

# Standard Protecting Groups Create Potent and Selective $\kappa$

## Opioids: Salvinorin B Alkoxyethyl Ethers

*Thomas A. Munro, Katharine K. Duncan, Wei Xu, Yulin Wang, Lee-Yuan Liu-Chen,*

*William A. Carlezon, Jr., Bruce M. Cohen, and Cécile Béguin.*

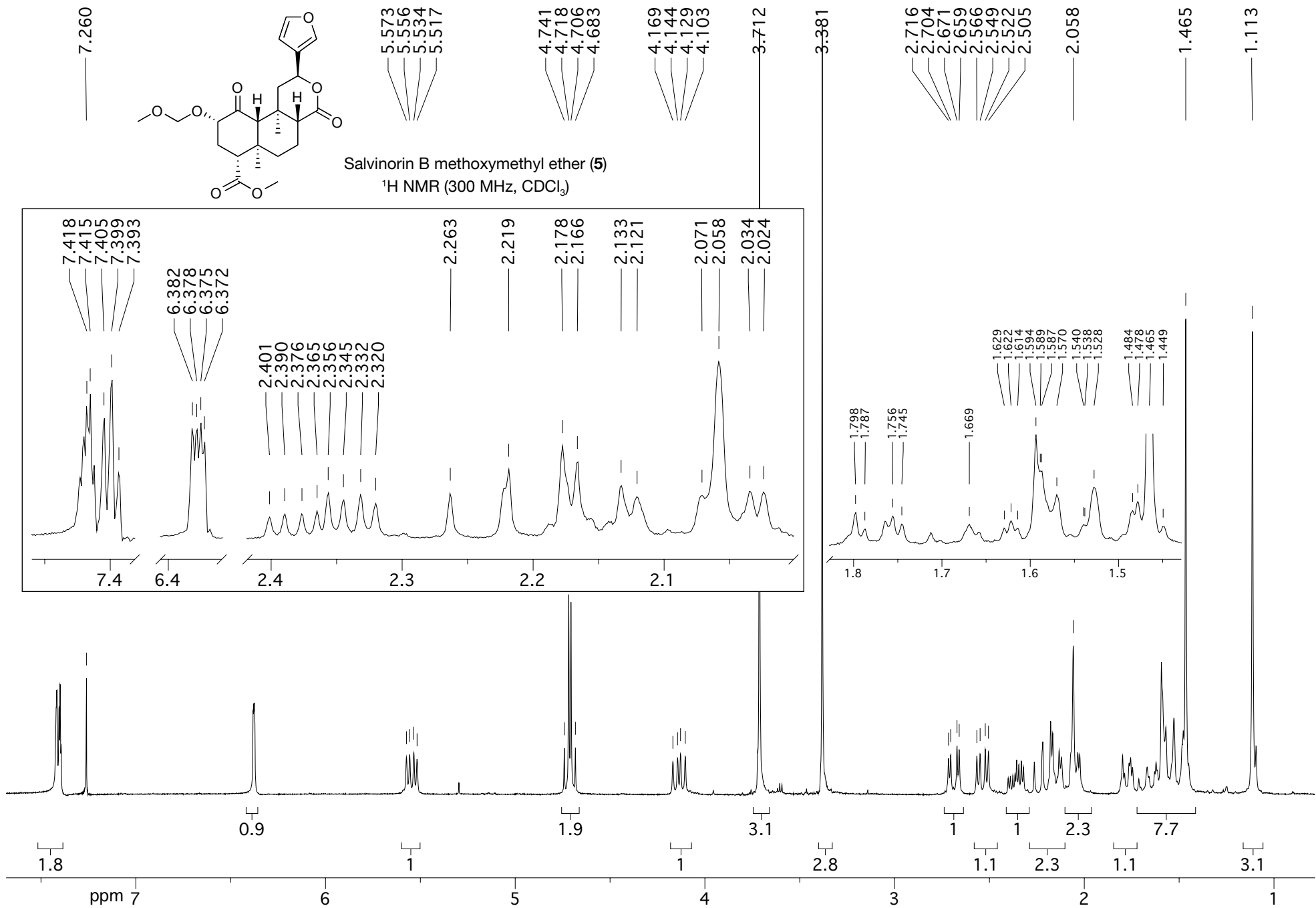
### Supporting information

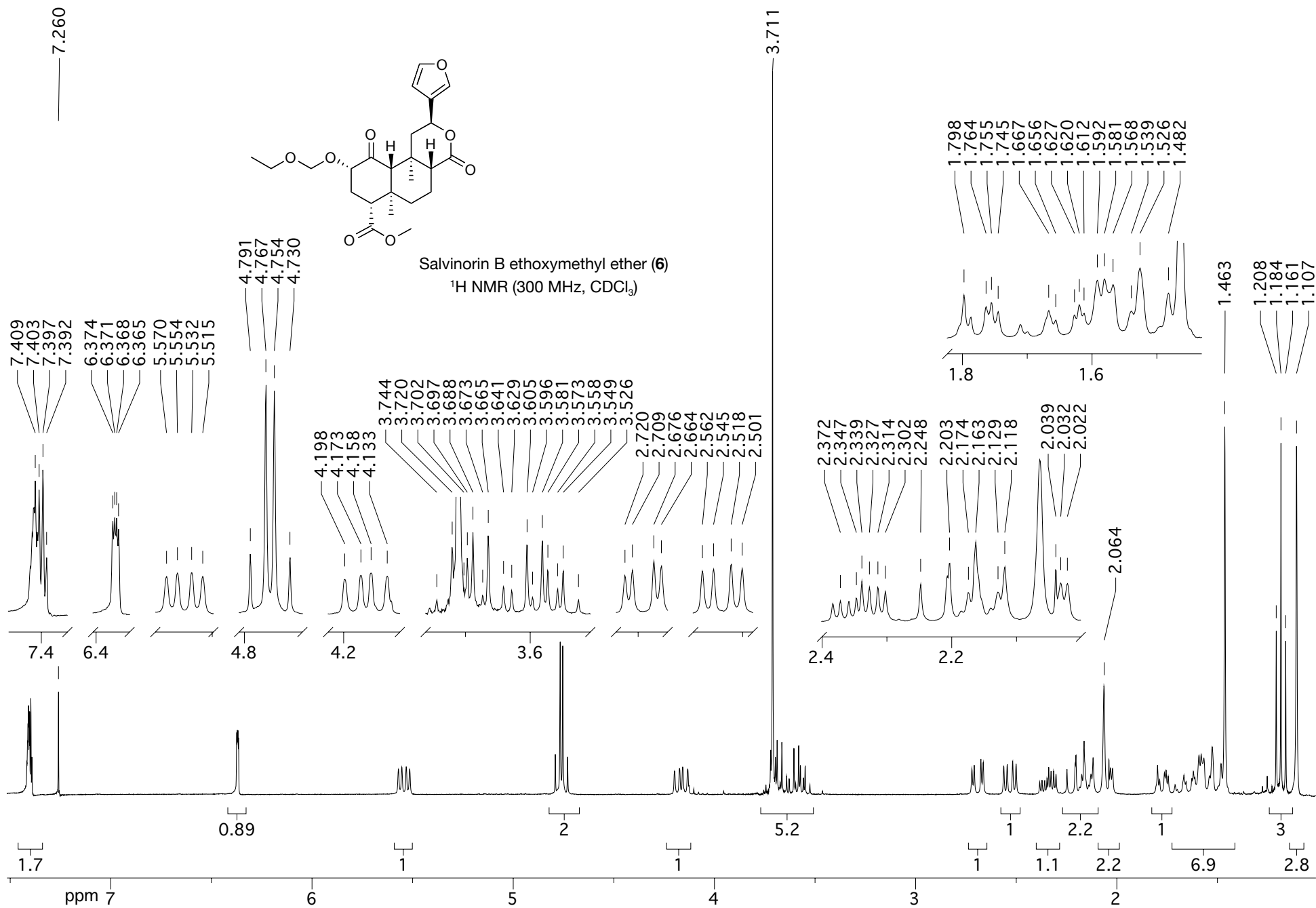
#### Table of Contents

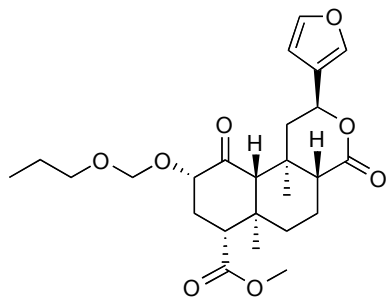
Compound	<sup>1</sup> H NMR spectrum	<sup>13</sup> C NMR spectrum
<b>5</b>	2	19
<b>6</b>	3	19
<b>7</b>	4	20
<b>8</b>	5	20
<b>9</b>	6	21
<b>10</b>	7	21
<b>11</b>	8	22
<b>12</b>	9	22
<b>13</b>	10	23
<b>14</b>	11	23
<b>15</b>	12	24
<b>16</b>	13	24
<b>17</b>	14	25
<b>18a</b>	15	25
<b>18b</b>	16	26
<b>19</b>	17	26
<b>20</b>	18	27

Statement of author contributions 28

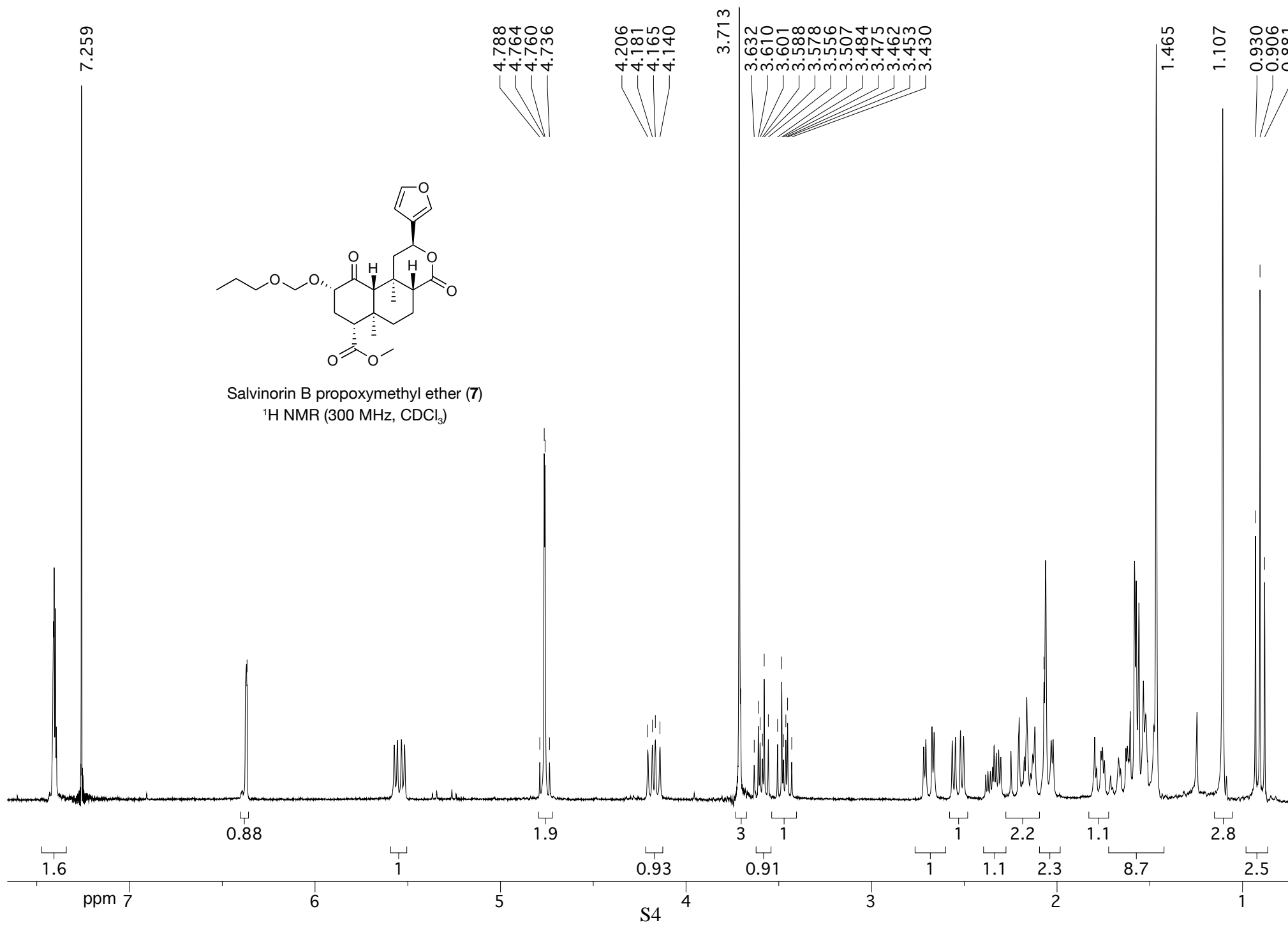
IUPAC International Chemical Identifiers (InChIs) 29







Salvinorin B propoxymethyl ether (**7**)  
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)



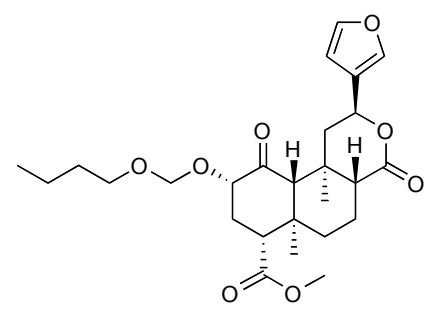
4.780  
4.756  
4.751  
4.727

4.197  
4.172  
4.156  
4.131

3.665  
3.643  
3.633  
3.621  
3.611  
3.589  
3.549  
3.527  
3.517  
3.505  
3.495  
3.473

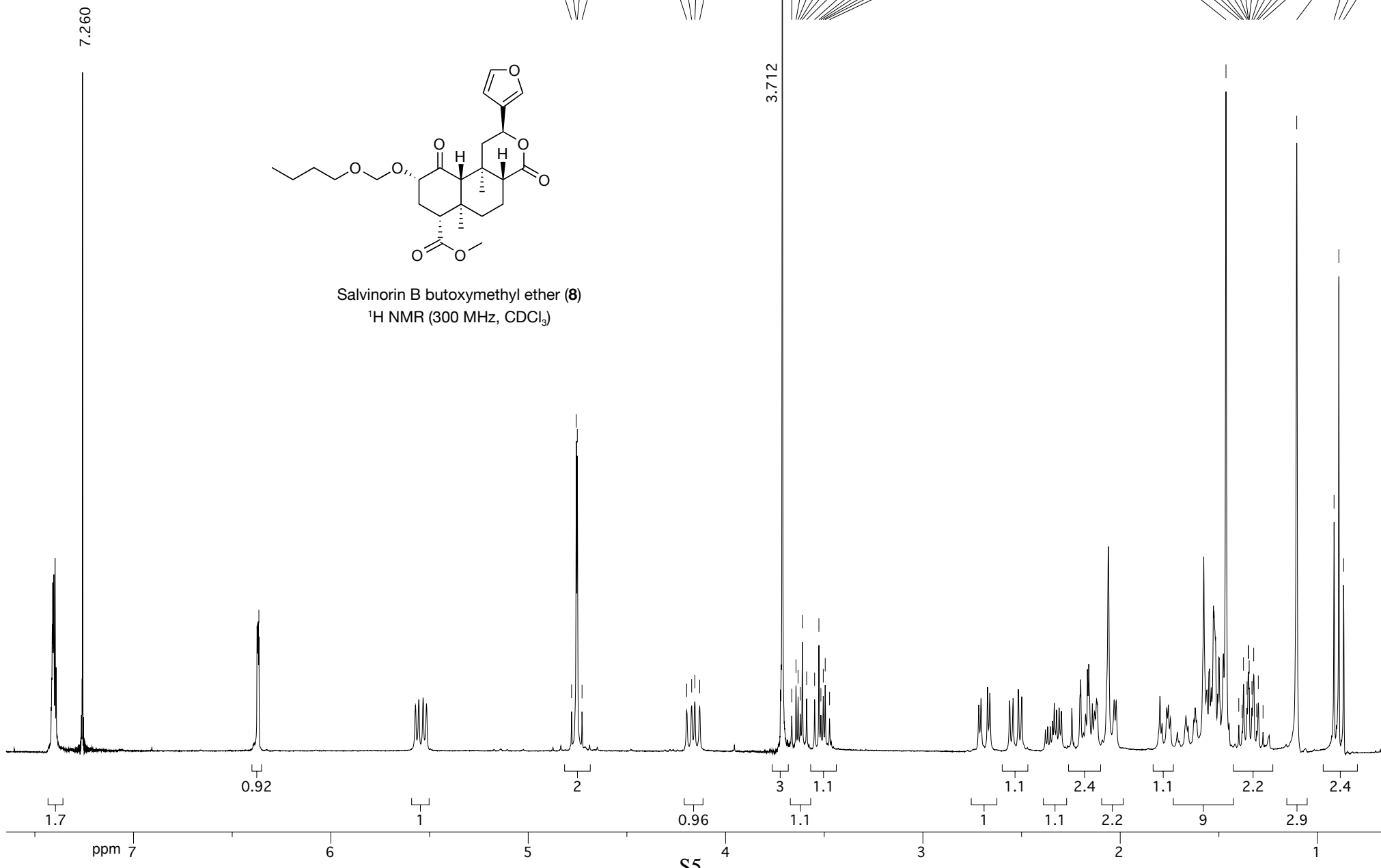
1.464  
1.389  
1.382  
1.375  
1.357  
1.351  
1.350  
1.347  
1.333  
1.324  
1.309  
1.276  
1.300  
1.106  
0.916  
0.892  
0.868

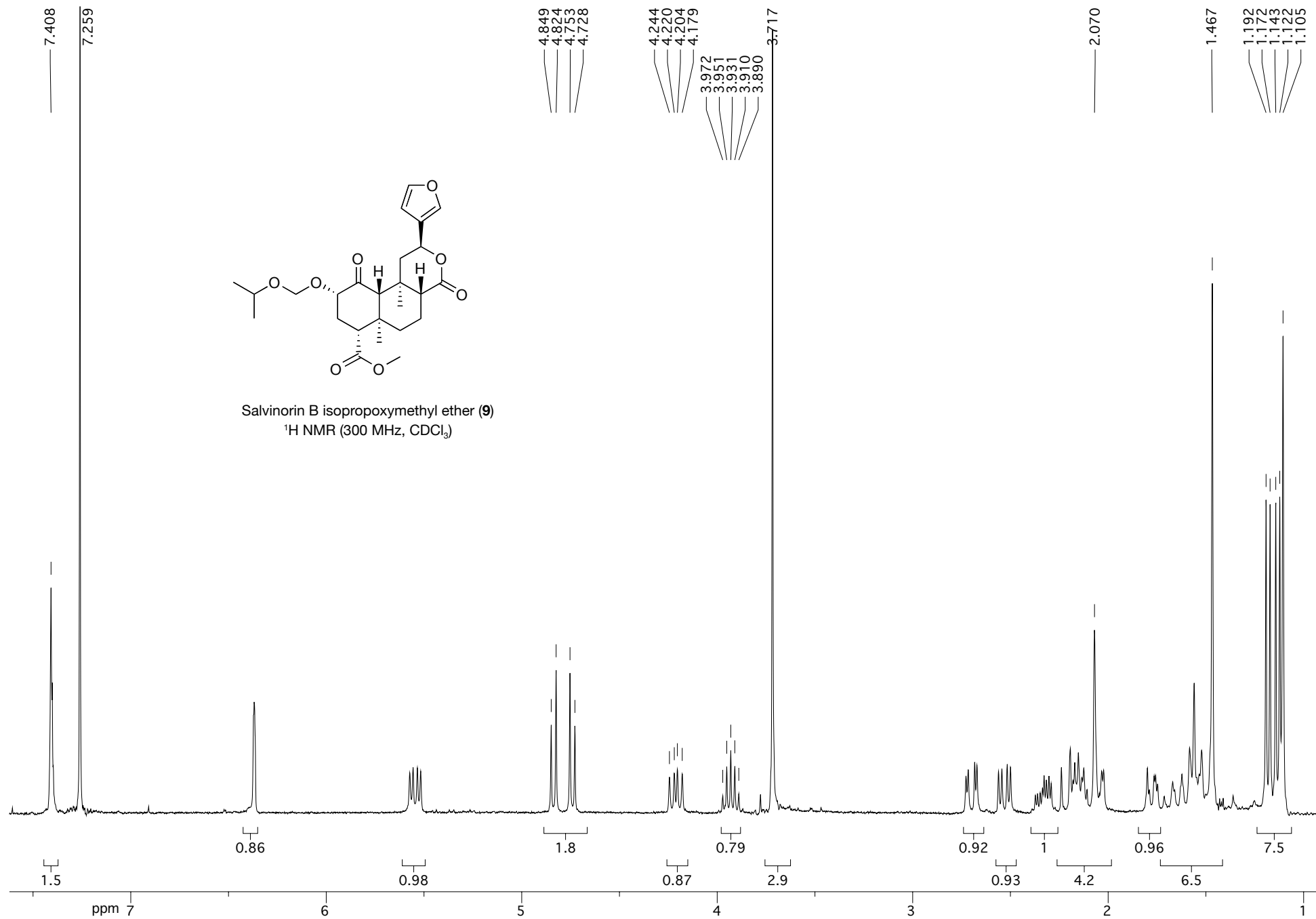
7.260

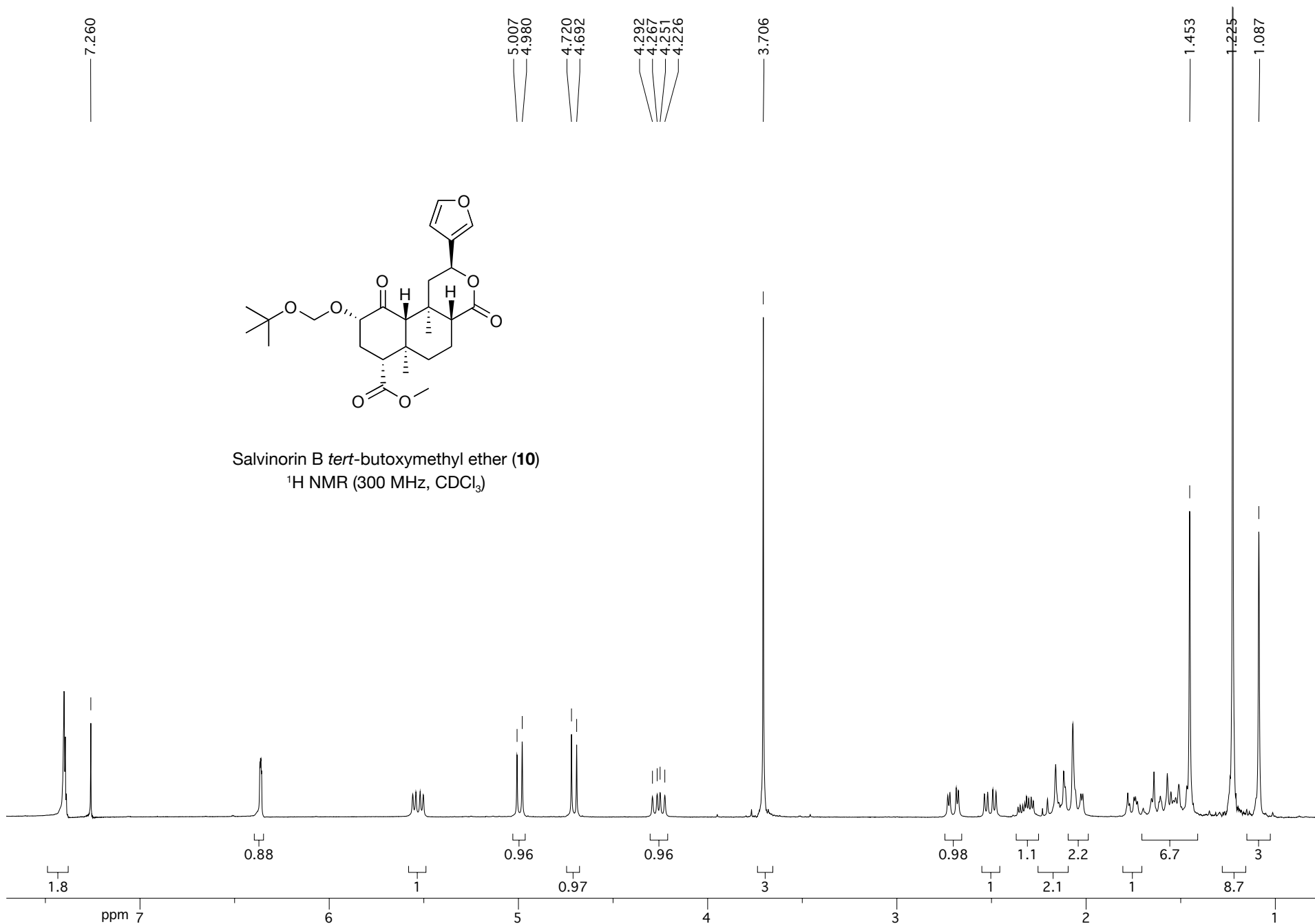


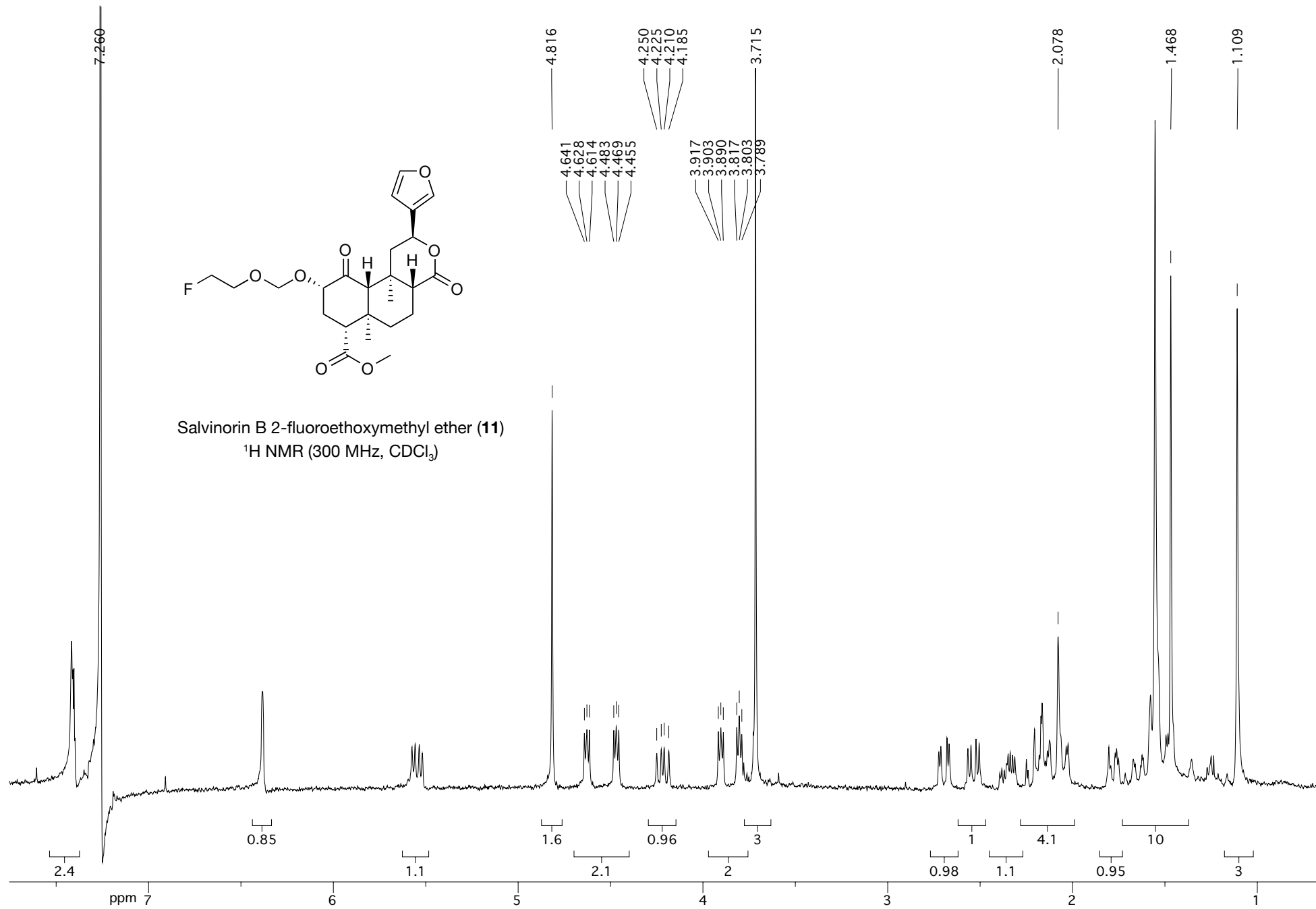
Salvinorin B butoxymethyl ether (**8**)  
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)

3.712

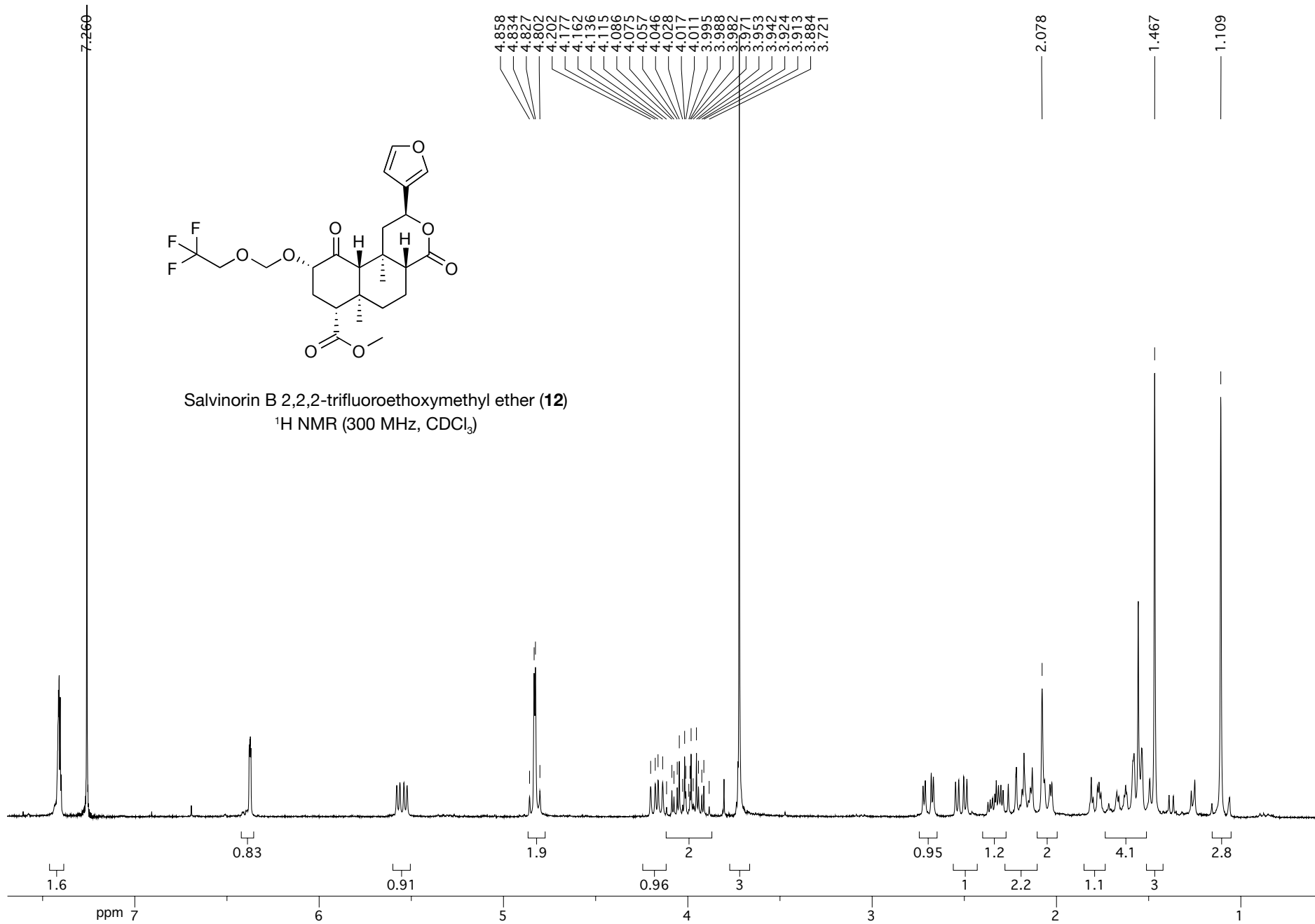


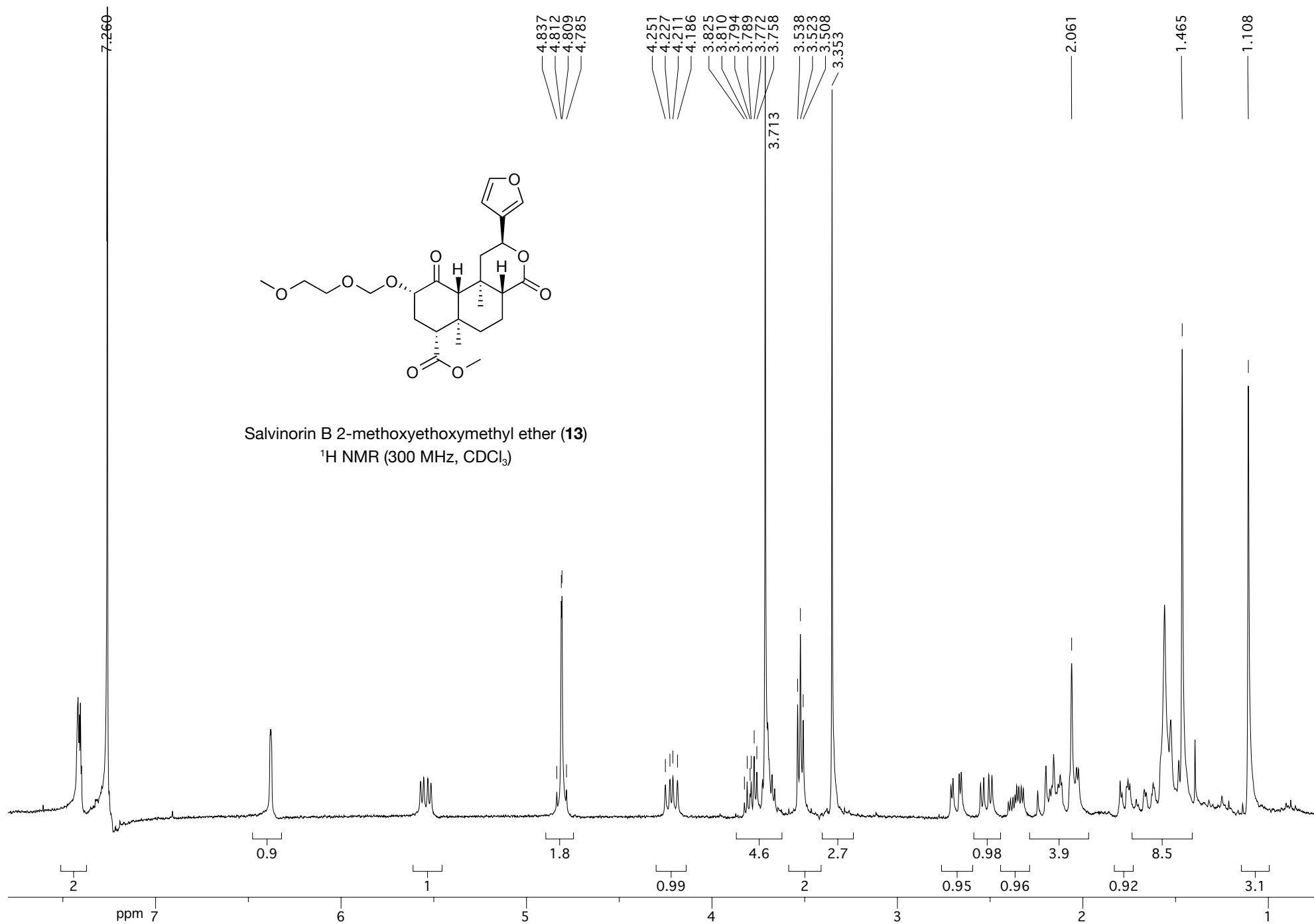


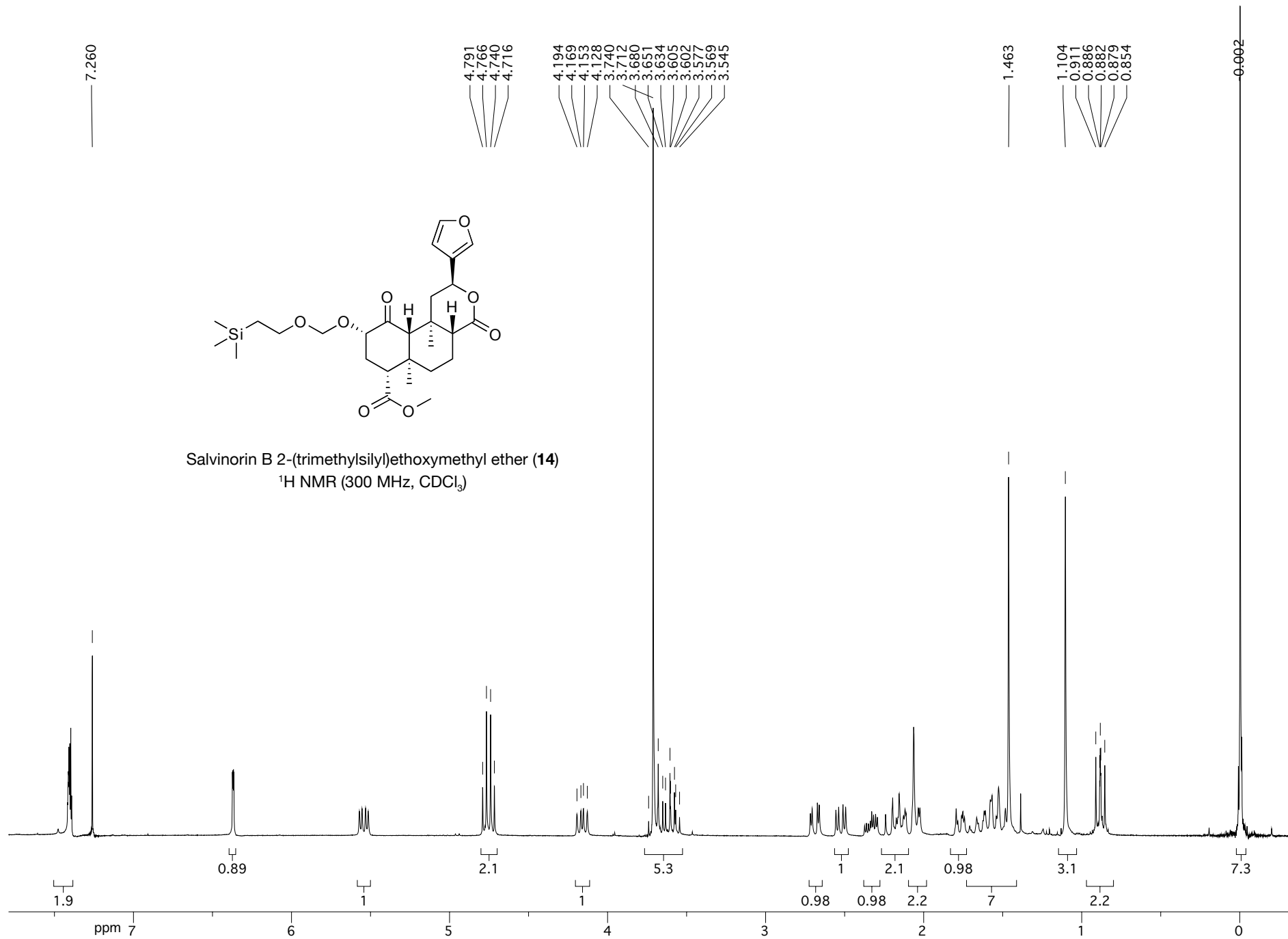


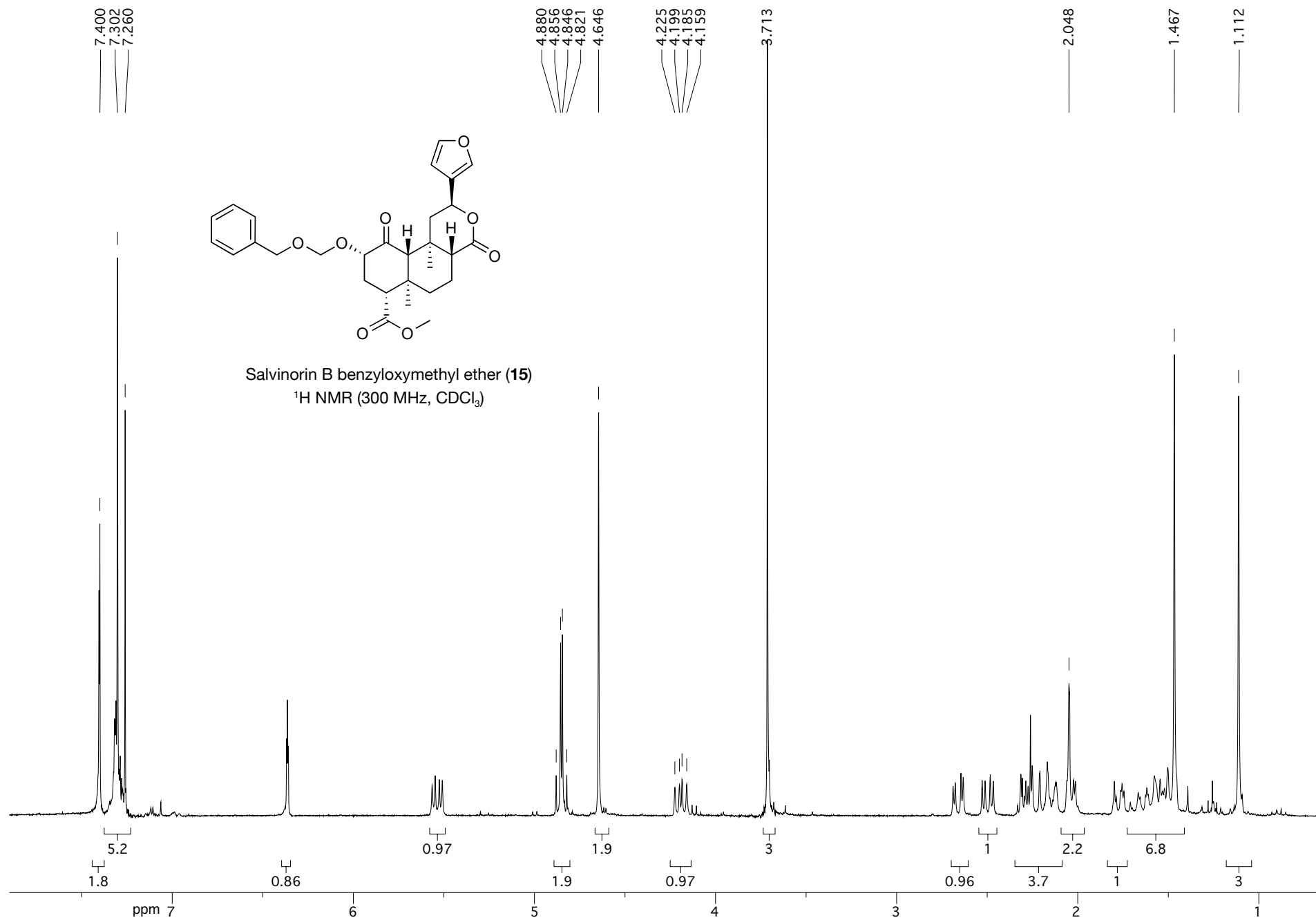


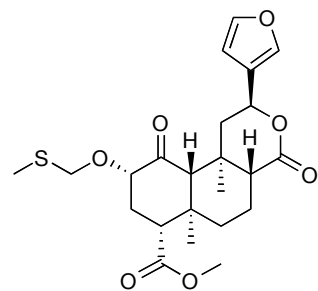






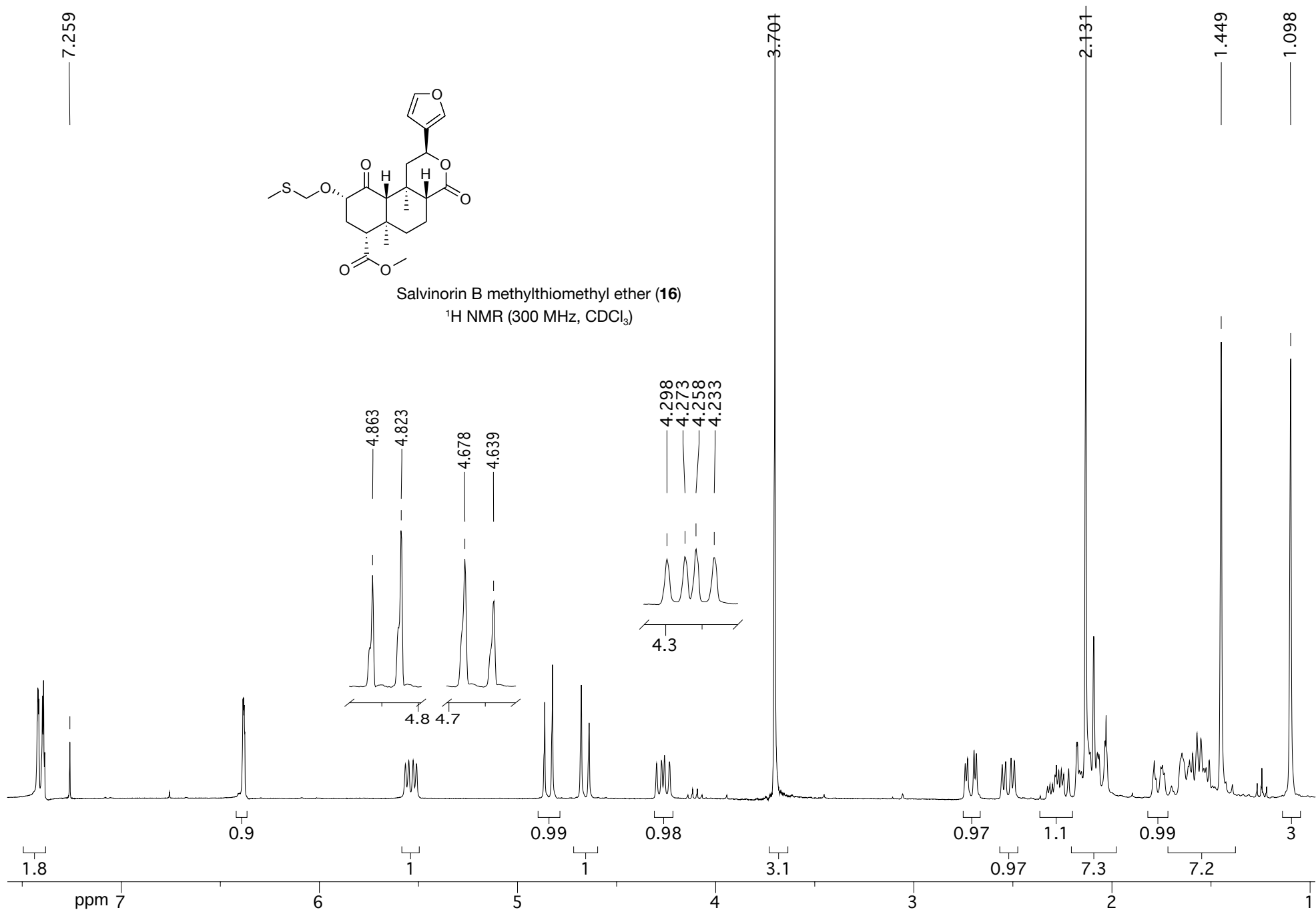


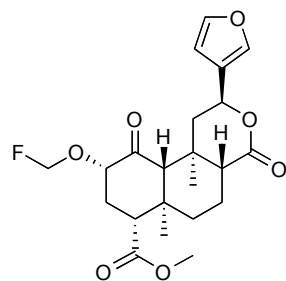




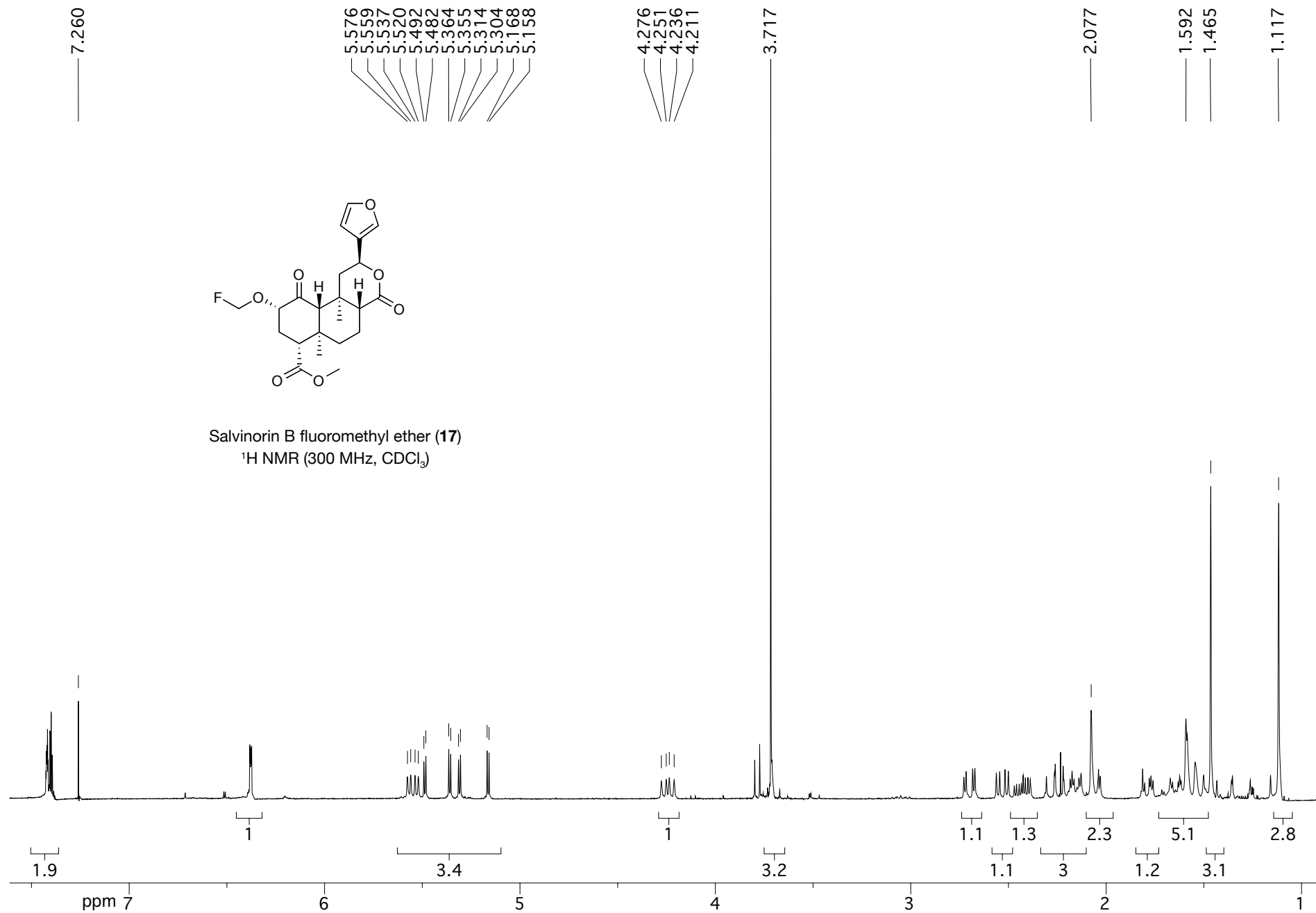
Salvinorin B methylthiomethyl ether (**16**)

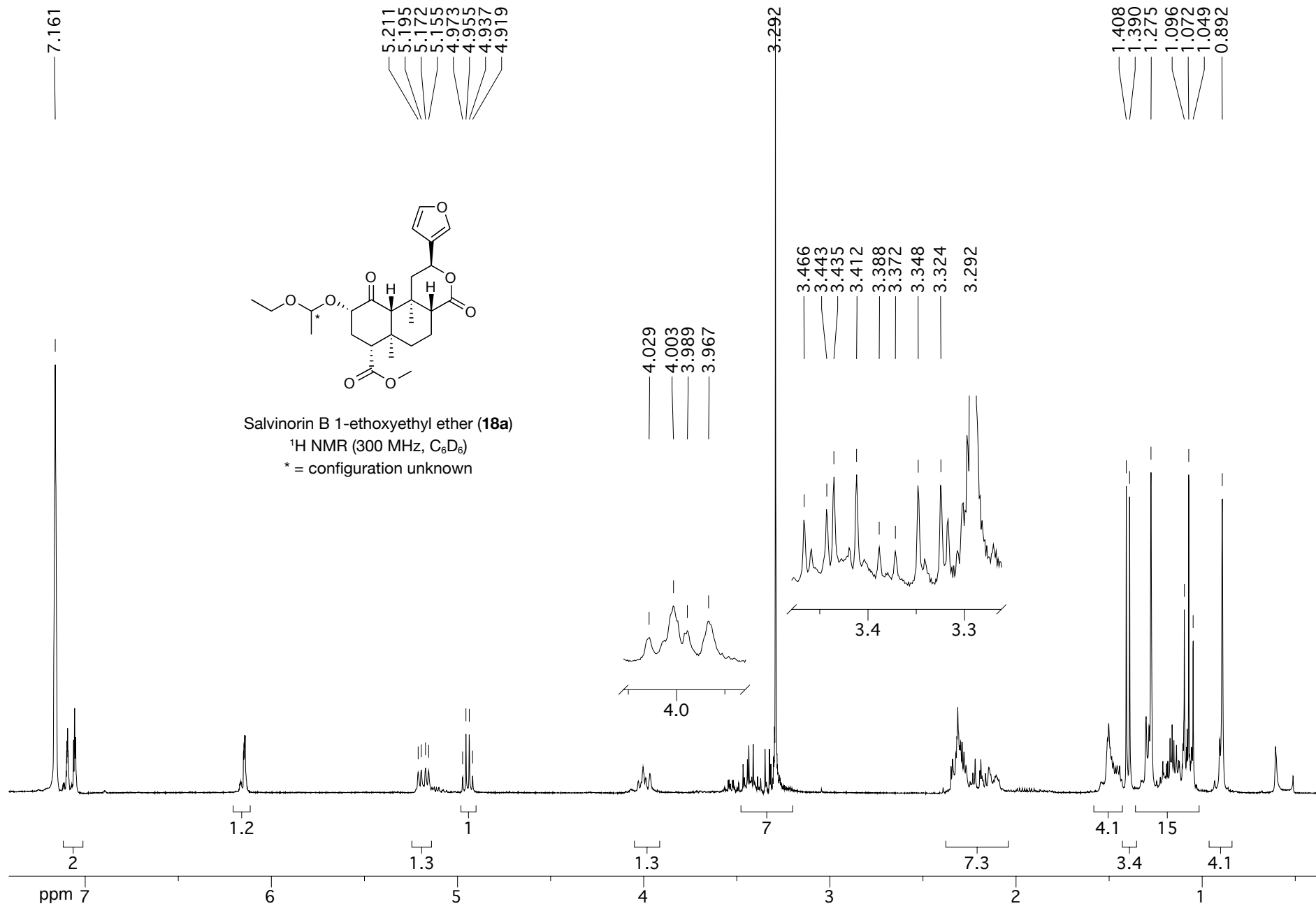
$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )

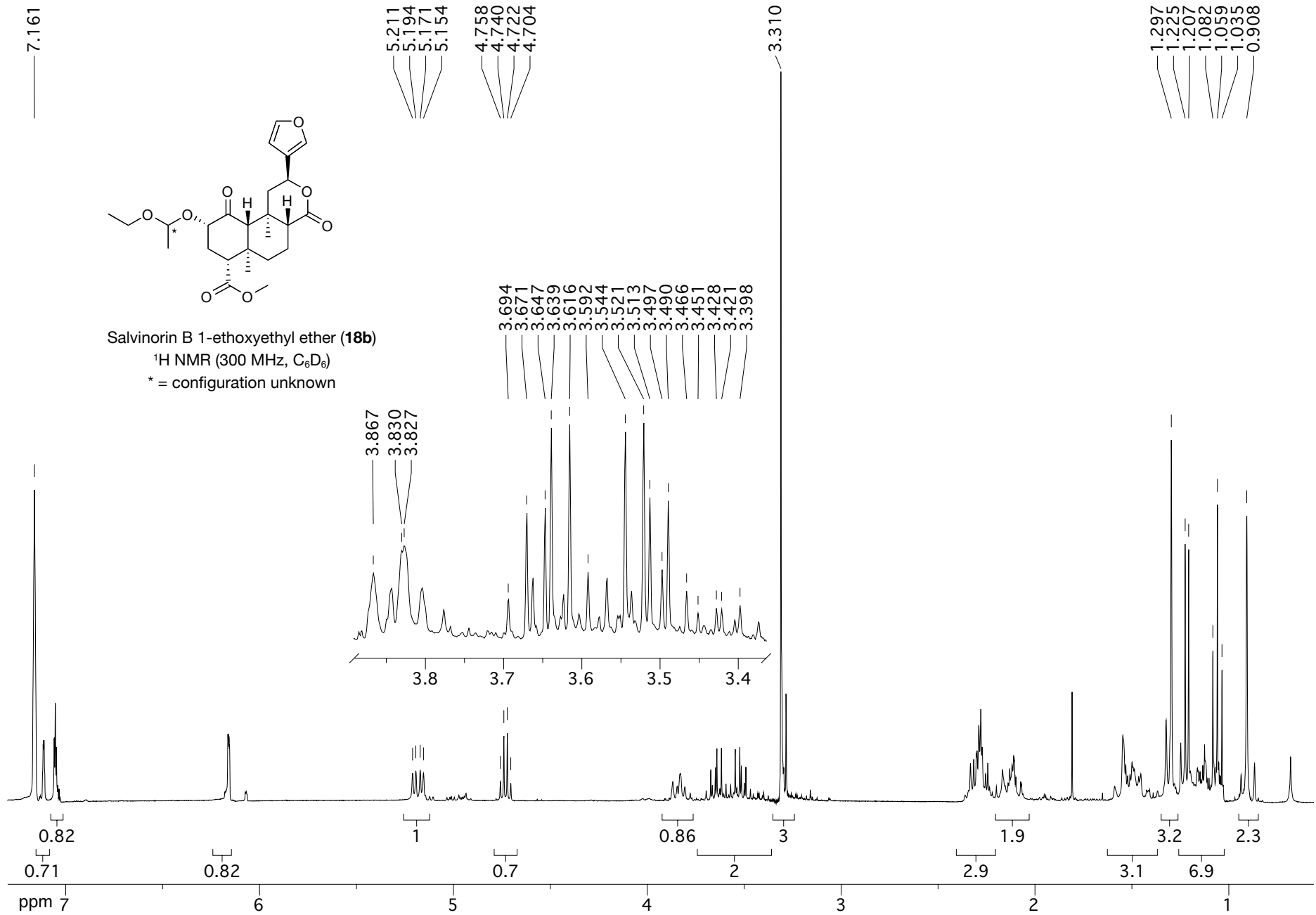




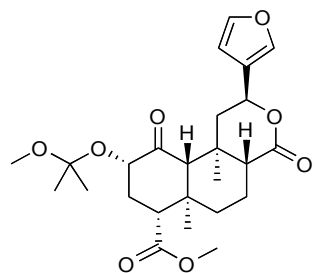
Salvinator B fluoromethyl ether (**17**)  
 $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )



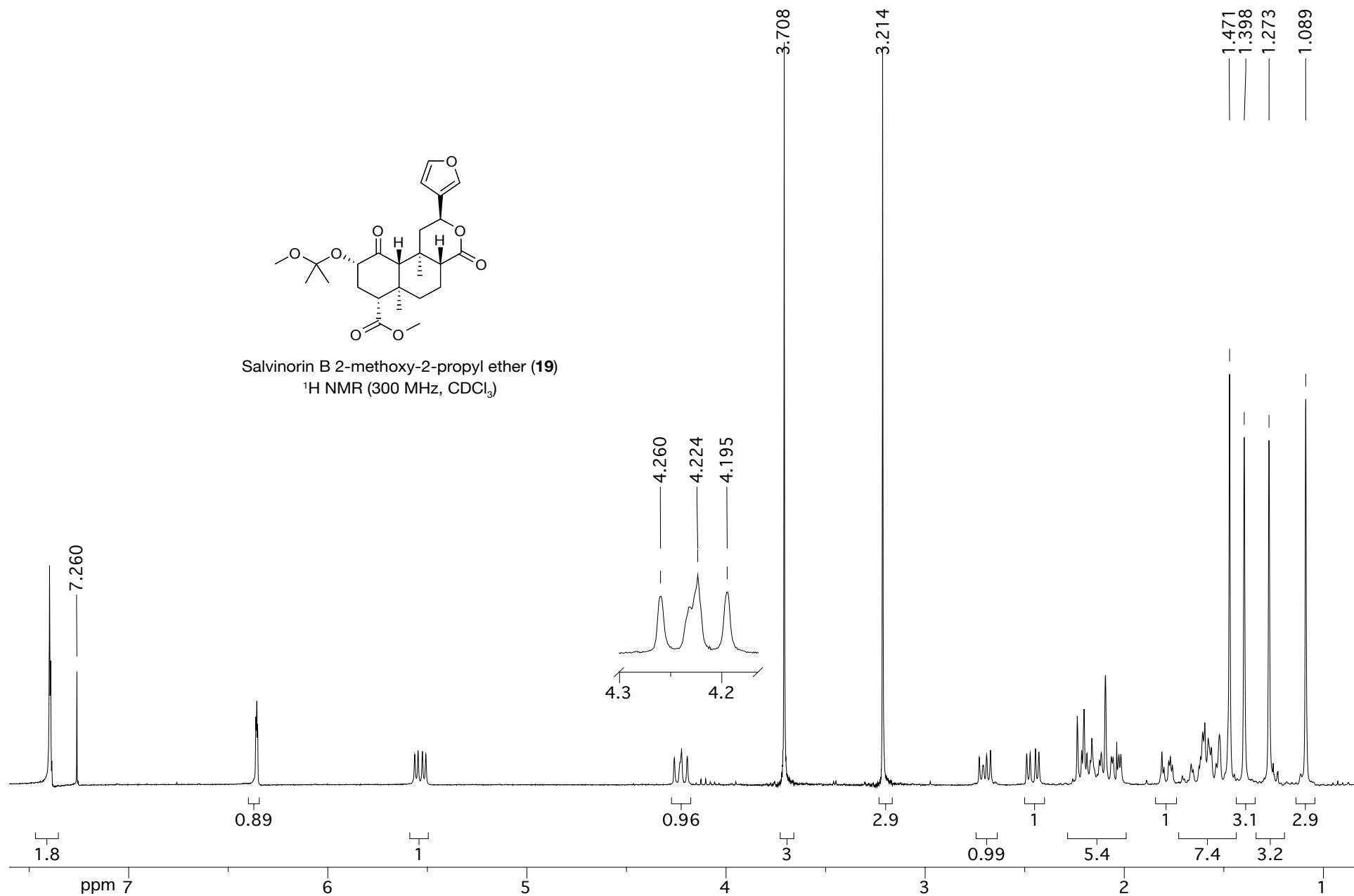


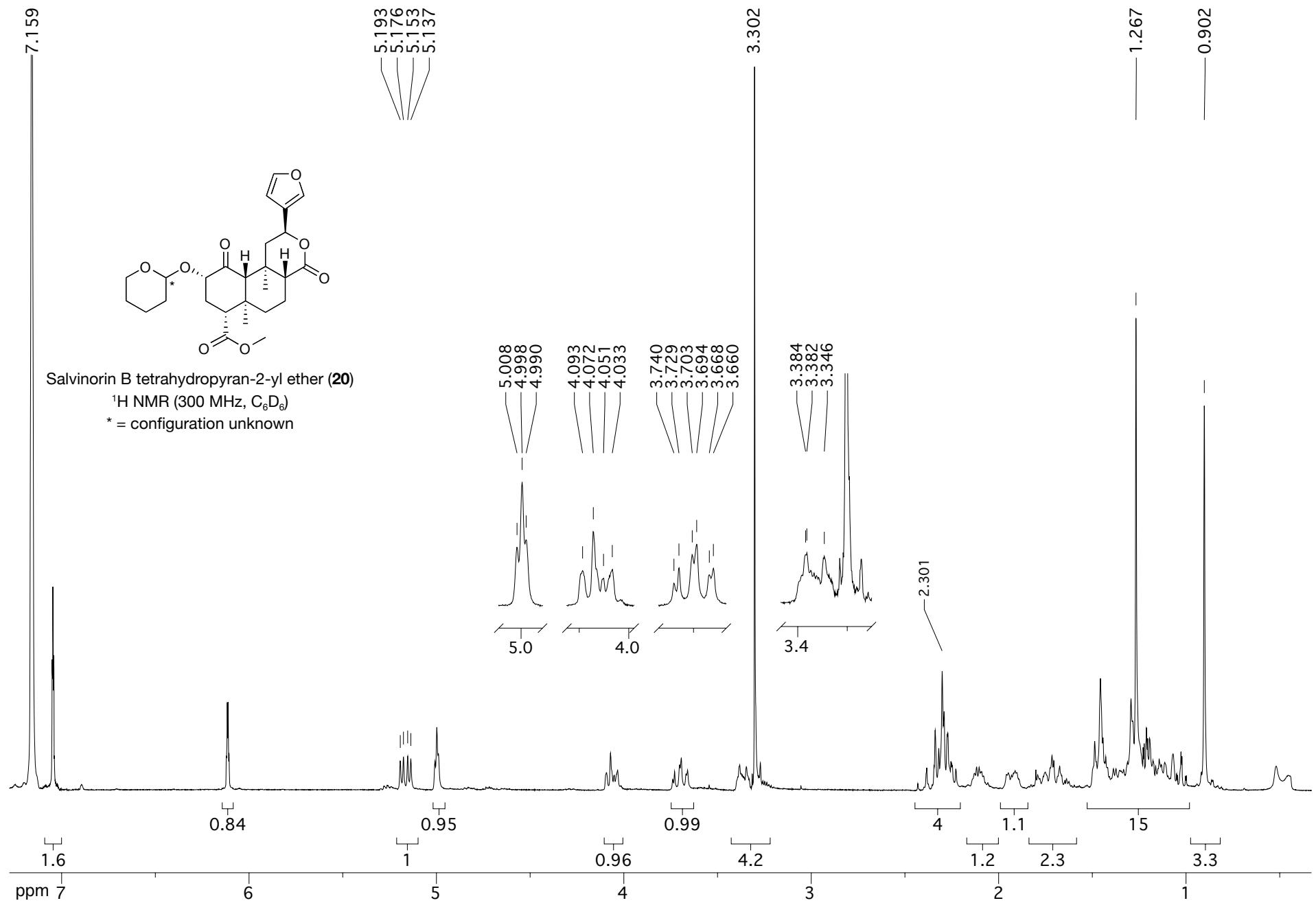


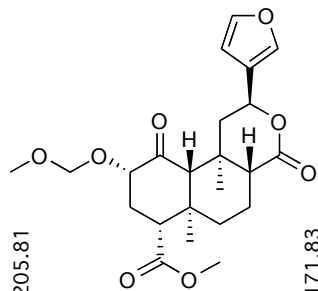




Salvinorin B 2-methoxy-2-propyl ether (**19**)  
 $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )

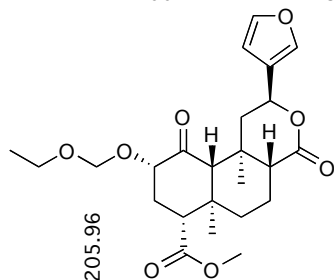
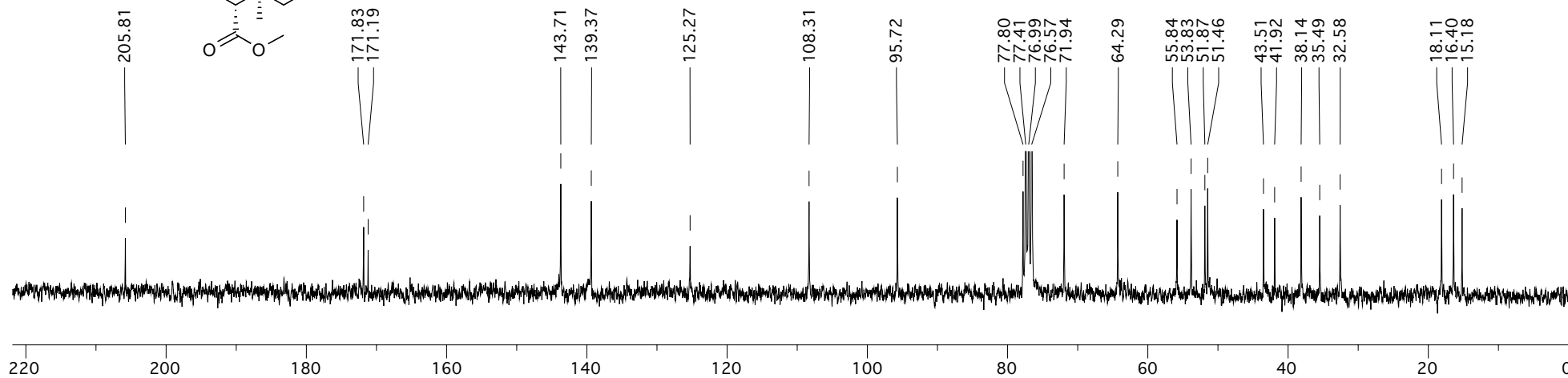




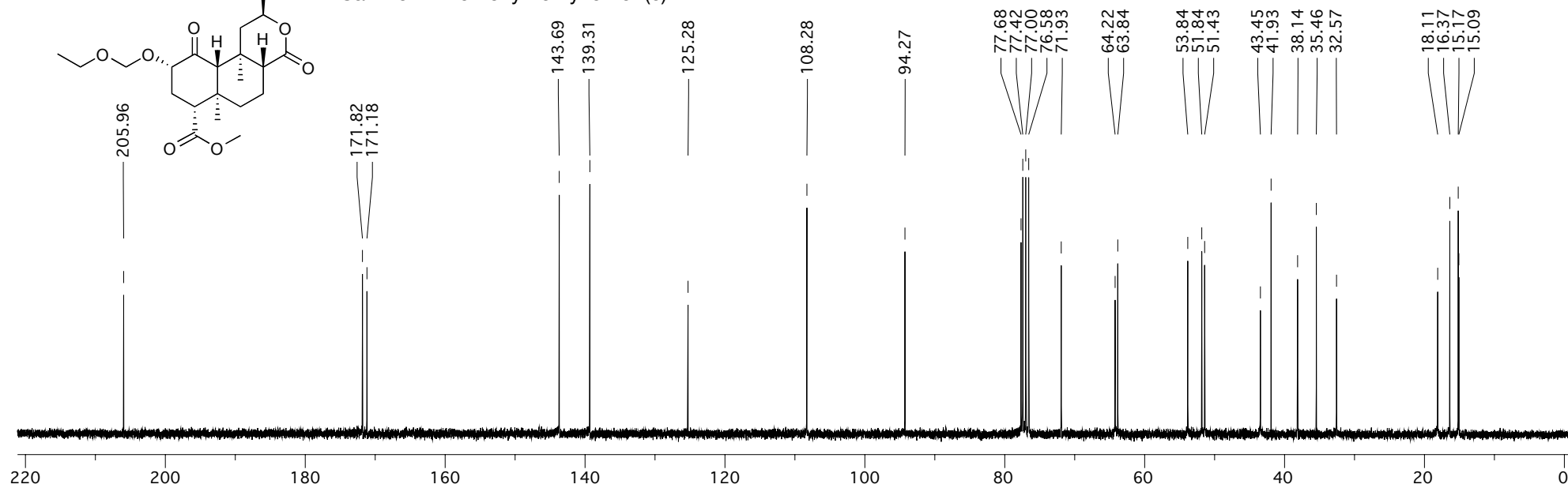


Salvinorin B methoxymethyl ether (**5**)

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )

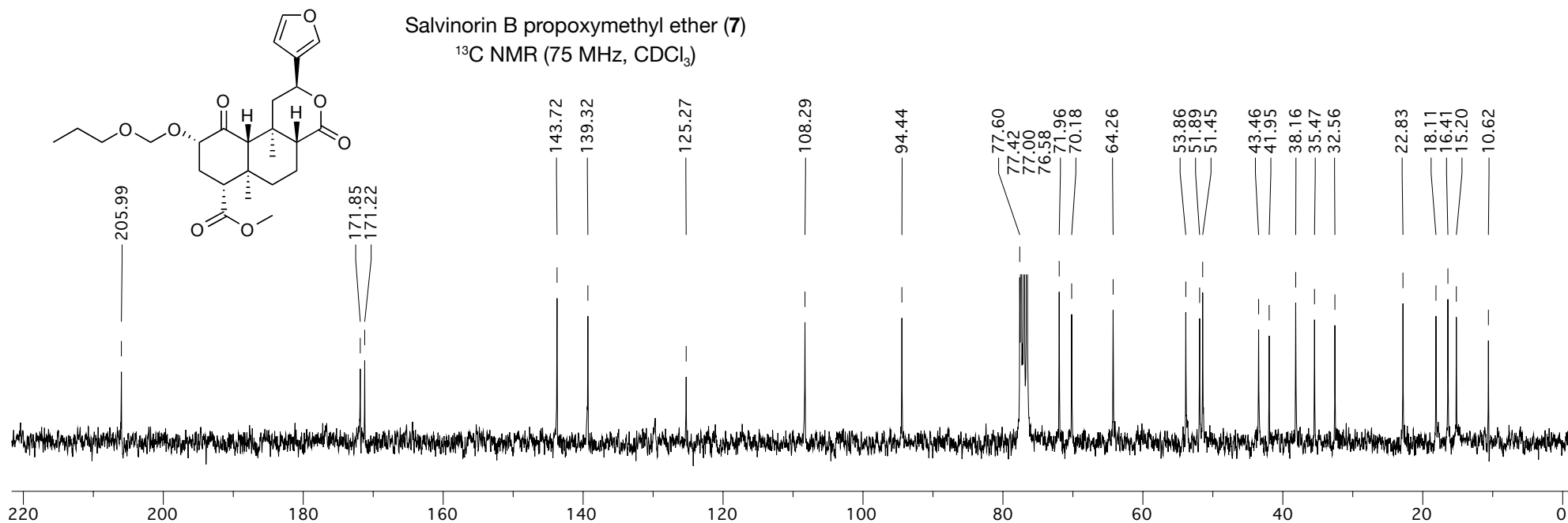


Salvinorin B ethoxymethyl ether (**6**)

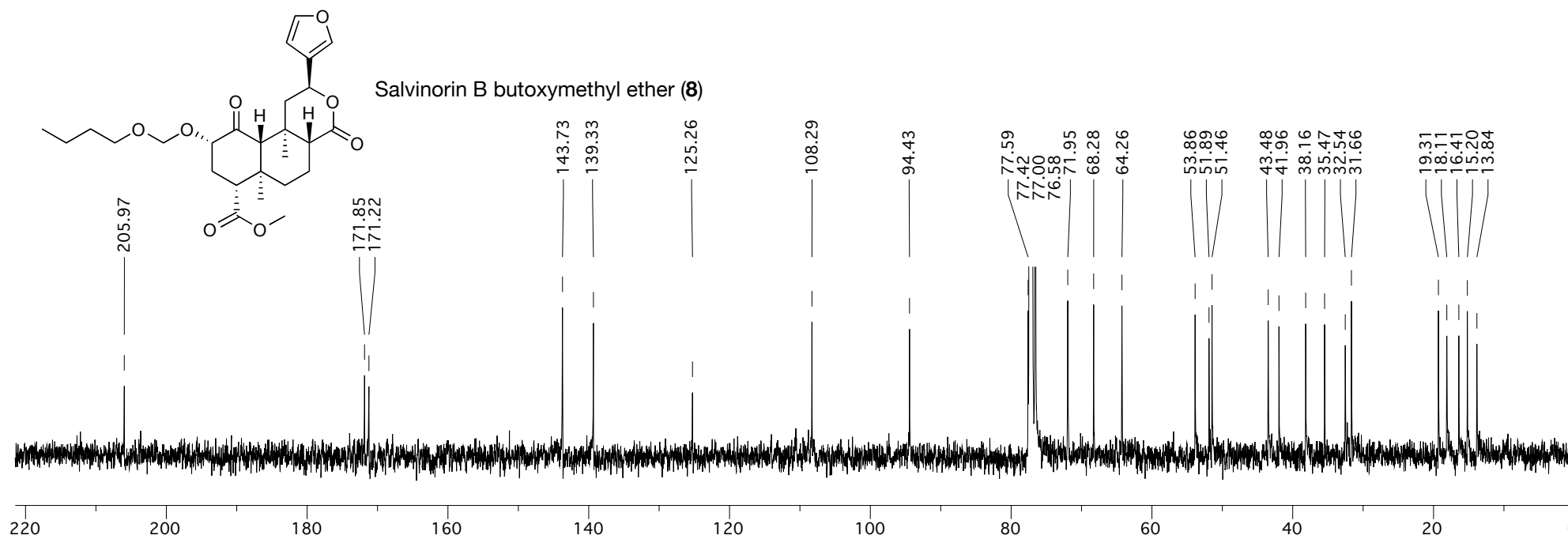


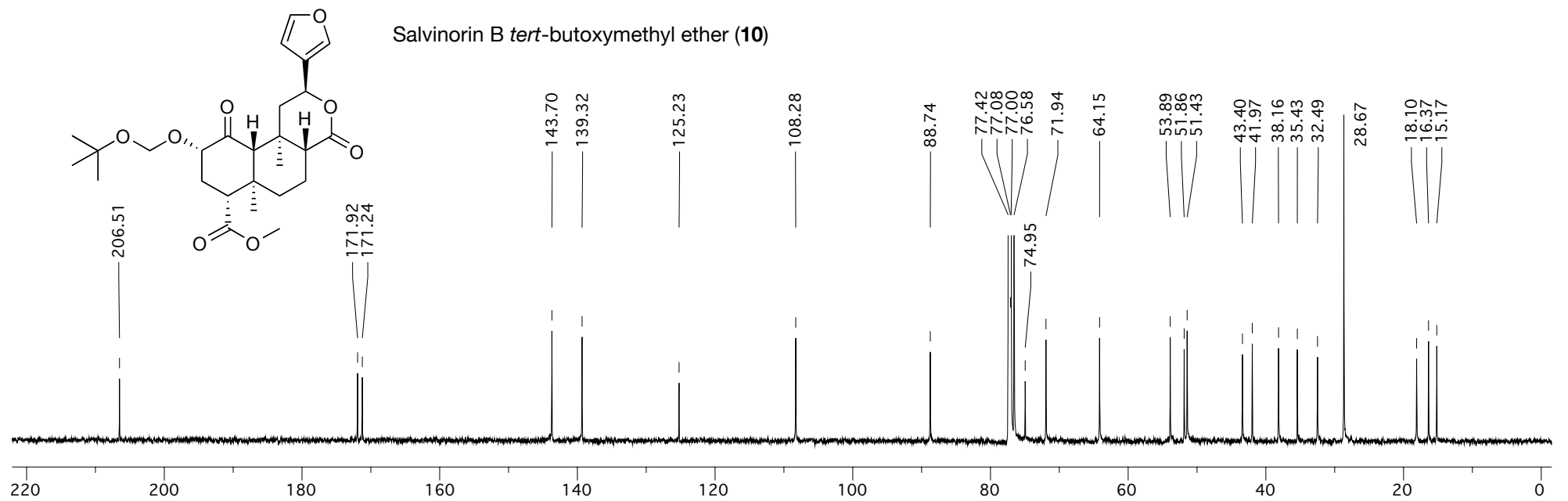
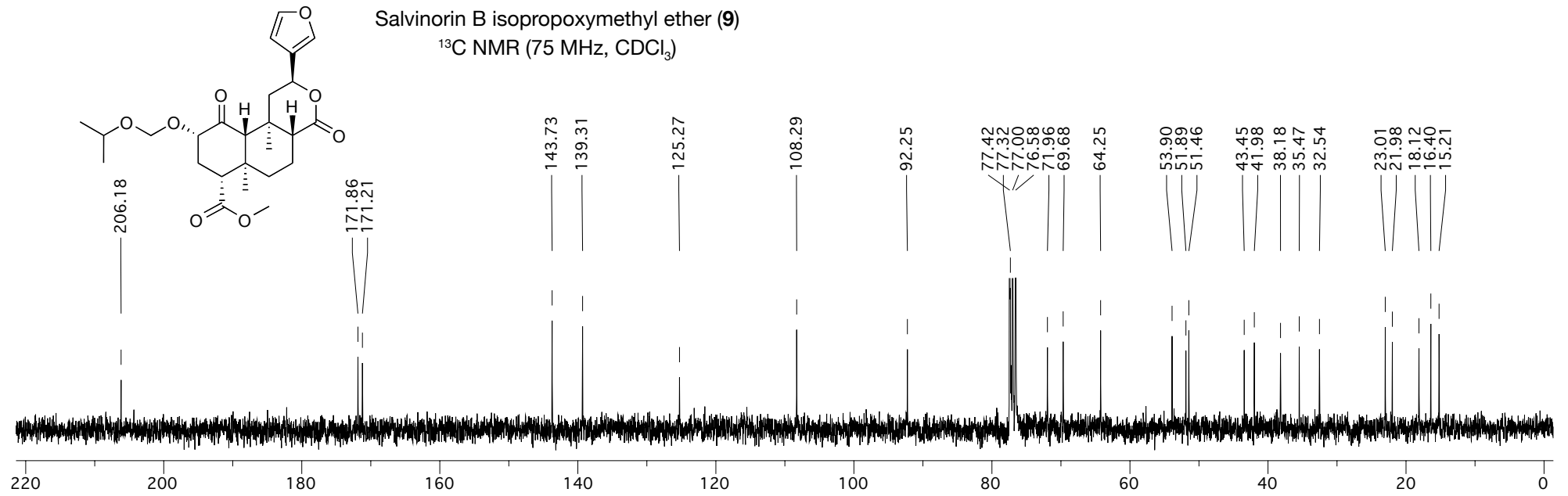
Salvinorin B propoxymethyl ether (**7**)

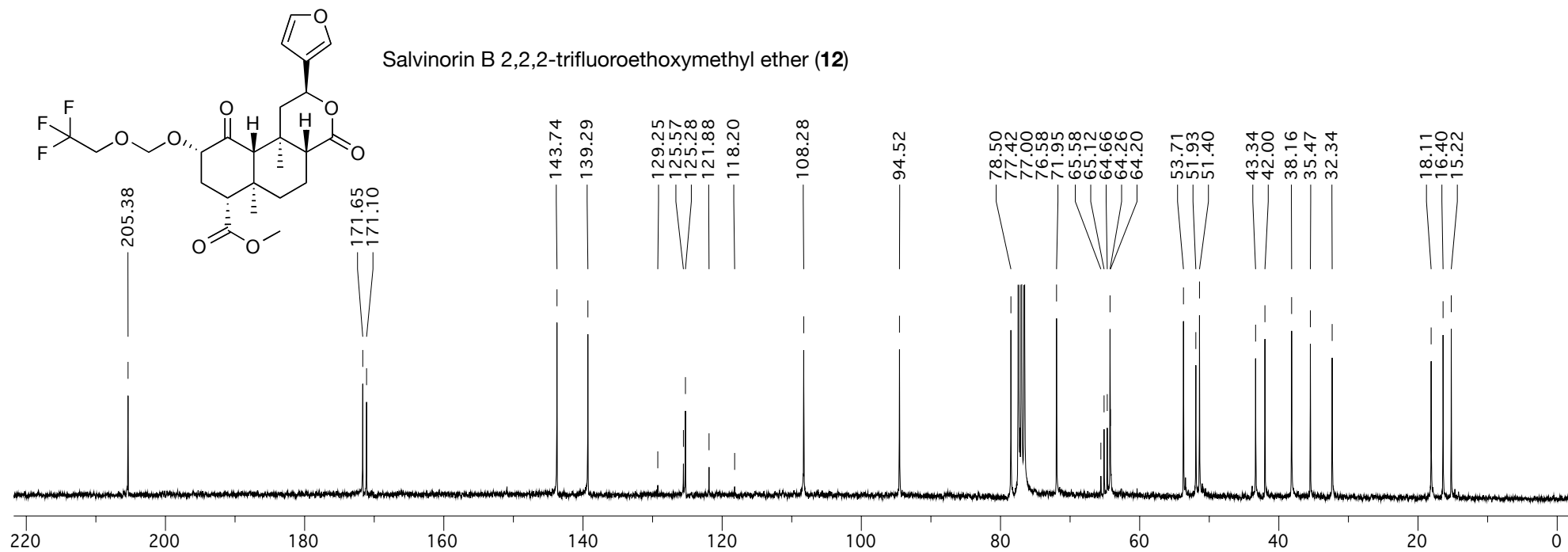
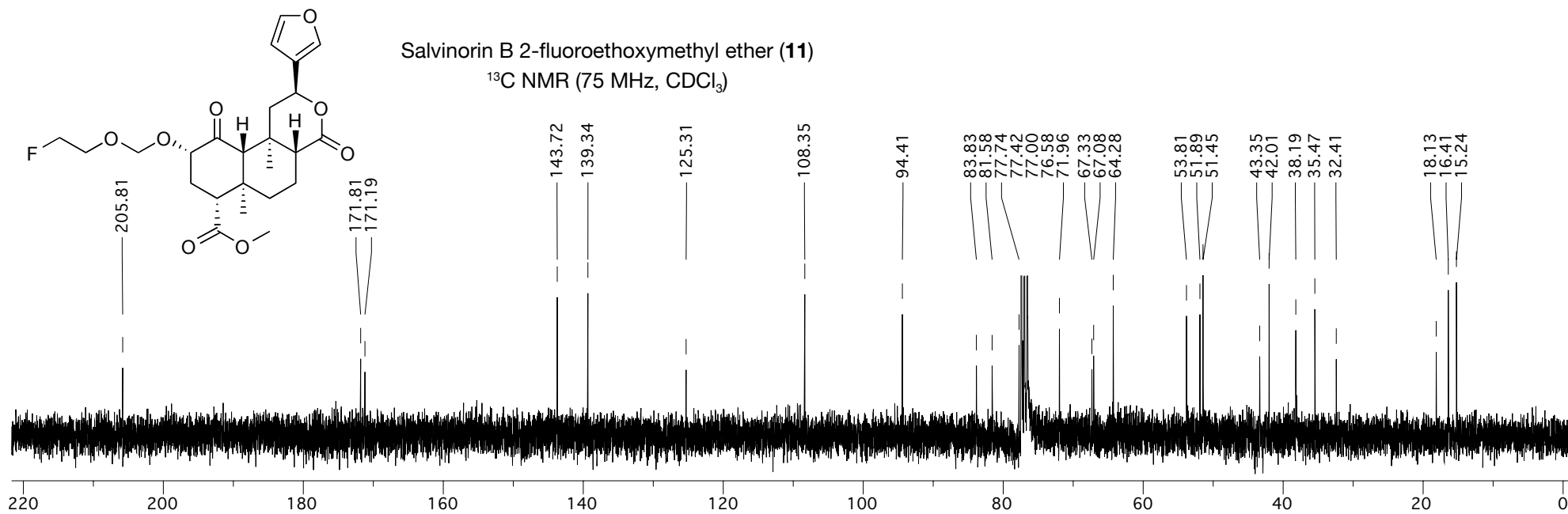
$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )

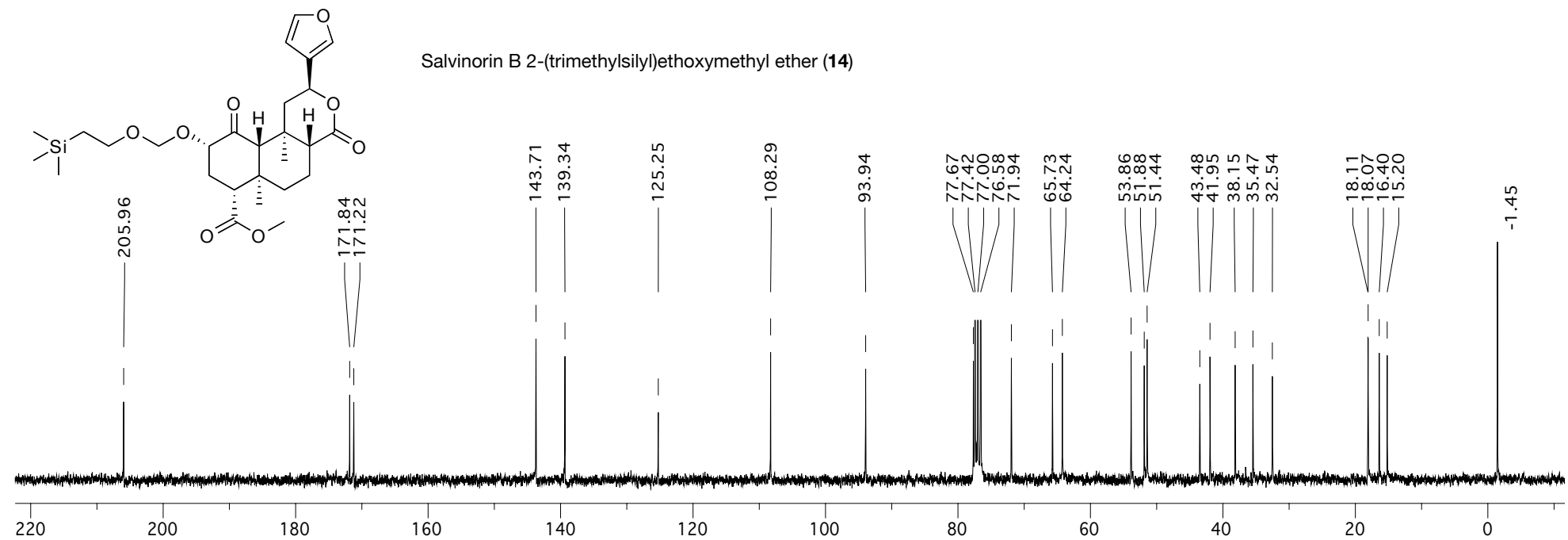
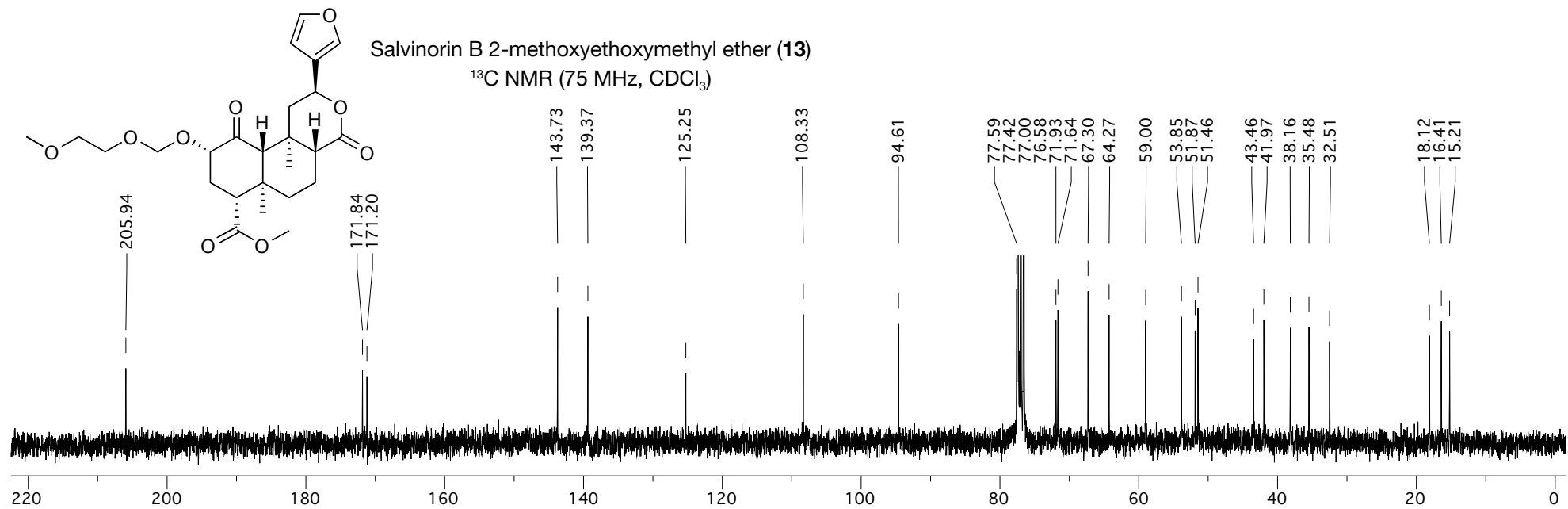


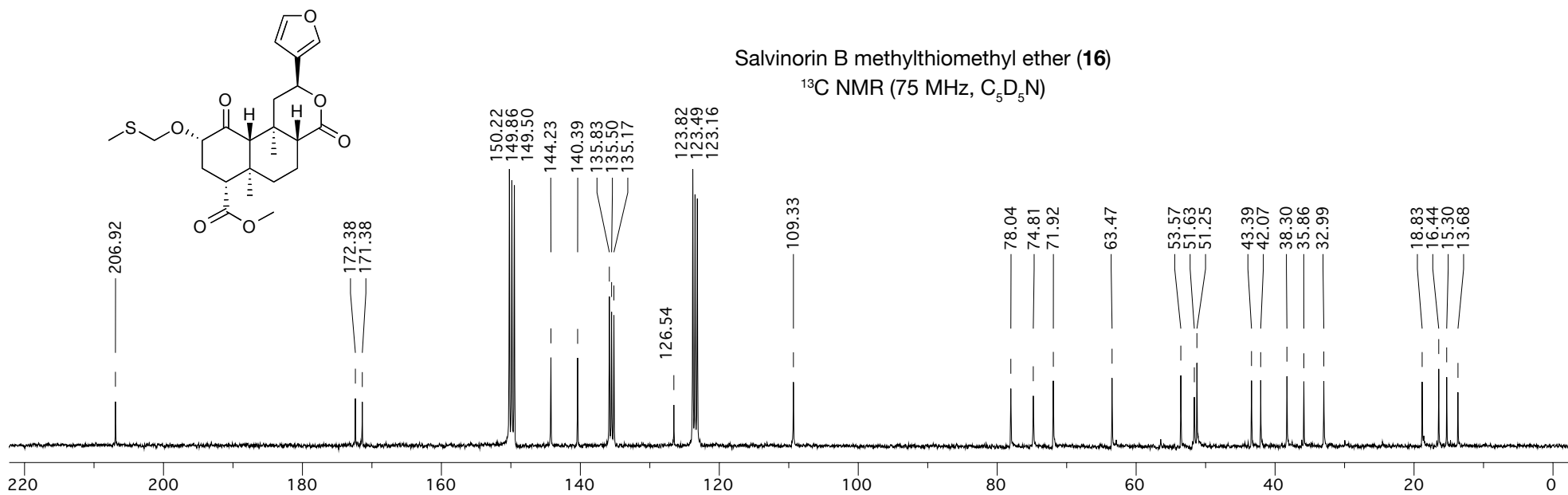
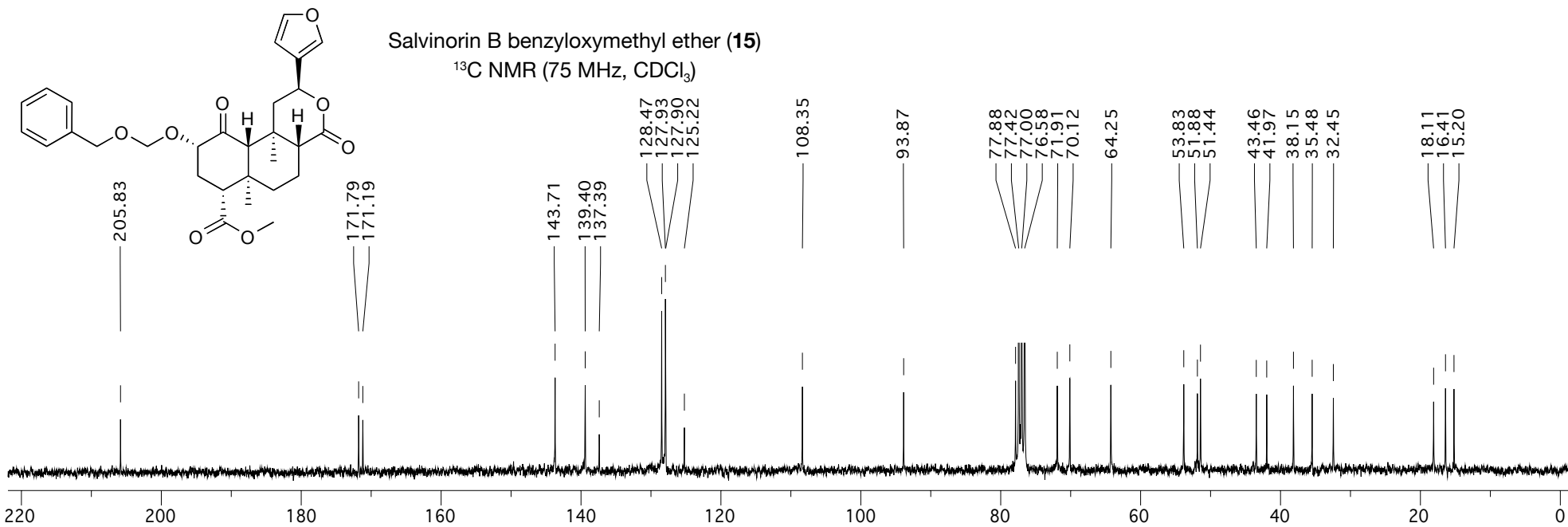
Salvinorin B butoxymethyl ether (**8**)





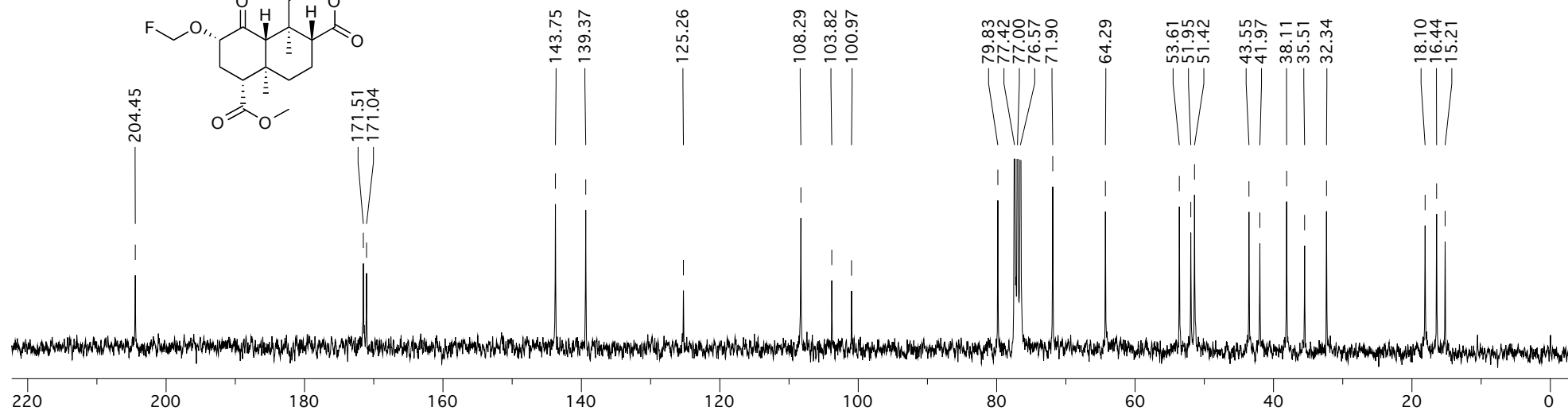






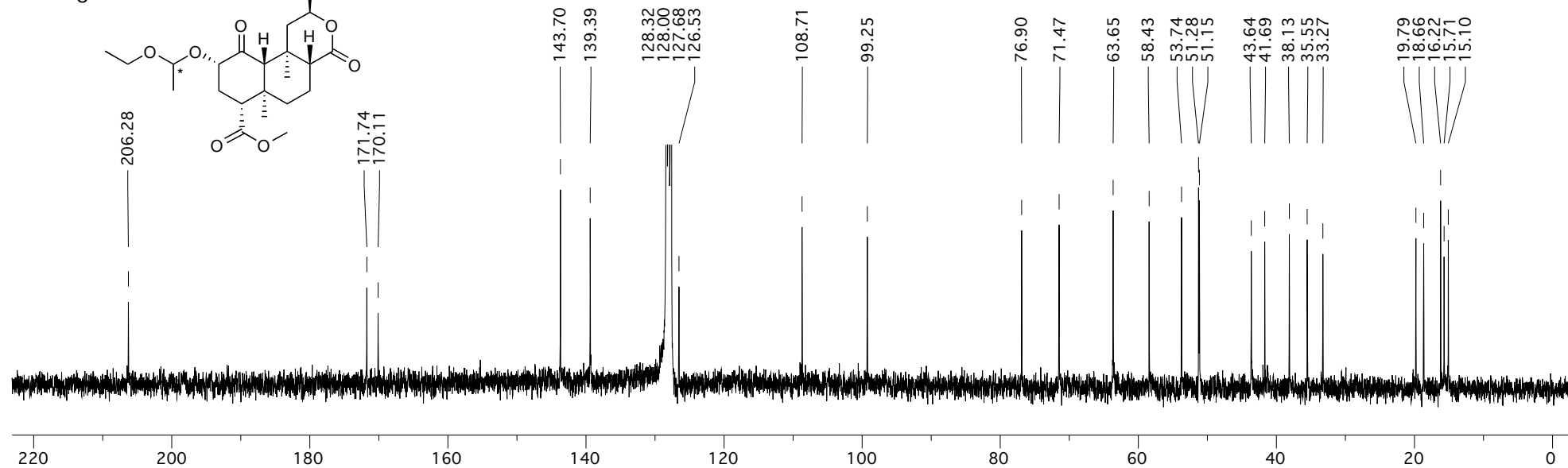


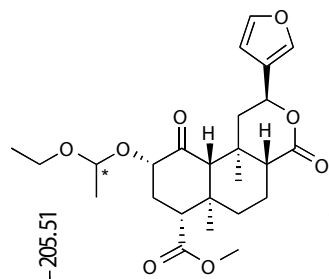
Salvinorin B fluoromethyl ether (**17**)  
 $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )



\* = configuration unknown

Salvinorin B 1-ethoxyethyl ether (**18a**)  
 $^{13}\text{C}$  NMR (75 MHz,  $\text{C}_6\text{D}_6$ )





Salvinator B 1-ethoxyethyl ether (18b)

$^{13}\text{C}$  NMR (75 MHz,  $\text{C}_6\text{D}_6$ )

205.51  
171.79  
170.10  
\* = configuration unknown

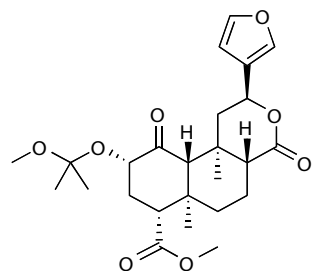
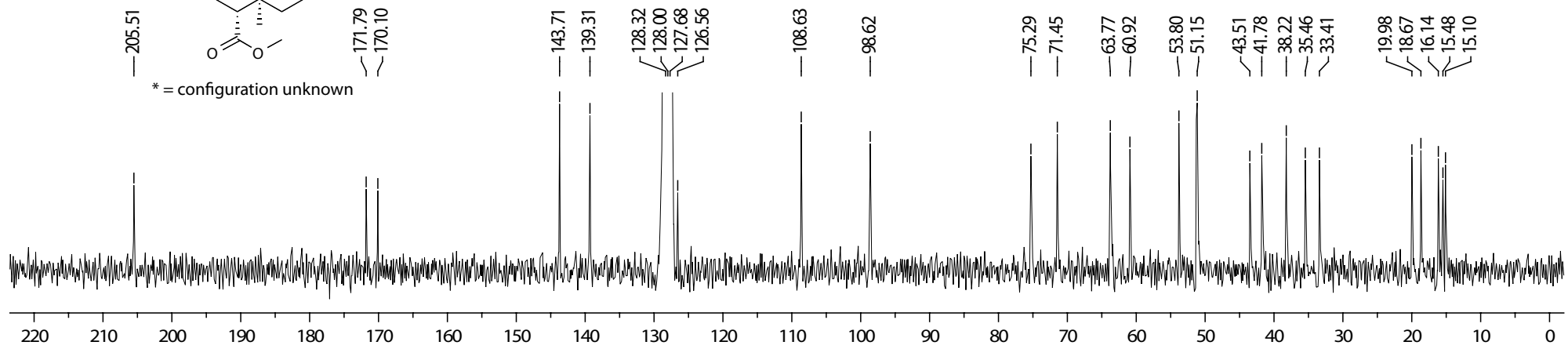
143.71  
139.31  
128.32  
128.00  
127.68  
126.56

108.63  
98.62

75.29  
71.45  
63.77  
60.92

53.80  
51.15  
43.51  
41.78  
38.22  
35.46  
33.41

19.98  
18.67  
16.14  
15.48  
15.10



Salvinator B 2-methoxy-2-propyl ether (19)

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )

206.55  
171.88  
171.18

143.69  
139.38  
125.29

108.30  
101.33

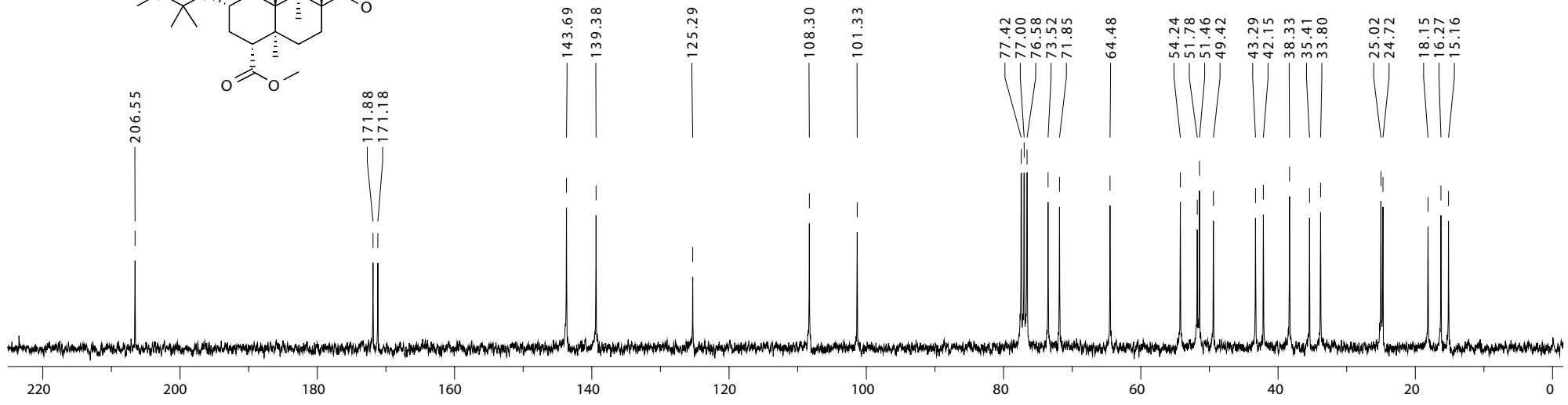
77.42  
77.00  
76.58  
73.52  
71.85

64.48

54.24  
51.78  
51.46  
49.42

43.29  
42.15  
38.33  
35.41  
33.80

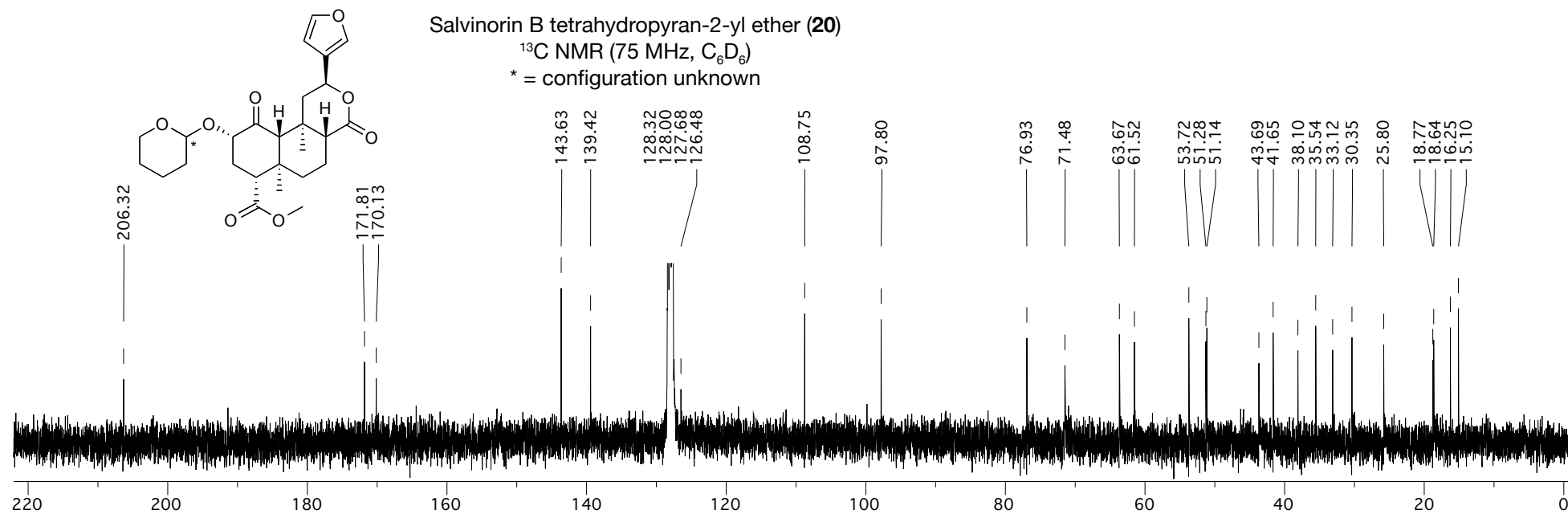
25.02  
24.72  
18.15  
16.27  
15.16



Salvinorin B tetrahydropyran-2-yl ether (**20**)

$^{13}\text{C}$  NMR (75 MHz,  $\text{C}_6\text{D}_6$ )

\* = configuration unknown



## Statement of author contributions

Munro selected the targets and synthetic routes, prepared compounds **5**, **7**, **8**, **16** and **17**, and wrote the manuscript. Duncan prepared compounds **6**, **9–15**, and **18–20**. Xu and Wang performed the binding assays and analyzed the results. Liu-Chen supervised Xu and Wang. Béguin directed the work of Duncan and Munro. Carlezon rewrote parts of the manuscript. Cohen supervised and coordinated the project.

## IUPAC International Chemical Identifiers (InChIs)

**1:** InChI=1/C23H28O8/c1-12(24)30-16-9-15(20(26)28-4)22(2)7-5-14-21(27)31-17  
(13-6-8-29-11-13)10-23(14,3)19(22)18(16)25/h6,8,11,14-17,19H,5,7,9-10H2,1-  
4H3/t14-,15-,16-,17-,19-,22-,23-/m0/s1

**2:** InChI=1/C21H26O7/c1-20-6-4-12-19(25)28-15(11-5-7-27-10-11)9-21(12,2)17  
(20)16(23)14(22)8-13(20)18(24)26-3/h5,7,10,12-15,17,22H,4,6,8-9H2,1-3H3/  
t12-,13-,14-,15-,17-,20-,21-/m0/s1

**3:** InChI=1/C22H26O8/c1-21-6-4-13-20(26)30-16(12-5-7-28-10-12)9-  
22(13,2)18(21)17(24)15(29-11-23)8-14(21)19(25)27-3/h5,7,10-11,13-16,18H,4,6,8-  
9H2,1-3H3/t13-,14-,15-,16-,18-,21-,22-/m0/s1

**4:** InChI=1/C23H30O7/c1-5-29-16-10-15(20(25)27-4)22(2)8-6-14-21(26)30-17(13-7-  
9-28-12-13)11-23(14,3)19(22)18(16)24/h7,9,12,14-17,19H,5-6,8,10-11H2,1-4H3/t14-  
,15-,16-,17-,19-,22-,23-/m0/s1

**5:** InChI=1/C23H30O8/c1-22-7-5-14-21(26)31-17(13-6-8-29-11-13)10-23(14,2)19(22)18(24)16(30-12-27-3)9-15(22)20(25)28-4/h6,8,11,14-17,19H,5,7,9-10,12H2,1-4H3/t14-,15-,16-,17-,19-,22-,23-/m0/s1

**6:** InChI=1/C24H32O8/c1-5-29-13-31-17-10-16(21(26)28-4)23(2)8-6-15-22(27)32-18(14-7-9-30-12-14)11-24(15,3)20(23)19(17)25/h7,9,12,15-18,20H,5-6,8,10-11,13H2,1-4H3/t15-,16-,17-,18-,20-,23-,24-/m0/s1

**7:** InChI=1/C25H34O8/c1-5-9-31-14-32-18-11-17(22(27)29-4)24(2)8-6-16-23(28)33-19(15-7-10-30-13-15)12-25(16,3)21(24)20(18)26/h7,10,13,16-19,21H,5-6,8-9,11-12,14H2,1-4H3/t16-,17-,18-,19-,21-,24-,25-/m0/s1

**8:** InChI=1/C26H36O8/c1-5-6-10-32-15-33-19-12-18(23(28)30-4)25(2)9-7-17-24(29)34-20(16-8-11-31-14-16)13-26(17,3)22(25)21(19)27/h8,11,14,17-20,22H,5-7,9-10,12-13,15H2,1-4H3/t17-,18-,19-,20-,22-,25-,26-/m0/s1

**9:** InChI=1/C25H34O8/c1-14(2)31-13-32-18-10-17(22(27)29-5)24(3)8-6-16-23(28)33-19(15-7-9-30-12-15)11-25(16,4)21(24)20(18)26/h7,9,12,14,16-19,21H,6,8,10-11,13H2,1-5H3/t16-,17-,18-,19-,21-,24-,25-/m0/s1

**10:** InChI=1/C26H36O8/c1-24(2,3)33-14-32-18-11-17(22(28)30-6)25(4)9-7-16-23(29)34-19(15-8-10-31-13-15)12-26(16,5)21(25)20(18)27/h8,10,13,16-19,21H,7,9,11-12,14H2,1-6H3/t16-,17-,18-,19-,21-,25-,26-/m0/s1

**11:** InChI=1/C24H31FO8/c1-23-6-4-15-22(28)33-18(14-5-8-30-12-14)11-24(15,2)20(23)19(26)17(32-13-31-9-7-25)10-16(23)21(27)29-3/h5,8,12,15-18,20H,4,6-7,9-11,13H2,1-3H3/t15-,16-,17-,18-,20-,23-,24-/m0/s1

**12:** InChI=1/C24H29F3O8/c1-22-6-4-14-21(30)35-17(13-5-7-32-10-13)9-23(14,2)19(22)18(28)16(8-15(22)20(29)31-3)34-12-33-11-24(25,26)27/h5,7,10,14-17,19H,4,6,8-9,11-12H2,1-3H3/t14-,15-,16-,17-,19-,22-,23-/m0/s1

**13:** InChI=1/C25H34O9/c1-24-7-5-16-23(28)34-19(15-6-8-31-13-15)12-25(16,2)21(24)20(26)18(11-17(24)22(27)30-4)33-14-32-10-9-29-3/h6,8,13,16-19,21H,5,7,9-12,14H2,1-4H3/t16-,17-,18-,19-,21-,24-,25-/m0/s1

**14:** InChI=1/C27H40O8Si/c1-26-9-7-18-25(30)35-21(17-8-10-32-15-17)14-27(18,2)23(26)22(28)20(13-19(26)24(29)31-3)34-16-33-11-12-36(4,5)6/h8,10,15,18-21,23H,7,9,11-14,16H2,1-6H3/t18-,19-,20-,21-,23-,26-,27-/m0/s1

**15:** InChI= 1/C29H34O8/c1-28-11-9-20-27(32)37-23(19-10-12-34-16-19)14-29(20,2)25(28)24(30)22(13-21(28)26(31)33-3)36-17-35-15-18-7-5-4-6-8-18/h4-8,10,12,16,20-23,25H,9,11,13-15,17H2,1-3H3/t20-,21-,22-,23-,25-,28-,29-/m0/s1

**16:** InChI=1/C23H30O7S/c1-22-7-5-14-21(26)30-17(13-6-8-28-11-13)10-23(14,2)19(22)18(24)16(29-12-31-4)9-15(22)20(25)27-3/h6,8,11,14-17,19H,5,7,9-10,12H2,1-4H3/t14-,15-,16-,17-,19-,22-,23-/m0/s1

**17:** InChI=1/C22H27FO7/c1-21-6-4-13-20(26)30-16(12-5-7-28-10-12)9-22(13,2)18(21)17(24)15(29-11-23)8-14(21)19(25)27-3/h5,7,10,13-16,18H,4,6,8-9,11H2,1-3H3/t13-,14-,15-,16-,18-,21-,22-/m0/s1

**18:** InChI=1/C25H34O8/c1-6-31-14(2)32-18-11-17(22(27)29-5)24(3)9-7-16-23(28)33-19(15-8-10-30-13-15)12-25(16,4)21(24)20(18)26/h8,10,13-14,16-19,21H,6-7,9,11-12H2,1-5H3/t14u,16-,17-,18-,19-,21-,24-,25-/m0/s1

**19:** InChI=1/C25H34O8/c1-23(2,30-6)33-17-11-16(21(27)29-5)24(3)9-7-15-22(28)32-18(14-8-10-31-13-14)12-25(15,4)20(24)19(17)26/h8,10,13,15-18,20H,7,9,11-12H2,1-6H3/t15-,16-,17-,18-,20-,24-,25-/m0/s1

**20:** InChI=1/C26H34O8/c1-25-9-7-16-24(29)34-19(15-8-11-31-14-15)13-26(16,2)22(25)21(27)18(12-17(25)23(28)30-3)33-20-6-4-5-10-32-20/h8,11,14,16-20,22H,4-7,9-10,12-13H2,1-3H3/t16-,17-,18-,19-,20u,22-,25-,26-/m0/s1