

## **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

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

**1. Artemisinin:**

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

**2. Dihydroartemisinin (DHA):**

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

**3. Anhydrodihydroartemisinin:**

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

**4. 1,3-Dihydroxy-2-propanone  $\beta,\beta$ -DHA acetal dimer:**

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

**5. 1,2,3-Propanetriol  $\beta,\beta$ -DHA acetal dimer:**

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

**6. 3,5-Dihydroxybenzyl alcohol  $\beta,\beta$ -DHA acetal dimer:**

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

**7. 3-Aminophenol  $\beta,\beta$ -DHA acetal dimer:**

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

**8. *cis*-2-Butene-1,4-diol  $\beta,\beta$ -DHA acetal dimer:**

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

**9. (*S*)-(-)-1-Butene-3,4-diol  $\beta,\beta$ -DHA acetal dimer:**

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

**10. (*S*)-(-)-1,2,4-Butanetriol  $\beta,\beta$ -DHA acetal dimer:**

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

**11. (2*R*<sup>\*</sup>,3*S*<sup>\*</sup>)-1,2,3,4-Butanetetraol  $\beta,\beta$ -DHA acetal dimer:**

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

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

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

**13. (*R*<sup>\*</sup>,*S*<sup>\*</sup>)-2,3-Epoxy-1,4-butanediol  $\beta,\beta$ -DHA acetal dimer:**

(3*R*,3'*R*,5*aS*,5*a'S*,6*R*,6'*R*,8*aS*,8*a'S*,9*R*,9'*R*,10*S*,10'*S*,12*R*,12'*R*,12*aR*,12*a'R*)-10,10'-[(*R*<sup>\*</sup>,*S*<sup>\*</sup>)-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*,5*aS*,5*a'S*,6*R*,6'*R*,8*aS*,8*a'S*,9*R*,9'*R*,10*S*,10'*S*,12*R*,12'*R*,12*aR*,12*a'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*,5*aS*,6*R*,8*aS*,9*R*,10*S*,12*R*,12*aR*)-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:**

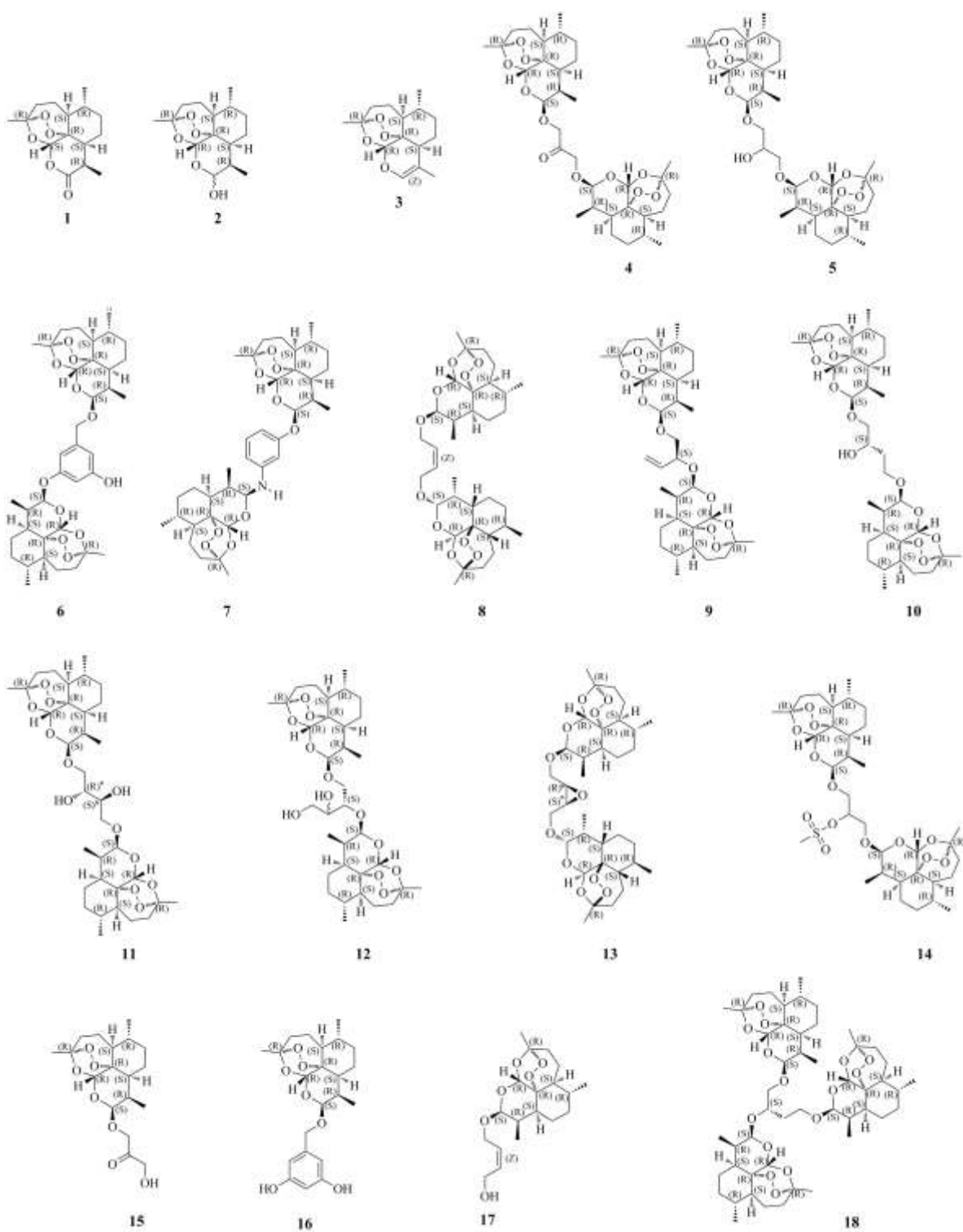
(3*R*,5*aS*,6*R*,8*aS*,9*R*,10*S*,12*R*,12*aR*)-10-(3,5-dihydroxybenzyloxy)-decahydro-3,6,9-trimethyl-3,12-epoxy-12H-pyrano[4,3-*j*]-1,2-benzodioxepin

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

(3*R*,5*aS*,6*R*,8*aS*,9*R*,10*S*,12*R*,12*aR*)-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*,5*aS*,5*a'S*,5*a''S*,6*R*,6'*R*,6''*R*,8*aS*,8*a'S*,8*a''S*,9*R*,9'*R*,9''*R*,10*S*,10'*S*,10''*S*,12*R*,12'*R*,12''*R*,12*aR*,12*a'R*,12*a''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]



Antifungal activity of **1–18**

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

IC<sub>50</sub>: concentration causing 50% growth inhibition. NA: not active. NT: not tested.

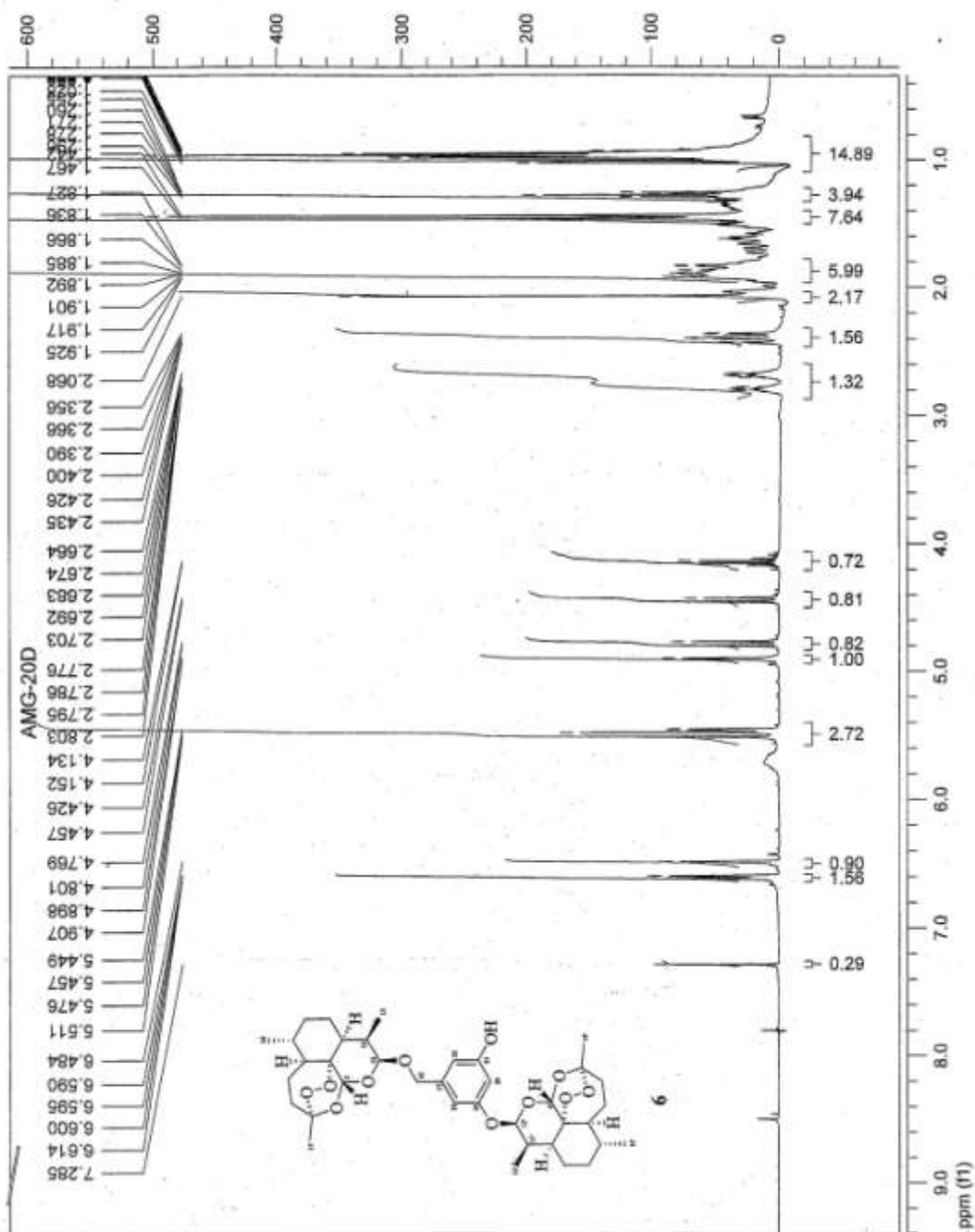
<sup>a</sup> Control.

Antibacterial activity of **1–18**

Compound	<i>S. aureus</i>	MRSa	<i>E. coli</i>	<i>P. aeruginosa</i>	<i>M. intracellulare</i>
	IC <sub>50</sub> (μM)				
<b>1</b>	NT	NA	NT	NT	NA
<b>2</b>	NT	NA	NT	NT	NA
<b>3</b>	NT	NA	NT	NT	56.32
<b>4</b>	NT	NA	NT	NT	NA
<b>5</b>	NT	NA	NT	NT	NA
<b>6</b>	NT	NA	22.29	NA	NA
<b>7</b>	NT	NA	8.57	NA	NA
<b>8</b>	NT	NA	NA	NA	NA
<b>9</b>	NT	NA	NA	NA	NA
<b>10</b>	16.52	> 31.31	13.60	NA	> 31.31
<b>11</b>	NT	NA	15.27	NA	NA
<b>12</b>	NT	22.91	7.64	NA	15.27
<b>13</b>	NA	NA	NA	> 31.41	NA
<b>14</b>	NT	NA	NA	NA	NA
<b>15</b>	NA	NA	NA	NA	NA
<b>16</b>	NA	NA	48.59	NA	> 49.20
<b>17</b>	NT	NA	NA	NA	NA
<b>18</b>	NA	NA	NA	NA	> 22.10
<b>ciprofloxacin<sup>a</sup></b>	<b>0.36</b>	<b>0.36</b>	<b>0.01</b>	<b>0.22</b>	<b>1.27</b>

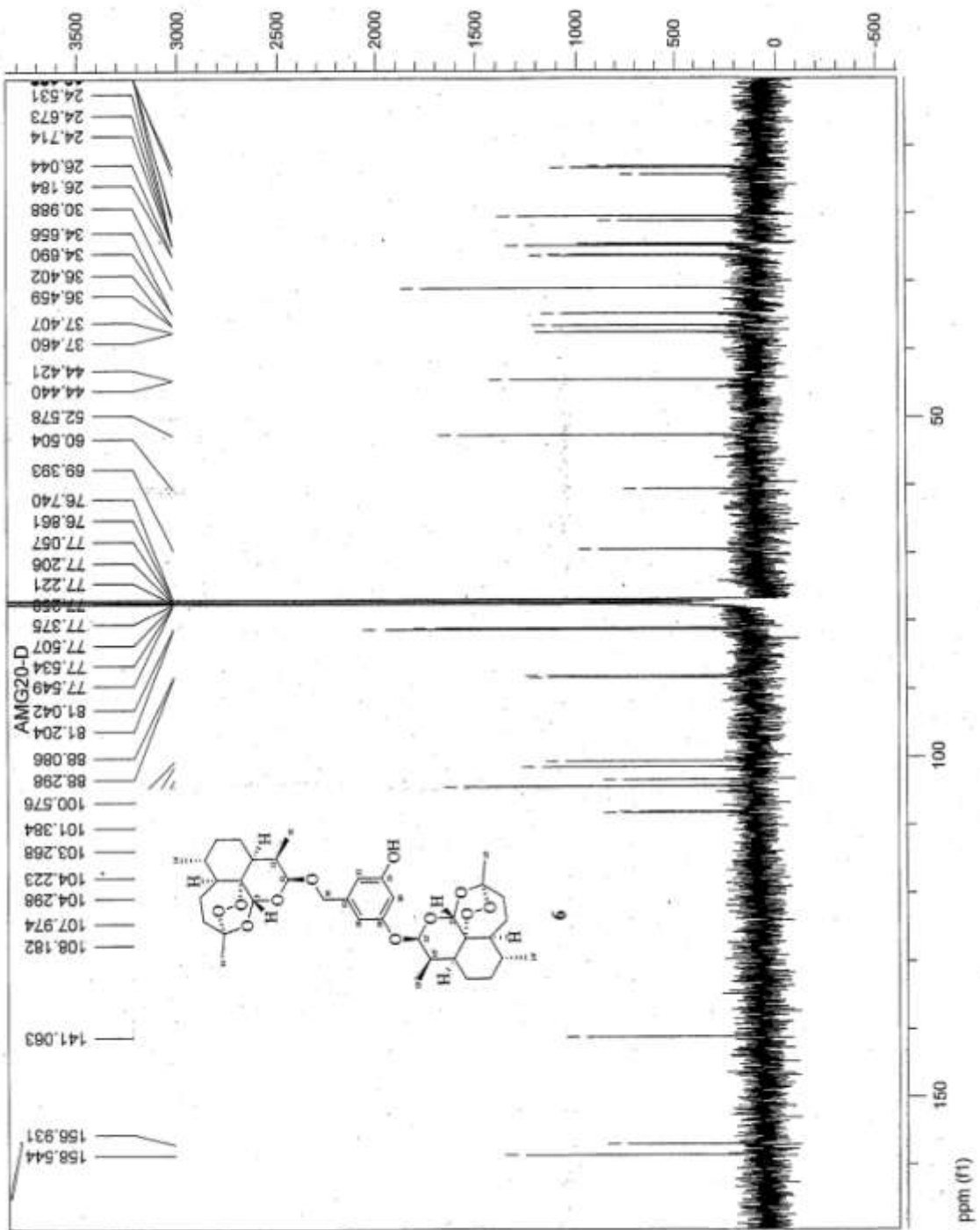
IC<sub>50</sub>: concentration causing 50% growth inhibition. NA: not active. NT: not tested.

<sup>a</sup> Control.



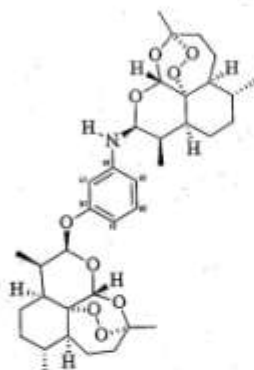
$^1\text{H}$  NMR spectrum for 6.



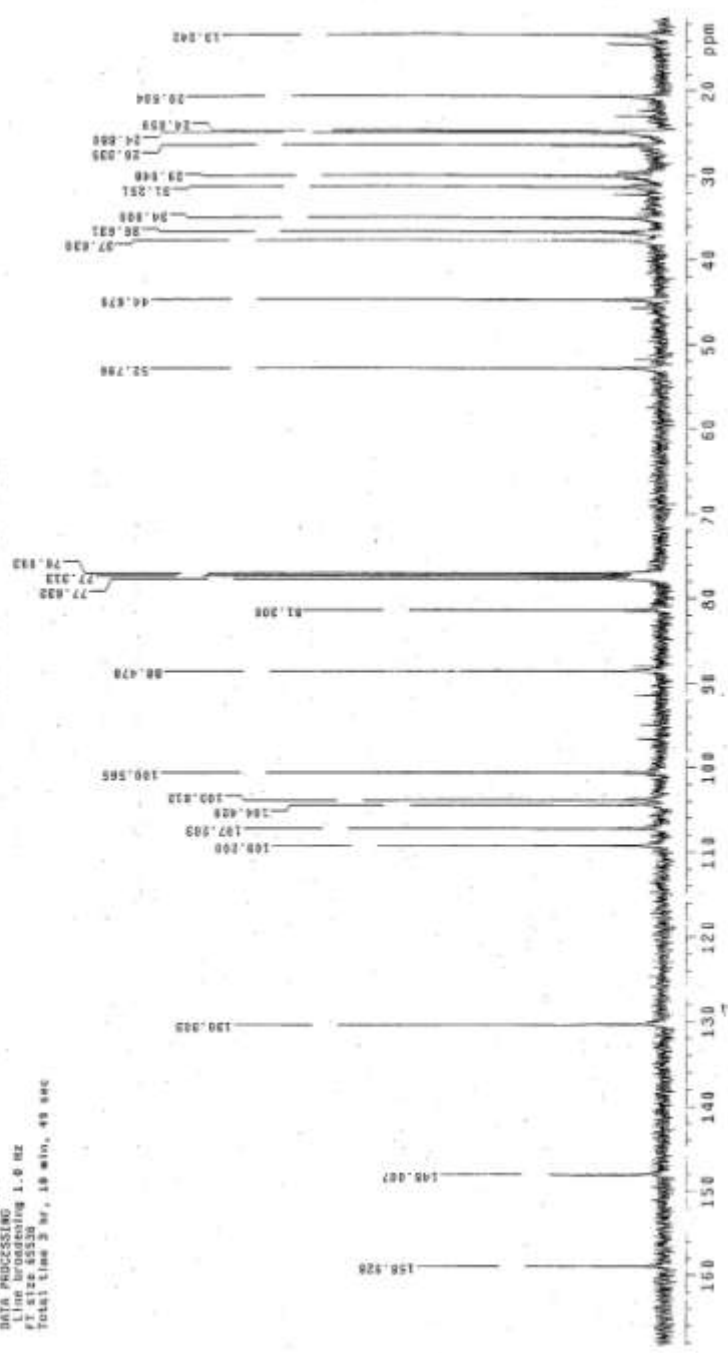


$^{13}\text{C}$  NMR spectrum for **6**.

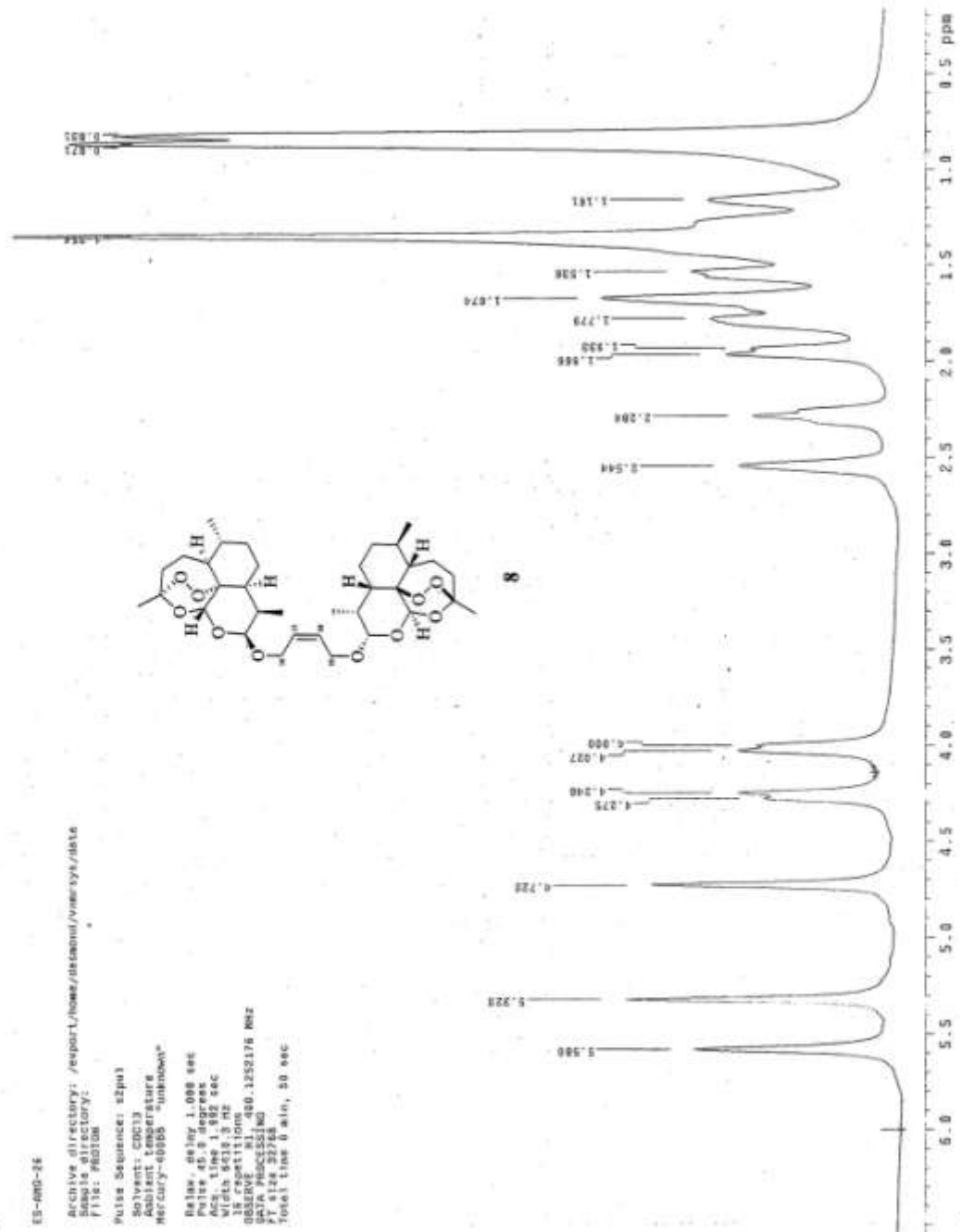




ES-486-42  
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 Sample category:  
 File: CH2020  
 Pulse Sequence: zgpg30  
 Solvent: CDCl3  
 Ambient Temperature  
 NUC1: 13C-10135 "irradiate"  
 Relax delay: 1.000 sec  
 Acq. delay: 0.000 sec  
 Acq. time: 1.151 sec  
 Width: 25125.2 Hz  
 01000 repetitions  
 01000 scans  
 DDCGPRG: 01. 100.1272240 MHz  
 Power: 38 dB  
 Continuously on  
 B1: 100.625145 MHz  
 B12: 100.625145 MHz  
 Linear: 0.000000  
 FT size: 55536  
 Total time: 3 hr, 10 min, 45 sec

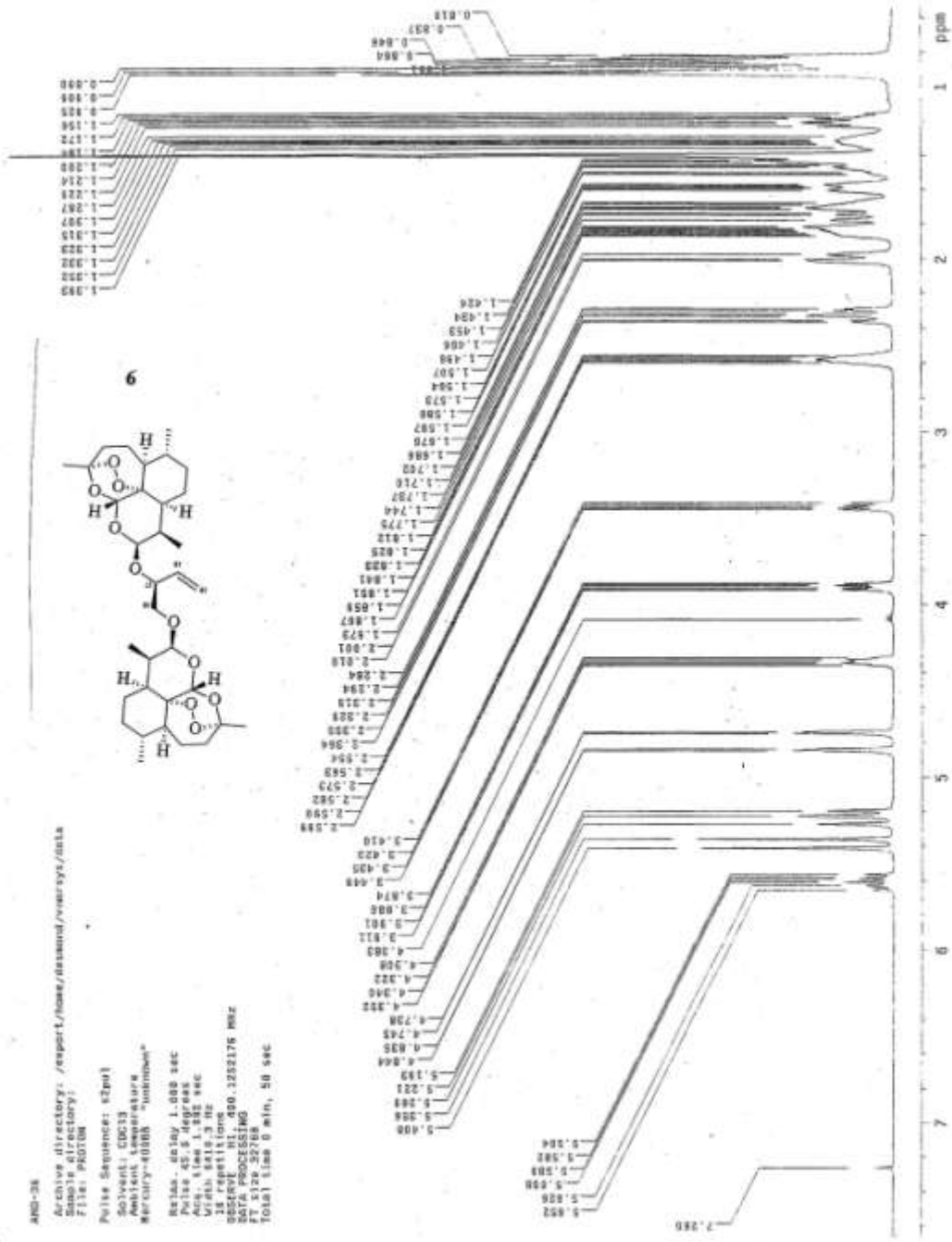


<sup>13</sup>C NMR spectrum for 7.



<sup>1</sup>H NMR spectrum for **8**.



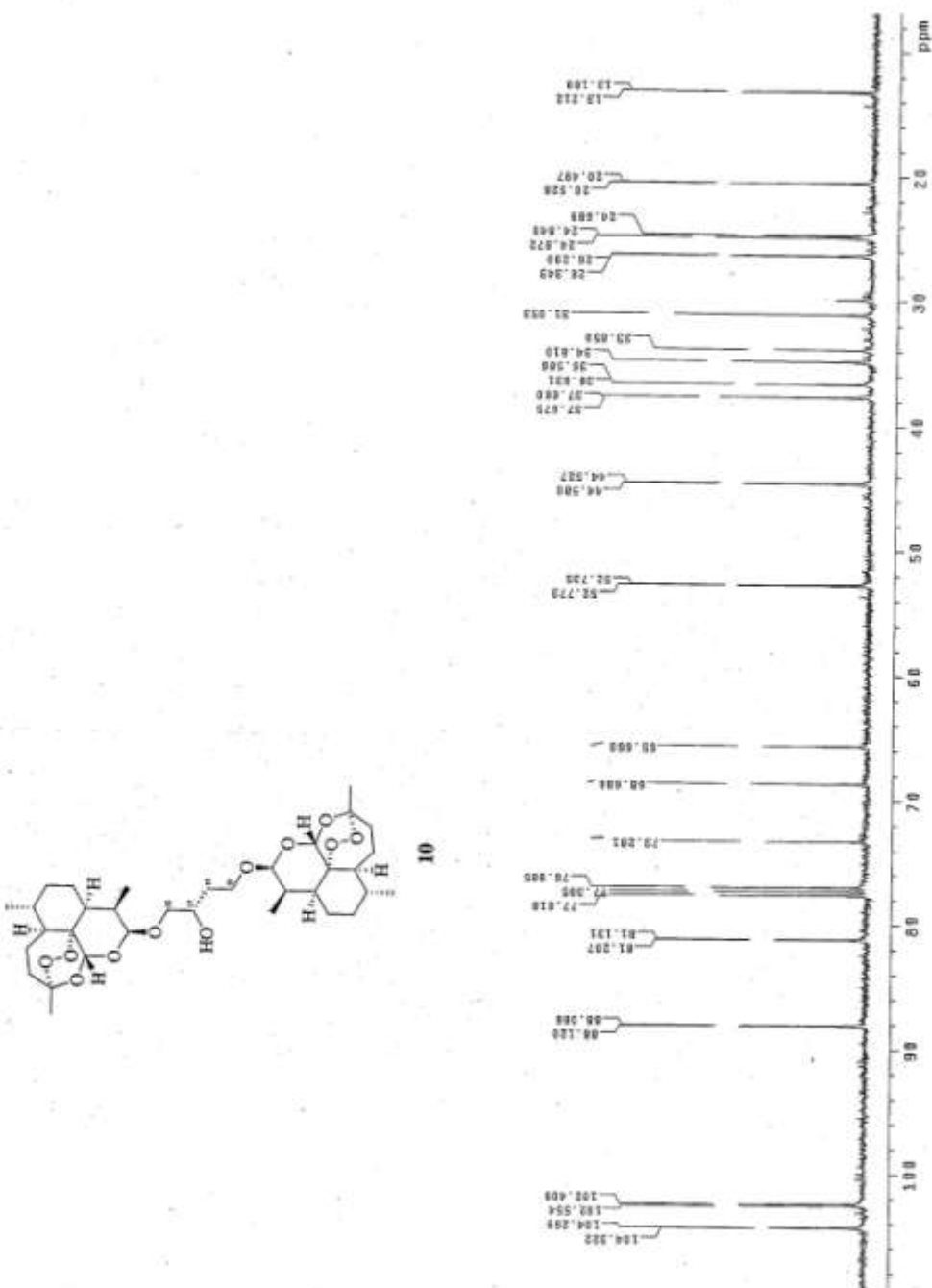


<sup>1</sup>H NMR spectrum for 9.



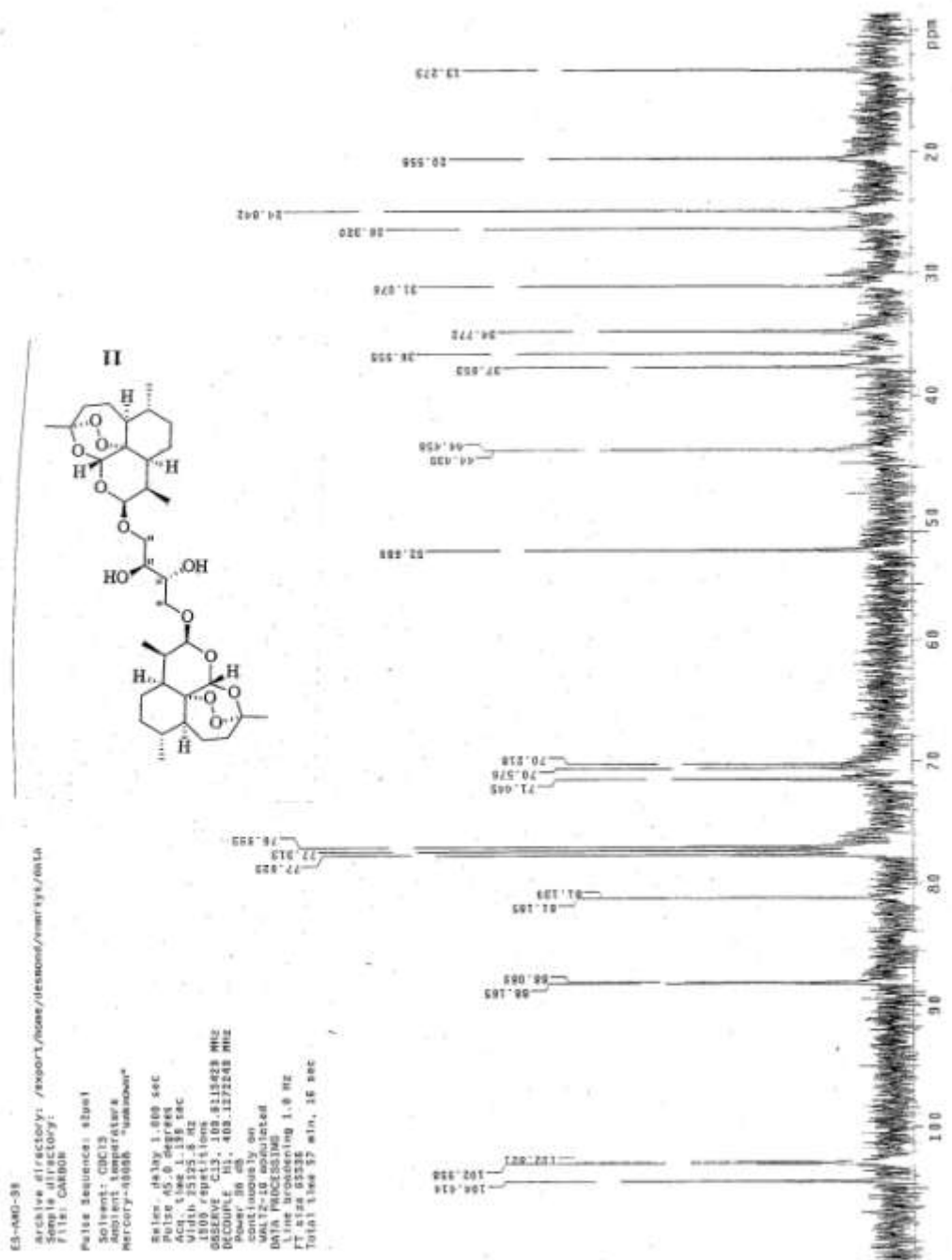




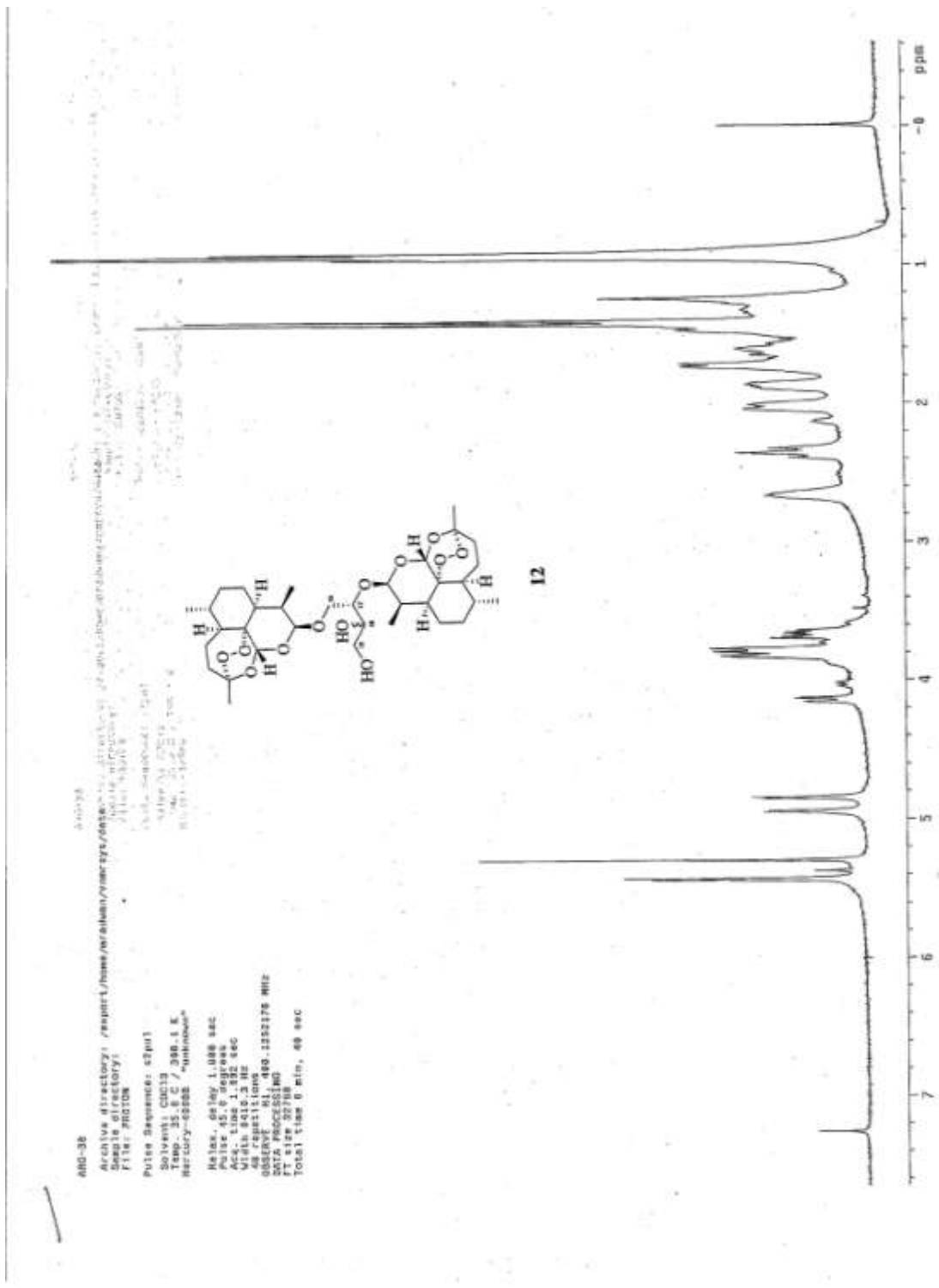


<sup>13</sup>C NMR spectrum for **10**.

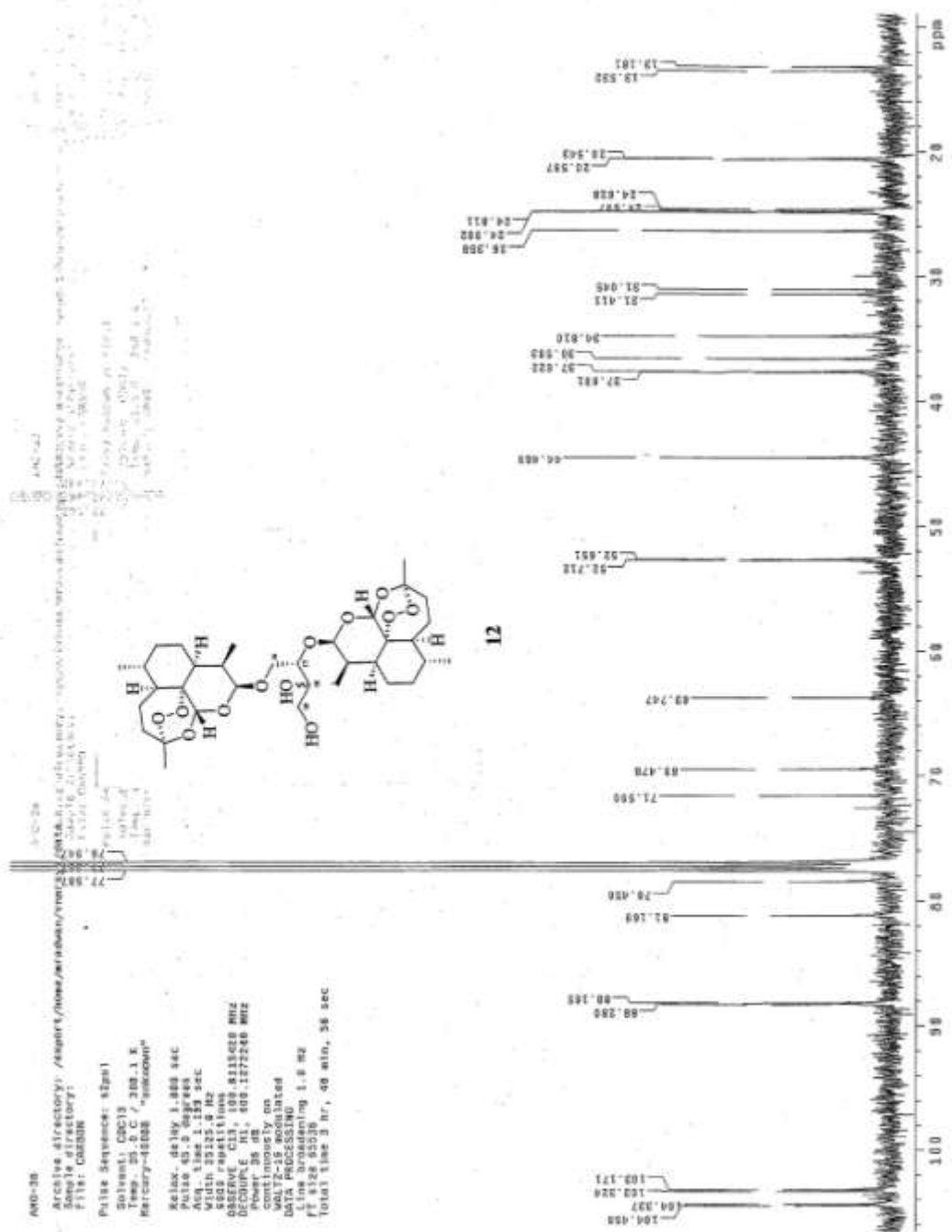




<sup>13</sup>C NMR spectrum for 11.



<sup>1</sup>H NMR spectrum for **12**.



<sup>13</sup>C NMR spectrum for **12**.



4110-25-Epoxy

MNO-De-Loxy

Archive directory: /export/fools/williams/williams/

Sample directory:

File: CARBON

Pulse Sequence: zgpg30

Solvent: CDCl3

Temperature: 300.2 K

Nucleus: 13C

Relaxation delay: 3.000 sec

Pulse delay: 0.000 sec

Acquisition time: 1.000 sec

Number of scans: 800

Observed frequency: 101.625 MHz

Reference: TMS

Processing: F2, 400.132548 MHz

Continuously on

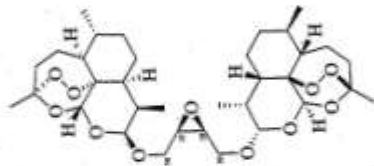
MULTI-SCAN

DATA PROCESSING

Line broadening: 1.0 Hz

Phase shift: 0.000

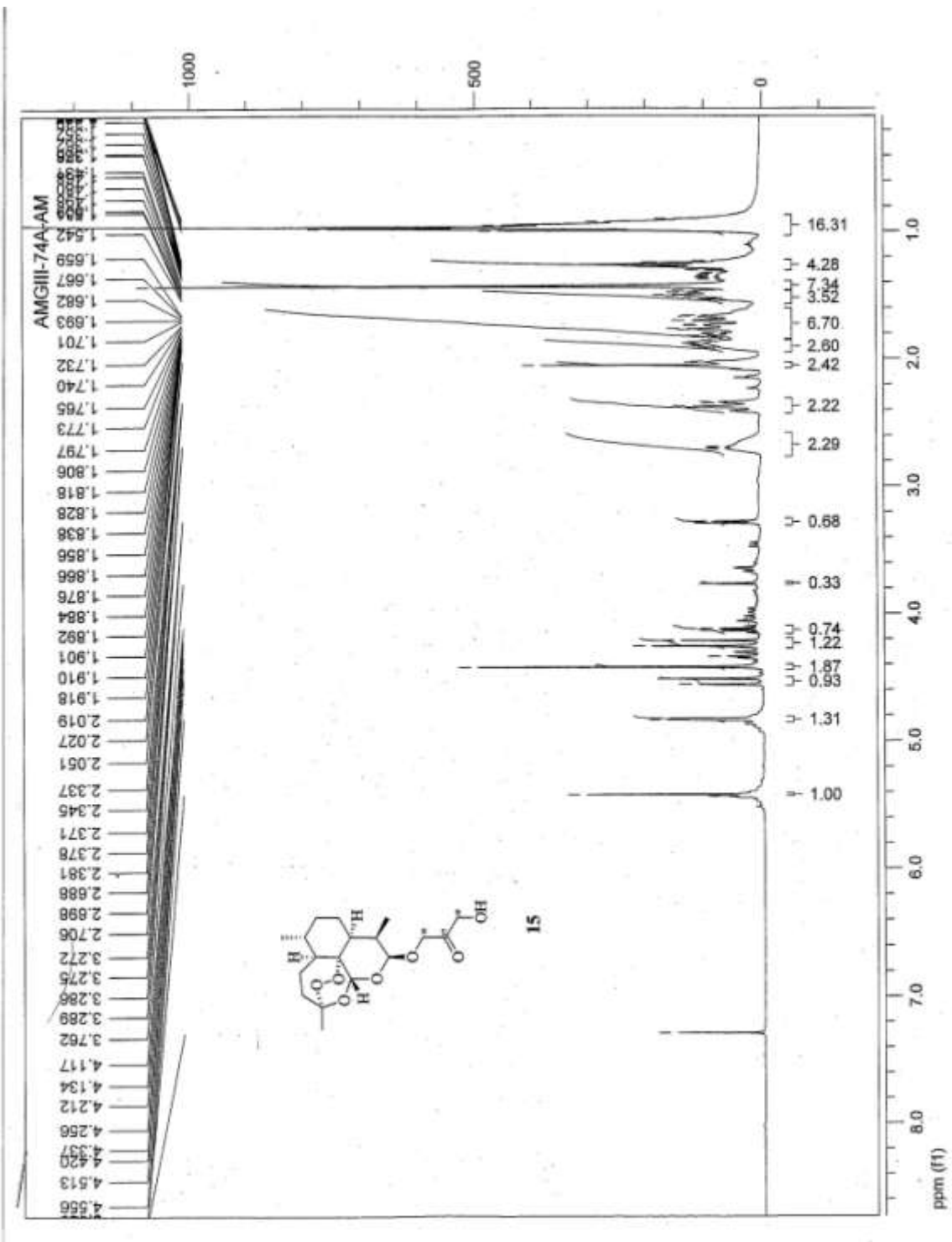
Total time: 3.00 hr, 48 min, 56 sec



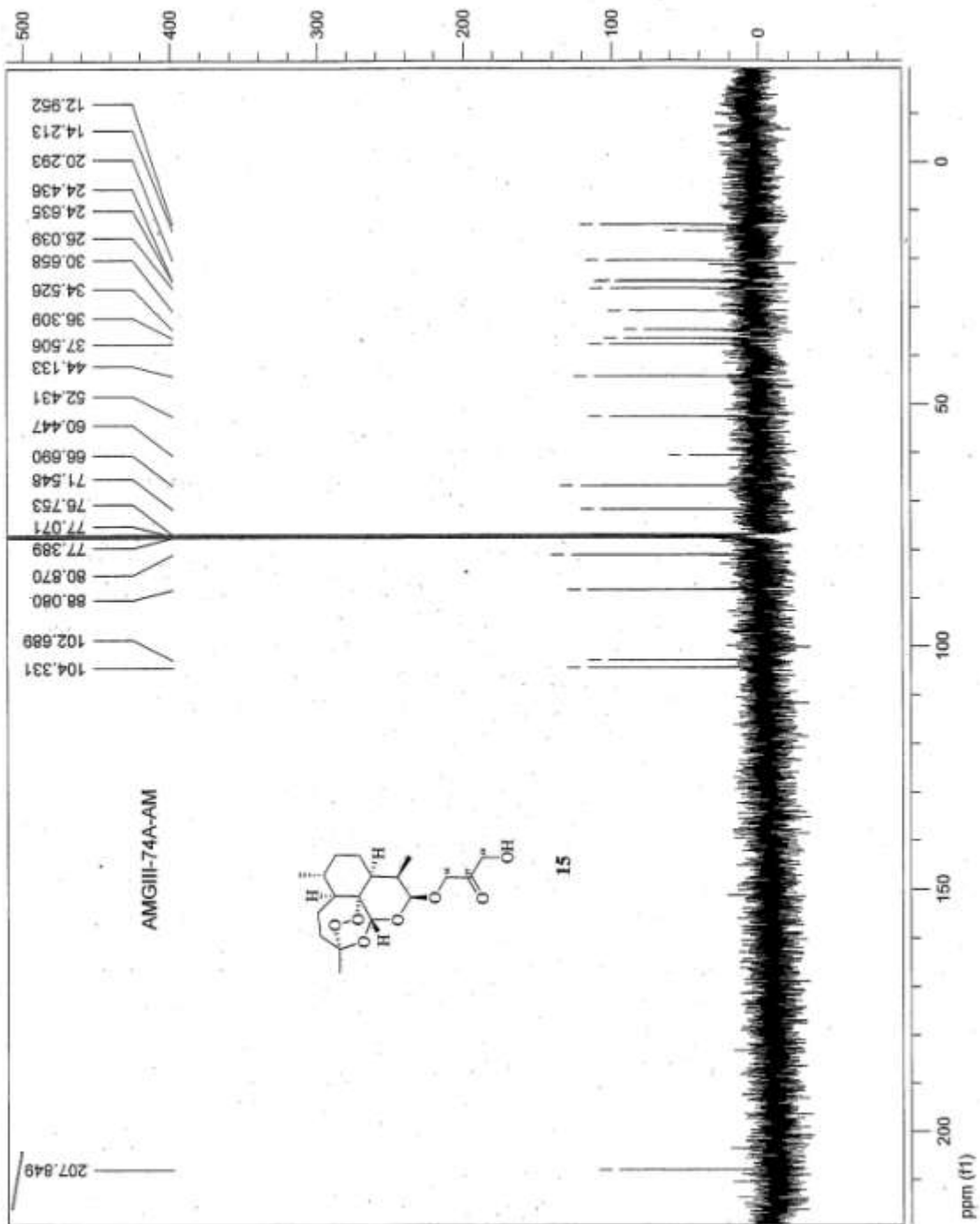






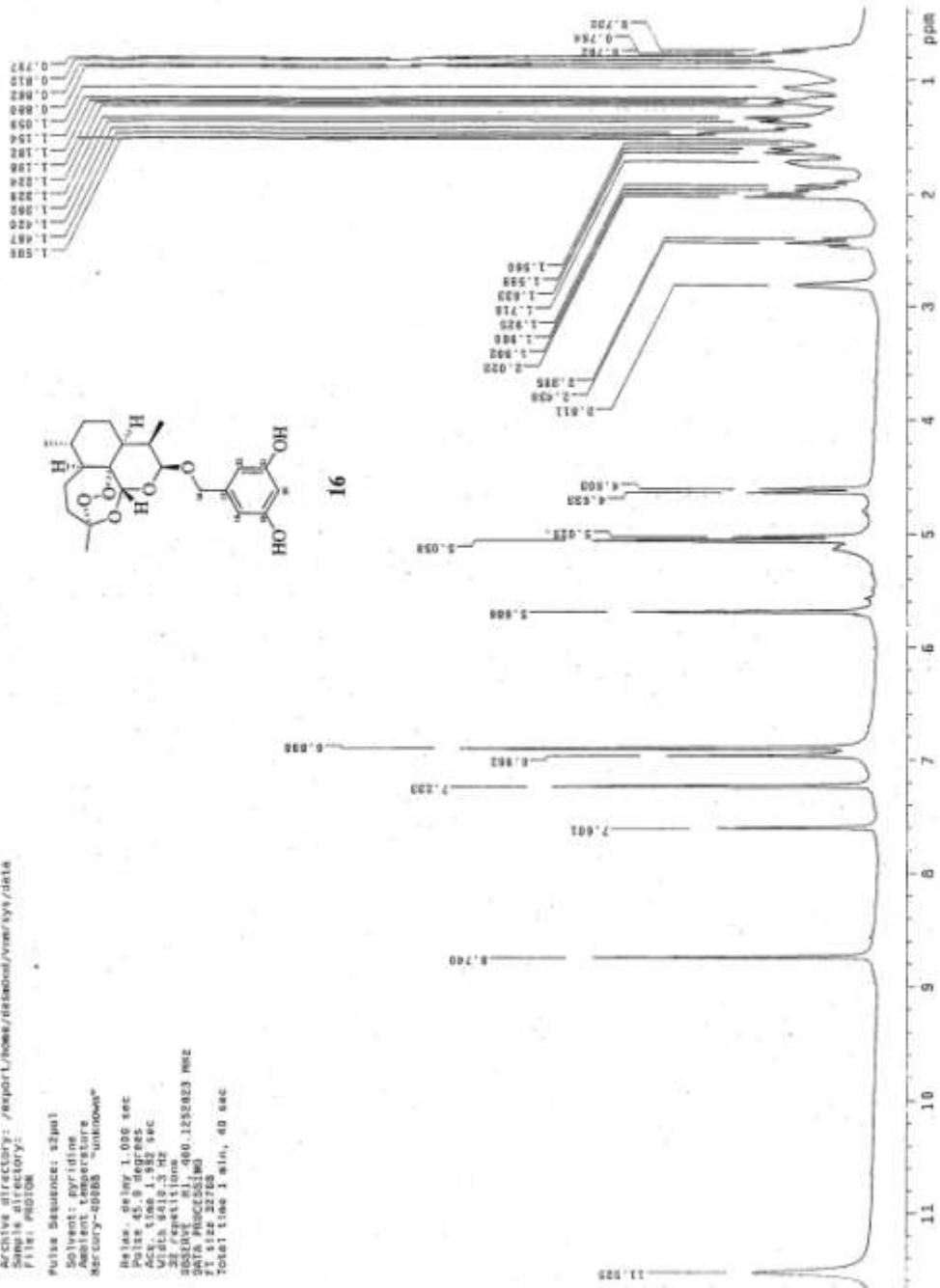
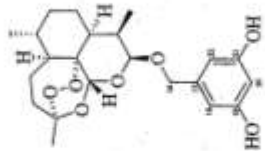


$^1\text{H}$  NMR spectrum for **15**.



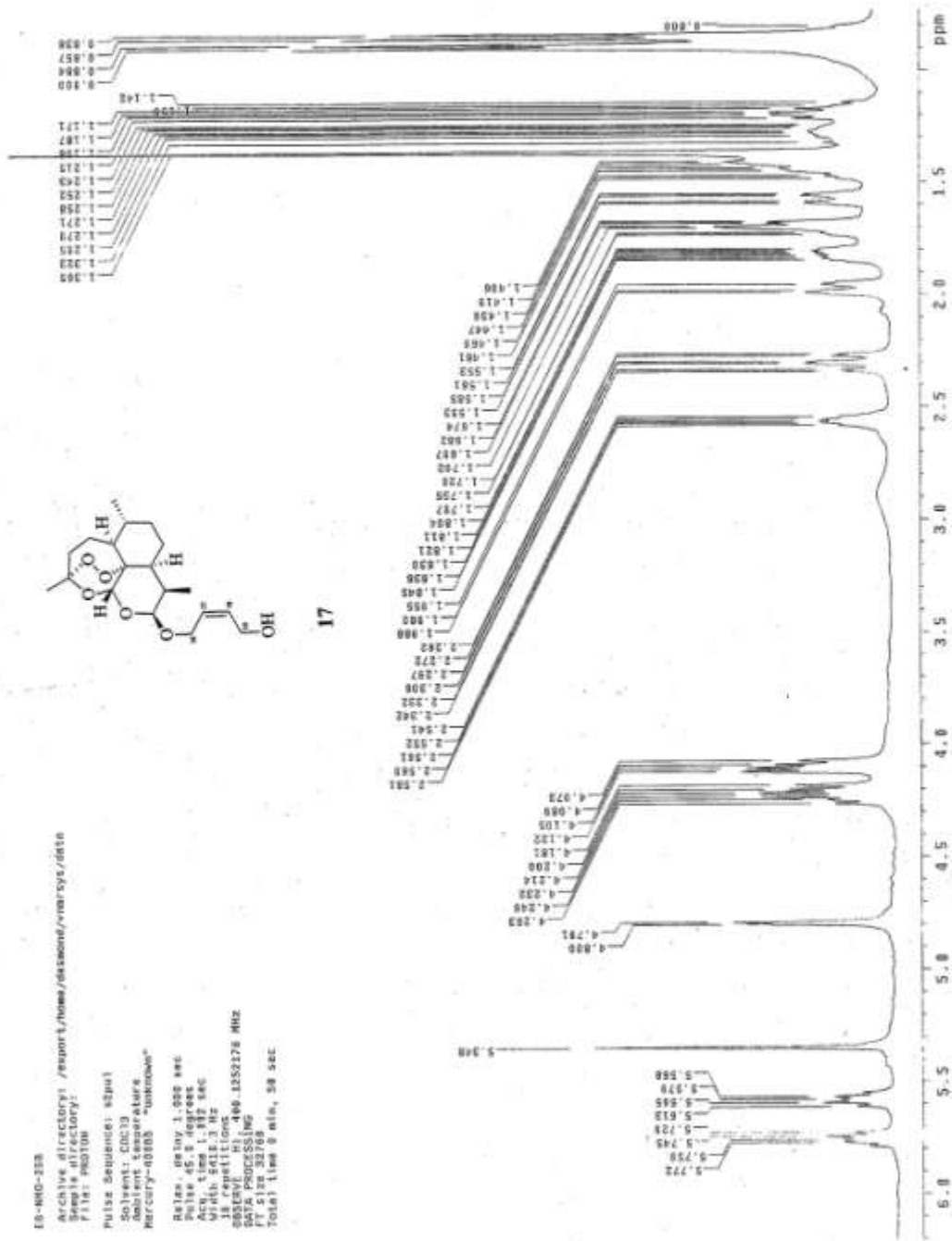
$^{13}\text{C}$  NMR spectrum for **15**.

ES-MHC-28  
 Archive directory: /nsport/home/relamond/ramfyy/data  
 Sample directory:  
 File: PROTON  
 Pulse Sequence: zgpg30  
 Solvent: pyridine  
 Reference: 4-methylpyridine  
 NSC000-0000 UNKNOWN\*  
 Relax. delay 1.000 sec  
 Pulse 45.0 degrees  
 Acq. time 1.592 sec  
 Date\_ Time 11-11-2009 12:00:00  
 32 repetitions  
 F2 (MHz) 400.1255823 MHz  
 DATA PROCESSING  
 F1 SIZE 32768  
 Total time 1 min, 40 sec



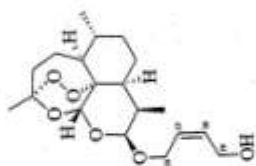
$^1\text{H}$  NMR spectrum for **16**.



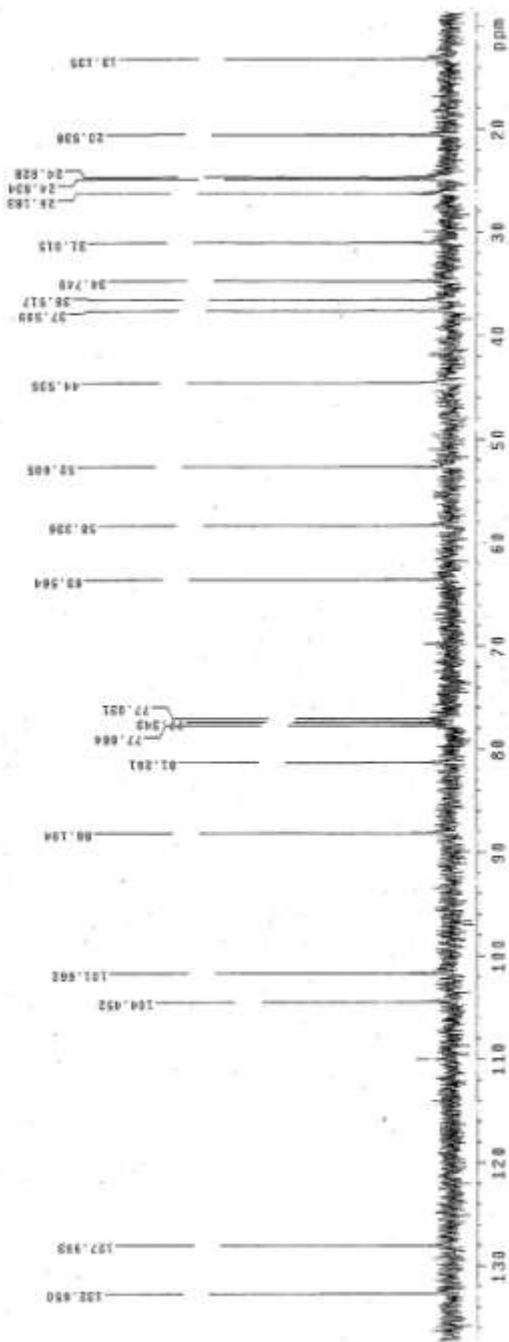


<sup>1</sup>H NMR spectrum for **17**.

ES-HMO-338  
 Archive directory: /export/home/edmond/vmr/sys/data  
 Sample directory:  
 File: CMB38  
 Pulse Sequence: zgpg30  
 Solvent: CDCl3  
 Ambient temperature  
 Mercury-100MS "mnohnu"  
 Relax delay 1.000 sec  
 Pulse 45.0 degree  
 Width 18.000 sec  
 Width 25.125 sec  
 138 repetitions  
 OBSERVE C13, 100.6115420 MHz  
 DECOUPLE H1, 400.1272240 MHz  
 continuously on  
 WALTZ-16 modulated  
 DATA PROCESSING  
 FT use decoupling 1.0 Hz  
 FT use 45.000 MHz  
 Total time 26 min, 42 sec



17



$^{13}\text{C}$  NMR spectrum for 17.

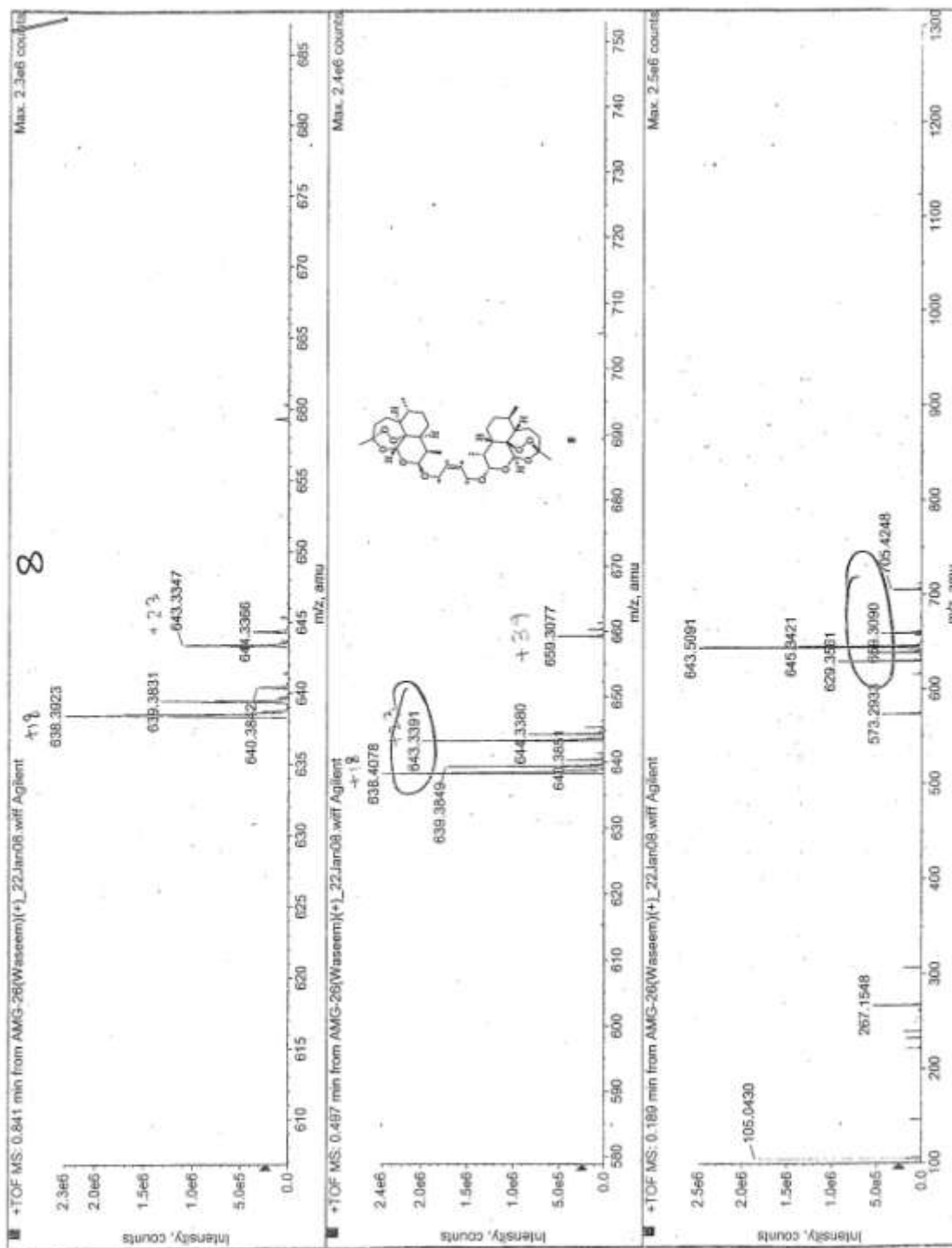




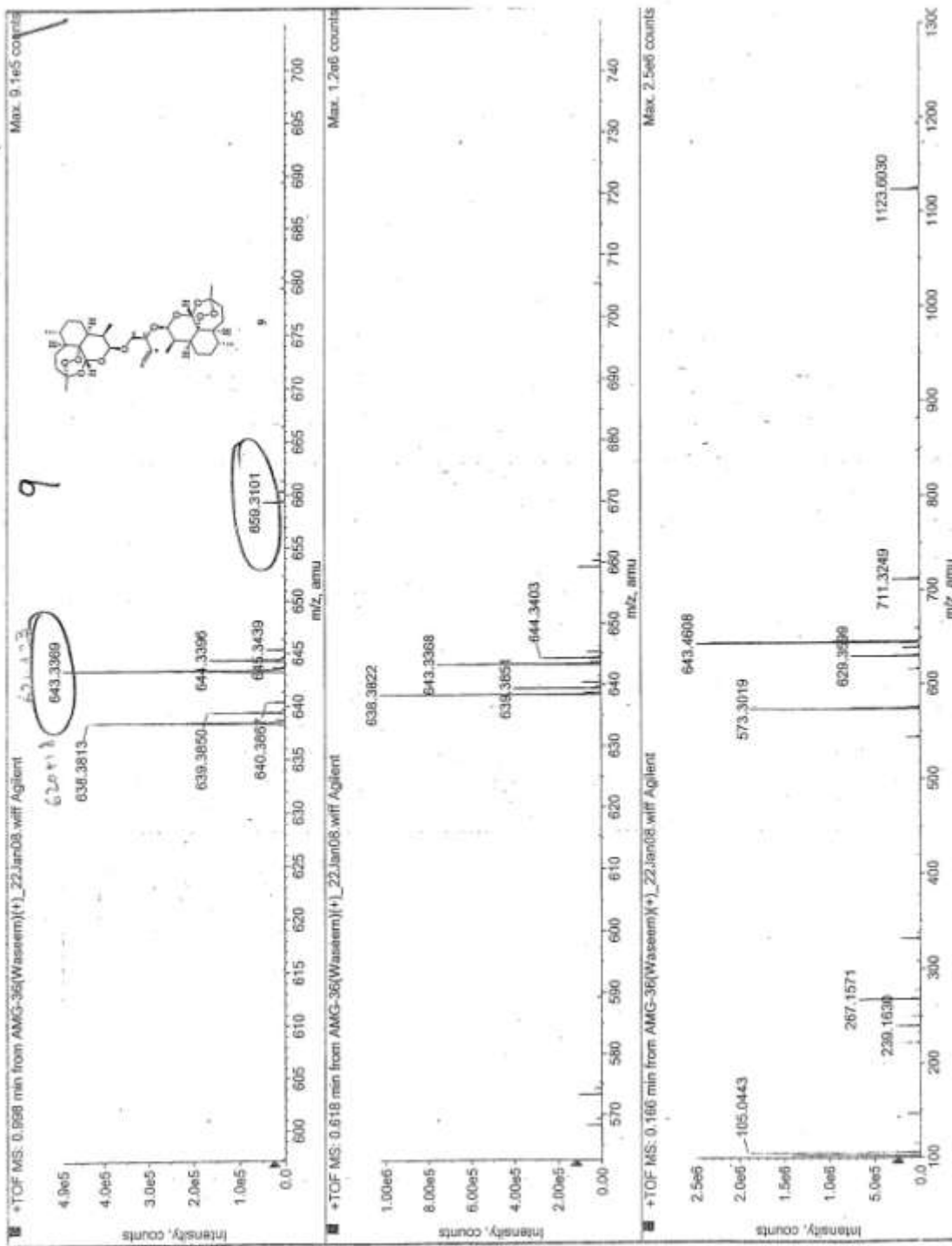




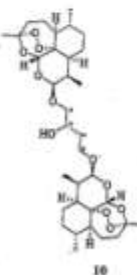
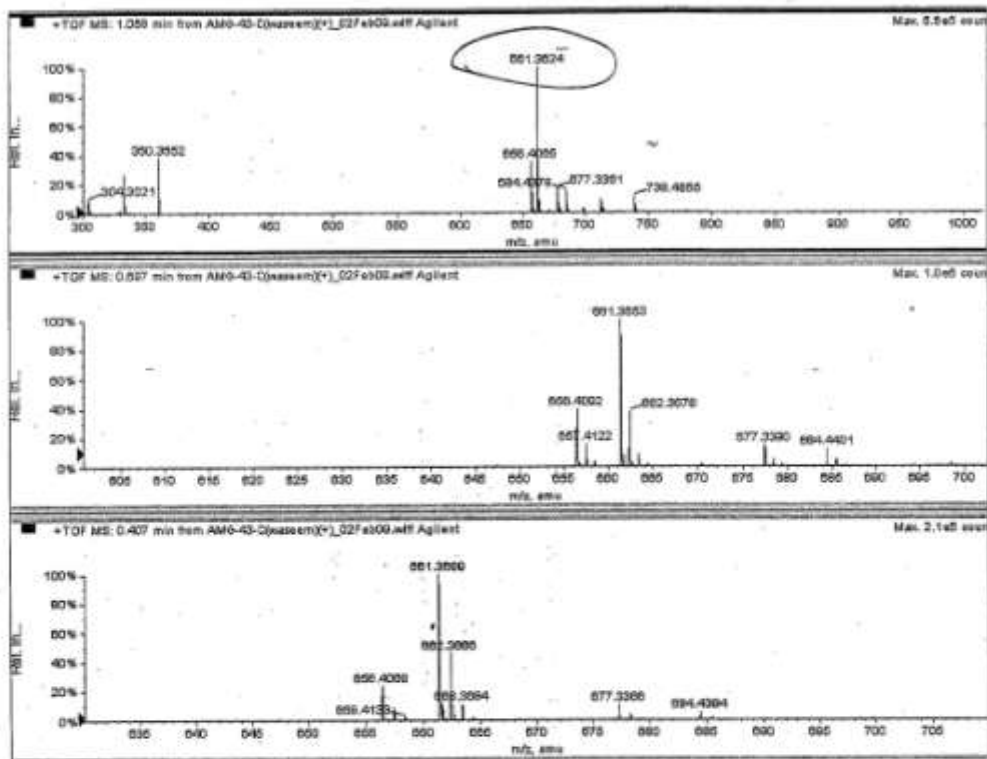




HRMS spectrum for 8.



HRMS spectrum for **9**.

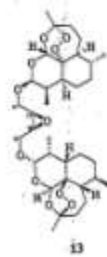
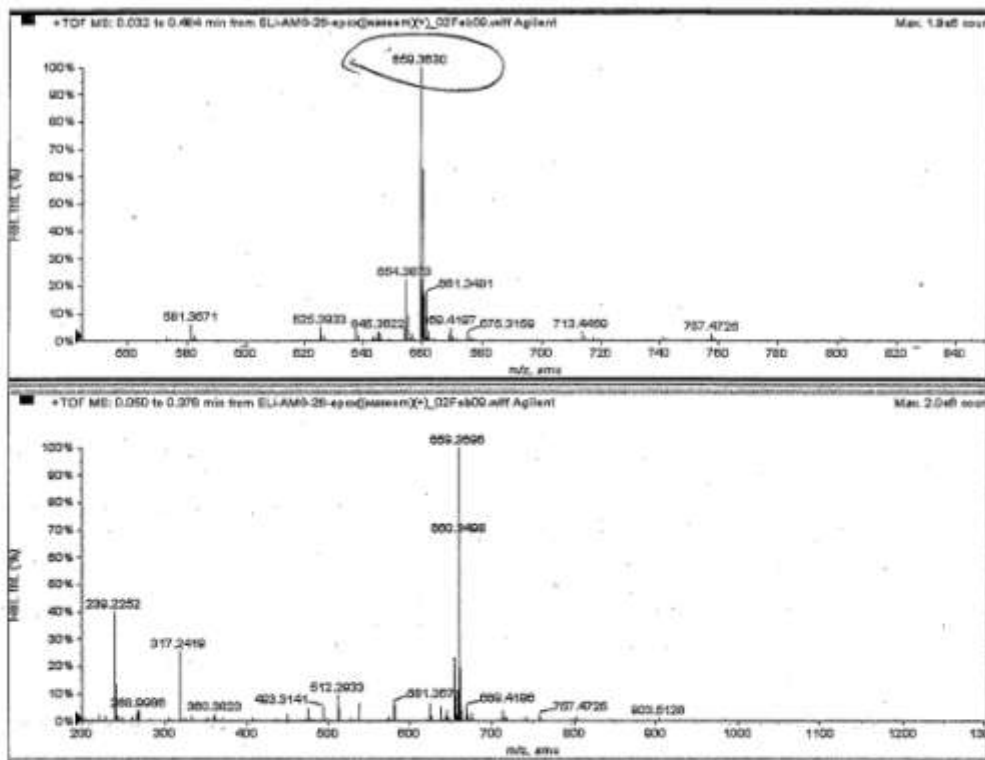


HRMS spectrum for **10**.



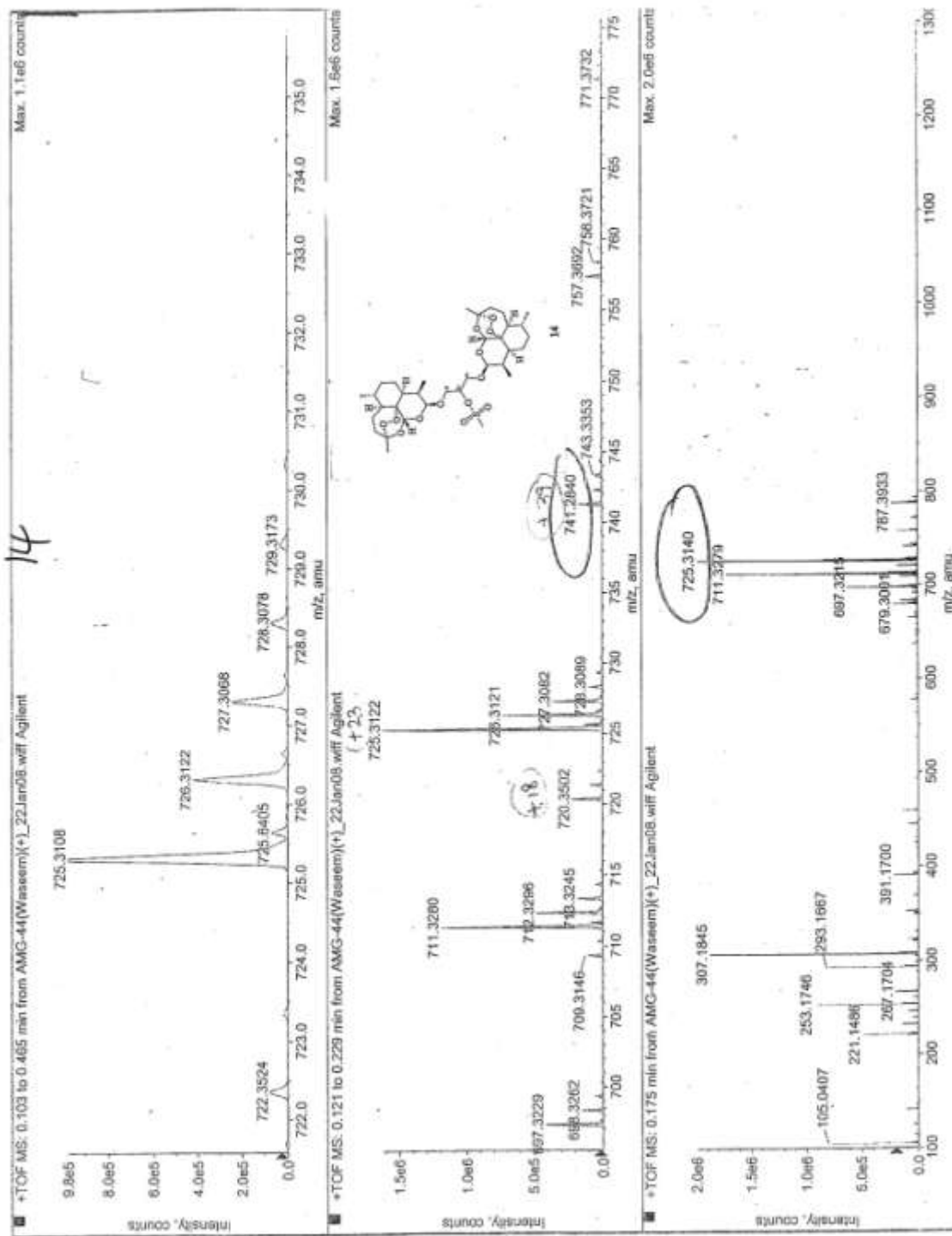






13

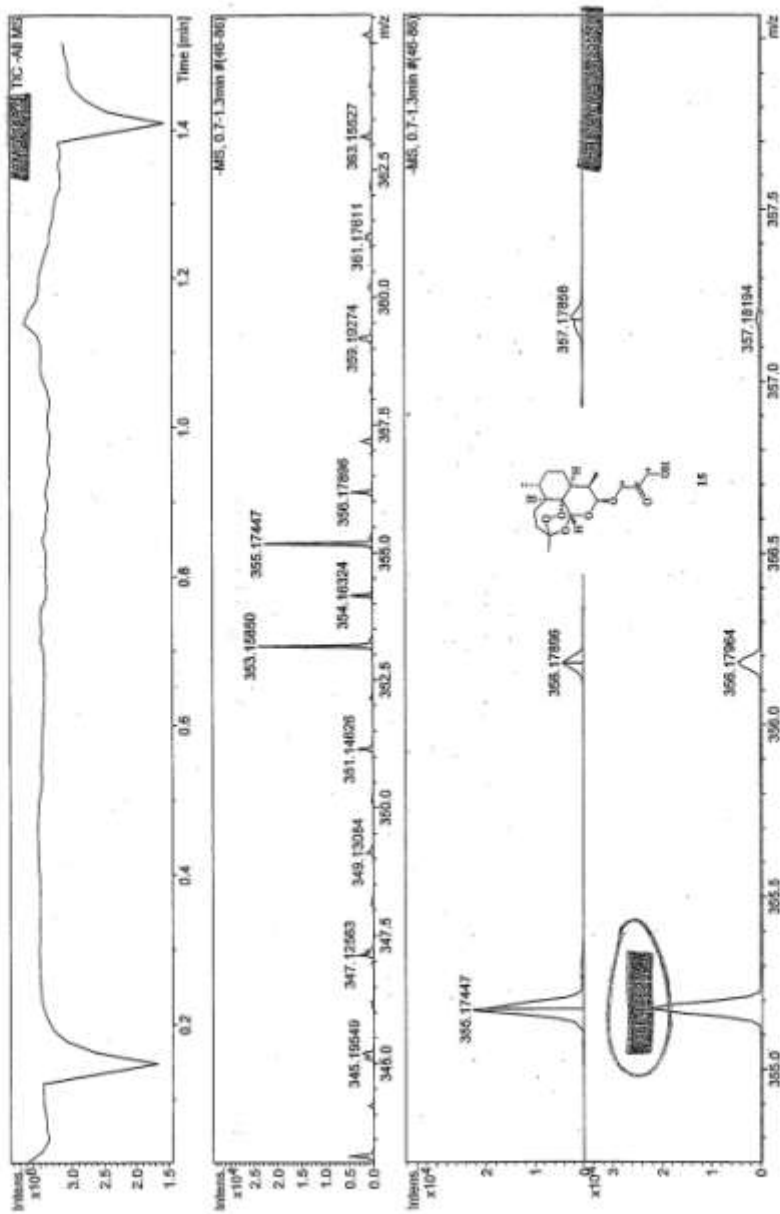
HRMS spectrum for 1



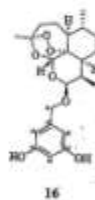
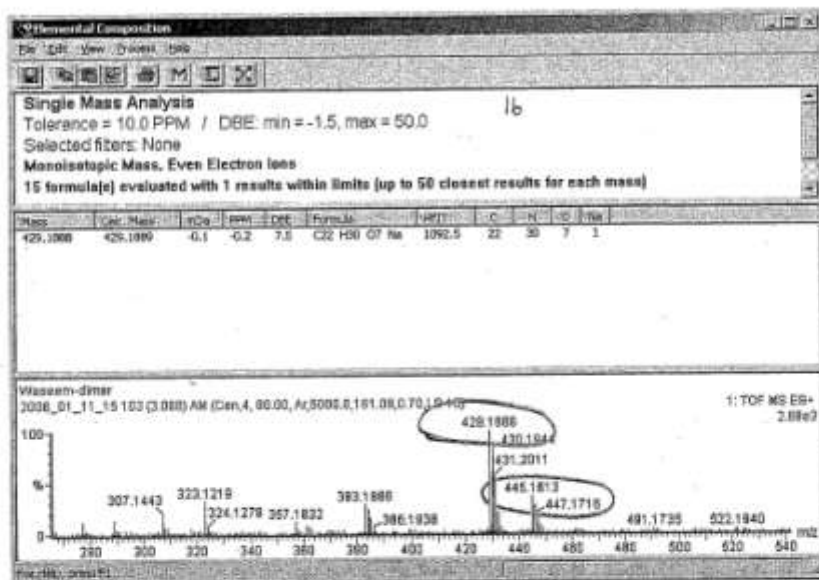
HRMS spectrum for 14.

15

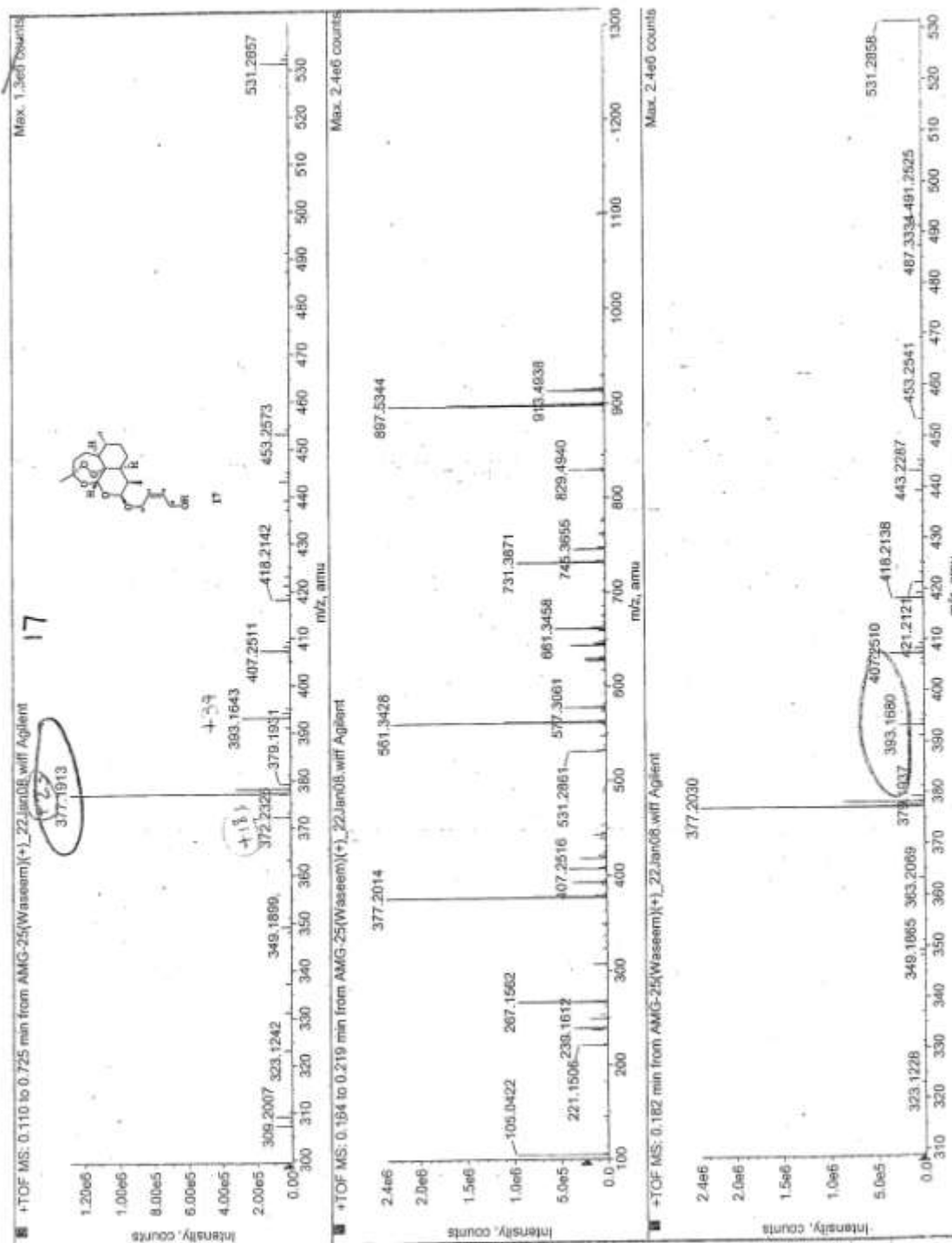
Generic Display Report (all)



HRMS spectrum for 15.



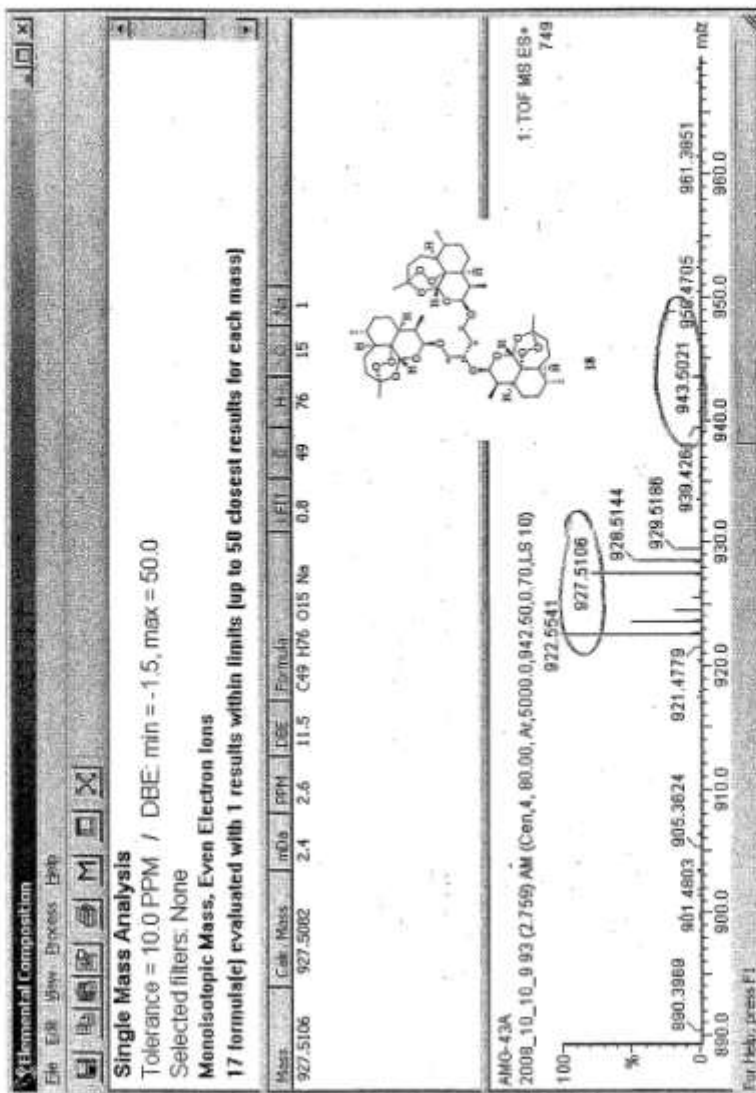
HRMS spectrum for **16**.



HRMS spectrum for 17.

18

A



HRMS spectrum for 18.