Supplementary data

Antiprotozoal, anticancer and antimicrobial activities of dihydroartemisinin acetal dimers and monomers

Desmond Slade, Ahmed M. Galal, Waseem Gul, Mohamed M. Radwan, Safwat A. Ahmed, Shabana I. Khan, Babu L. Tekwani, Melissa R. Jacob, Samir A. Ross, Mahmoud A. ElSohly

Contents **Page**

List S1. IUPAC nomenclature for **1**–**20**.

1. **Artemisinin:**

   (3*R*,5a*S*,6*R*,8a*S*,9*R*,12*S*,12a*R*)-octahydro-3,6,9-trimethyl-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepin-10(3H)-one

2. **Dihydroartemisinin (DHA):**

   (3*R*,5a*S*,6*R*,8a*S*,9*R*,12*R*,12a*R*)-decahydro-3,6,9-trimethyl-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepin-10-ol

3. **Anhydrodihydroartemisinin:**

   (3*R*,5a*S*,6*R*,8a*S*,12*R*,12a*R*)-3,4,5,5a,6,7,8,8a-octahydro-3,6,9-trimethyl-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepin

4. **1,3-Dihydroxy-2-propanone β,β-DHA acetal dimer:**

   (3*R*,3'*R*,5a*S*,5a'*S*,6*R*,6'*R*,8a*S*,8a'*S*,9*R*,9'*R*,10*S*,10'*S*,12*R*,12'*R*,12a*R*,12a'*R*)-10,10'-[2-keto-1,3-propanediylbis(oxy)]bis[decahydro-3,6,9-trimethyl-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepin]

5. **1,2,3-Propanetriol β,β-DHA acetal dimer:**

   (3*R*,3'*R*,5a*S*,5a'*S*,6*R*,6'*R*,8a*S*,8a'*S*,9*R*,9'*R*,10*S*,10'*S*,12*R*,12'*R*,12a*R*,12a'*R*)-10,10'-[2-hydroxy-1,3-propanediylbis(oxy)]bis[decahydro-3,6,9-trimethyl-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepin]

6. **3,5-Dihydroxybenzyl alcohol β,β-DHA acetal dimer:**

   3-[(3*R*,5a*S*,6*R*,8a*S*,9*R*,10*S*,12*R*,12a*R*)-decahydro-3,6,9-trimethyl-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepin-10-oxymethyl]-5-[(3*R*,5a*S*,6*R*,8a*S*,9R,10*S*,12*R*,12a*R*)-decahydro-3,6,9-trimethyl-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepin-10-oxy]phenol

7. **3-Aminophenol β,β-DHA acetal dimer:**

N-[(3*R*,5a*S*,6*R*,8a*S*,9*R*,10*S*,12*R*,12a*R*)-decahydro-3,6,9-trimethyl-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepin-10-yl]-3-[(3*R*,5a*S*,6*R*,8a*S*,9*R*,10*S*,12*R*,12a*R*)-decahydro-3,6,9-trimethyl-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepin-10-oxy]aniline

8. ***cis*-2-Butene-1,4-diol β,β-DHA acetal dimer:**

(3*R*,3'*R*,5a*S*,5a'*S*,6*R*,6'*R*,8a*S*,8a'*S*,9*R*,9'*R*,10*S*,10'*S*,12*R*,12'*R*,12a*R*,12a'*R*)-10,10'-[1,4-*cis*-but-2-enediylbis(oxy)]bis[decahydro-3,6,9-trimethyl-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepin]

9. **(*S*)-(–)-1-Butene-3,4-diol β,β-DHA acetal dimer:**

(3*R*,3'*R*,5a*S*,5a'*S*,6*R*,6'*R*,8a*S*,8a'*S*,9*R*,9'*R*,10*S*,10'*S*,12*R*,12'*R*,12a*R*,12a'*R*)-10,10'-[(*S*)-1-vinyl-1,2-ethanediylbis(oxy)]bis[decahydro-3,6,9-trimethyl-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepin]

10. **(*S*)-(–)-1,2,4-Butanetriol β,β-DHA acetal dimer:**

(3*R*,3'*R*,5a*S*,5a'*S*,6*R*,6'*R*,8a*S*,8a'*S*,9*R*,9'*R*,10*S*,10'*S*,12*R*,12'*R*,12a*R*,12a'*R*)-10,10'-[(*S*)-2-hydroxy-1,4-butanediylbis(oxy)]bis[decahydro-3,6,9-trimethyl-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepin]

11. **(2*R**,3*S**)-1,2,3,4-Butanetetraol β,β-DHA acetal dimer:**

(3*R*,3'*R*,5a*S*,5a'*S*,6*R*,6'*R*,8a*S*,8a'*S*,9*R*,9'*R*,10*S*,10'*S*,12*R*,12'*R*,12a*R*,12a'*R*)-10,10'-[(*R**,*S**)-2,3-dihydroxy-1,4-butanediylbis(oxy)]bis[decahydro-3,6,9-trimethyl-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepin]

12. **(2*S*)-1,2,3,4-Butanetetraol β,β-DHA acetal dimer:**

(3*R*,3'*R*,5a*S*,5a'*S*,6*R*,6'*R*,8a*S*,8a'*S*,9*R*,9'*R*,10*S*,10'*S*,12*R*,12'*R*,12a*R*,12a'*R*)-10,10'-[(*S*)-1-(1,2-dihydroxyethyl)-1,2-ethanediylbis(oxy)]bis[decahydro-3,6,9-trimethyl-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepin]

13. **(*R**,*S**)-2,3-Epoxy-1,4-butanediol β,β-DHA acetal dimer:**

(3*R*,3'*R*,5a*S*,5a'*S*,6*R*,6'*R*,8a*S*,8a'*S*,9*R*,9'*R*,10*S*,10'*S*,12*R*,12'*R*,12a*R*,12a'*R*)-10,10'-[(R^*,S^*)-2,3-epoxy-1,4-butanediylbis(oxy)]bis[decahydro-3,6,9-trimethyl-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepin]

14. **2-Methoxysulfonyl-1,3-propanediol β,β-DHA acetal dimer:**

(3*R*,3'*R*,5a*S*,5a'*S*,6*R*,6'*R*,8a*S*,8a'*S*,9*R*,9'*R*,10*S*,10'*S*,12*R*,12'*R*,12a*R*,12a'*R*)-10,10'-[2-methoxysulfonyl-1,3-propanediylbis(oxy)]bis[decahydro-3,6,9-trimethyl-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepin]

15. **1,3-Dihydroxy-2-propanone β-DHA acetal monomer:**

(3*R*,5a*S*,6*R*,8a*S*,9*R*,10*S*,12*R*,12a*R*)-10-(3-hydroxy-2-keto-1-propanoxy)-decahydro-3,6,9-trimethyl-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepin

16. **3,5-Dihydroxybenzyl alcohol β-DHA acetal monomer:**

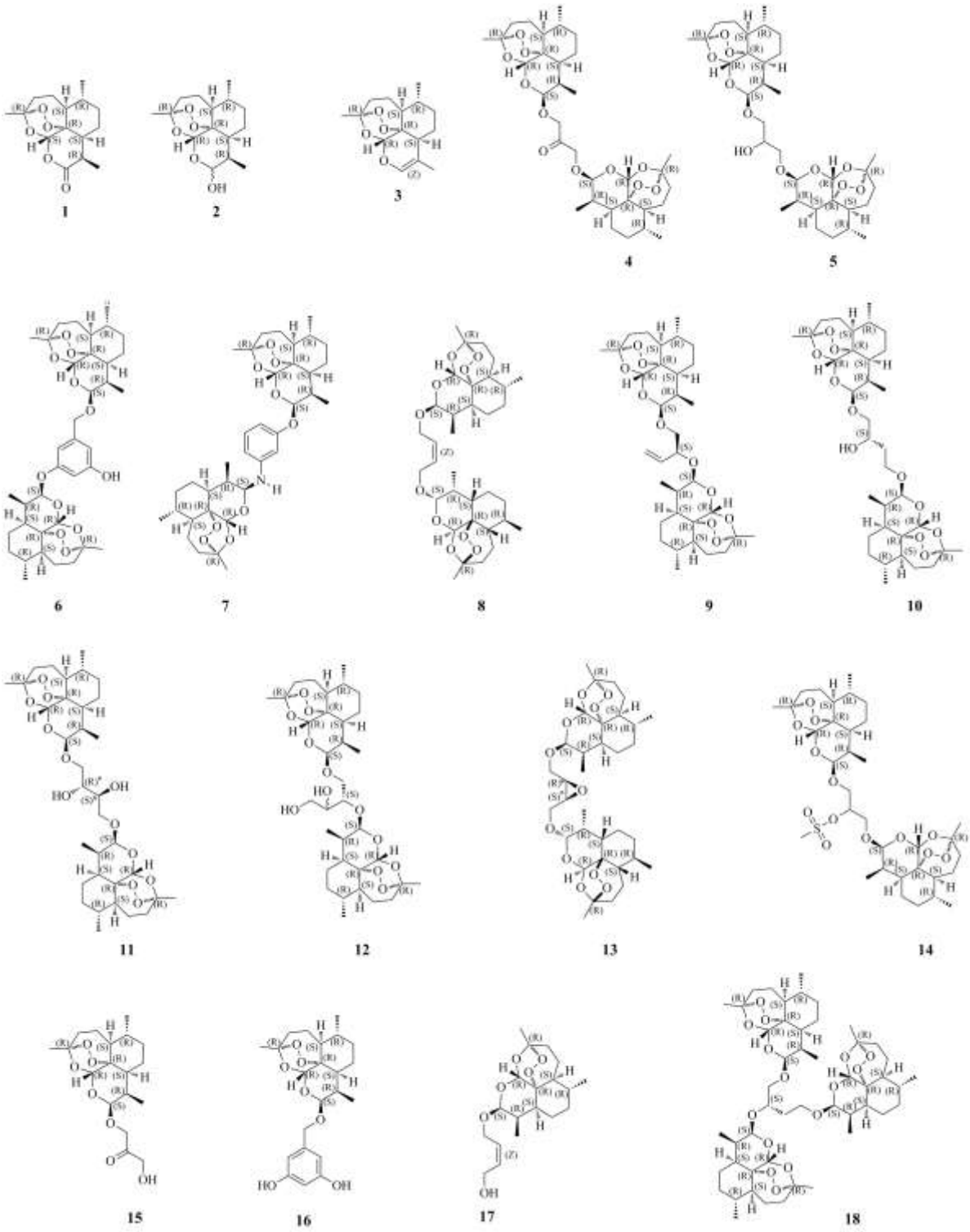
(3*R*,5a*S*,6*R*,8a*S*,9*R*,10*S*,12*R*,12a*R*)-10-(3,5-dihydroxybenzyloxy)-decahydro-3,6,9-trimethyl-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepin

17. ***cis*-2-Butene-1,4-diol β-DHA acetal monomer:**

(3*R*,5a*S*,6*R*,8a*S*,9*R*,10*S*,12*R*,12a*R*)-10-(*cis*-4-hydroxybut-2-enoxy)-decahydro-3,6,9-trimethyl-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepin

18. **(*S*)-(–)-1,2,4-Butanetriol β,β,β-DHA acetal trimer:**

(3*R*,3'*R*,3"*R*,5a*S*,5a'*S*,5a"*S*,6*R*,6'*R*,6"*R*,8a*S*,8a'*S*,8a"*S*,9*R*,9'*R*,9"*R*,10*S*,10'*S*,10"*S*,12*R*,12'*R*,12"*R*,12a*R*,12a'*R*,12a"*R*)-10,10',10"-[(*S*)-1,2,4-butanetriyltris(oxy)]tris[decahydro-3,6,9-trimethyl-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepin]



Supplementary 5

Antifungal activity of **1**–**18**

Compound	*C. albicans*	*C. glabrata*	*C. krusei*	*C. neoformans*	*A. fumigatus*
			IC_{50} (μM)		
1	NA	NA	14.17	0.25	NA
2	0.88	NA	28.13	0.28	NA
3	NA	NA	56.32	0.30	NA
4	2.41	NA	0.88	0.88	32.12
5	0.80	NA	0.40	0.32	NA
6	NA	NT	NT	1.49	NA
7	NA	NT	NT	0.16	NA
8	NA	NT	NT	24.16	NA
9	1.45	NT	NT	6.44	16.11
10	10.25	> 31.31	> 31.31	1.60	5.24
11	6.11	NT	NT	1.22	30.54
12	0.92	NT	NT	0.53	7.64
13	> 31.41	> 31.41	NA	> 31.41	> 31.41
14	4.27	NT	NT	1.42	NA
15	> 56.12	NA	> 56.11	6.48	NA
16	NA	NA	NA	18.60	NA
17	NA	NT	NT	0.56	NA
18	NA	NA	NA	16.57	NA
amphotericin B[a]	**0.37**	**0.46**	**0.85**	**0.78**	**1.12**

IC_{50}: concentration causing 50% growth inhibition. NA: not active. NT: not tested.

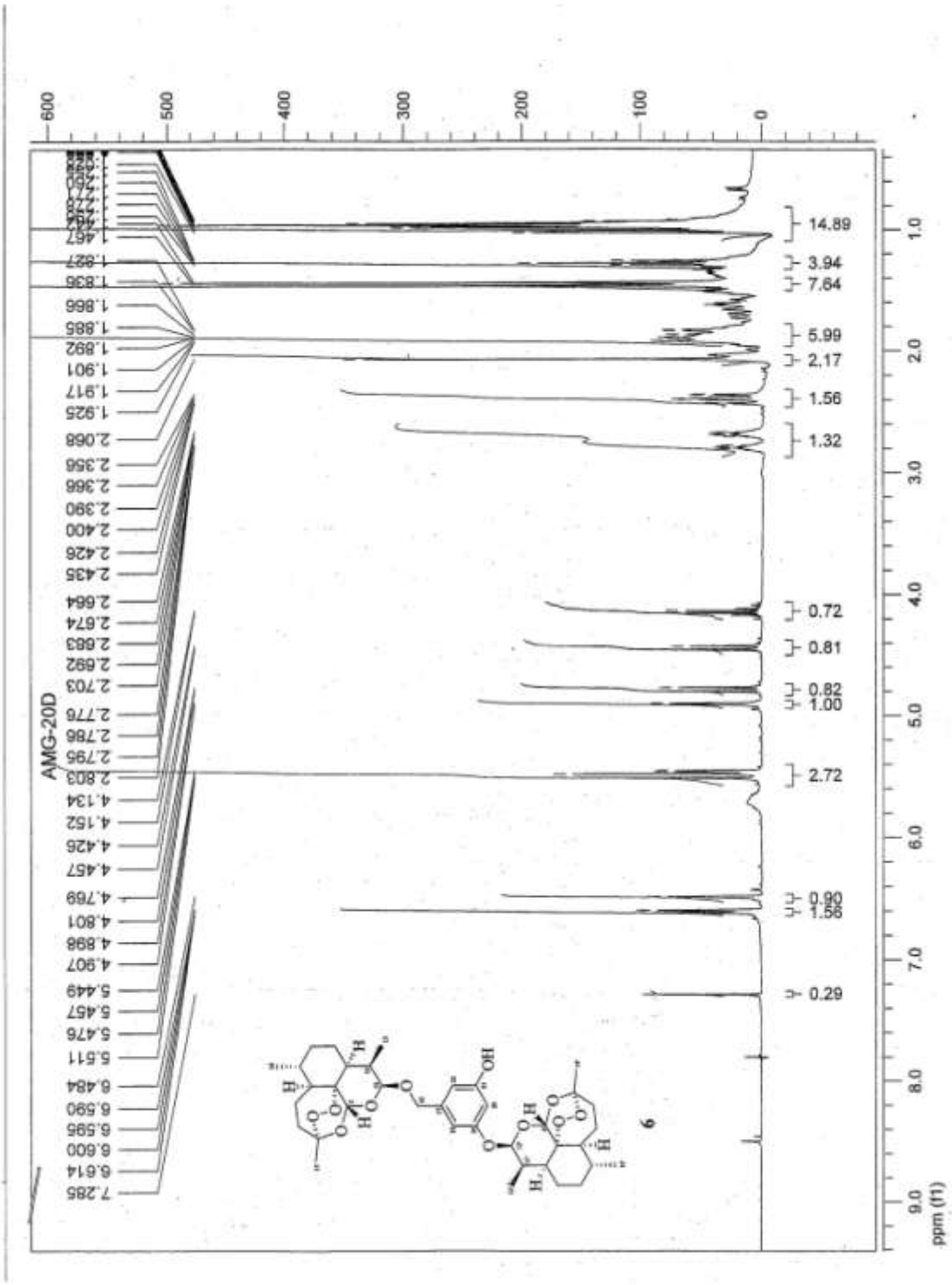
[a] Control.

Antibacterial activity of **1**–**18**

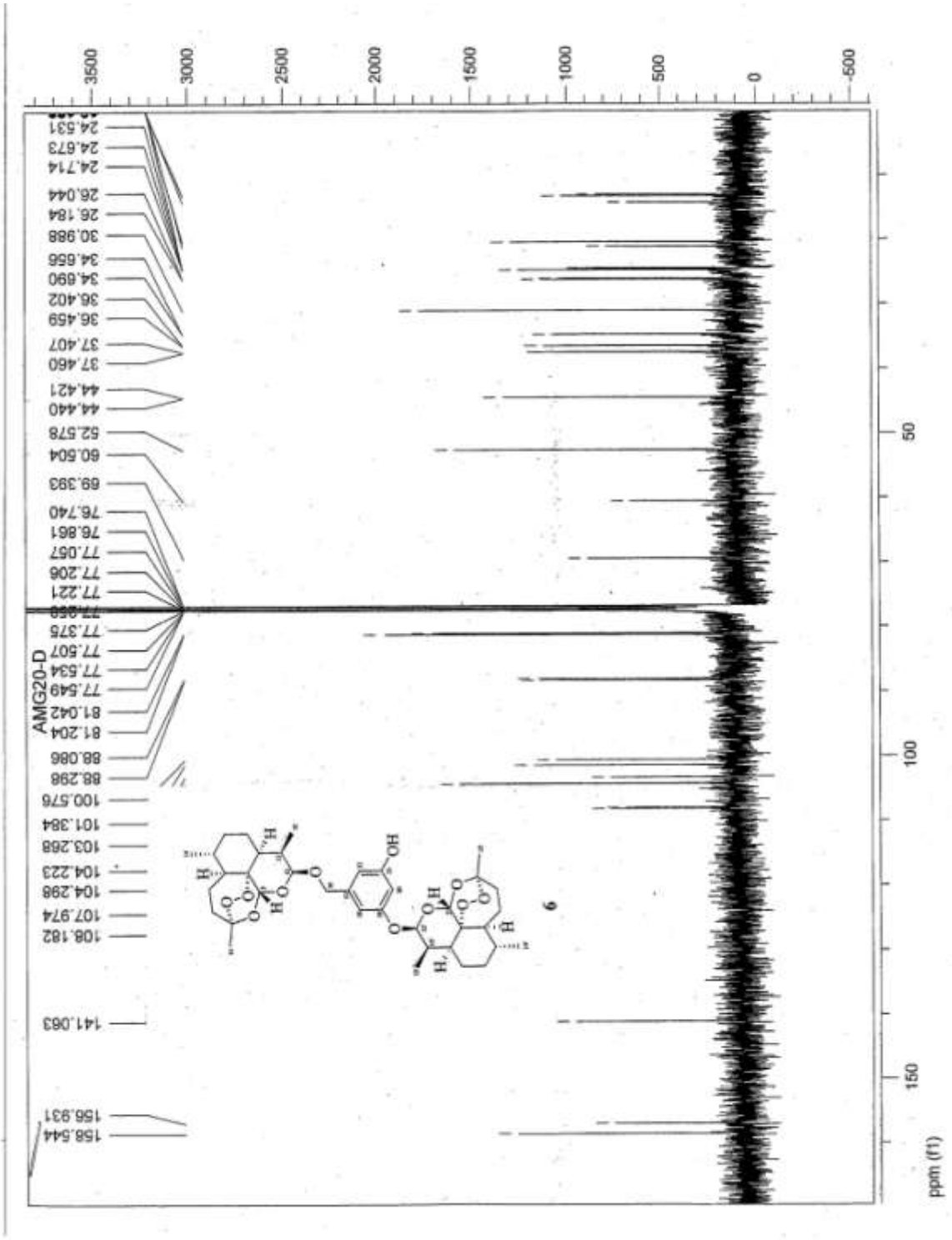
Compound	*S. aureus*	MR*Sa*	*E. coli*	*P. aeruginosa*	*M. intracellulare*
	IC_{50} (μM)				
1	NT	NA	NT	NT	NA
2	NT	NA	NT	NT	NA
3	NT	NA	NT	NT	56.32
4	NT	NA	NT	NT	NA
5	NT	NA	NT	NT	NA
6	NT	NA	22.29	NA	NA
7	NT	NA	8.57	NA	NA
8	NT	NA	NA	NA	NA
9	NT	NA	NA	NA	NA
10	16.52	> 31.31	13.60	NA	> 31.31
11	NT	NA	15.27	NA	NA
12	NT	22.91	7.64	NA	15.27
13	NA	NA	NA	> 31.41	NA
14	NT	NA	NA	NA	NA
15	NA	NA	NA	NA	NA
16	NA	NA	48.59	NA	> 49.20
17	NT	NA	NA	NA	NA
18	NA	NA	NA	NA	> 22.10
ciprofloxacin[a]	**0.36**	**0.36**	**0.01**	**0.22**	**1.27**

IC_{50}: concentration causing 50% growth inhibition. NA: not active. NT: not tested.

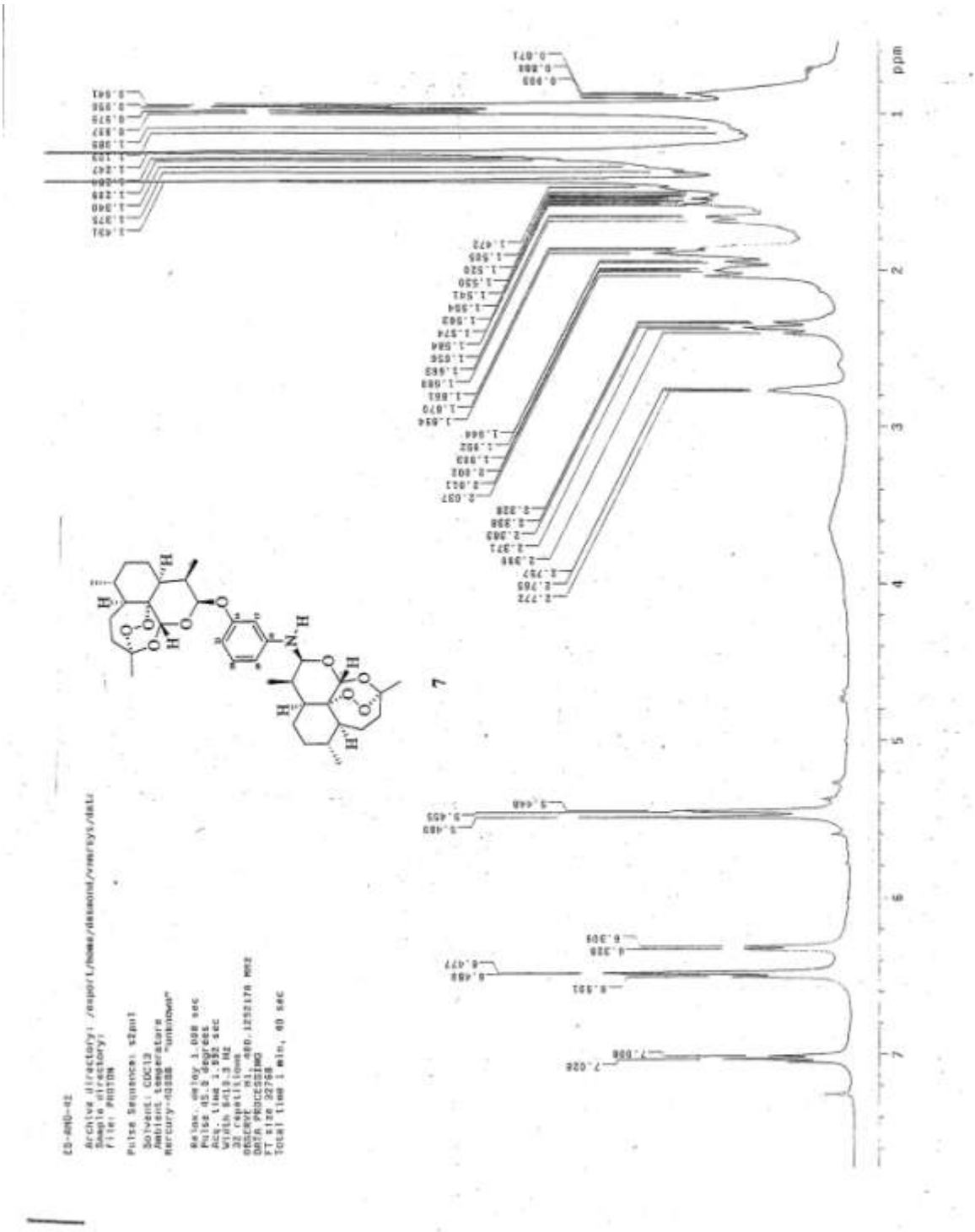
[a] Control.



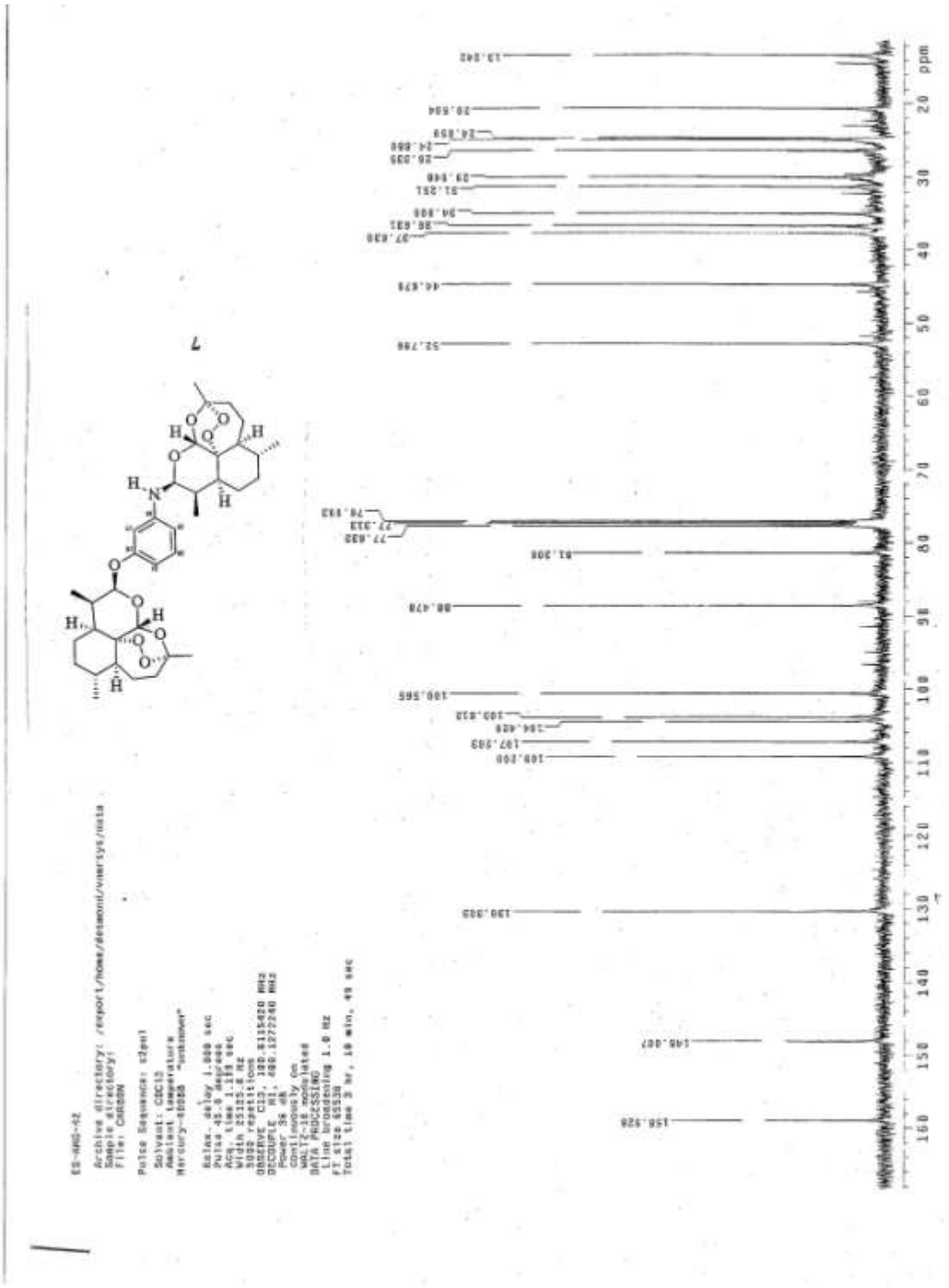
^{1}H NMR spectrum for **6**.



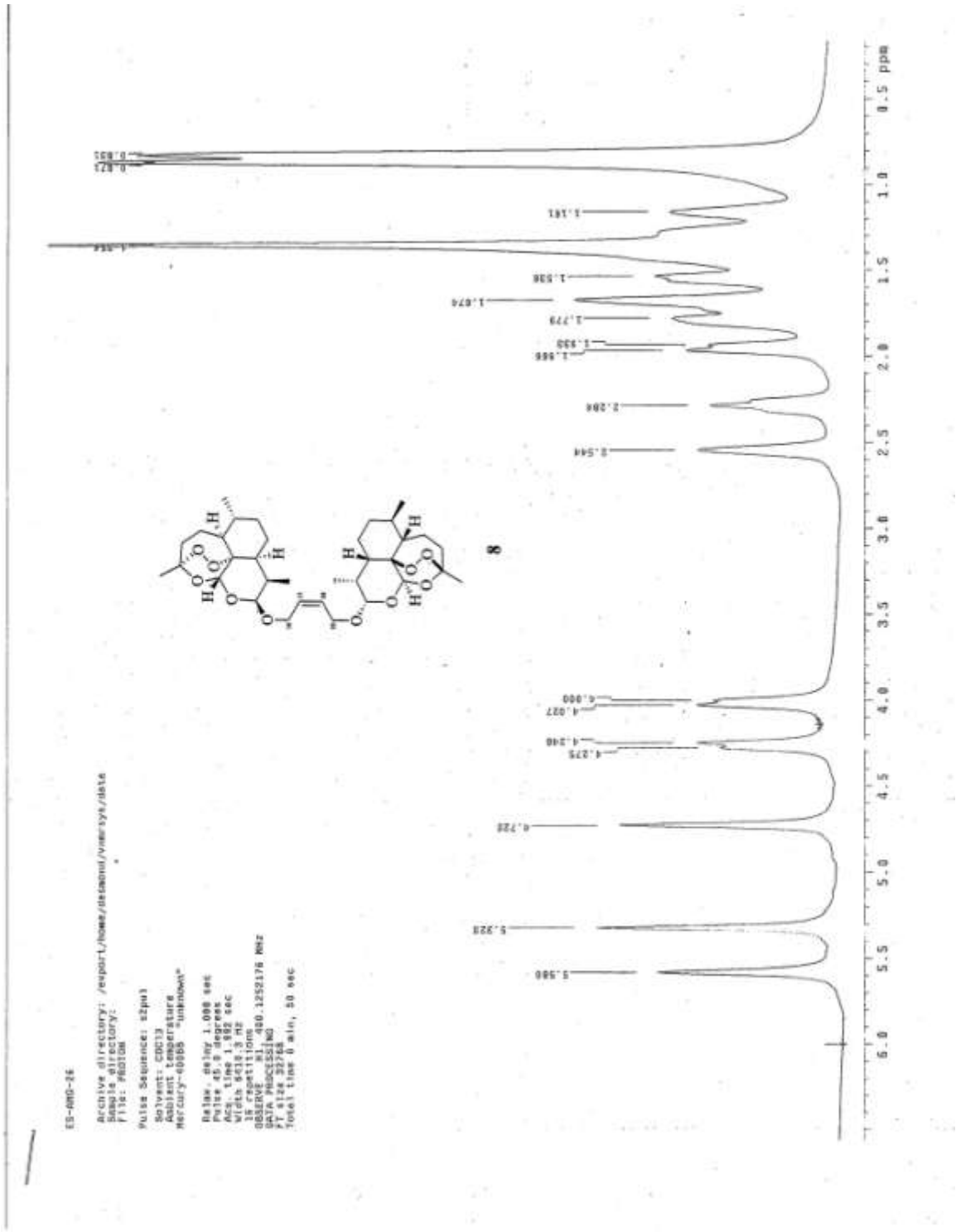
^{13}C NMR spectrum for **6**.



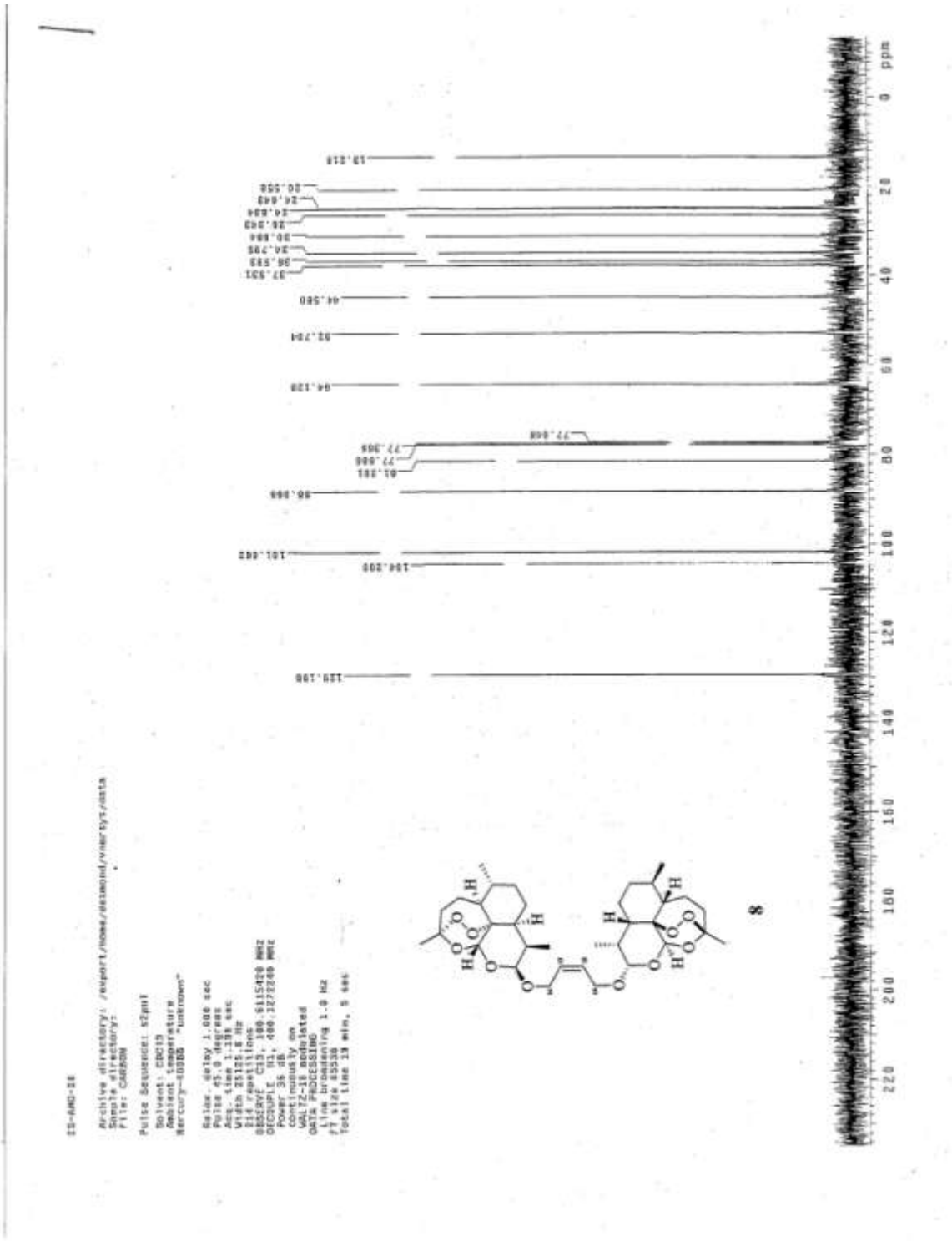
^{1}H NMR spectrum for **7**.



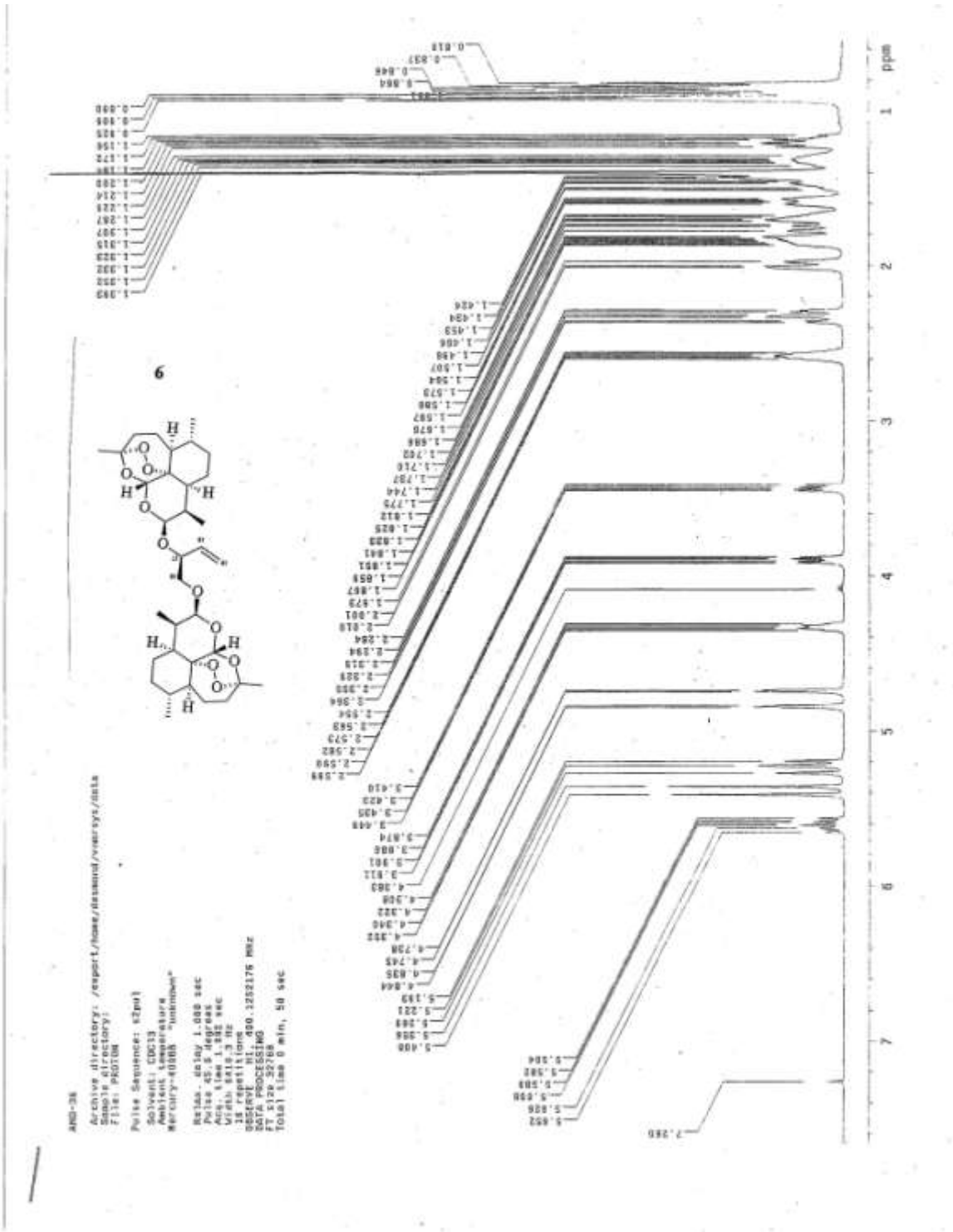
^{13}C NMR spectrum for **7**.



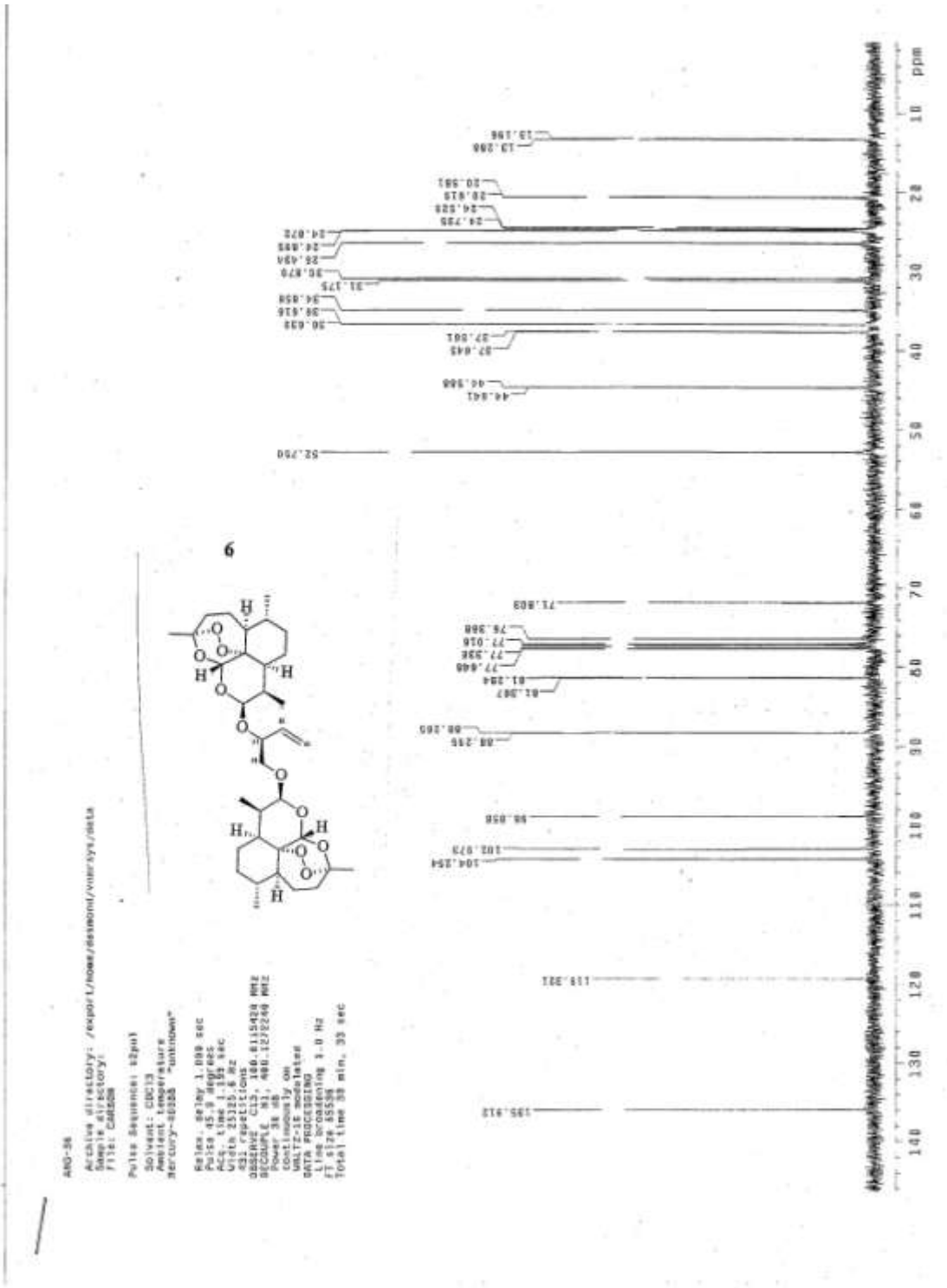
^{1}H NMR spectrum for **8**.



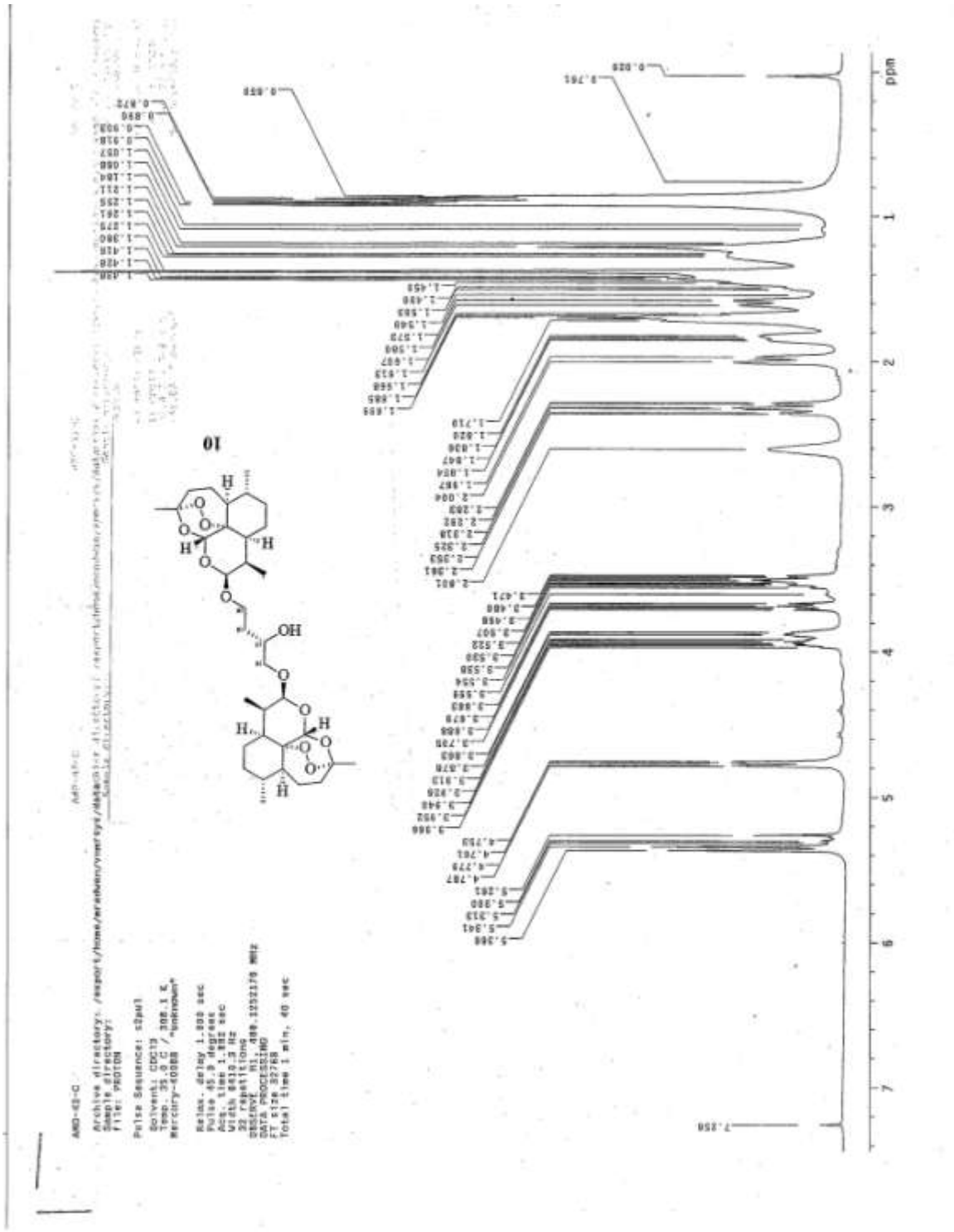
^{13}C NMR spectrum for **8**.



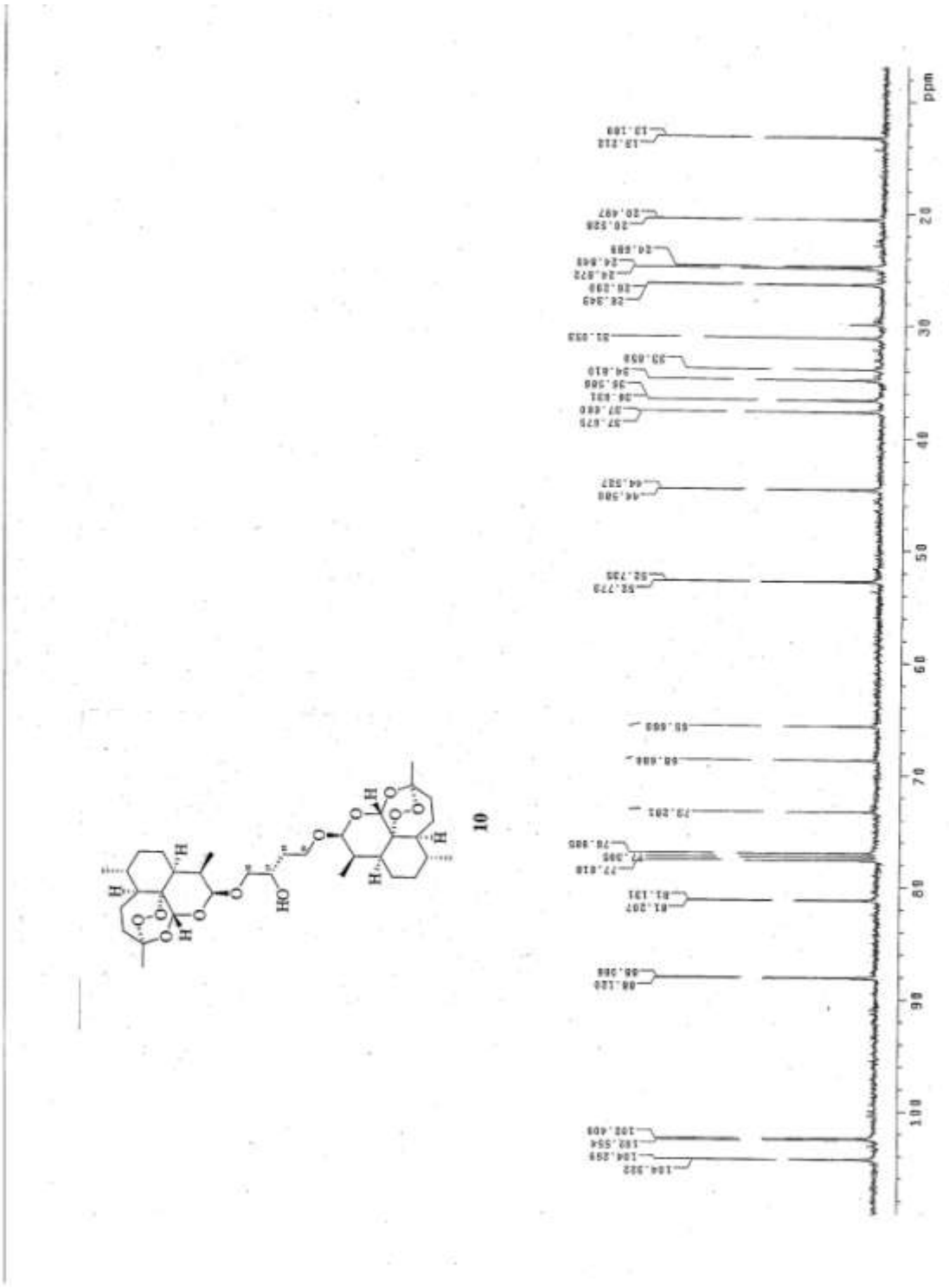
^{1}H NMR spectrum for **9**.



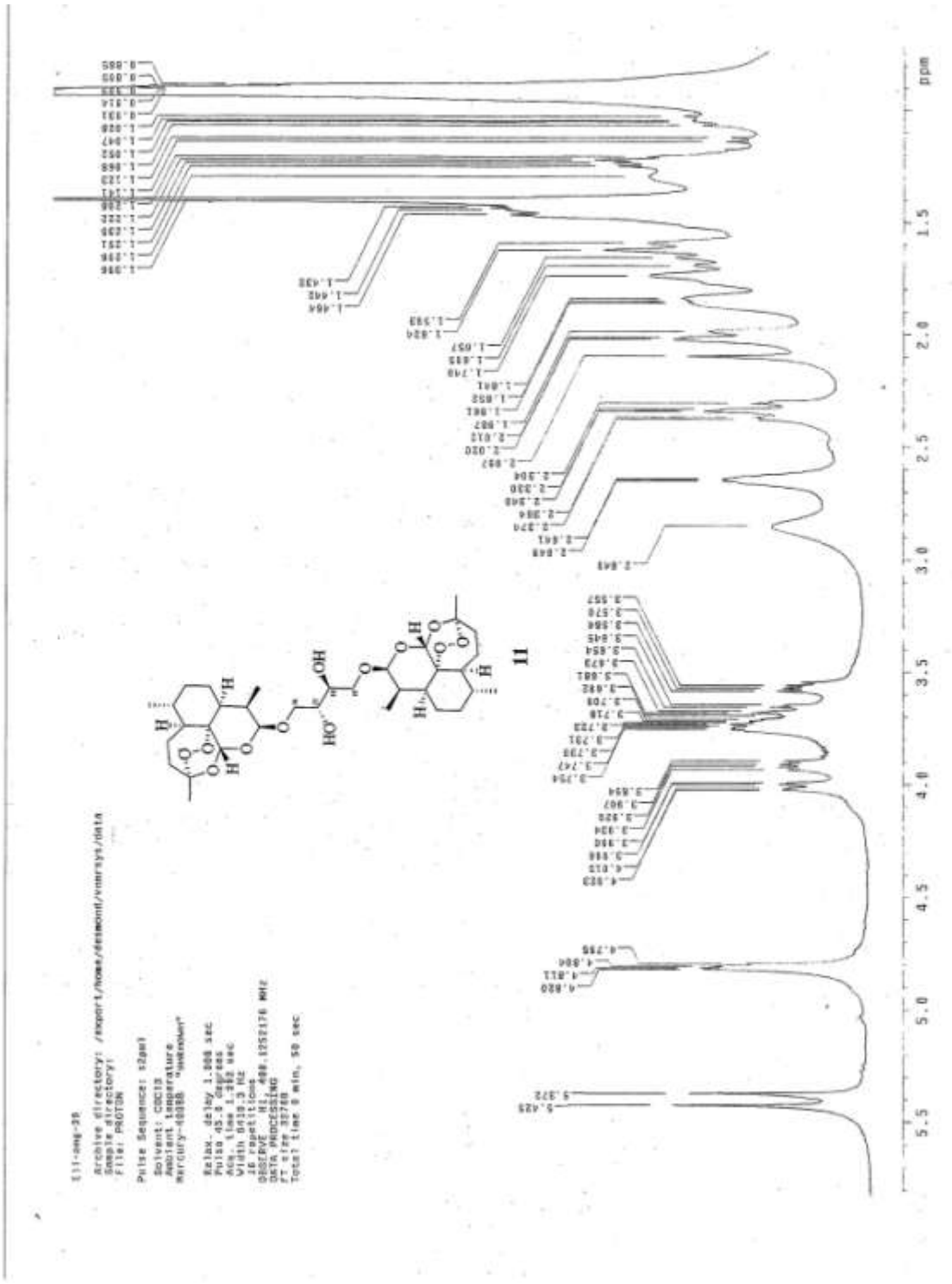
^{13}C NMR spectrum for **9**.



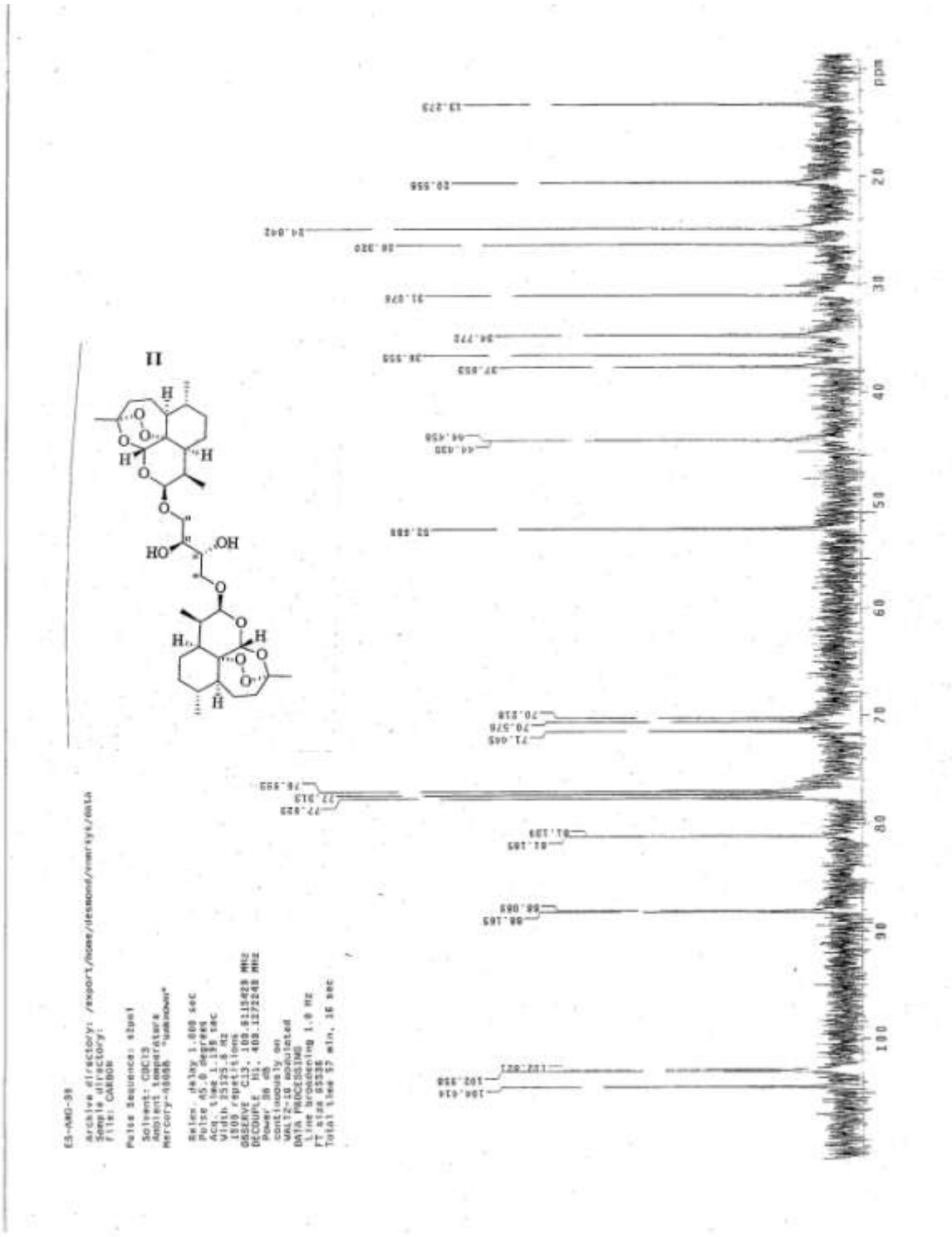
^{1}H NMR spectrum for **10**.



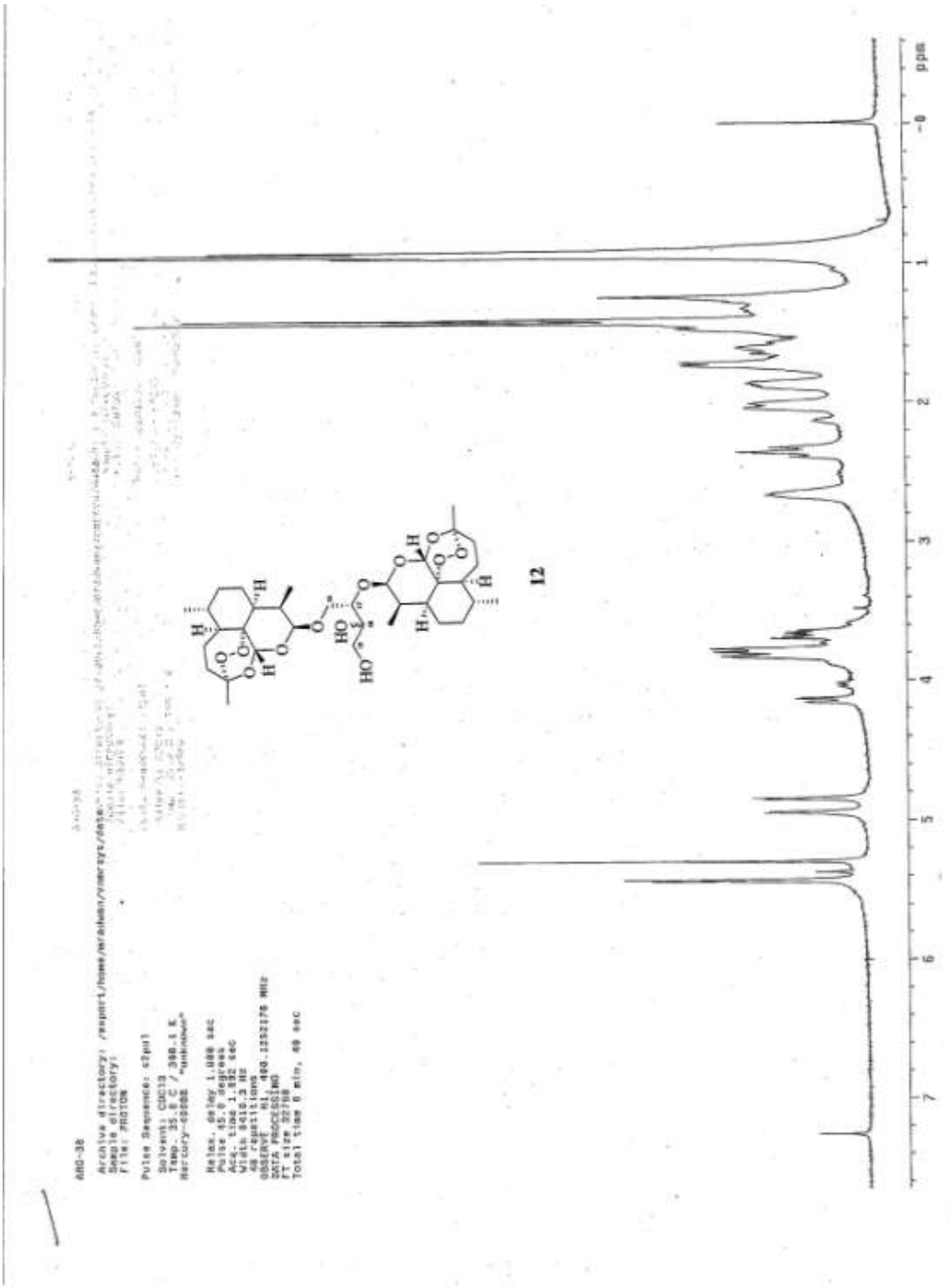
^{13}C NMR spectrum for **10**.



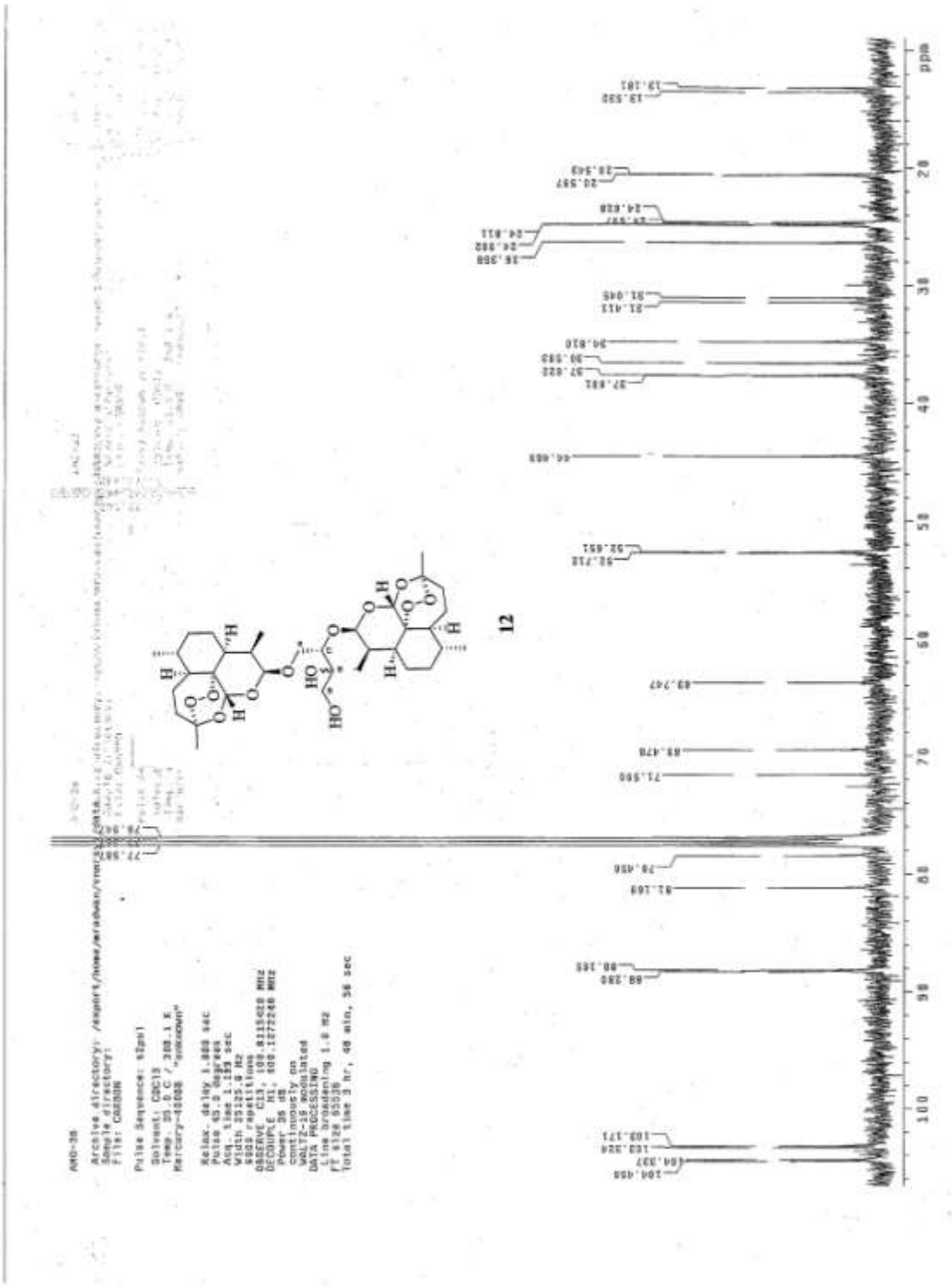
^{1}H NMR spectrum for **11**.



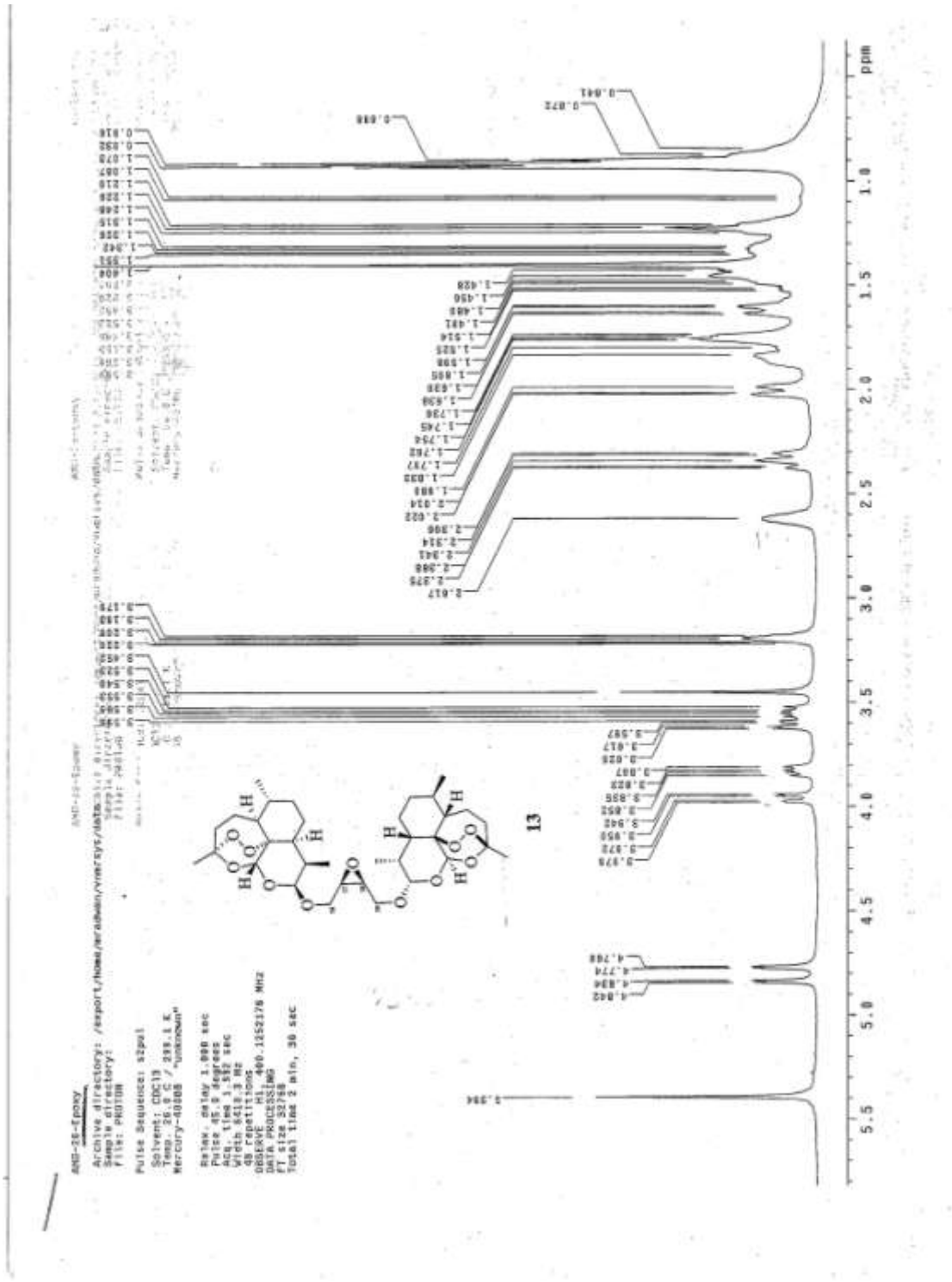
^{13}C NMR spectrum for **11**.



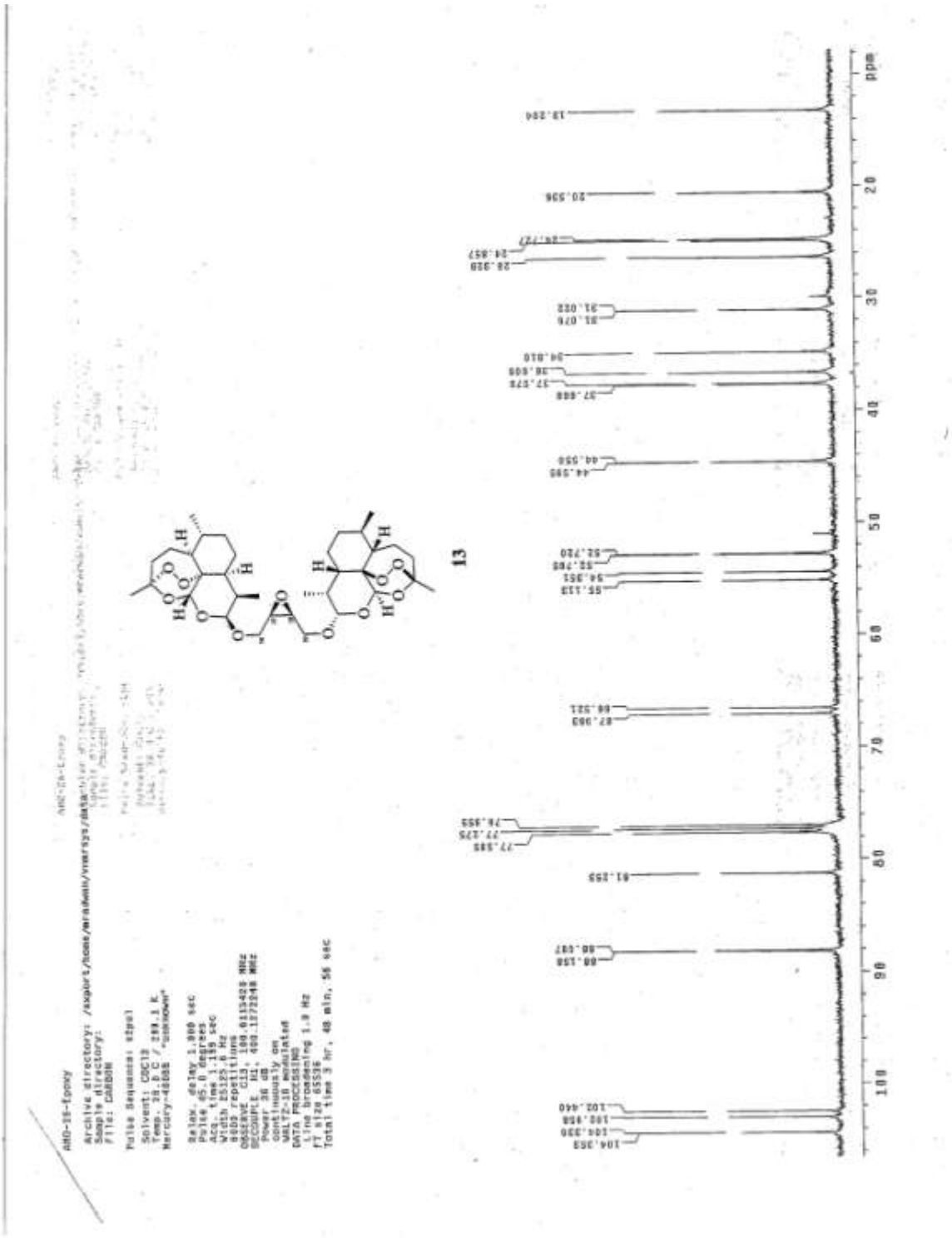
^{1}H NMR spectrum for **12**.



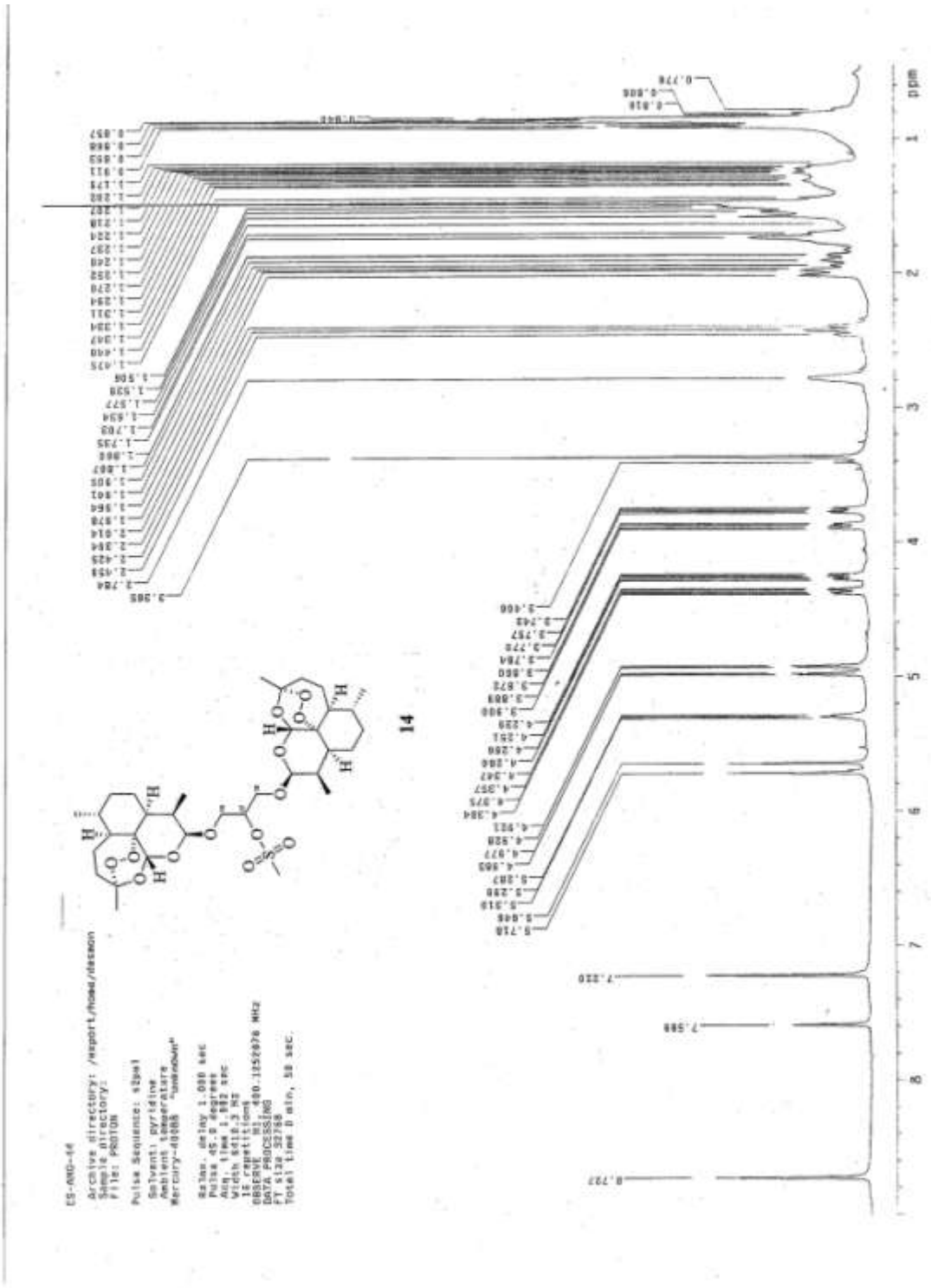
^{13}C NMR spectrum for **12**.



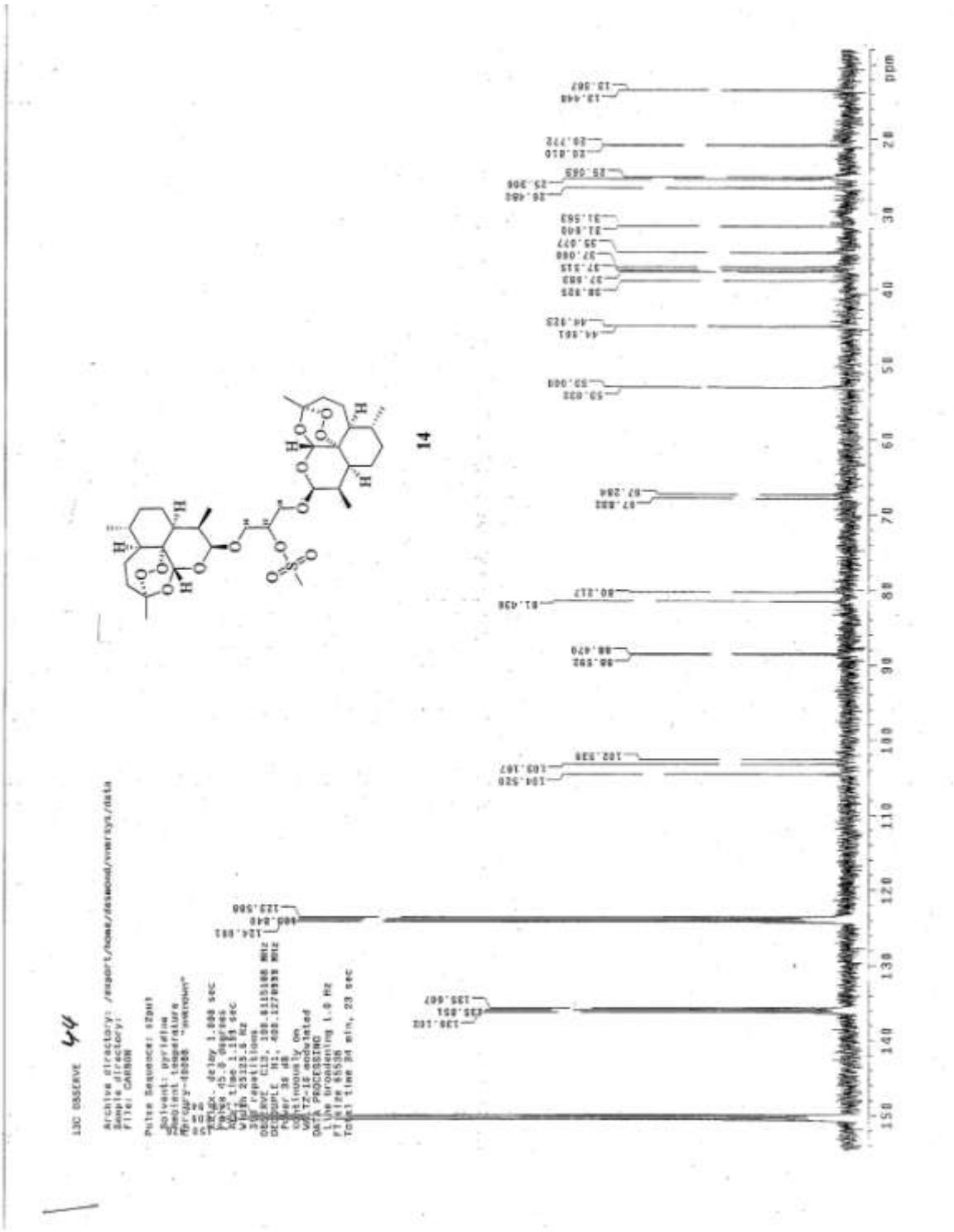
^{1}H NMR spectrum for **13**.



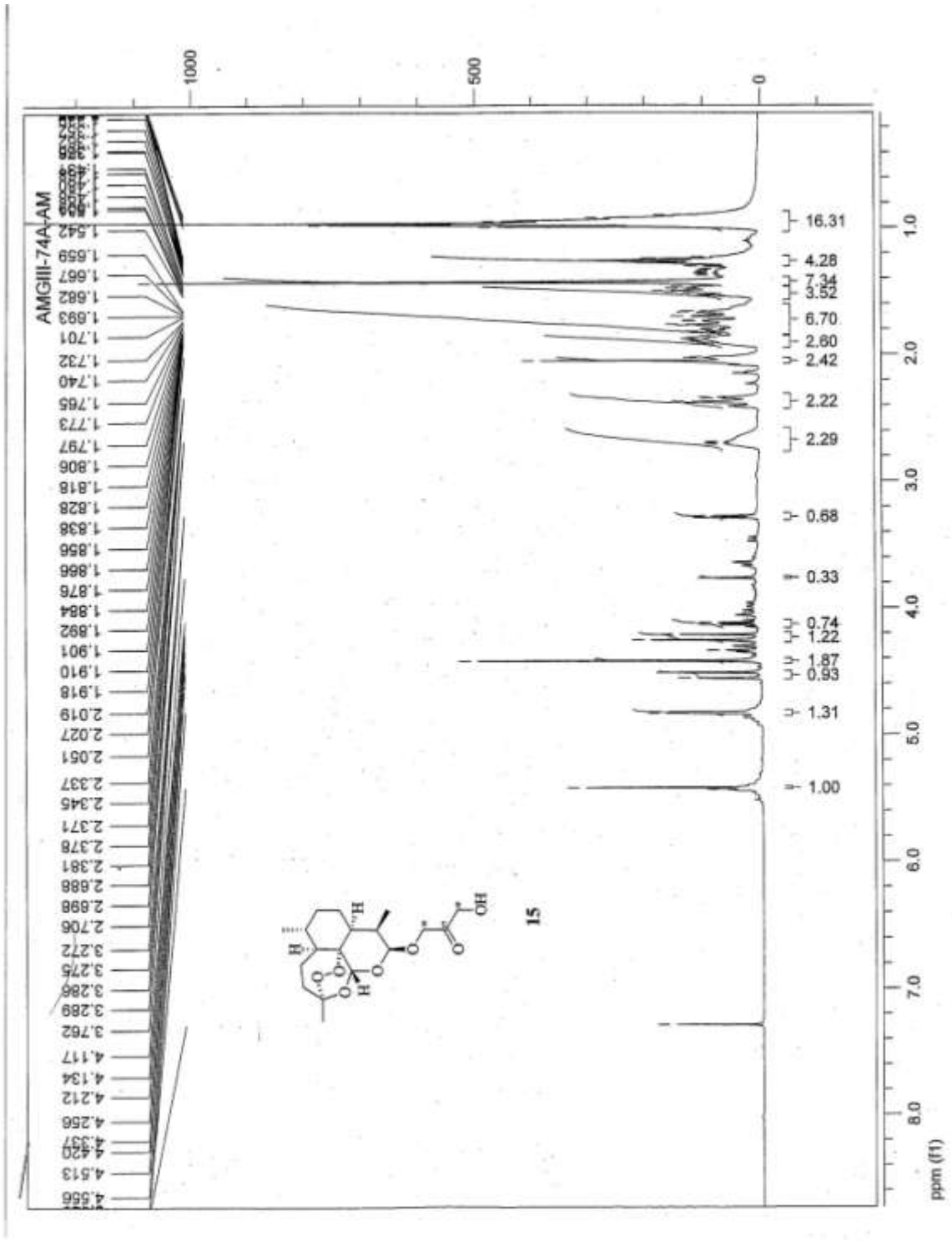
^{13}C NMR spectrum for **13**.



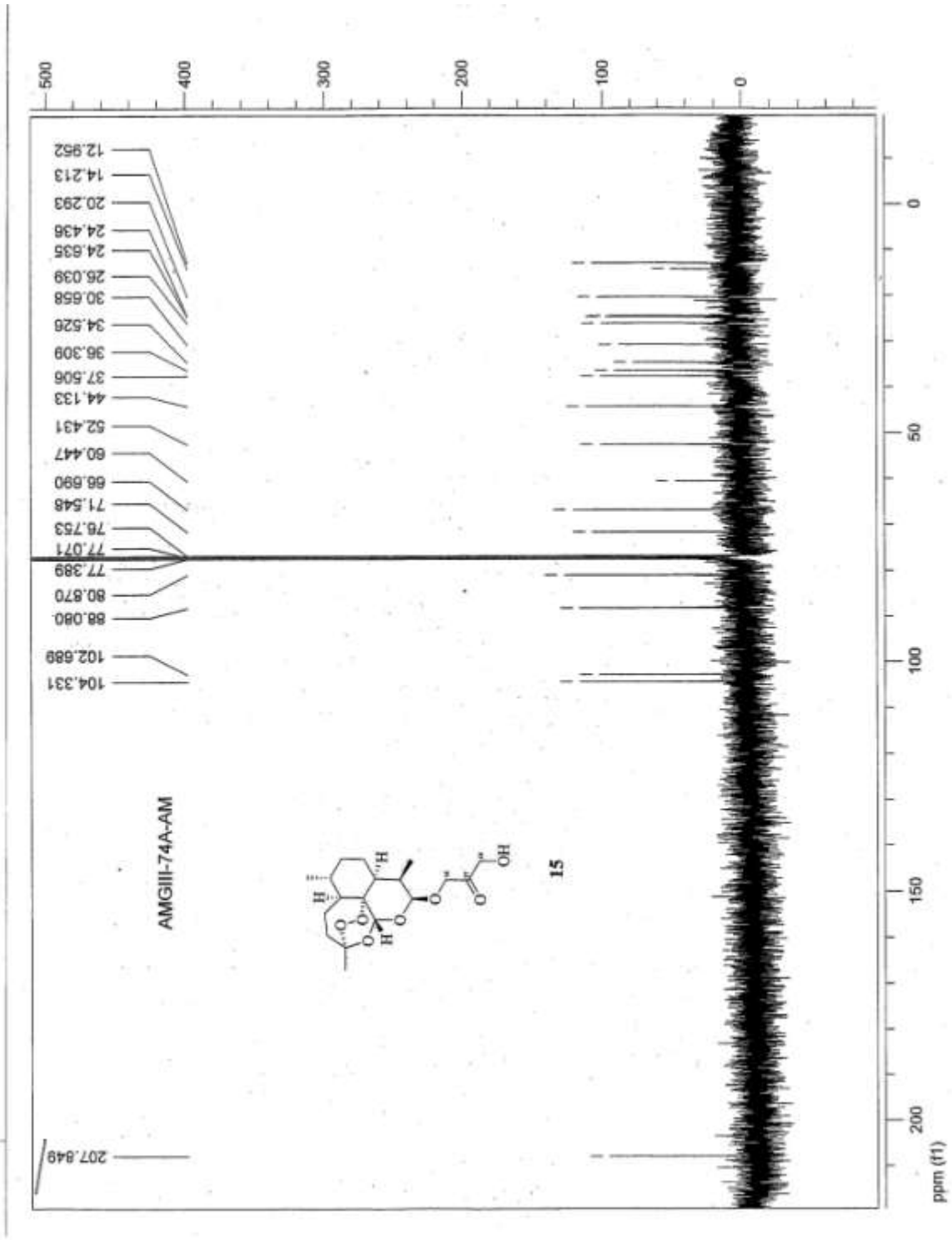
^{1}H NMR spectrum for **14**.



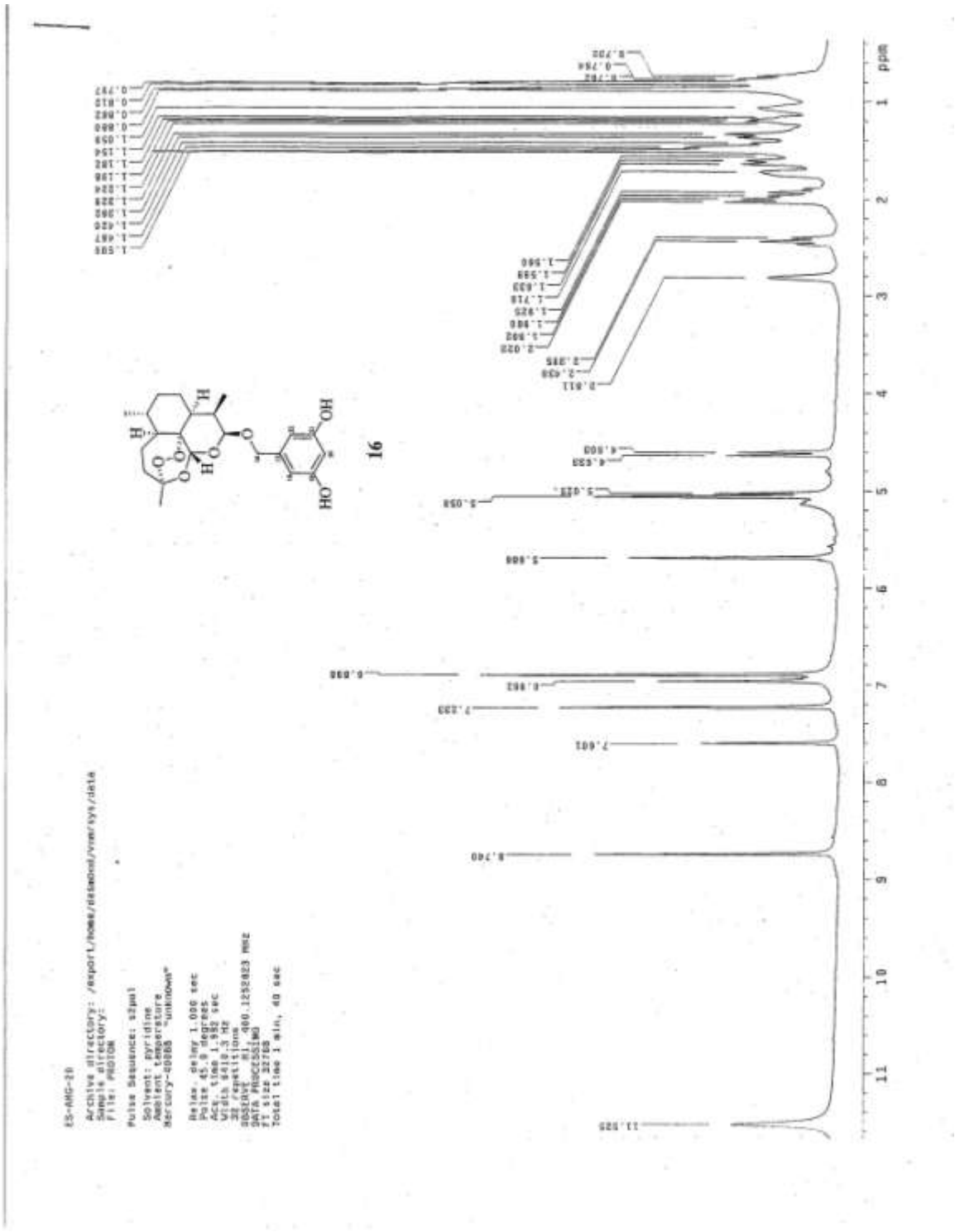
^{13}C NMR spectrum for **14**.



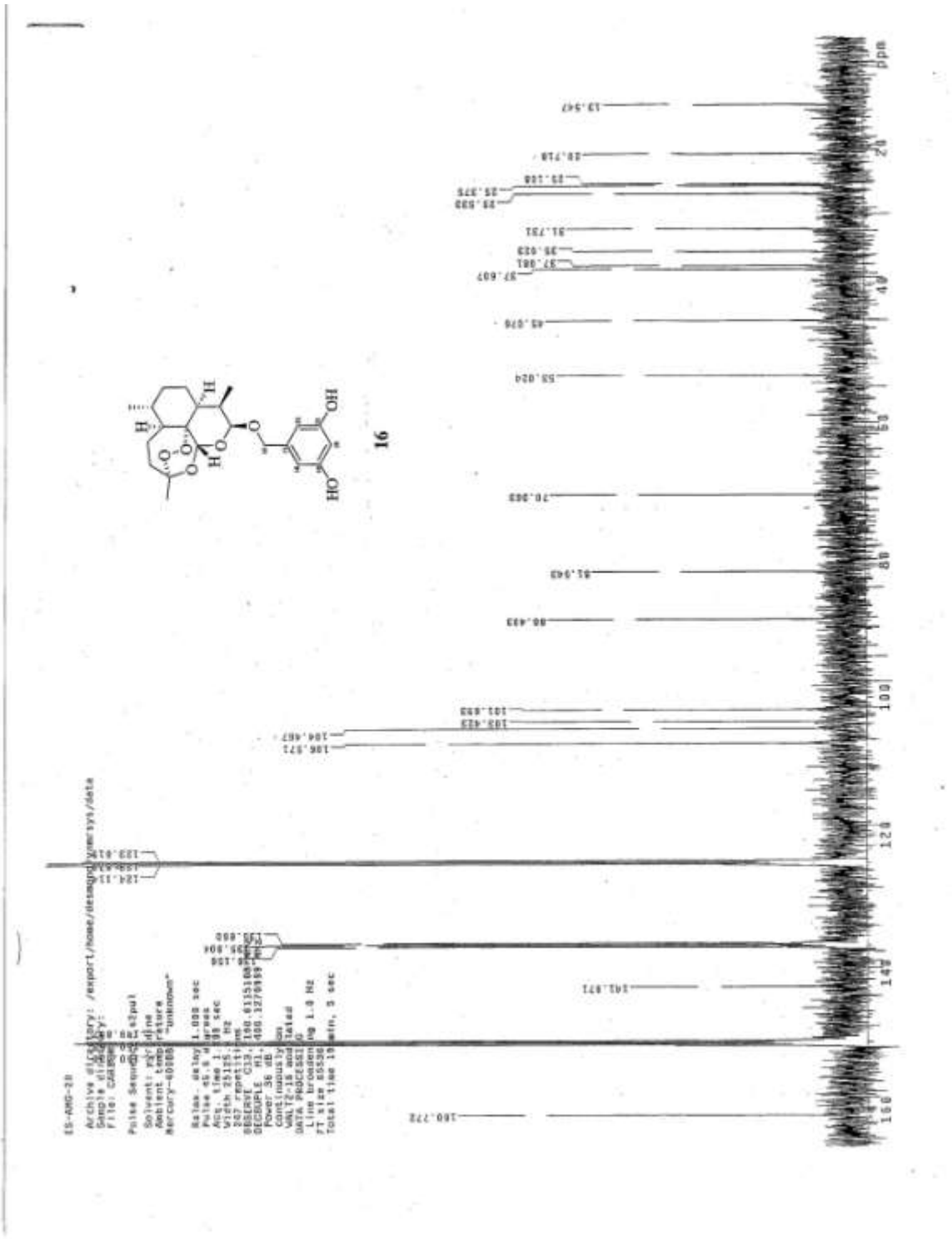
^{1}H NMR spectrum for **15**.



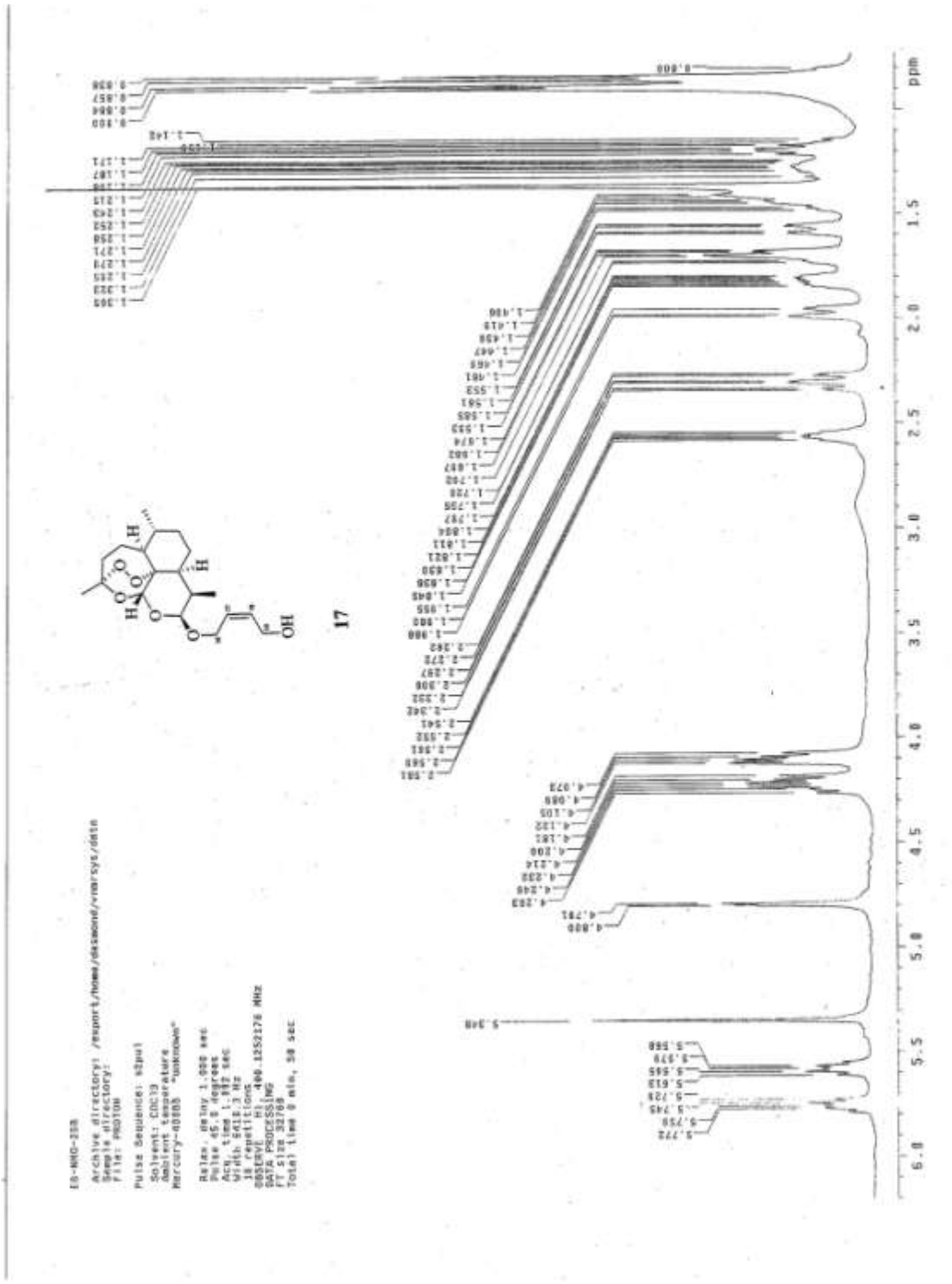
^{13}C NMR spectrum for **15**.



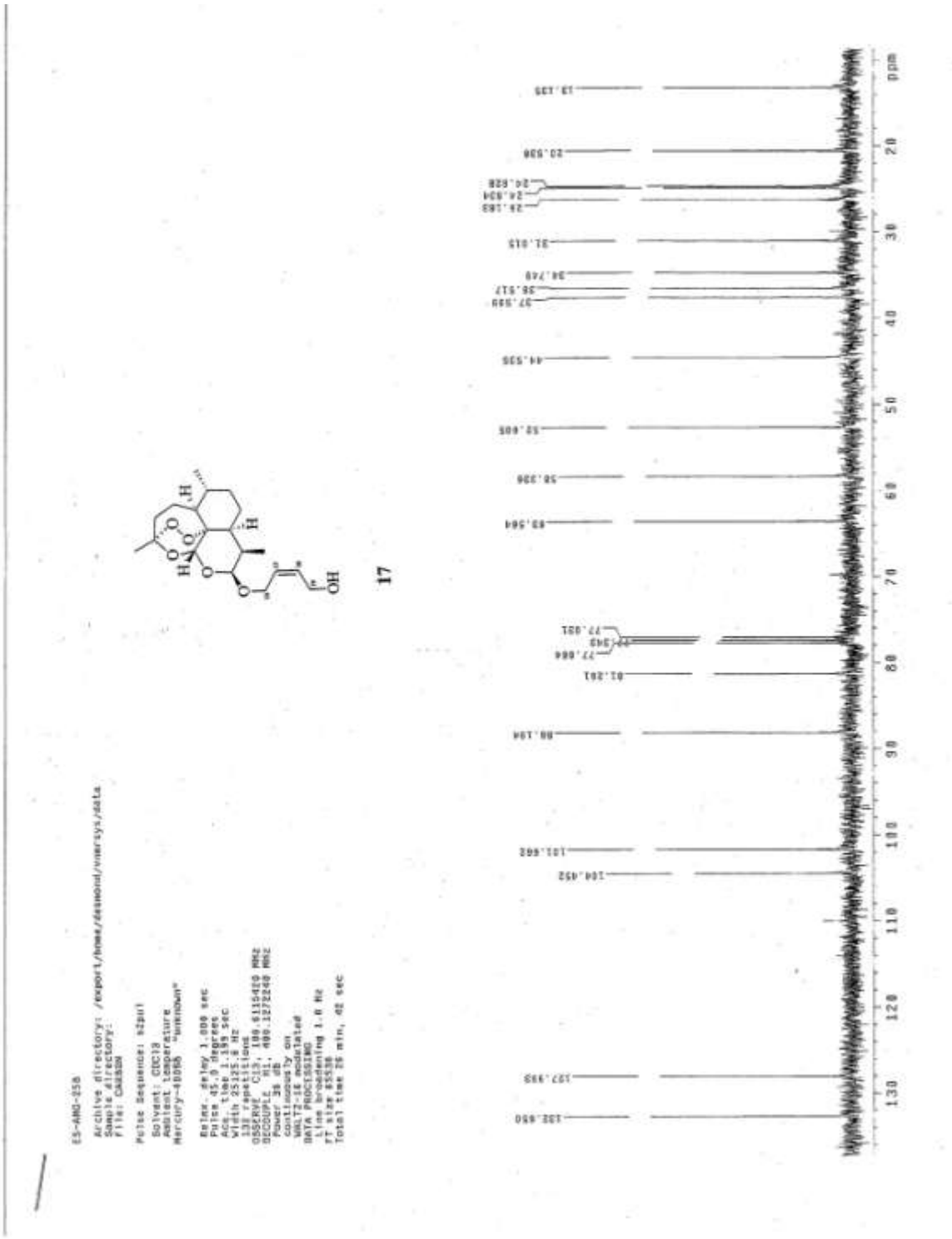
^{1}H NMR spectrum for **16**.



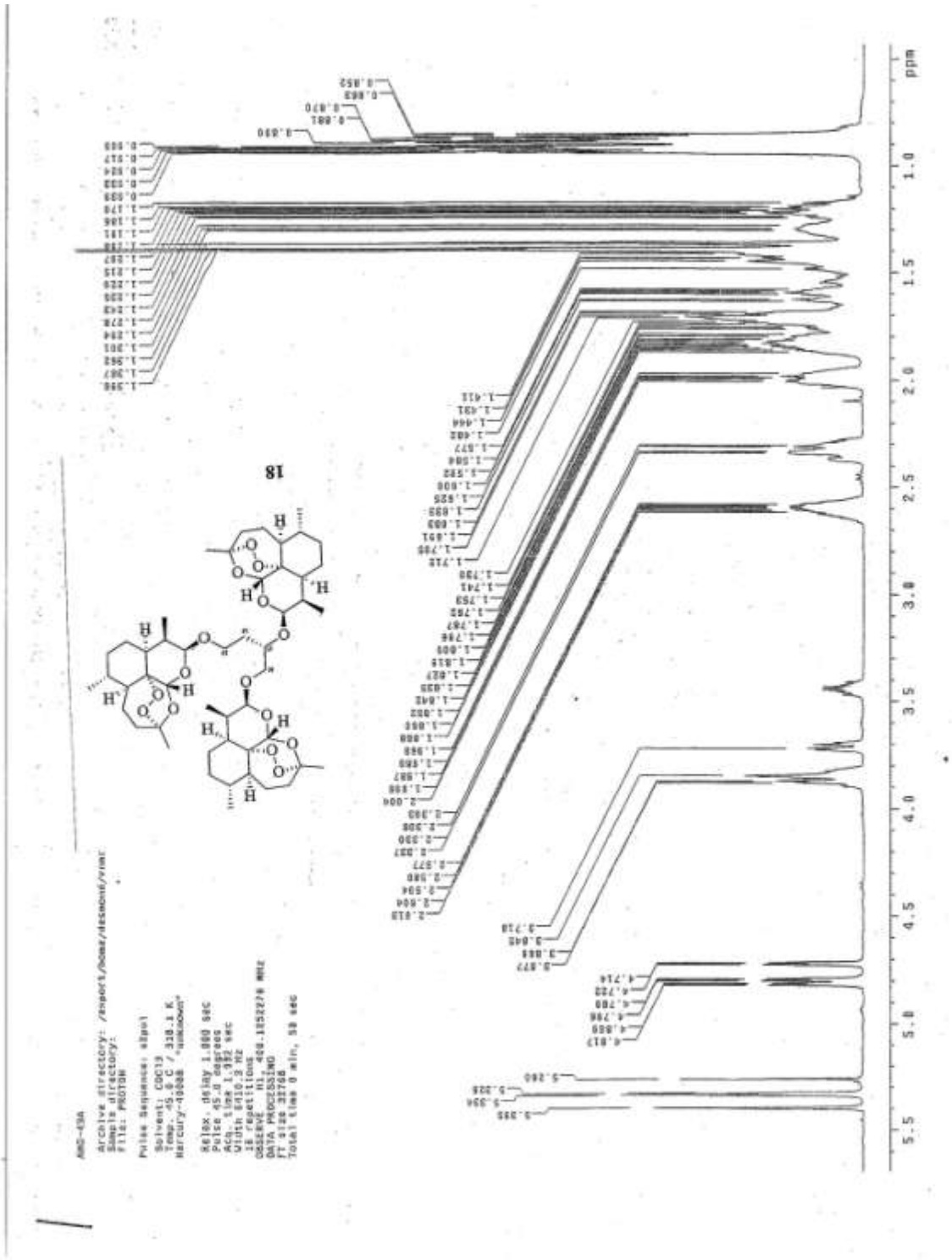
^{13}C NMR spectrum for **16**.



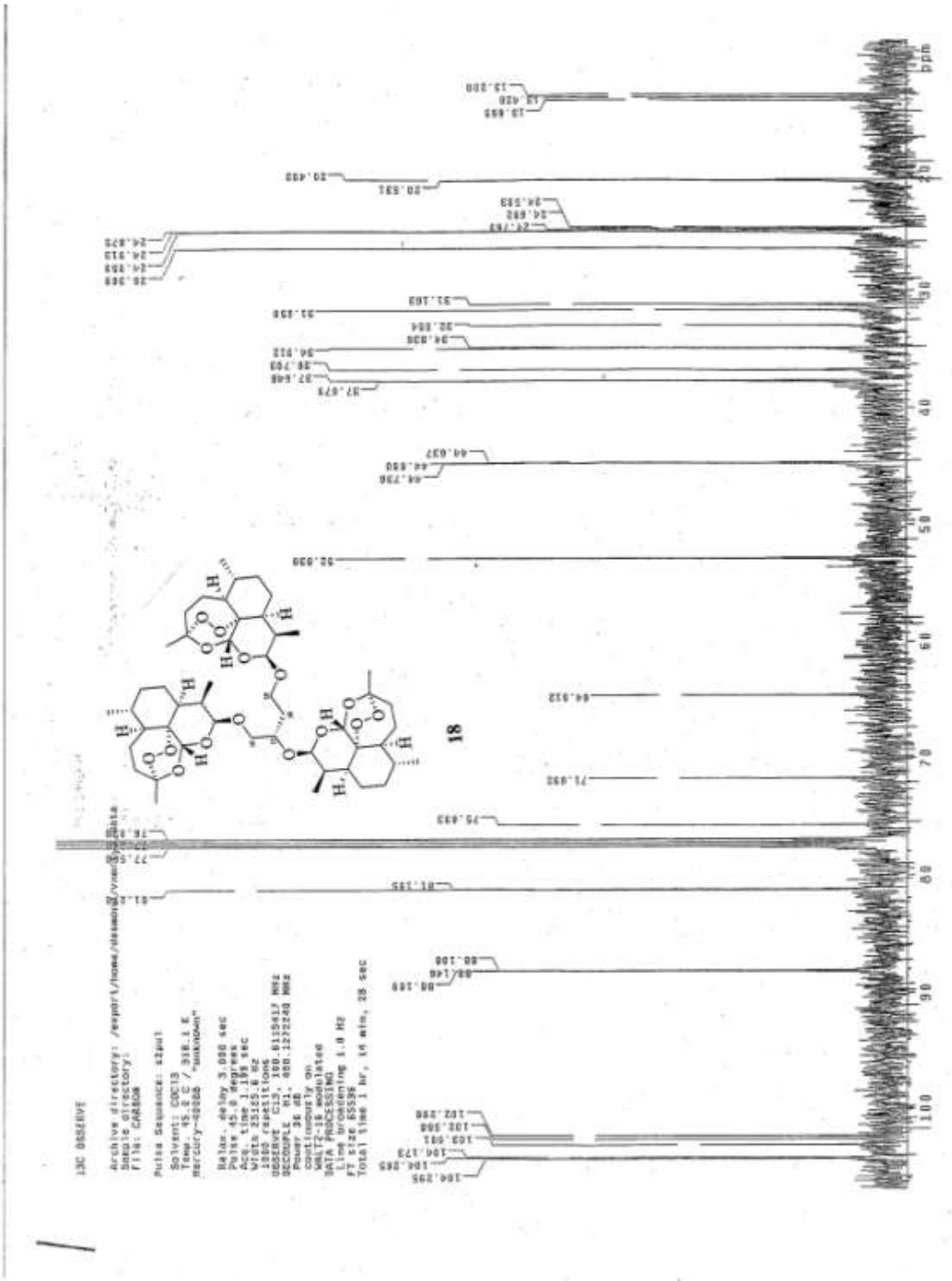
^{1}H NMR spectrum for **17**.



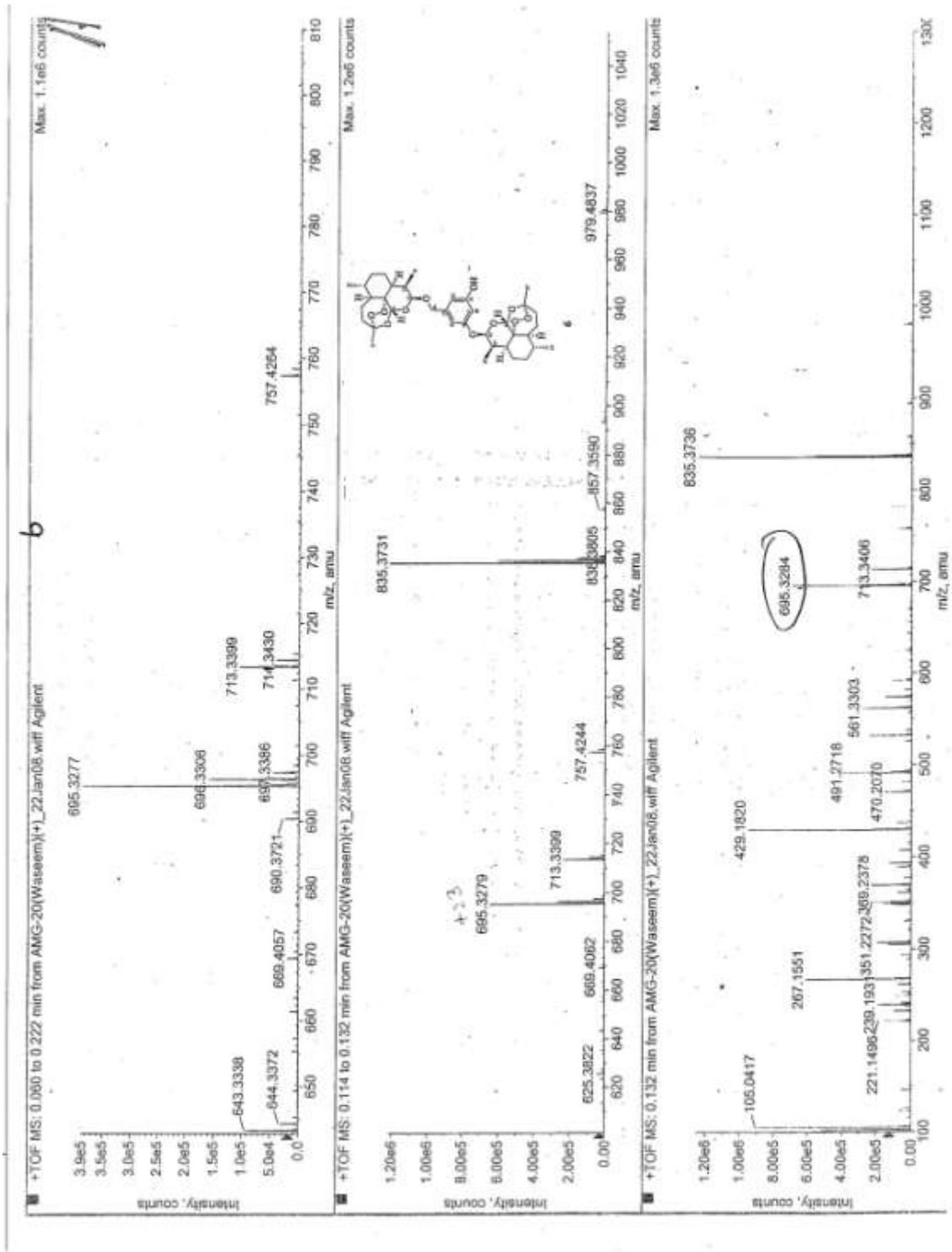
^{13}C NMR spectrum for **17**.



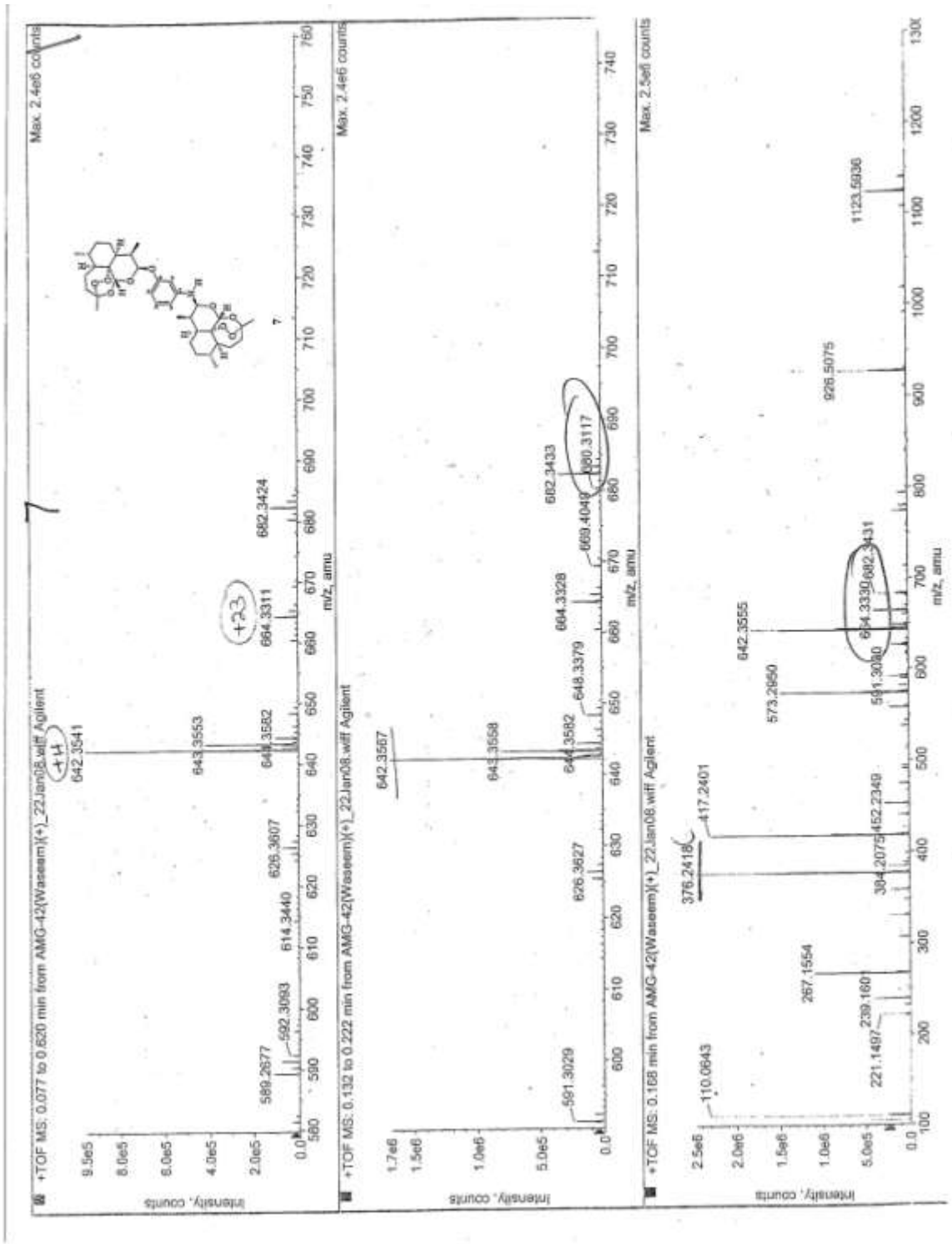
^{1}H NMR spectrum for **18**.



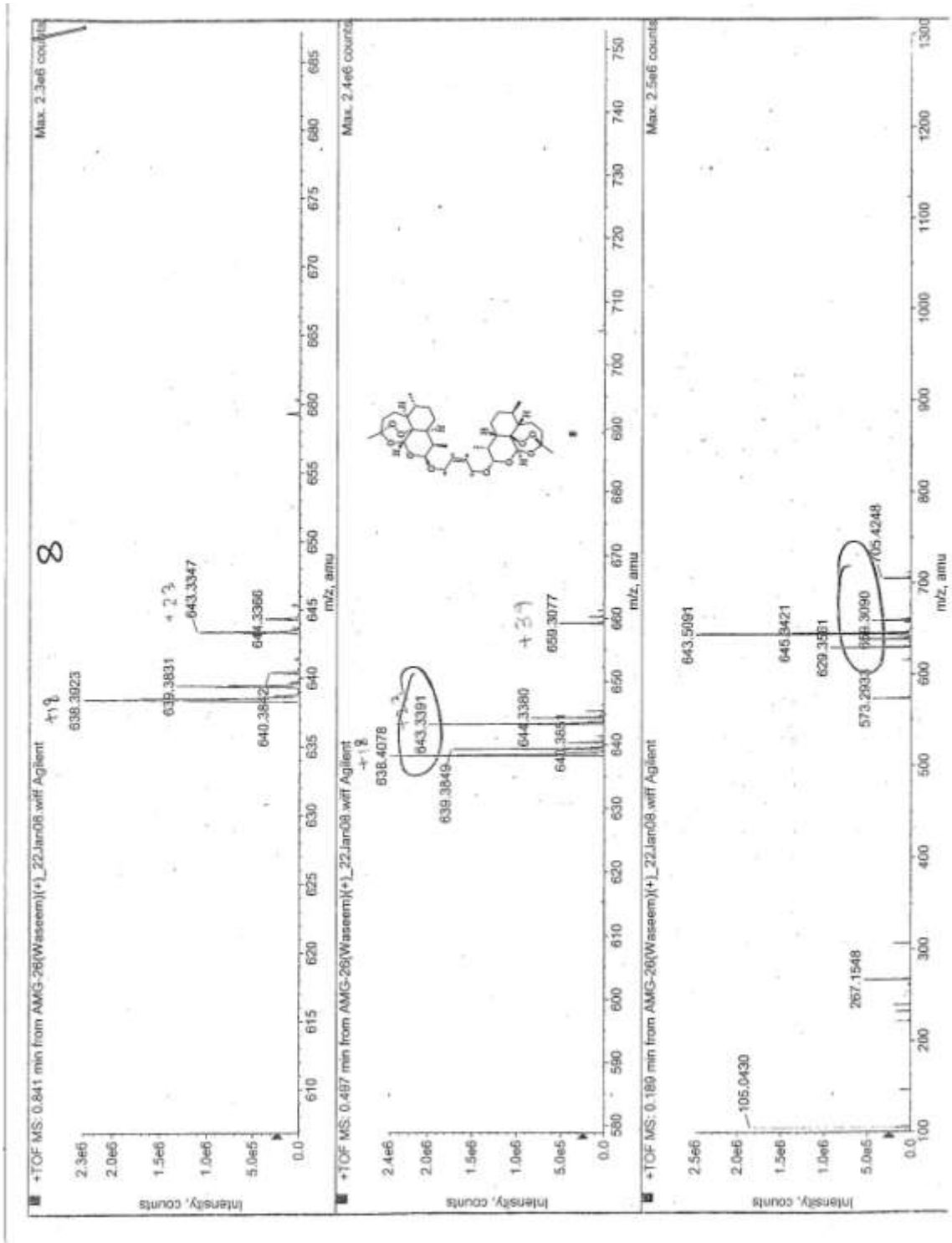
^{13}C NMR spectrum for **18**.



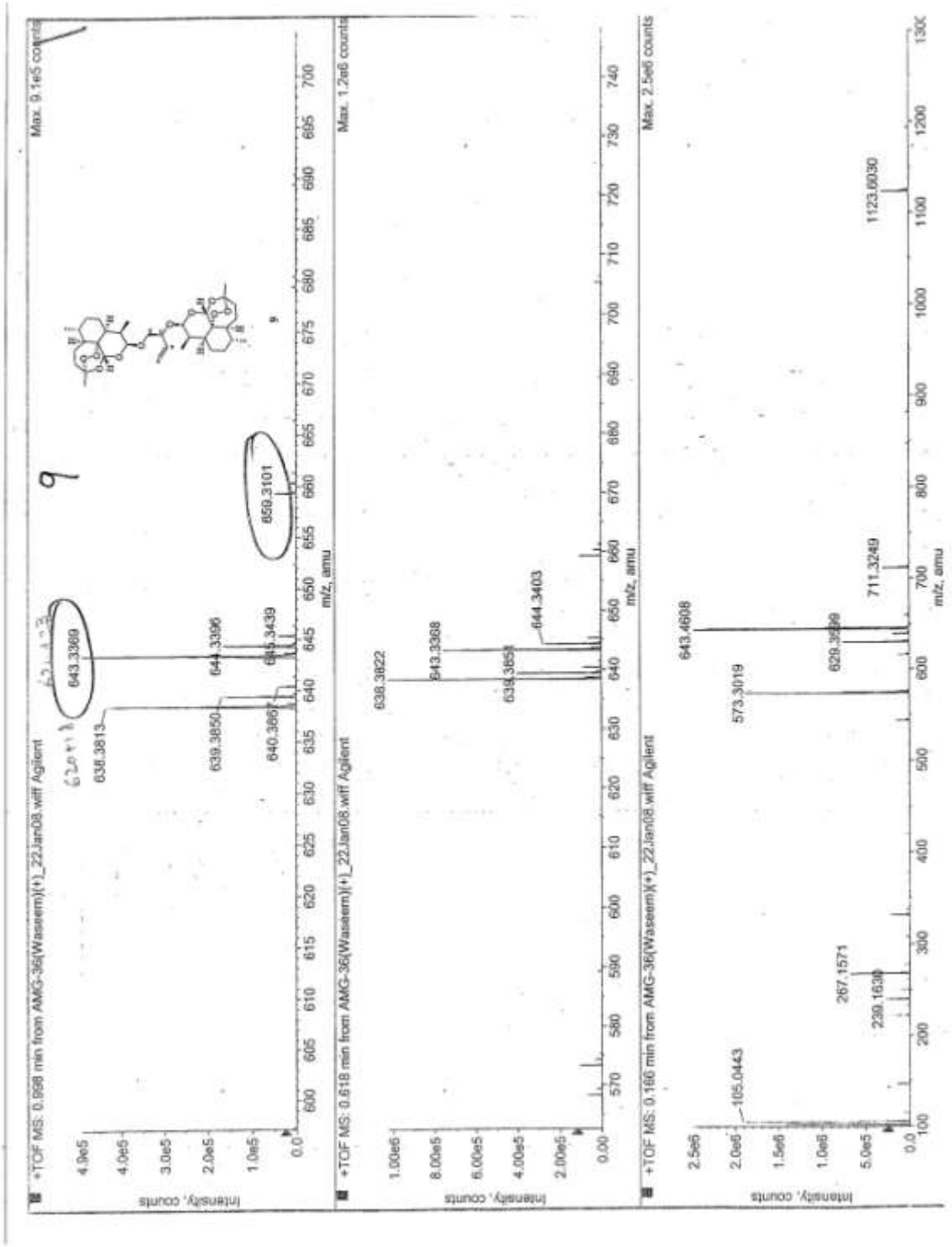
HRMS spectrum for **6**.



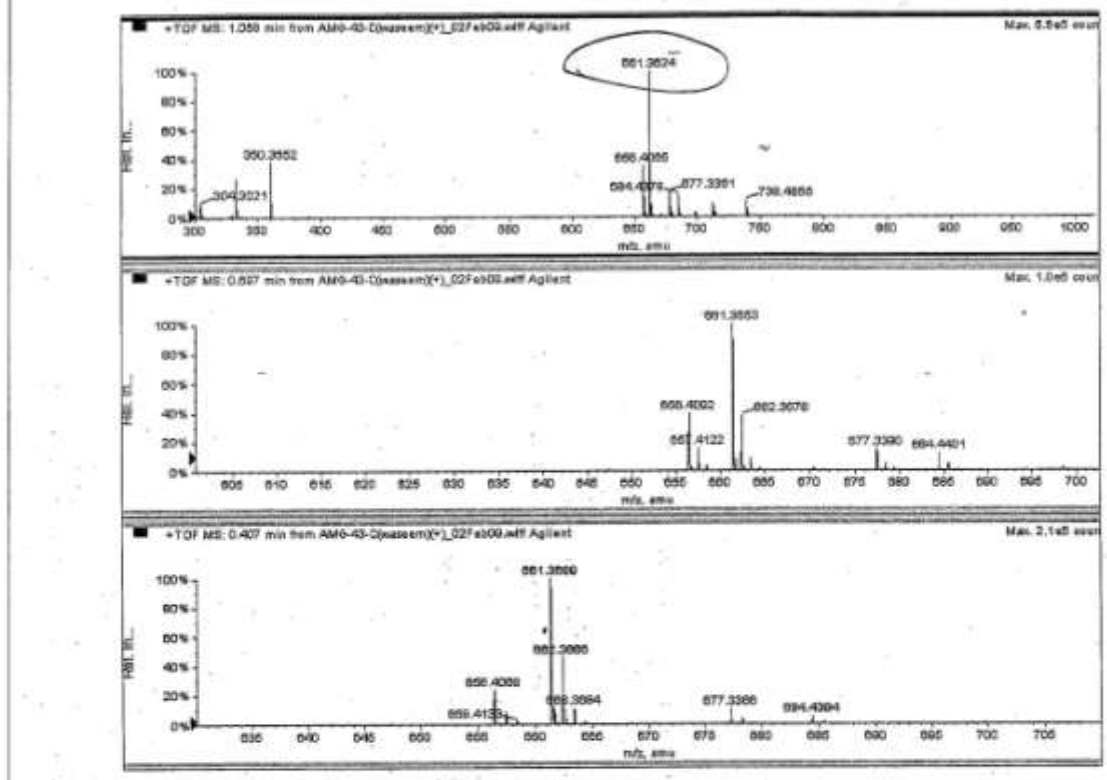
HRMS spectrum for **7**.



HRMS spectrum for **8**.



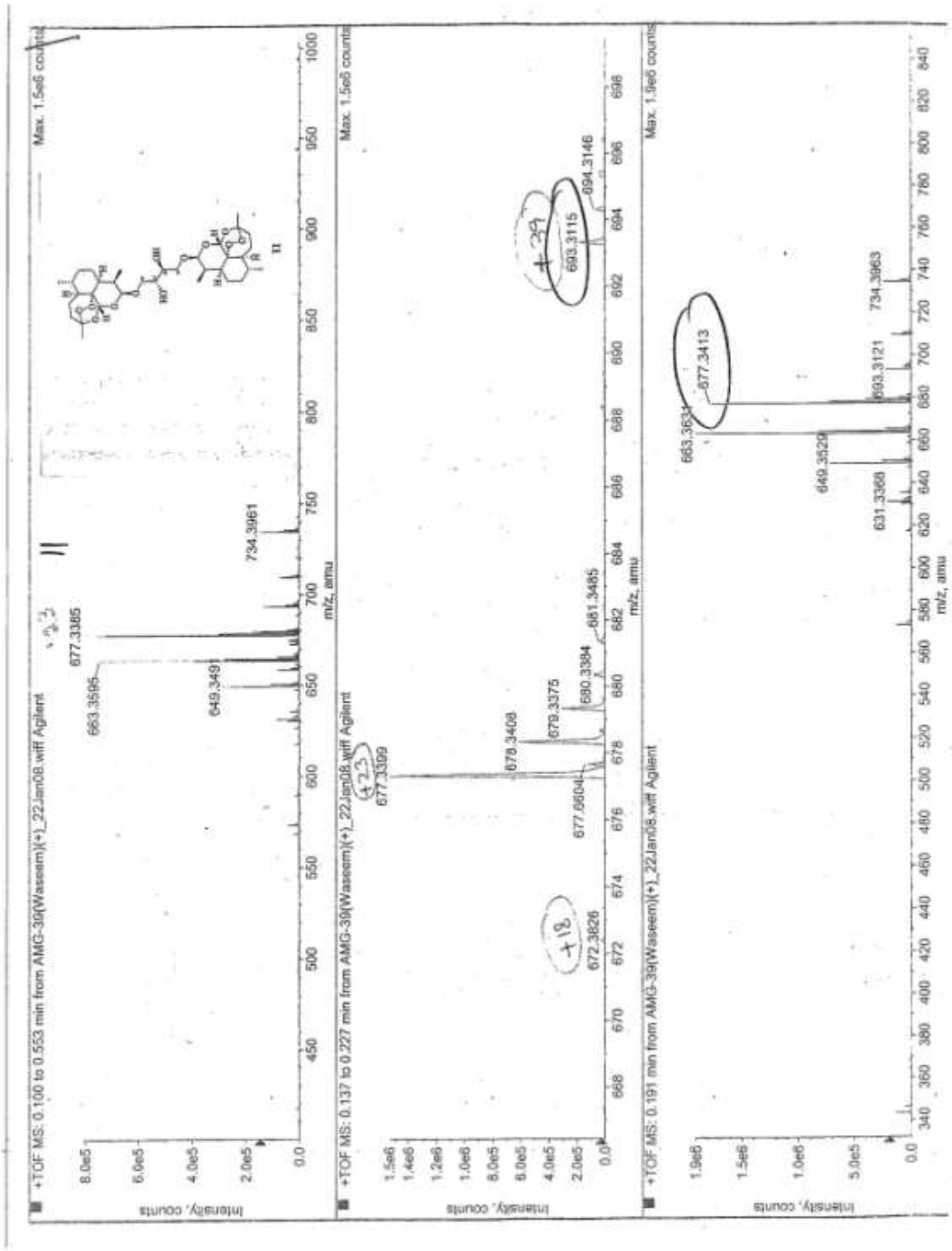
HRMS spectrum for **9**.



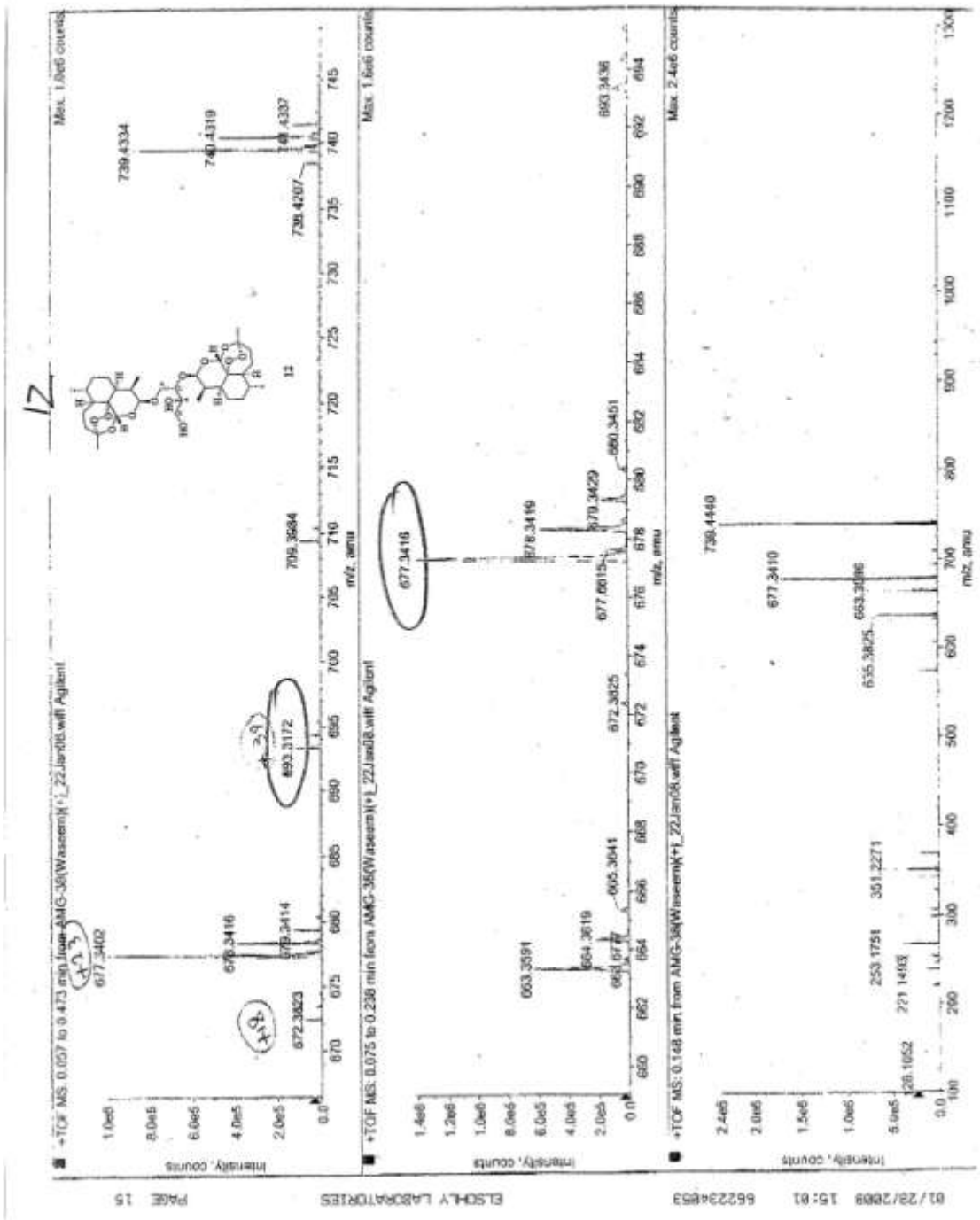
10

6

HRMS spectrum for **10**.

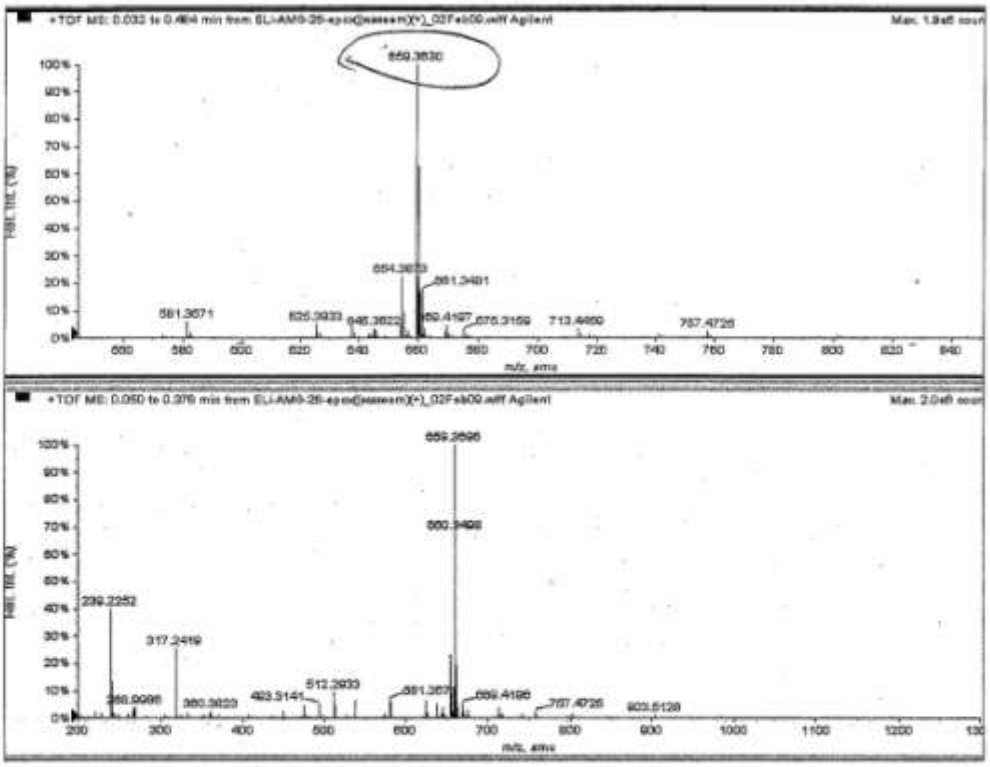


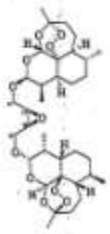
HRMS spectrum for **11**.



HRMS spectrum for **12**.

13

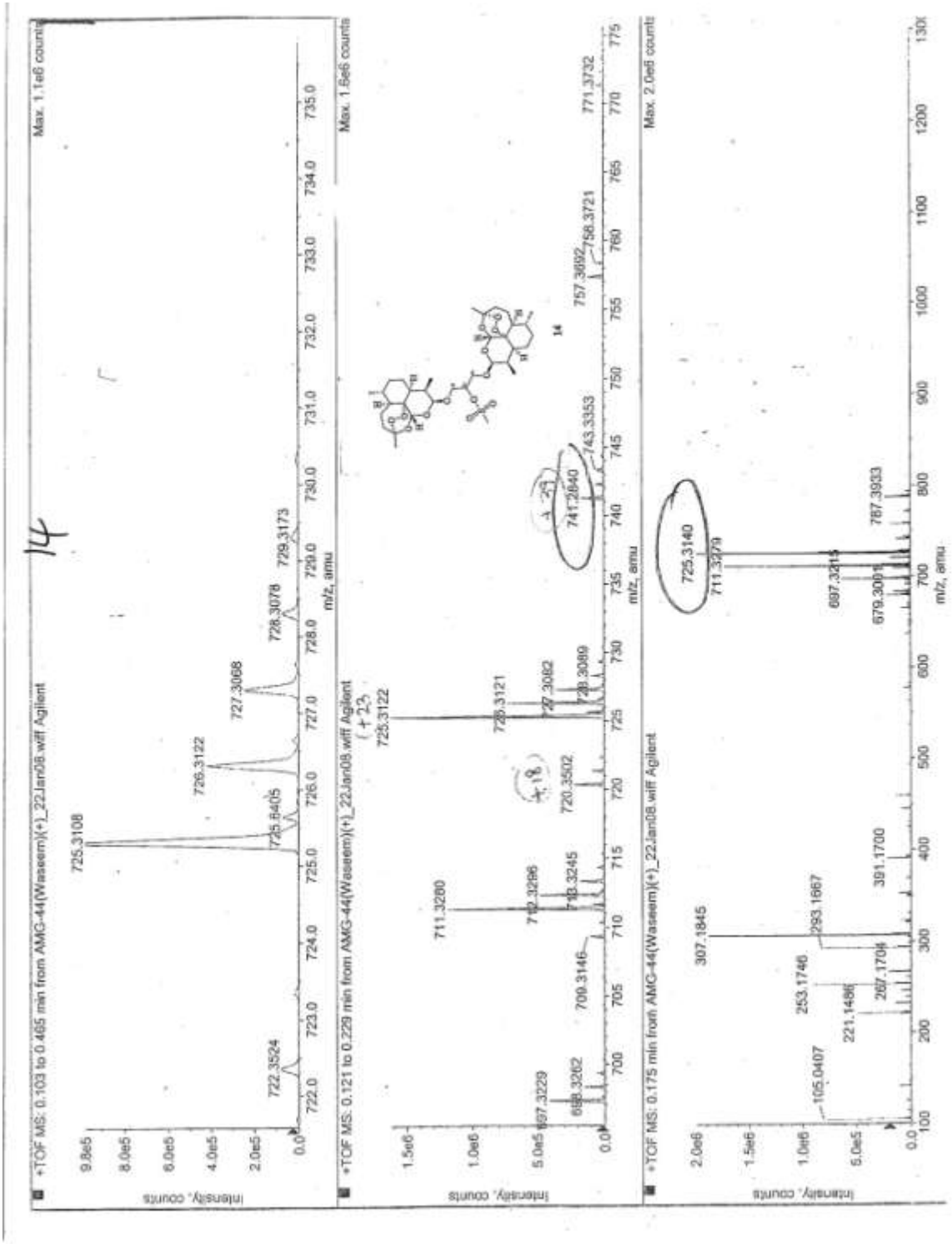




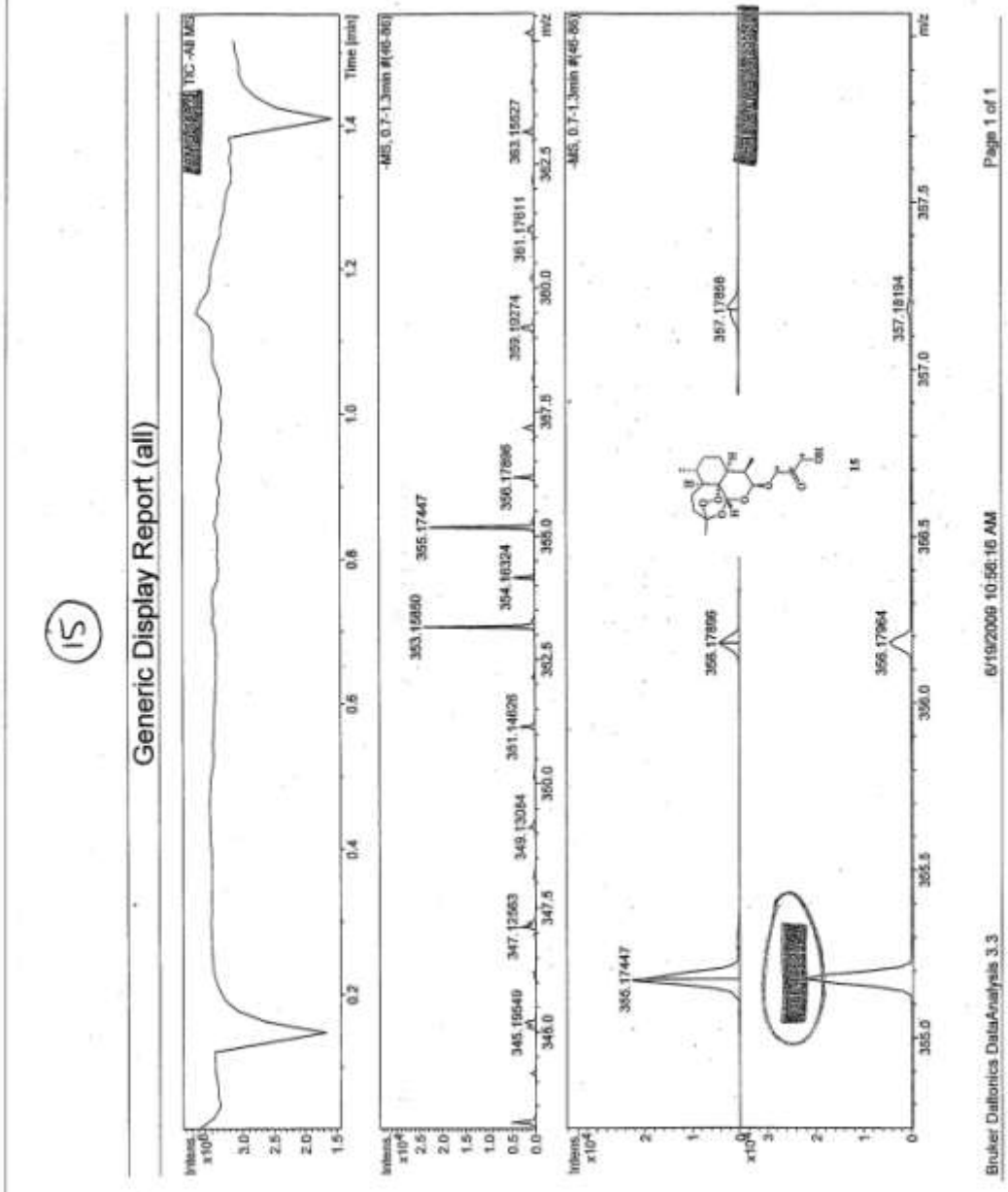
13

3

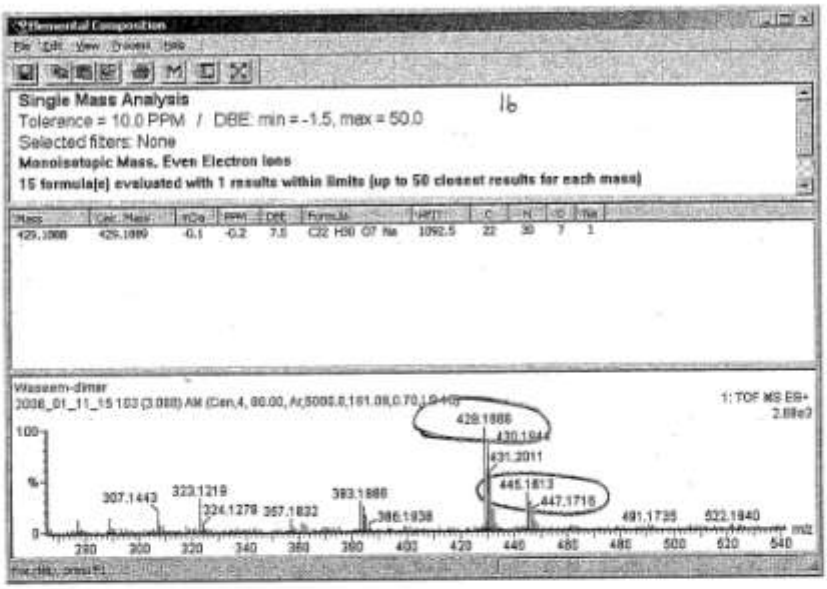
HRMS spectrum for **13**.

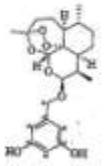


HRMS spectrum for **14**.



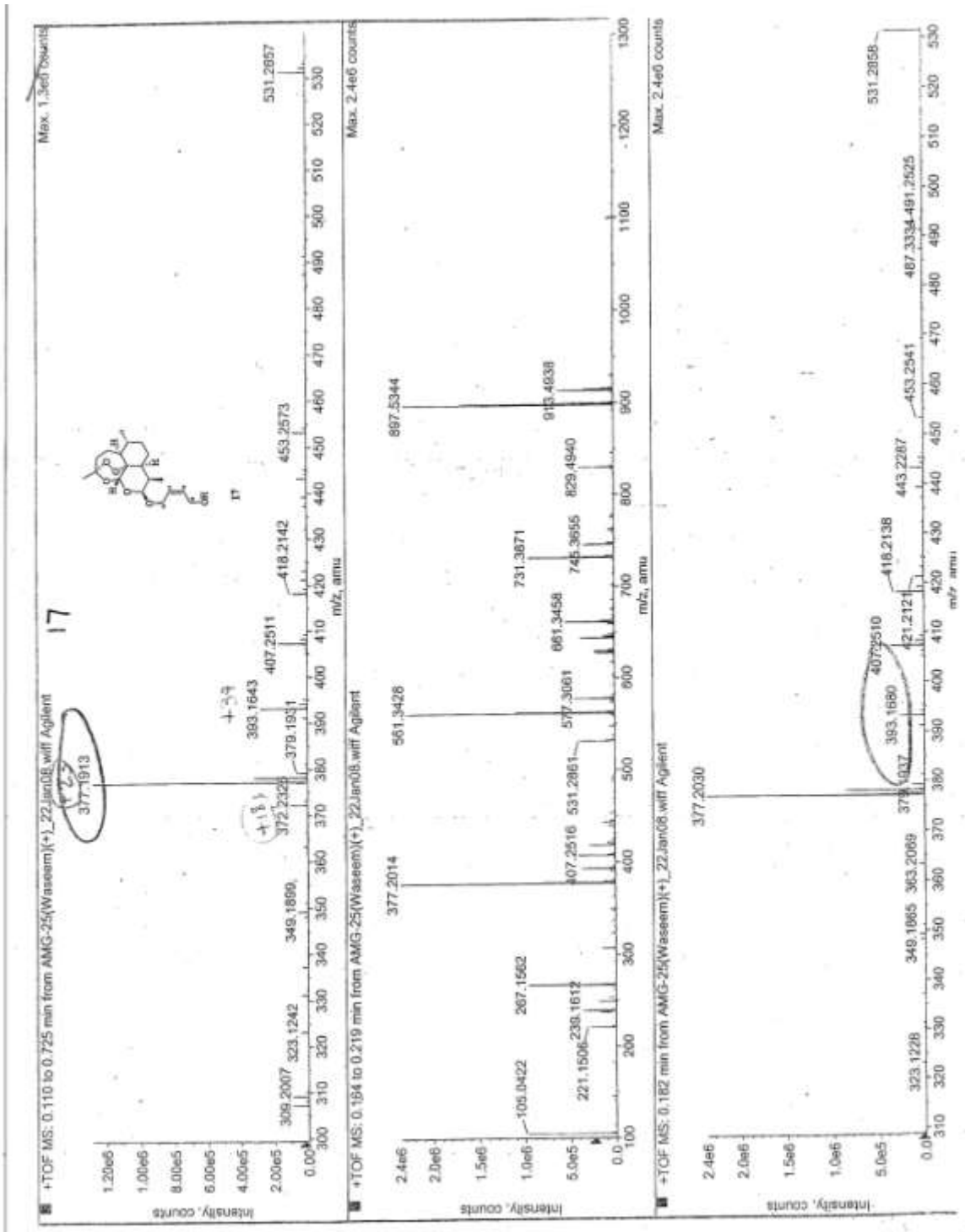
HRMS spectrum for **15**.



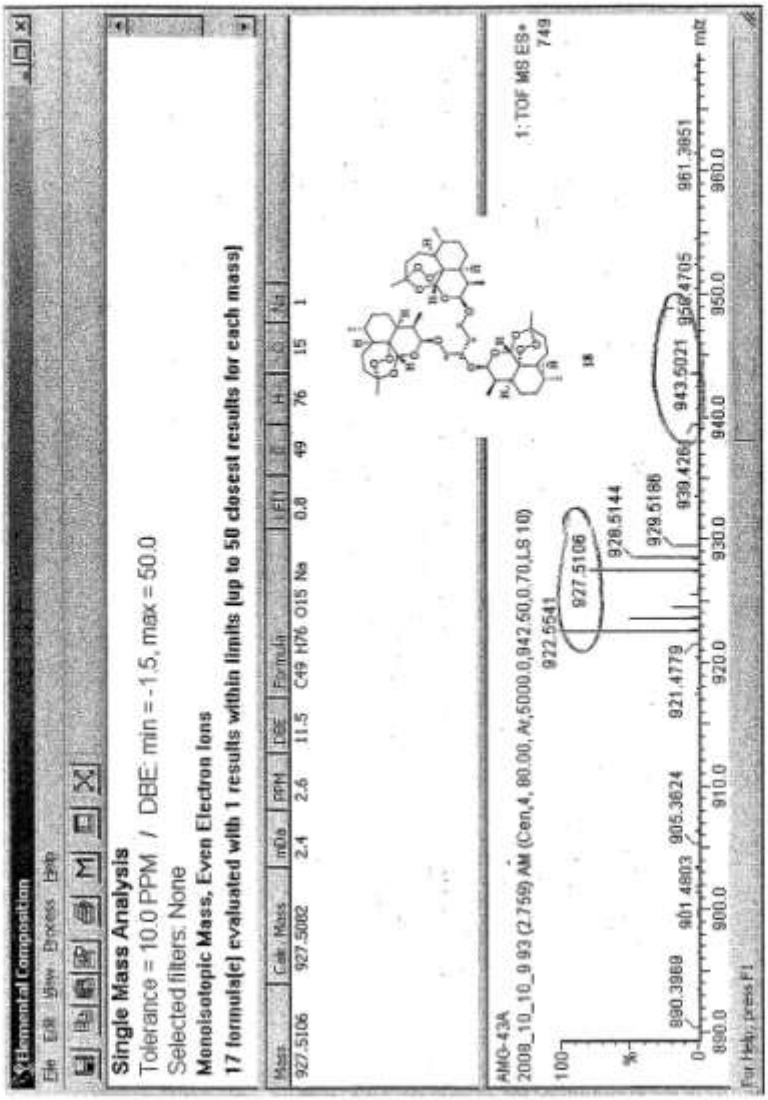


16

HRMS spectrum for **16**.



HRMS spectrum for **17**.



HRMS spectrum for **18**.