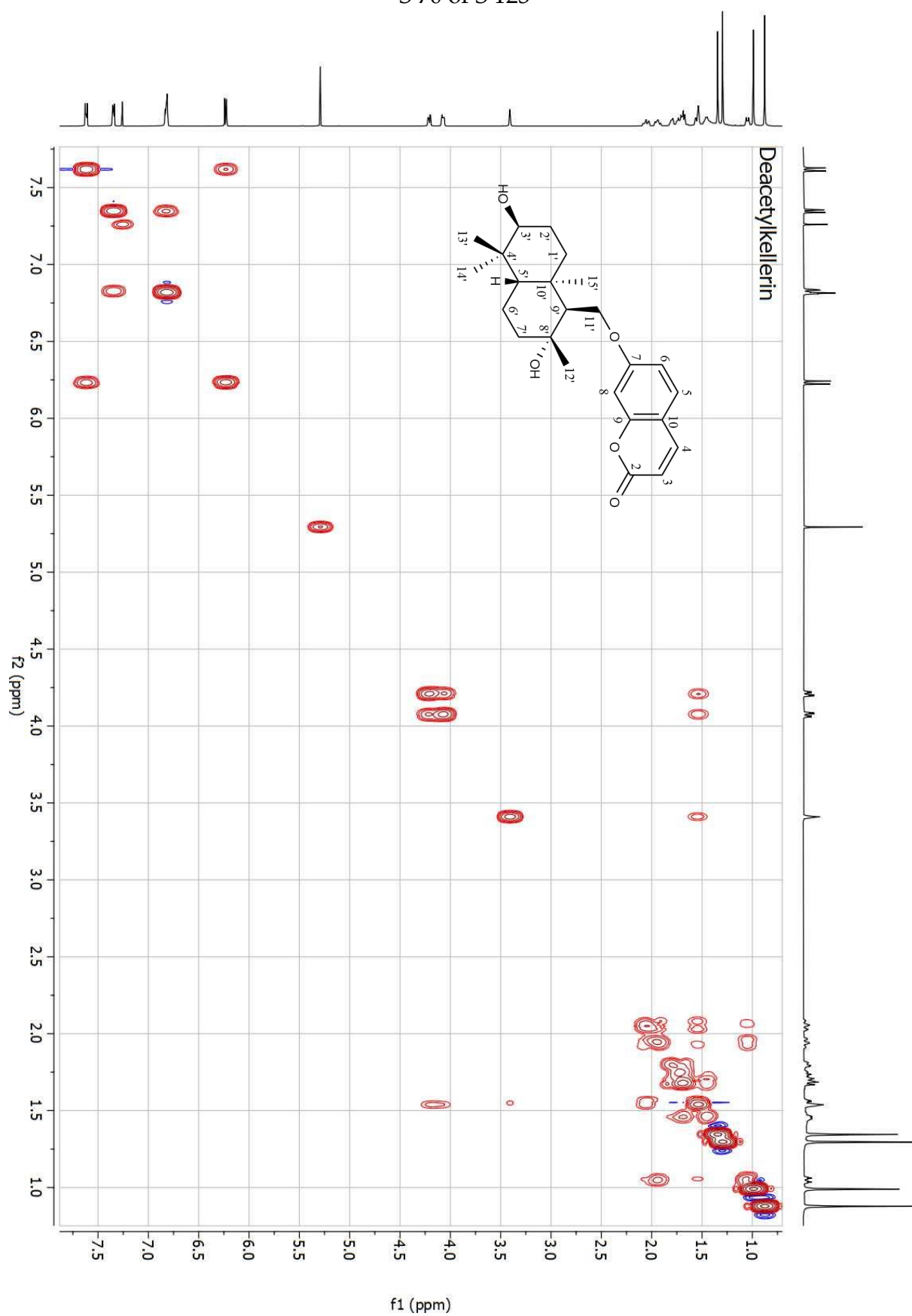


**Figure S62.**  $^1\text{H-NMR}$  spectrum (500 MHz,  $\text{CDCl}_3$ ) of deacetylkellerin (11)



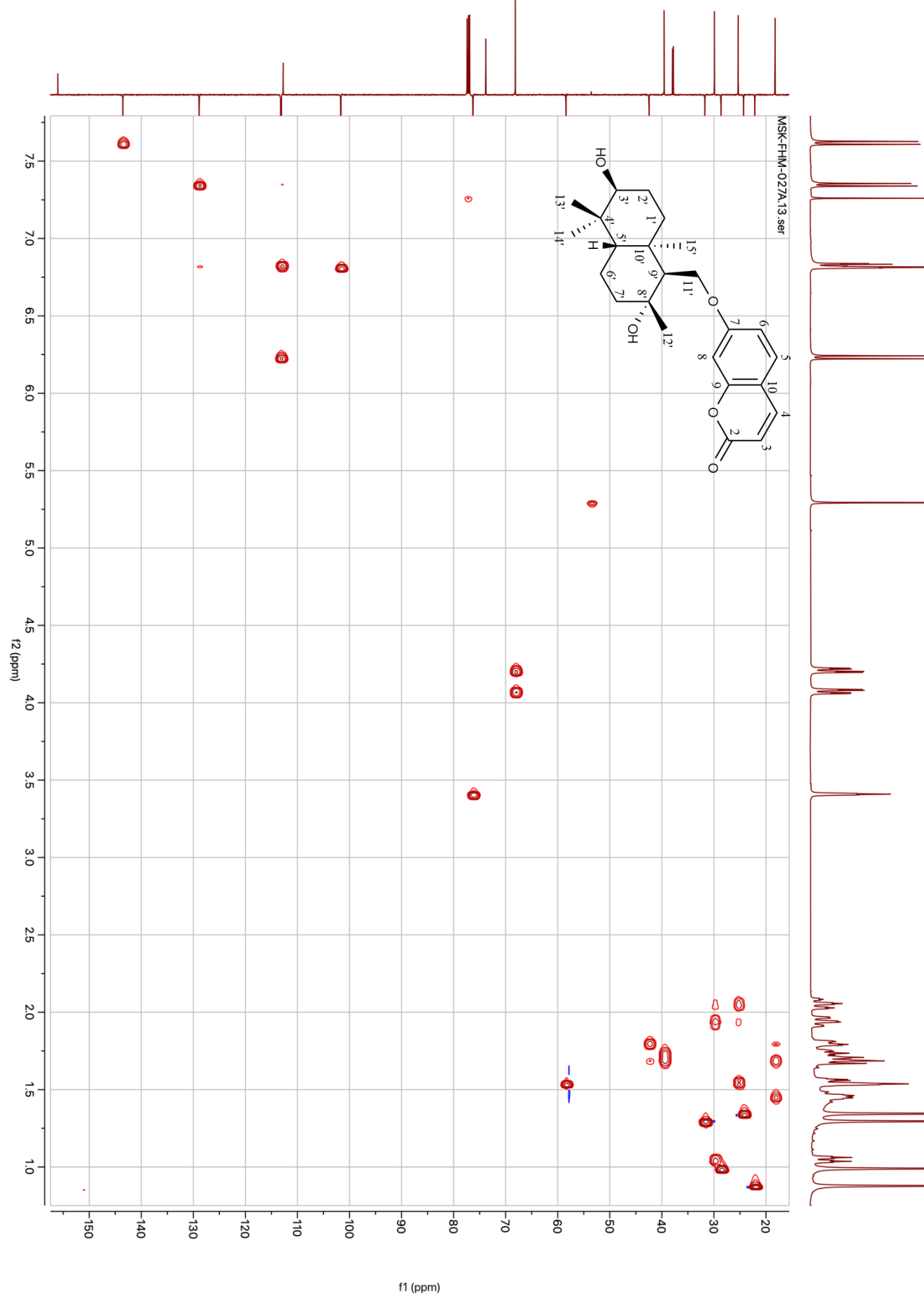
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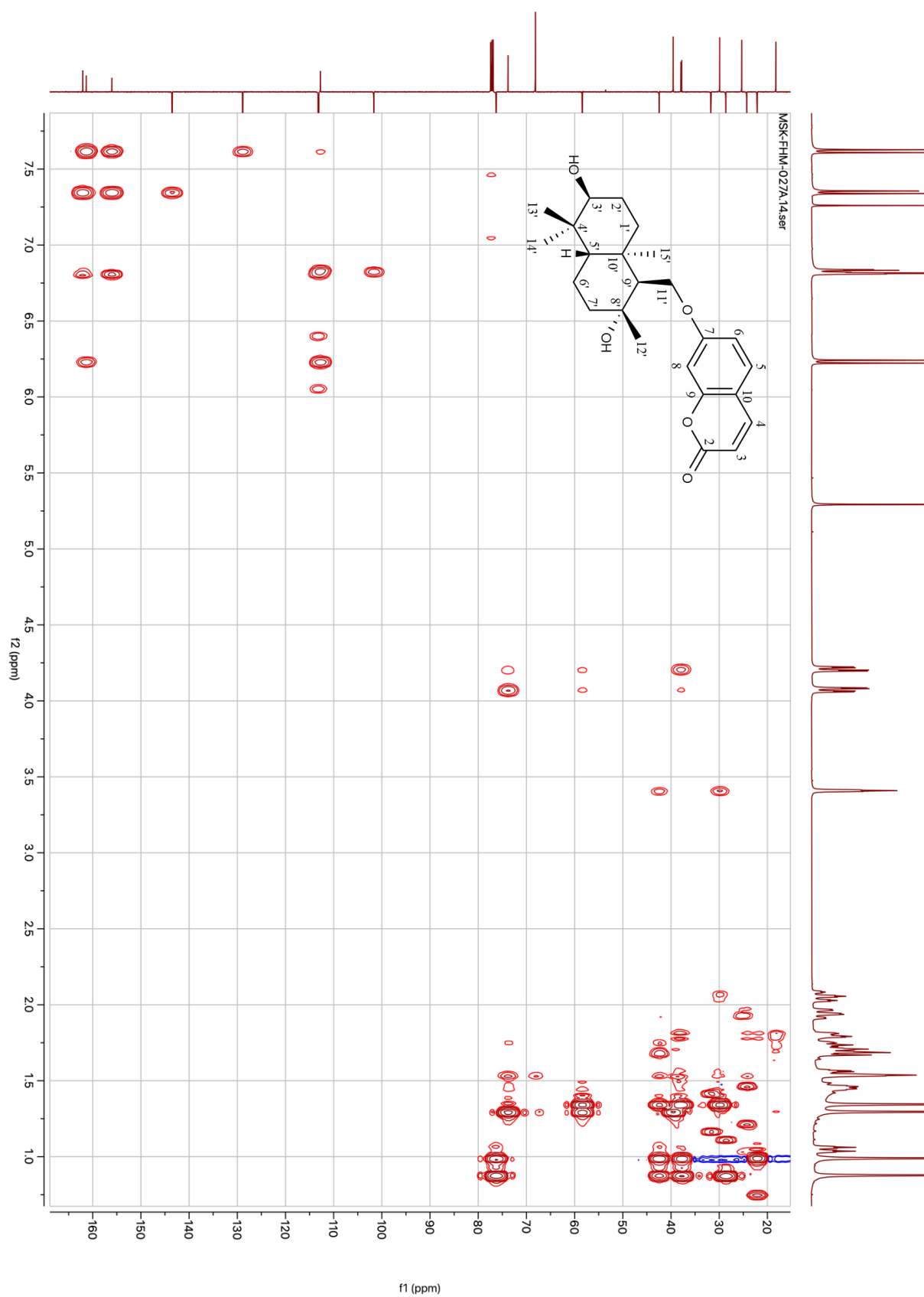
**Figure S63.**  $^{13}\text{C}$ -NMR (APT) spectrum (125 MHz,  $\text{CDCl}_3$ ) of deacetylkellerin (11)

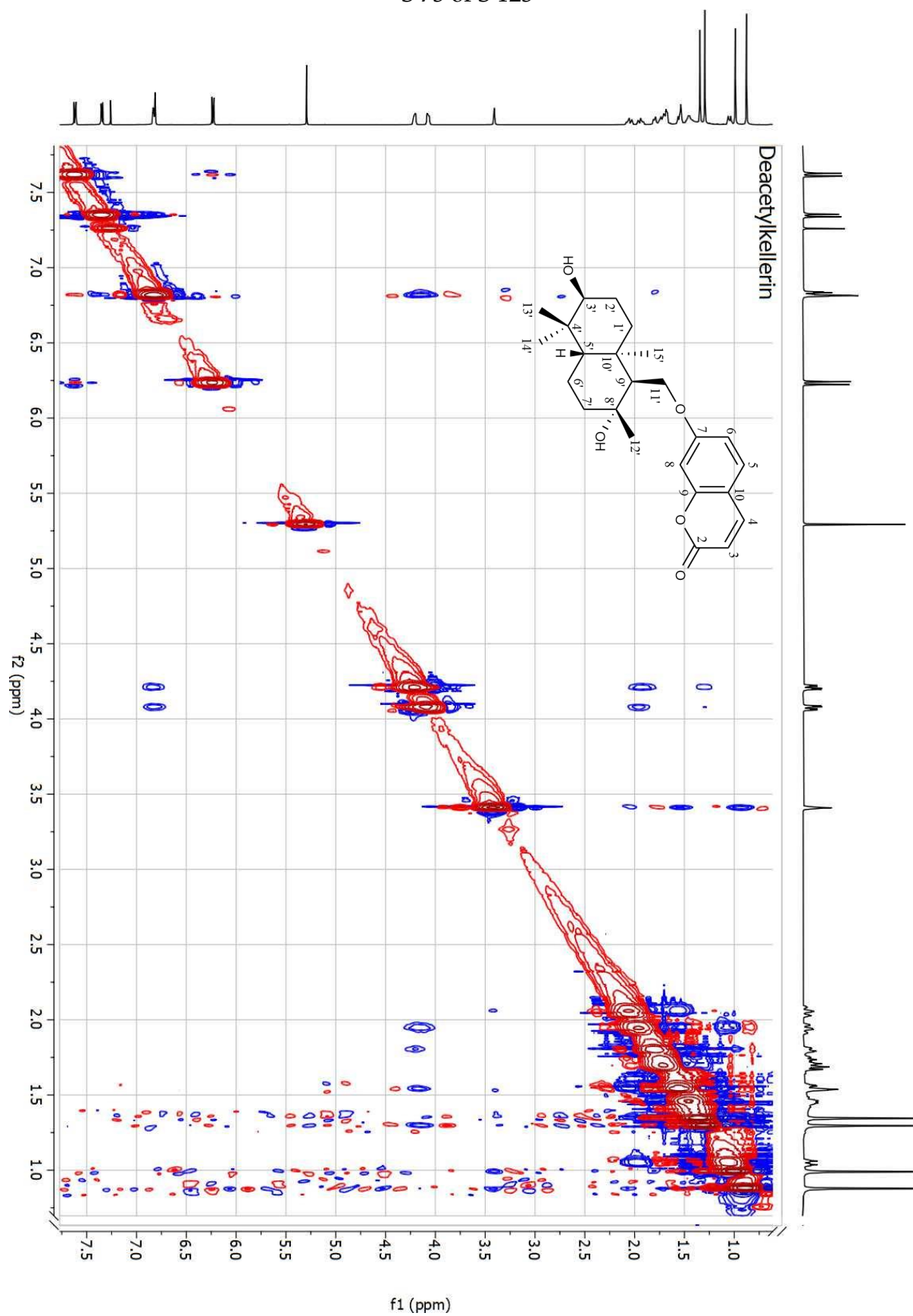


**Figure S64.** <sup>1</sup>H-<sup>1</sup>H COSY spectrum (CDCl<sub>3</sub>) of deacetylkellerin (11)

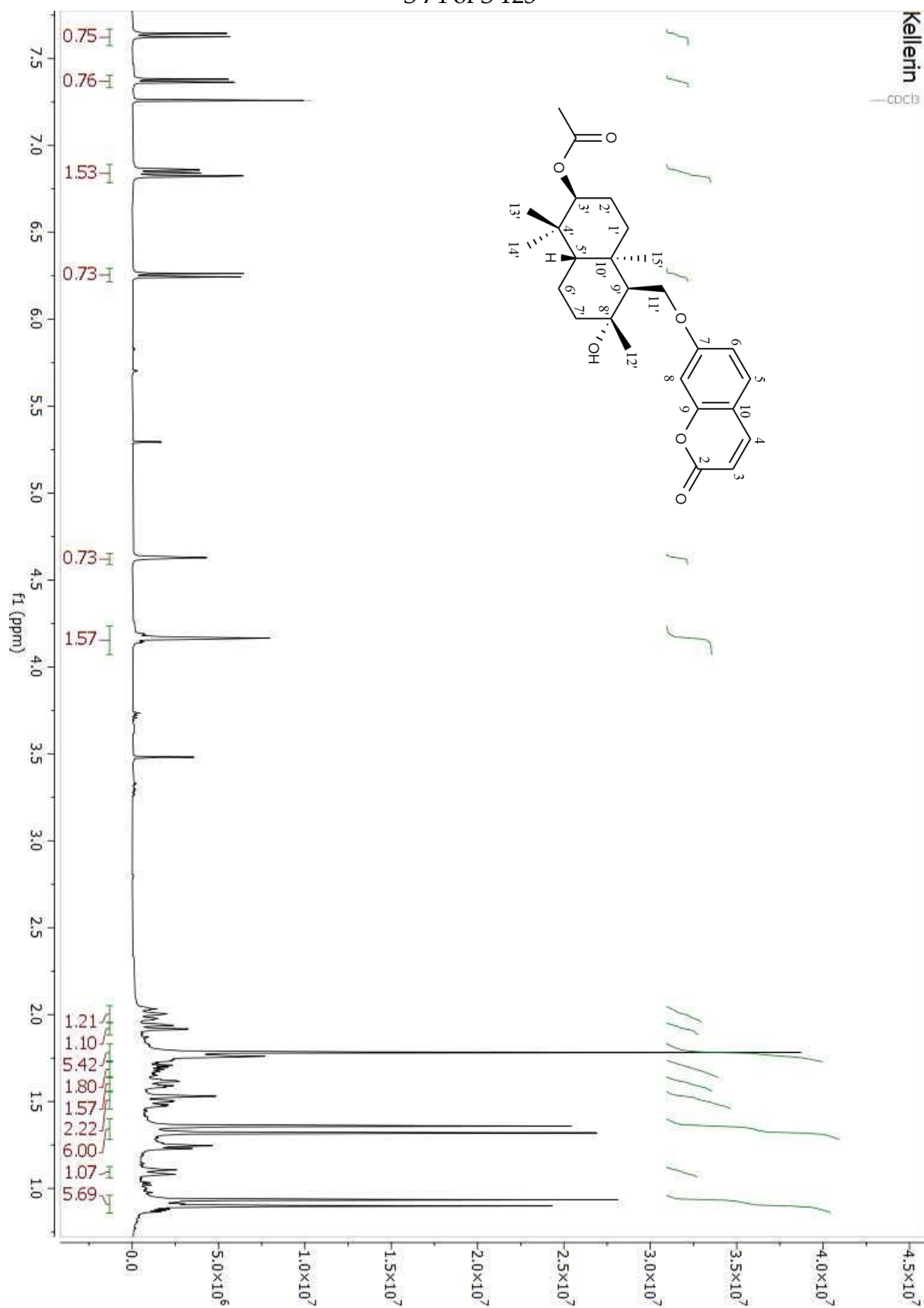
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**Figure S65.** HSQC spectrum ( $\text{CDCl}_3$ ) of deacetylkellerin (11)

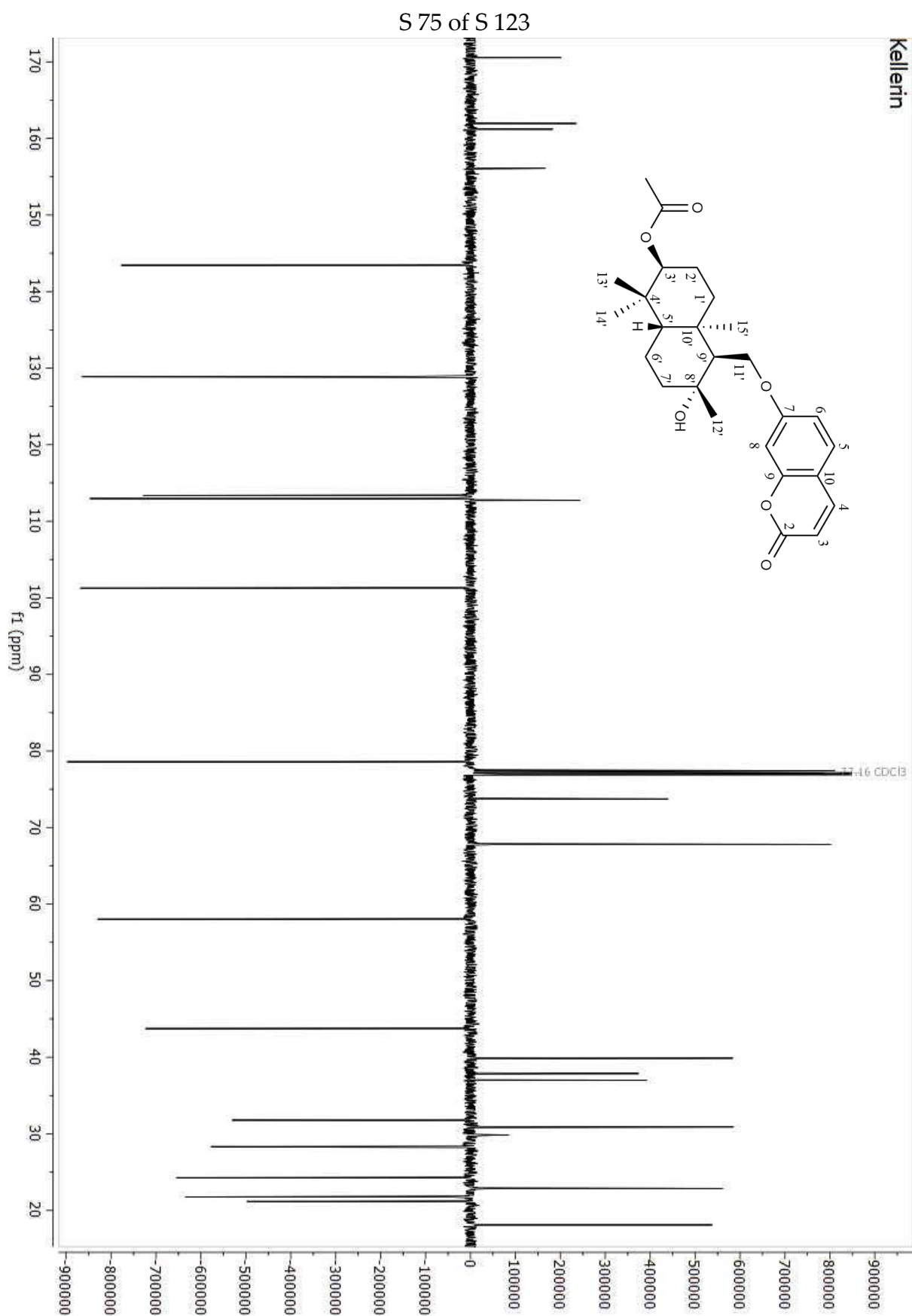
**Figure S66.** HMBC spectrum (CDCl<sub>3</sub>) of deacetylkellerin (11)



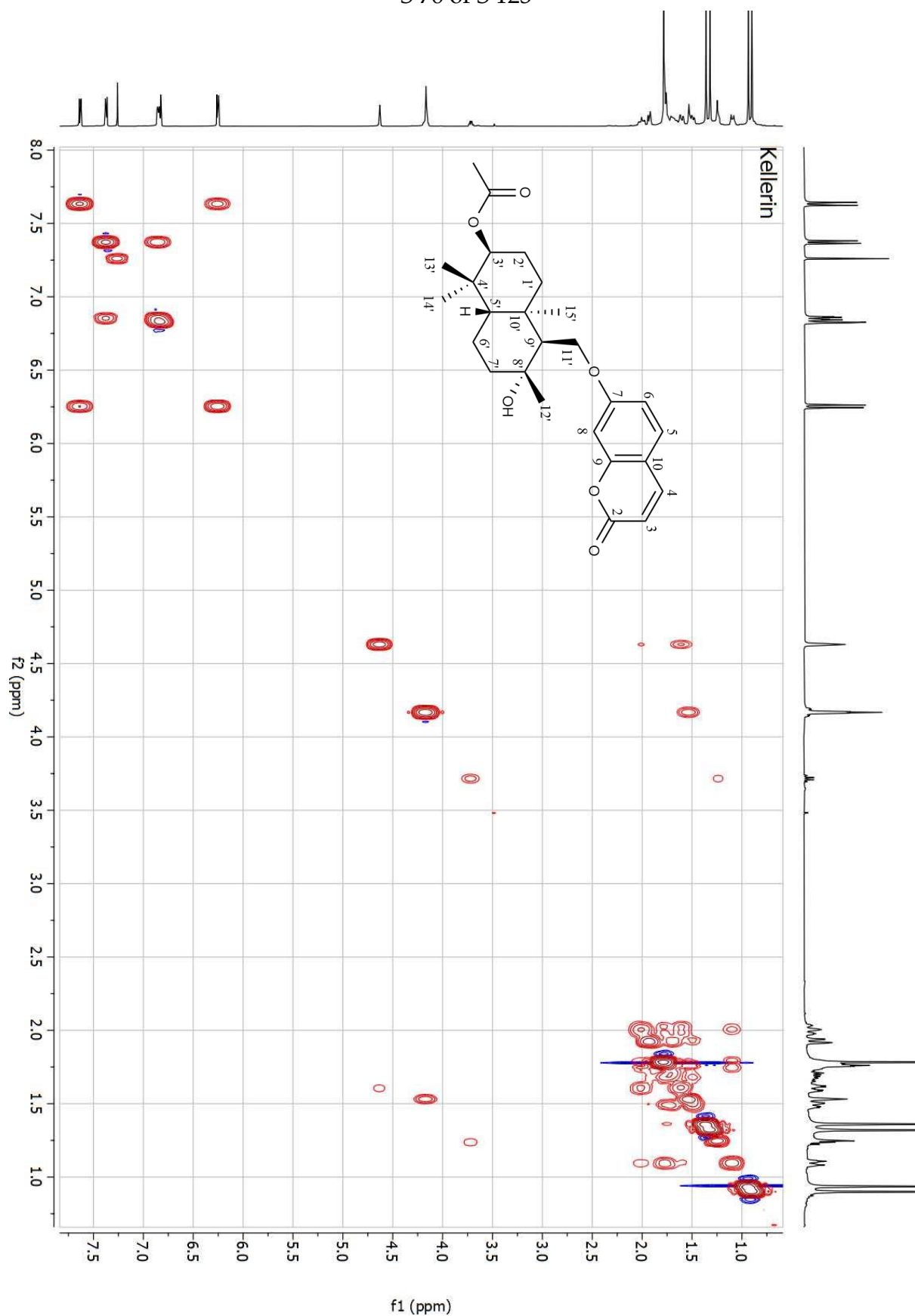
**Figure S67.** NOESY spectrum (CDCl<sub>3</sub>) of deacetylkellerin (11)



**Figure S68.** <sup>1</sup>H-NMR spectrum (500 MHz, CDCl<sub>3</sub>) of kellerin (12)

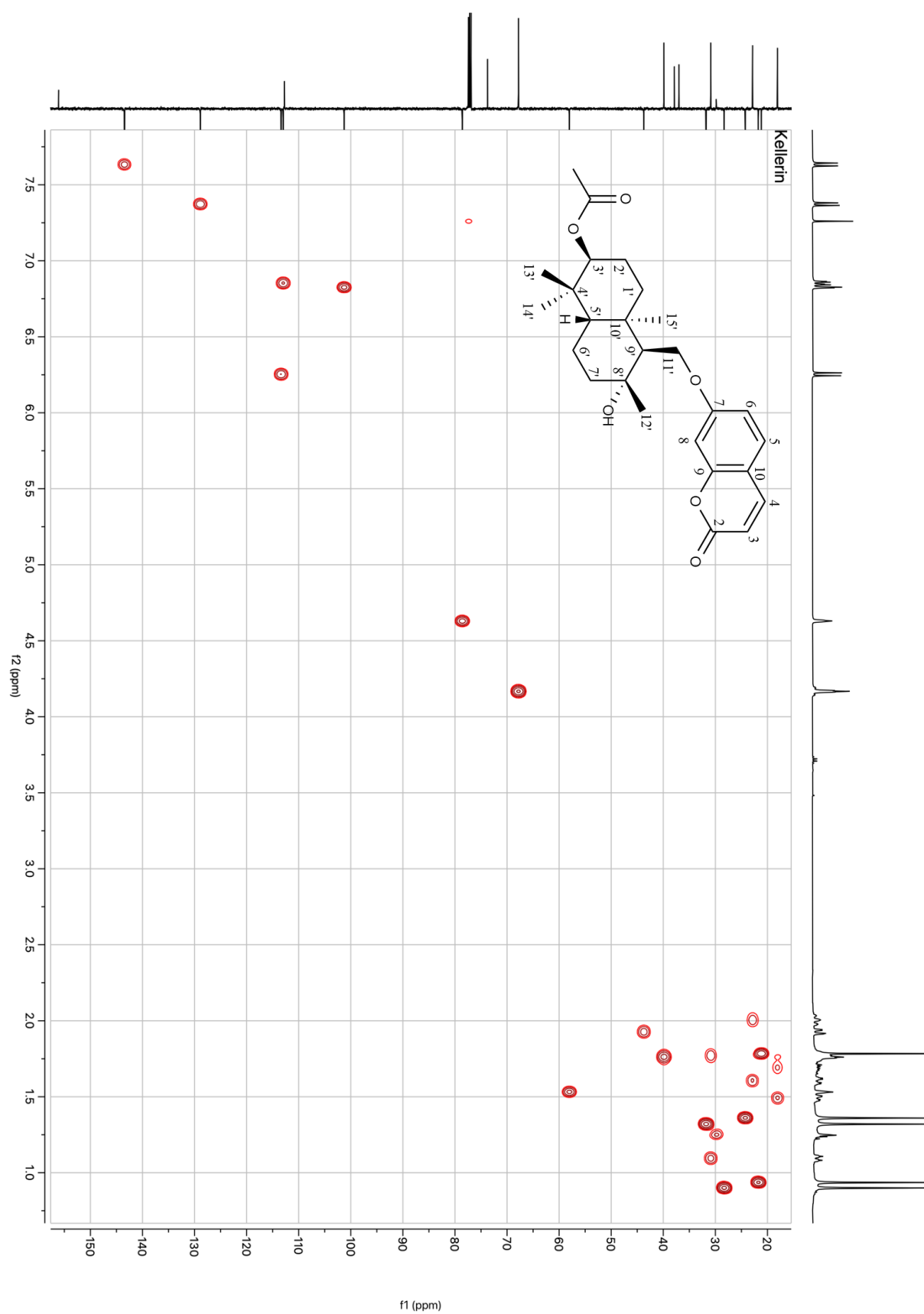


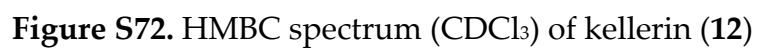
**Figure S69.**  $^{13}\text{C}$ -NMR (APT) spectrum (125 MHz,  $\text{CDCl}_3$ ) of kellerin (12)

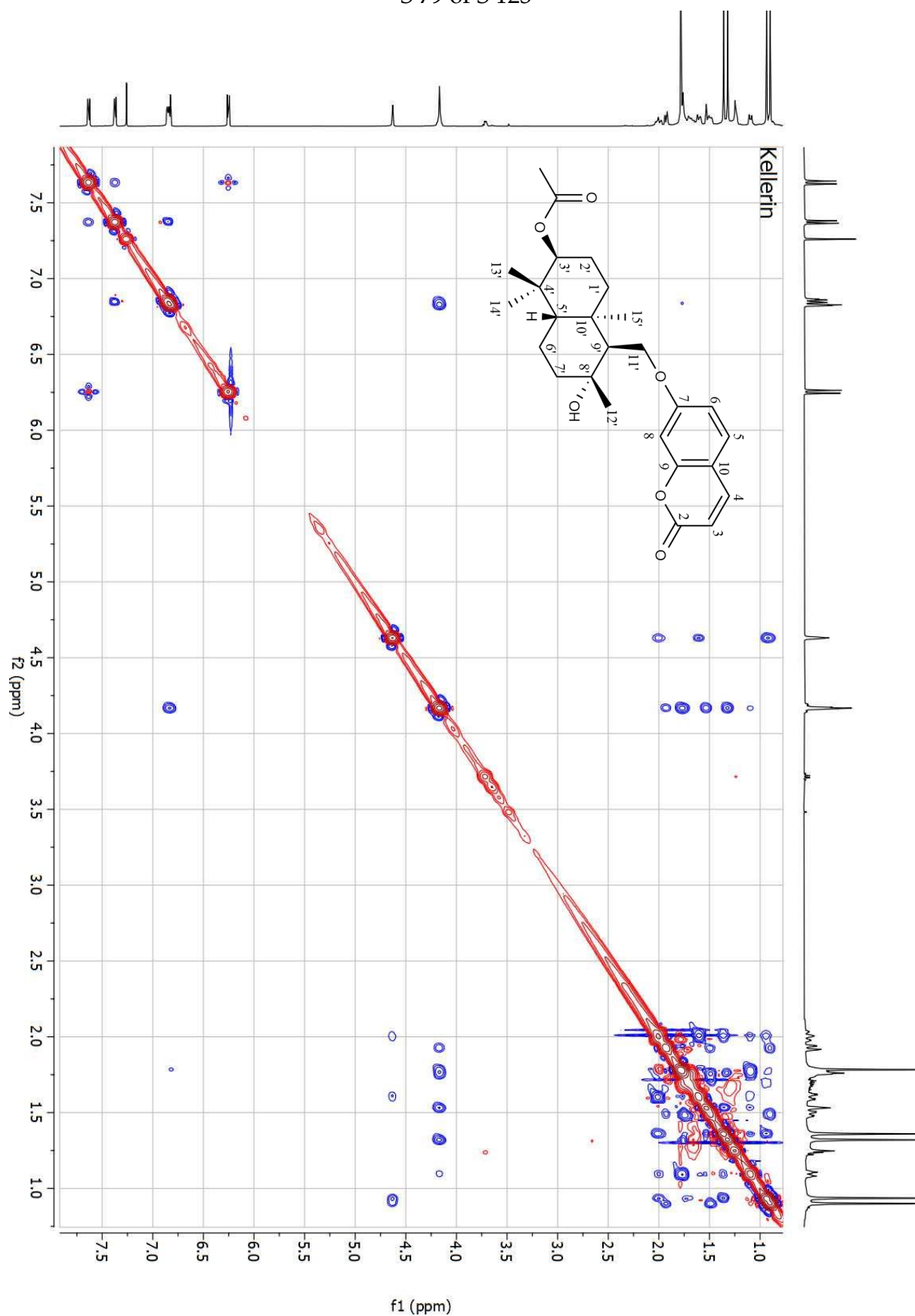
**Figure S70.**  $^1\text{H}$ - $^1\text{H}$  COSY spectrum ( $\text{CDCl}_3$ ) of kellerin (12)

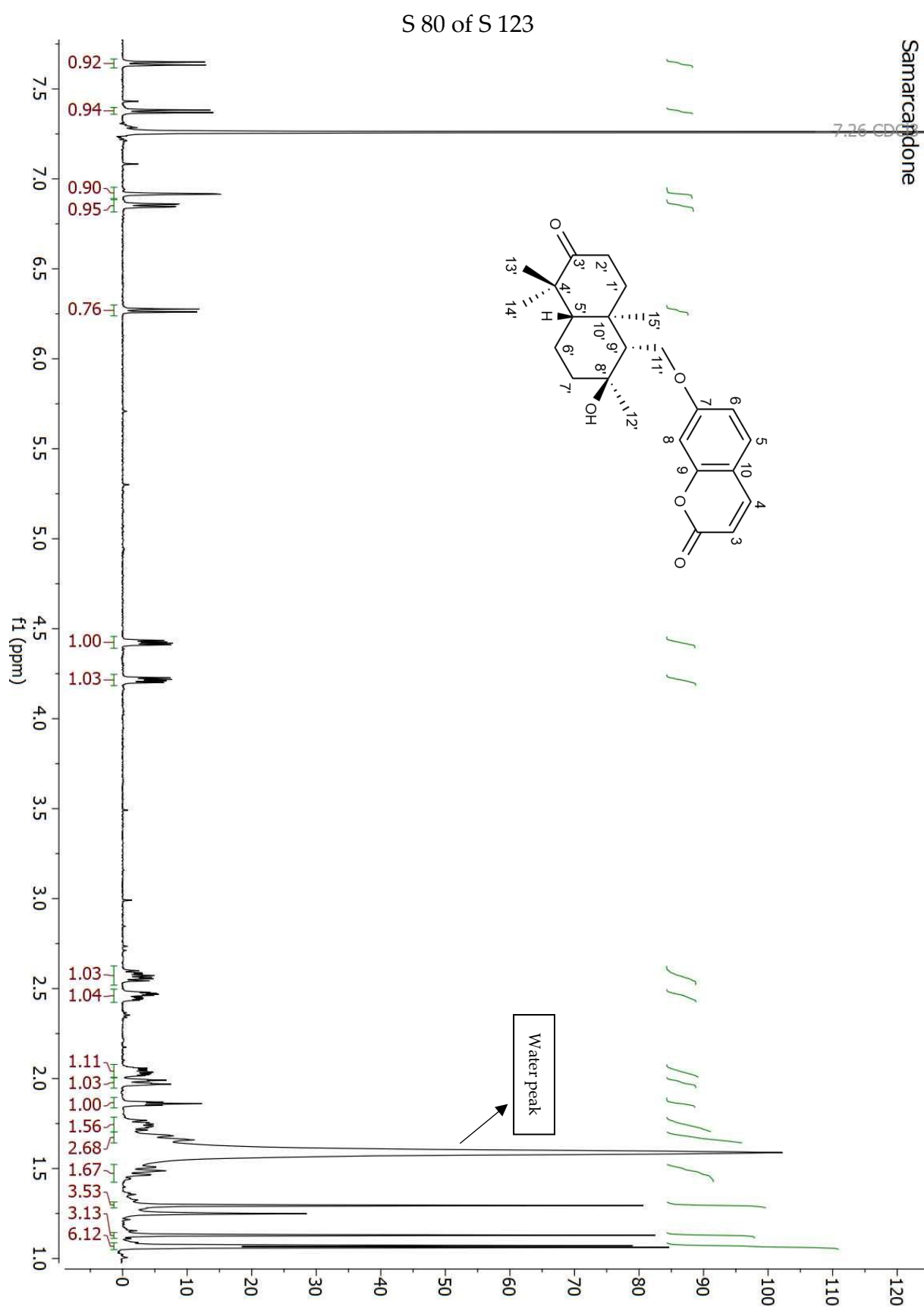


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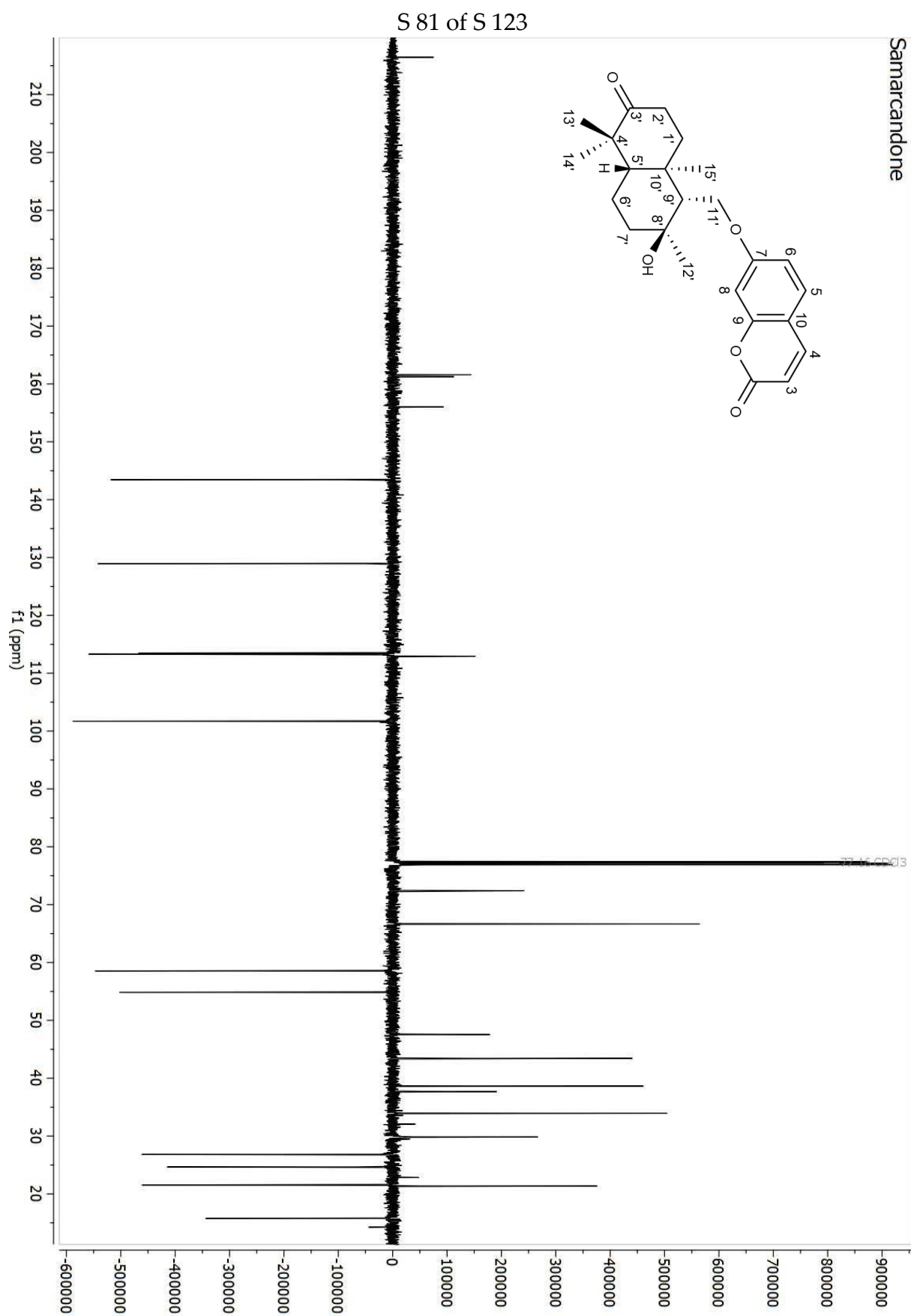
**Figure S71.** HSQC spectrum (CDCl<sub>3</sub>) of kellerin (12)



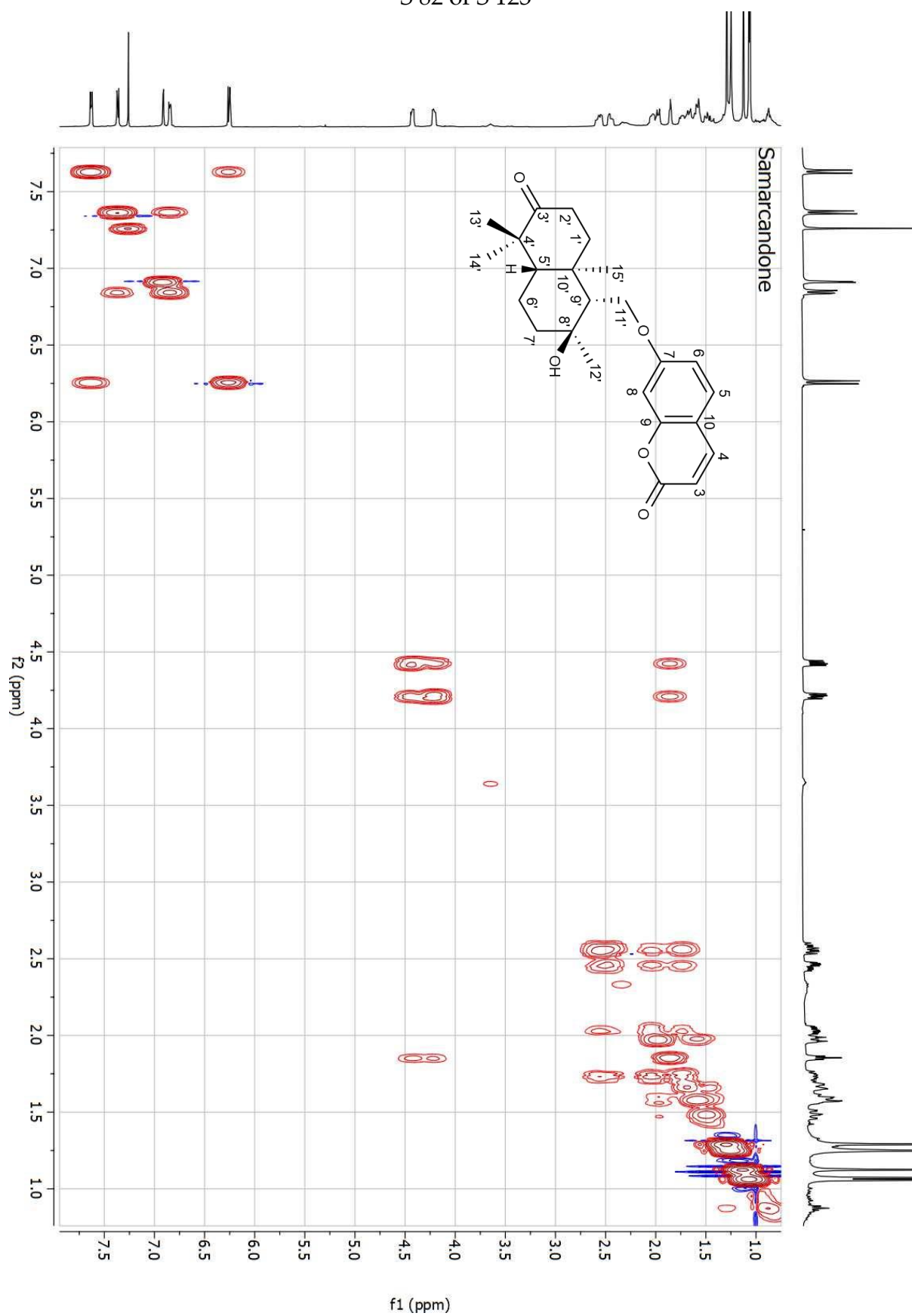
**Figure S73.** NOESY spectrum ( $\text{CDCl}_3$ ) of kellerin (12)



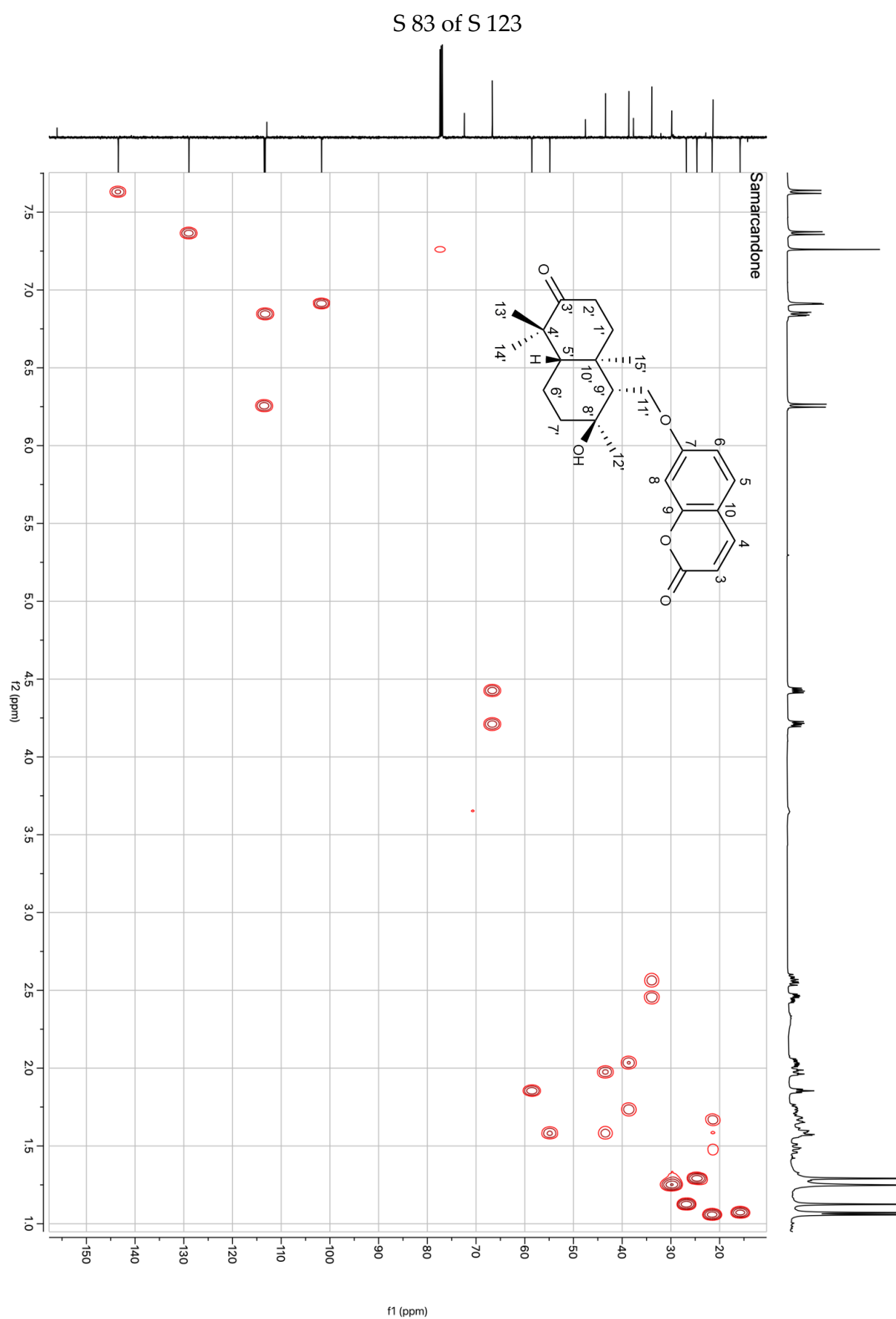
**Figure S74.**  $^1\text{H}$ -NMR spectrum (500 MHz,  $\text{CDCl}_3$ ) of samarcandone (13)



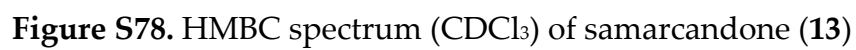
**Figure S75.**  $^{13}\text{C}$ -NMR (APT) spectrum (125 MHz,  $\text{CDCl}_3$ ) of samarcondone (13)



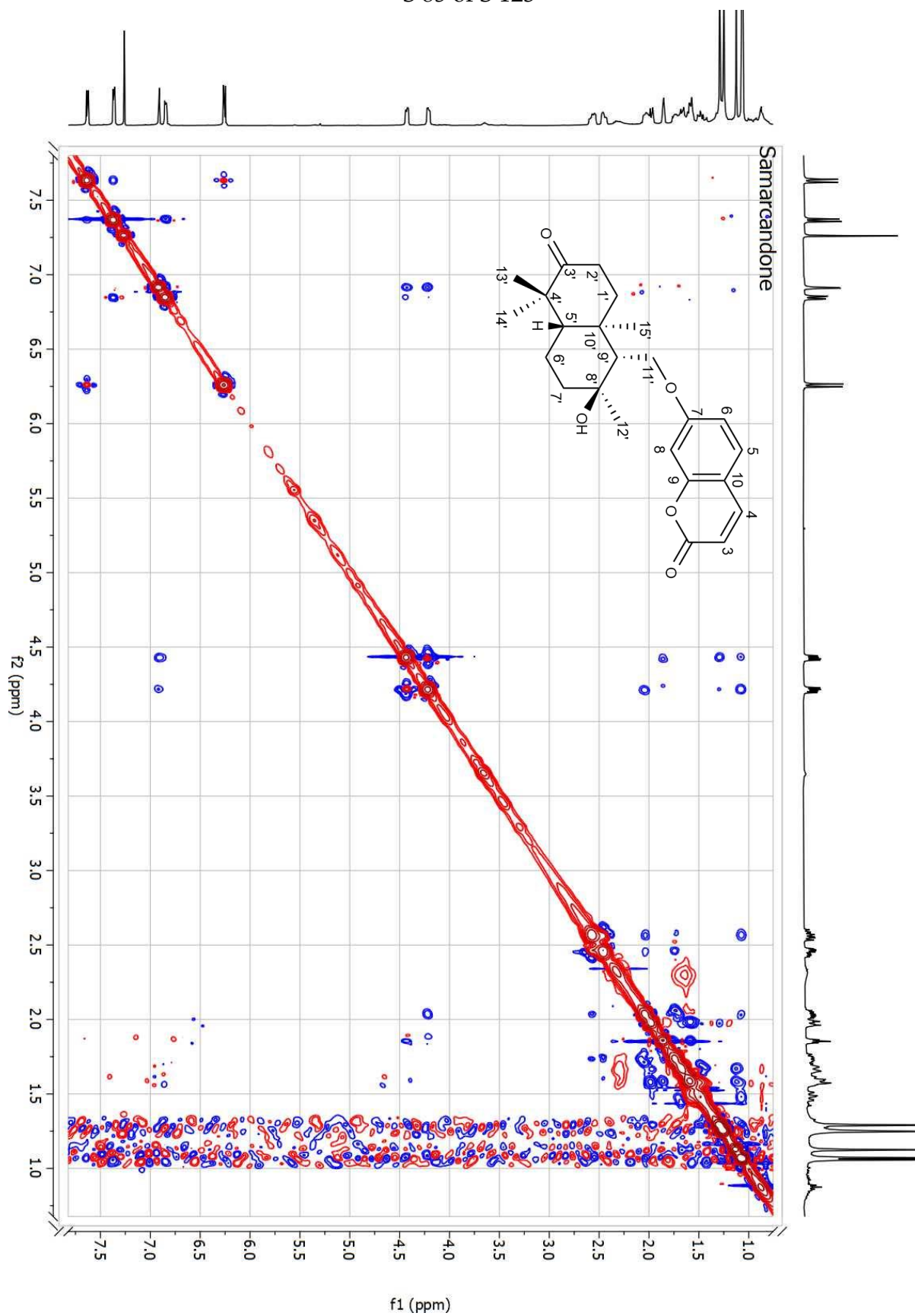
**Figure S76.** <sup>1</sup>H-<sup>1</sup>H COSY spectrum (CDCl<sub>3</sub>) of samarcondone (13)



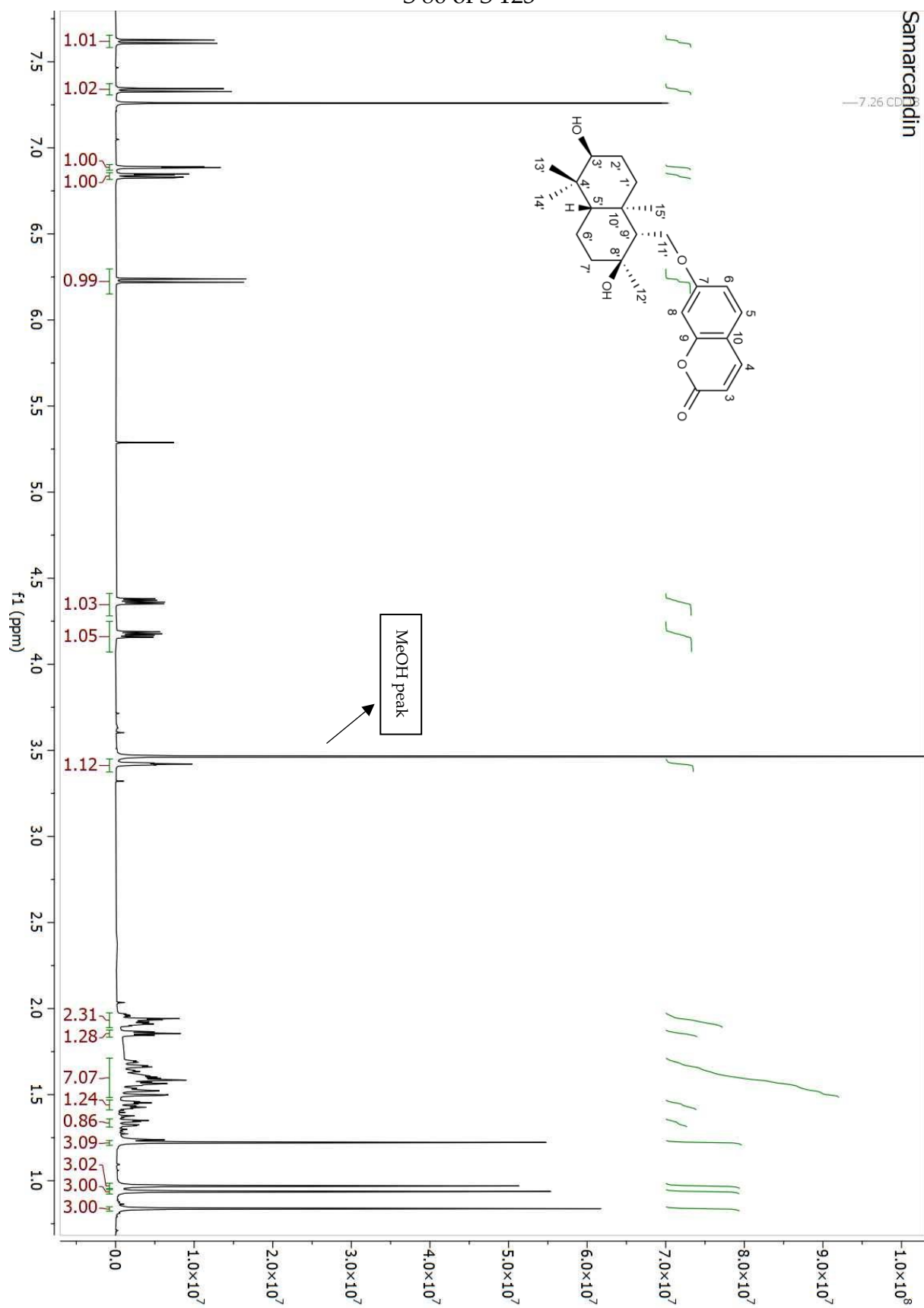
**Figure S77.** HSQC spectrum (CDCl<sub>3</sub>) of samarcandone (13)

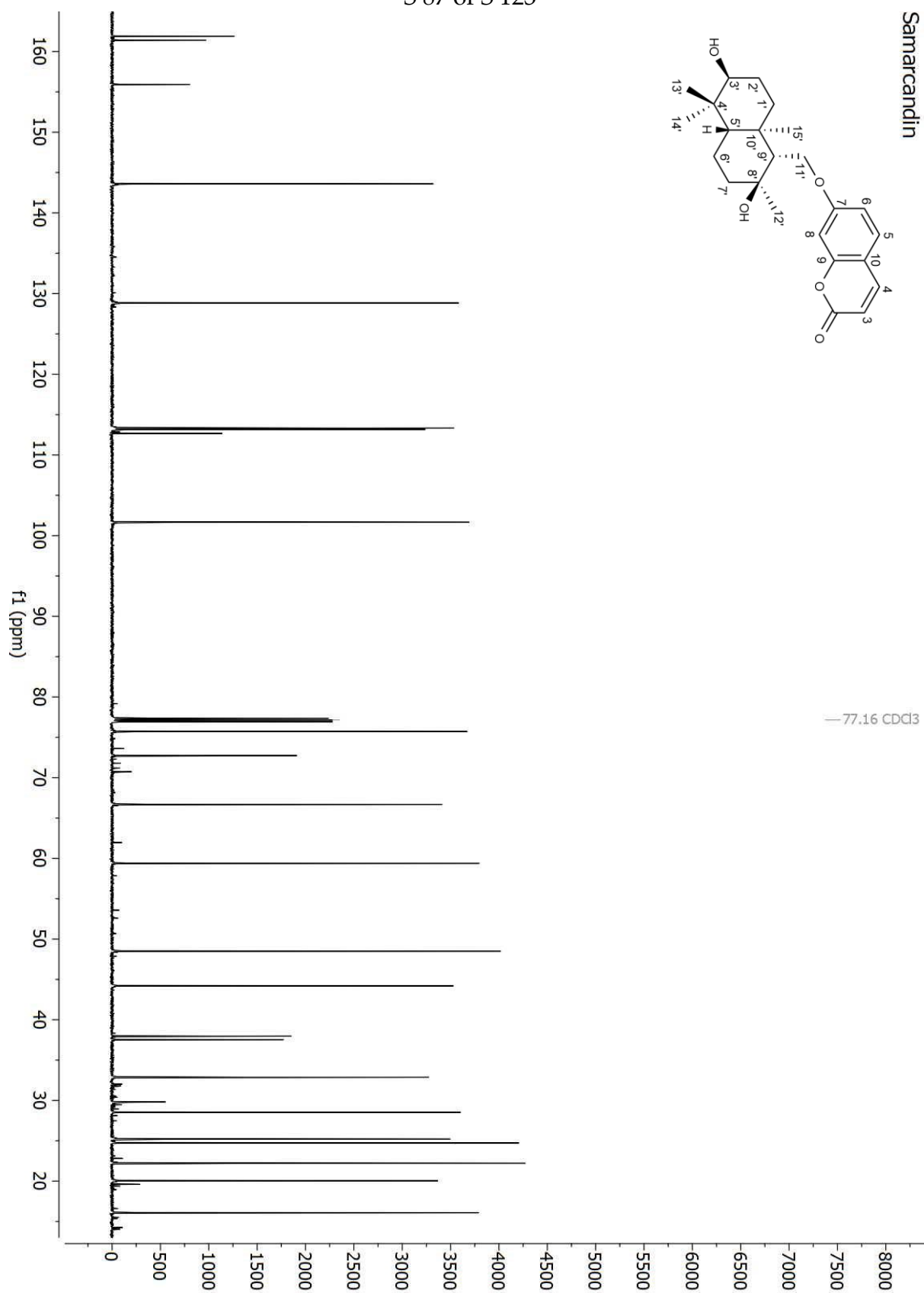




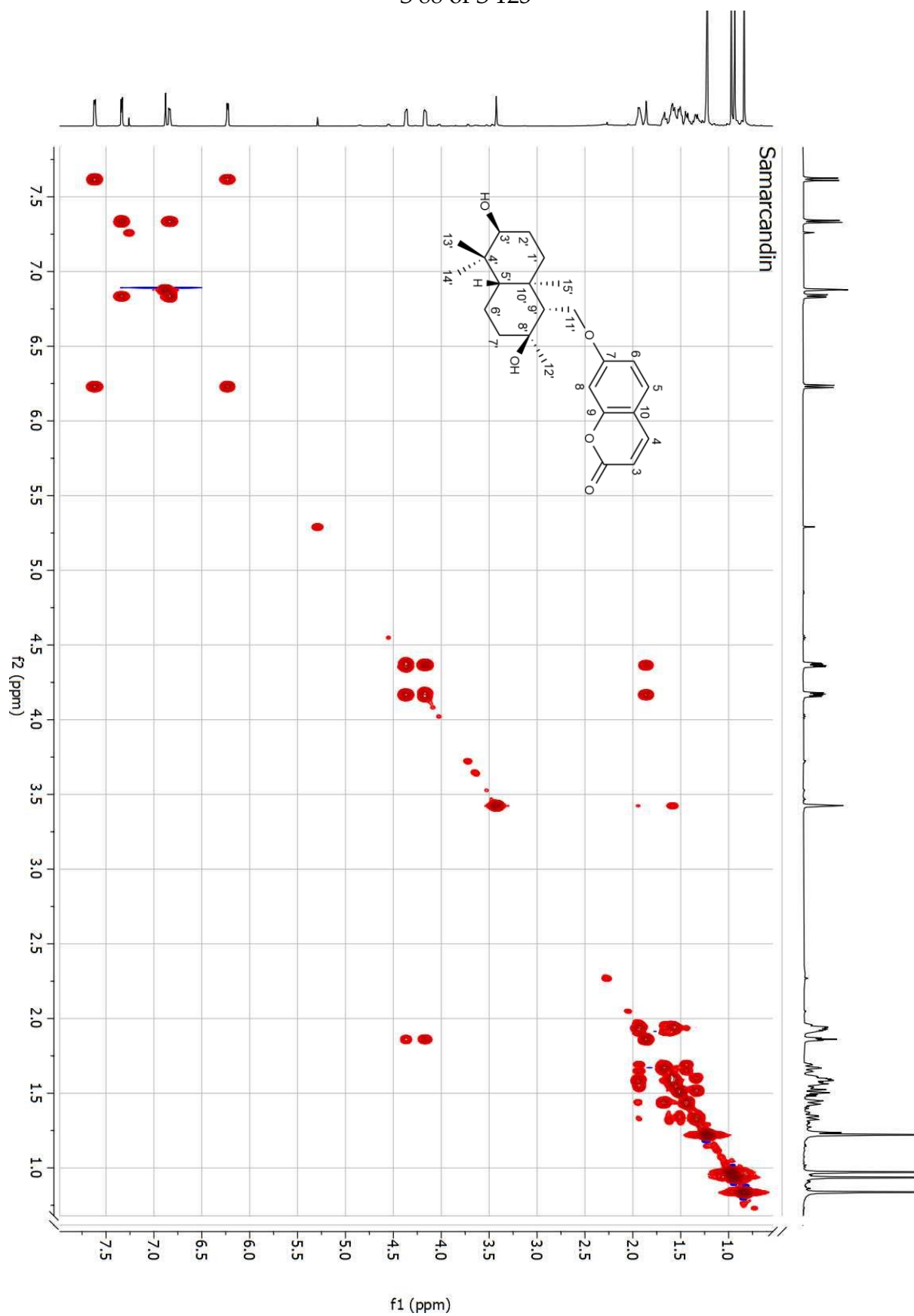


**Figure S79.** NOESY spectrum (CDCl<sub>3</sub>) of samarcandone (13)

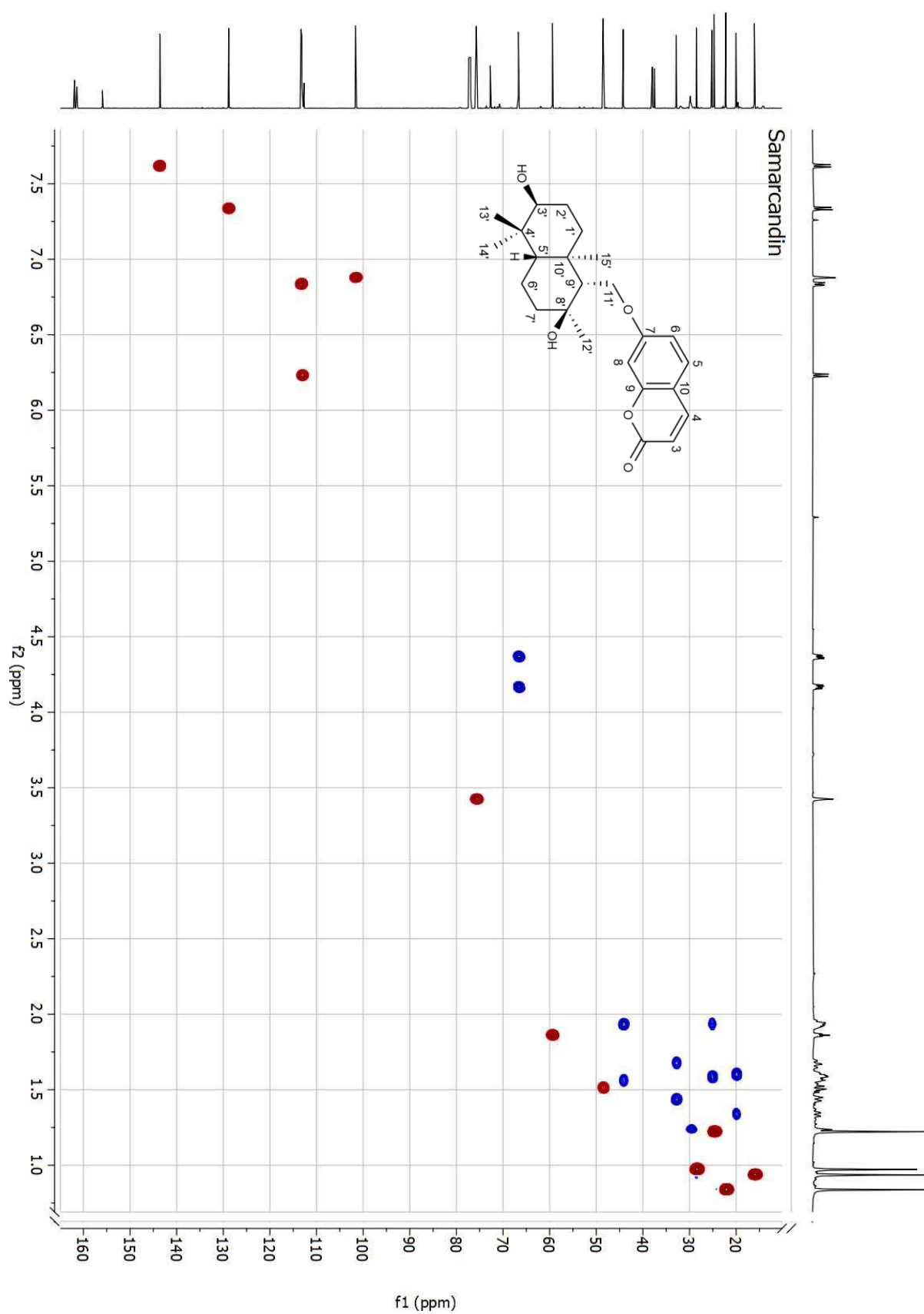
**Figure S80.** <sup>1</sup>H-NMR spectrum (500 MHz, CDCl<sub>3</sub>) of samarcandin (14)

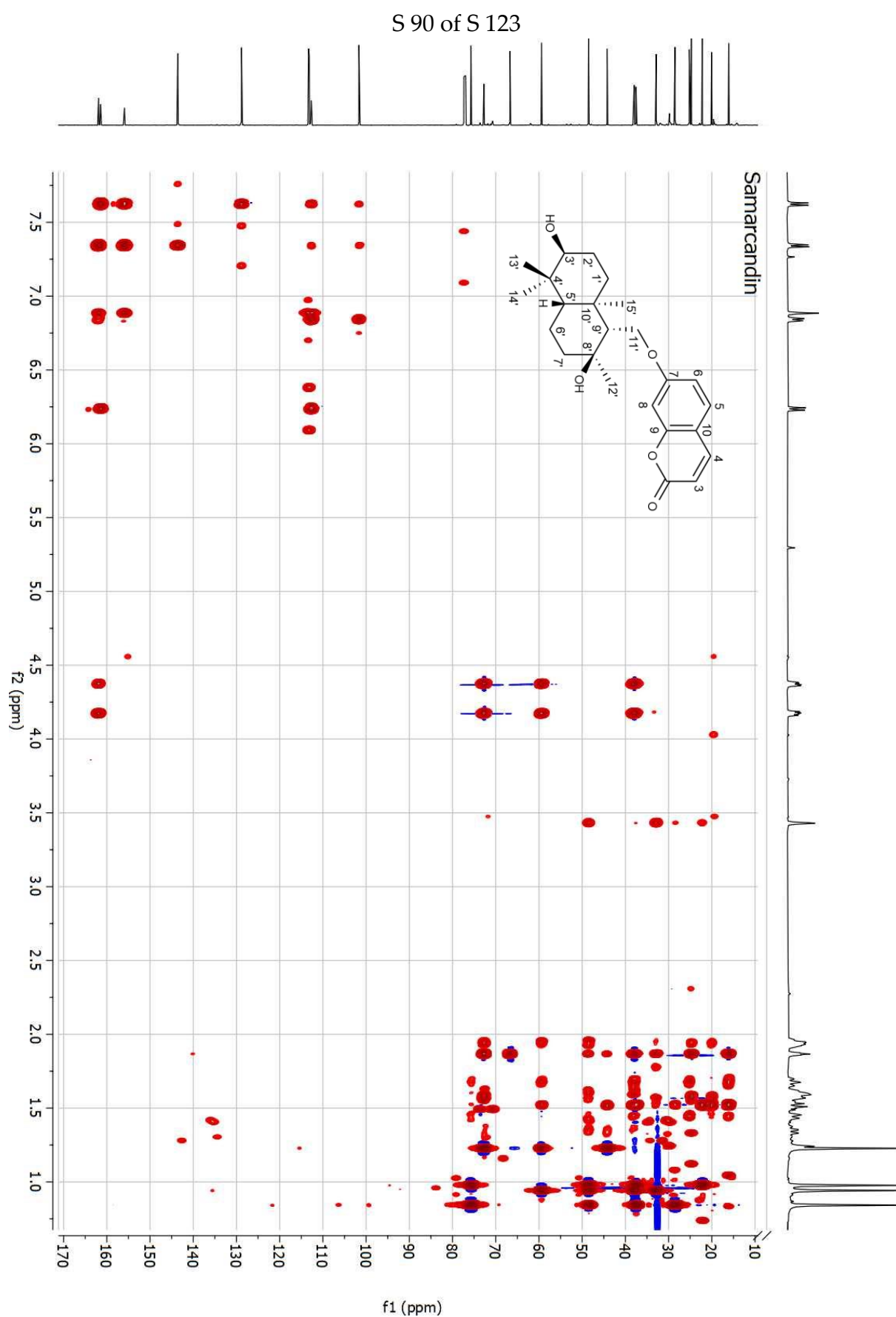


**Figure S81.**  $^{13}\text{C}$ -NMR spectrum (125 MHz,  $\text{CDCl}_3$ ) of samarcandin (14)

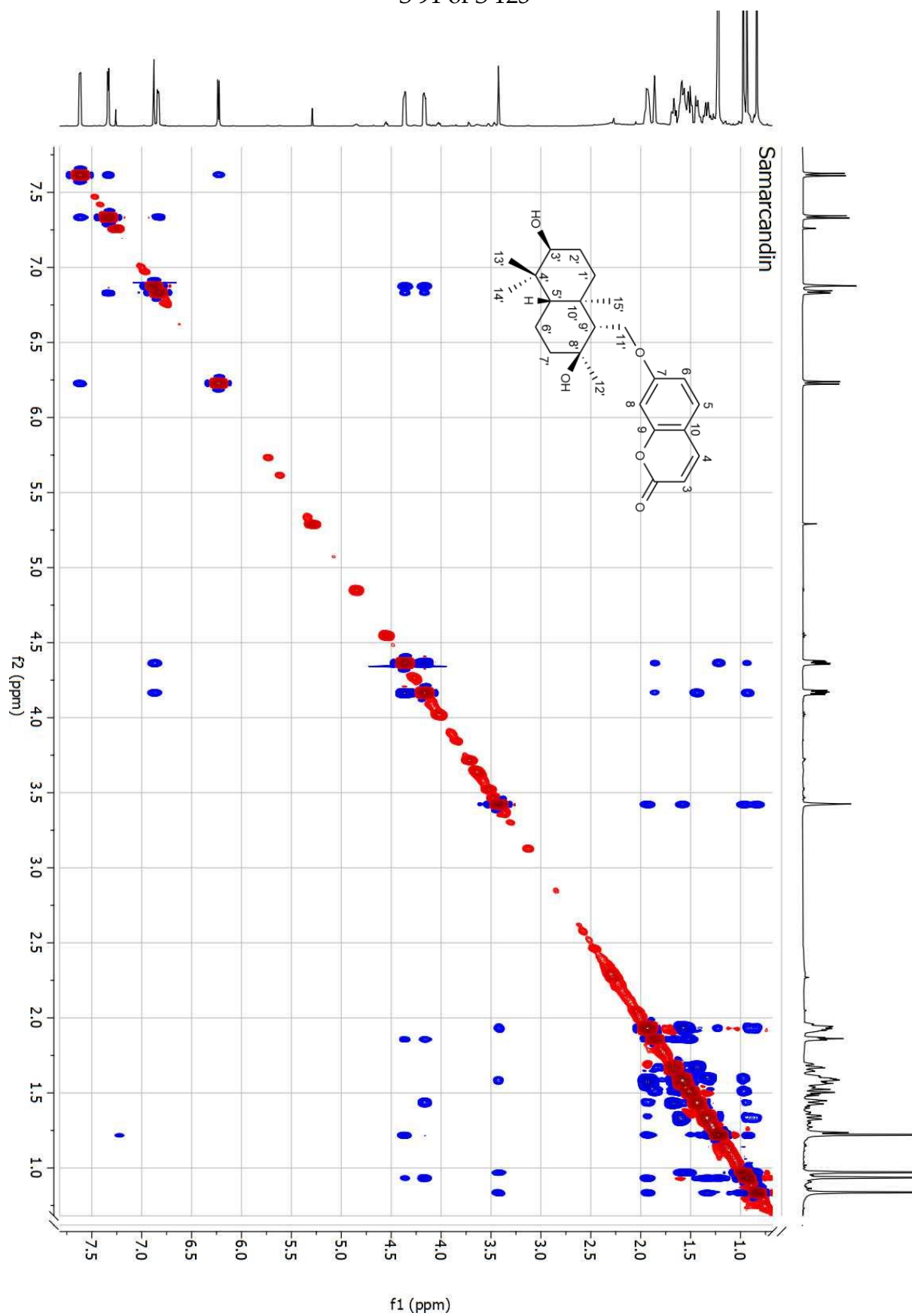


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**Figure S83.** HSQC spectrum ( $\text{CDCl}_3$ ) of samarcandin (14)

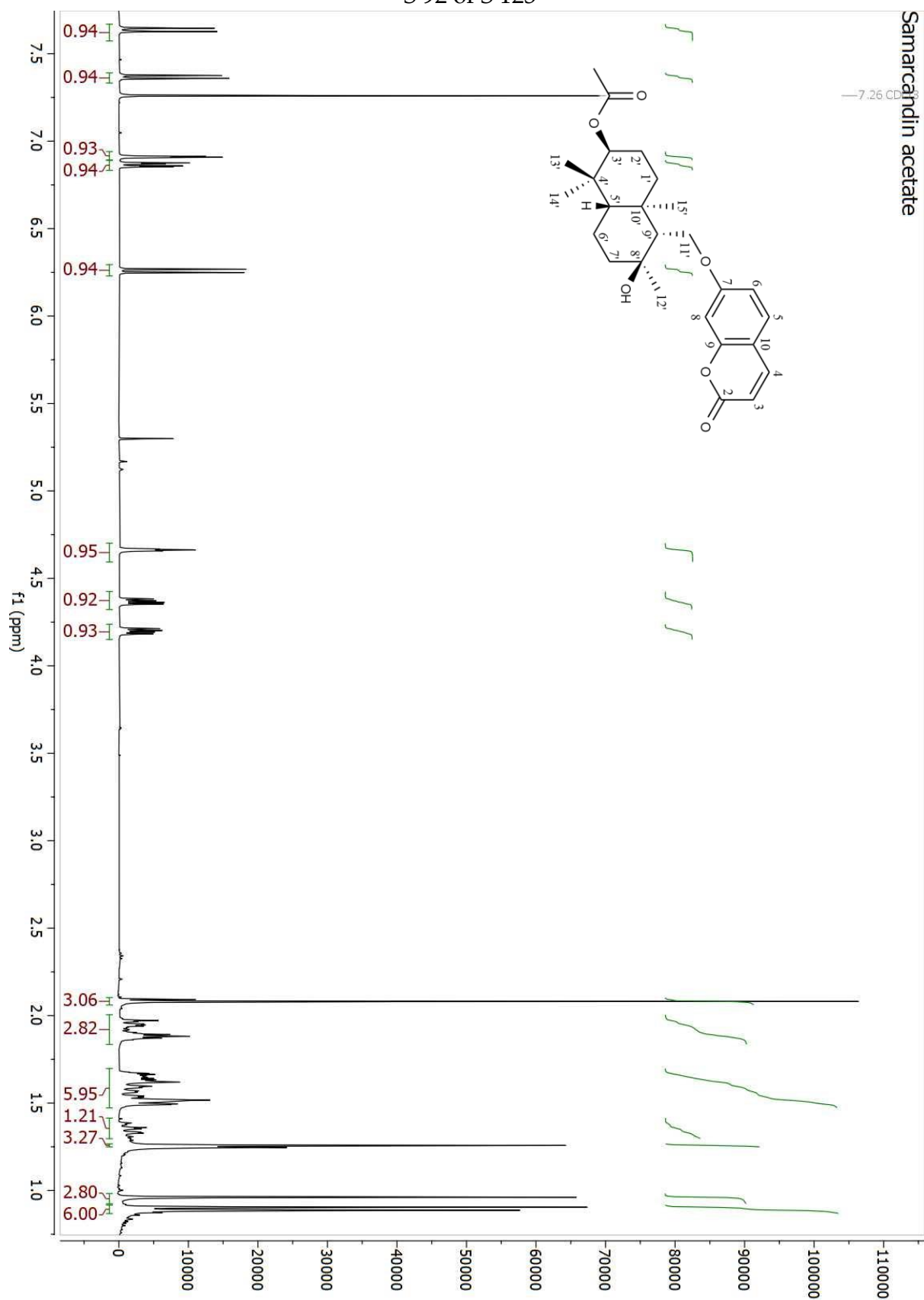


**Figure S84.** HMBC spectrum (CDCl<sub>3</sub>) of samarcandin (14)

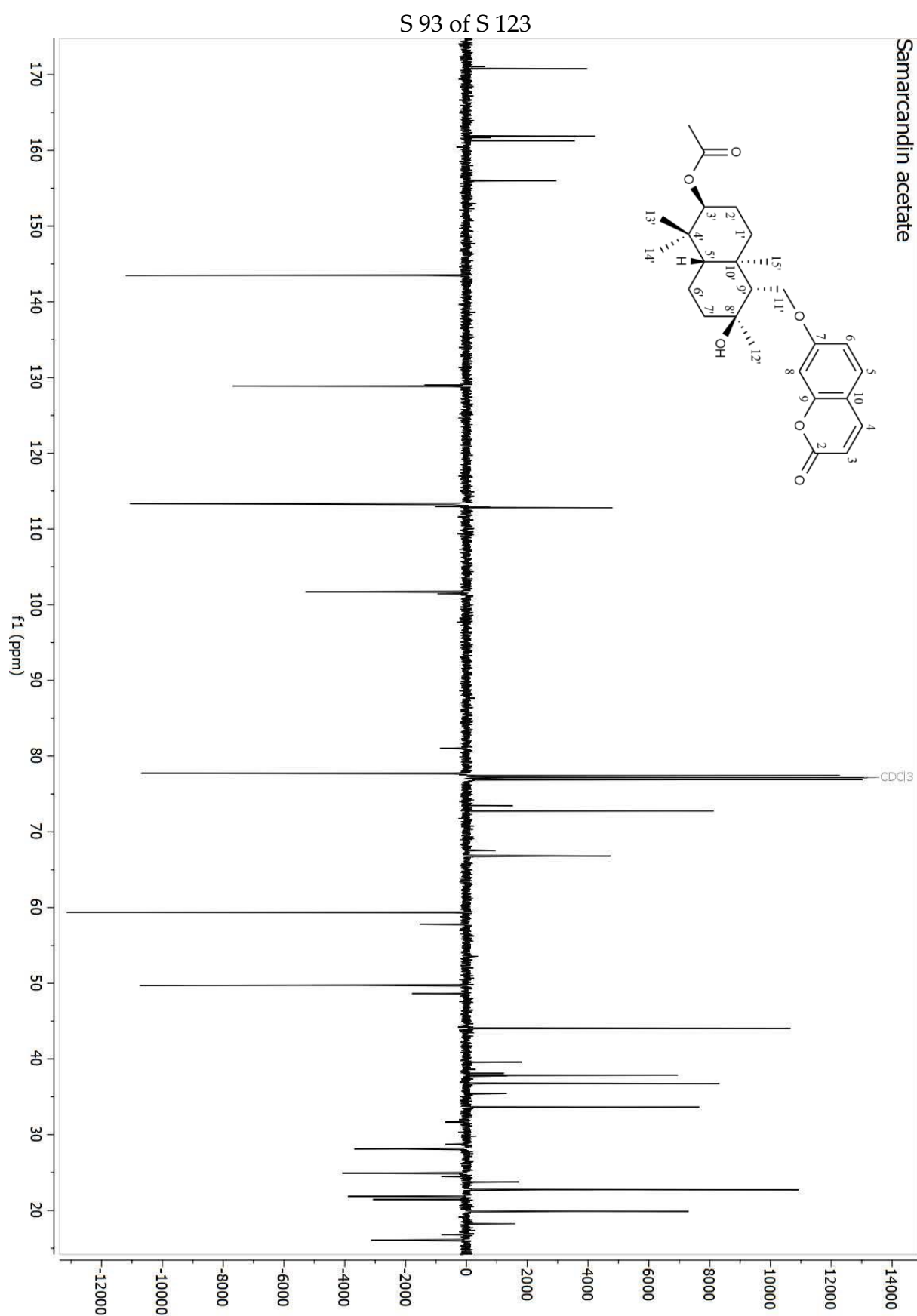


**Figure S85.** NOESY spectrum (CDCl<sub>3</sub>) of samarcandin (14)

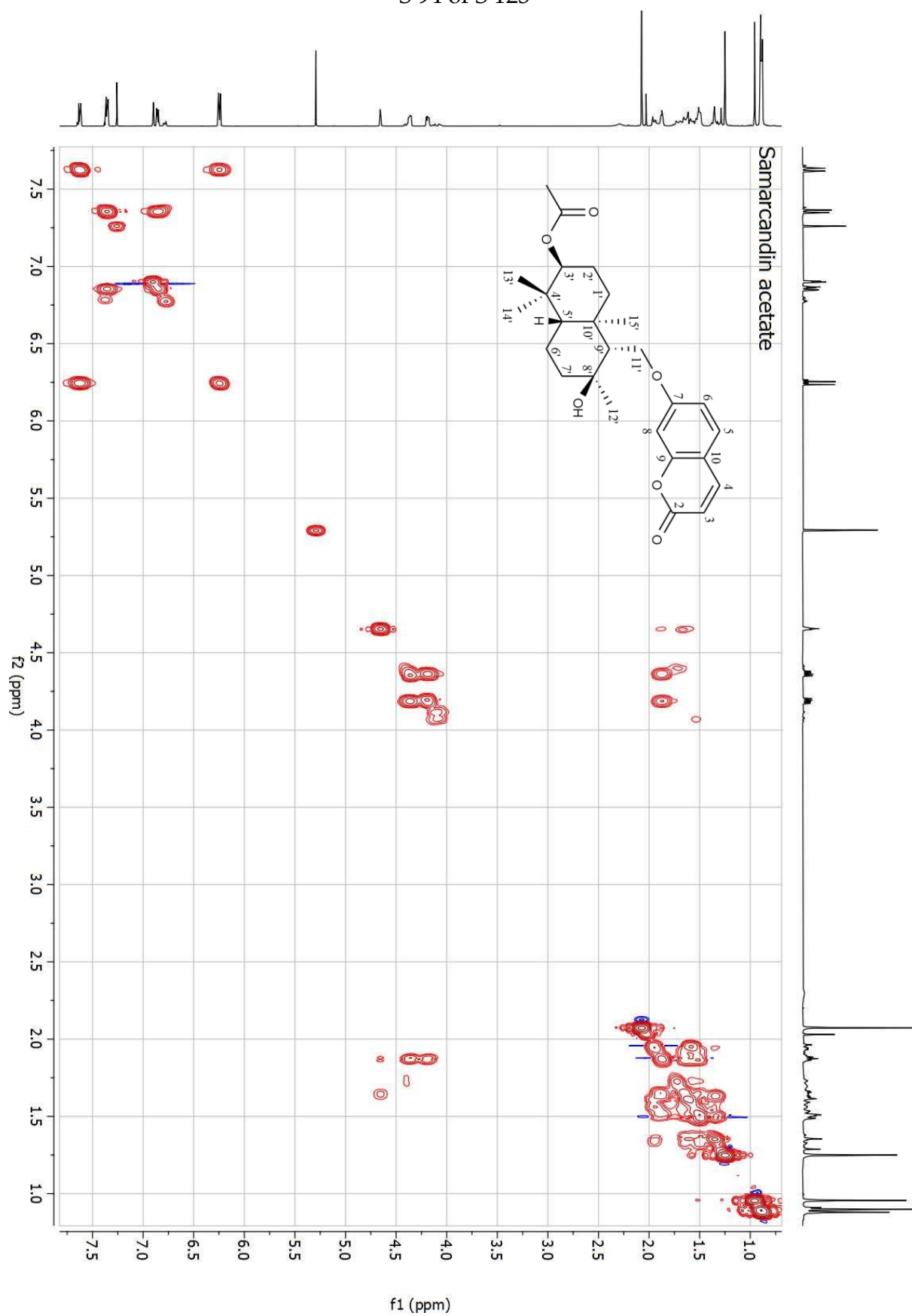
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**Figure S86.**  $^1\text{H}$ -NMR spectrum (500 MHz,  $\text{CDCl}_3$ ) of samarcandin acetate (15)

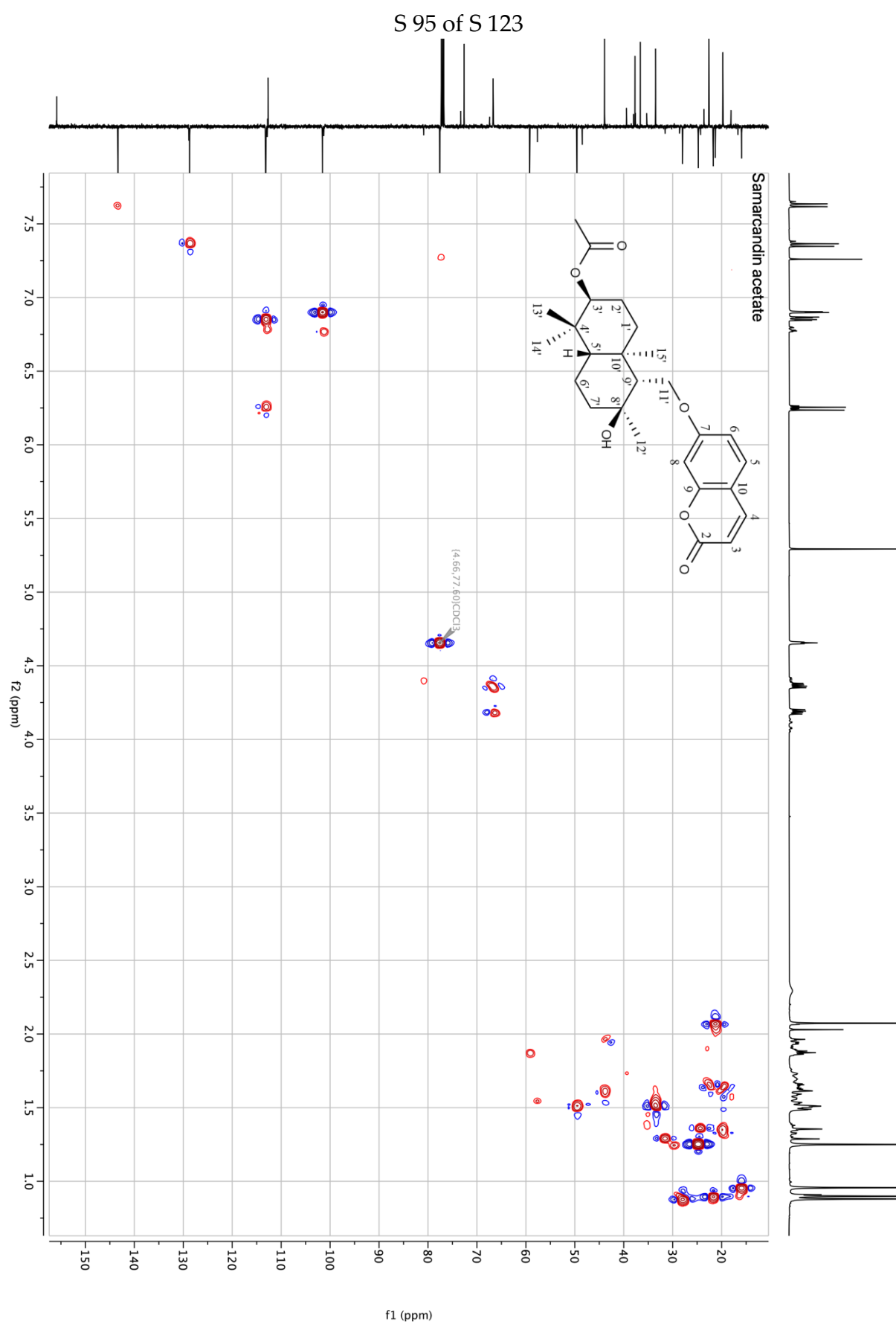




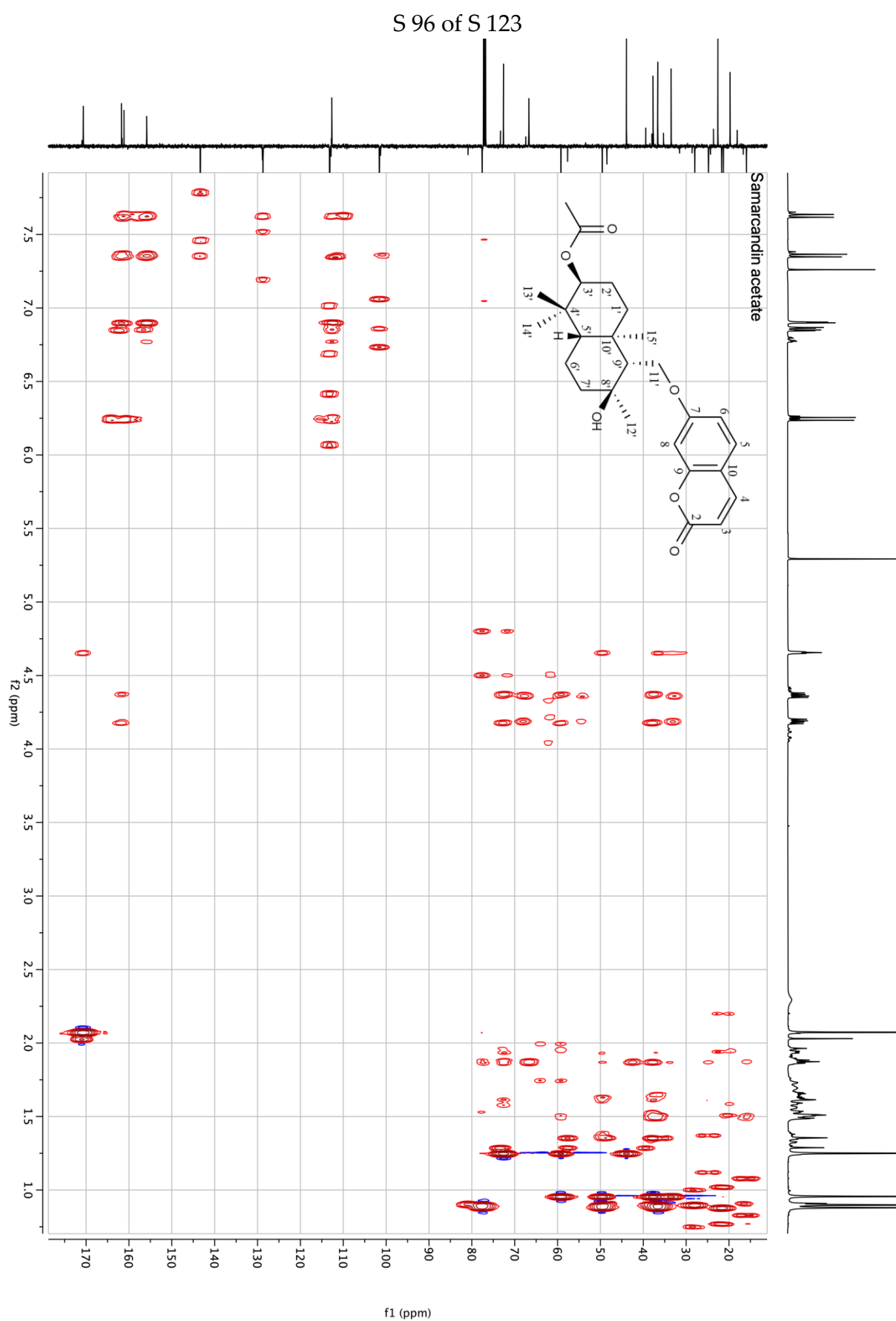
**Figure S87.** <sup>13</sup>C-NMR (APT) spectrum (125 MHz, CDCl<sub>3</sub>) of samarcandin acetate (15)



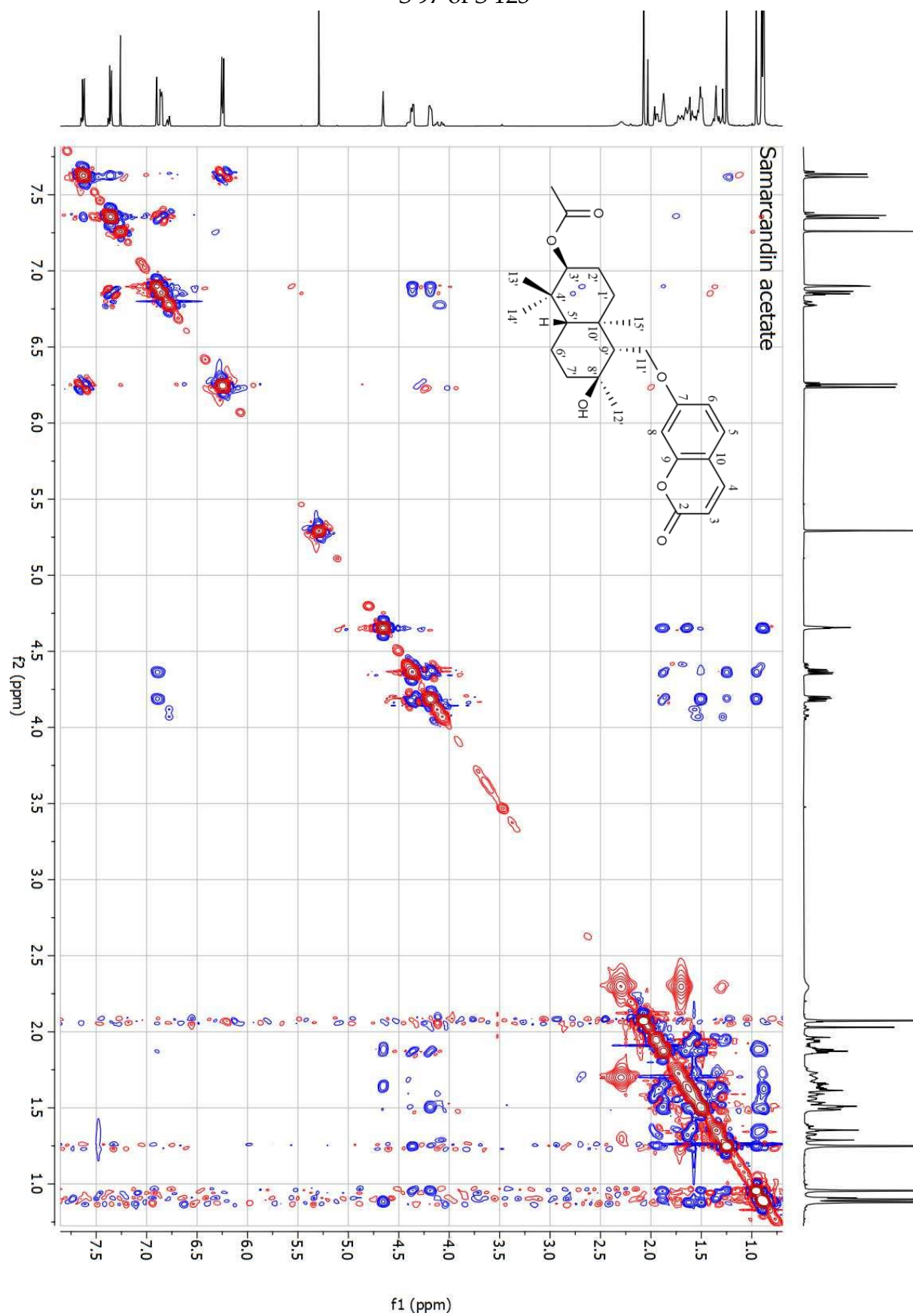
**Figure S88.**  $^1\text{H}$ - $^1\text{H}$  COSY spectrum (CDCl<sub>3</sub>) of samarcandin acetate (**15**)



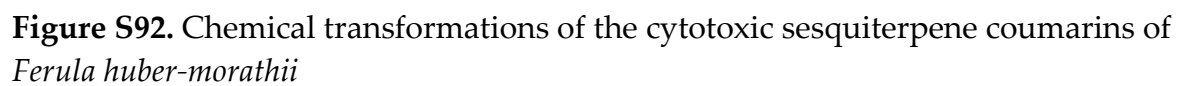
**Figure S89.** HSQC spectrum (CDCl<sub>3</sub>) of samarcandin acetate (15)

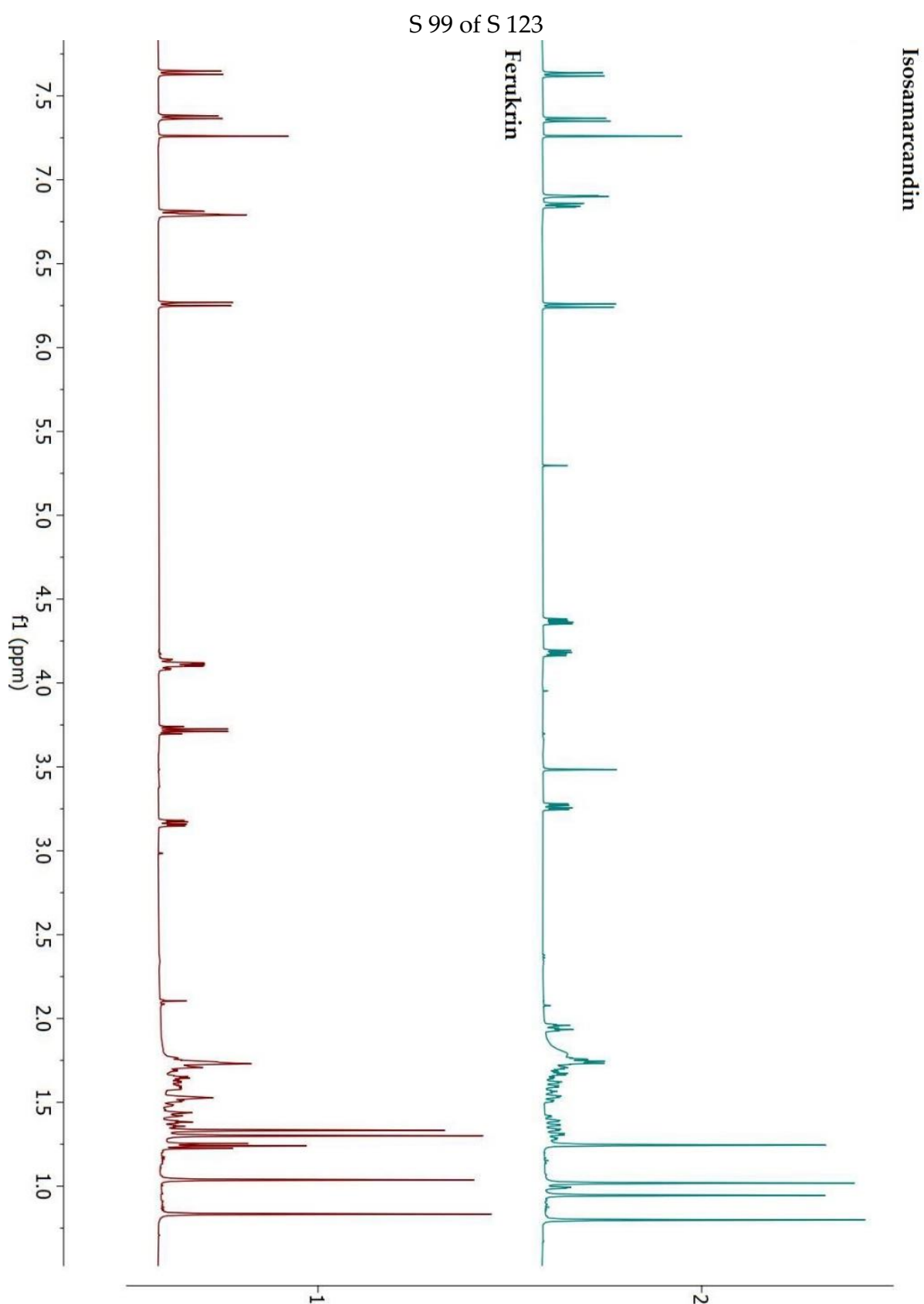


**Figure S90.** HMBC spectrum (CDCl<sub>3</sub>) of samarcandin acetate (15)

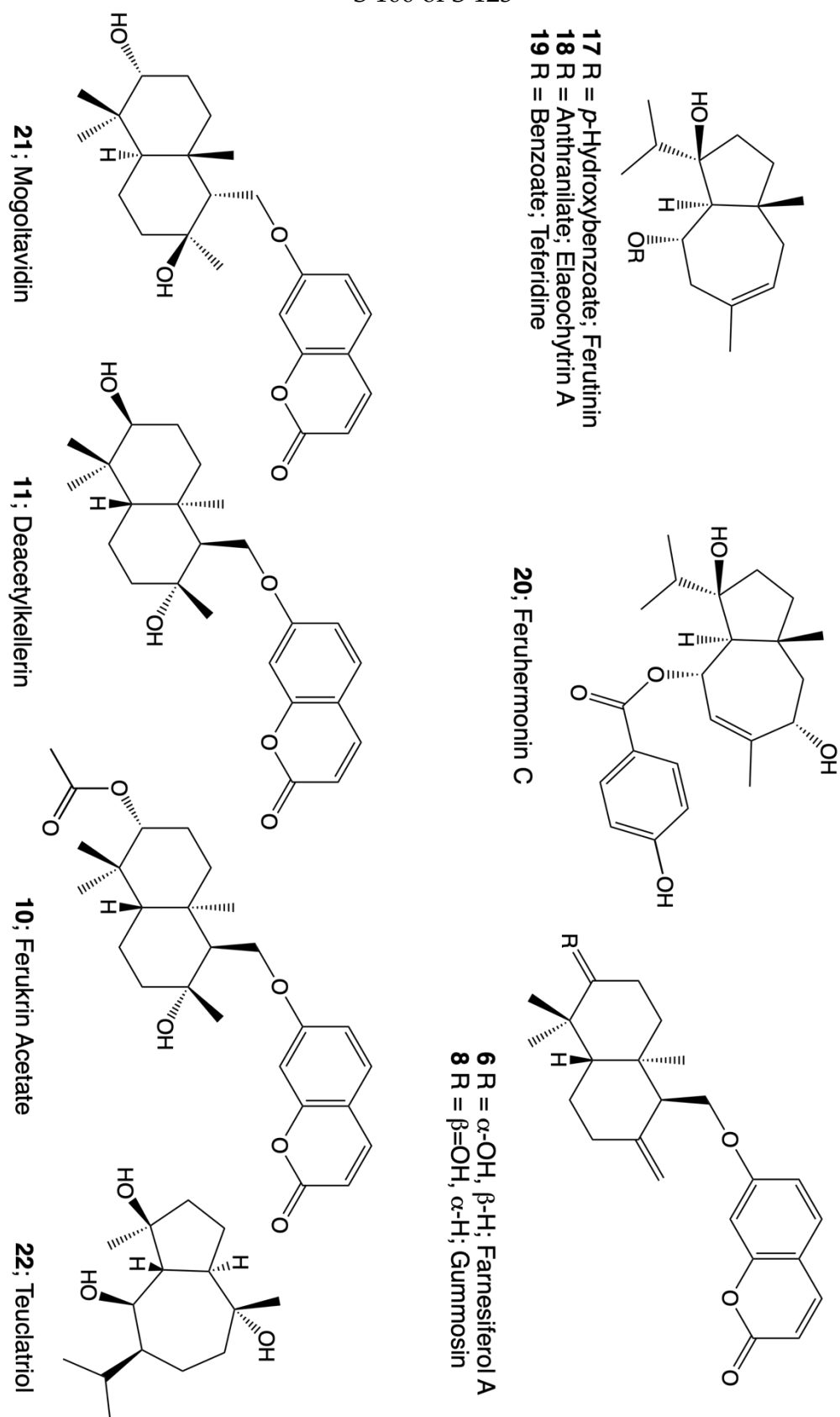


**Figure S91.** NOESY spectrum (CDCl<sub>3</sub>) of samarcandin acetate (15)



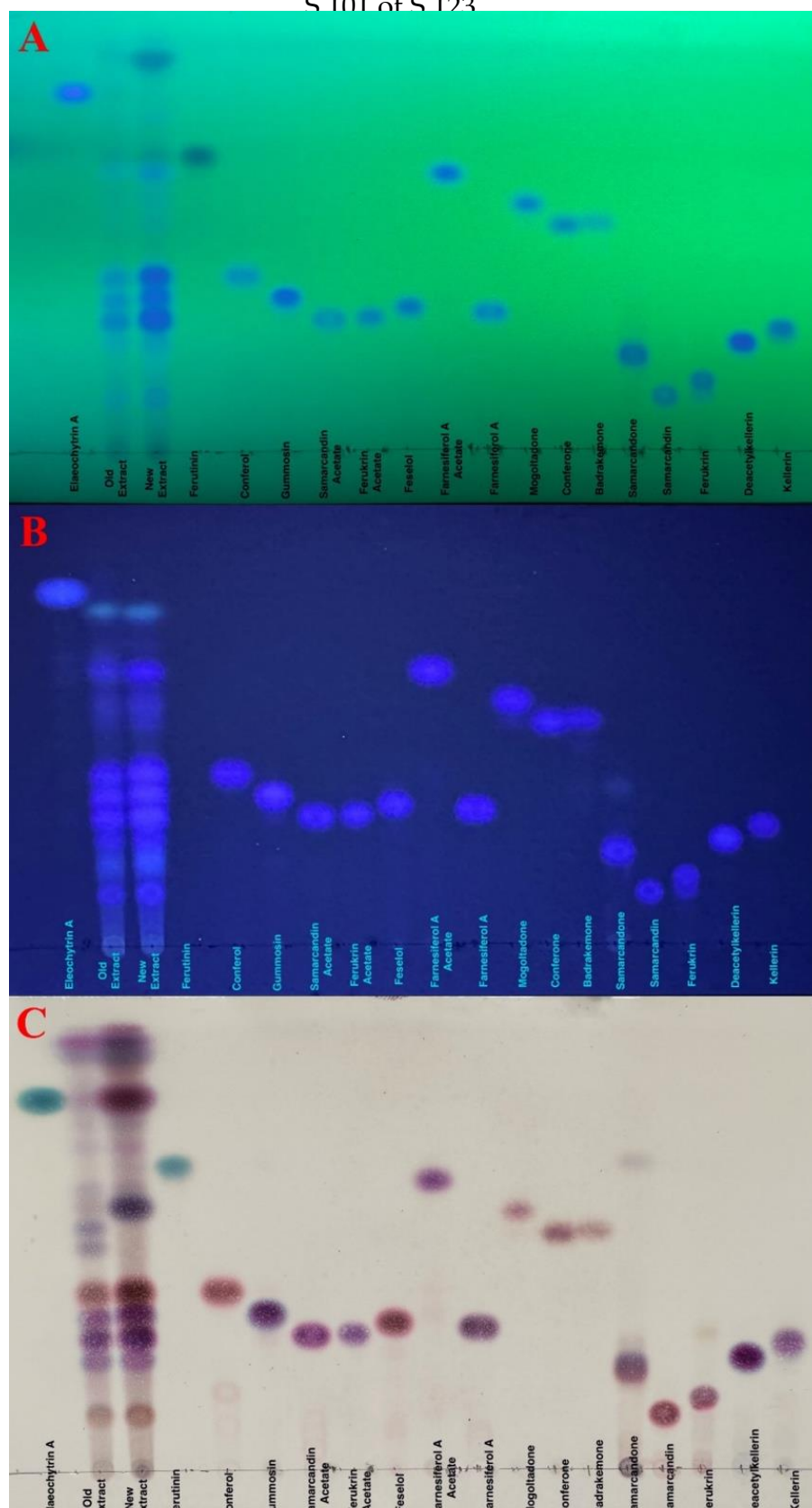


**Figure S93.** Comparison of  $^1\text{H}$ -NMR spectra of isosamarcandin (**16**) and ferukrin (**9**)



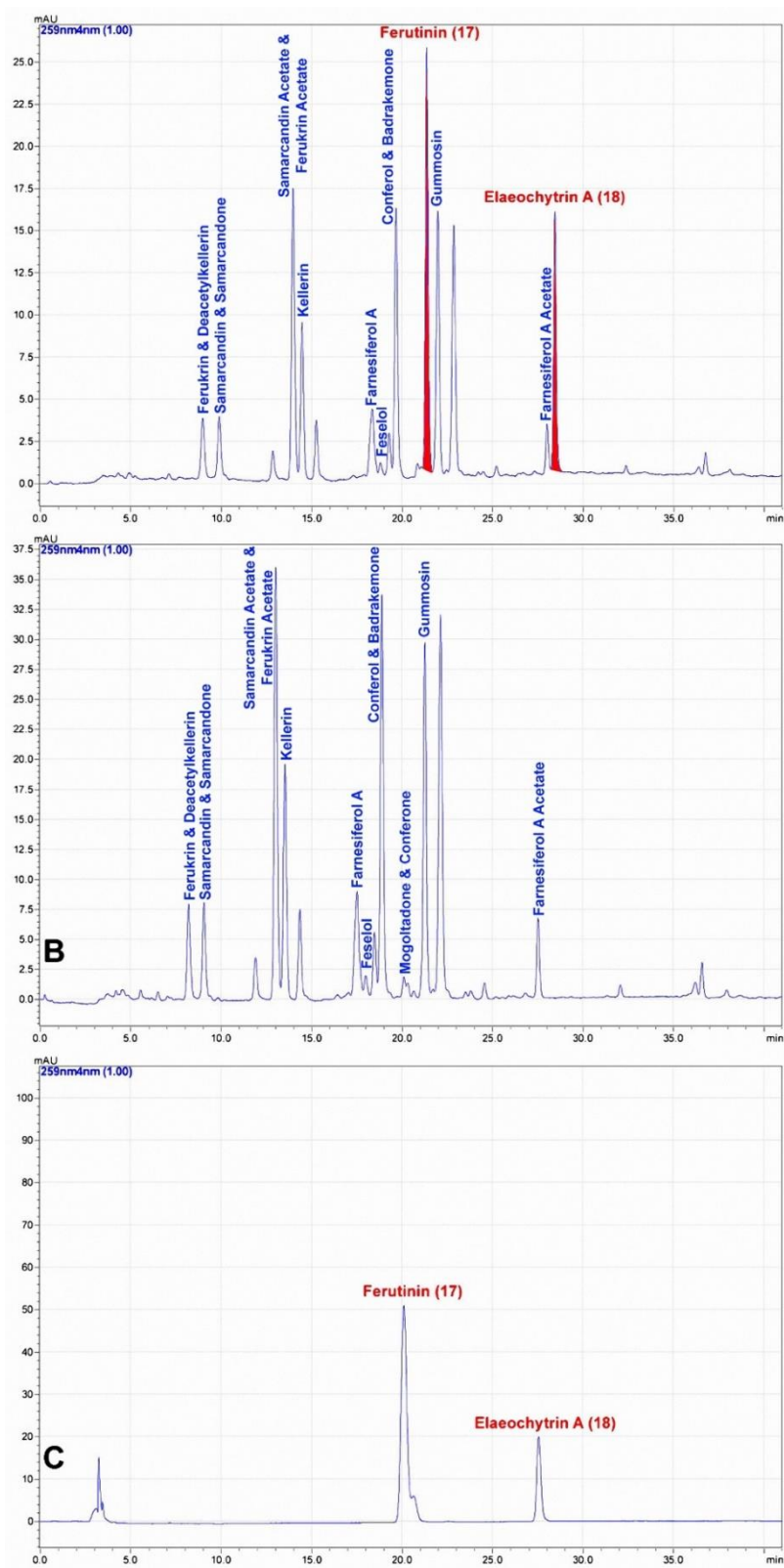
**Figure S94.** Previously proposed structures of sesquiterpene compounds isolated from the chloroform extract of *Ferula huber-morathii* [3]





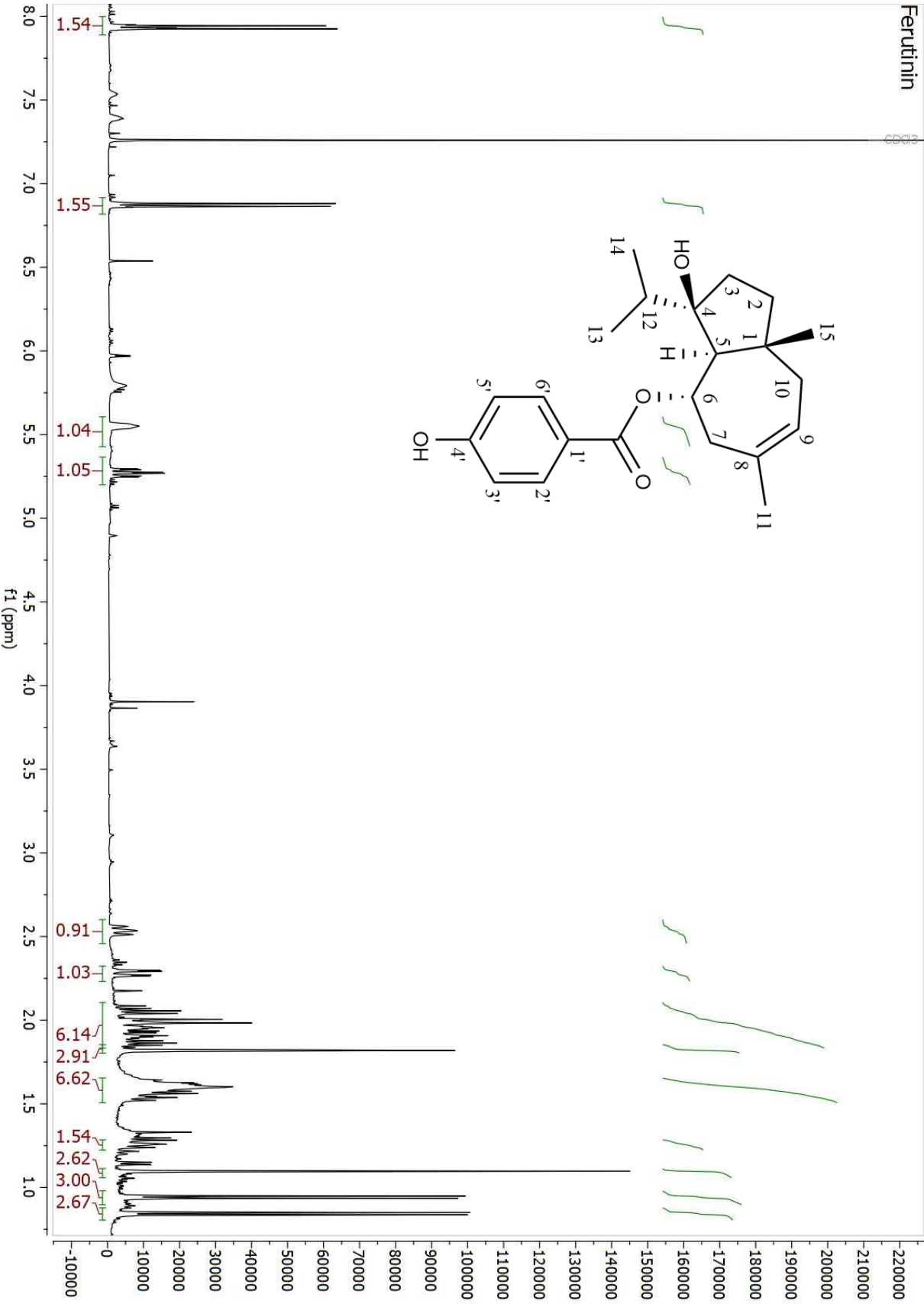
**Figure S95.** TLC comparison of the dichloromethane extracts of *Ferula huber-morathii* with reference compounds; elaeochoytrin A (18) and ferutinin (17), and isolated sesquiterpene coumarins (1-15), mobile phase; Hxn:EtOAc (6:4), detection; A: 254 nm; B: 366 nm; C: Anisaldehyde reagent

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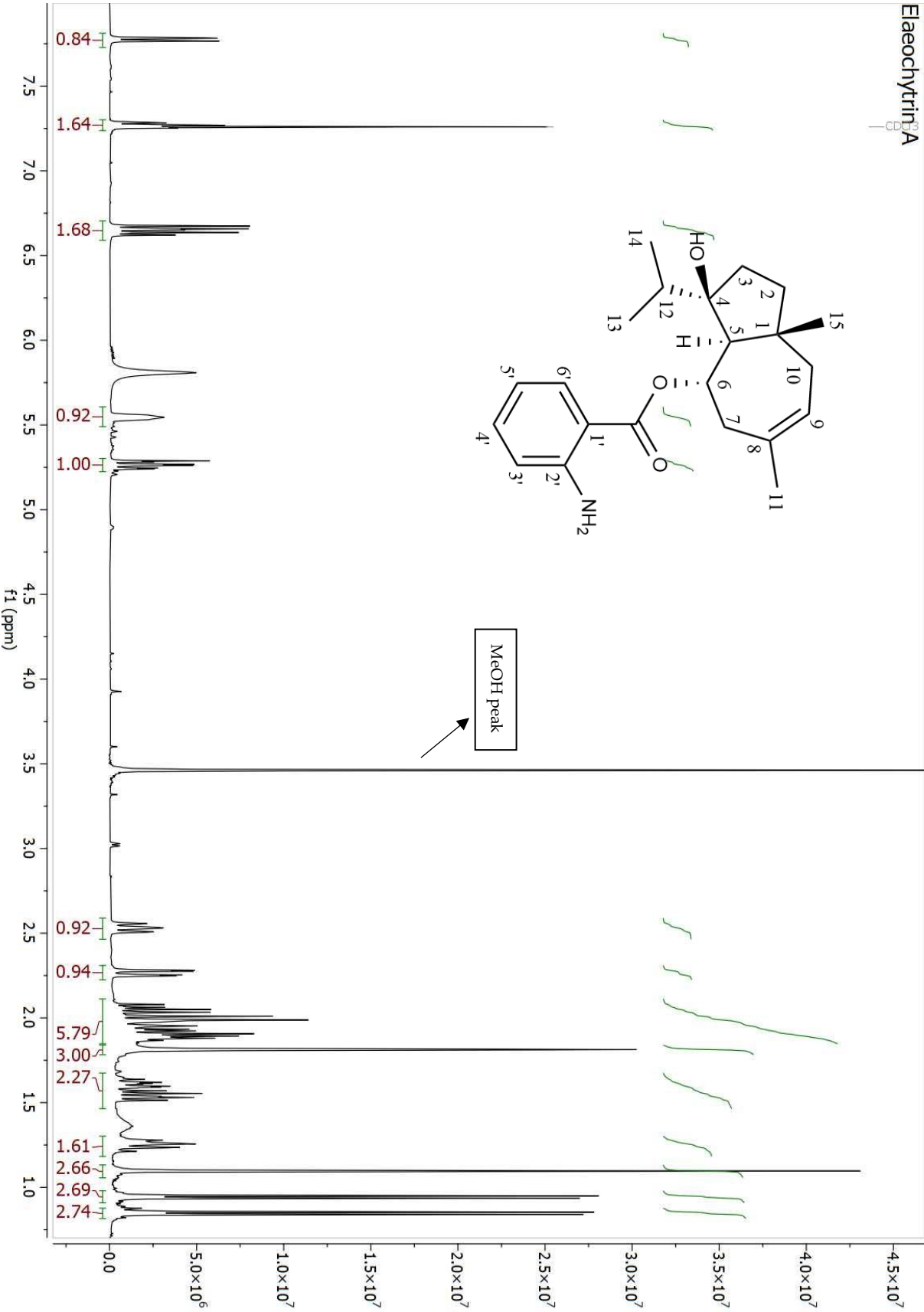


**Figure S96.** A. HPLC chromatogram of the dichloromethane root extract of *Ferula huber-morathii* spiked with reference compounds ferutin (17) and elaeochytrin A (18), B. HPLC chromatogram of the dichloromethane root extract of *F. huber-morathii*

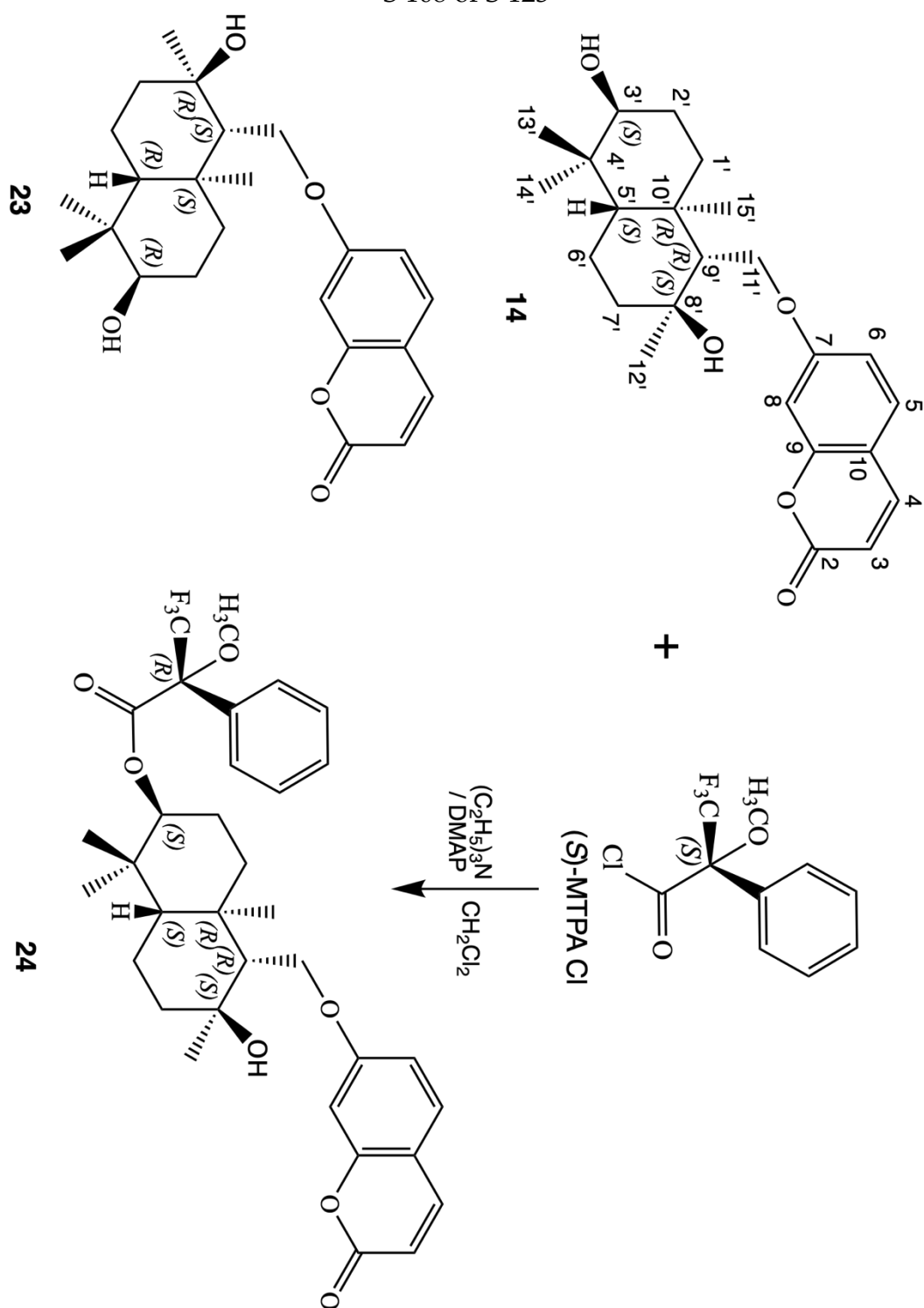
and **C.** HPLC chromatogram of the mixture of reference compounds ferutinin (**17**) and elaeochytrin A (**18**). Detection: UV detector at 259 nm



**Figure S97.**  $^1\text{H}$ -NMR spectrum (500 MHz,  $\text{CDCl}_3$ ) of reference compound ferutinin (17)



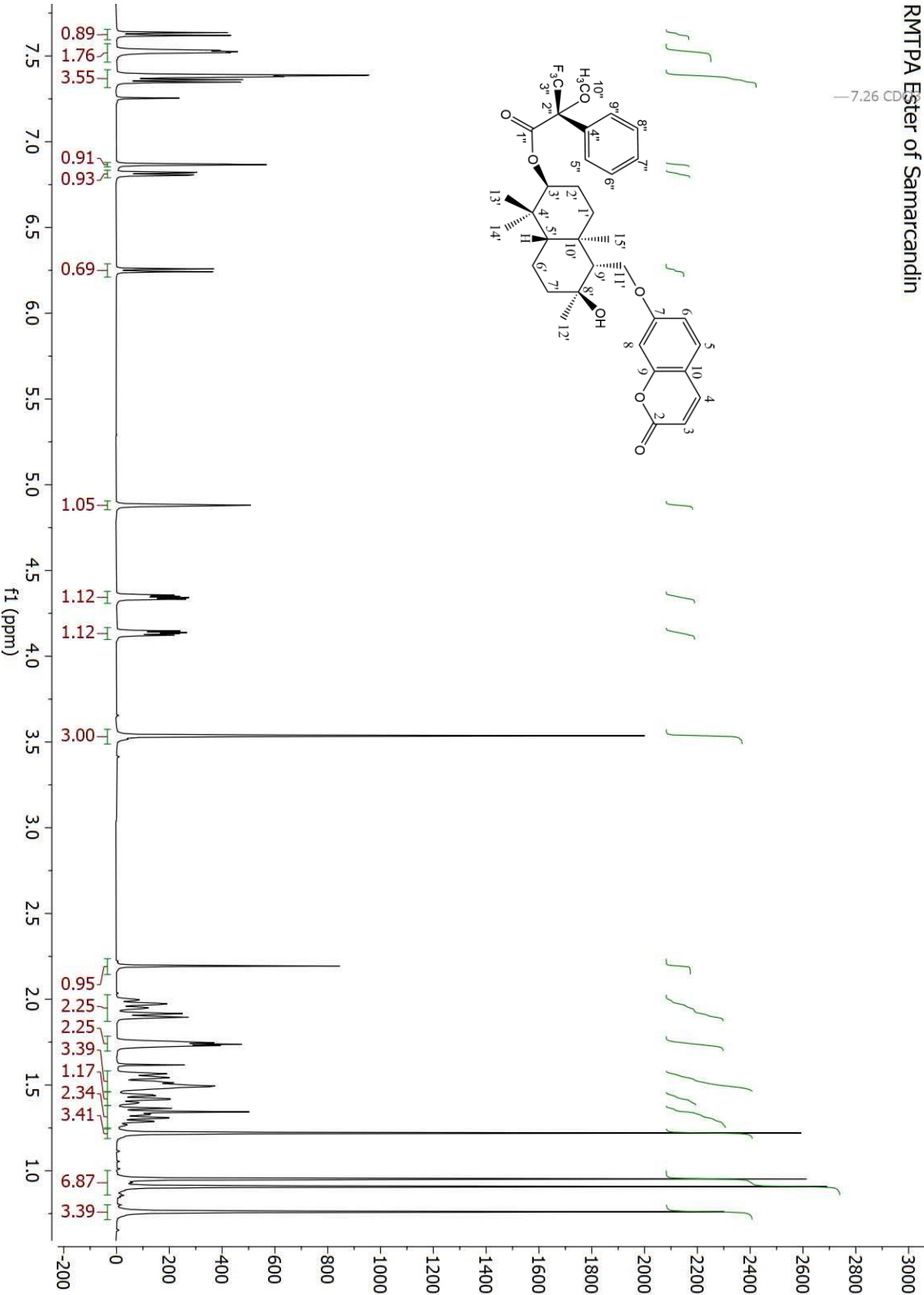
**Figure S98.**  $^1\text{H}$ -NMR spectrum (500 MHz,  $\text{CDCl}_3$ ) of reference compound elaeochtyrin A (**18**)



**Figure S99.** Preparation of the (R)-MTPA ester of samarcandin (**24**) and structure of *ent*-samarcandin (**23**)

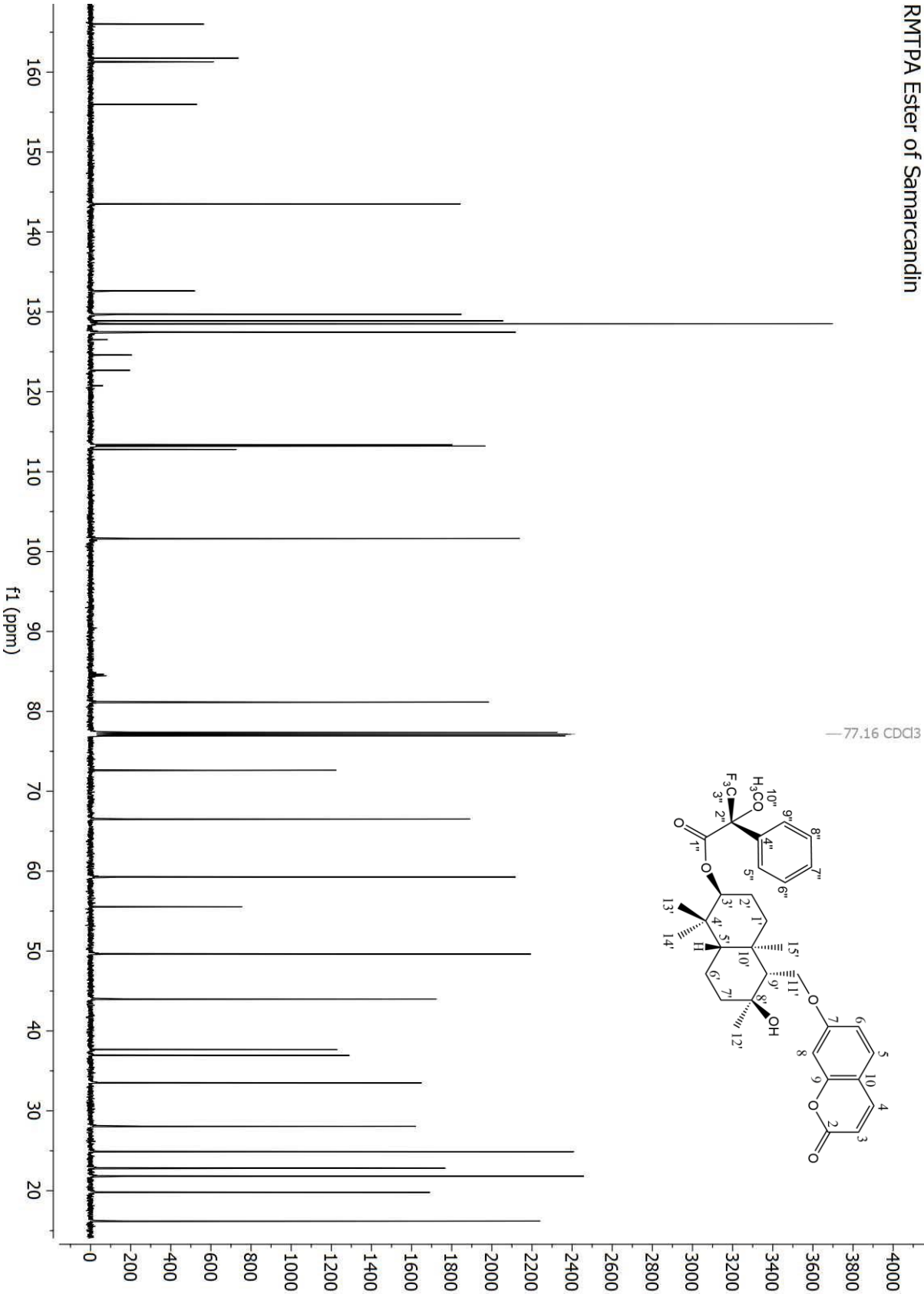


RMTPA Ester of Samarcandin



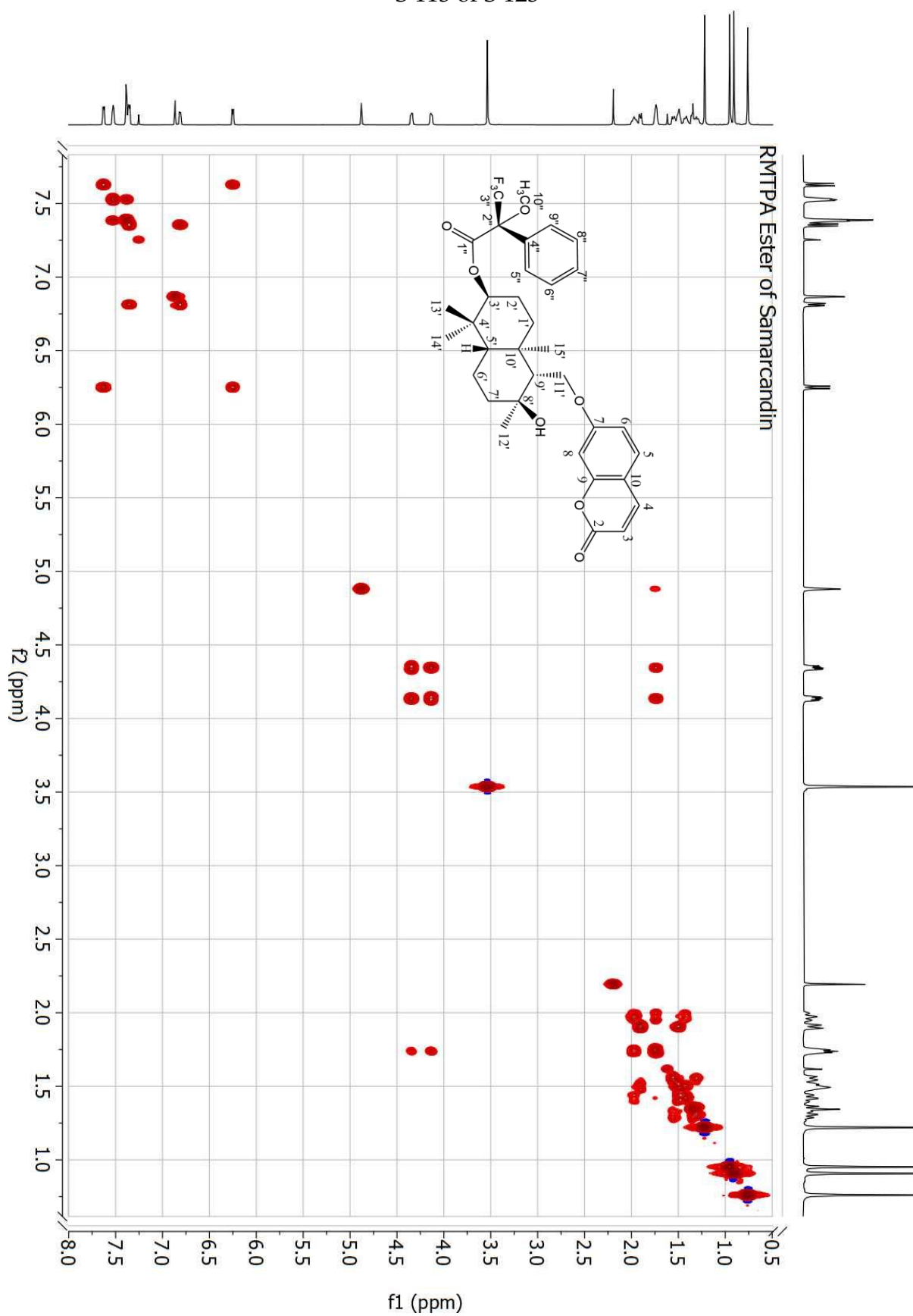
**Figure S100.**  $^1\text{H}$ -NMR spectrum (500 MHz,  $\text{CDCl}_3$ ) of (*R*)-MTPA ester of samarcandin (24)

RMTPA Ester of Samarcandin

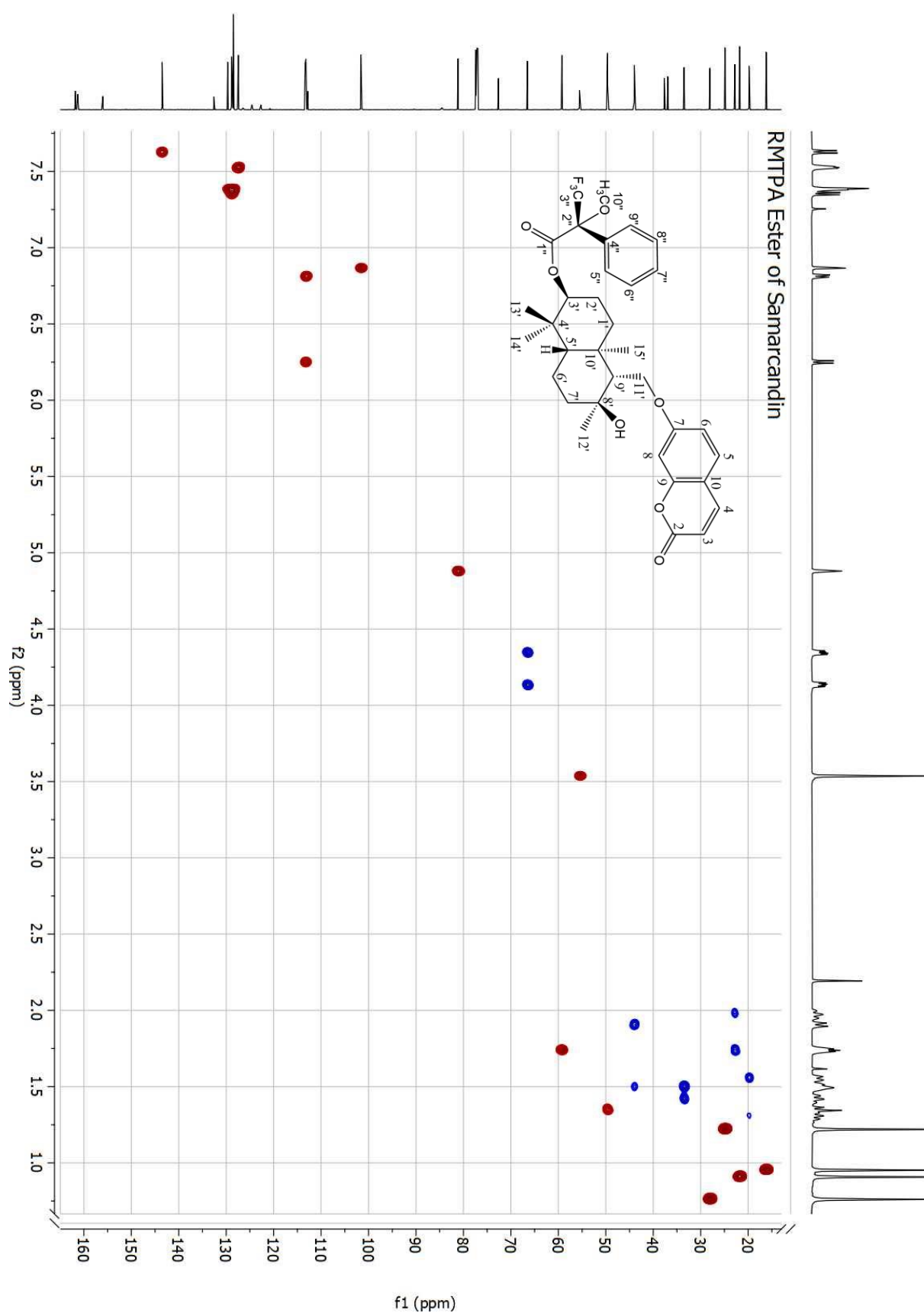


**Figure S101.**  $^{13}\text{C}$ -NMR spectrum (125 MHz,  $\text{CDCl}_3$ ) of (*R*)-MTPA ester of samarcandin (**24**)

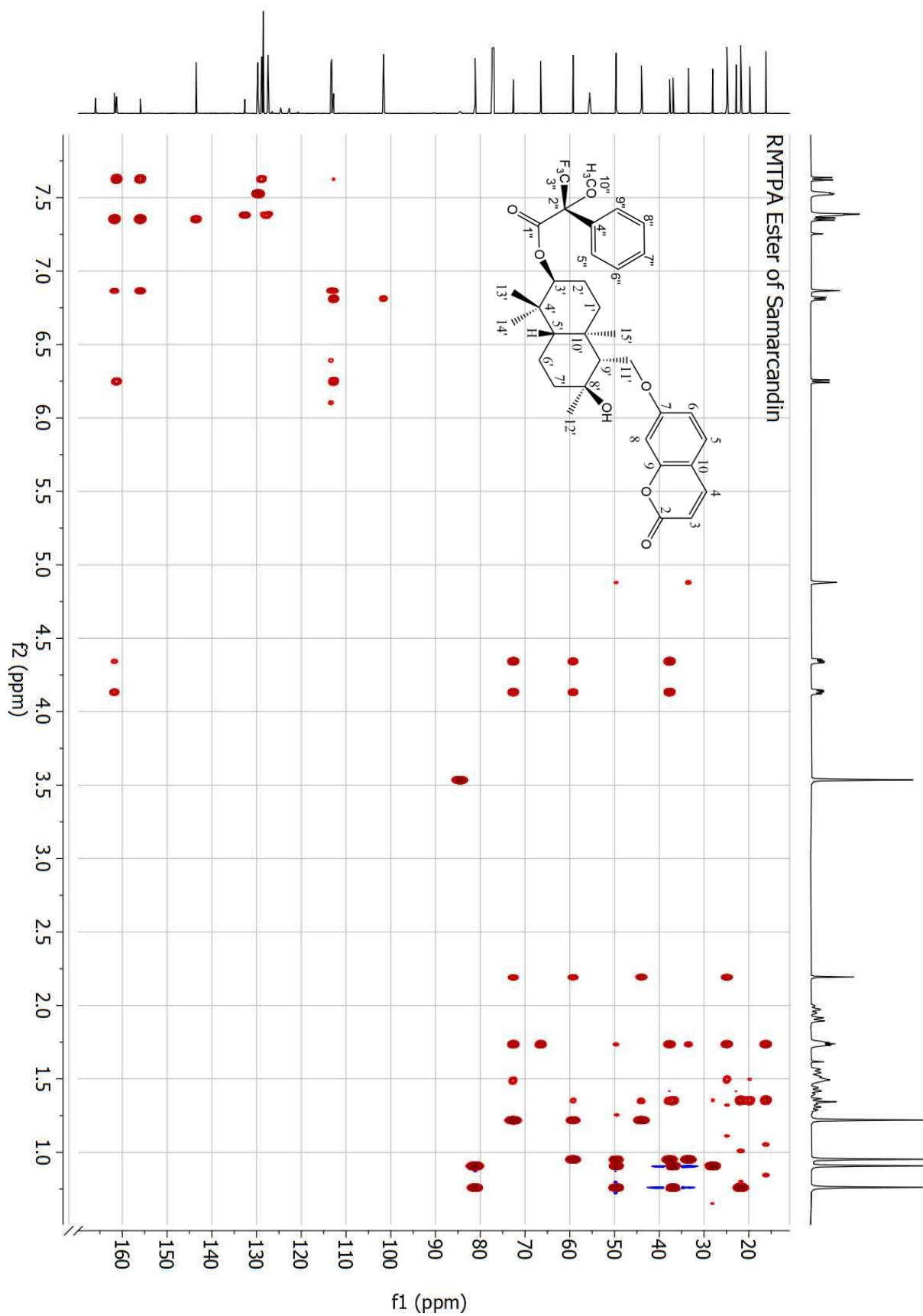
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**Figure S102.**  $^1\text{H}$ - $^1\text{H}$  COSY spectrum ( $\text{CDCl}_3$ ) of (R)-MTPA ester of samarcandin (24)

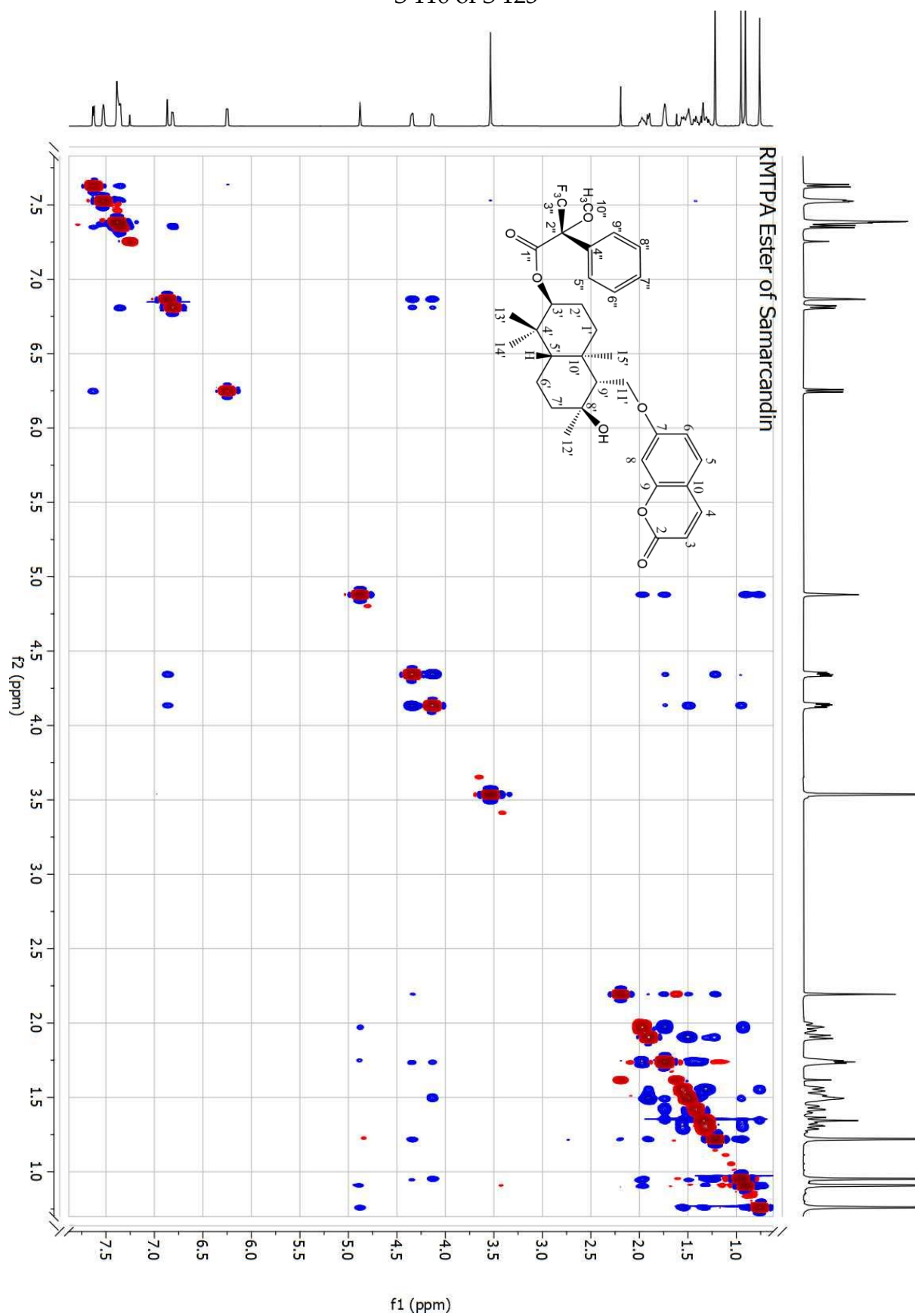
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**Figure S103.** HSQC spectrum of (*R*)-MTPA ester of samarcandin (**24**)

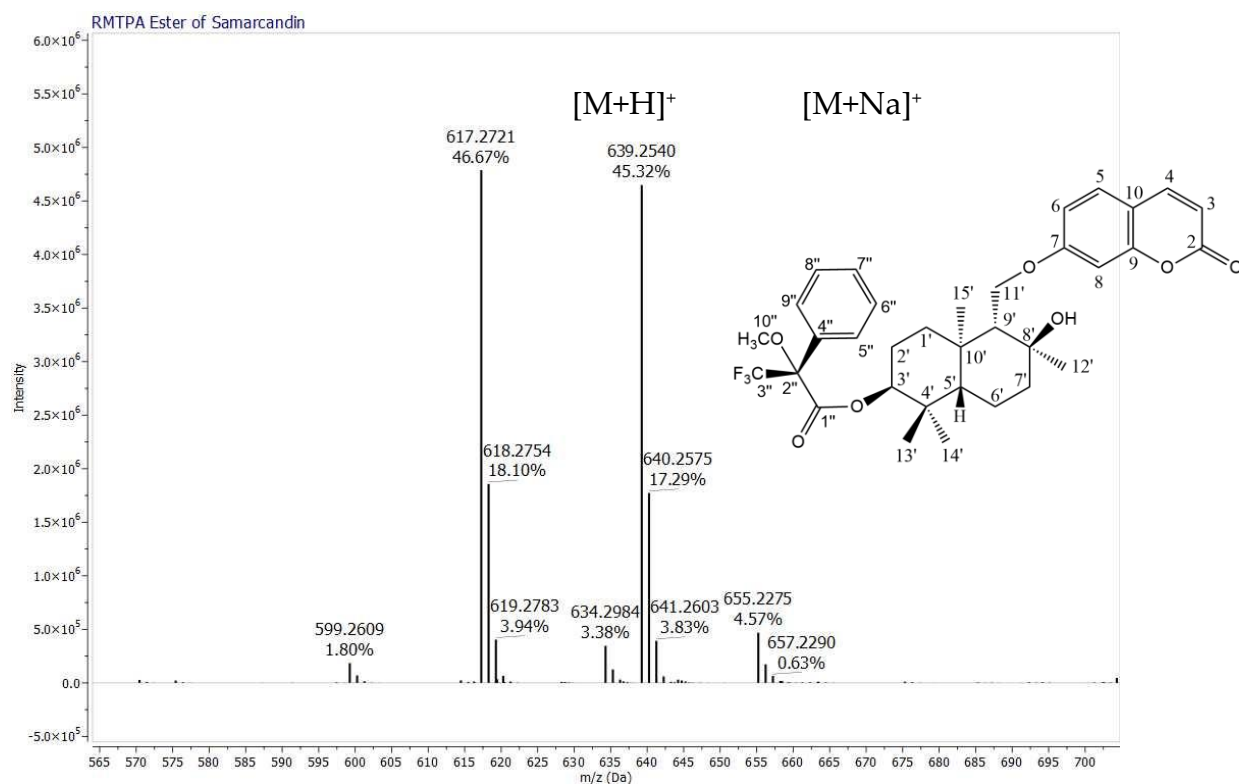
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**Figure S104.** HMBC spectrum of (R)-MTPA ester of samarcandin (24)

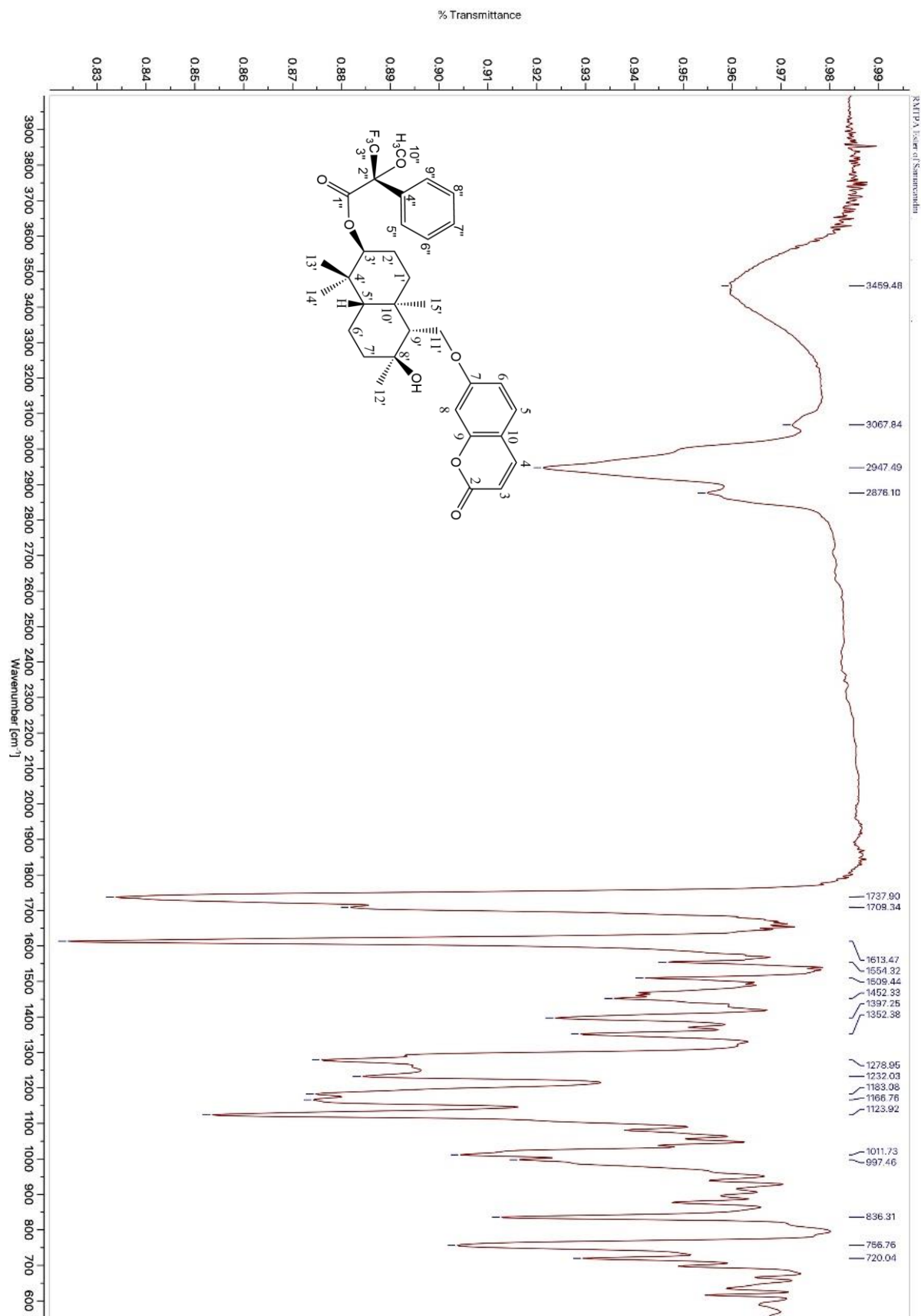
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**Figure S105.** NOESY spectrum of (R)-MTPA ester of samarcandin (24)

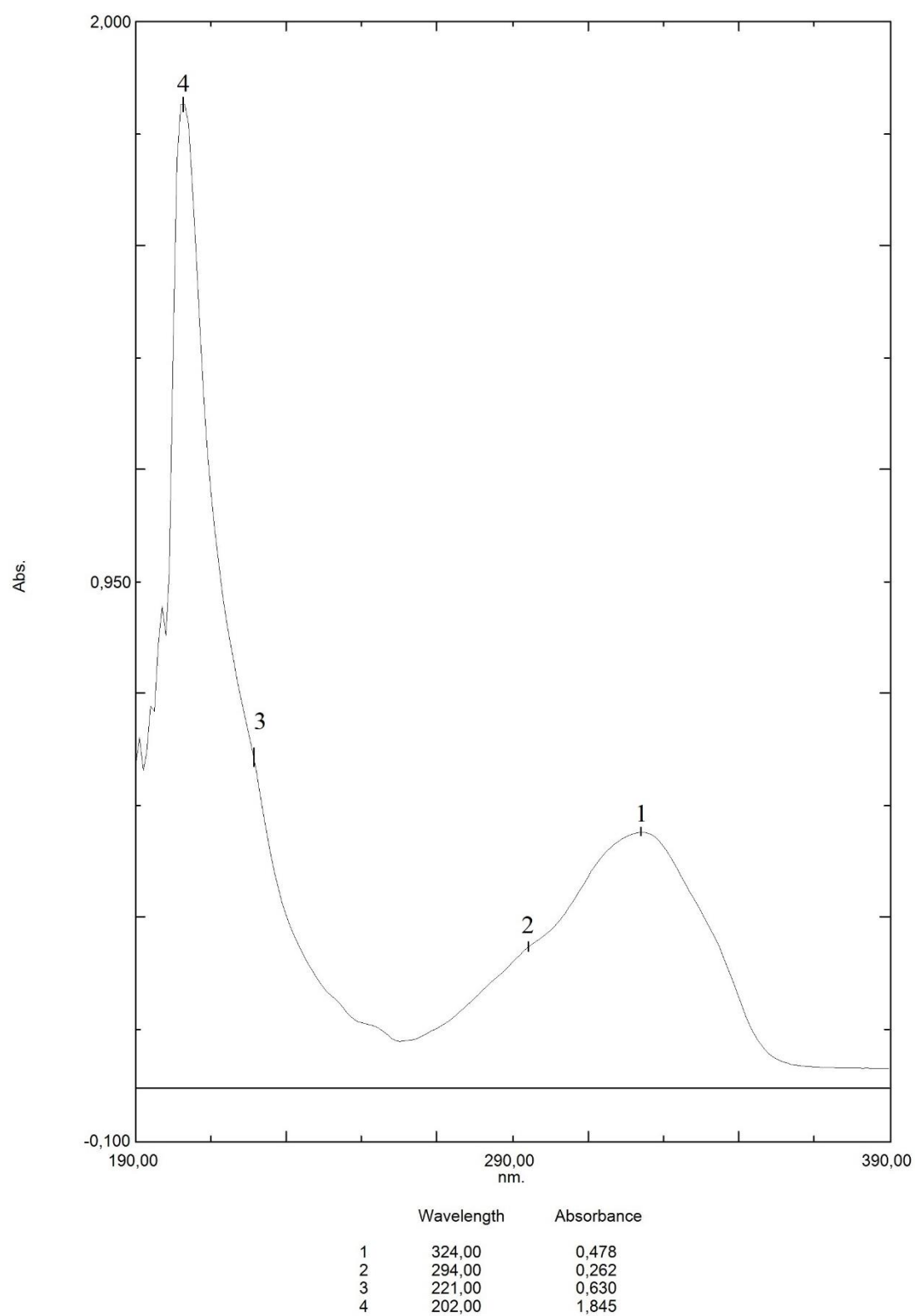




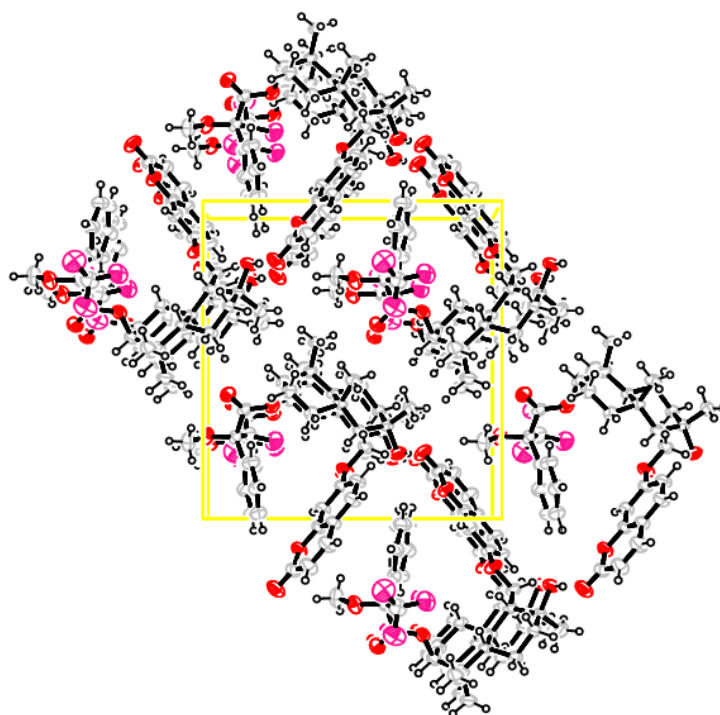
**Figure S106.** (+)-HRESIMS spectrum of (*R*)-MTPA ester of samarcandin (**24**)



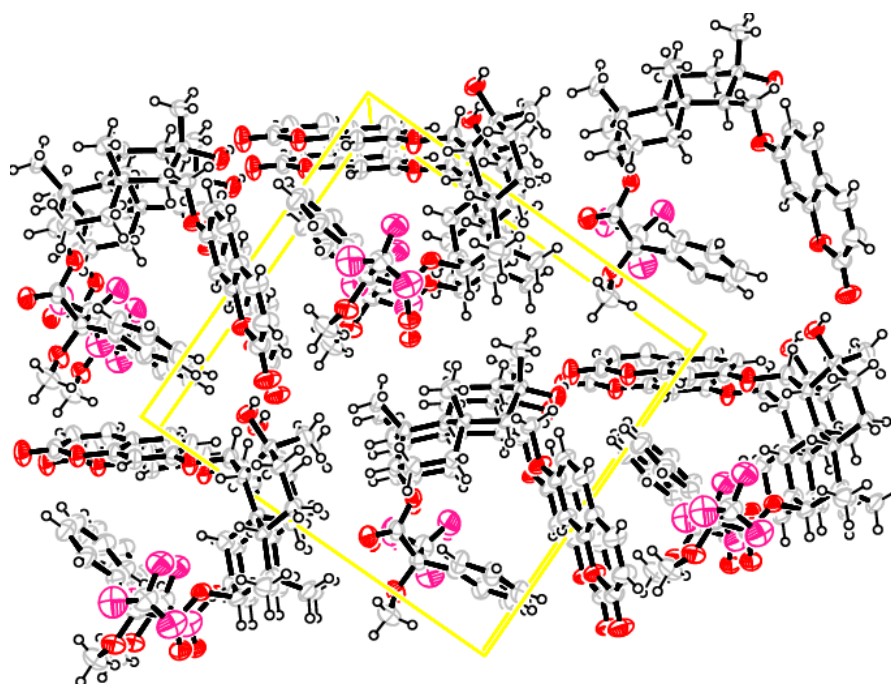
**Figure S107.** IR spectrum of (*R*)-MTPA ester of samarcandin (**24**)



**Figure S108.** UV spectrum of (R)-MTPA ester of samarcandin (24)



A



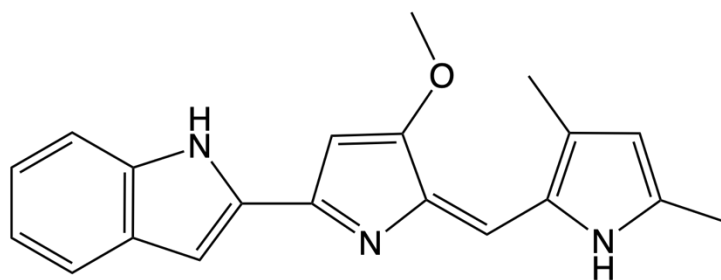
B

**Figure S109.** Packings of the (*R*)-MTPA ester of samarcandin (**24**) in unit cell

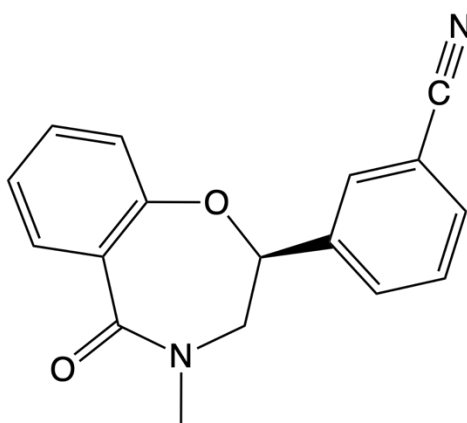
**Table S2.** Crystal data and details of the structure determination of (*R*)-MTPA ester of samarcandin (**24**)

Crystal formula	C <sub>34</sub> H <sub>39</sub> F <sub>3</sub> O <sub>7</sub>
Formula weight	616.15
Crystal dimensions, [mm <sup>3</sup> ]	0.5x0.2x0.2
Temp, [ K]	293(2)
Wavelength, [Å]	0.71073
Crystal system	Monoclinic
Space group; Z	P 2 <sub>1</sub> ; 2
a, [Å]	7.31110(10)
b, [Å]	14.0819(4)
c, [Å]	14.9790(10)
β, [°]	97.977(6)
Volume [Å <sup>3</sup> ]	1527.23(11)
Dcalc [g.cm <sup>-3</sup> ]	1.341
F(000)	652.0
Abs. coefficient (μ, mm <sup>-1</sup> )	0.104
Range of θ, [°]	3.10 to 27.47
Reflections collected	36935
Reflections used in refinement	6992
No. of refined parameters	413
Absorption correction	Multi-scan
Refinement method	Full matrix
R / R <sub>w</sub> values	0.0379/ 0.1049
GOF	1.056
Final shift	0.000
(Δρ) <sub>min</sub> , (Δρ) <sub>max</sub> (e Å <sup>-3</sup> )	0.252, - 0.203

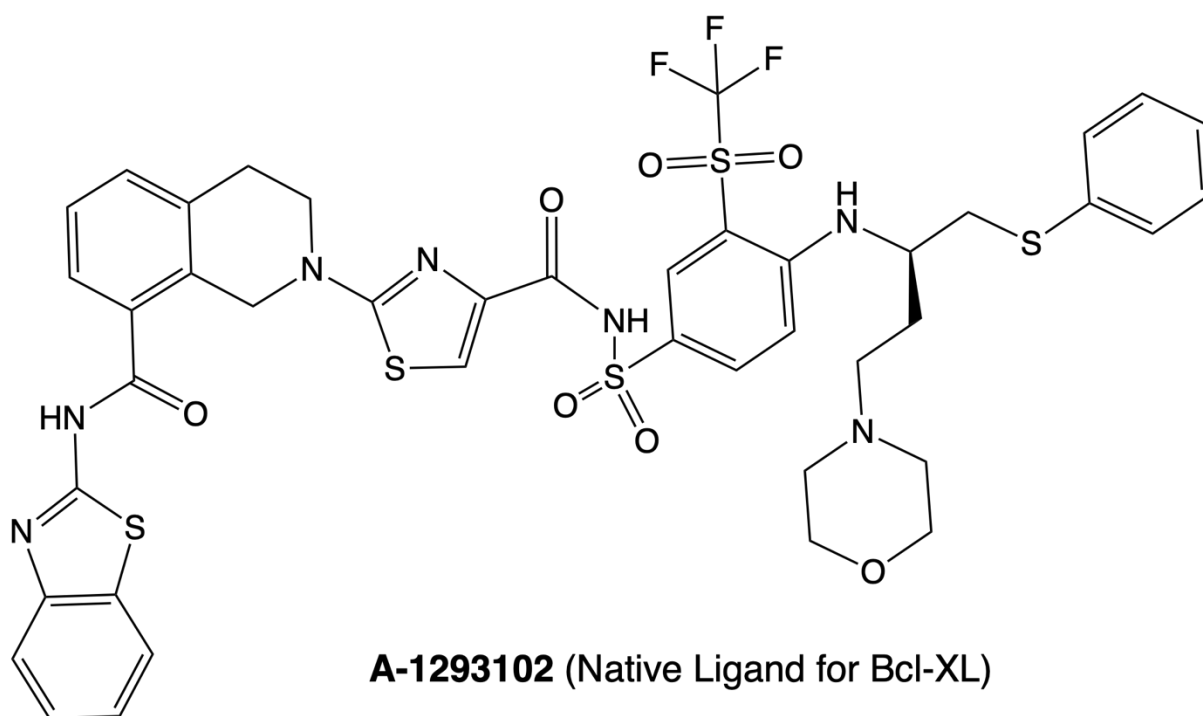
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**Obatoclax** (Reference Compound for Bcl-XL &  $\beta$ -Catenin)

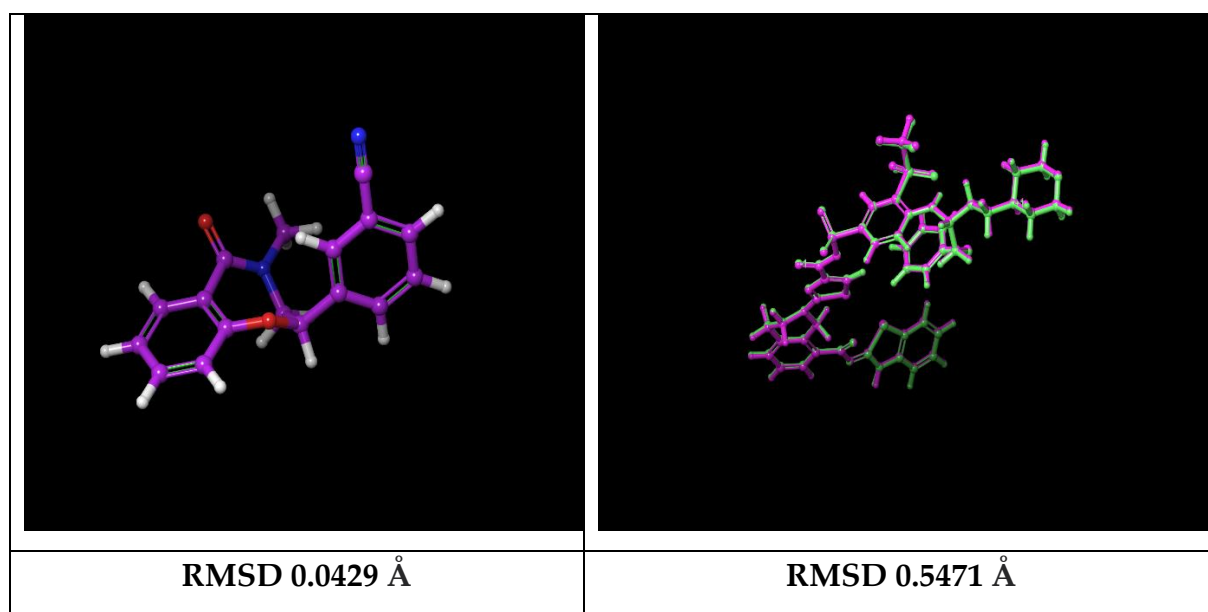


**Compound 6** (Co-crystalized Ligand for  $\beta$ -Catenin)



**A-1293102** (Native Ligand for Bcl-XL)

**Figure S110.** Structures of Bcl-XL and  $\beta$ -Catenin ligands



**Figure S111.** Validation of the docking models. Superposition of docked pose and experimental binding conformation (green) of Native Ligands in the binding pocket of 7AFW (left), 7LH7 (right)

## References

1. Abd El-Razek, M.H.; Ohta, S.; Hirata, T. Terpenoid coumarins of the genus *Ferula*. *Heterocycles* **2003**, *60*(3), 689 - 716.
2. Ban'kovskii, A.I.; Ermatov, N.E.; Perel'son, M.E.; Bubeva-Ivanova, L.; Pavlova, N.S. Structure of the coumarins colladin and colladonin. II. *Chem. Nat. Compd.* **1970**, *6*, 170-176.
3. Aydogan, F.; Baykan, S.; Soliman, G.A.; Yusufoglu, H.; Bedir, E. Evaluation of the potential aphrodisiac activity of sesquiterpenoids from roots of *Ferula huber-morathii* Peşmen in male rats. *J. Ethnopharmacol.* **2020**, *257*, 112868.