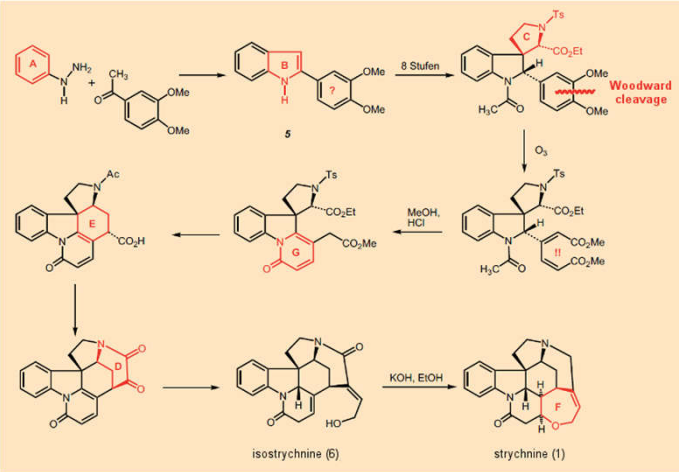
Total Synthesis of Strychnine



Heinrich O. Wieland
(1877-1957) 1927 NP

Woodward total synthesis of strychnine (1954)

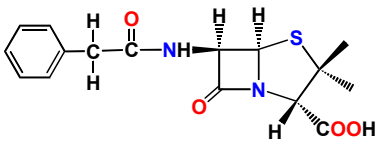
Structure and Synthesis of Penicillin

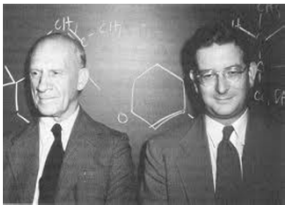
没有结构一切无从谈起

- For three decades after the discovery of natural penicillin by Sir Alexander Fleming, the source of the antibiotic hardly changed. Scientists made the drug by natural fermentation of *Penicillium* mold. However, during World War II, the United States government undertook a massive effort to determine the chemical structure of penicillin and to chemically synthesize it in large quantities.
- The scale of this project was compared to the development of the atomic bomb. This stemmed from the dire need for the antibiotic to treat soldiers on the battlefield. More than a thousand chemists working at thirty-nine laboratories were involved in the project. Despite the huge investment by the government, none proved to be successful in solving this elusive problem.

82

A well-known dispute about the Structure of Penicillin

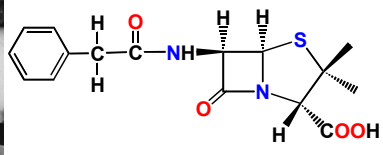


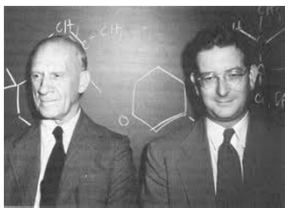


This incident is significant because Robinson refused to give much credence to spectroscopic data, while Woodward was a pioneer in using it for organic structure determination. It displays the generational gap between two of the greatest synthetic organic chemists of the twentieth century.

83

Structure of Penicillin



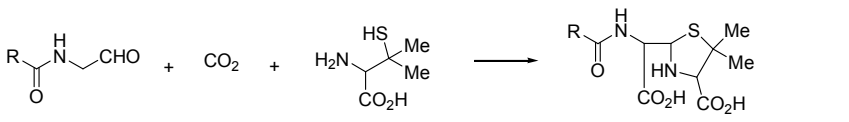


Penicillin G was proposed by Woodward in 1944 to contain a novel b-lactam in its structure based on degradation products, reaction profiles, and UV studies.

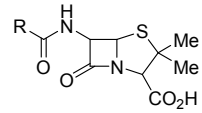
二战时期，英、美两国合作青霉素计划，化学组由R. Robinson 领导。但他的结构与伍德沃德的不同。伍德沃德的内酰胺(β-lactam)结构由钱恩(E. Chain)告诉罗氏，而后者老羞成怒，将桌上墨水瓶向钱恩掷去，幸未击中。青霉素的分子式，经X光晶体衍射求正，正如伍德沃德所想的一样。

84

Structure of Penicillin



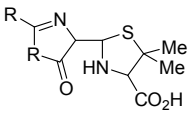
1944, 27岁



Abraham's correct structure

Woodward

OR



Robinson's incorrect structure

1944, 58岁

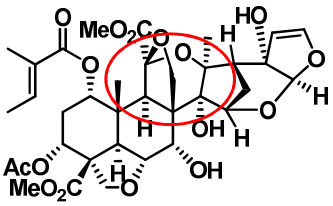
- Scheme 1. The notional reconstruction of penicillin from its degradation products.
- R = pent-2-enyl for the penicillin grown by fermentation in Oxford; R = benzyl for that grown in America. The difference was slightly confusing until clarified in 1943, but it did not affect the structural debates.

Edward Penley Abraham proposed b-lactam but opposed by Robinson

85

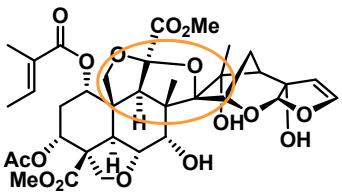
Azadirachtin印楝素

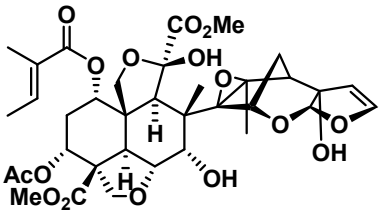
The First Complete Structure



Nakanishi's Azadirachtin 1975

Ley's Modification 1985





Correct Structure

X-ray 1986 by Ley

Broughton, H. B.; Ley, S. V. *J. Chem. Soc. Chem. Commun.* **1986**, 46.

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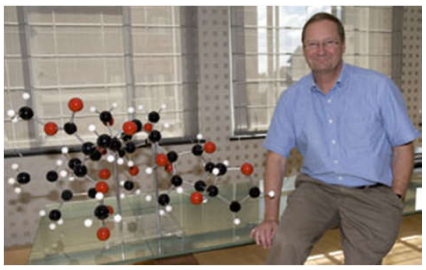
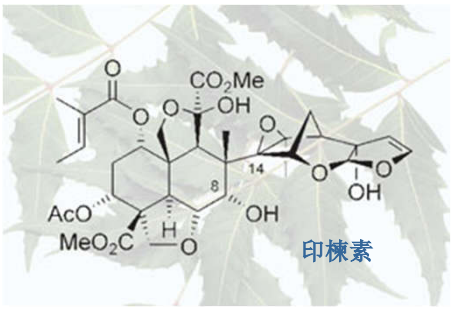
Azadirachtin sees first total synthesis

10 August 2007





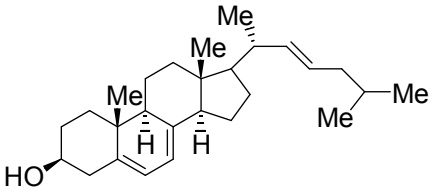
A complex natural product has finally succumbed to its first total synthesis after 22 years of attempts by eminent organic chemists.

87

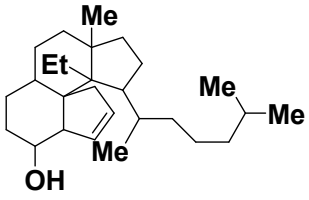
Heinrich O. Wieland

汪猷

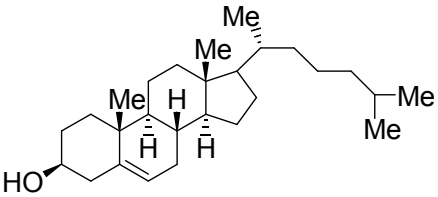
朱子清



Structure for Ergsterol 1932



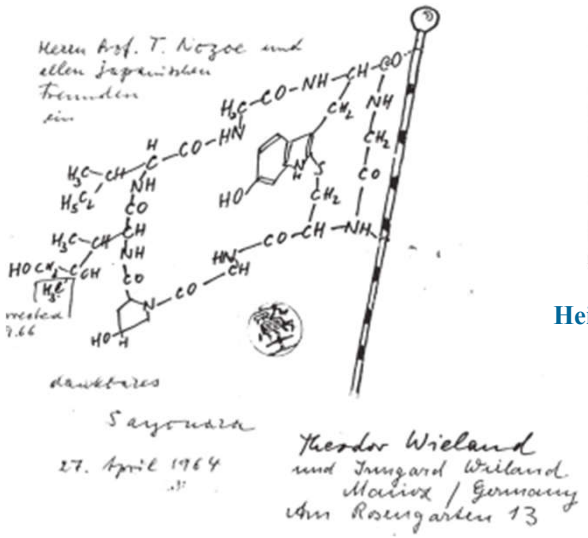
Structure for Cholesterol
Wieland/Windaus 1927 NP



Structure for Cholesterol 1932

Bernal, J. D. *Nature,* **1932**, *129*, 721.

88



Heinrich Otto Wieland

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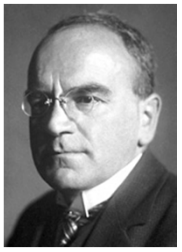
朱子清



H. O. Wieland 27 NP

Fritz Pregl 23NP

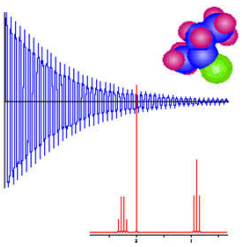
１９２９年在美国伊利诺大学研究院求学。１９３３年他获哲学博士学位。同年由伊利诺大学研究院化学系主任亚当斯（Ｒ·Ａｄａｍｓ）推荐，赴德国明兴大学从名师维兰德（Ｈ·Ｗｉｅｌａｎｄ）继续进行有机化学研究。１９３４年转赴奥地利格拉兹大学，跟随微量化学的首创人、诺贝尔奖金获得者普雷格尔（Ｆ·Ｐｒｅｇｌ）学习微量分析。１９３５年朱子清学成回国。１９５５年首先确定了该类植物碱的基本骨架为变型甾体。

90

波 谱 学

What we will learn?

How to use them?



91

An Historical Glance

Before 60's — **Chemistry** (gram quantities)
- Degradation
- Derivatization

Between 60-80's — **Spectra** (mg)
- UV, IR
- MS
- ^{1}H-NMR
- ^{13}C-NMR
- NOE, DEPT

After 80's — **2D NMR** (mg-μg)
- ^{1}H-^{1}H COSY
- HMQC (HSQC)
- HMBC
- NOESY (ROESY)
- INADEQUATE

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Strategy of Structure Elucidation

UV
IR
HR-MS
→ 化合物类型和共轭体系
官能团
分子式:双键, 环数, 杂原子

1D NMR

^{1}H-NMR
^{13}C-NMR
NOE
DEPT
→ H的个数和相互关系
C的个数和SP, SP^2, SP^3
H的空间关系
C的种类C, CH, CH_2, CH_3

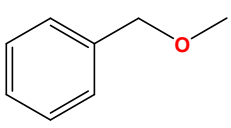
2D NMR

^{1}H-^{1}H COSY H-C-C-H
HMQC H-C
HMBC H-C-C, H-C-C-C, H-C-C=C-C
NOESY (ROESY) H-H conformation
INADEQUATE C-C

93

What Differences Between Them

$C_8H_{10}O$



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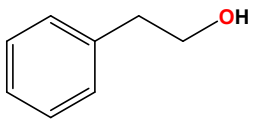
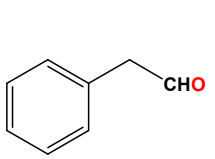


2

94

What Differences Between Them

C_8H_8O



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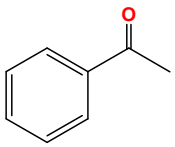
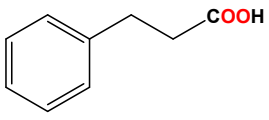


2

95

What Differences Between Them

$C_9H_{10}O_2$



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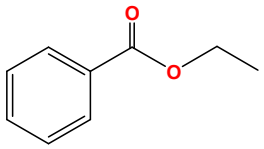

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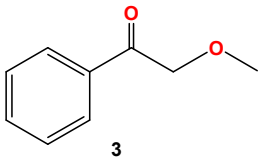

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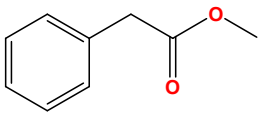

4

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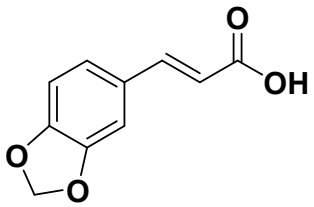
Structure Elucidation



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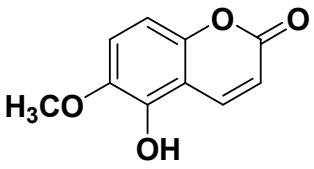


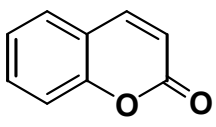
2

$C_{10}H_8O_4$

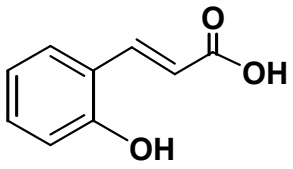
Difference of IR, ^{1}H-NMR, ^{13}C-NMR

97

1. How to Distinguish the Structures of A and B?



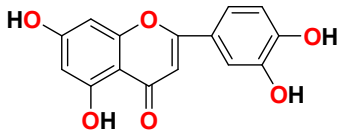
A



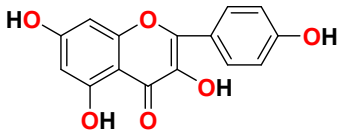
B

98

2. How to Distinguish the Structures of 1 and 2?



1

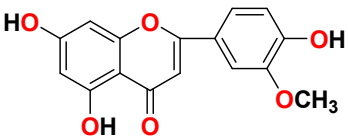


2

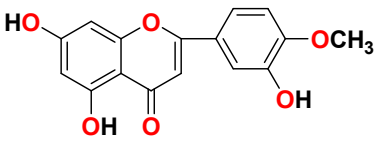
^{1}H-NMR?

99

3. How to Distinguish the Structures of 1 and 2?



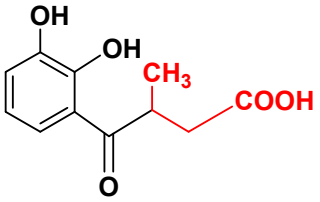
1



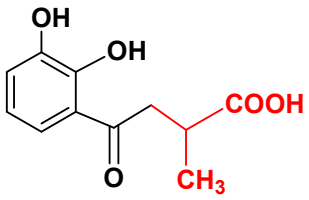
2

100

4. How to Distinguish A and B Using NMR?



(A)

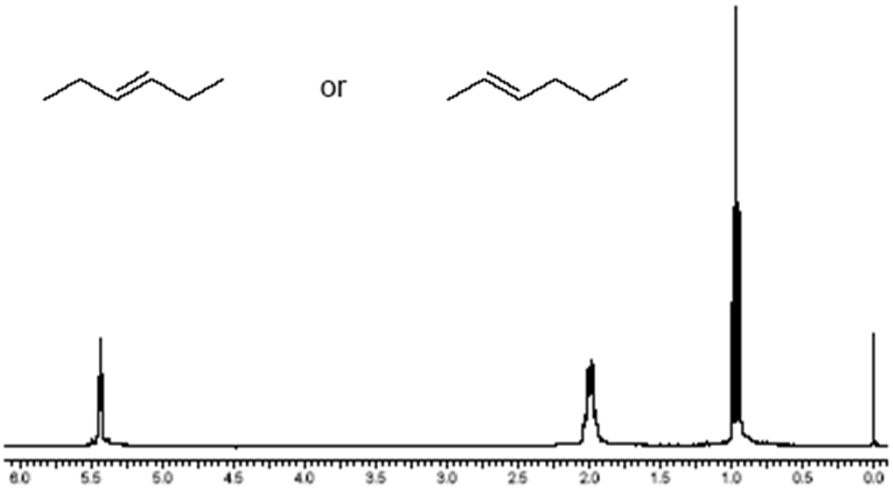


(B)

101

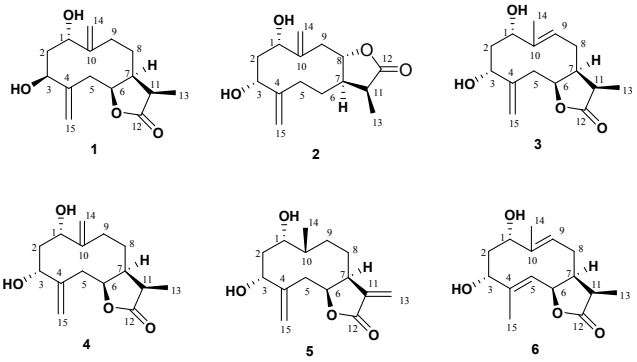
5. For each spectrum below, chose between the alternative compounds. Give your reasons.

or



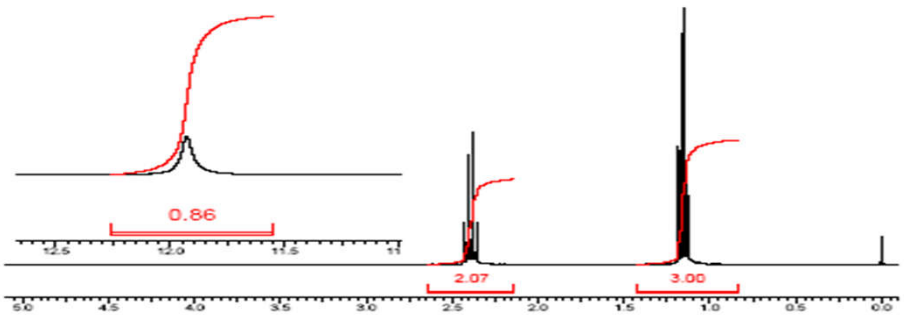
6. What Differences Between Them

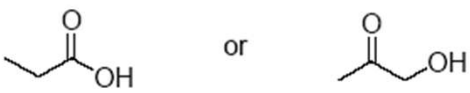
$C_{15}H_{22}O_4$



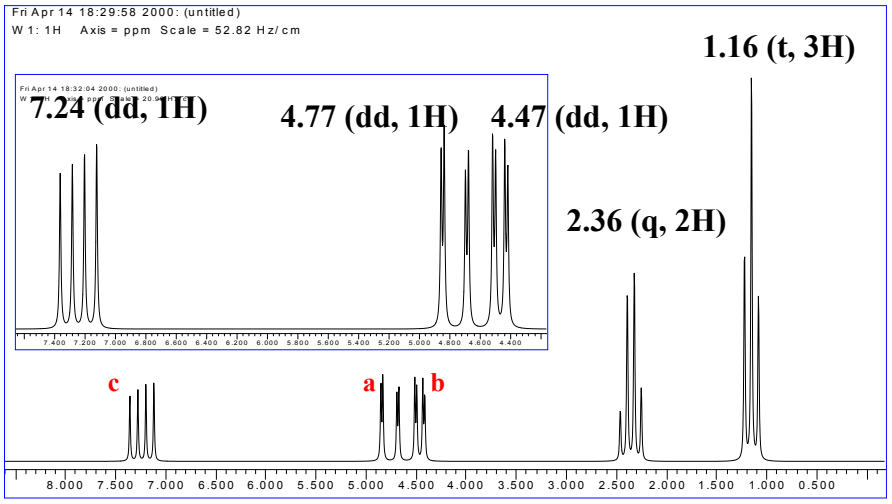
103

7. For each spectrum below, chose between the alternative compounds. Give your reasons.

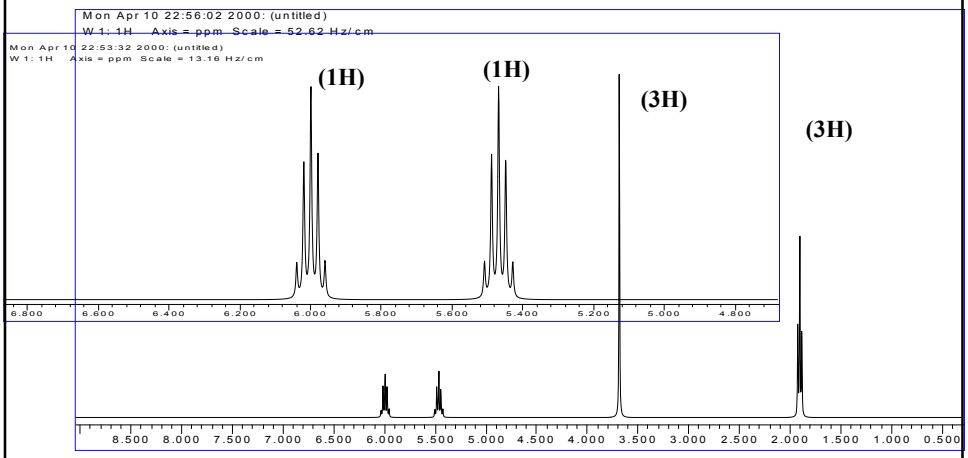




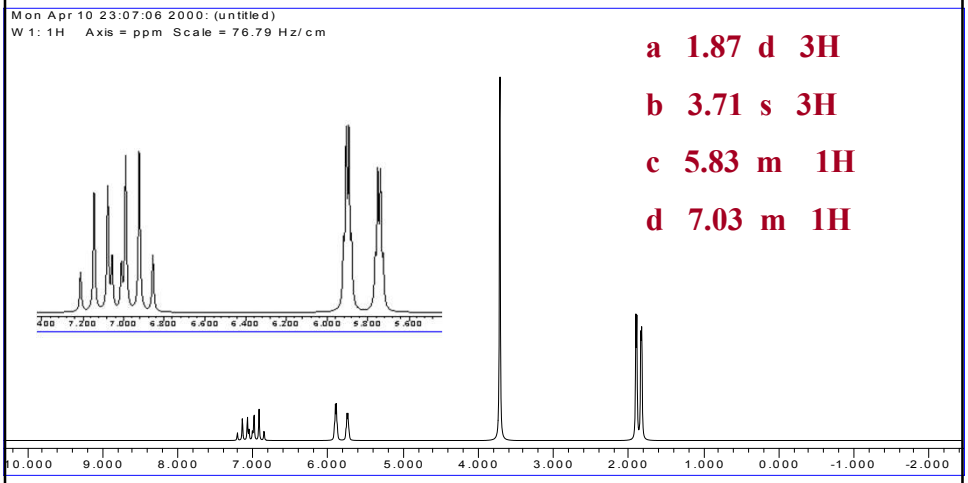
8. $C_5H_8O_2$的^{1}H-NMR谱如下, 推导其结构



9. $C_5H_8O_2$两种异构体的 ^{1}H-NMR谱如下，确定其结构　A 图



B 图 $C_5H_8O_2$



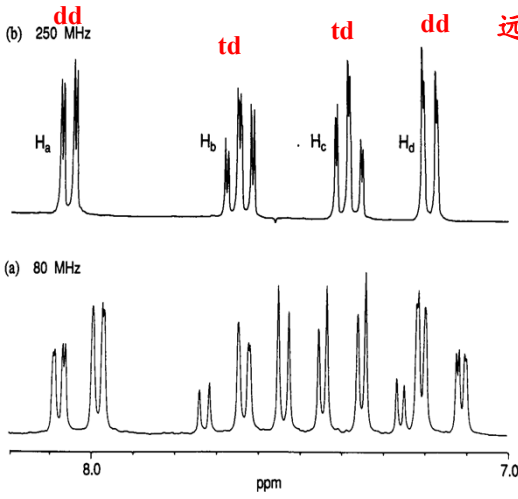
a 1.87 d 3H

b 3.71 s 3H

c 5.83 m 1H

d 7.03 m 1H

10. Assigin H_a, H_b, H_c and H_d of Aspirin?



远程耦合常数

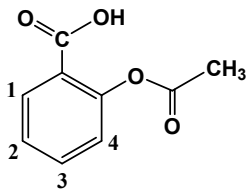
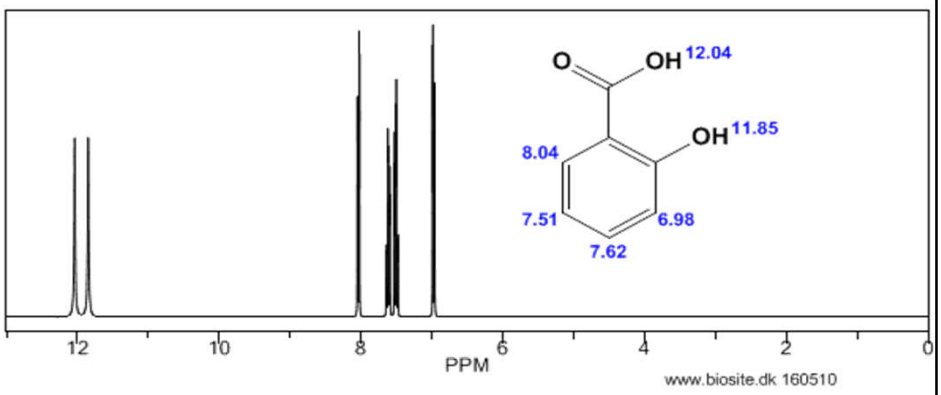
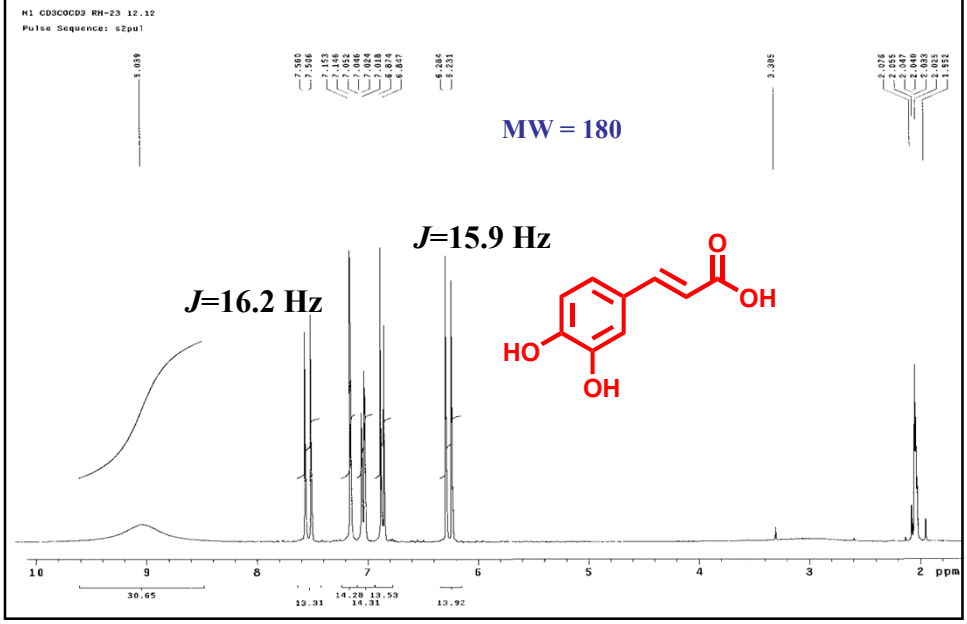


Fig. 0.1. (a) 80 and (b) 250 MHz ^1H spectra of aspirin in acetone-d_6 solution.

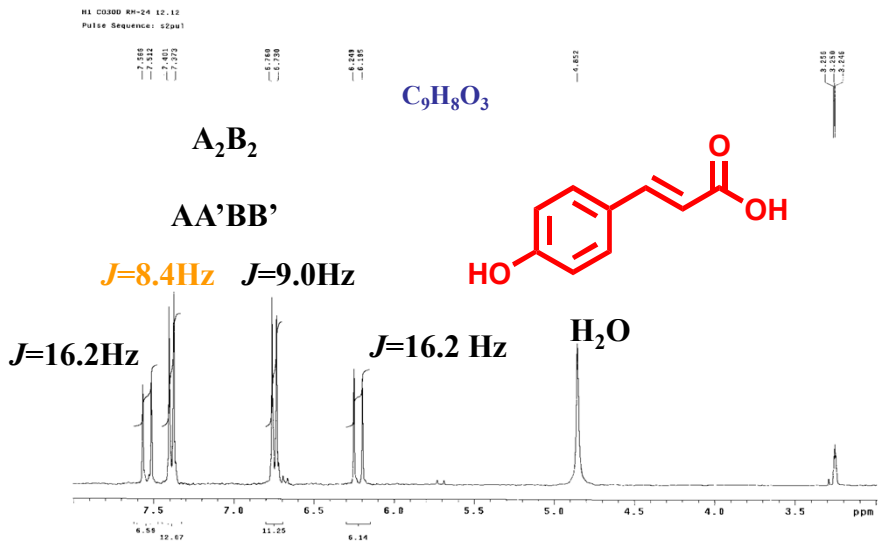
^{1}H-NMR of Salicylic Acid



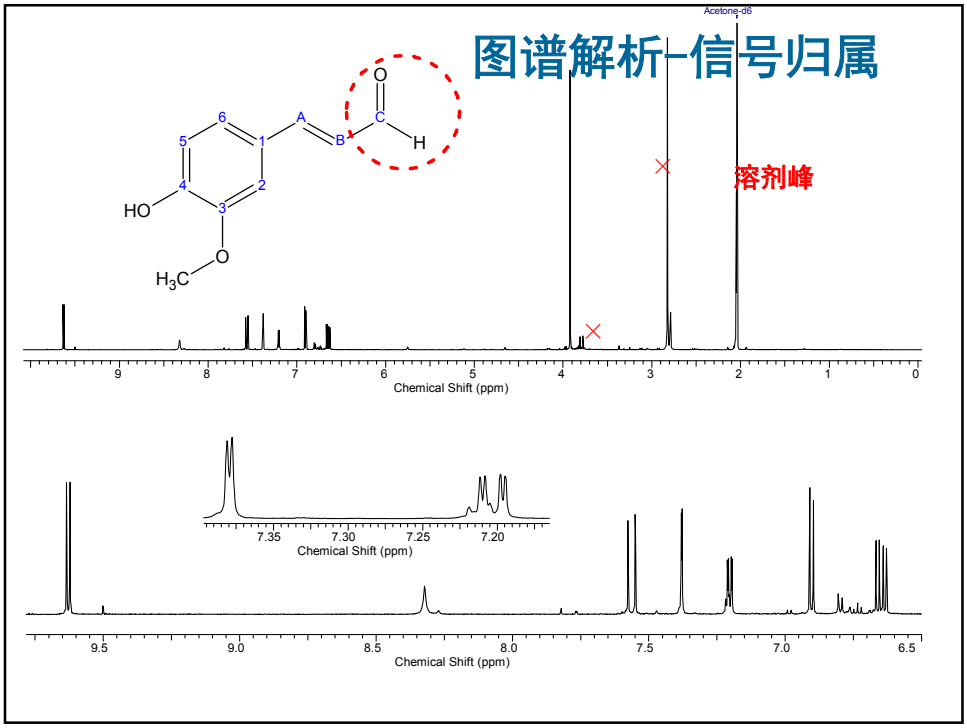
11. 图谱解析-信号归属



图谱解析-信号归属



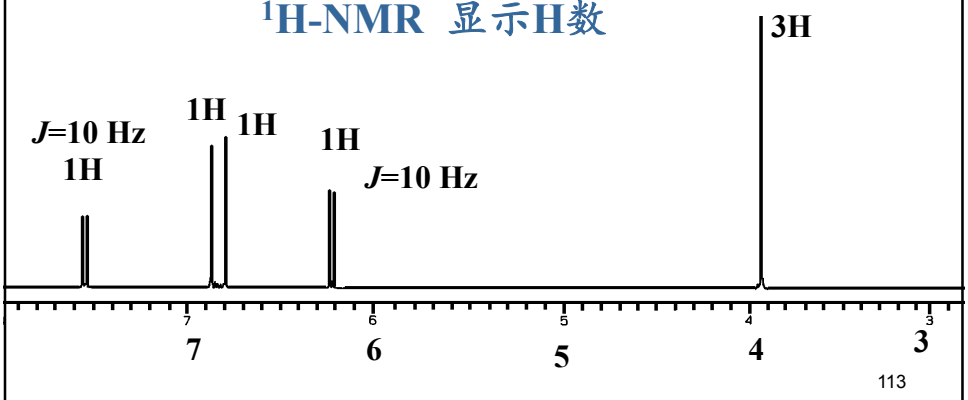
图谱解析-信号归属



12. 推断结构

从某一豆科植物中分离出一化合物，分子式为 $C_{10}H_8O_4$, *m/z*:192. 根据下列信息，推断其可能的结构。

^{1}H-NMR 显示H数



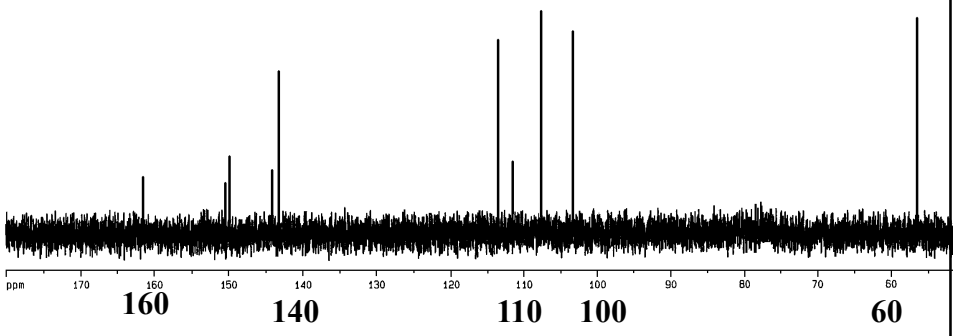
113

推断结构

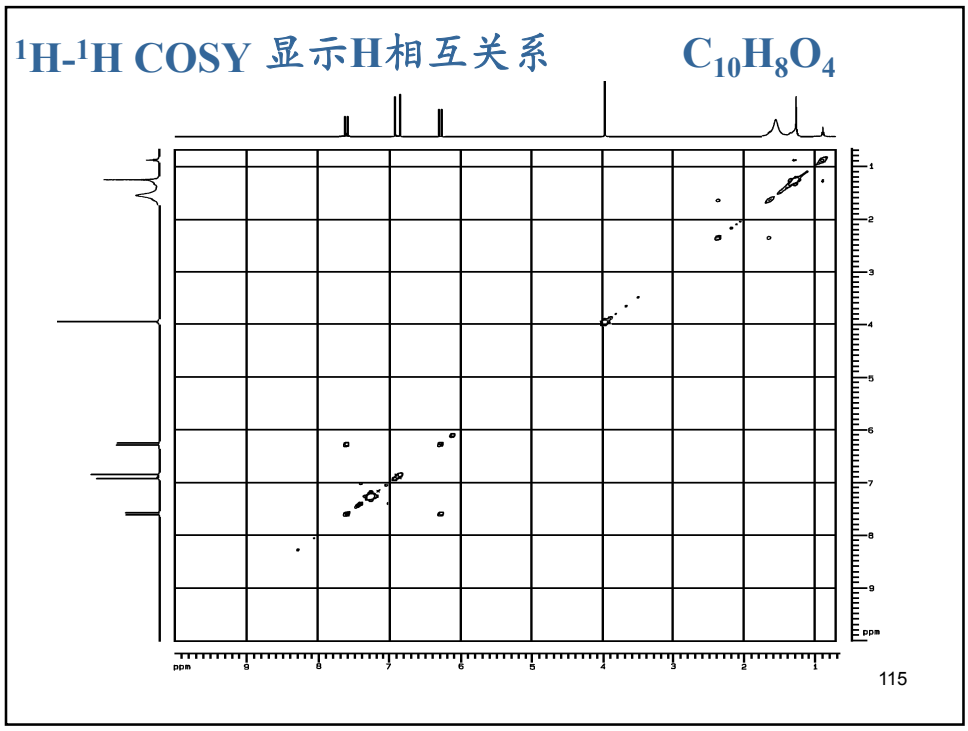
^{13}C-NMR

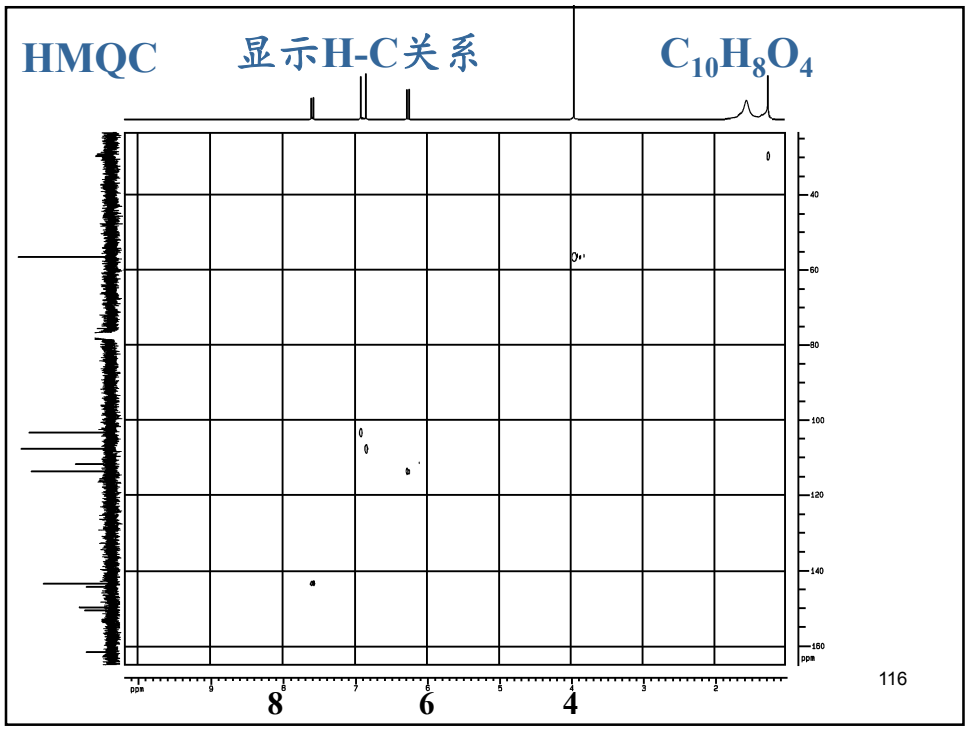
$C_{10}H_8O_4$

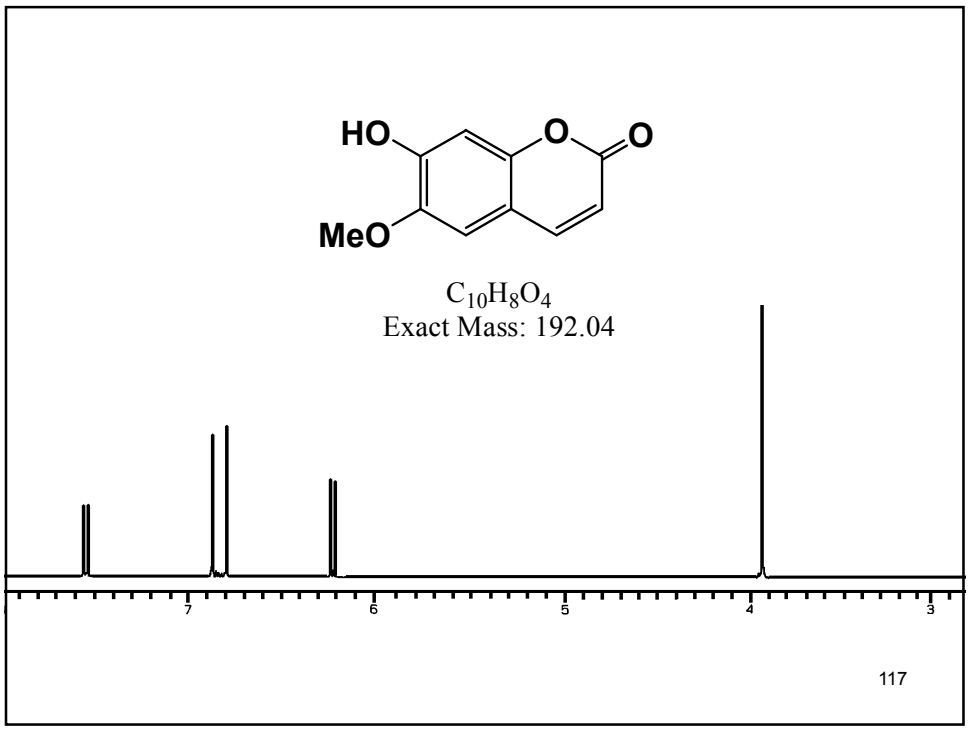
^{13}C-NMR 显示C数

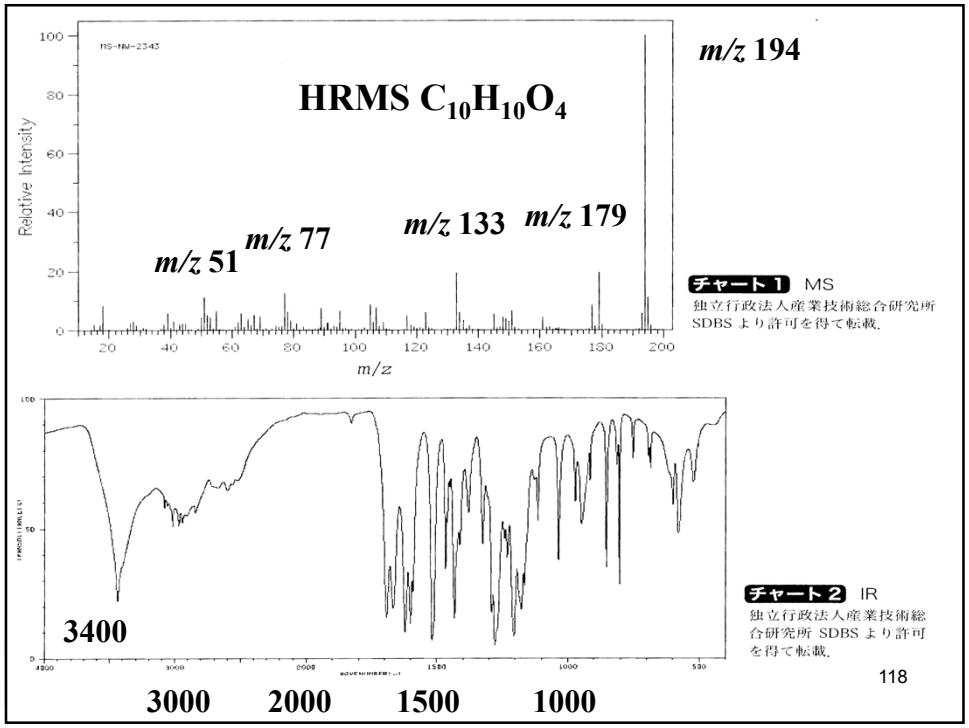


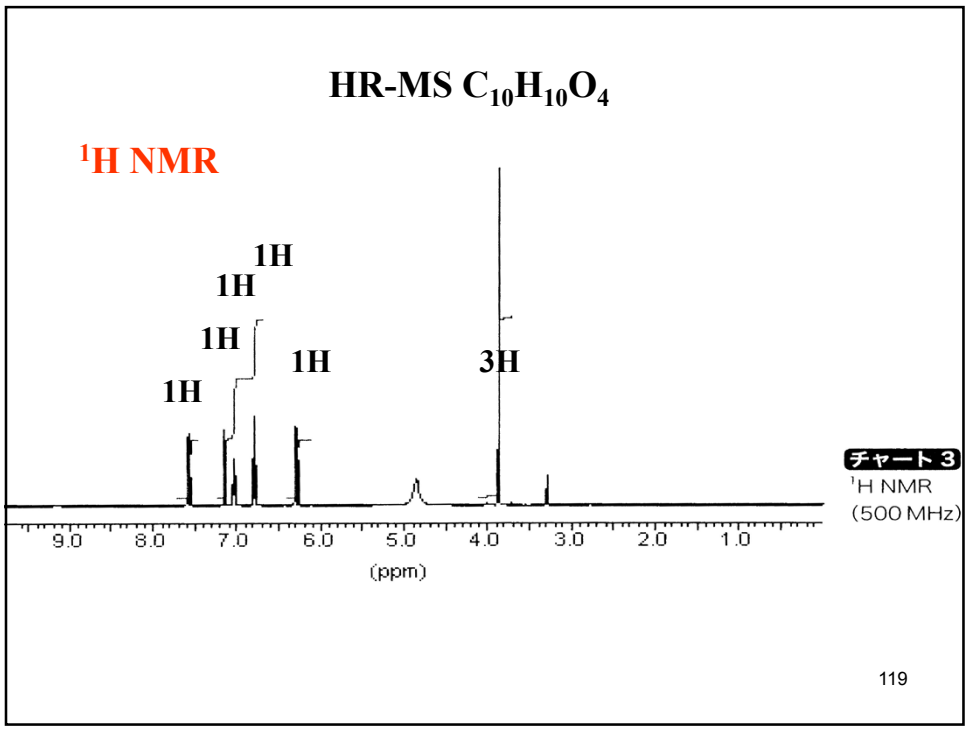
114

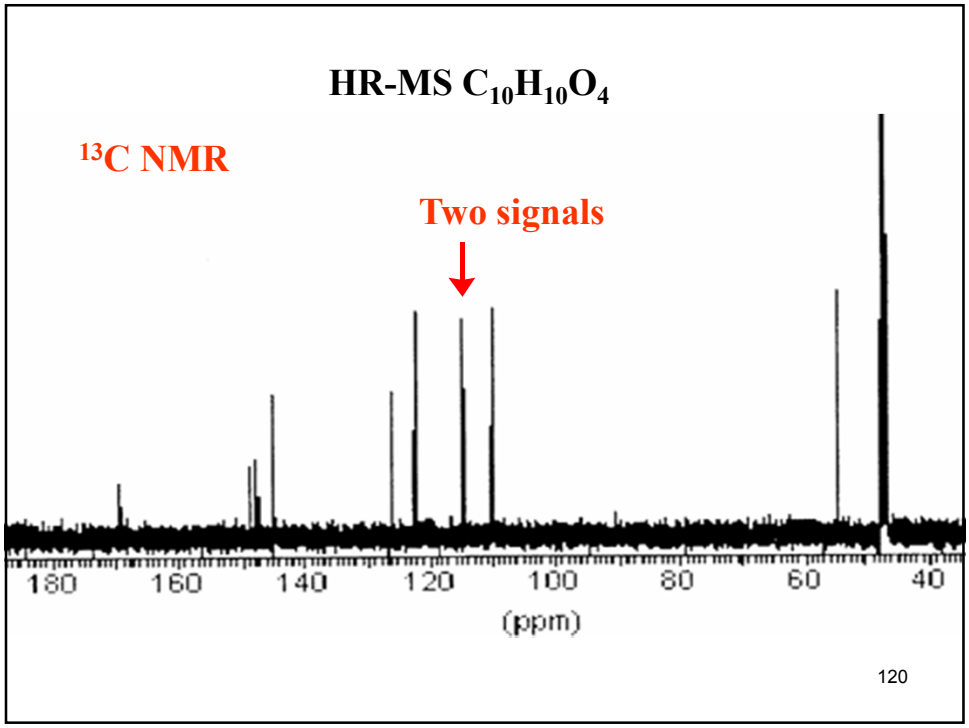

^{1}H-^{1}H COSY 显示H相互关系
$C_{10}H_8O_4$
115


HMQC
显示H-C关系
$C_{10}H_8O_4$
116

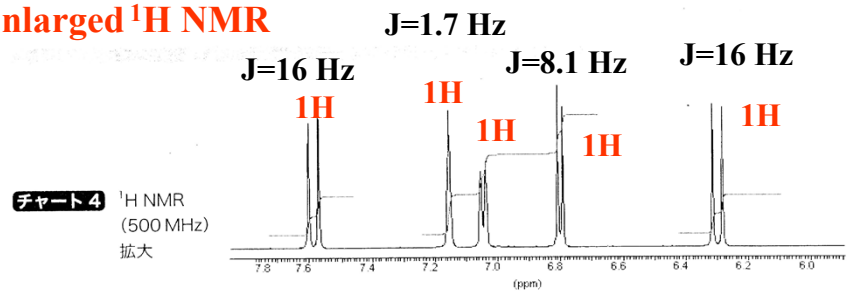

HO
O
O
MeO
$C_{10}H_8O_4$
Exact Mass: 192.04
7
6
5
4
3
117


HRMS $C_{10}H_{10}O_4$
m/z 194
m/z 51
m/z 77
m/z 133
m/z 179
Relative Intensity
m/z
チャート1 MS
独立行政法人産業技術総合研究所 SDBS より許可を得て転載.
3400
3000
2000
1500
1000
チャート2 IR
独立行政法人産業技術総合研究所 SDBS より許可を得て転載.
118

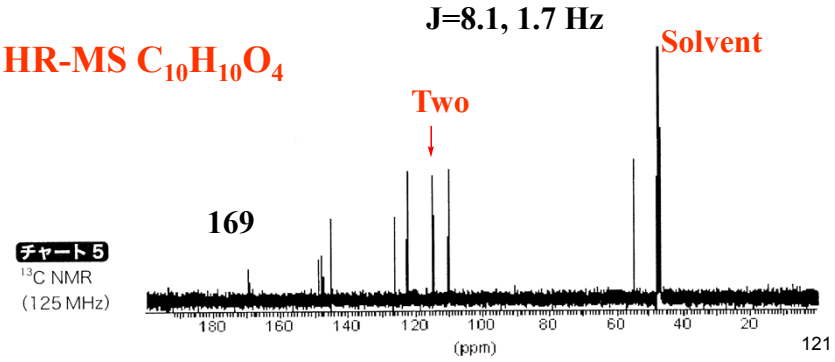

HR-MS $C_{10}H_{10}O_4$
^{1}H NMR
1H
1H
1H
1H
1H
3H
チャート 3
^{1}H NMR
(500 MHz)
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
(ppm)
119


HR-MS $C_{10}H_{10}O_4$
^{13}C NMR
Two signals
180
160
140
120
100
80
60
40
(ppm)
120

Enlarged ^{1}H NMR

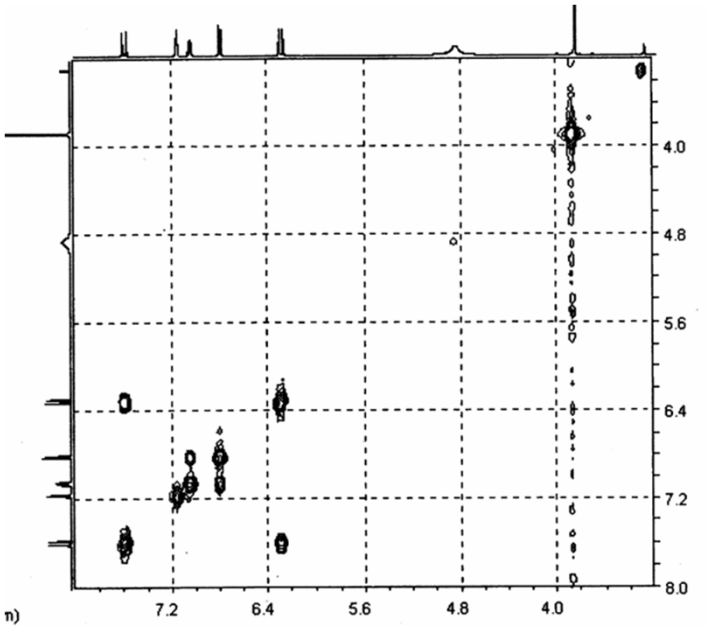


HR-MS $C_{10}H_{10}O_4$

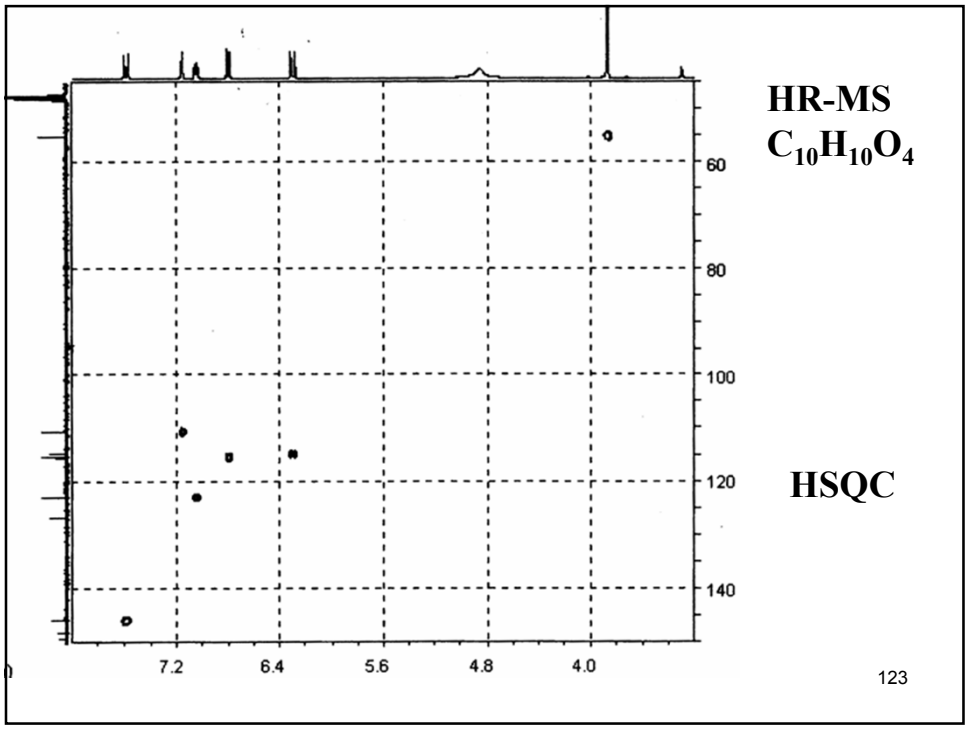


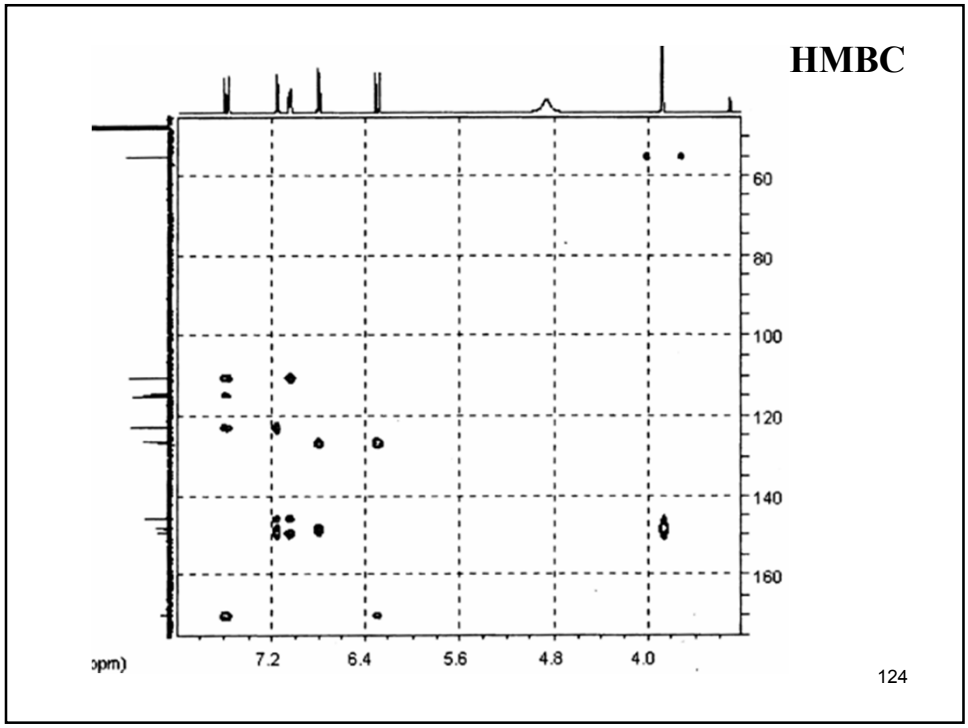
121

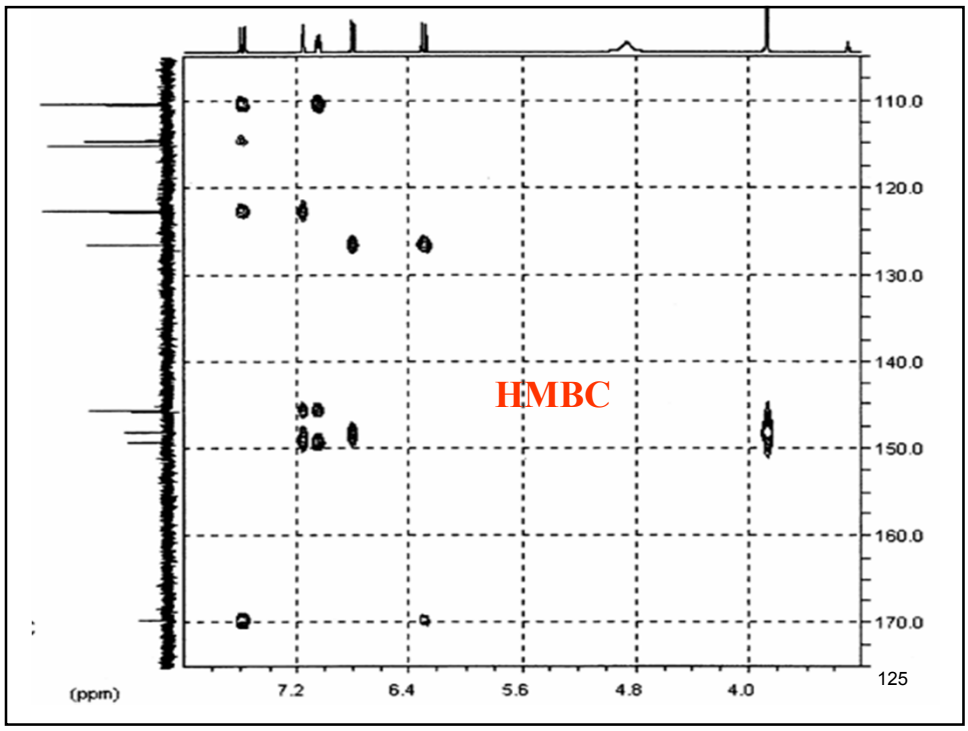
^{1}H-^{1}H COSY

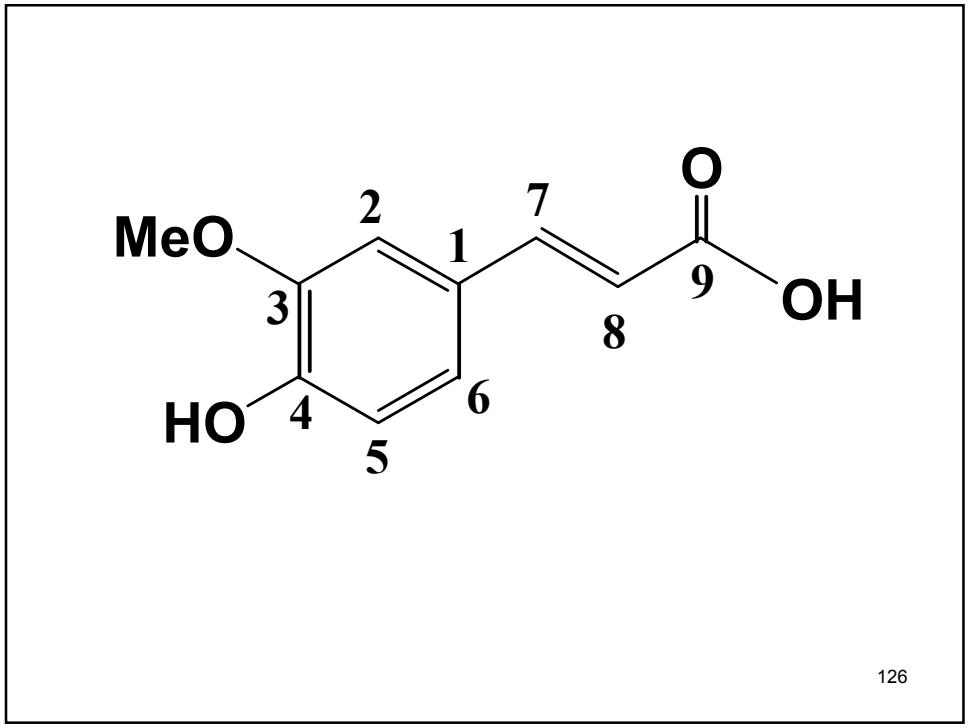


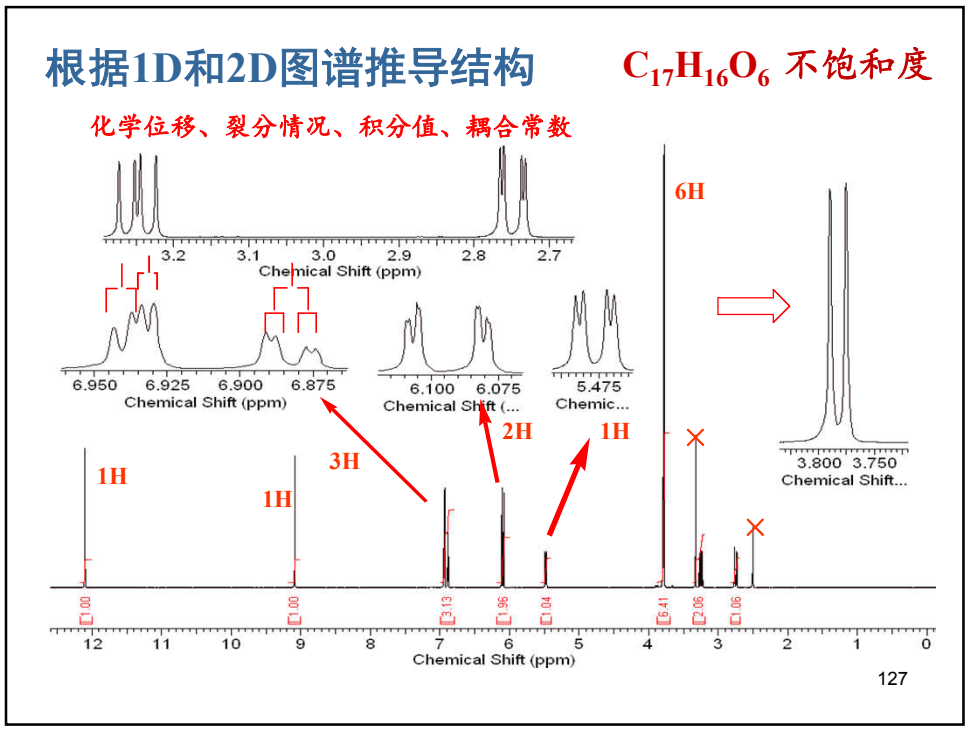
122

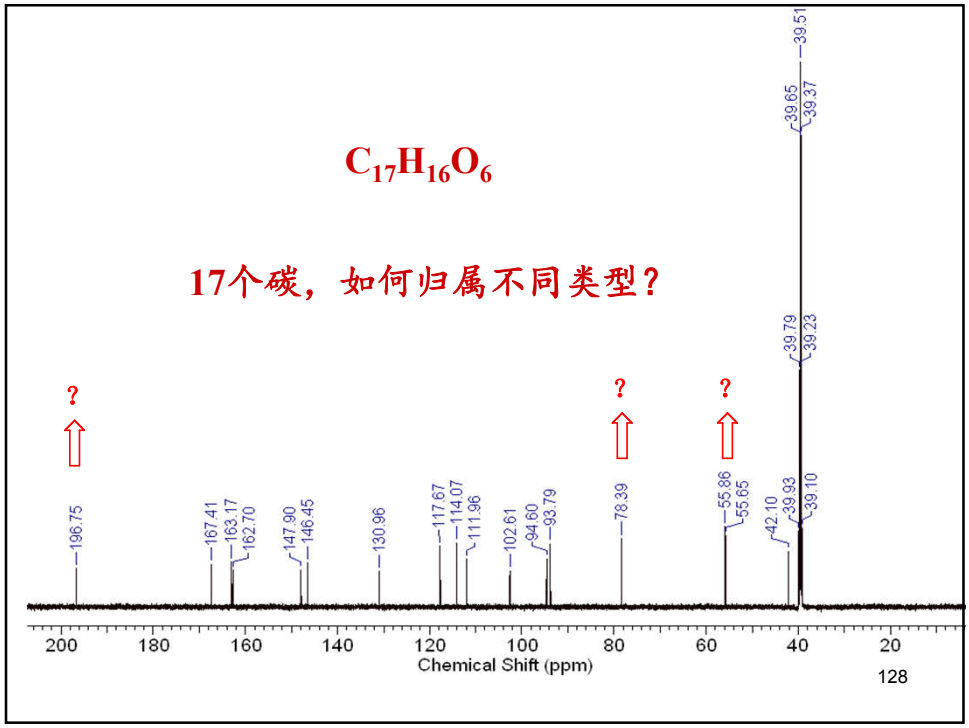

HR-MS
$C_{10}H_{10}O_4$
HSQC
60
80
100
120
140
7.2
6.4
5.6
4.8
4.0
123


HMBC
60
80
100
120
140
160
7.2
6.4
5.6
4.8
4.0
124

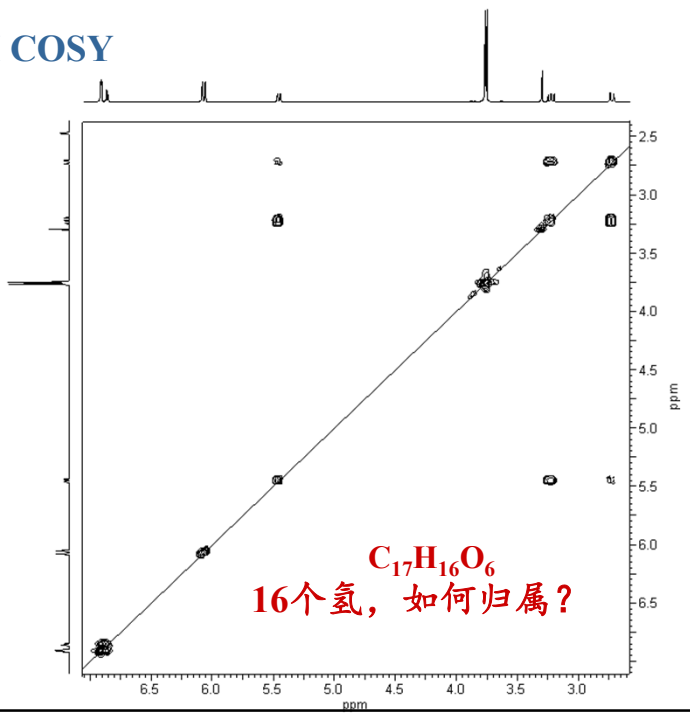

HMBC
110.0
120.0
130.0
140.0
150.0
160.0
170.0
(ppm)
7.2
6.4
5.6
4.8
4.0
125


MeO
HO
OH
O
1
2
3
4
5
6
7
8
9
126


根据1D和2D图谱推导结构
$C_{17}H_{16}O_6$ 不饱和度
化学位移、裂分情况、积分值、耦合常数
6H
1H
1H
3H
2H
1H
Chemical Shift (ppm)
127


$C_{17}H_{16}O_6$
17个碳，如何归属不同类型？
?
?
?
Chemical Shift (ppm)
128

^1H-^1H COSY

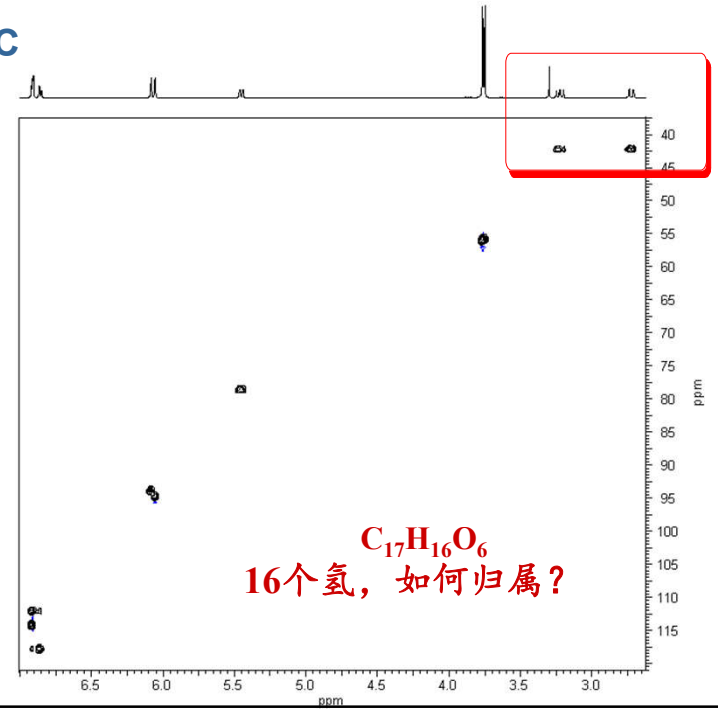


$C_{17}H_{16}O_6$

16个氢，如何归属？

129

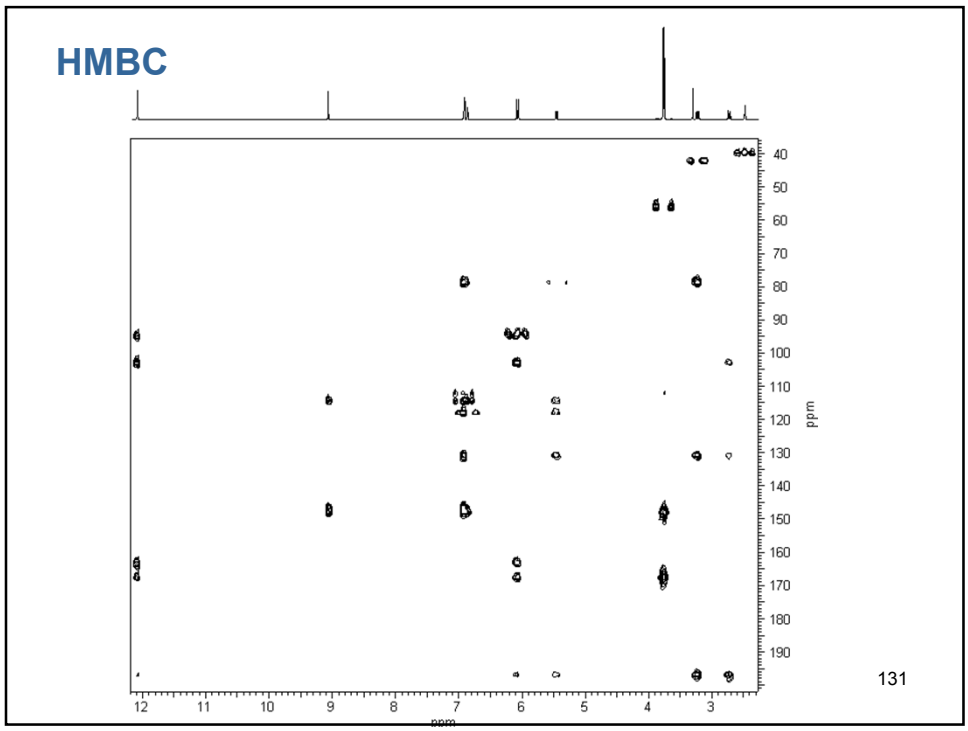
HMQC

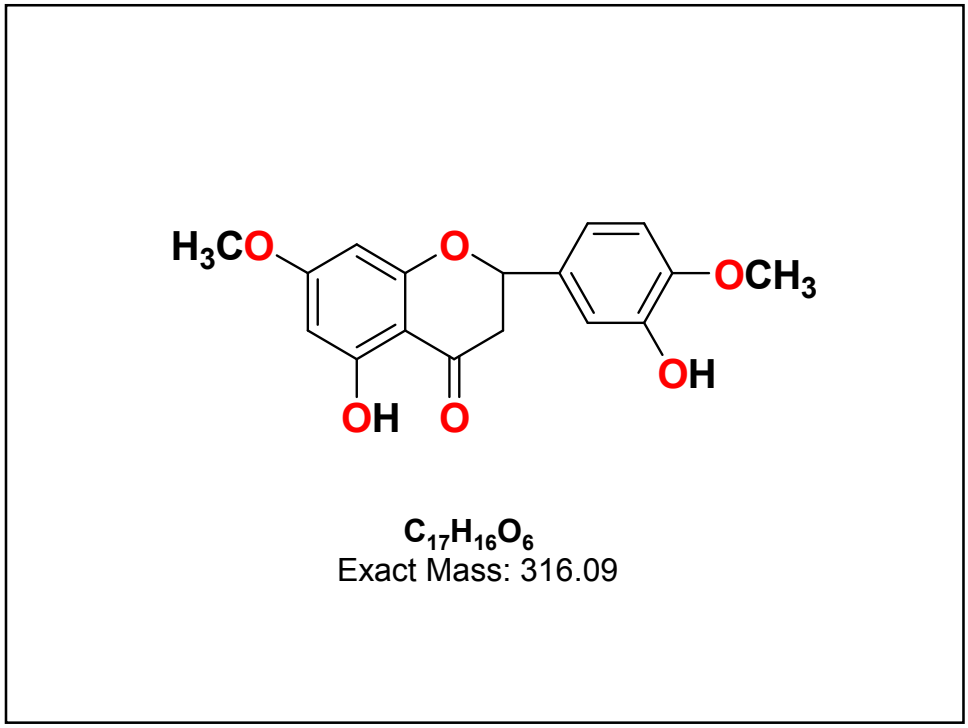


$C_{17}H_{16}O_6$

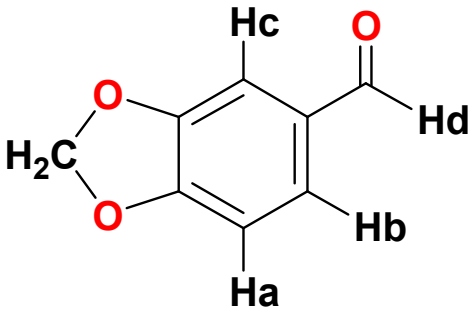
16个氢，如何归属？

130


HMBC
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
ppm
12
11
10
9
8
7
6
5
4
3
ppm
131


H3CO
O
OCH3
OH
OH
O
C17H16O6
Exact Mass: 316.09

1. Please draw a NMR chart for the following structure. And give your reasons.



133

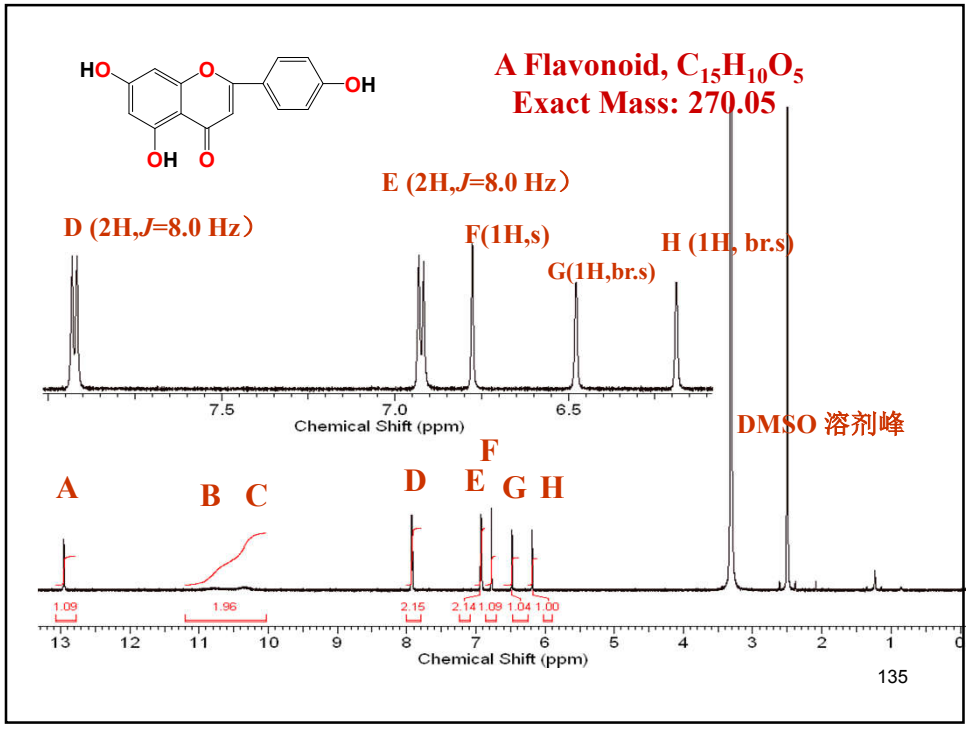
核磁共振氢谱、碳谱

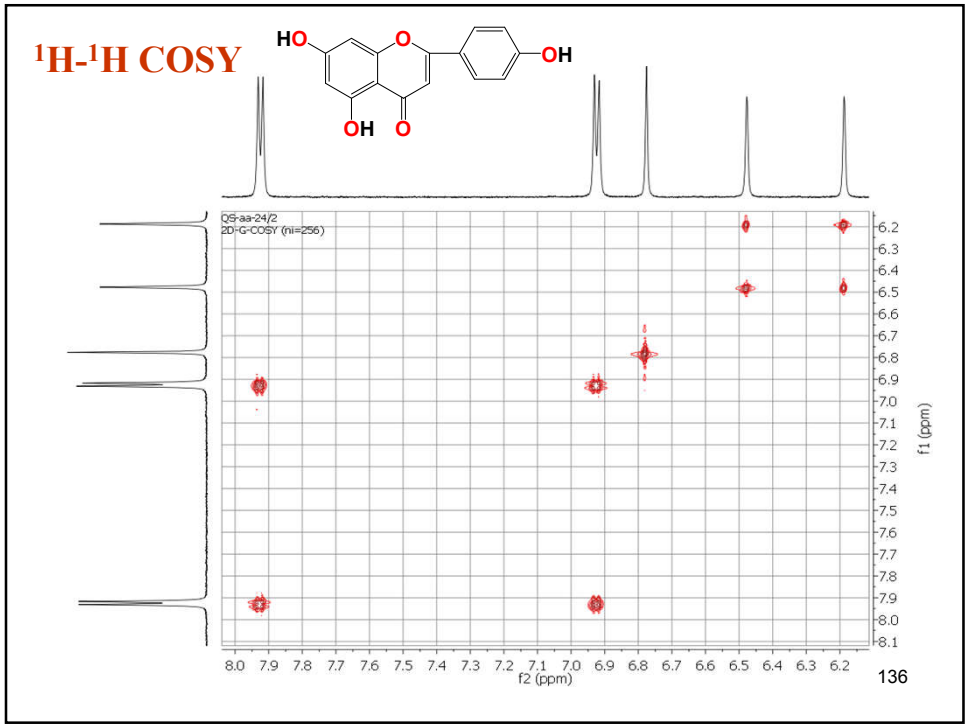
Nuclear Magnetic Resonance

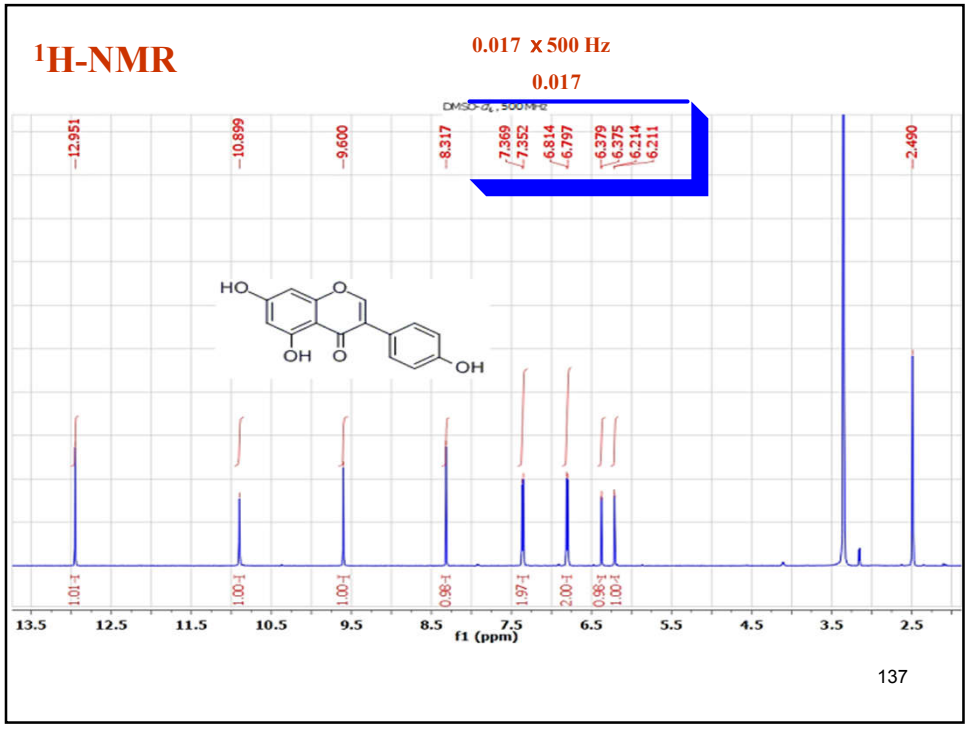
^{1}H- and ^{13}C-NMR

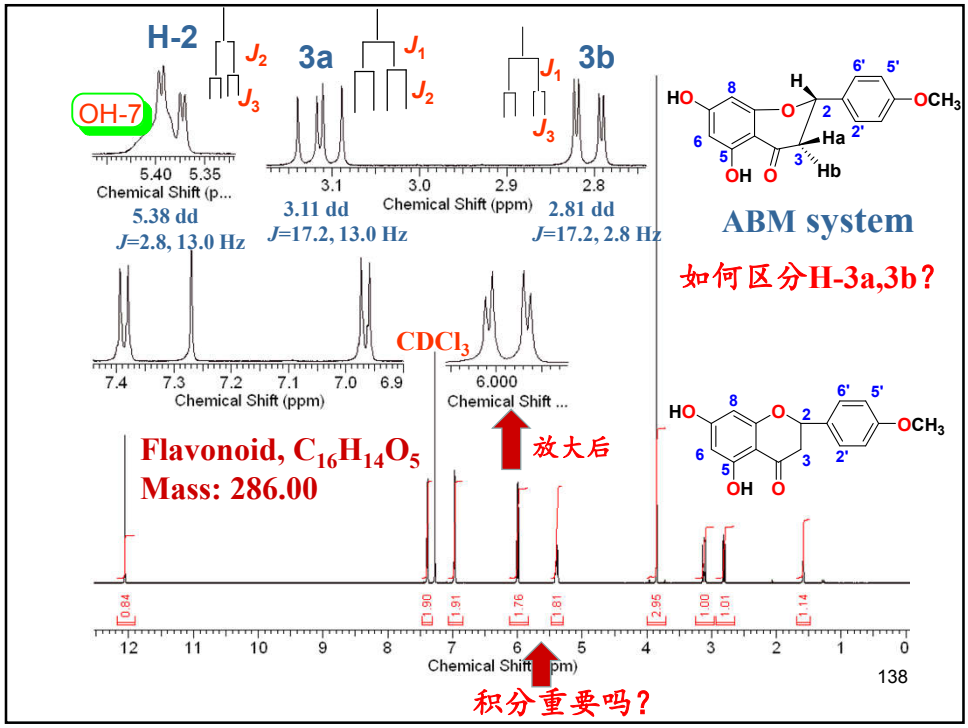
An indispensable tool for structural elucidation

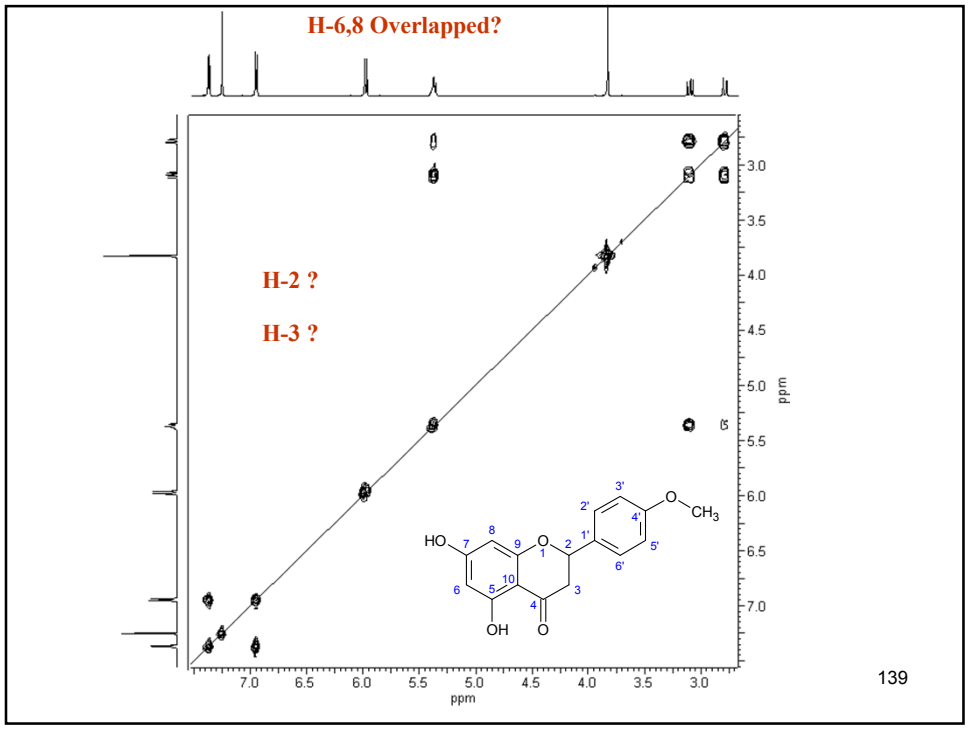
134

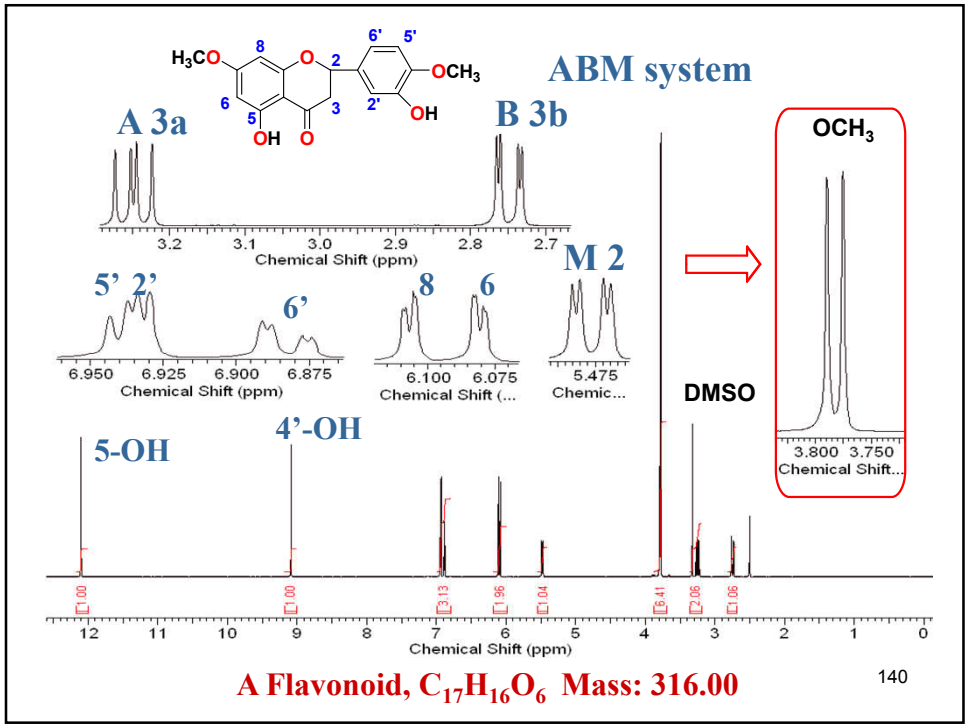

A Flavonoid, $C_{15}H_{10}O_5$
Exact Mass: 270.05
E (2H,J=8.0 Hz）
D (2H,J=8.0 Hz）
F(1H,s)
H (1H, br.s)
G(1H,br.s)
DMSO 溶剂峰
Chemical Shift (ppm)
A
B C
D
E
F
G H
Chemical Shift (ppm)
135

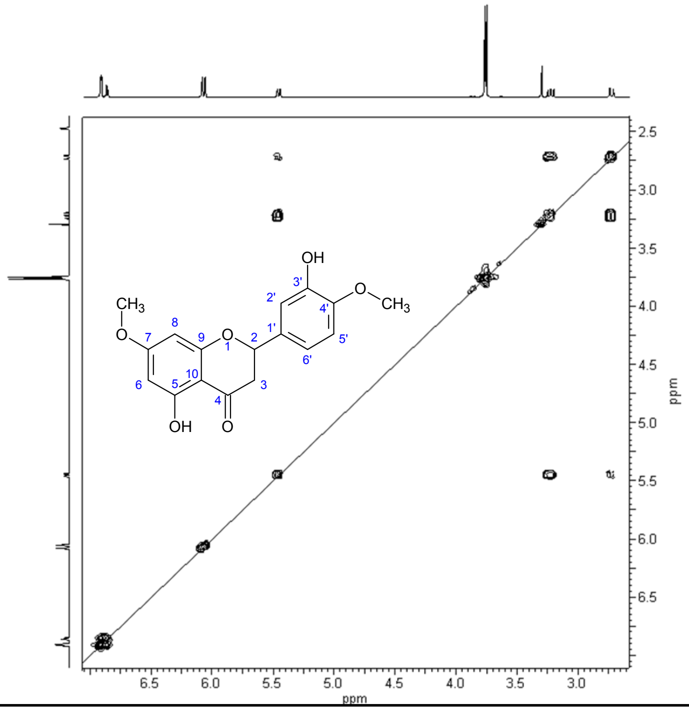

^1H-^1H COSY
f2 (ppm)
f1 (ppm)
136


1H-NMR
0.017 x 500 Hz
0.017
-12.951
-10.899
-9.600
-8.317
7.369
7.352
6.814
6.797
6.379
6.375
6.214
6.211
-2.490
HO
OH
O
OH
1.01
1.00
1.00
0.98
1.97
2.00
0.98
1.00
13.5
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
f1 (ppm)
137


H-2
J2
J3
OH-7
5.40 5.35
Chemical Shift (p...
5.38 dd
J=2.8, 13.0 Hz
3a
J1
J2
3.1
3.0
2.9
2.8
Chemical Shift (ppm)
3.11 dd
J=17.2, 13.0 Hz
J1
J3
3b
2.81 dd
J=17.2, 2.8 Hz
HO
H
6'
5'
8
O
2
OCH3
6
Ha
2'
5
3
OH
O
Hb
ABM system
如何区分H-3a,3b?
7.4
7.3
7.2
7.1
7.0
6.9
Chemical Shift (ppm)
CDCl3
6.000
Chemical Shift ...
放大后
Flavonoid, C16H14O5
Mass: 286.00
0.84
0.90
1.91
1.76
0.81
2.95
1.00
1.01
1.14
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)
积分重要吗?
138

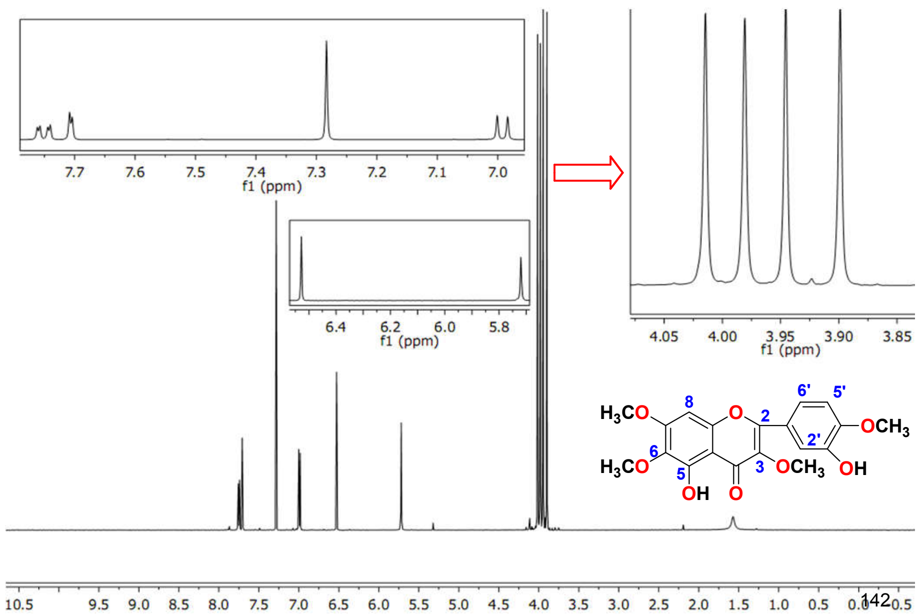

H-6,8 Overlapped?
H-2 ?
H-3 ?
ppm
ppm
HO
OH
O
O
CH3
139


H3CO
OCH3
OH
OH
O
ABM system
A 3a
B 3b
M 2
5' 2'
6'
8
6
OCH3
DMSO
5-OH
4'-OH
Chemical Shift (ppm)
A Flavonoid, C17H16O6 Mass: 316.00
140

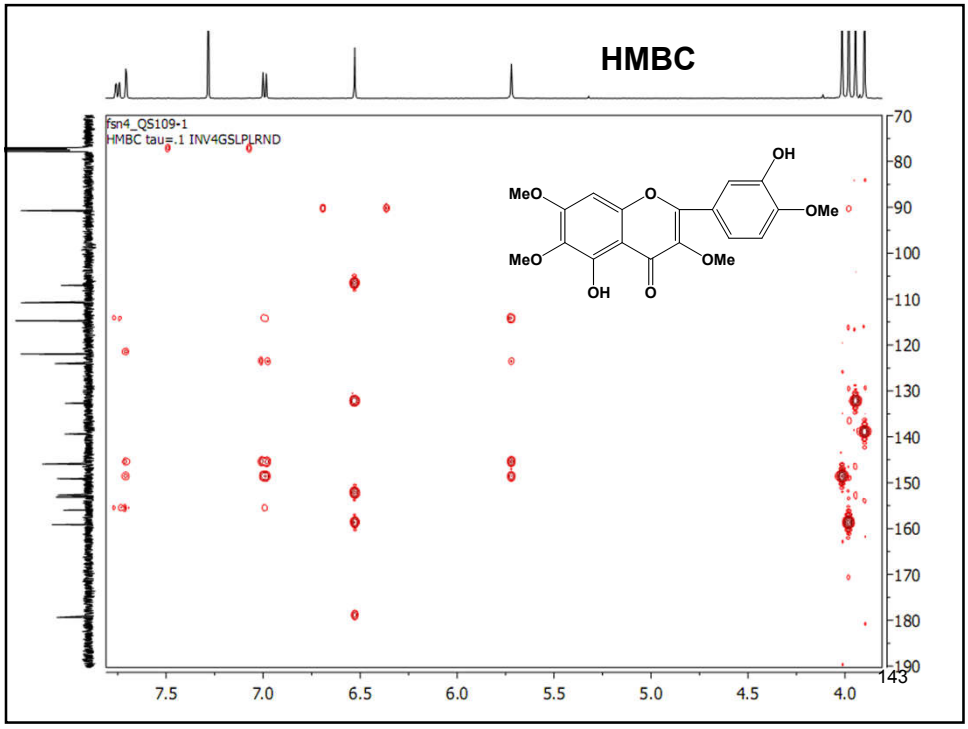


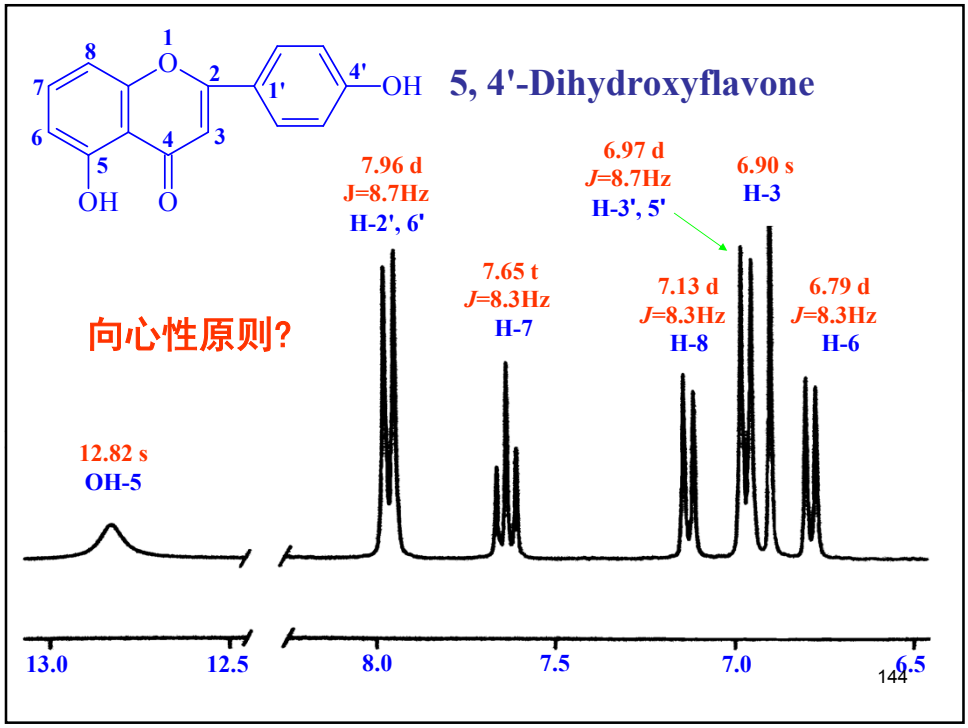
141

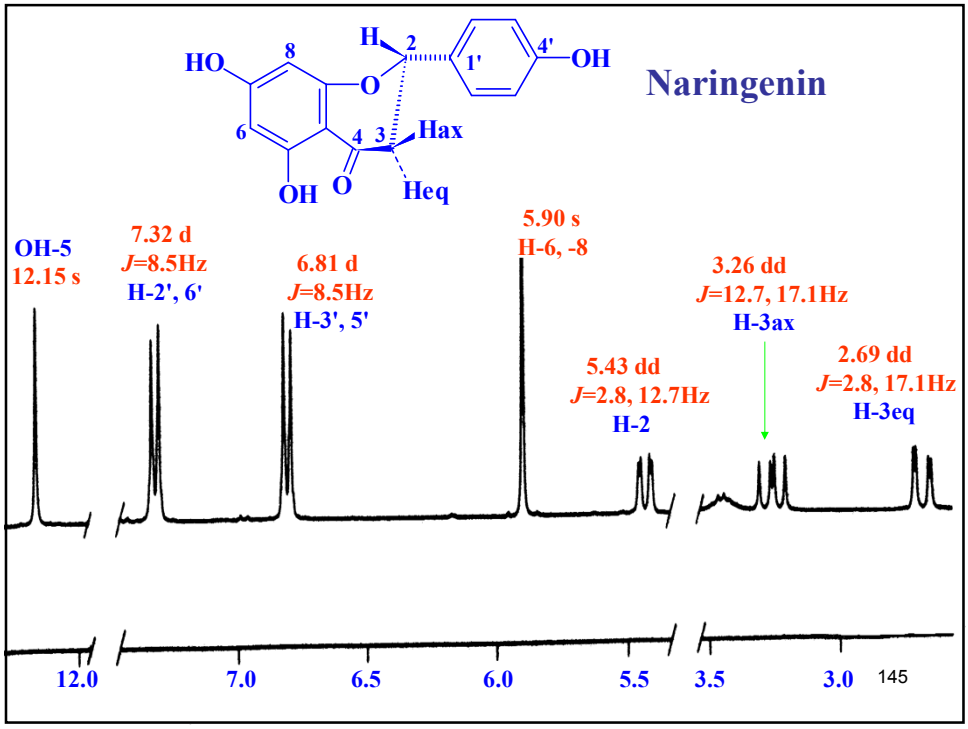
A Flavonoid, $C_{19}H_{18}O_{8}$ Mass: 374.34

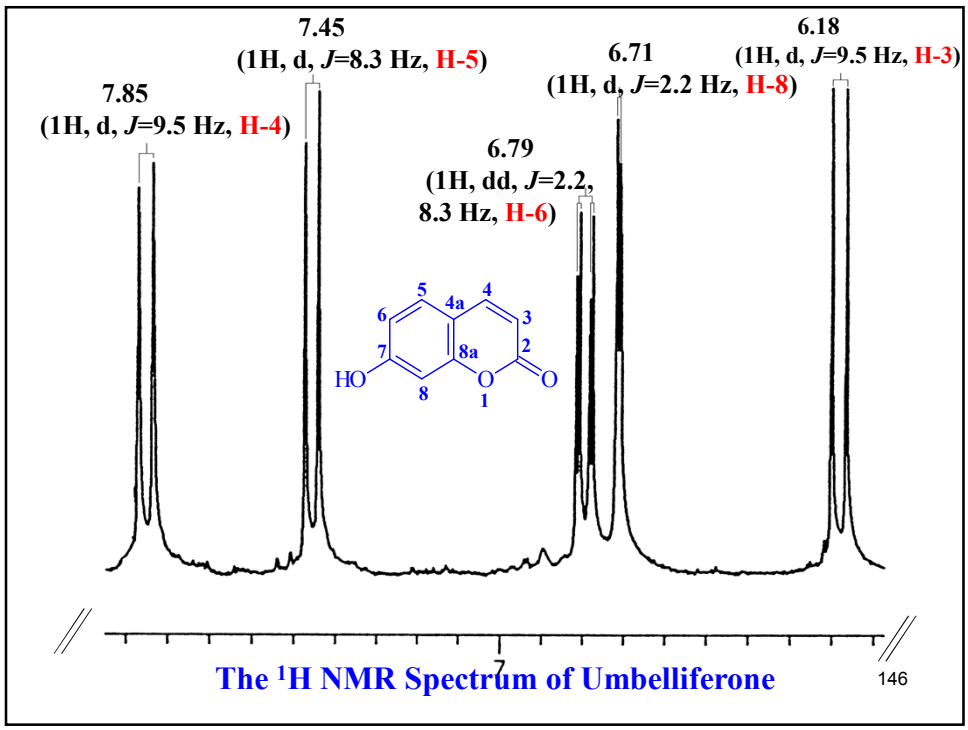


142

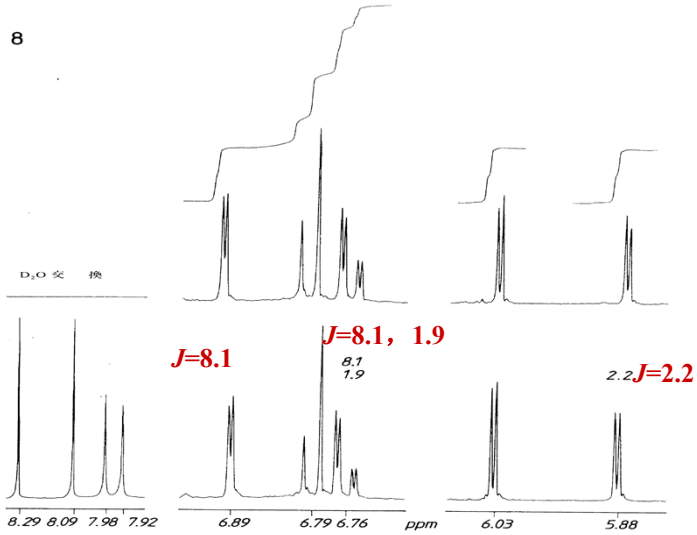

HMBC
fsn4_QS109-1
HMBC tau=.1 INV4GSLPLRND
MeO
MeO
OH
OMe
OMe
OH
O
O
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
143


5, 4'-Dihydroxyflavone
OH
OH
O
7.96 d
J=8.7Hz
H-2', 6'
6.97 d
J=8.7Hz
H-3', 5'
6.90 s
H-3
7.65 t
J=8.3Hz
H-7
7.13 d
J=8.3Hz
H-8
6.79 d
J=8.3Hz
H-6
向心性原则?
12.82 s
OH-5
13.0
12.5
8.0
7.5
7.0
6.5
144

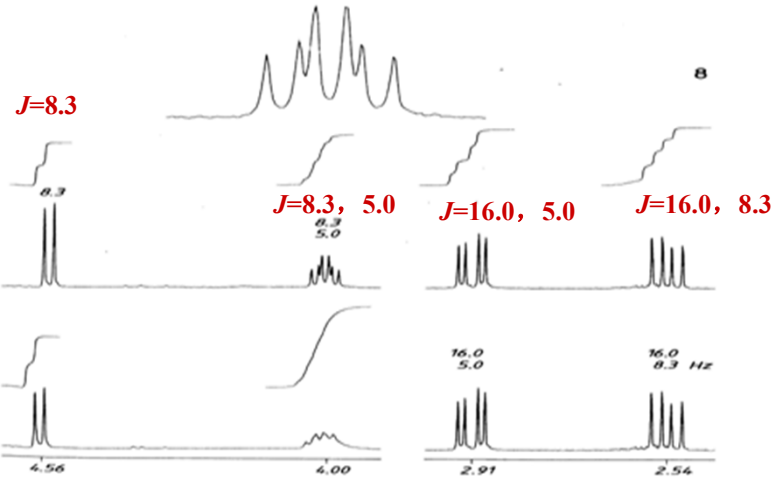

Naringenin
OH-5
12.15 s
7.32 d
J=8.5Hz
H-2', 6'
6.81 d
J=8.5Hz
H-3', 5'
5.90 s
H-6, -8
5.43 dd
J=2.8, 12.7Hz
H-2
3.26 dd
J=12.7, 17.1Hz
H-3ax
2.69 dd
J=2.8, 17.1Hz
H-3eq
12.0
7.0
6.5
6.0
5.5
3.5
3.0
145


7.85
(1H, d, J=9.5 Hz, H-4)
7.45
(1H, d, J=8.3 Hz, H-5)
6.79
(1H, dd, J=2.2,
8.3 Hz, H-6)
6.71
(1H, d, J=2.2 Hz, H-8)
6.18
(1H, d, J=9.5 Hz, H-3)
7
The 1H NMR Spectrum of Umbelliferone
146

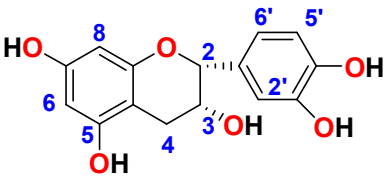
从某一中药中分离出一个化合物，初步鉴定其为一个黄烷醇类化合物，$C_{15}H_{14}O_6$，根据提供的波谱数据（如下图，ppm为化学位移，积分值和偶合常数见标示）写出其最可能的结构。



147

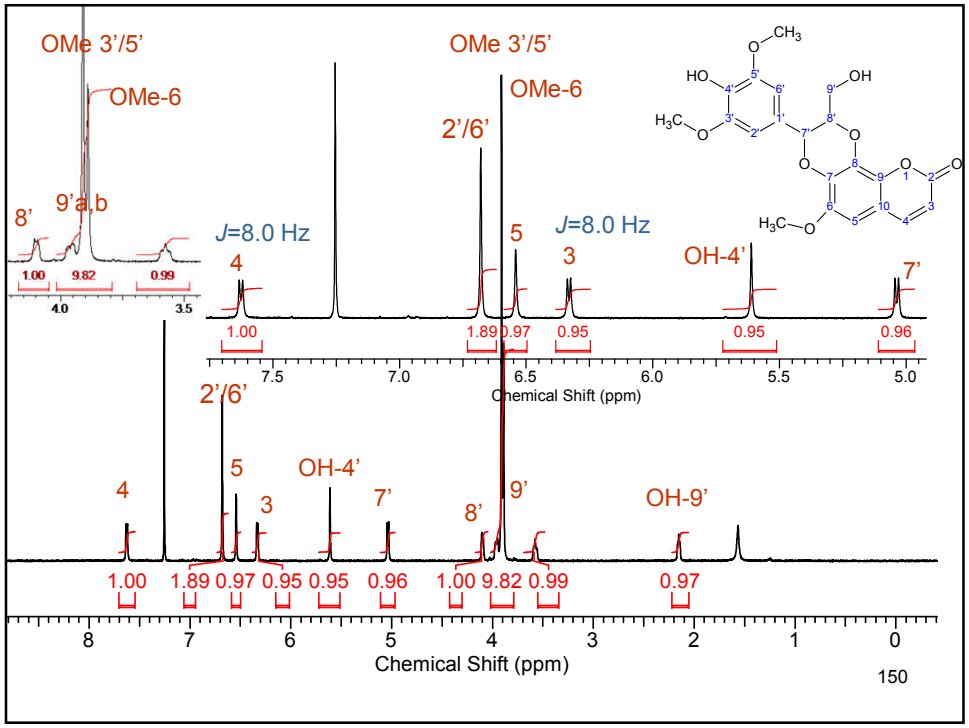


148

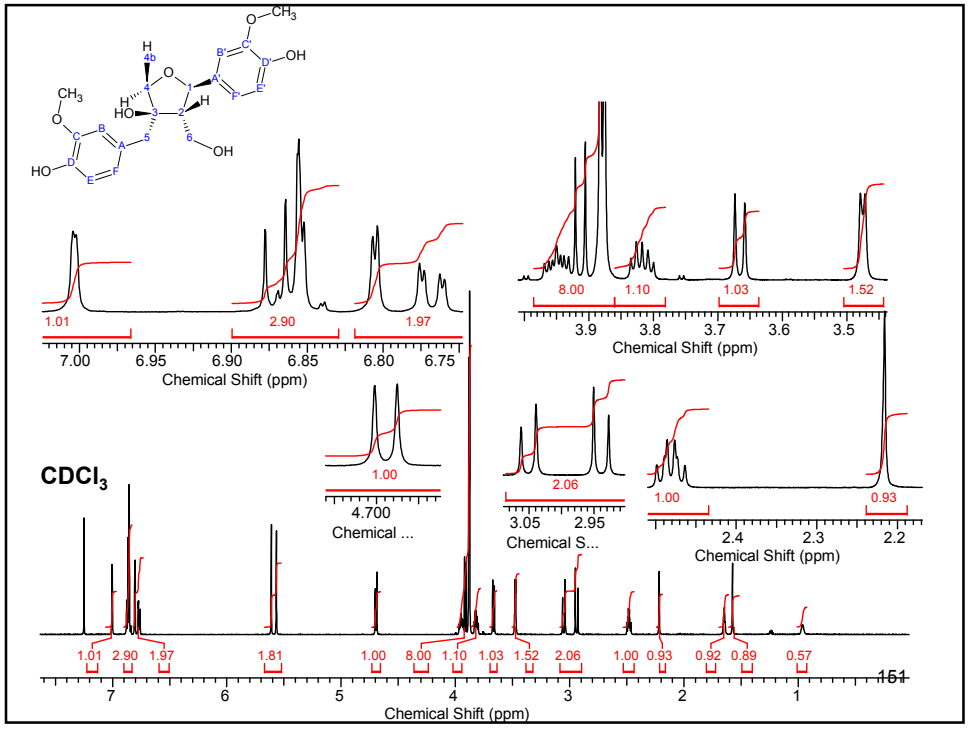


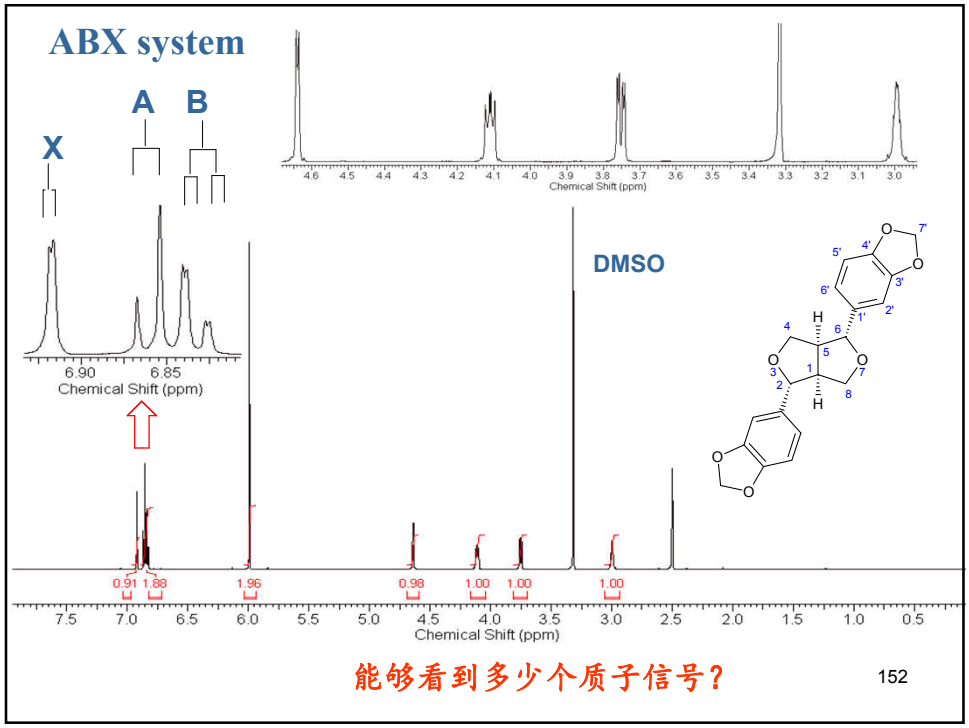
$C_{15}H_{14}O_6$
Exact Mass: 290.08

149

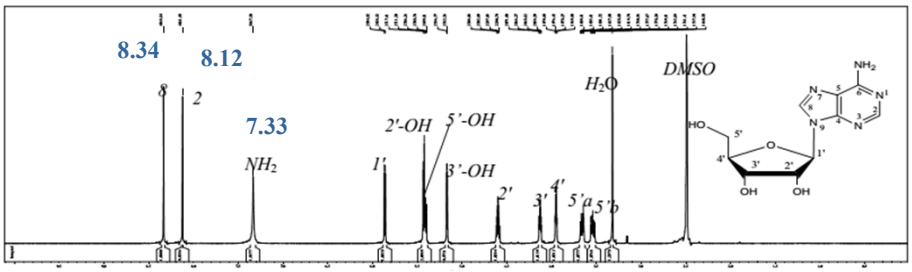


150


CDCl3
Chemical Shift (ppm)
151

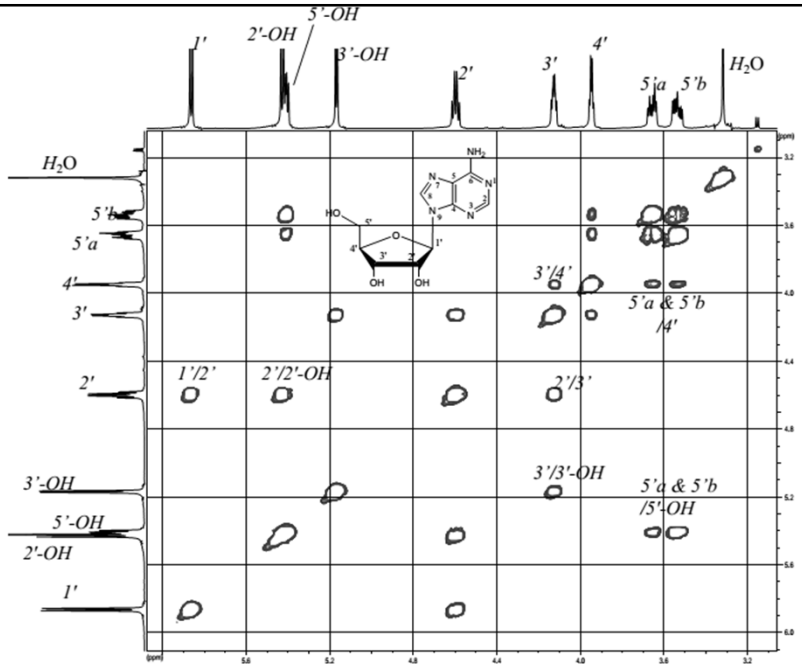

ABX system
A
B
X
DMSO
Chemical Shift (ppm)
能够看到多少个质子信号？
152

如何确定是活泼H？



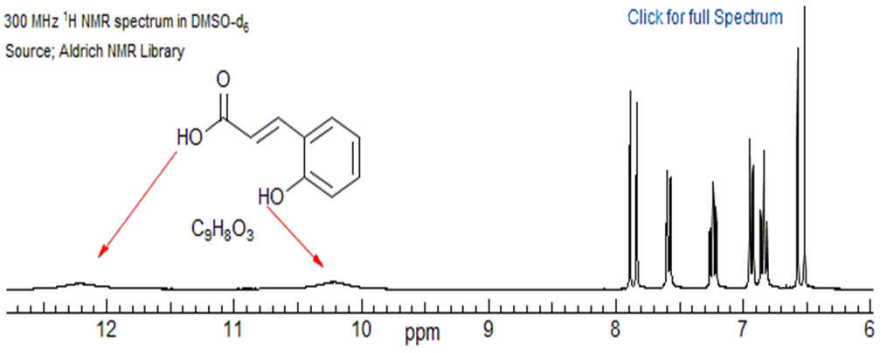
2	8.12 (s)
8	8.34 (s)
6-NH_2	7.33 (s)
1'	5.86 (d, *J* =6.3)
2'	4.60 (dd, *J*=11.35, 6.3)
2'-OH	5.43(d, *J* =6.3)
3'	4.13 (dd, *J* =7.88, 4.73)
3'-OH	5.17 (d, *J* =4.41)
4'	3.95 (dd, *J* =6.62, 3.47)
5'a	3.54 (ddd, *J* =3.47, 7.25, 11.67)
5'b	3.66 (ddd, *J* =4.09, 8.19, 11.98)
5'-OH	5.41 (dd, *J* =7.25, 4.73)

153



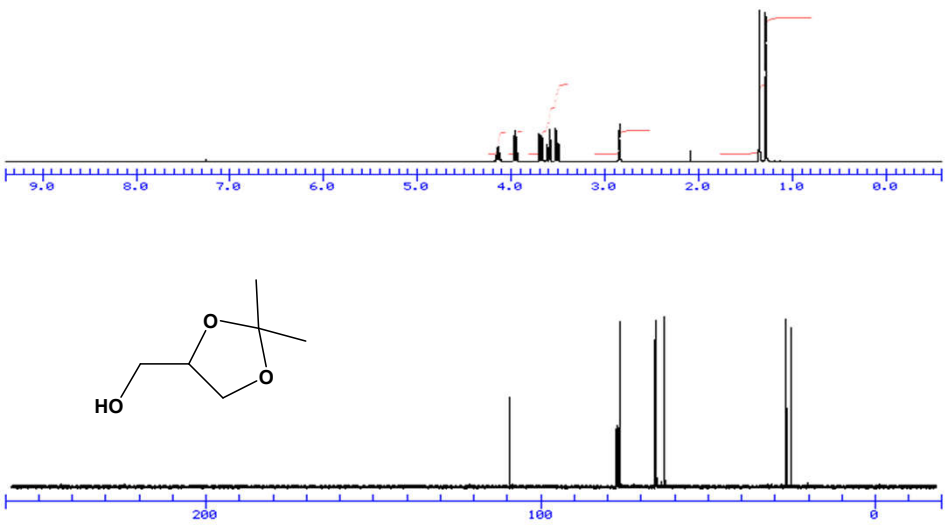
154

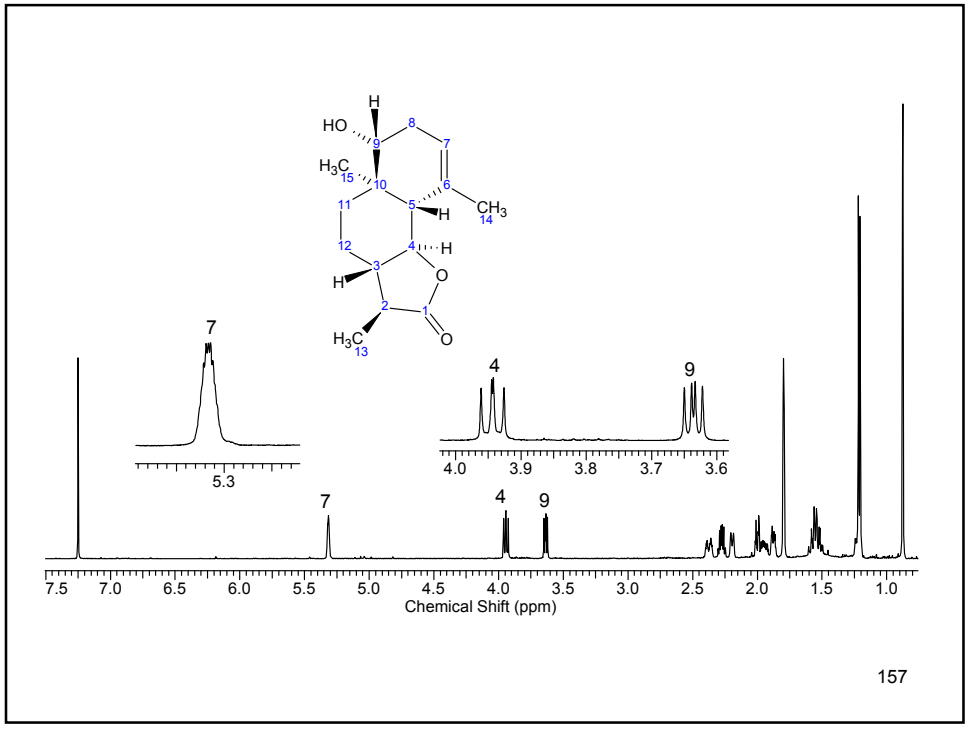
积分



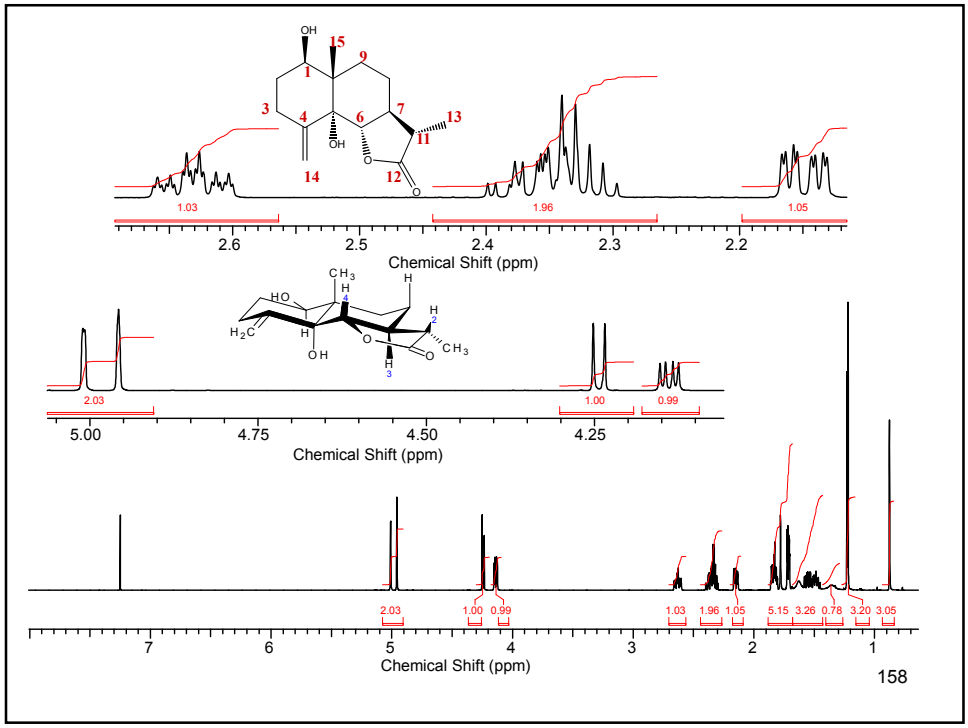
155

$C_6H_{12}O_3$
NMR Solvent: $CDCl_3$

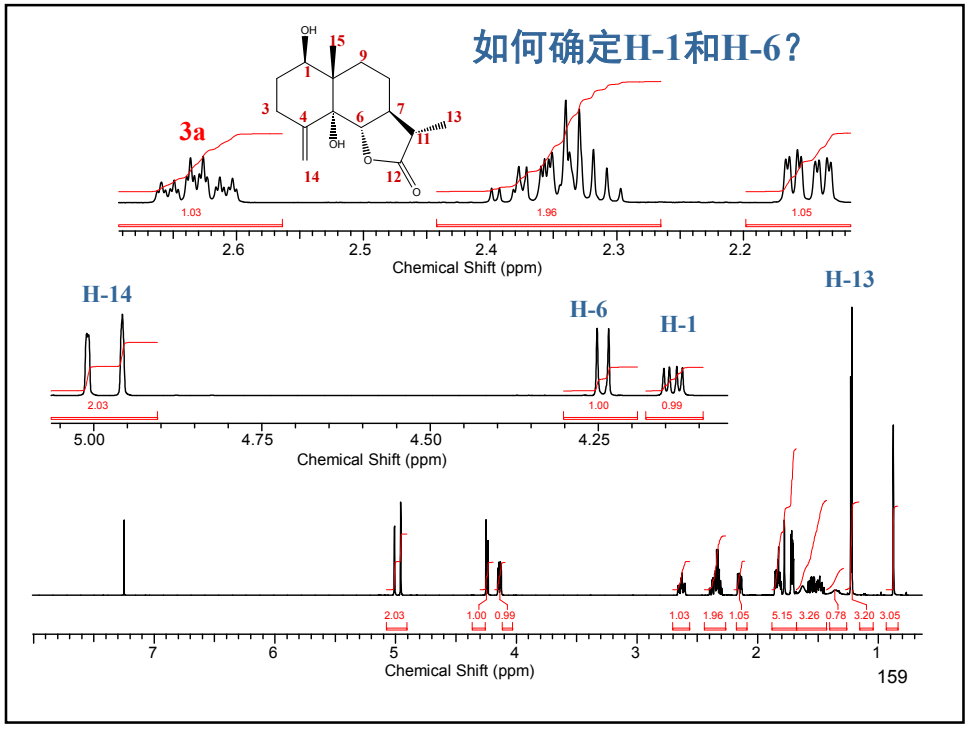


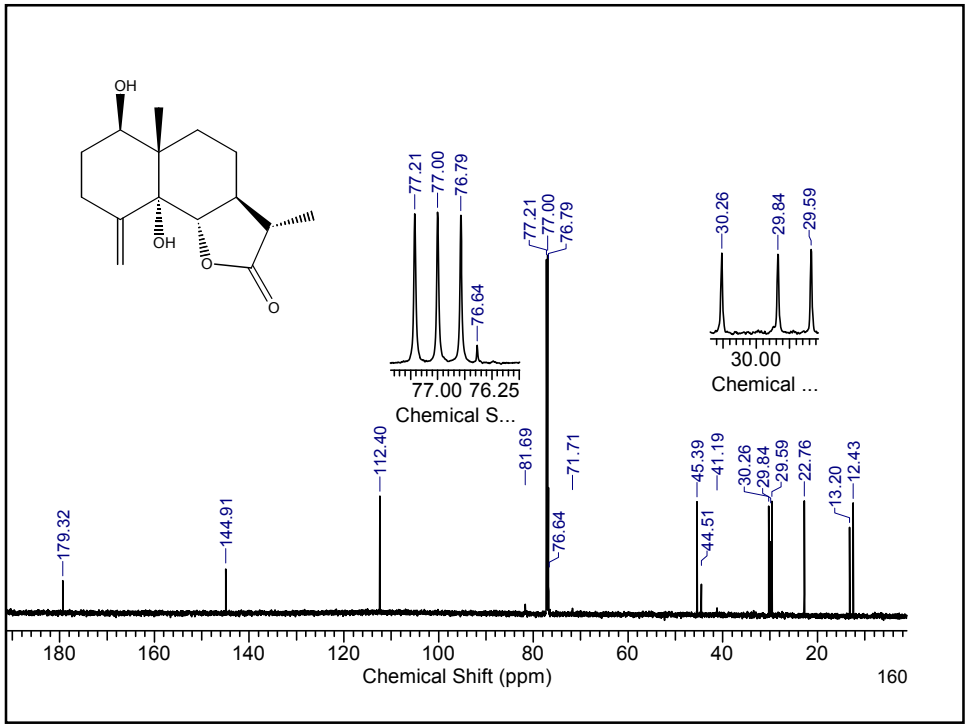

HO
H
H3C
CH3
O
7
4
9
5.3
4.0
3.9
3.8
3.7
3.6
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
Chemical Shift (ppm)

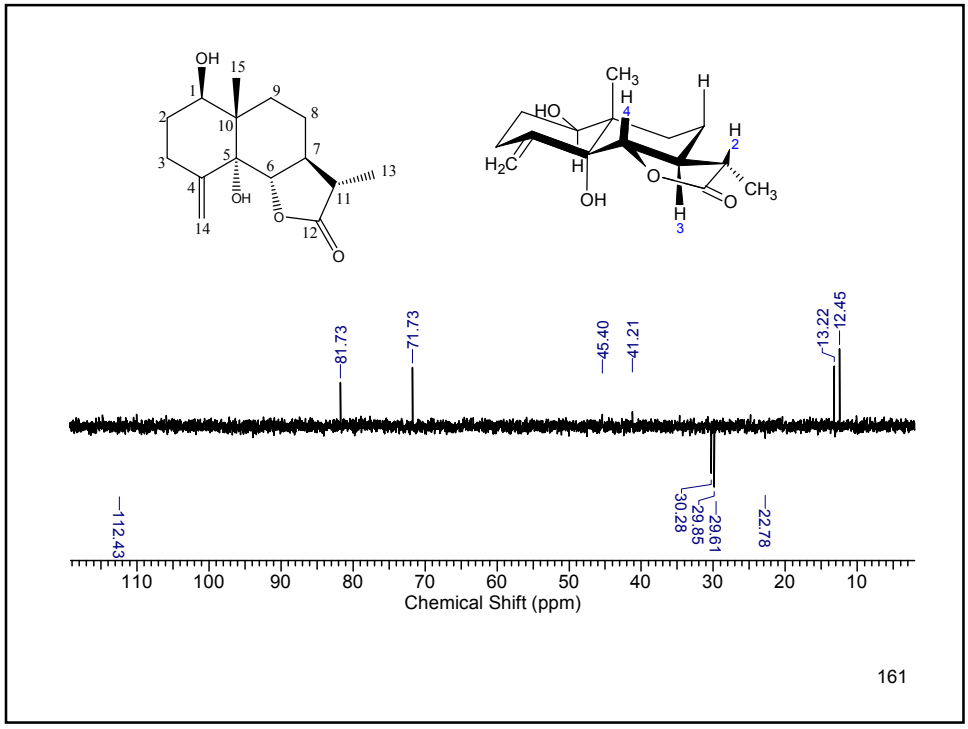
157


OH
1.03
1.96
1.05
2.6
2.5
2.4
2.3
2.2
Chemical Shift (ppm)
2.03
1.00
0.99
5.00
4.75
4.50
4.25
Chemical Shift (ppm)
2.03
1.00
0.99
1.03
1.96
1.05
5.15
3.26
0.78
3.20
3.05
7
6
5
4
3
2
1
Chemical Shift (ppm)

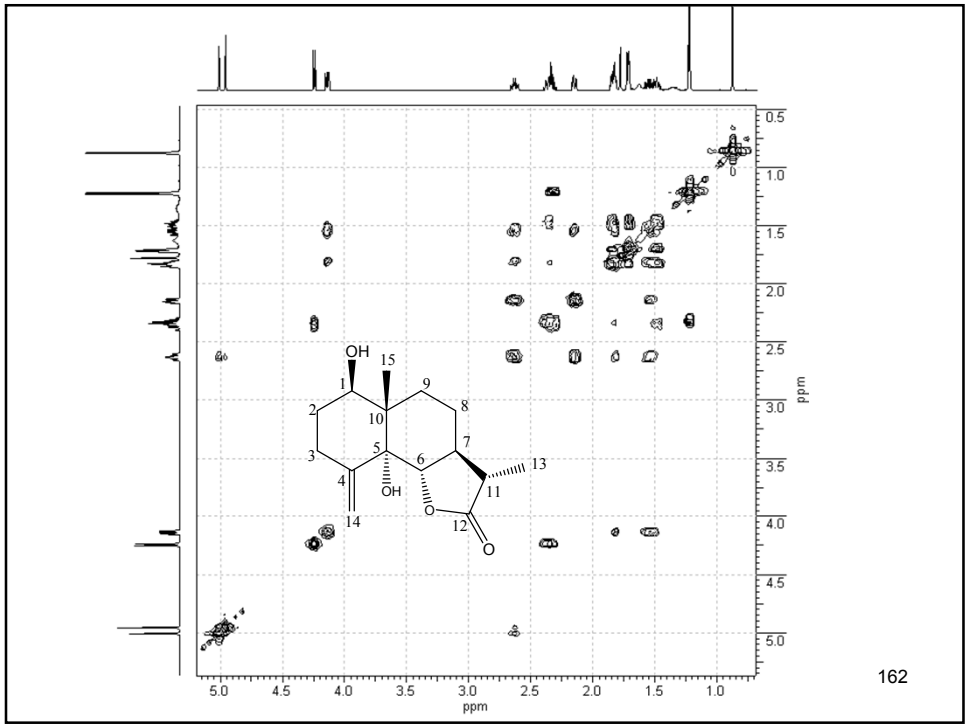
158


如何确定H-1和H-6？
3a
H-14
H-6
H-1
H-13
Chemical Shift (ppm)
159

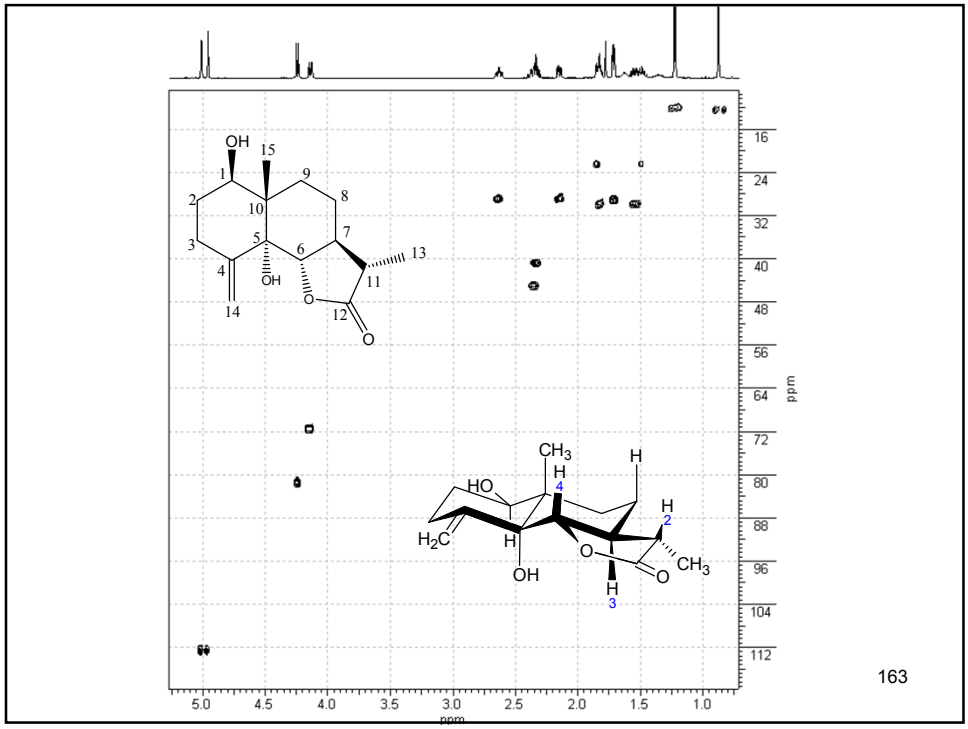

OH
179.32
144.91
112.40
81.69
77.21
77.00
76.79
76.64
71.71
45.39
44.51
41.19
30.26
29.84
29.59
22.76
13.20
12.43
Chemical Shift (ppm)
160


OH
15
1
9
2
8
10
7
3
5
6
13
4
OH
11
O
14
12
O
CH3
H
4
HO
H
H
2
H2C
H
OH
O
CH3
O
H
3
81.73
71.73
45.40
41.21
13.22
12.45
112.43
30.28
29.85
29.61
22.78
110
100
90
80
70
60
50
40
30
20
10
Chemical Shift (ppm)

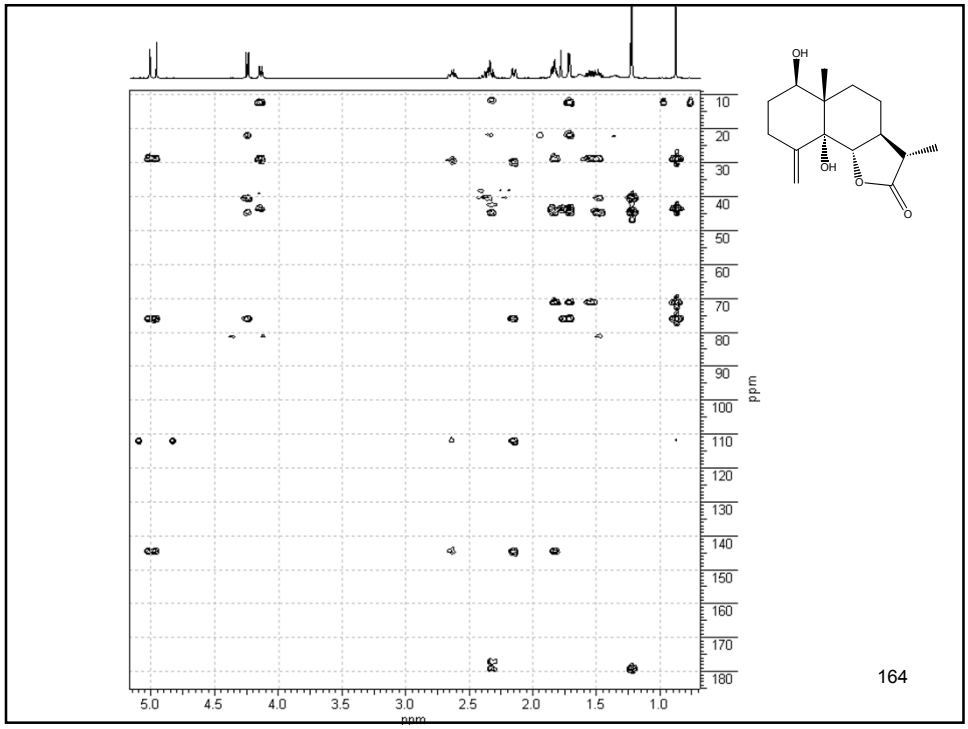
161


OH
15
1
9
2
8
10
7
3
5
6
13
4
OH
11
O
14
12
O
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
ppm
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

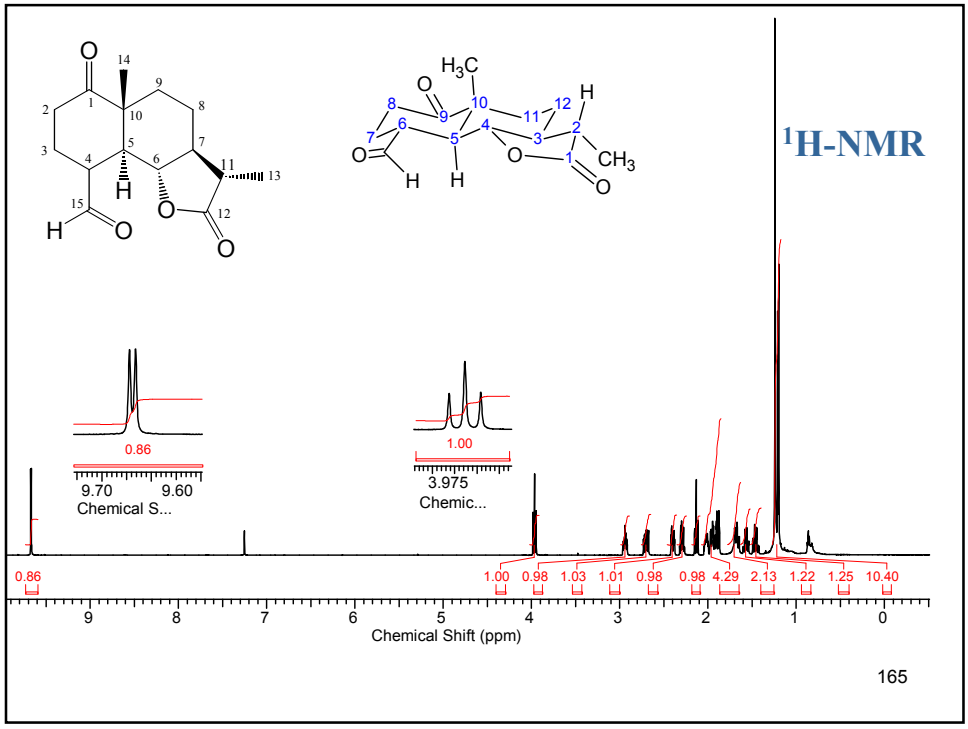
162

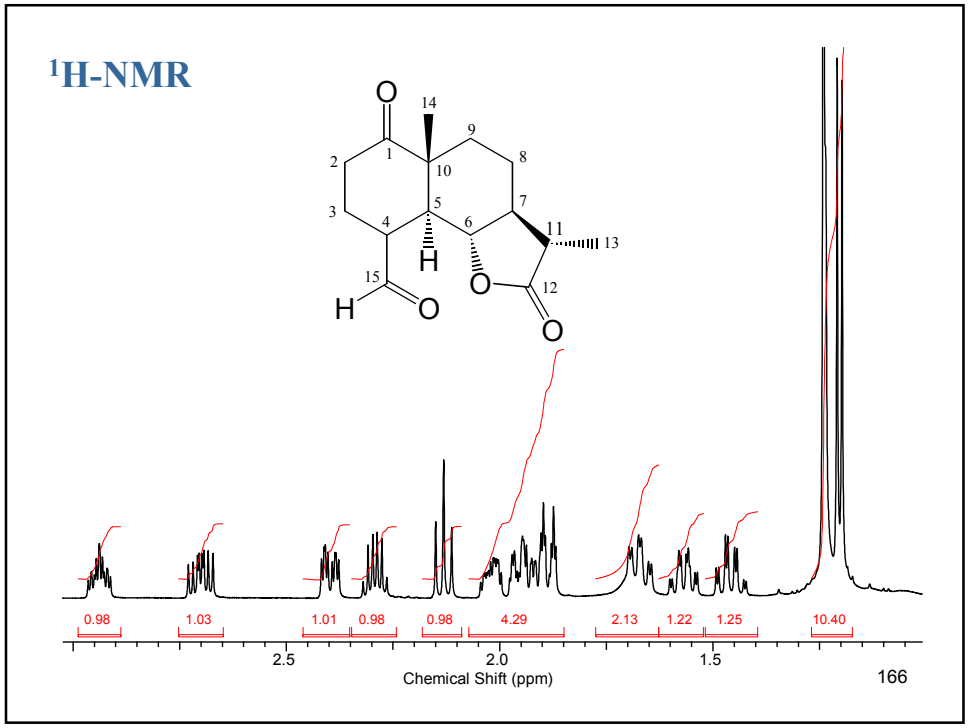

OH
15
1
9
2
8
10
7
3
5
6
13
4
OH
11
O
14
12
O
CH3
H
H
4
HO
H
2
H2C
H
O
CH3
OH
O
H
3
ppm
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0

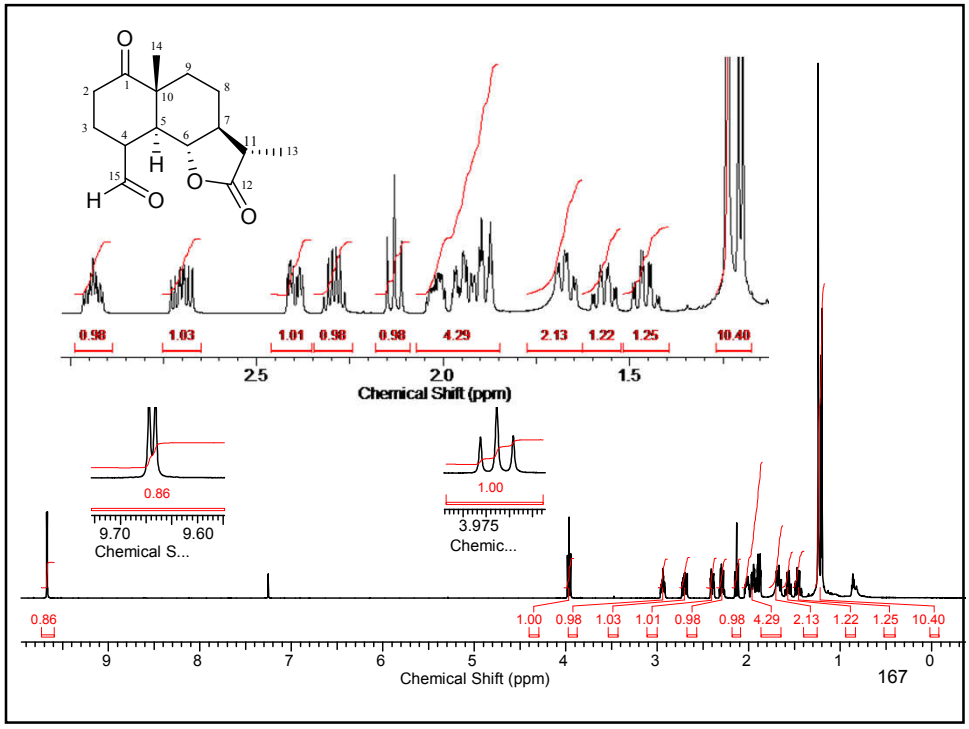
163

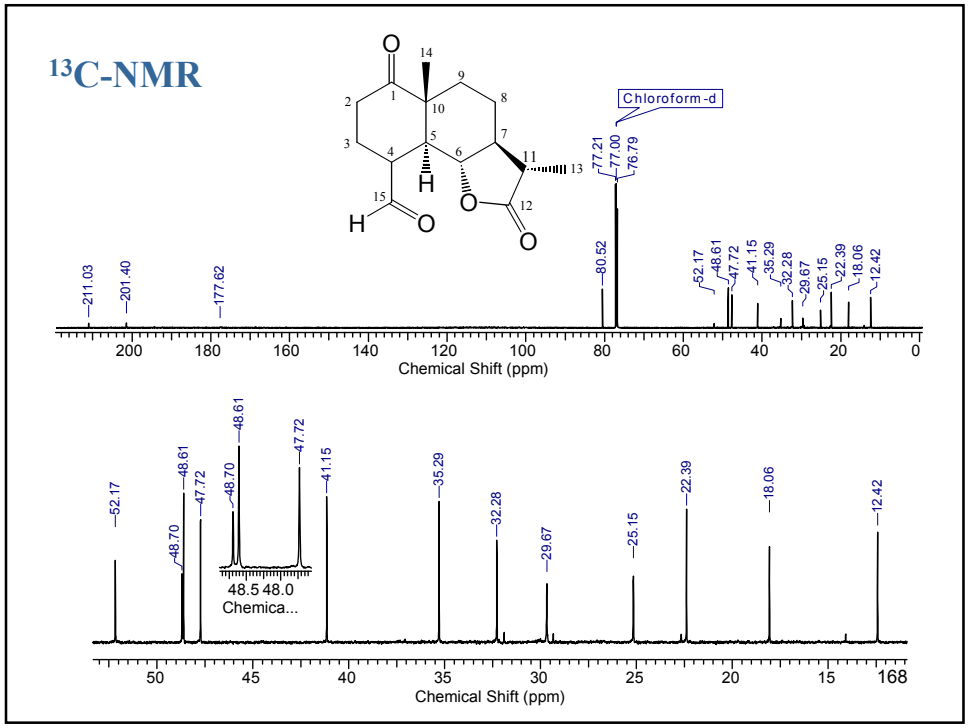

OH
OH
O
O
ppm
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0

164

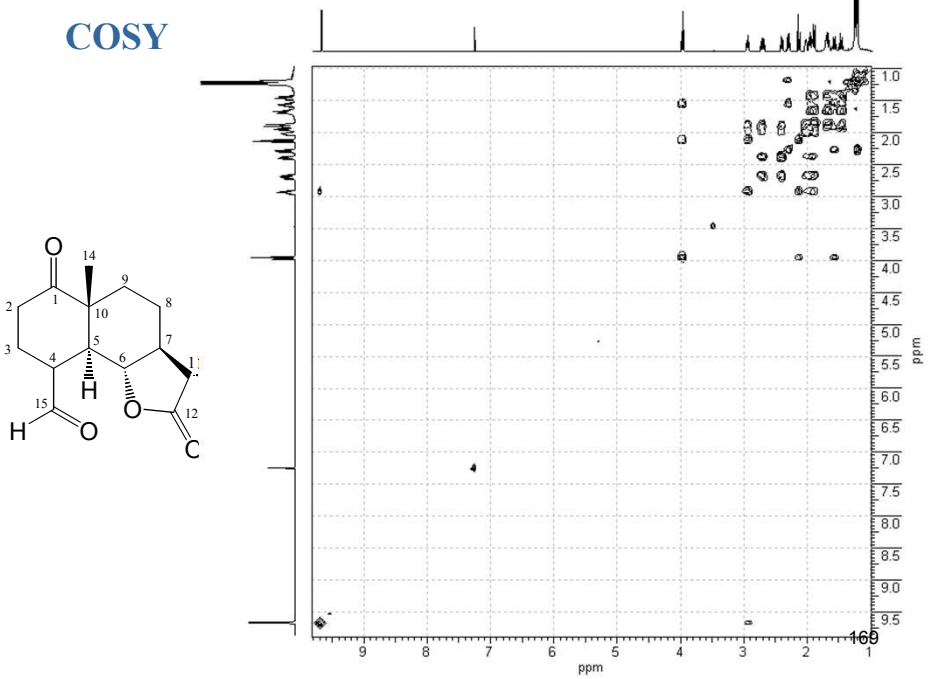

1H-NMR
0.86
9.70
9.60
Chemical S...
1.00
3.975
Chemic...
0.86
1.00 0.98 1.03 1.01 0.98 0.98 4.29 2.13 1.22 1.25 10.40
Chemical Shift (ppm)
165


1H-NMR
0.98 1.03 1.01 0.98 0.98 4.29 2.13 1.22 1.25 10.40
Chemical Shift (ppm)
166

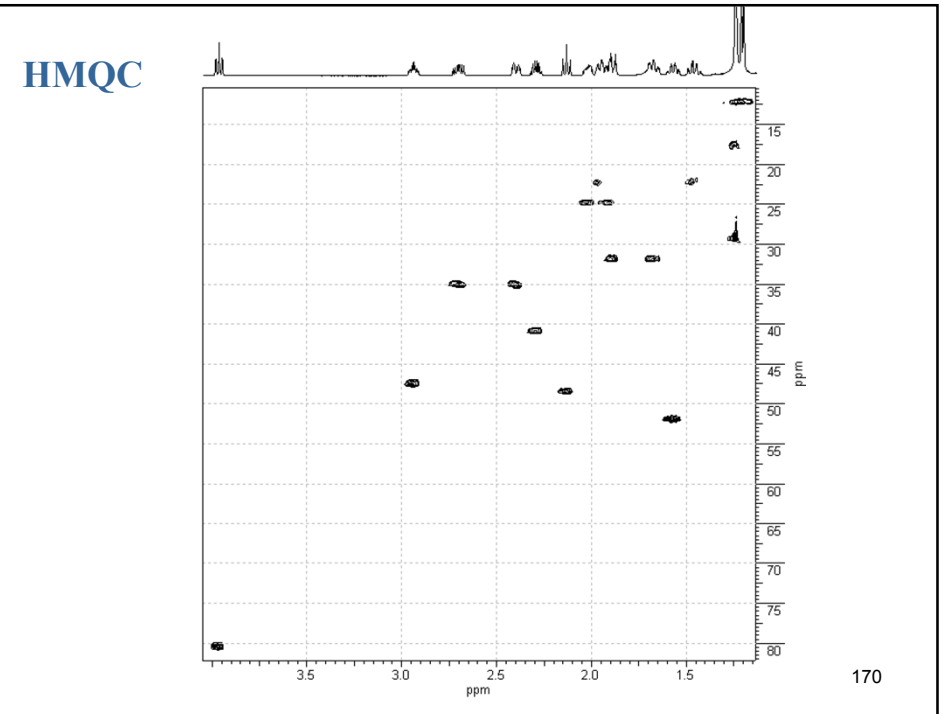

0.98 1.03 1.01 0.98 0.98 4.29 2.13 1.22 1.25 10.40
2.5 2.0 1.5
Chemical Shift (ppm)
0.86
9.70 9.60
Chemical S...
1.00
3.975
Chemic...
0.86 1.00 0.98 1.03 1.01 0.98 0.98 4.29 2.13 1.22 1.25 10.40
9 8 7 6 5 4 3 2 1 0
Chemical Shift (ppm)
167


13C-NMR
Chloroform-d
77.21
77.00
76.79
211.03
201.40
177.62
80.52
52.17
48.61
47.72
41.15
35.29
32.28
29.67
25.15
22.39
18.06
12.42
200 180 160 140 120 100 80 60 40 20 0
Chemical Shift (ppm)
48.5 48.0
Chemica...
50 45 40 35 30 25 20 15
Chemical Shift (ppm)
168

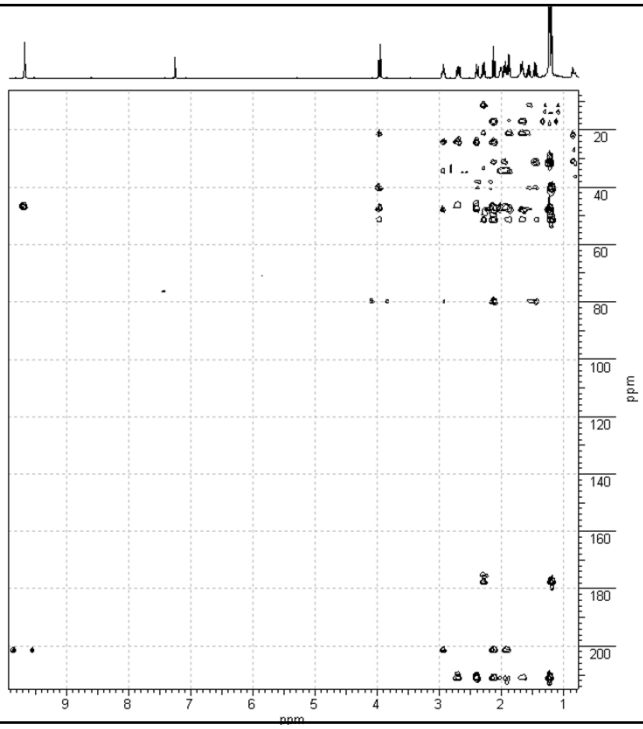
COSY



HMQC

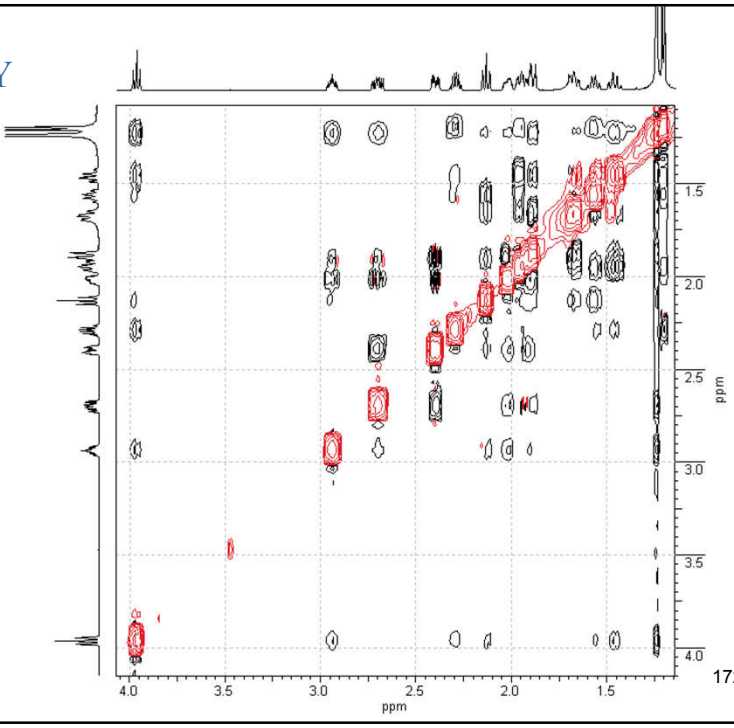


HMBC

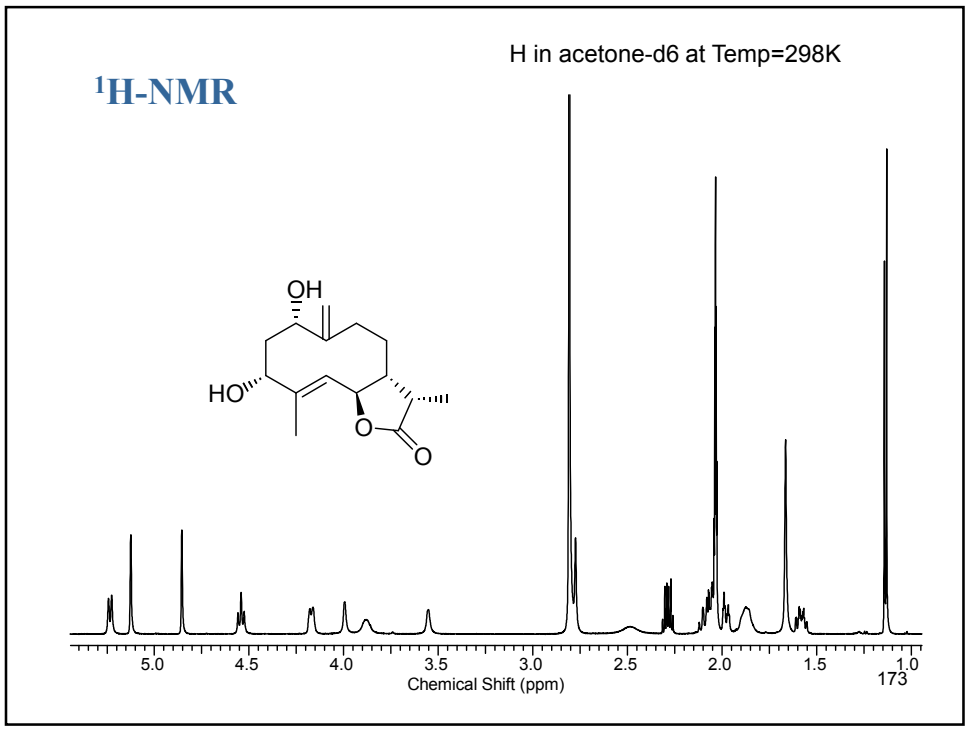


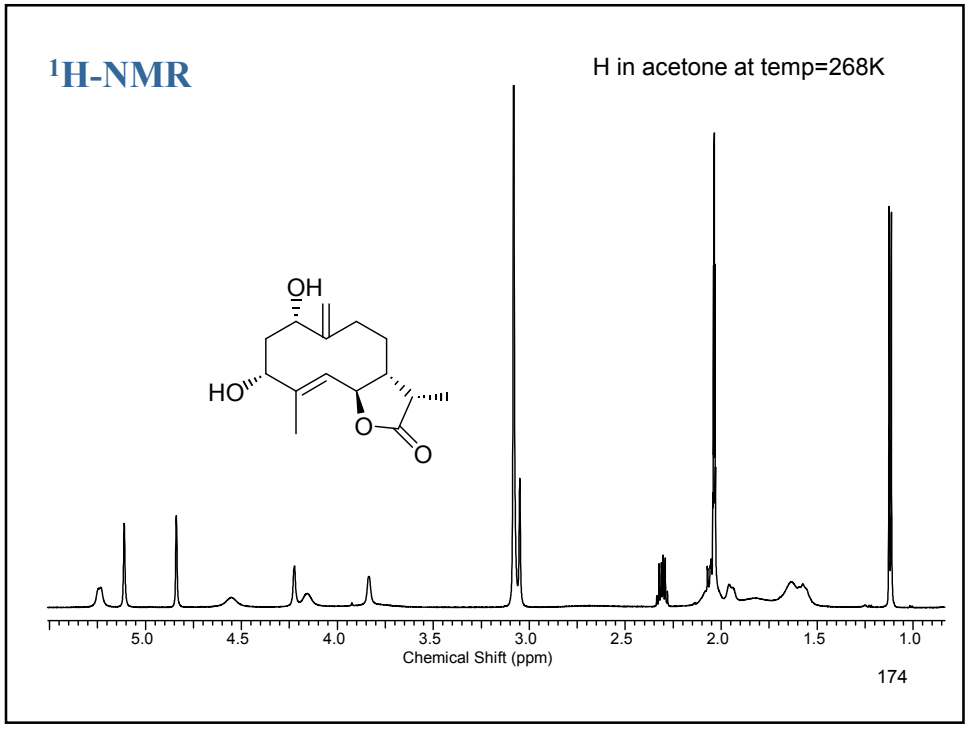
171

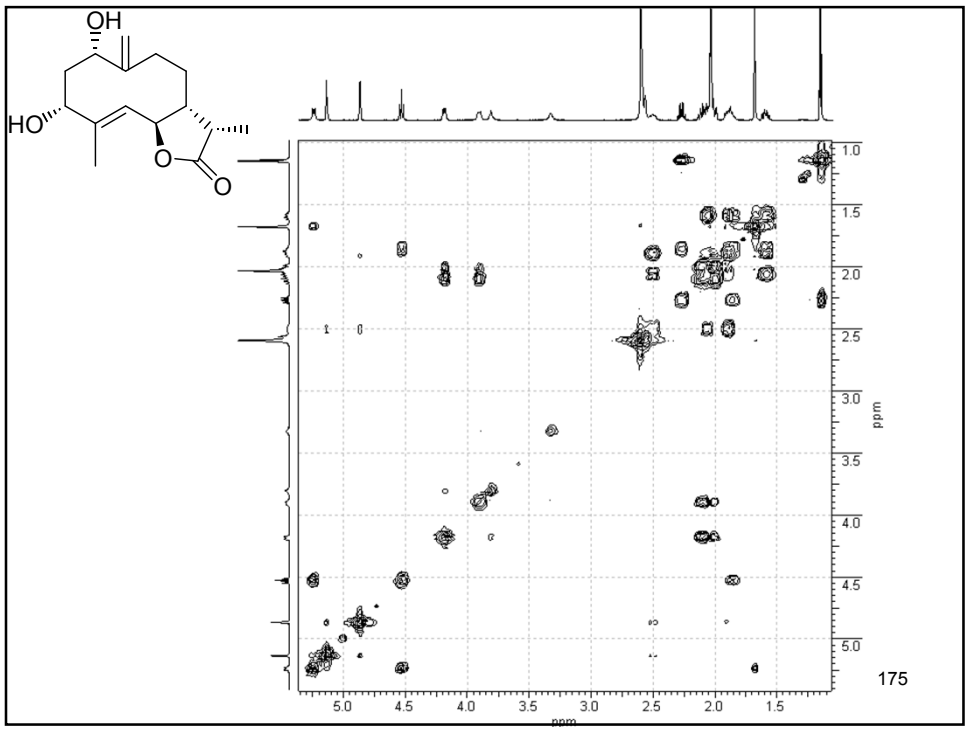
NOESY

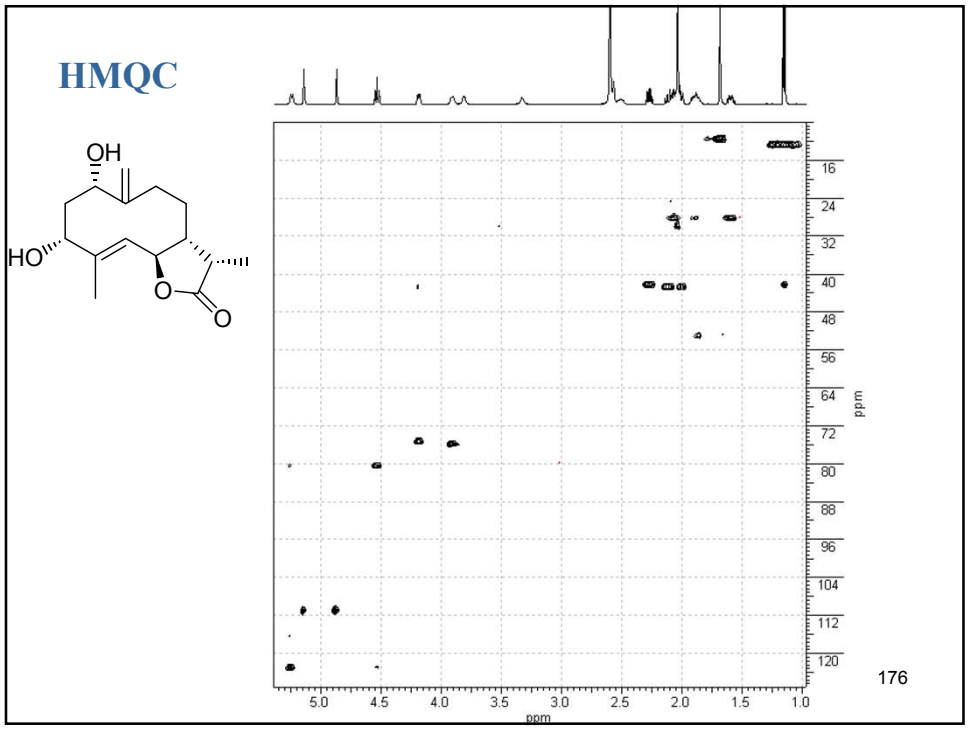


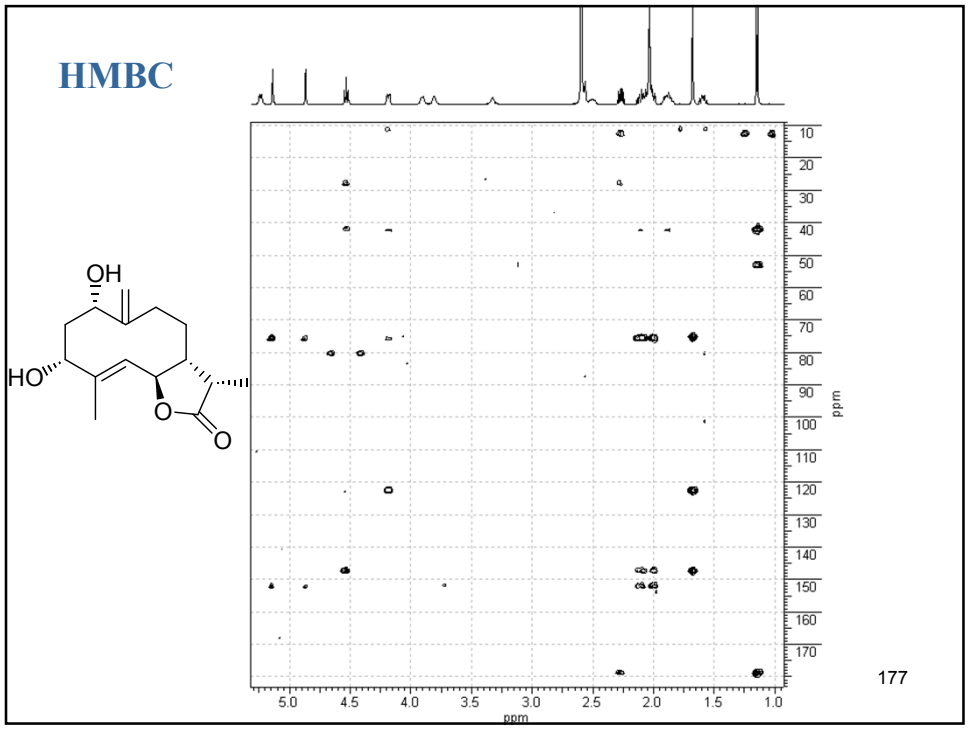
172

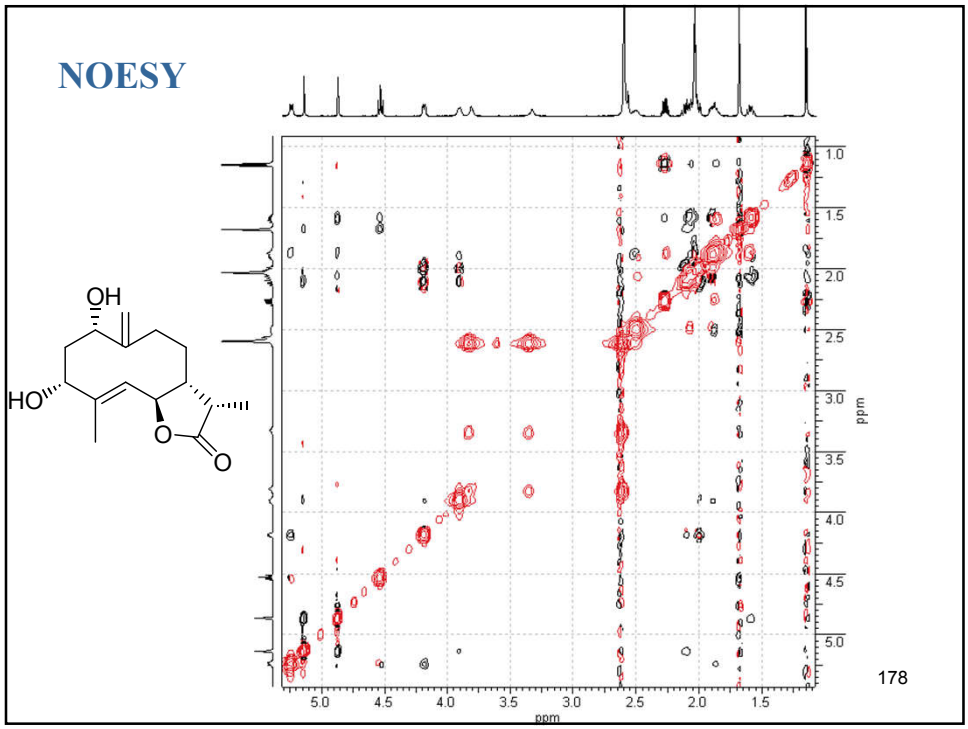

^{1}H-NMR
H in acetone-d6 at Temp=298K
OH
HO
O
O
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
Chemical Shift (ppm)
173

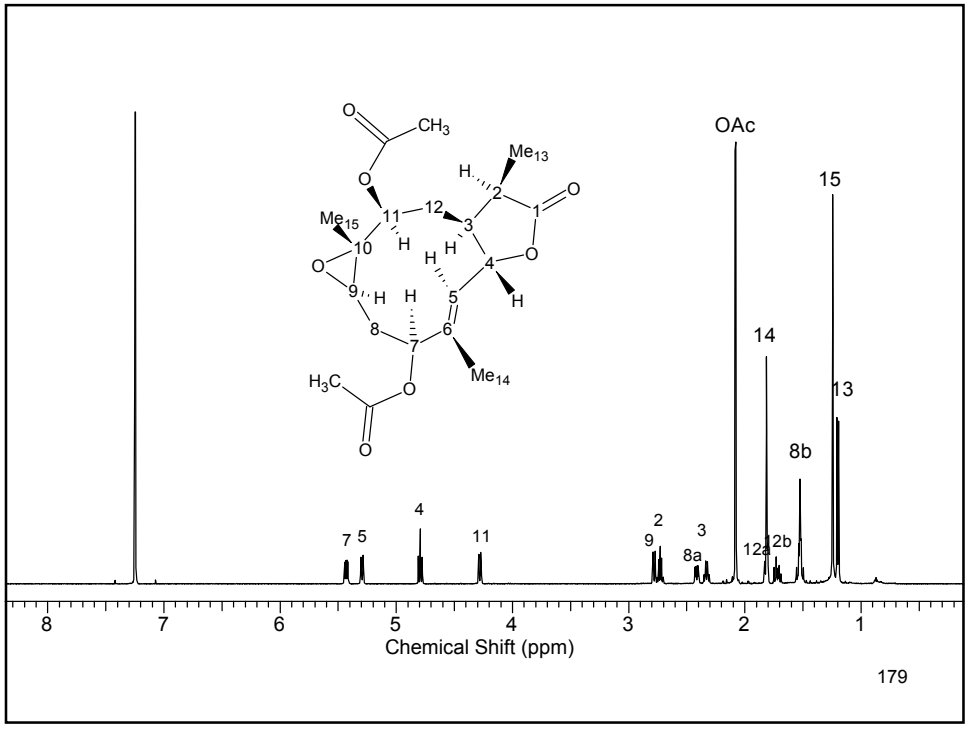

^{1}H-NMR
H in acetone at temp=268K
OH
HO
O
O
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
Chemical Shift (ppm)
174

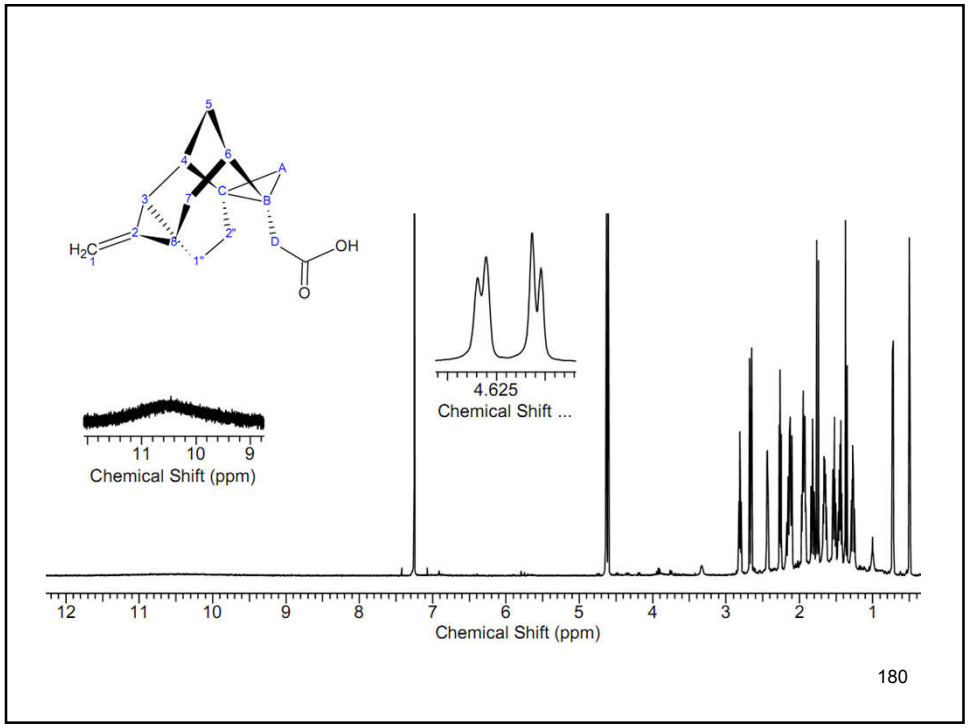

OH
HO
O
O
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
ppm
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
175


HMQC
OH
HO
O
O
16
24
32
40
48
56
64
72
80
88
96
104
112
120
ppm
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
176


HMBC
OH
HO
O
O
ppm
177


NOESY
OH
HO
O
O
ppm
178


OAc
15
14
13
8b
4
7 5
11
9
2
8a
3
12a
12b
8
7
6
5
4
3
2
1
Chemical Shift (ppm)
179


4.625
Chemical Shift ...
11
10
9
Chemical Shift (ppm)
12
11
10
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)
180