Multidimensional NMR Experiments

Chem 4010/5326:
Organic Spectroscopic Analysis

2D NMR Spectroscopy
General Information

– More complicated experiments to set up than ^1H and ^{13}C

– Changes in pulses (#, length, angles, mixing times, etc.)

– Observe effects based on relationship of nuclei
> **Can be homonuclear (same nuclei) (e.g. H–H) or heteronuclear (different nuclei) (e.g. H–C, H–P, etc.)**

– Will only go over the what the experiments tell you and how to interpret, and only for the most common and widely used for solving organic structures
> – DEPT, H–H COSY, HMQC (HETCOR), HMBC, INADEQUATE

– There is a whole alphabet soup of other experiments (both 1D and 2D)
> – EXSY, TOCSY, HOHAHA, INEPT, WATERGATE, and many more

http://www.chem.ox.ac.uk/spectroscopy/nmr/acropage.htm

2D NMR Spectroscopy
Number of Protons on Carbon

<u>DEPT (*D*istortionless *E*nhancement by *P*olarisation *T*ransfer)</u>

- Used to be known as APT (<u>A</u>ttached <u>P</u>roton <u>T</u>est)
  - DEPT is ^{1}H-detected; APT is ^{13}C-detected

- Tells you how many protons are attached to a particular carbon
  - negative peaks = CH_2
  - positive peaks = CH and CH_3 (distinguishable with further processing)
  - "missing" peaks = carbons w/o protons

- With a little help from IR and chemical shift of ^{1}H and ^{13}C, can get a rough idea of molecular weight

2D NMR Spectroscopy
Number of Protons on Carbon

DEPT (*D*istortionless *E*nhancement by *P*olarisation *T*ransfer)

1 = Carbon spectrum   **2** = ↓ CH_2 **3** = ↑ CH
                                           ↑ CH, CH_3
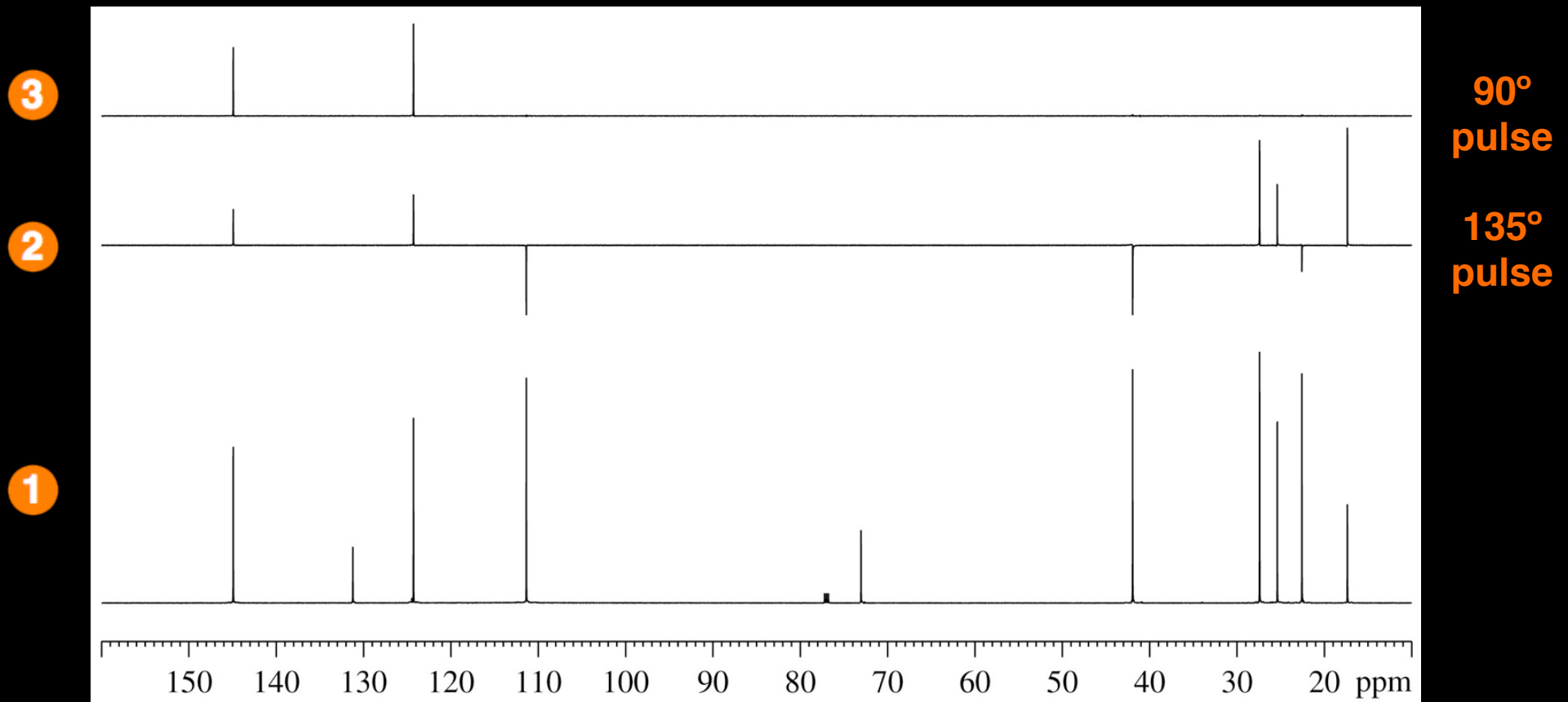
**90° pulse**

135° pulse

2D NMR Spectroscopy
Who is Talking to Who?

$^1H-^1H$ COSY (*C*orrelation *S*pectroscop*y*)
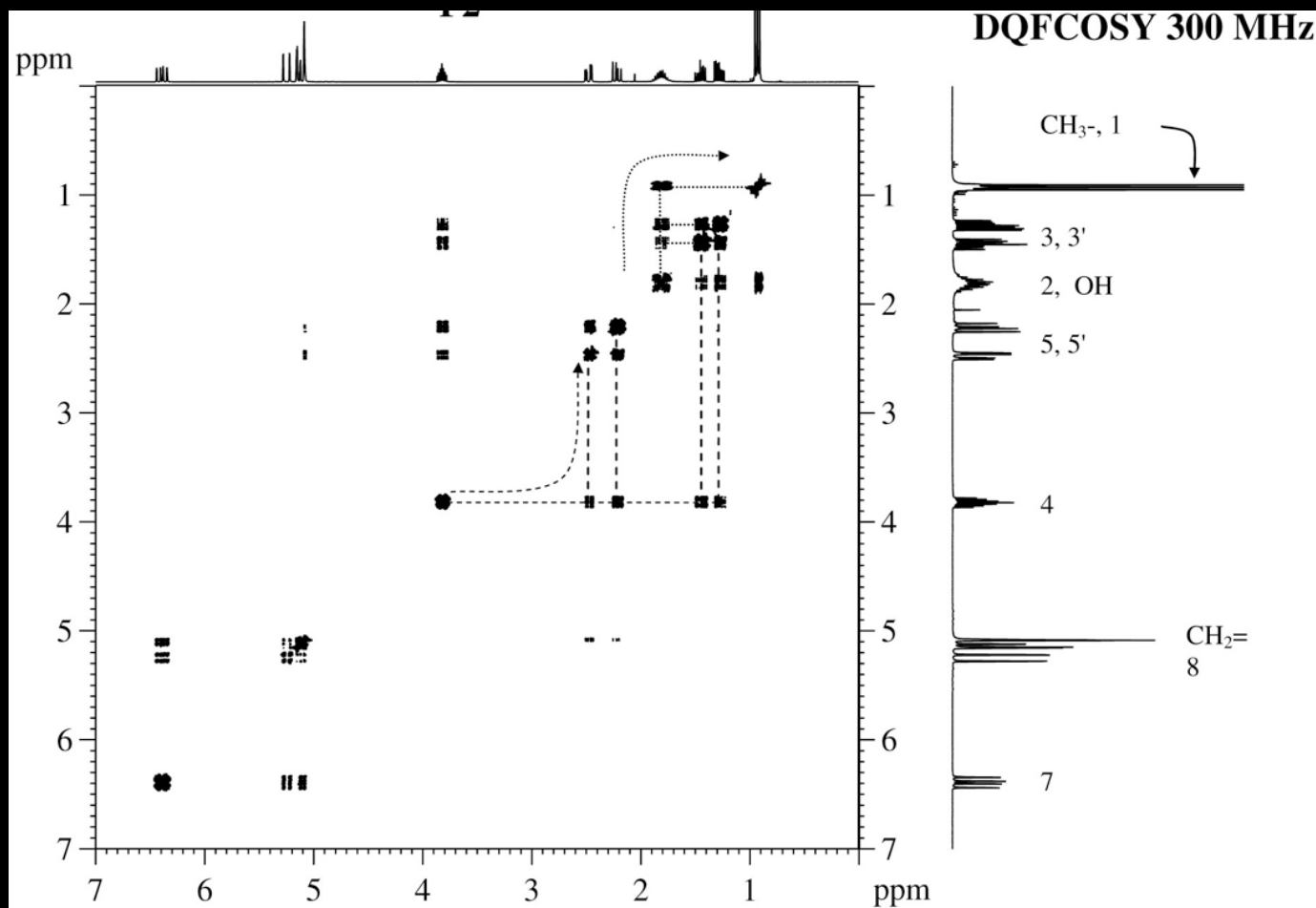
– Tells you which protons are coupled to one another

– Very useful when peaks are overlapping in ^1H NMR and you are unable to calculate coupling constants, or when there are a lot of similar coupling constants

– Cross peaks are coupled to each other

1 bond H–H coupling

COSY 600 MHz
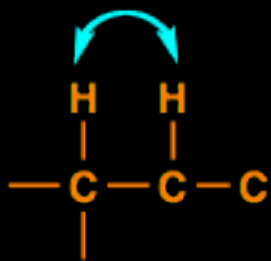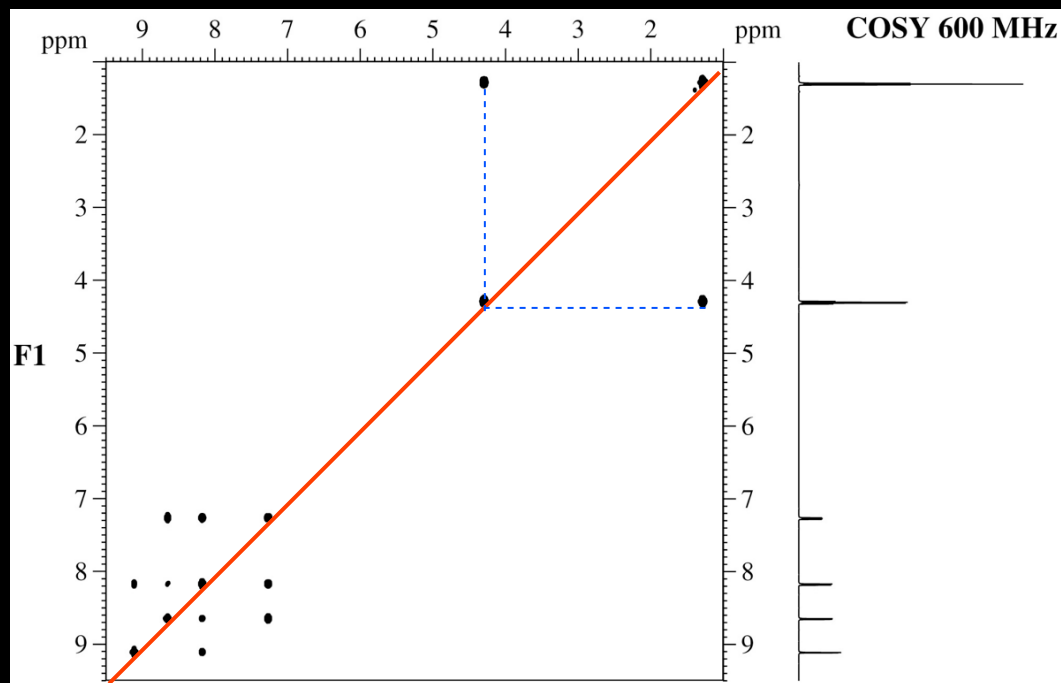
– Newer method is DQF (<u>D</u>ouble <u>Q</u>uantum <u>F</u>iltered)-COSY
  – same information, but looks "cleaner"

2D NMR Spectroscopy
Who is Talking to Who?

<u>^{1}H–^{1}H COSY (*C*orrelation *S*pectroscop*y*)</u>

– Overlapping protons and a lot of similar coupling constants
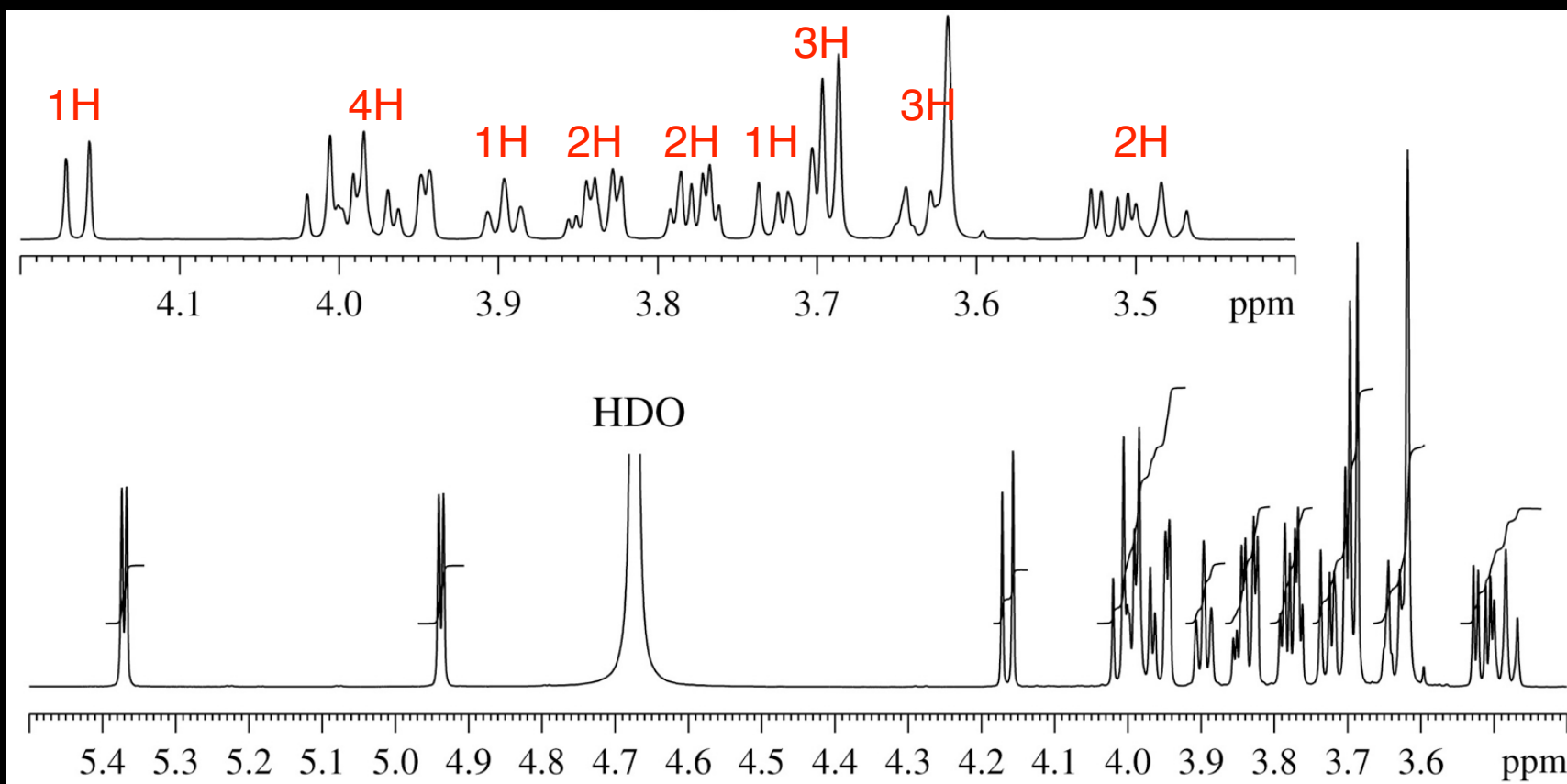
Raffinose–a trisaccharide

2D NMR Spectroscopy
Who is Talking to Who?

<u>$^1H–^1H$ COSY (*C*orrelation *S*pectroscop*y*)</u>

COSY 600 MHz

Raffinose–a trisaccharide

2D NMR Spectroscopy
Who is Talking to Who?

<u>^{1}H–^{1}H COSY (*C*orrelation *S*pectroscop*y*)</u>

2D NMR Spectroscopy
Who is Talking to Who?

$^1H–^1H$ COSY (*C*orrelation *S*pectroscop*y*)

– DQF-COSY: *D*ouble *Q*uantum *F*iltered COSY – cleans up the spectrum by reducing noncoupled systems (e.g. CH3 singlets)

Ipsenol

COSY 300 MHz

Diagonal peak

Symmetric cross peaks
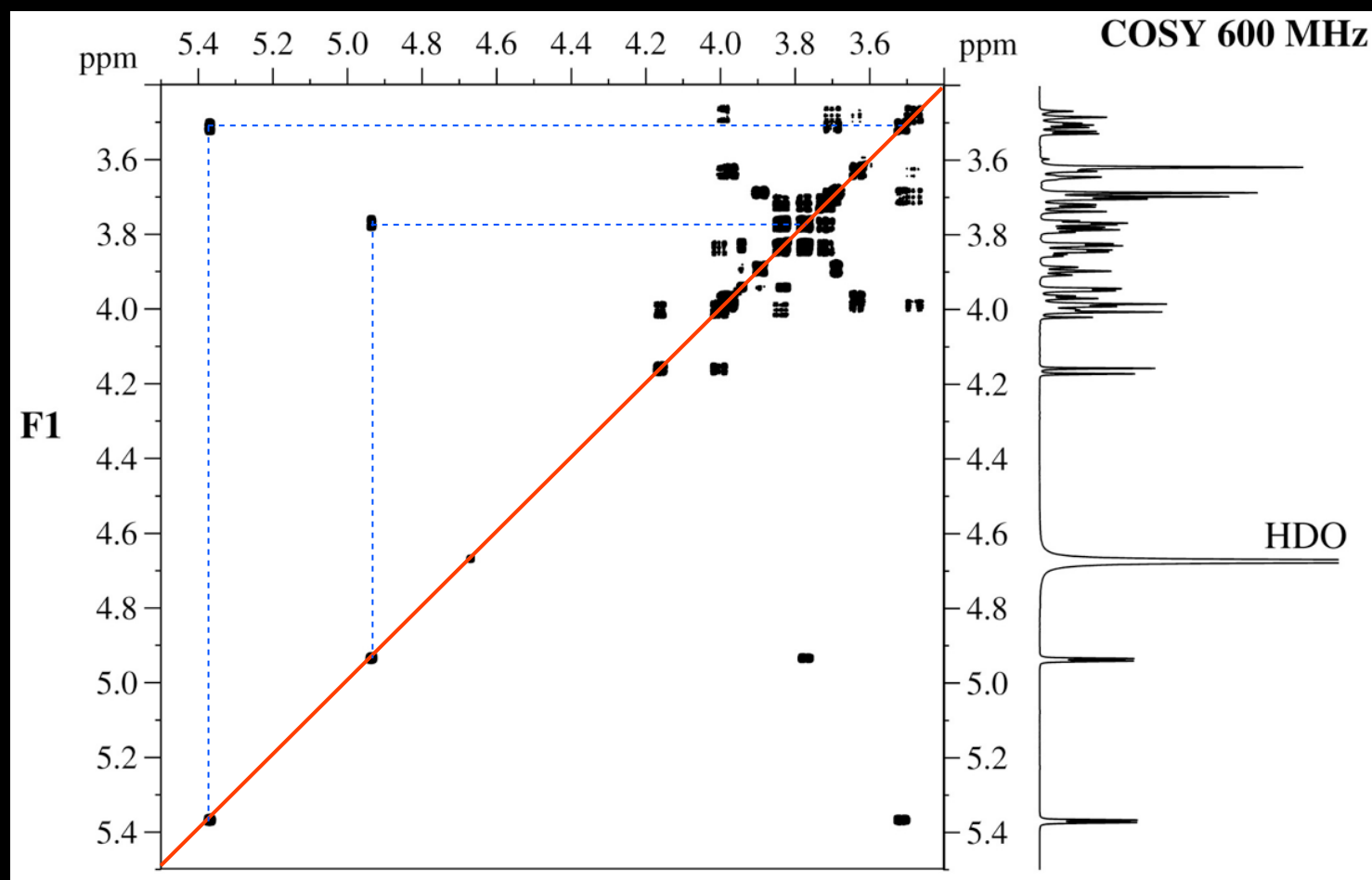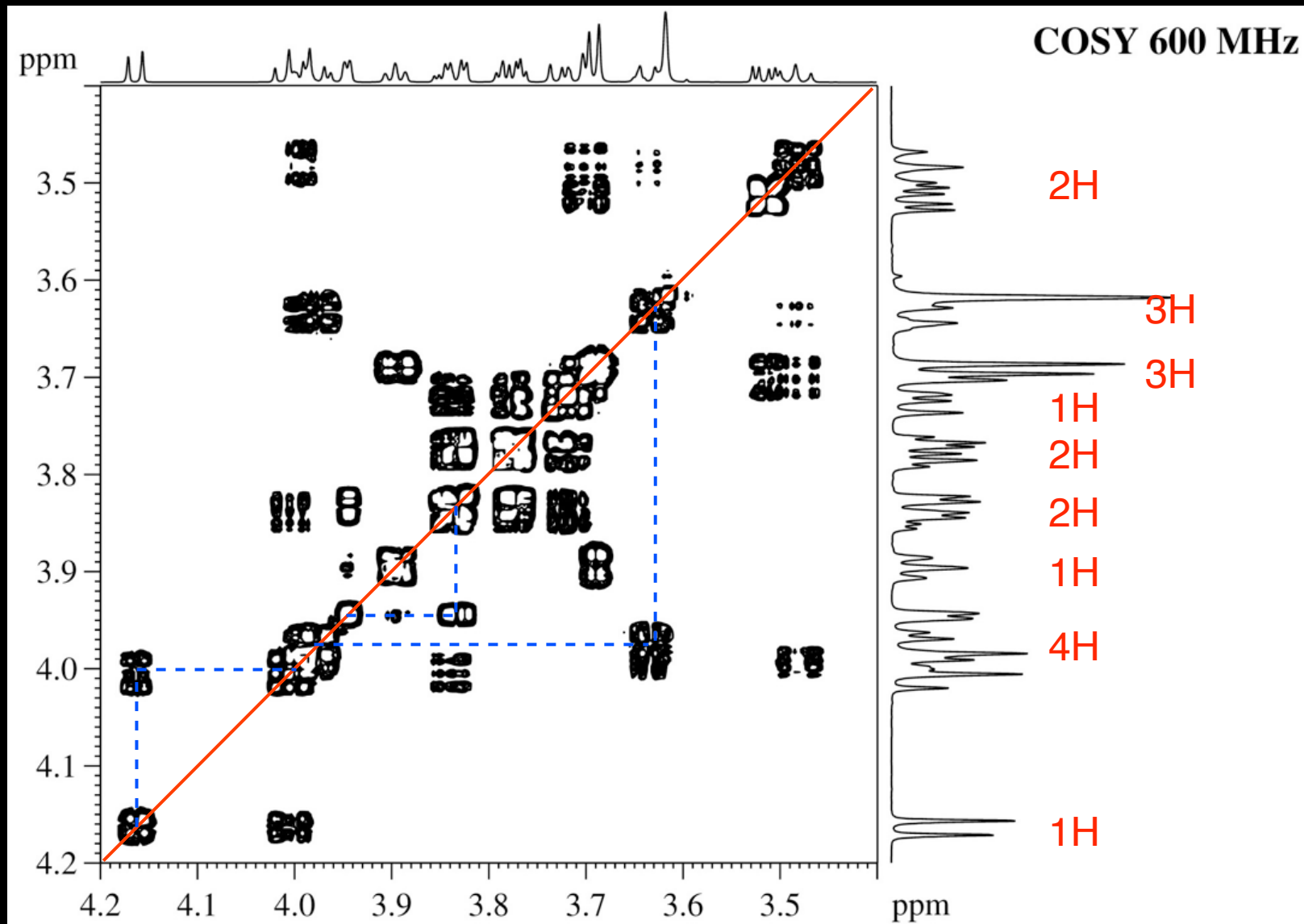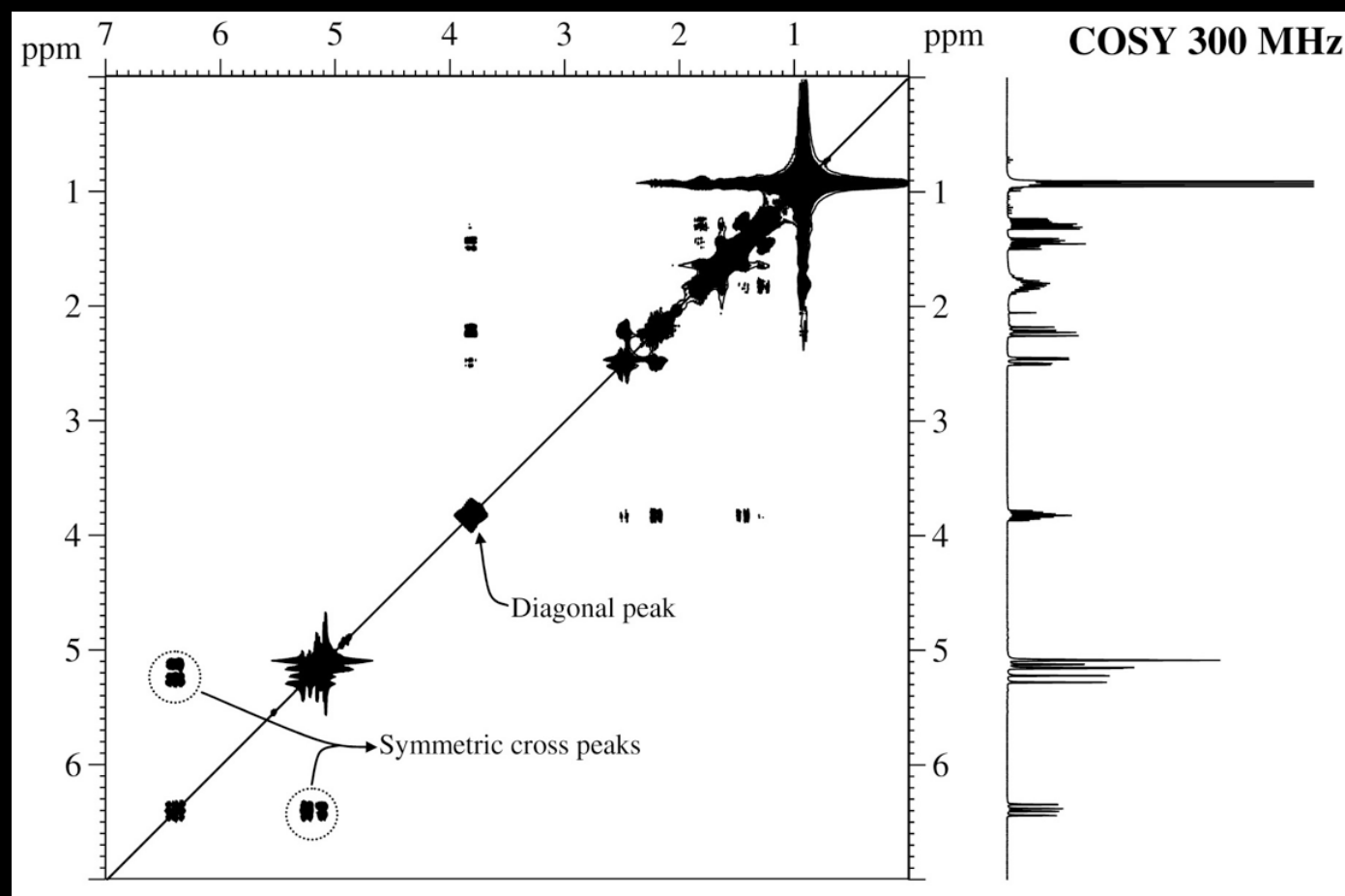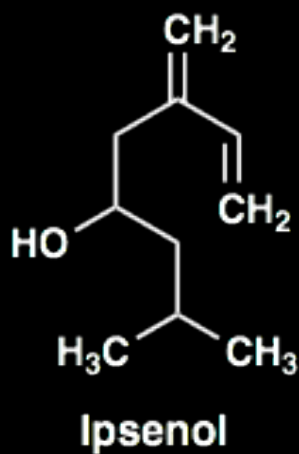
2D NMR Spectroscopy
Who is Talking to Who?

$^1H–^1H$ COSY (Correlation Spectroscopy)

– DQF-COSY: Double Quantum Filtered COSY – cleans up the spectrum by reducing noncoupled systems (e.g. CH3 singlets)

2D NMR Spectroscopy
Who is Talking to Who?

<u>$^1H-^1H$ COSY (*C*orrelation *S*pectroscop*y*)</u>

$C_6H_{10}O_2$
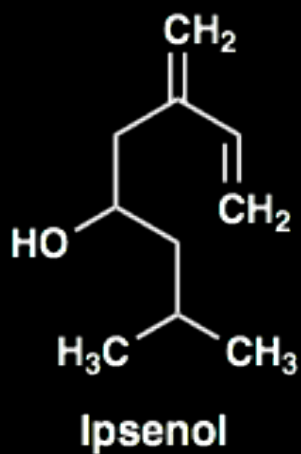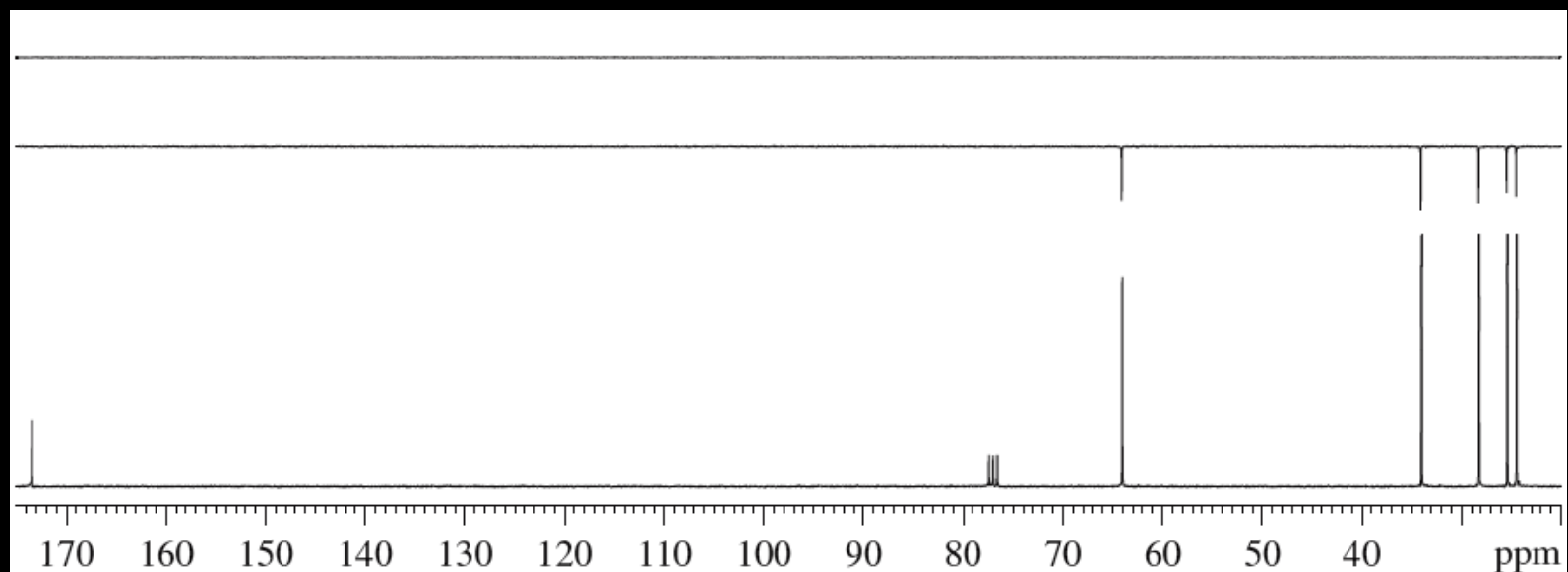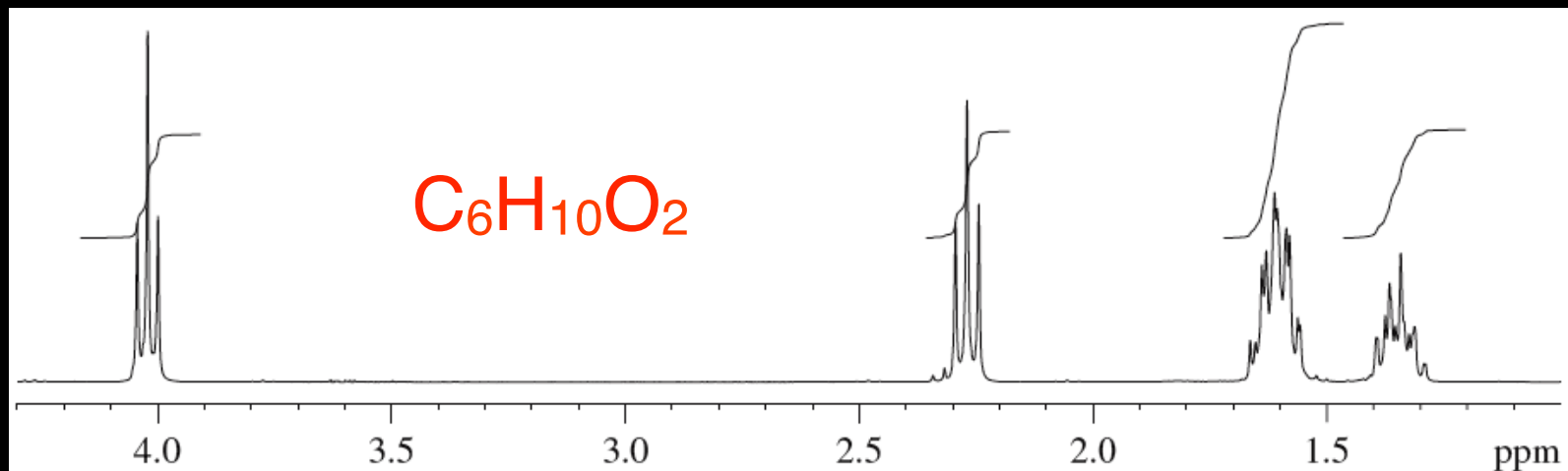
2D NMR Spectroscopy
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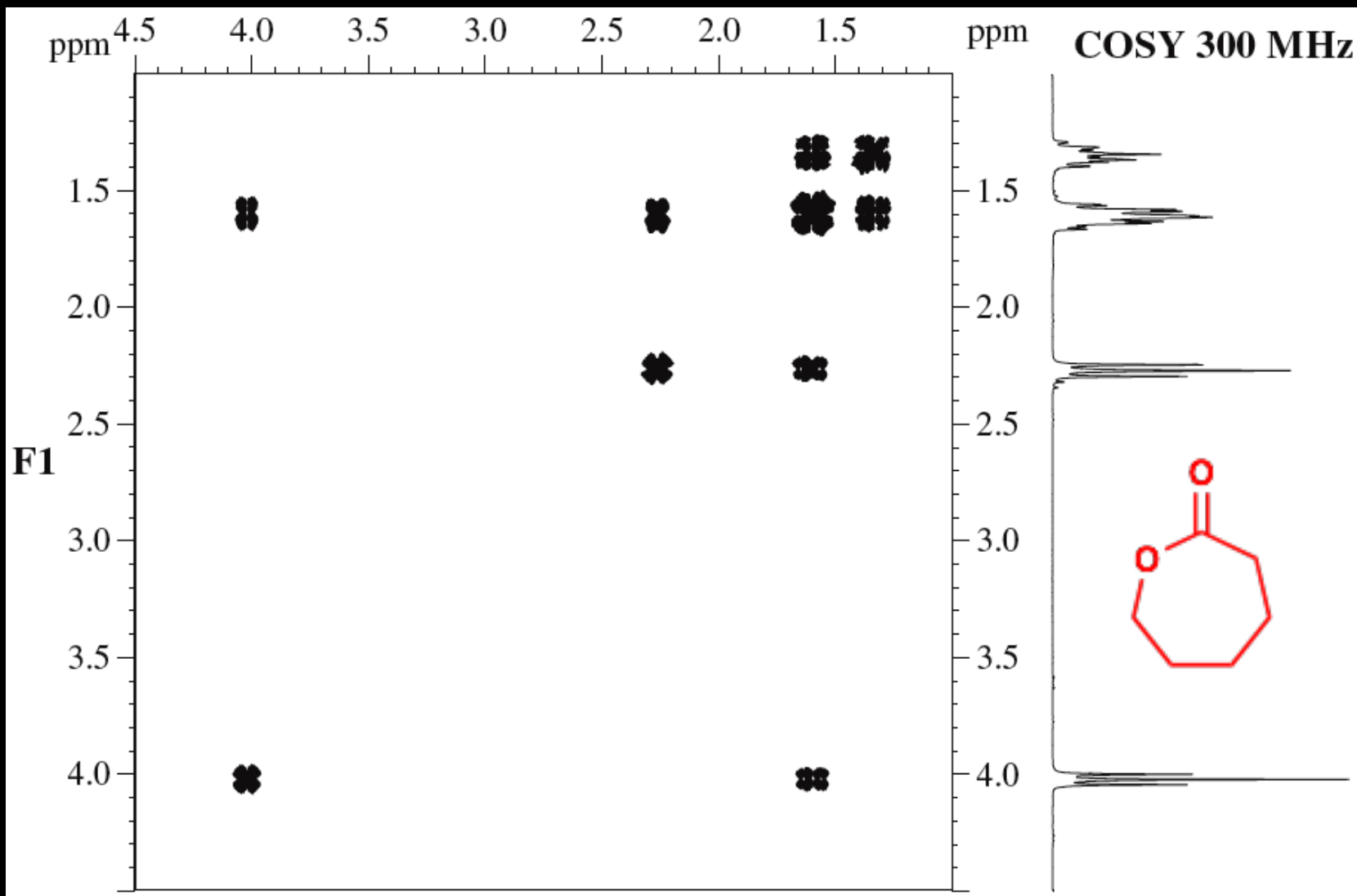
Recall...
¹H–¹H COSY

– Tells you which protons are coupled to one another

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– Cross peaks are coupled to each other
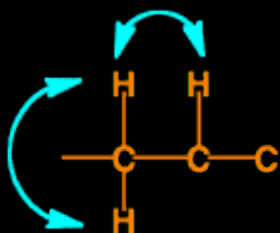
2 & 3 bond H–H coupling
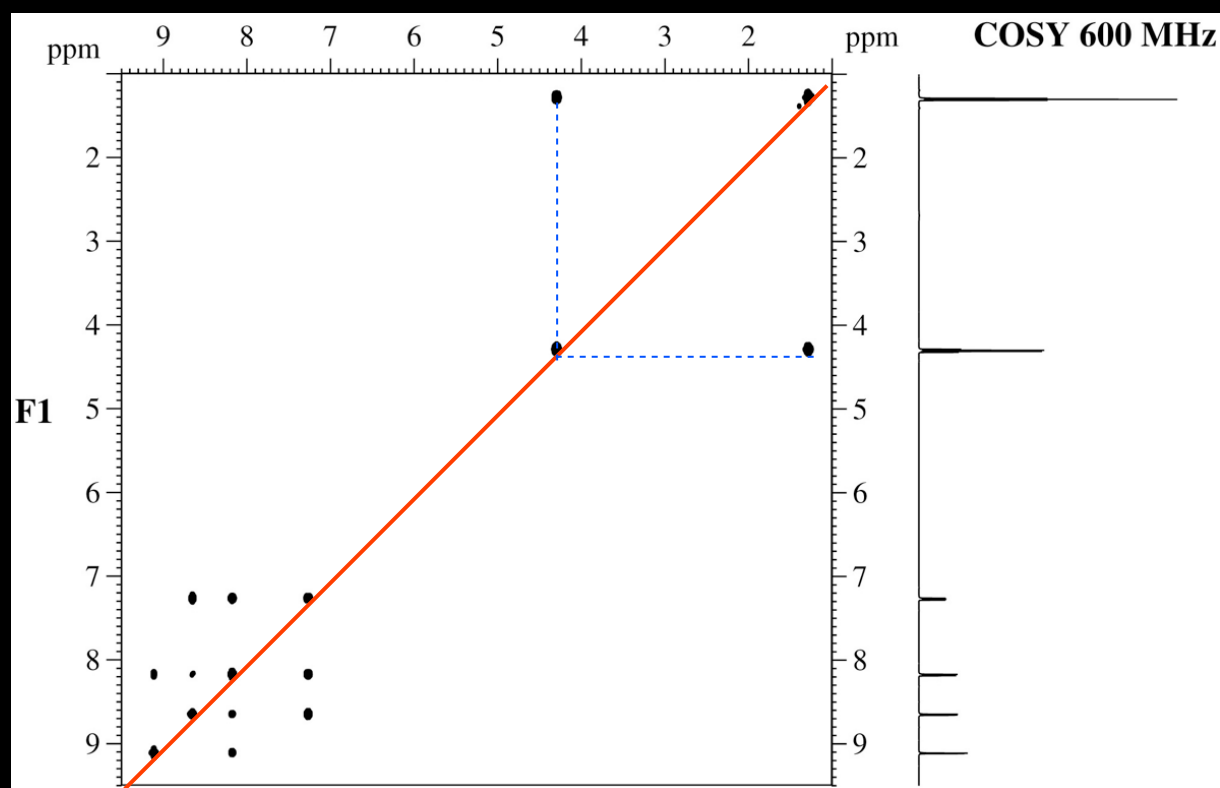
Recall...
¹H–¹H COSY

This can still cause ambiguities!

– Tells you which protons are coupled to one another

– Very useful when peaks are overlapping in ¹H NMR and you are unable to calculate coupling constants, or when there are a lot of similar coupling constants

– Cross peaks are coupled to each other
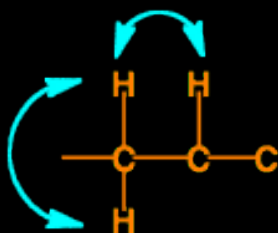
2 & 3 bond H–H coupling
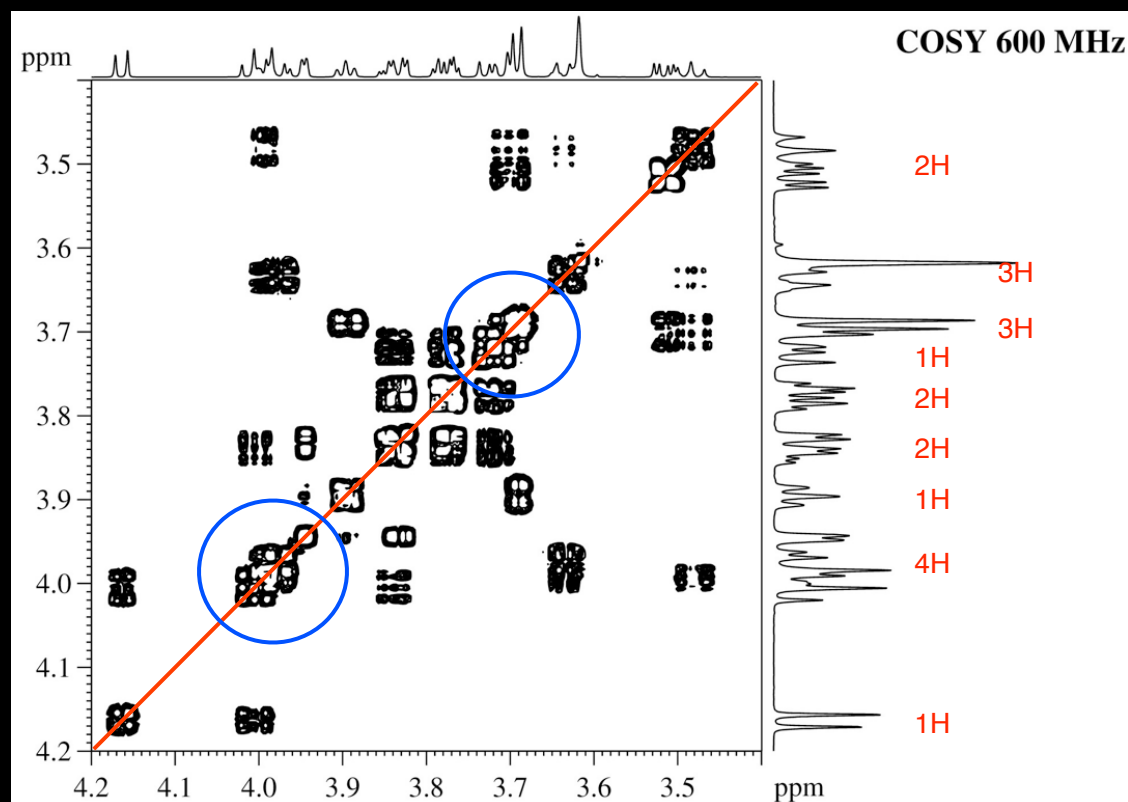
2D NMR Spectroscopy
Who is Talking to Who?

<u>^{1}H–^{1}H TOCSY (*T*otal *C*orrelation *S*pectroscopy)</u>

– Tells you which protons are in the same spin system (a continuous chain of spin-spin coupled protons)

– Magnetization from H_A is transferred to H_B, which then transfers to H_C and on down the line

– Can be run as either a 1D or 2D experiment

– Running as a 1D experiment greatly simplifies spectra with severe signal overlap

– Related experiment (HOHAHA) gives essentially the same information

– Can also observe one-bond ^{1}H–^{13}C couplings (HMQC-TOCSY, hetero-TOCSY, HEHAHA) - will not discuss

1D TOCSY
Spin System Identification

<u>$^1H–^1H$ TOCSY (*T*otal *C*orrelation *S*pectroscopy)</u>

– Irradiate at frequency of proton of interest

– Wait a period of time (typically 20 to 400 ms) and then collect 1D spectrum

– Only observe protons to which magnetization has been transferred

– Short periods of time (20 ms) will only give rise to "single step" transfers; longer periods of time allow magnetization to propagate further
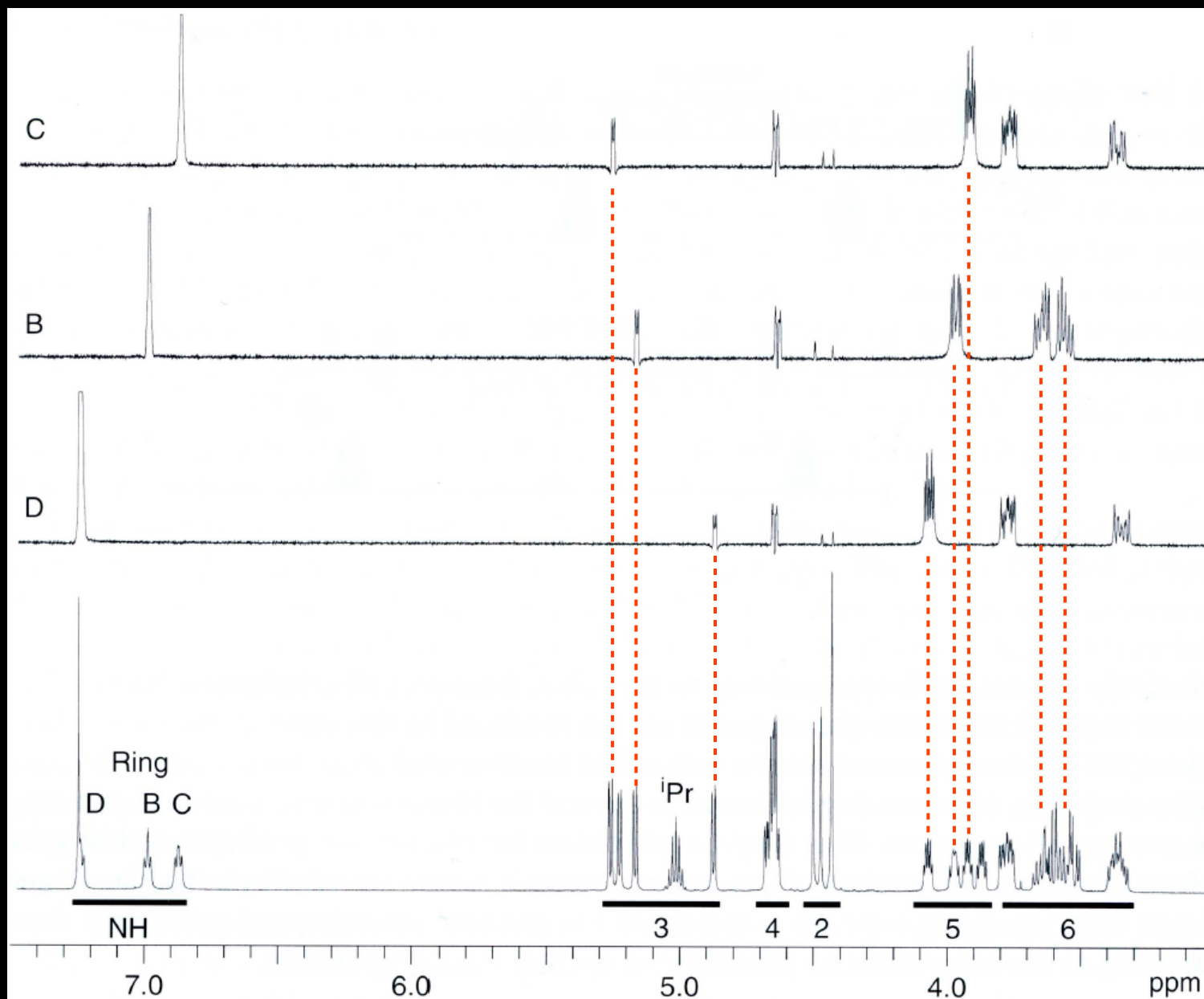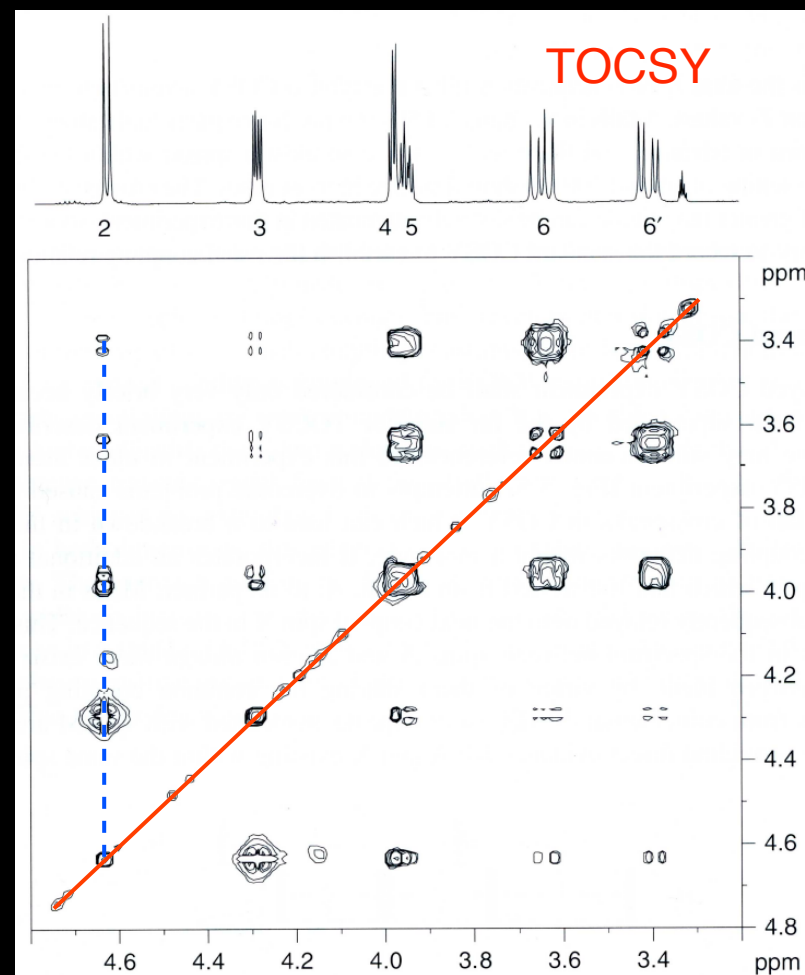

α- and β-lactose

1D TOCSY
Spin System Identification

β-lactose

H₁ ⟵ 4.67 ppm

Mixing time 400 ms β 1 irradiated

β6   β6'

Mixing time 120 ms

β5

Mixing time 80 ms

β4

Mixing time 40 ms

β3

Mixing time 20 ms

β2

¹H NMR 600 MHz

3.9   3.8   3.7   3.6   3.5   3.4   3.3   ppm

1D TOCSY

1D TOCSY

Claridge, T. D. W. *High-Resolution NMR Techniques in Organic Chemistry*, 2nd Ed., Elsevier, 2009.
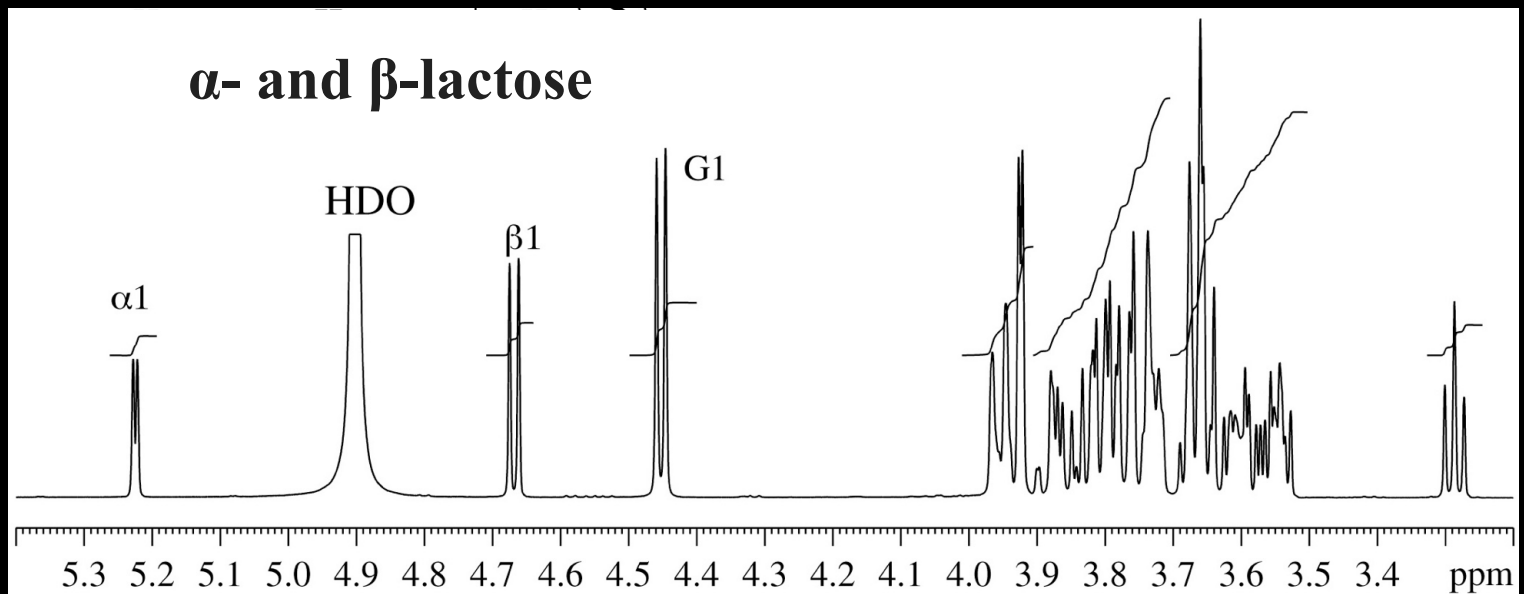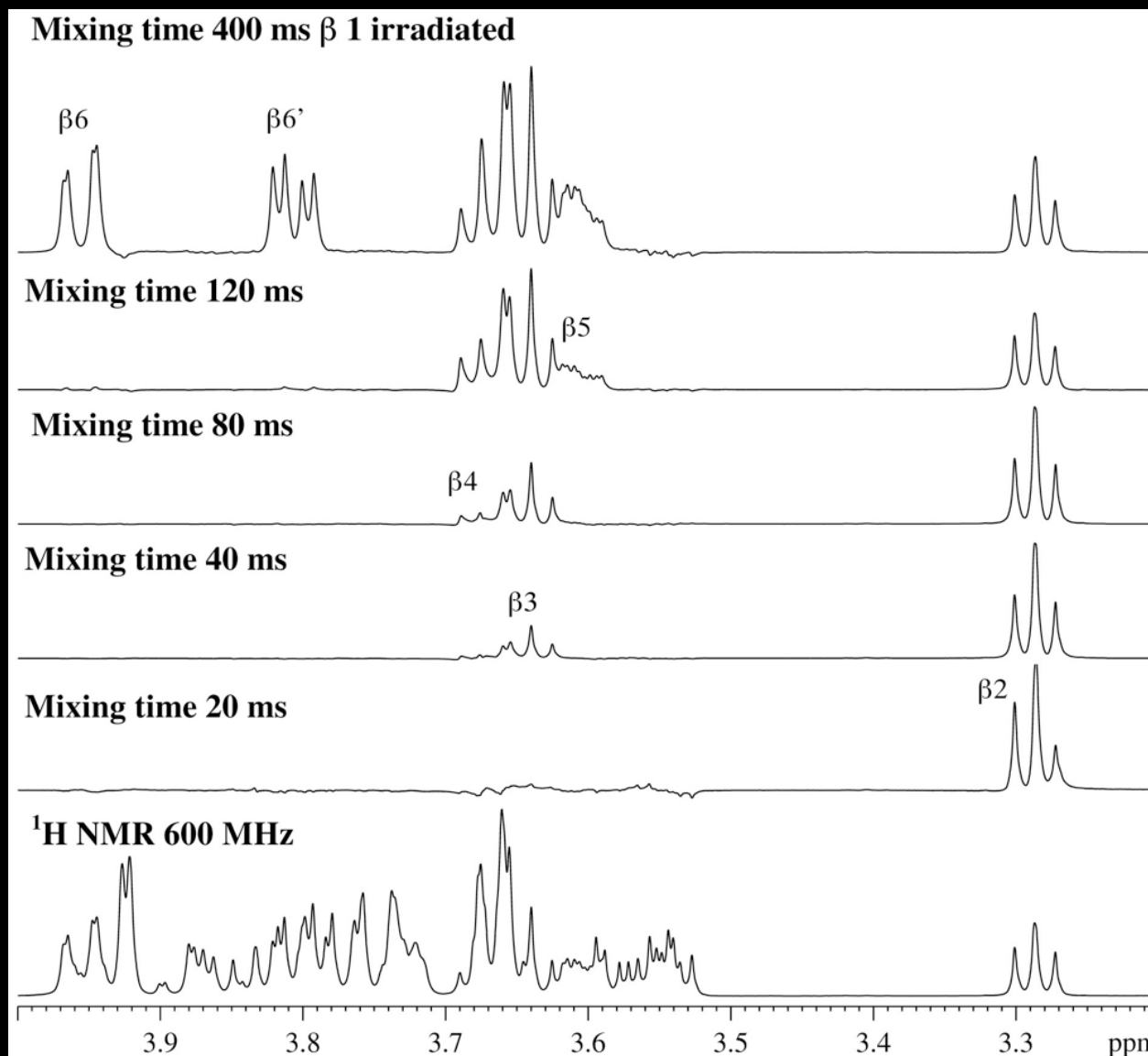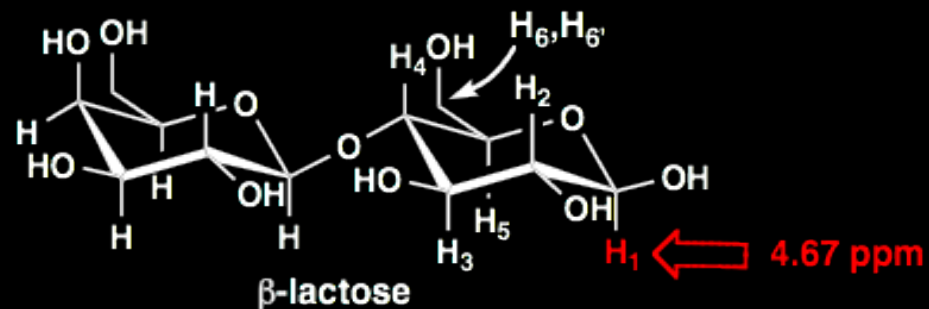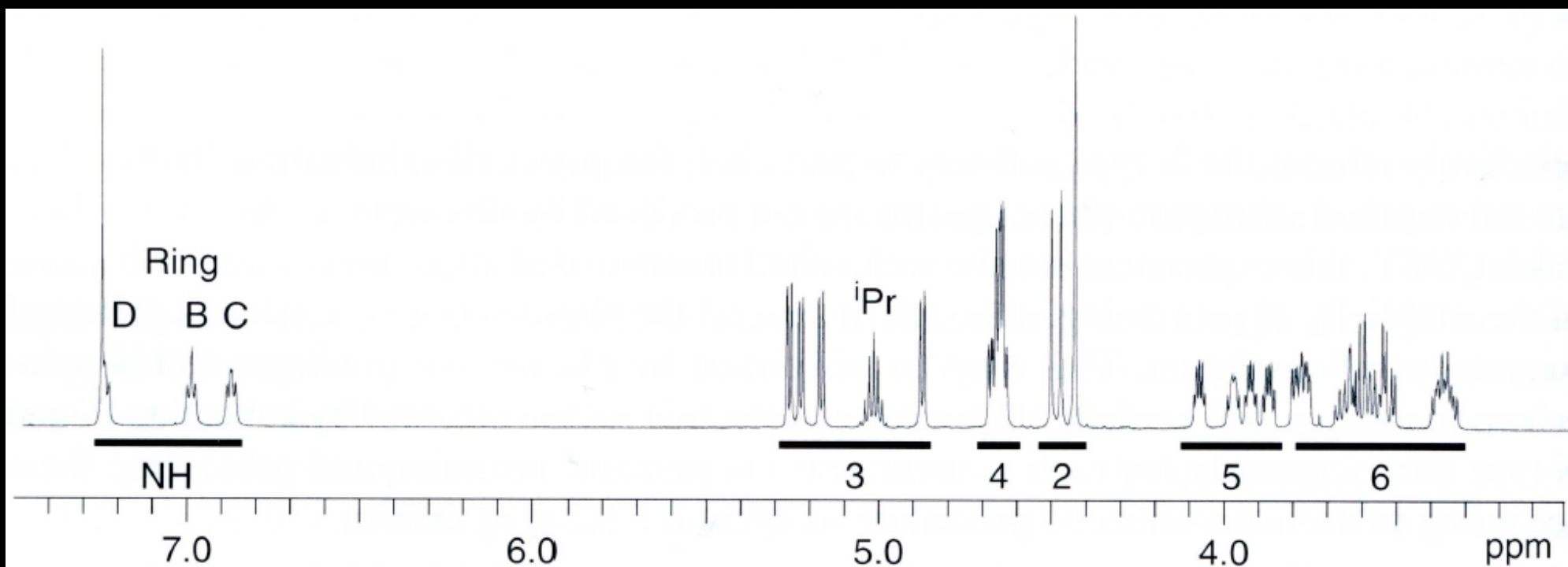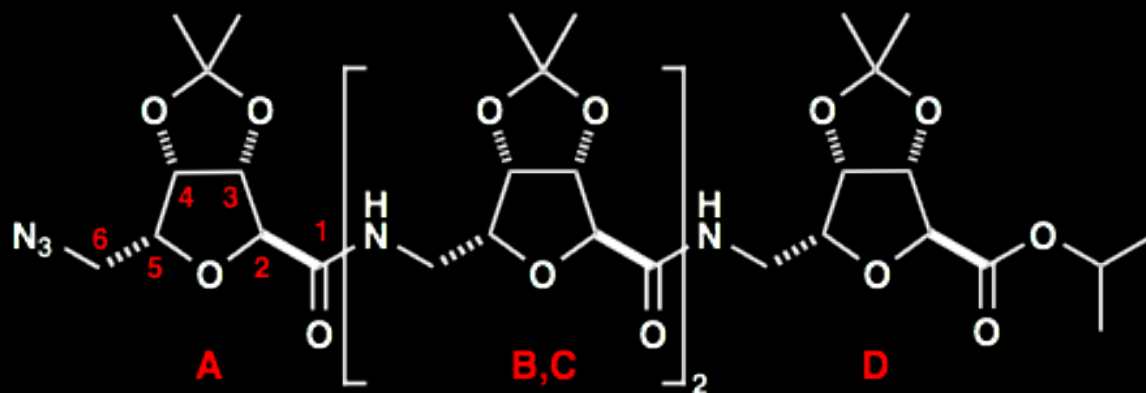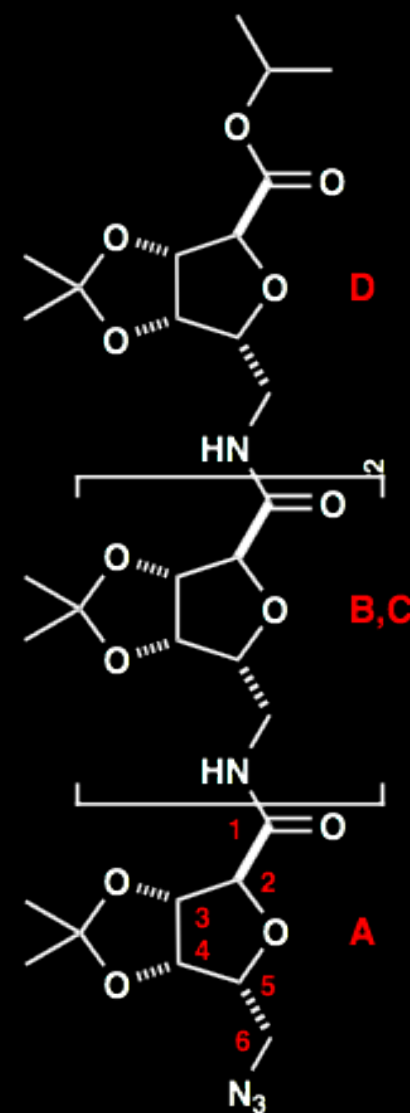
2D TOCSY
Spin System Identification

^{1}H–^{1}H TOCSY (*T*otal *C*orrelation *S*pectroscopy)

– Cross peaks are in the same spin system
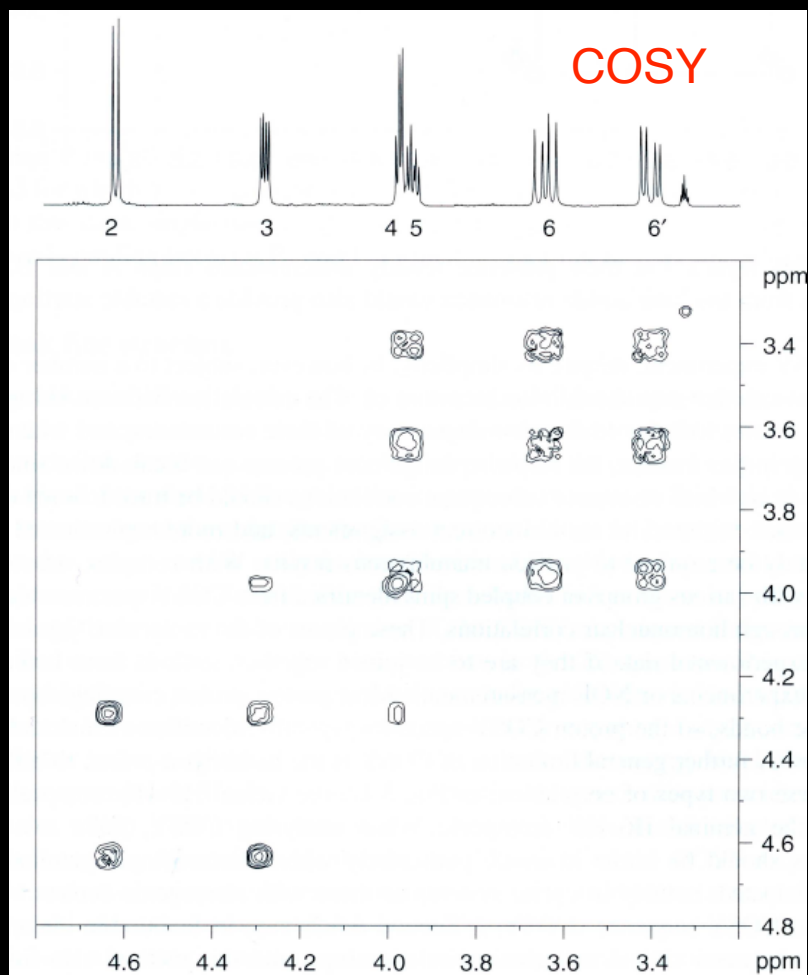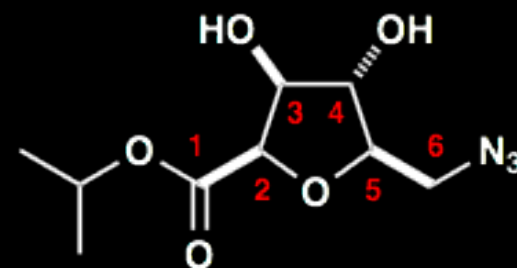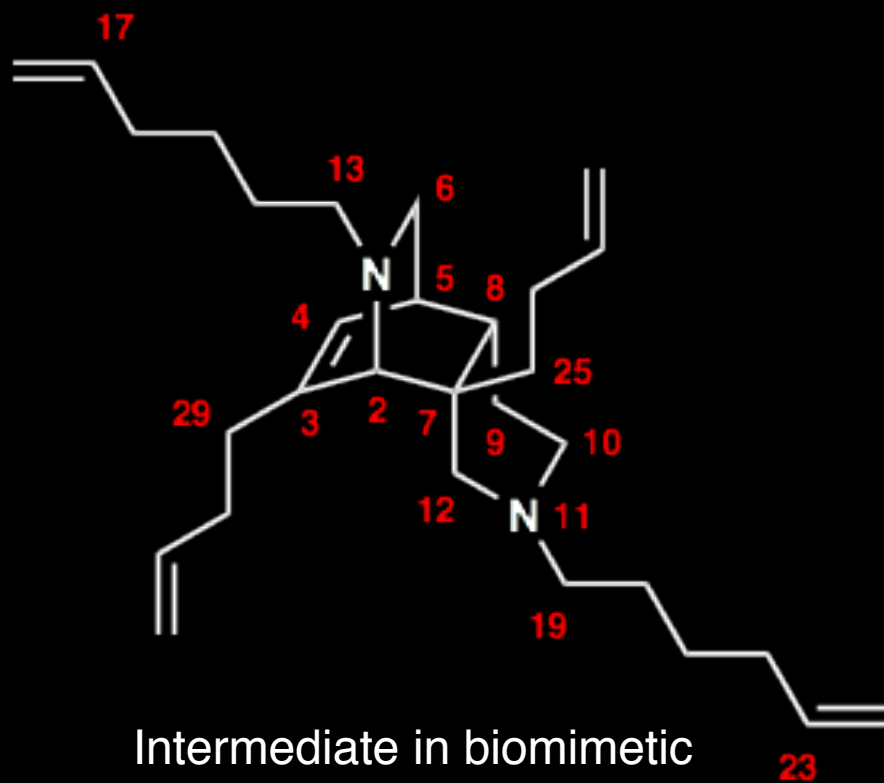
COSY

TOCSY

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2D TOCSY

– Cross peaks are in the same spin system

Intermediate in biomimetic
synthesis of manzamine

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2D TOCSY

– Cross peaks are in the same spin system

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2D TOCSY

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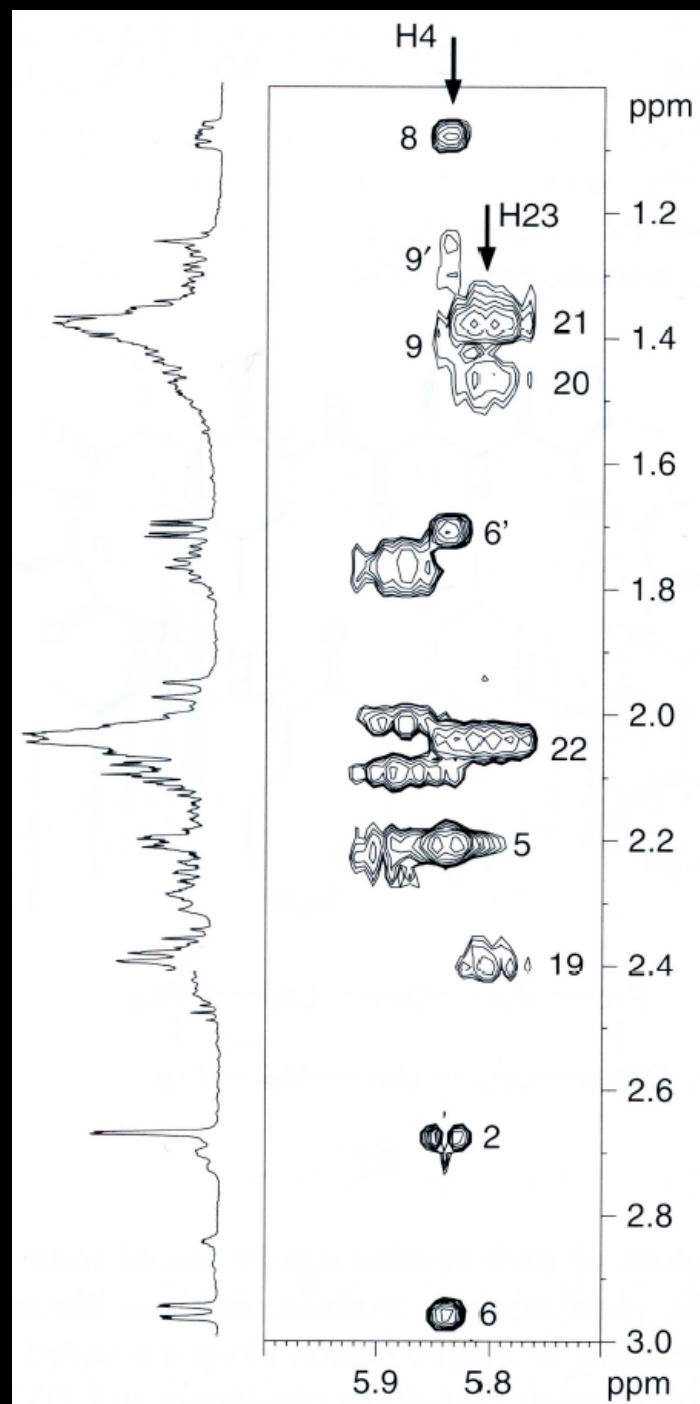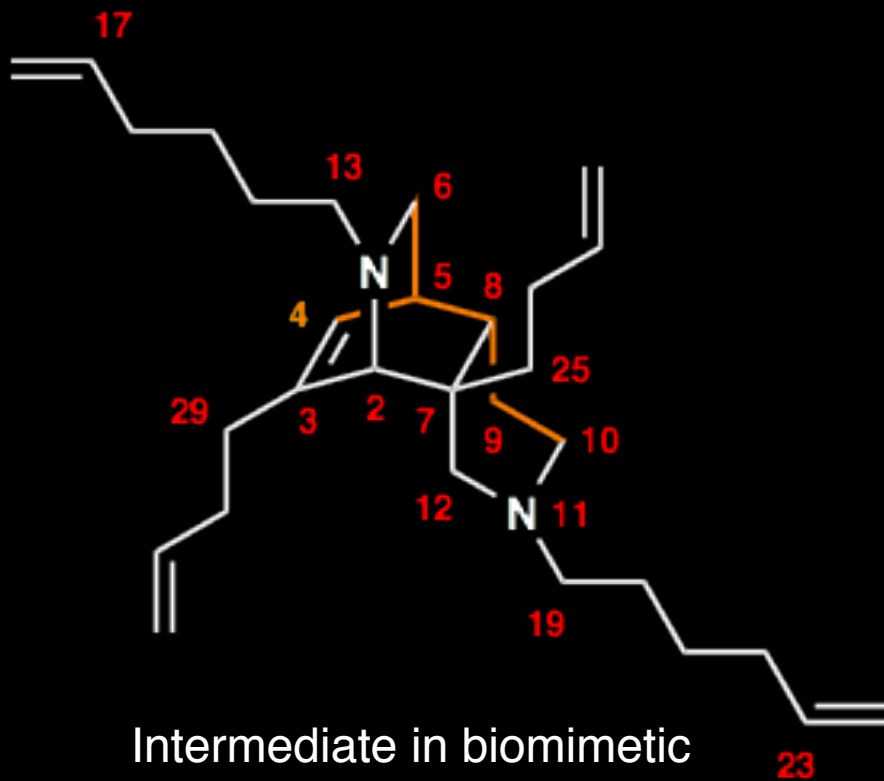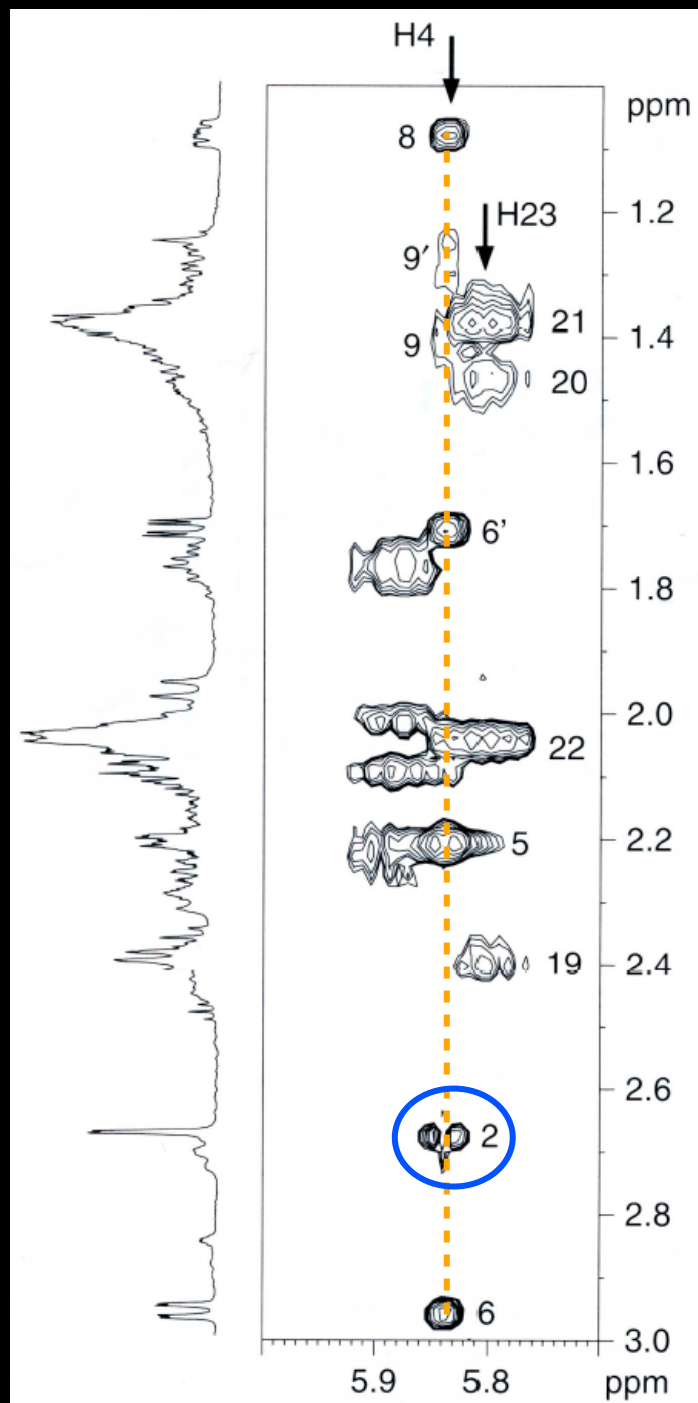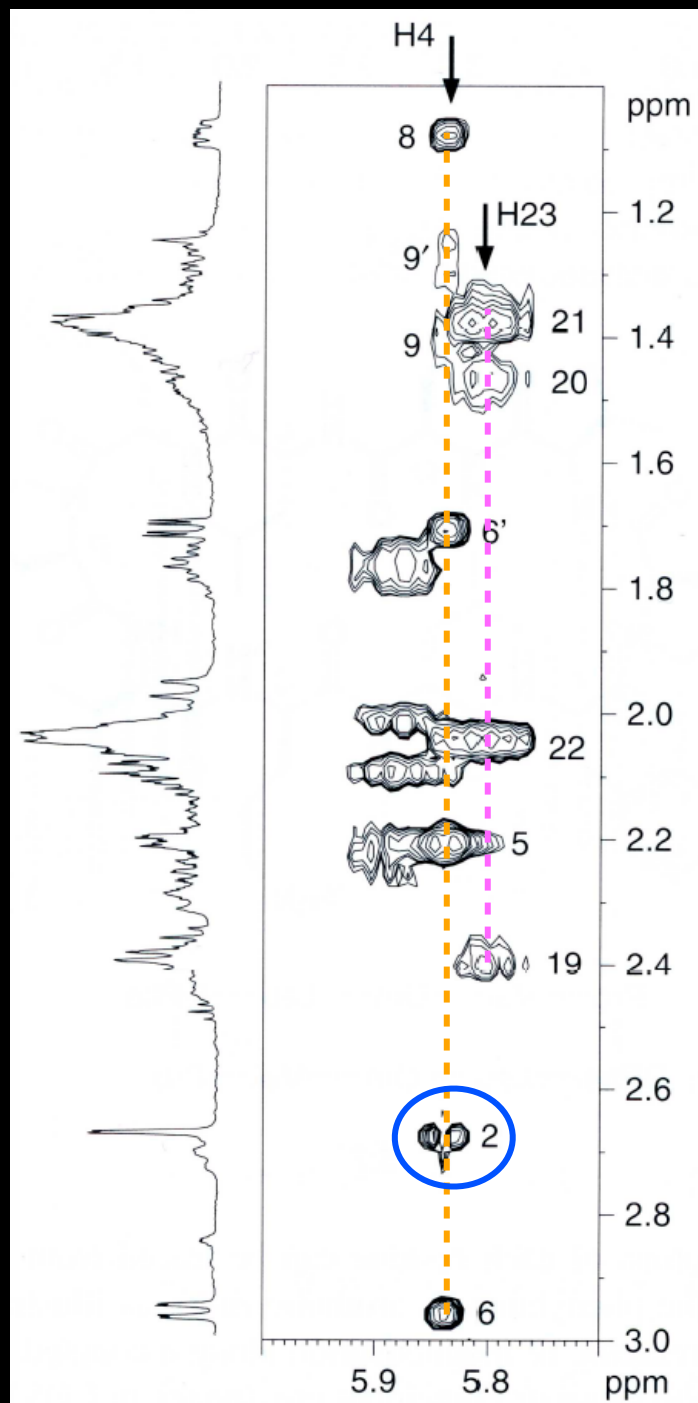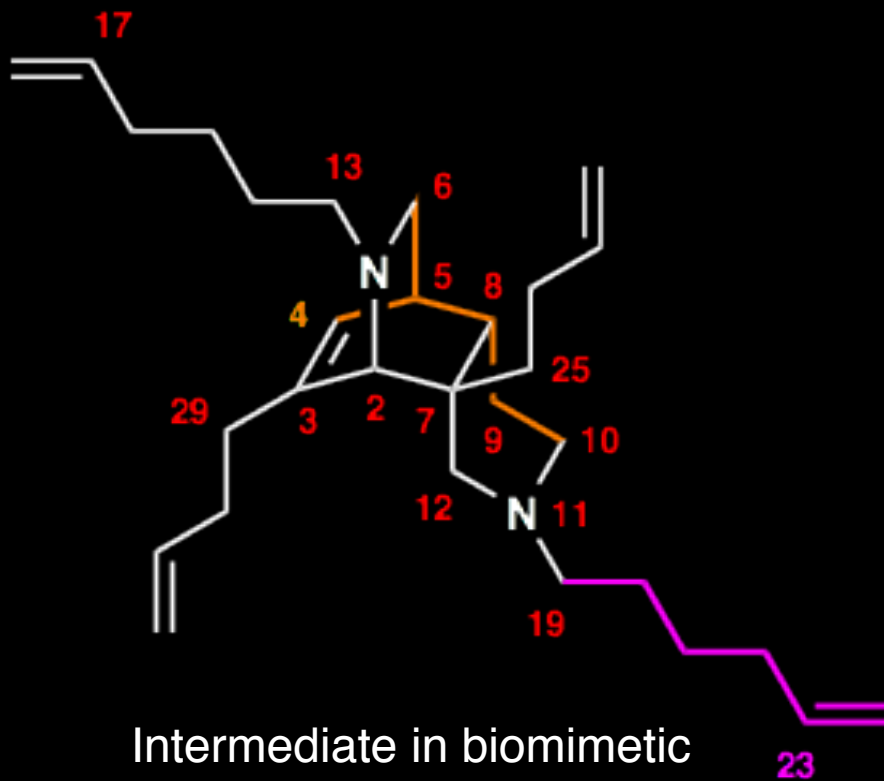
New Developments
Deconvolution via MDEC

MDEC (*M*ulti Frequency Homonuclear *De*coupling)

– Conceptually the same as the homonuclear decoupling experiment mentioned earlier, but allows multiple frequencies to be decoupled *at the same time*
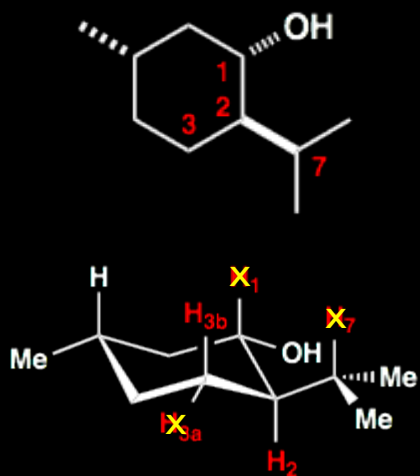
(a) ¹H NMR
(b) irr @ H-1
(c) irr @ H-1/H-7
(d) irr @ H-1/H-3a/H-7

J. Am. Chem. Soc. **2009**, *131*, 15994–15995
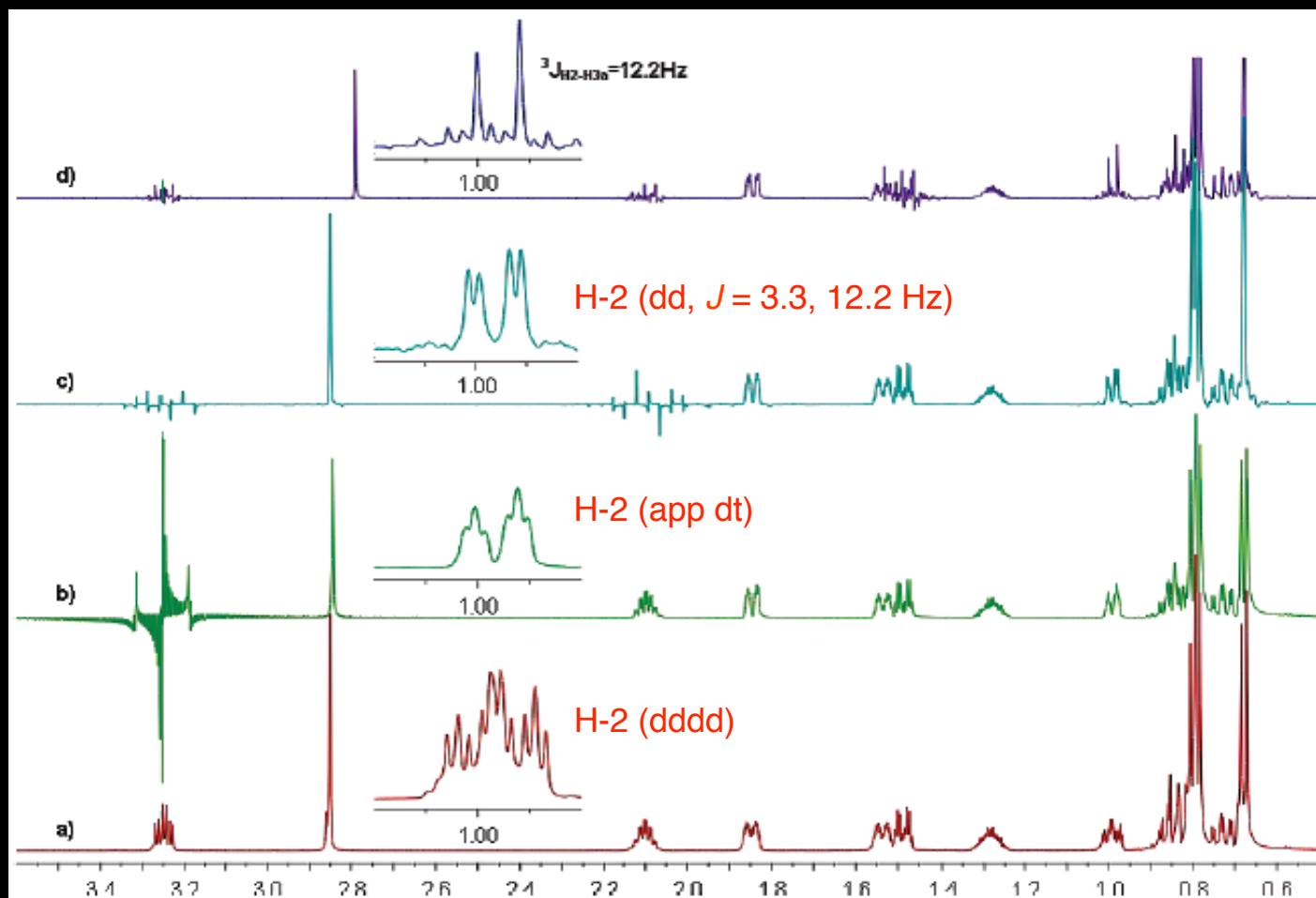
New Developments
Deconvolution via MDEC

1D-TOCSY-MDEC
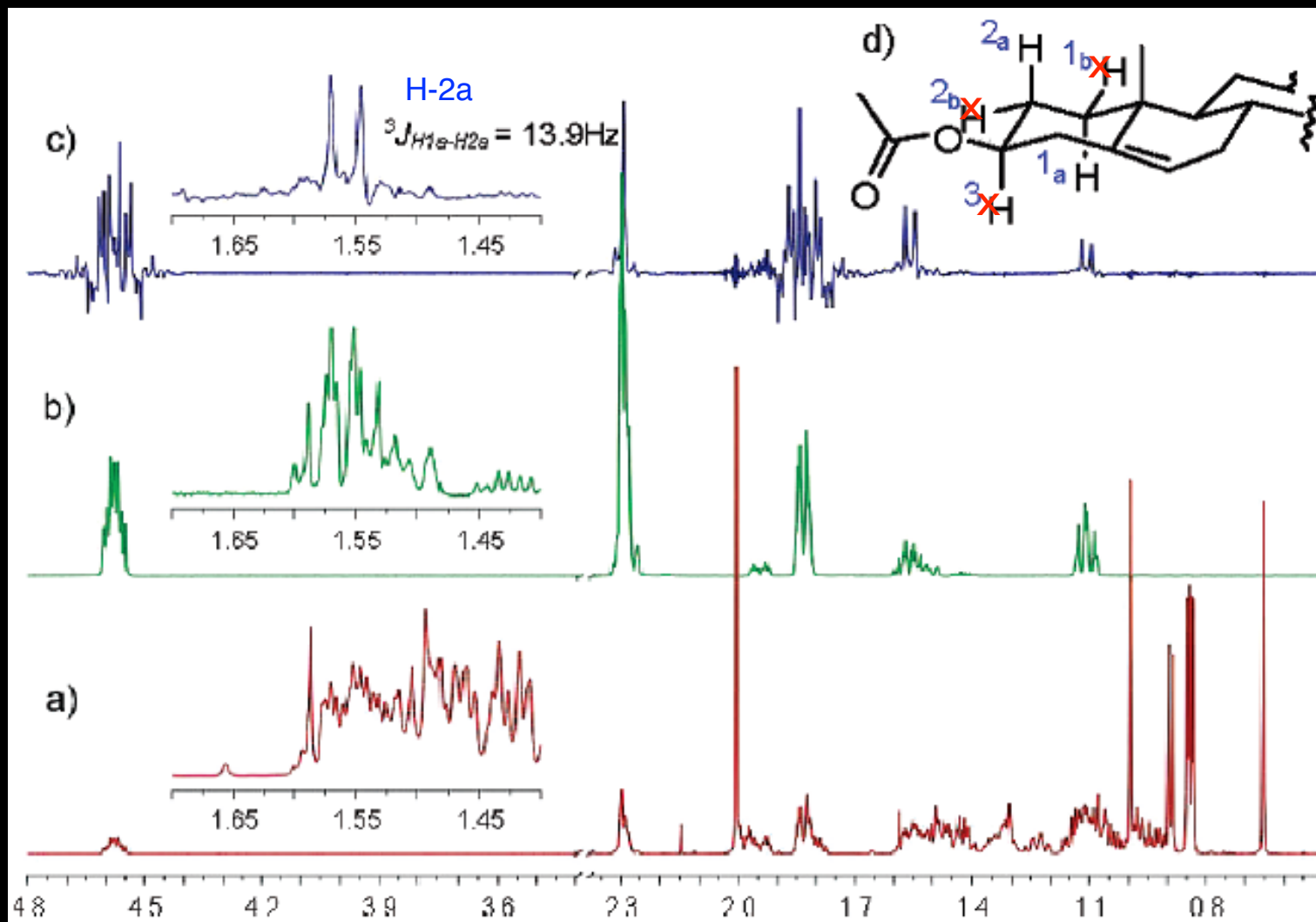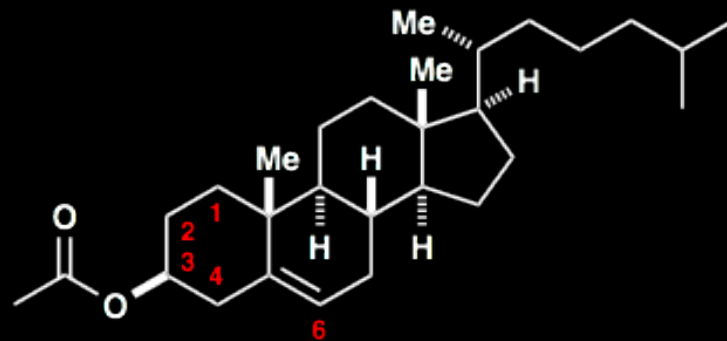
(a) ^{1}H NMR

(b) 1D-TOCSY
    irr @ H-3

(c) 1D-TOCSY
    irr @ H-3 with
    MDEC @ H-1b,
    H-2b, H-3

2D NMR Spectroscopy
Who is Talking to Who?

^{1}H–^{13}C COSY

– HETCOR (Heteronuclear Correlation)
   – older experiment; ^{13}C-detected

– HMQC (Heteronuclear Multiple Quantum Correlation) and
  HSQC (Heteronuclear Single Quantum Correlation)
   – newer experiments; ^{1}H-detected; largely replaced HETCOR

– Both give same information, experimentally very different

– Peaks have one-bond coupling (i.e. attached directly)

– Compliments DEPT

– Particularly useful for diastereotopic protons

1 bond H–C coupling

2D NMR Spectroscopy
Who is Talking to Who?
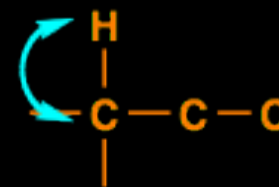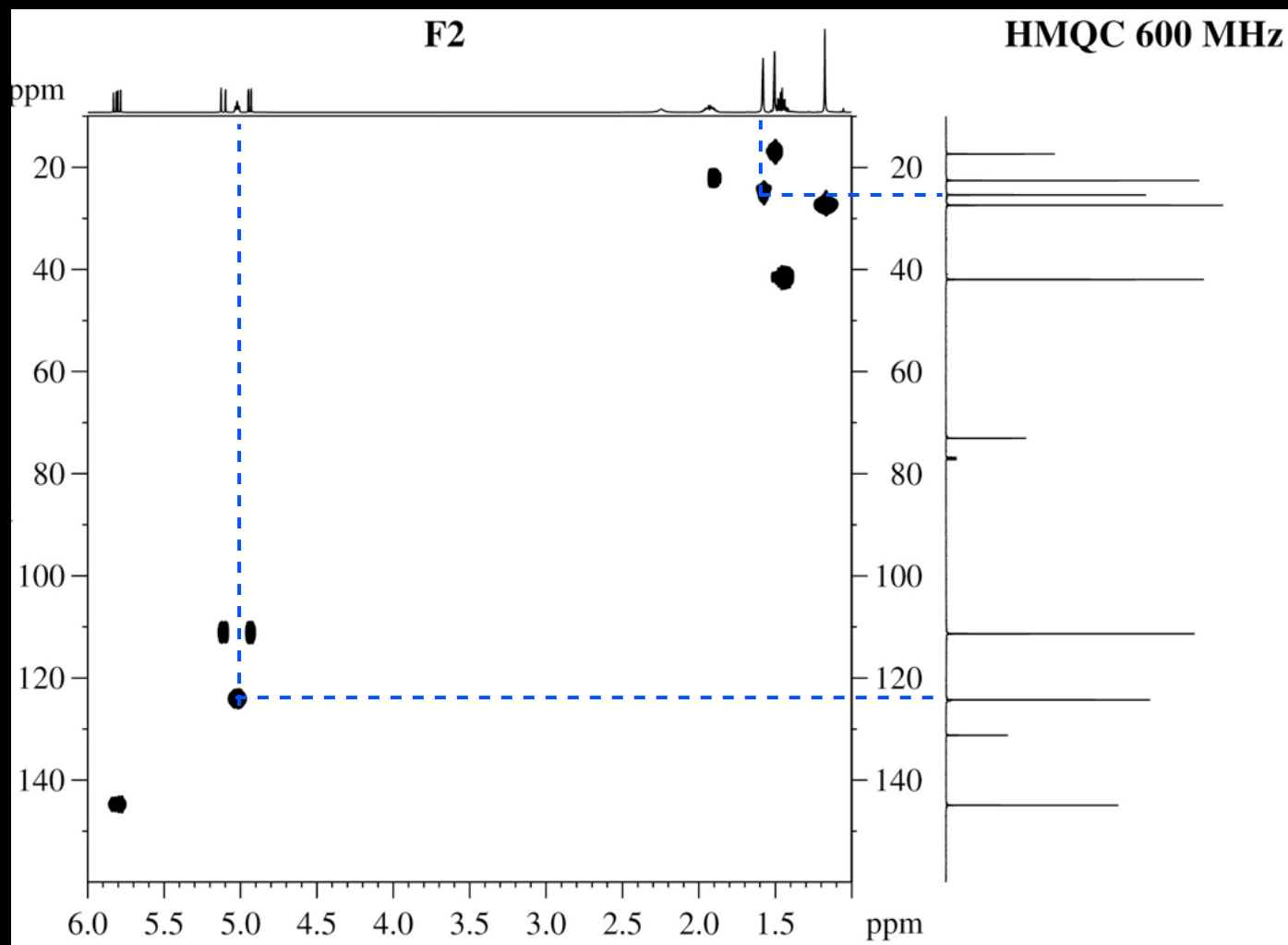
HMQC

2D NMR Spectroscopy
Who is Talking to Who?

<u>HMQC</u>

Diastereotopic Protons

1 bond H–C coupling
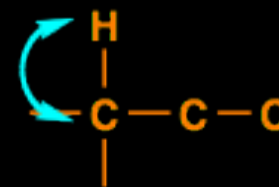
2D NMR Spectroscopy
Who is Talking to Who?

Caryophyllene Oxide
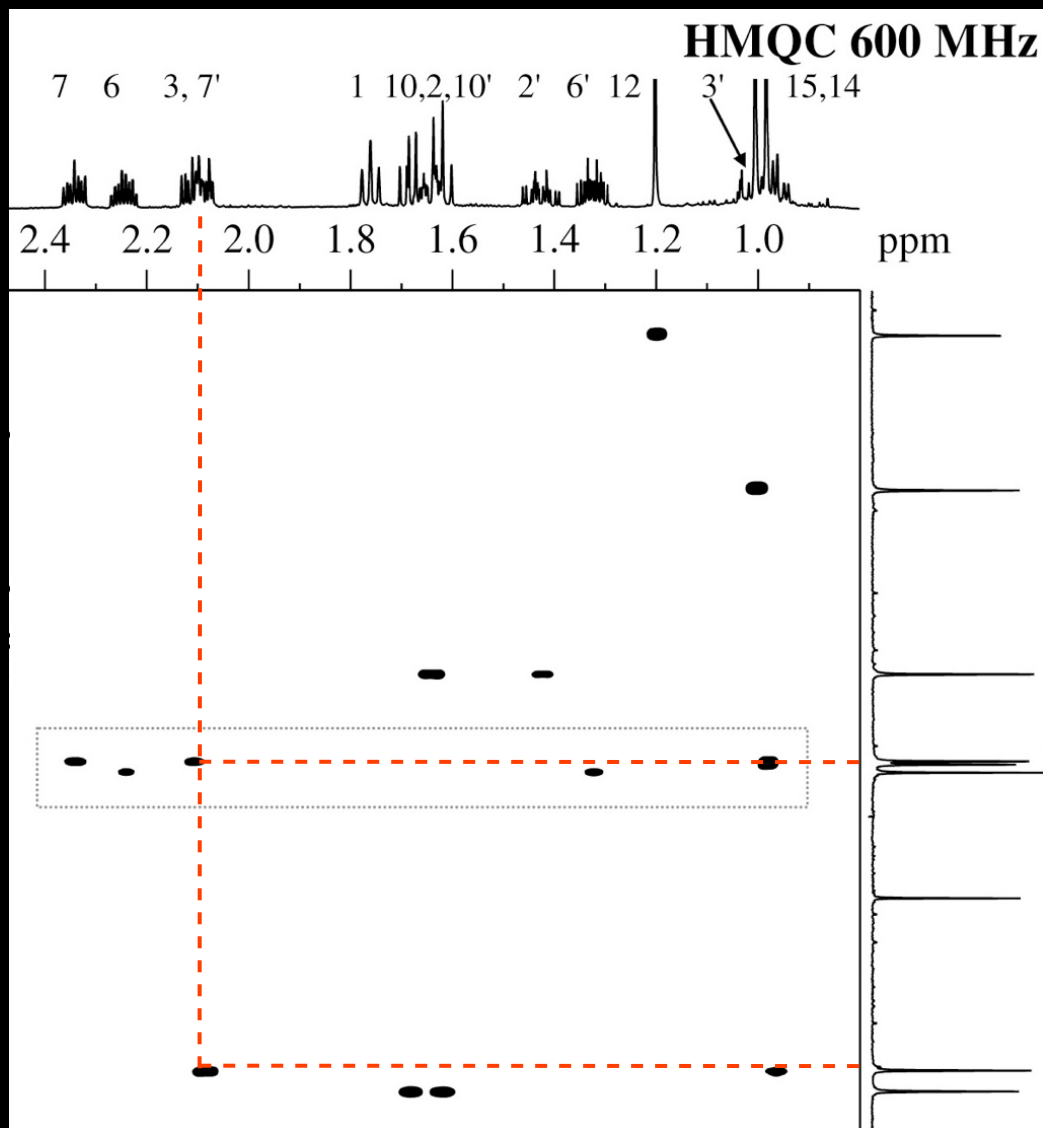
HMQC

Can "see into" multiplets
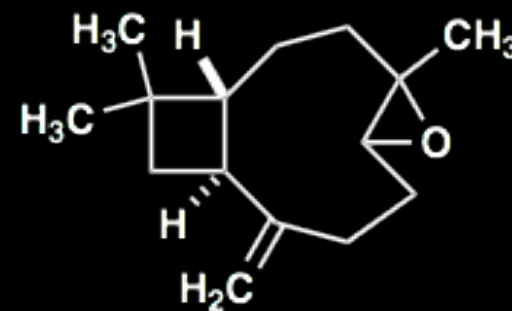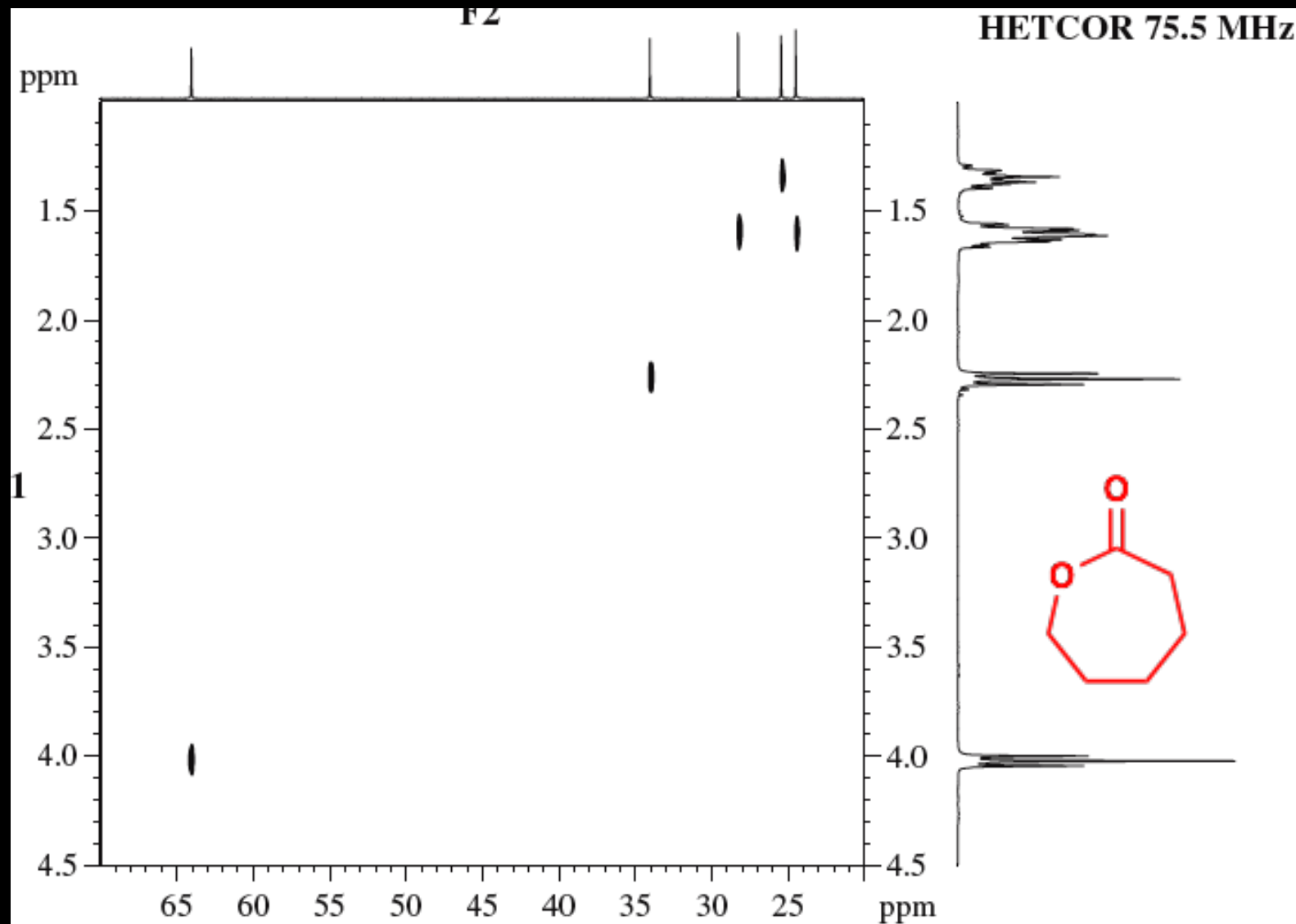
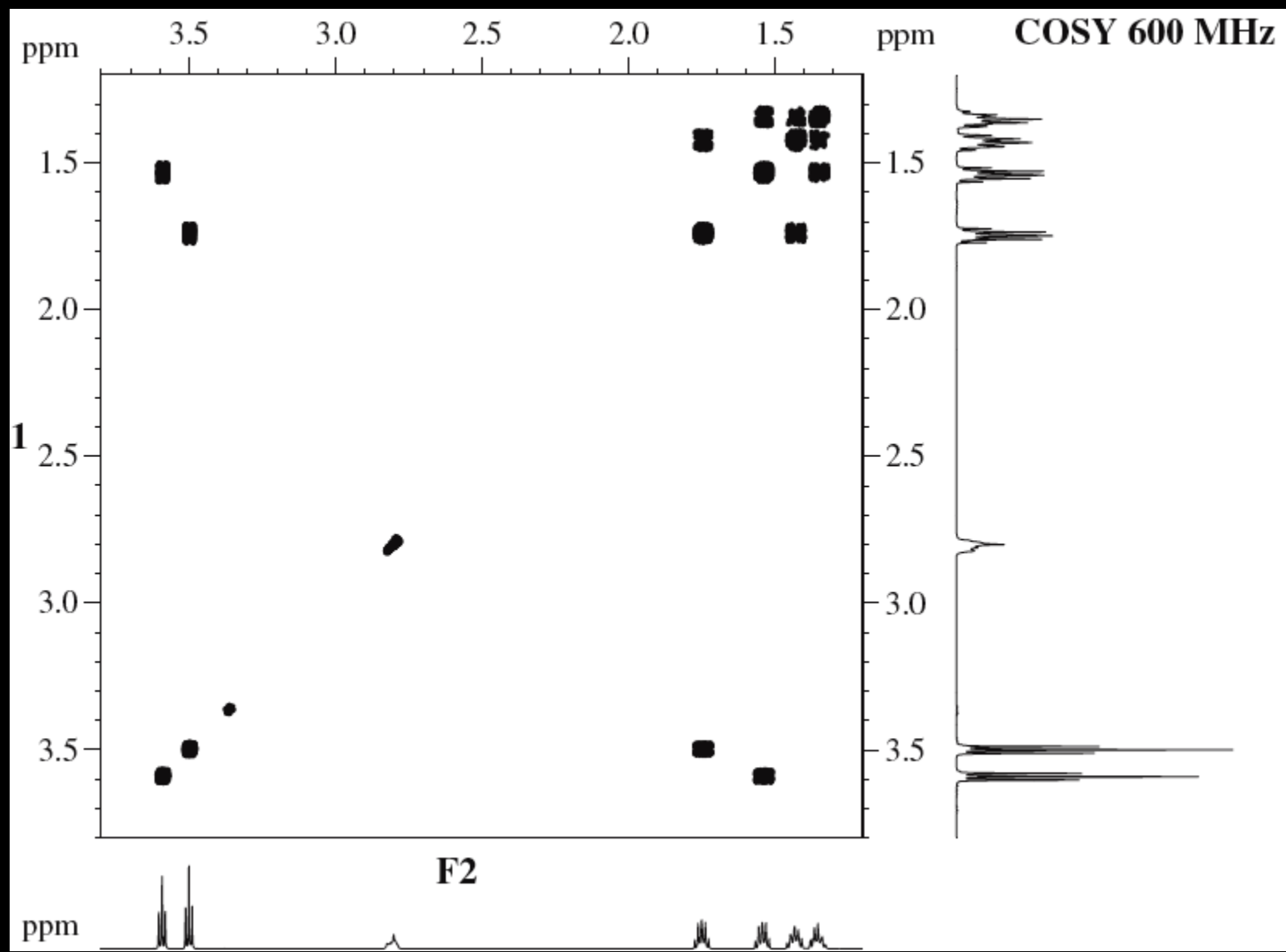# 2D NMR Spectroscopy
Who is Talking to Who?

HMQC

2D NMR Spectroscopy
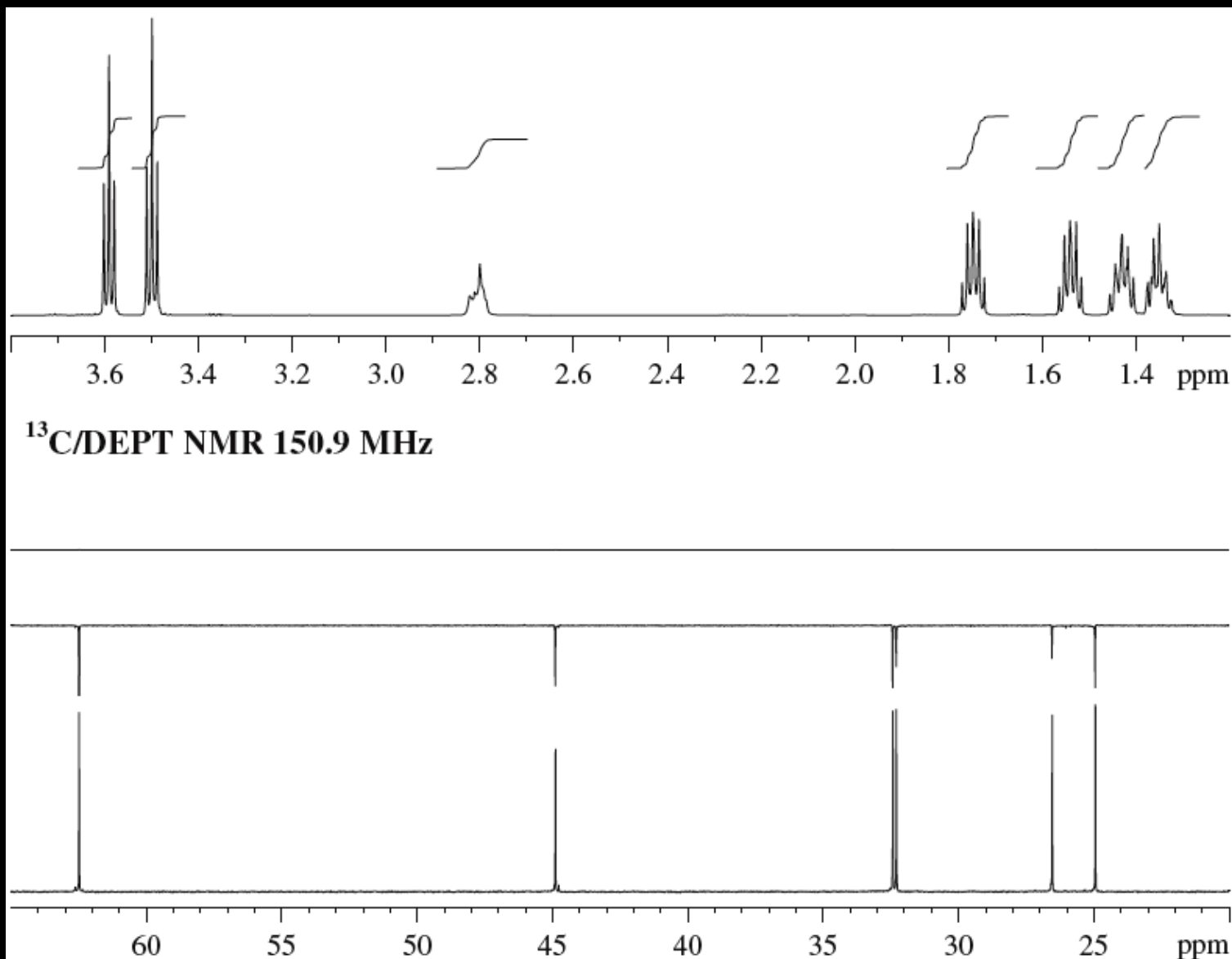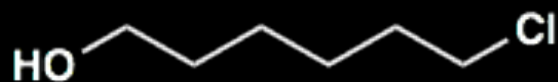
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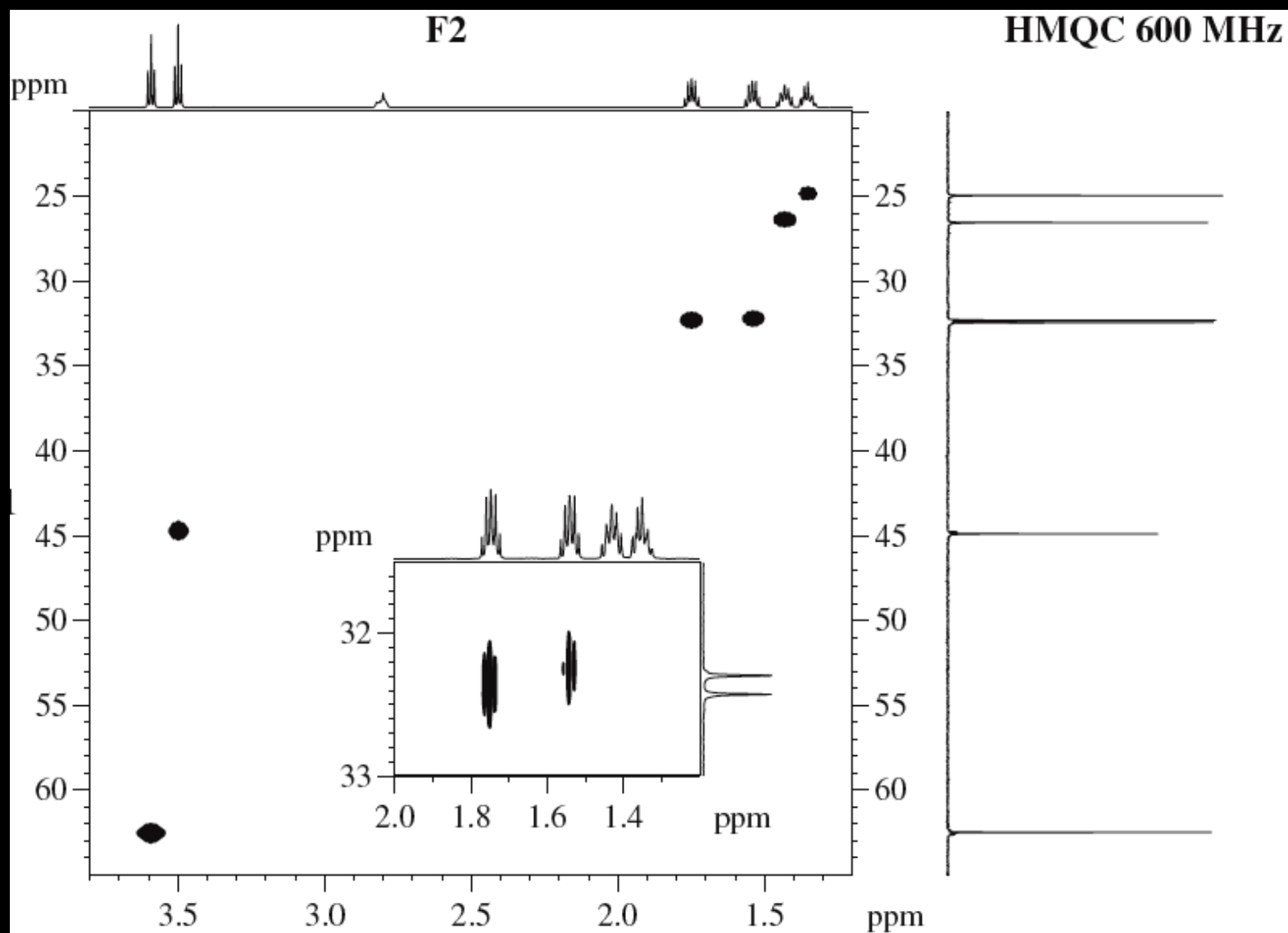
2D NMR Spectroscopy

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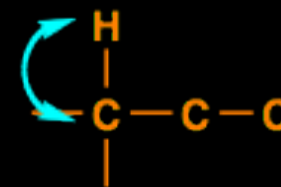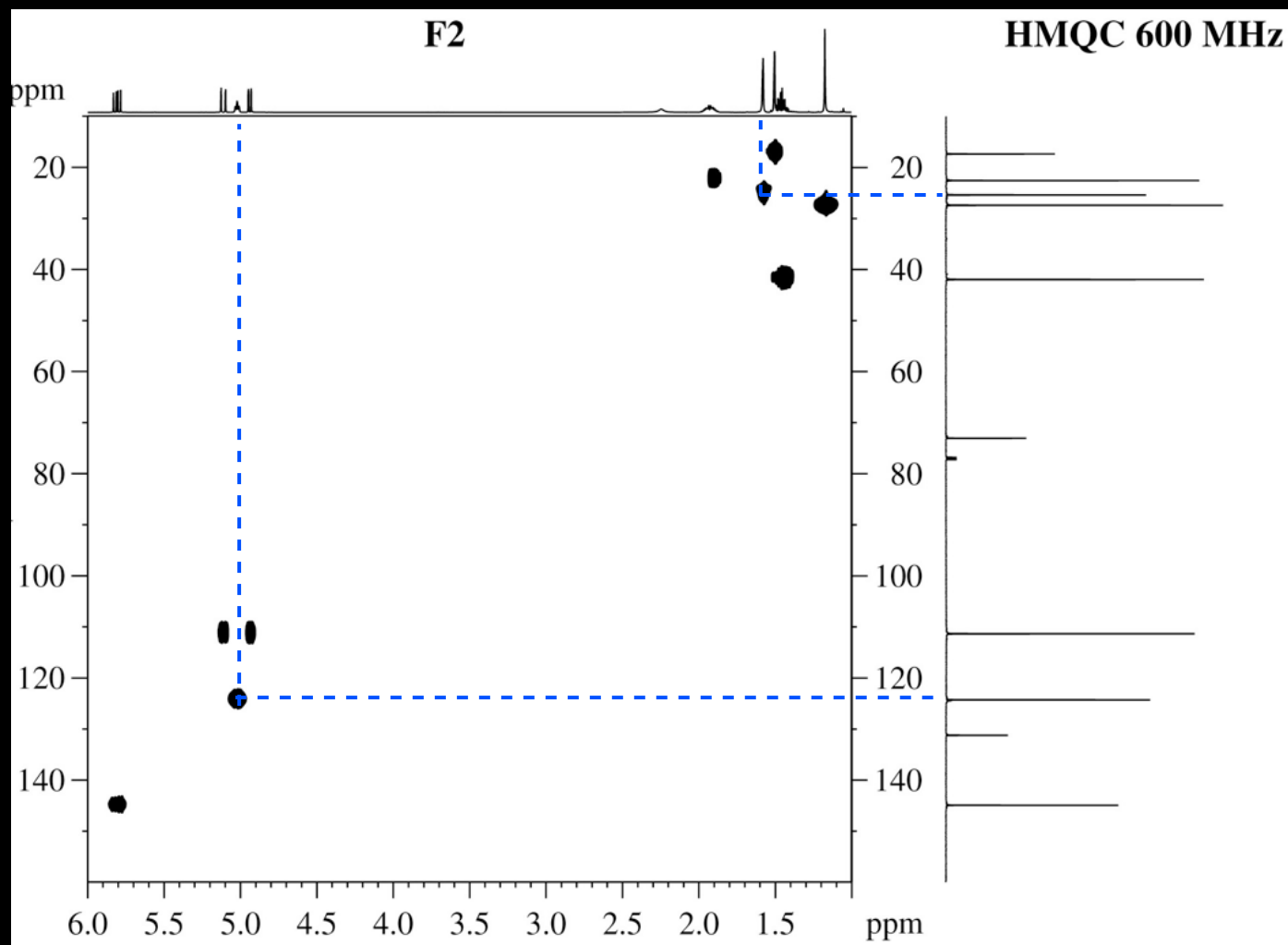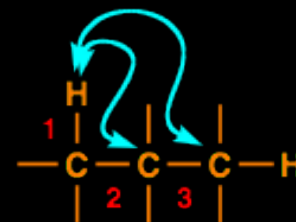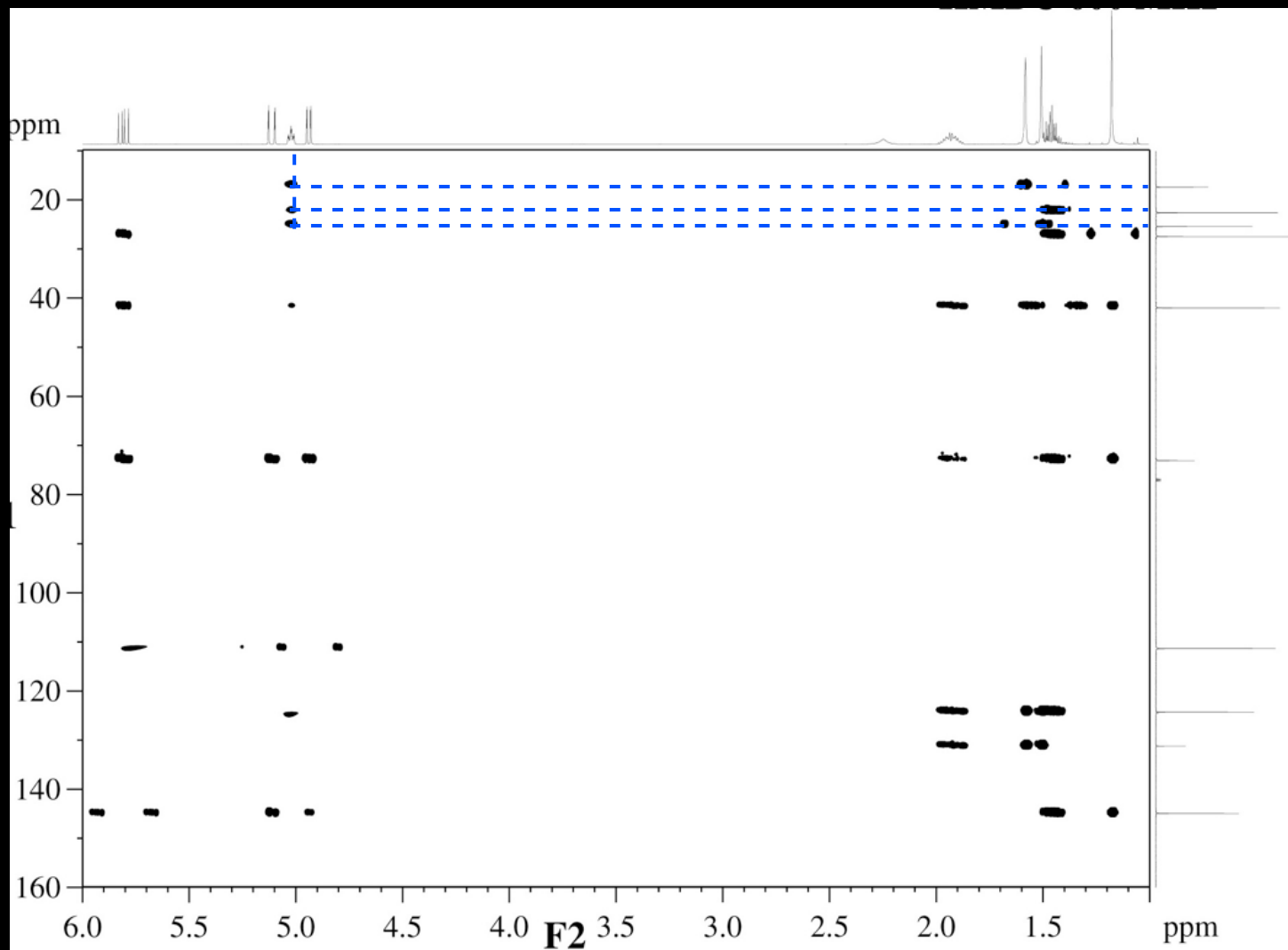## Who is Talking to Who?

– COLOC (Correlated spectroscopy for Long range Couplings)
  – older experiment; ^{13}C-detected

– HMBC (Heteronuclear Multiple Bond Coherence)
  – newer experiment; ^{1}H-detected; completely replaced COLOC

– Both give same information, experimentally very different

– Peaks have two- or three-bond coupling

– "Sees through" heteroatoms and quaternary carbons

– Can be very complicated, but is very powerful
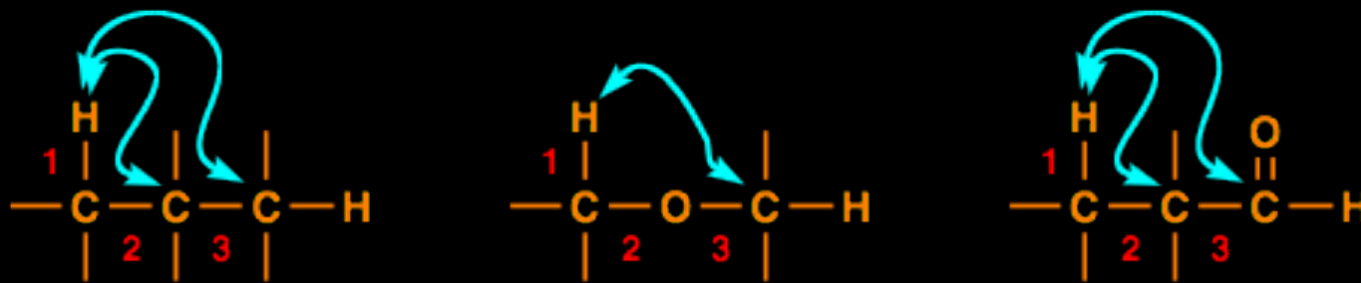

2 and 3 bond H–C couplings

2D NMR Spectroscopy
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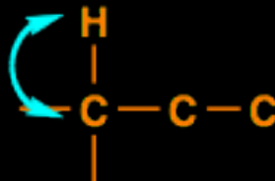
1 bond H–C coupling

2D NMR Spectroscopy
Who is Talking to Who?

HMQC

1 bond H–C coupling

2D NMR Spectroscopy
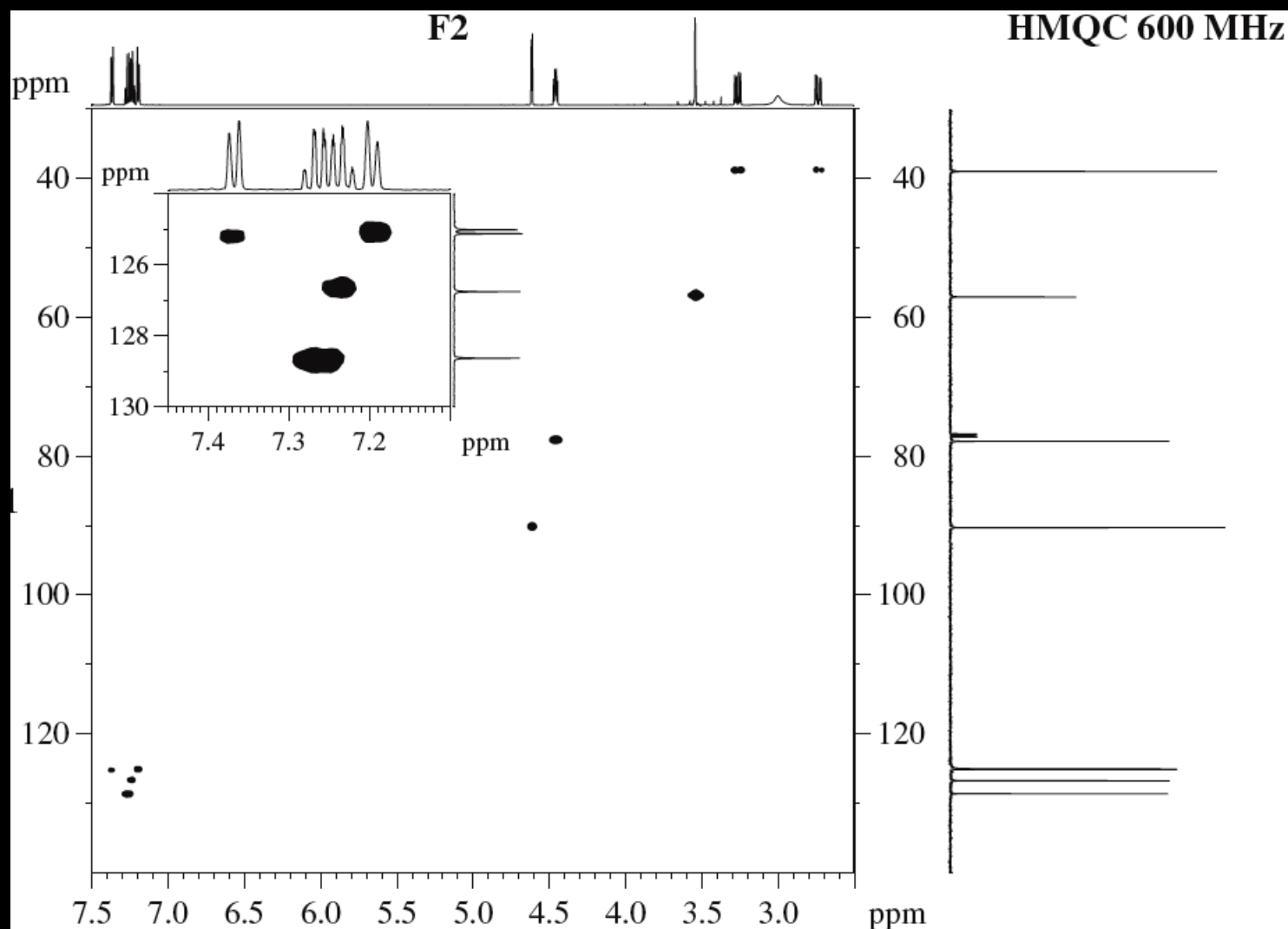## Who is Talking to Who?

HMBC
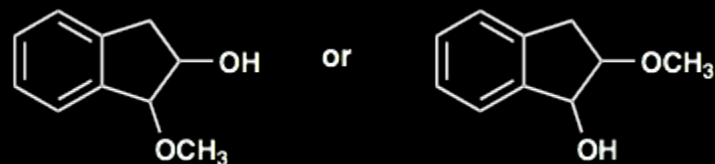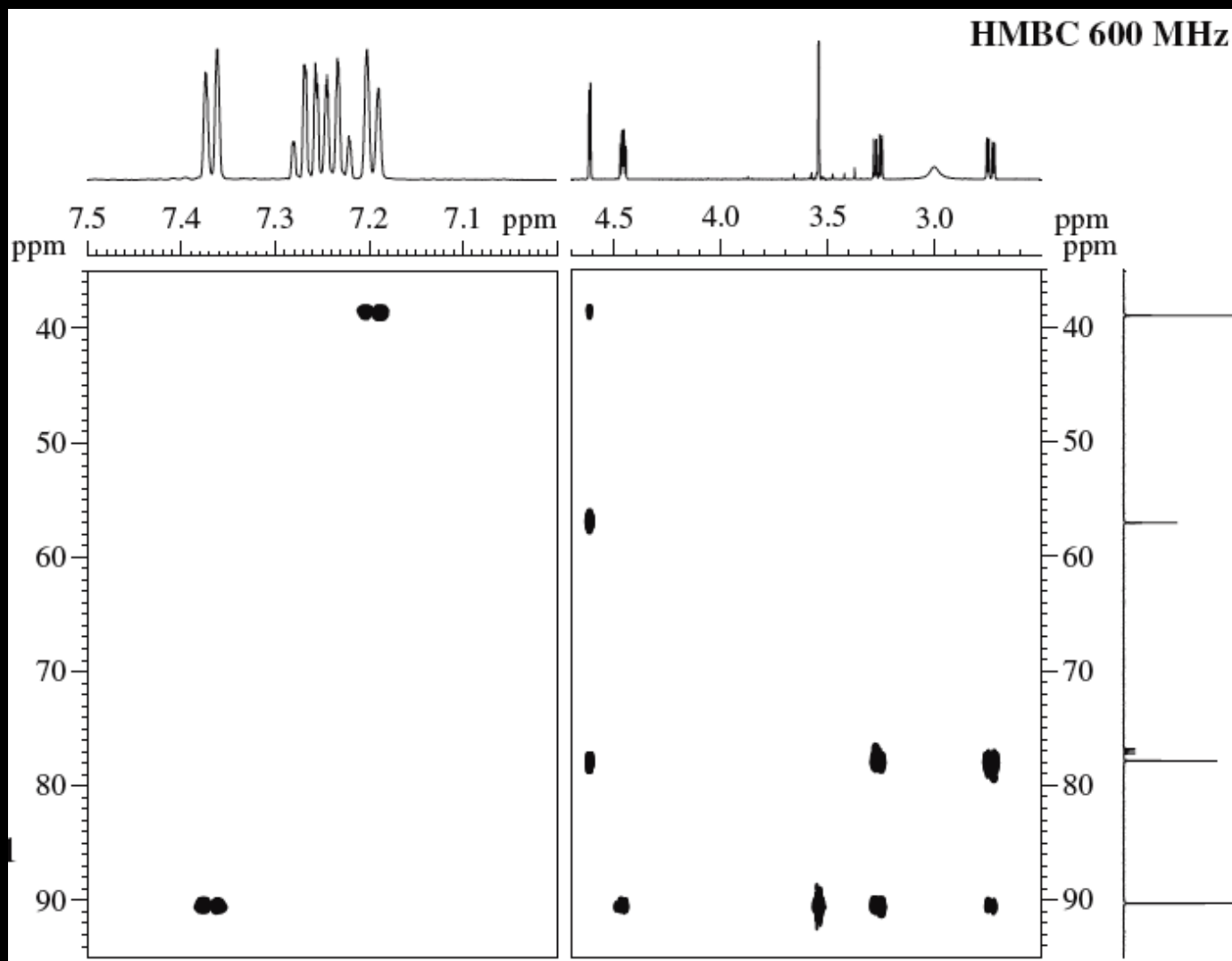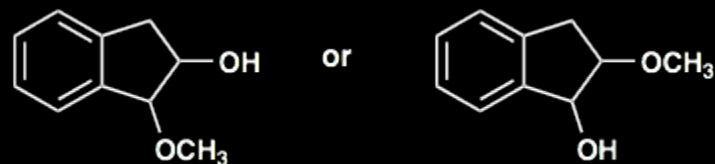

2 and 3 bond H–C couplings
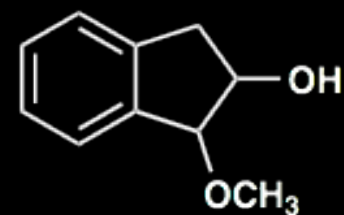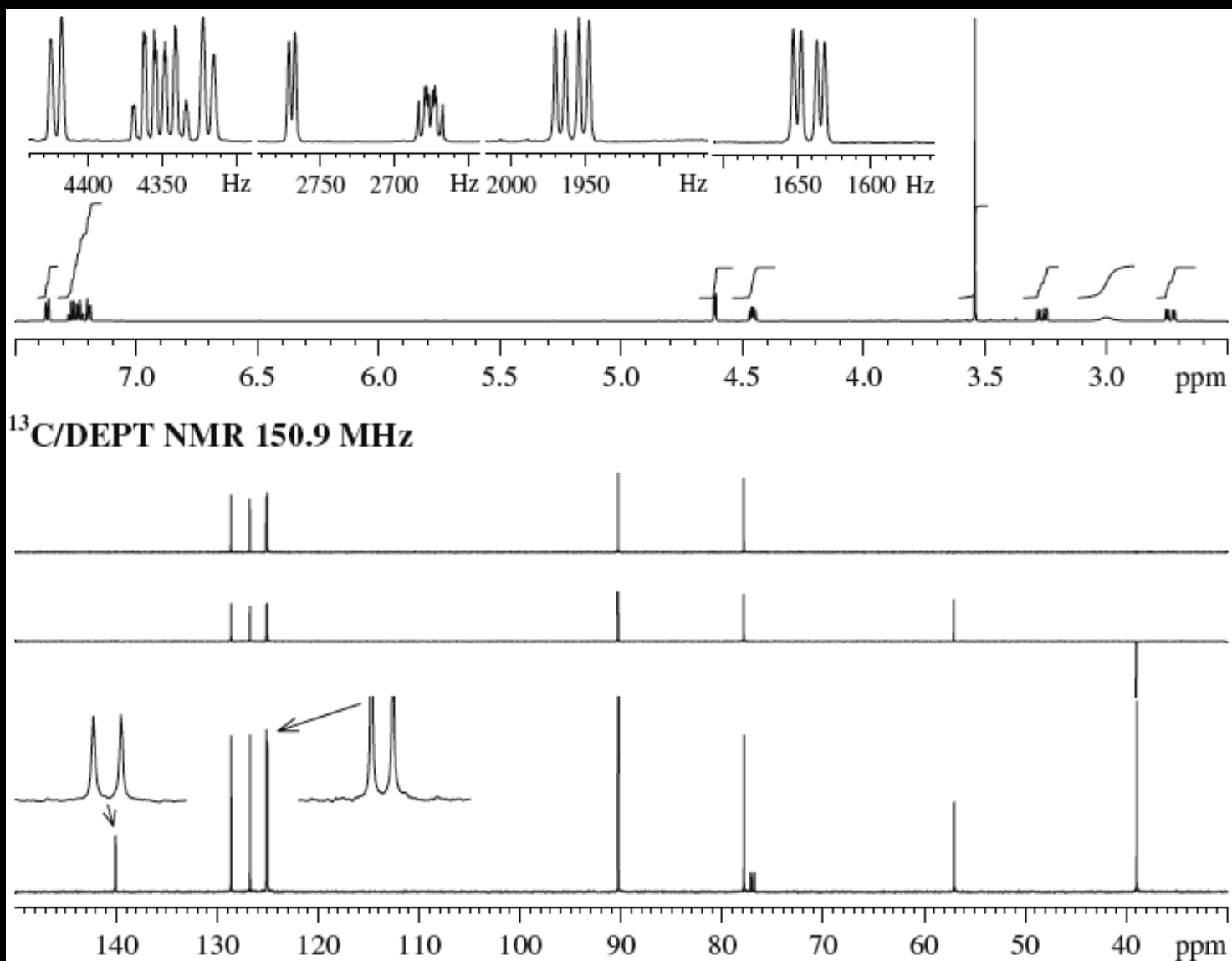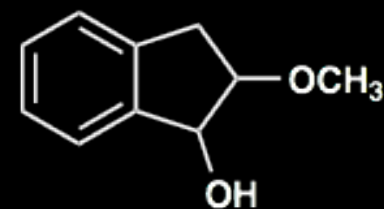
2D NMR Spectroscopy
Who is Talking to Who?

2D NMR Spectroscopy
Who is Talking to Who?
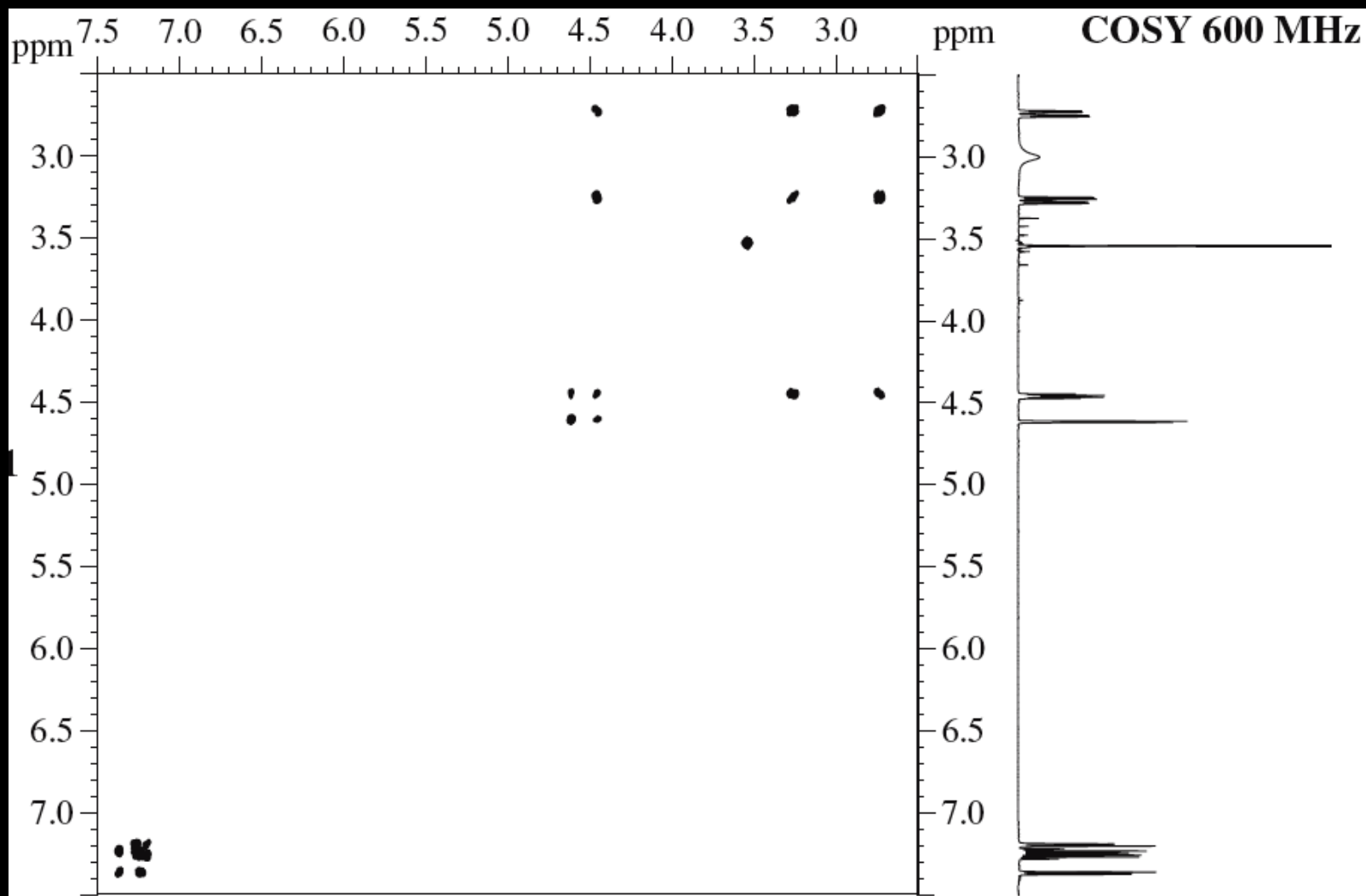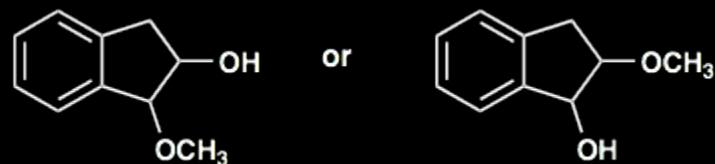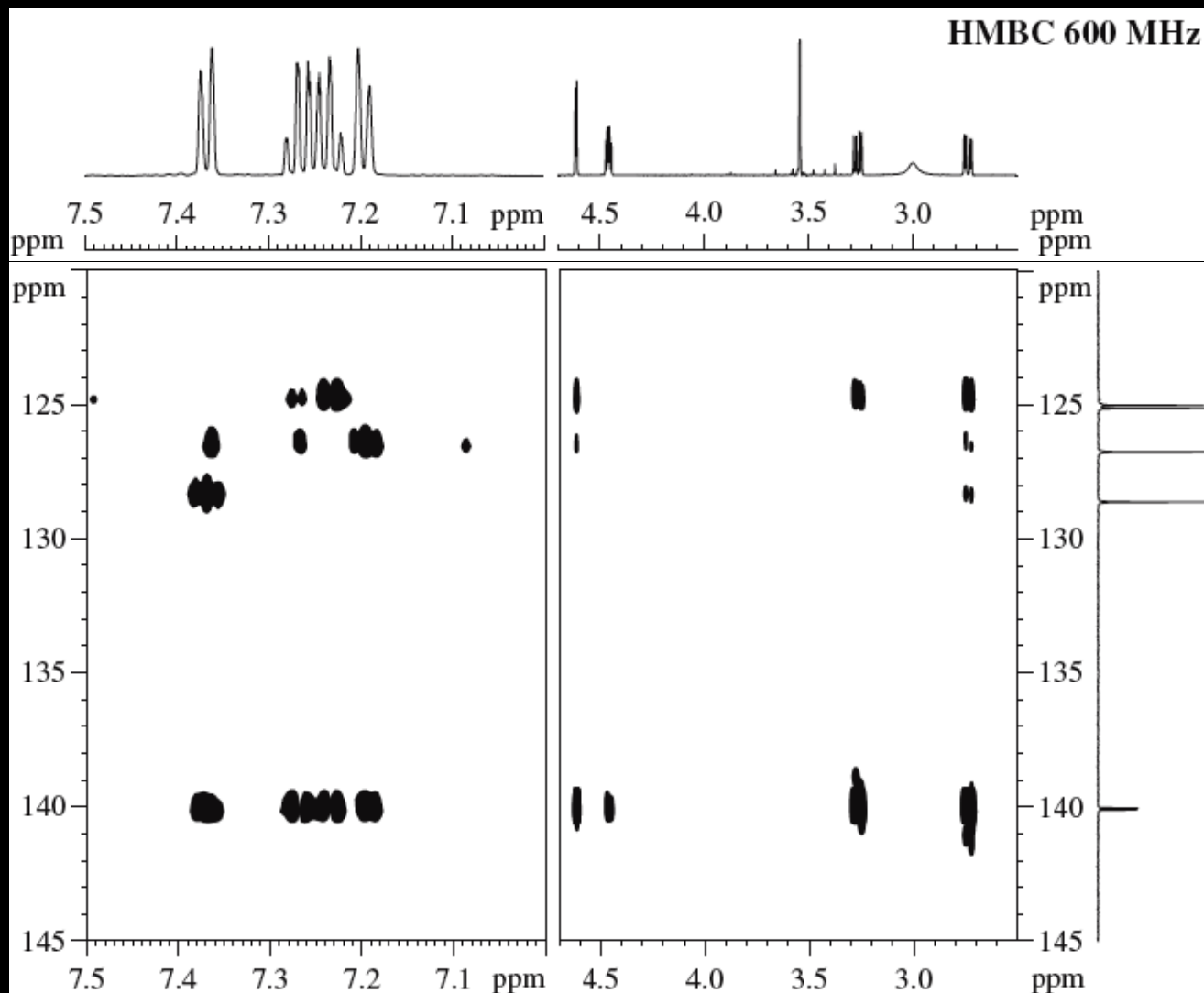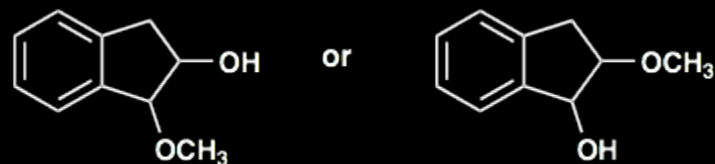
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^{13}C–^{13}C COSY

- INADEQUATE (Incredible Natural Abundance Double Quantum Transfer Experiment)

- tells what carbons are attached to each other

- if you know what type of carbon it is (C, C=O, CH, CH_2, CH_3, etc.) from DEPT, you can almost write down the entire gross structure by running two NMR experiments

- **_BUT_** it is ^{13}C–^{13}C coupling

  - probability of one ^{13}C is 0.01

  - two next to each other 0.01x0.01 = 0.0001
  (~1 molecule in 10,000)

- Need lots of sample and instrument time to overcome
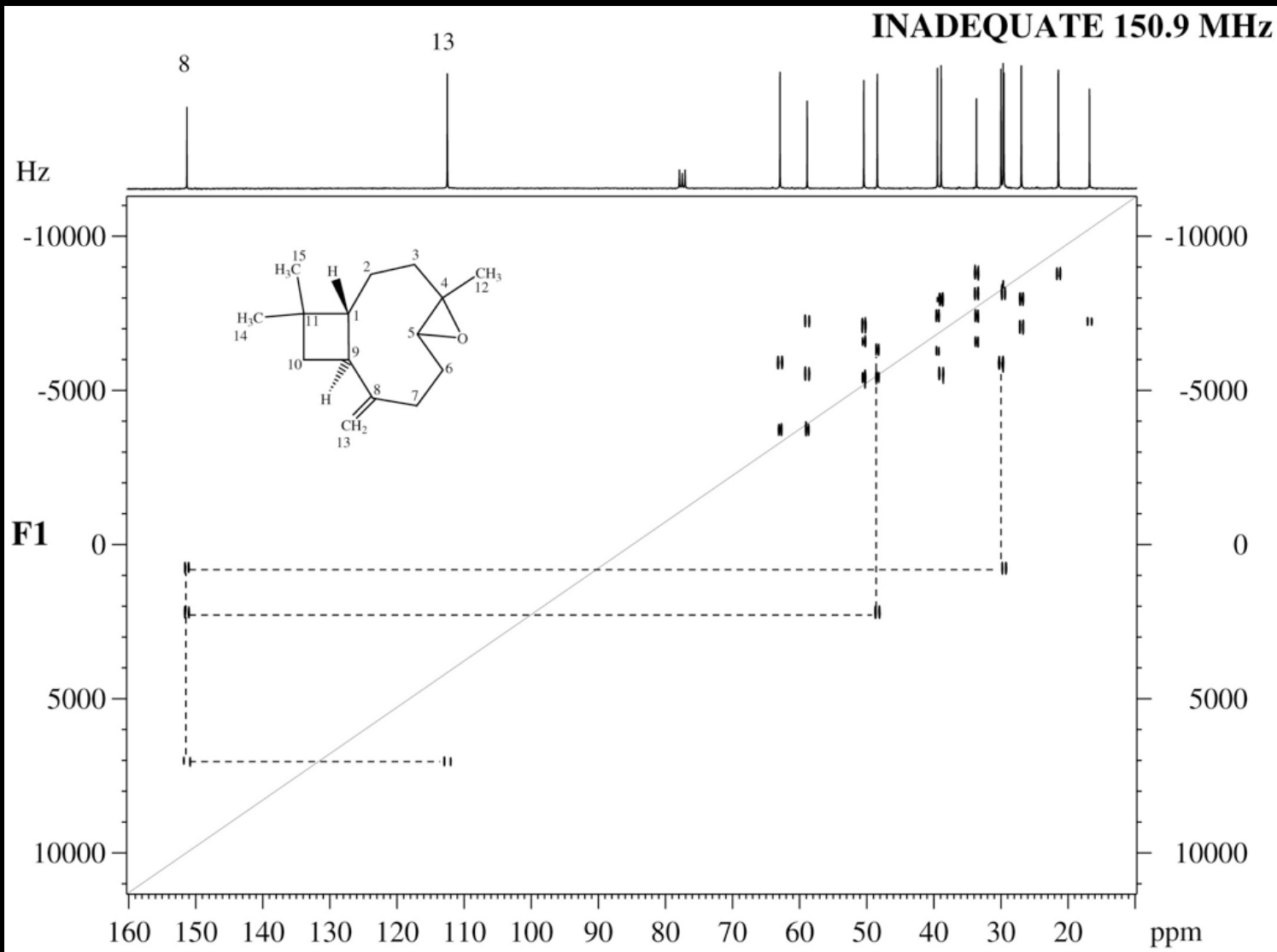
- In our facility: 80% v/v, overnight, 500 MHz = nothing
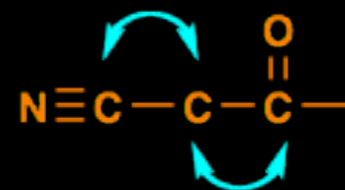
1 bond C–C coupling

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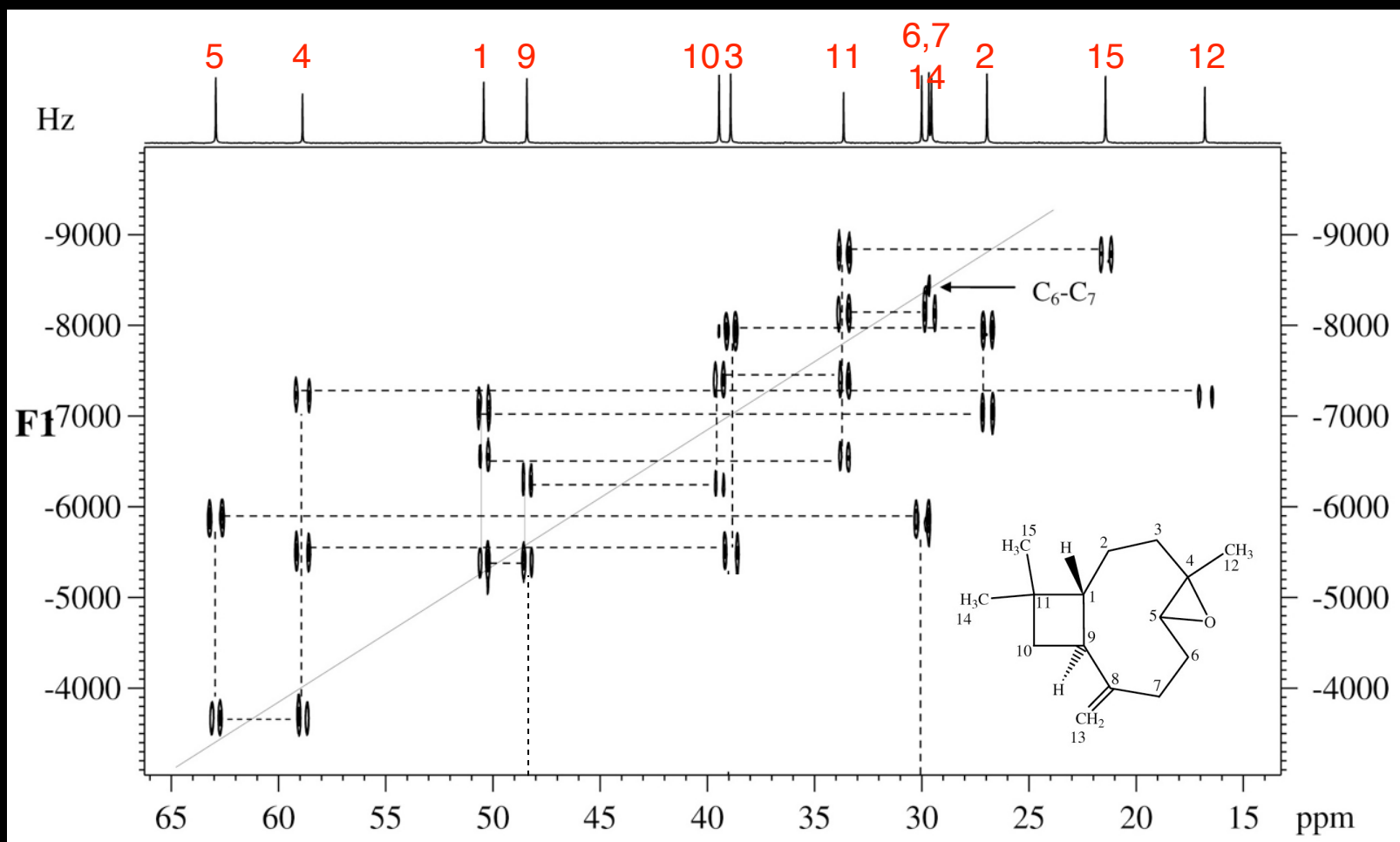## Who is Talking to Who?
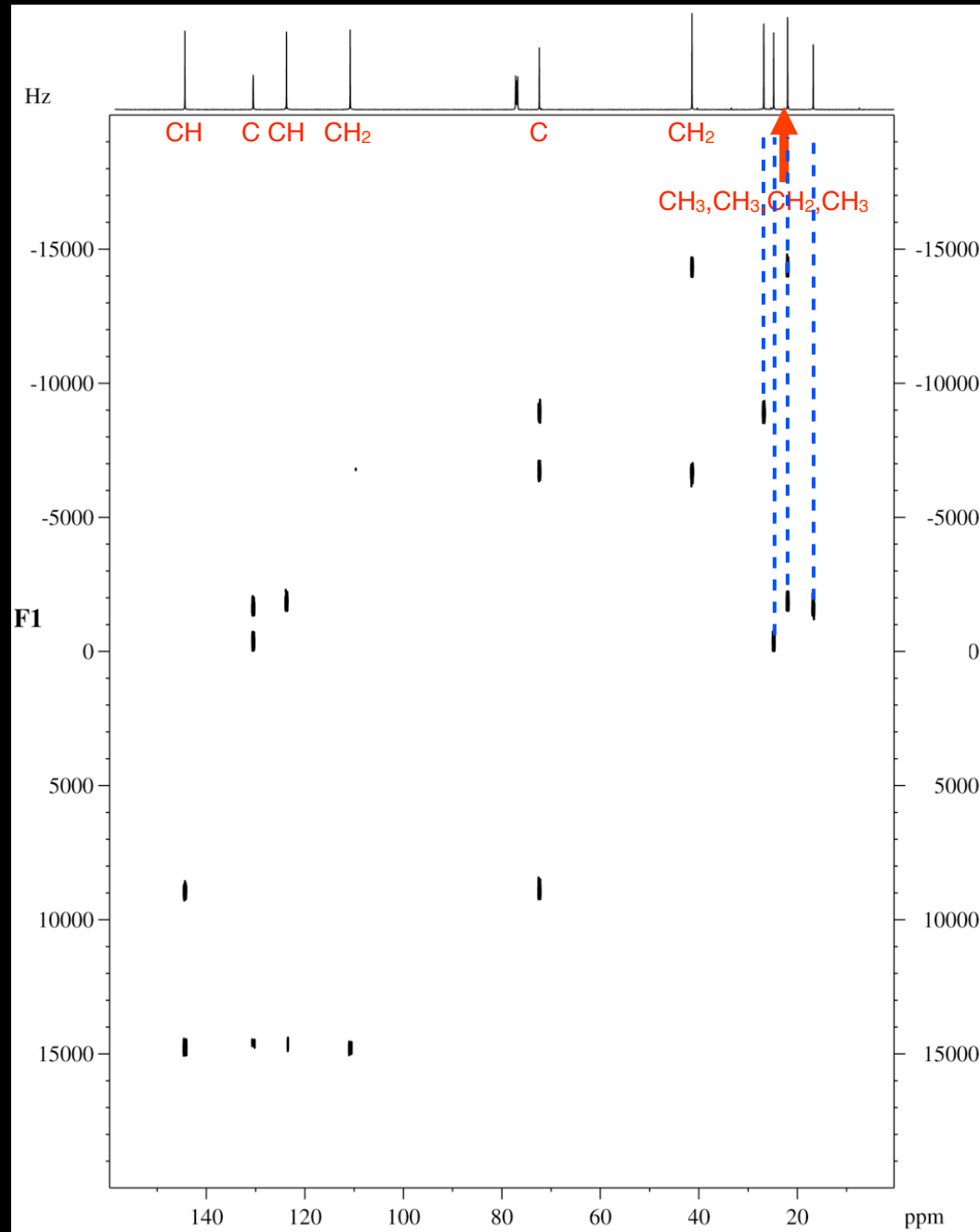
INADEQUATE

2D NMR Spectroscopy
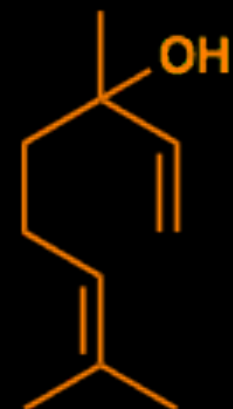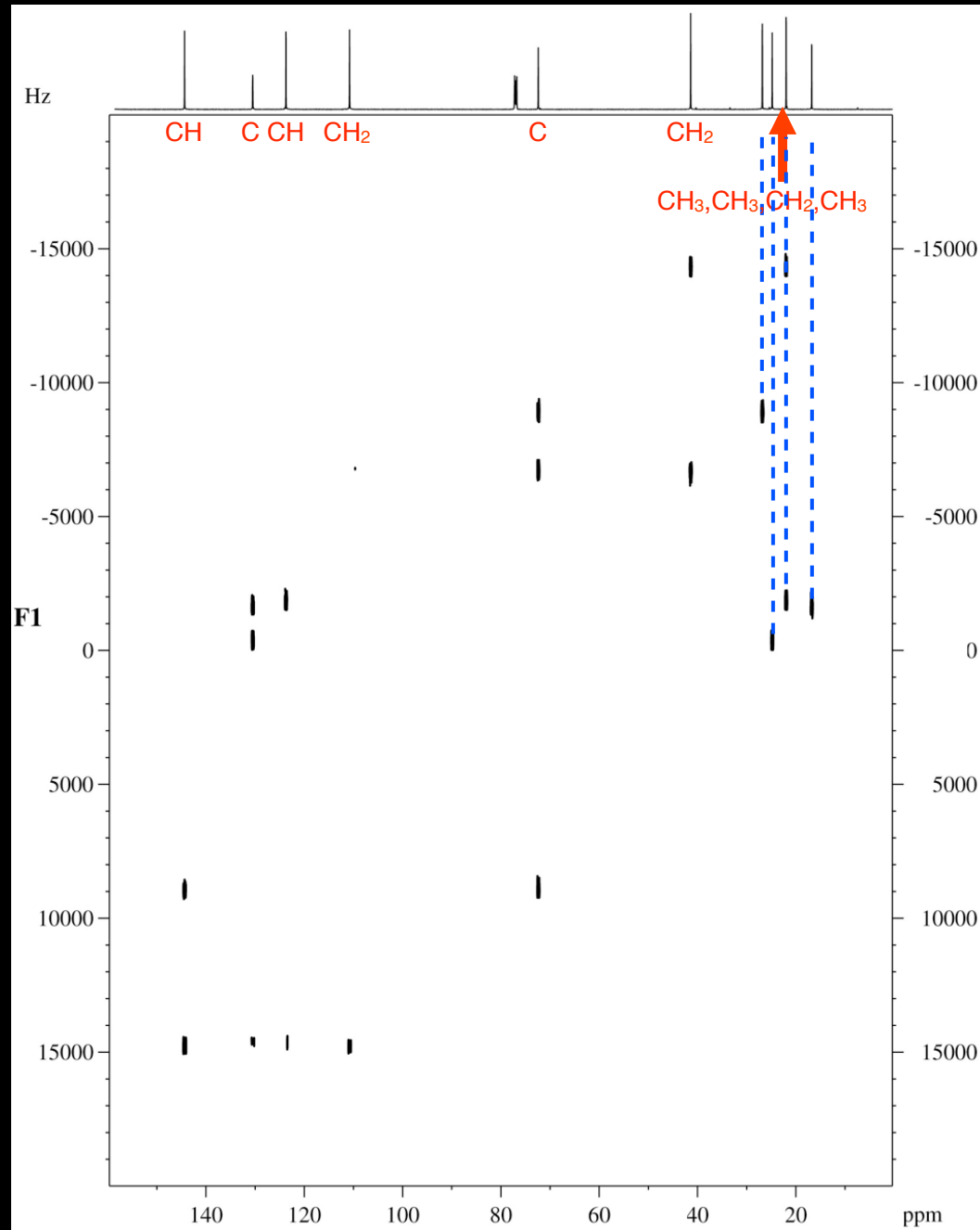## Who is Talking to Who?

INADEQUATE

– Cross peaks show up as doublets = J_{CC}

– Diagonal is midway between the two doublets
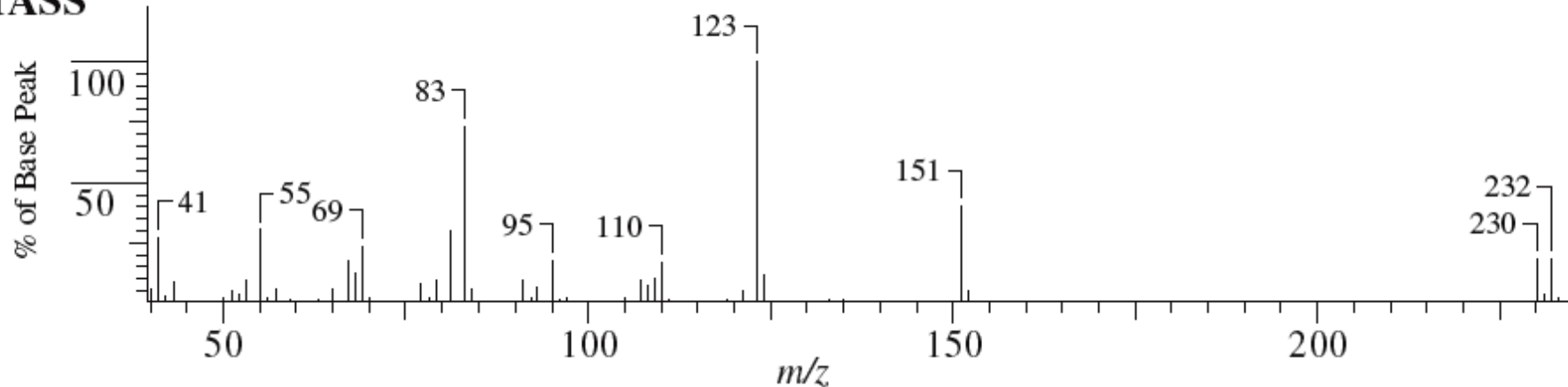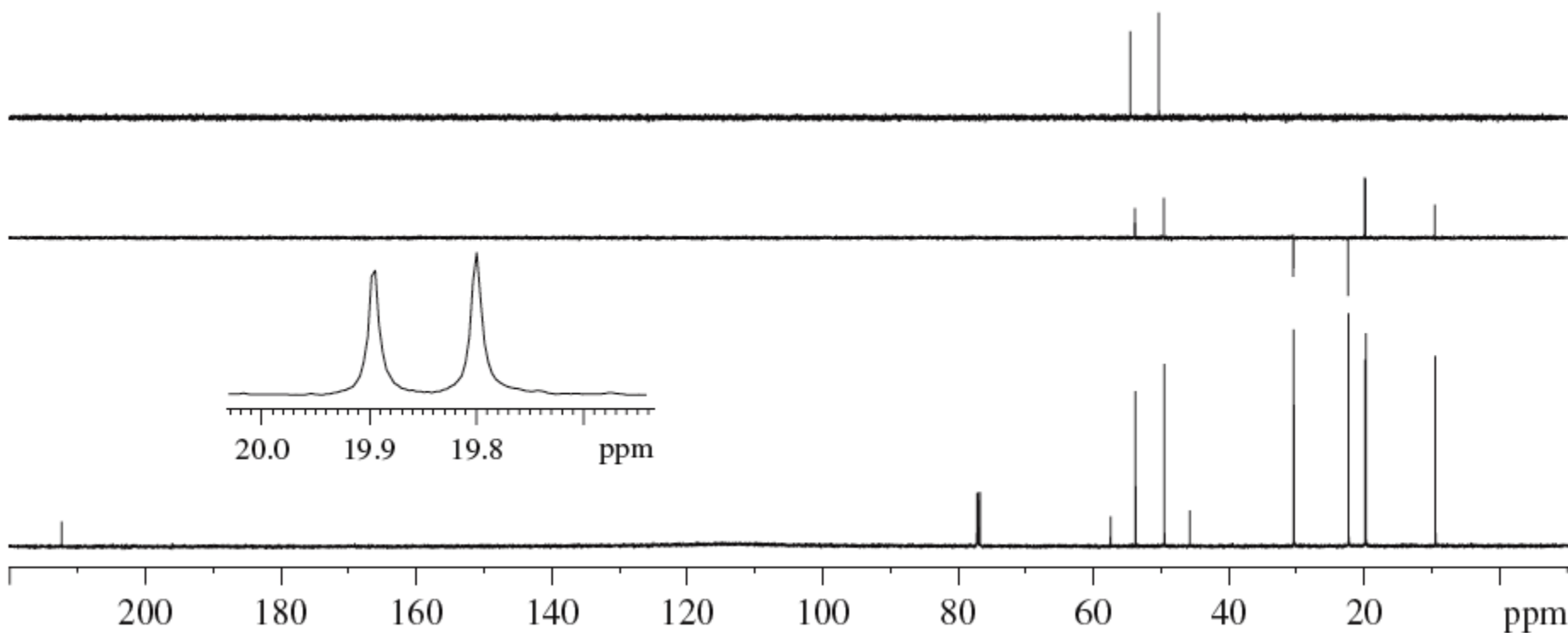
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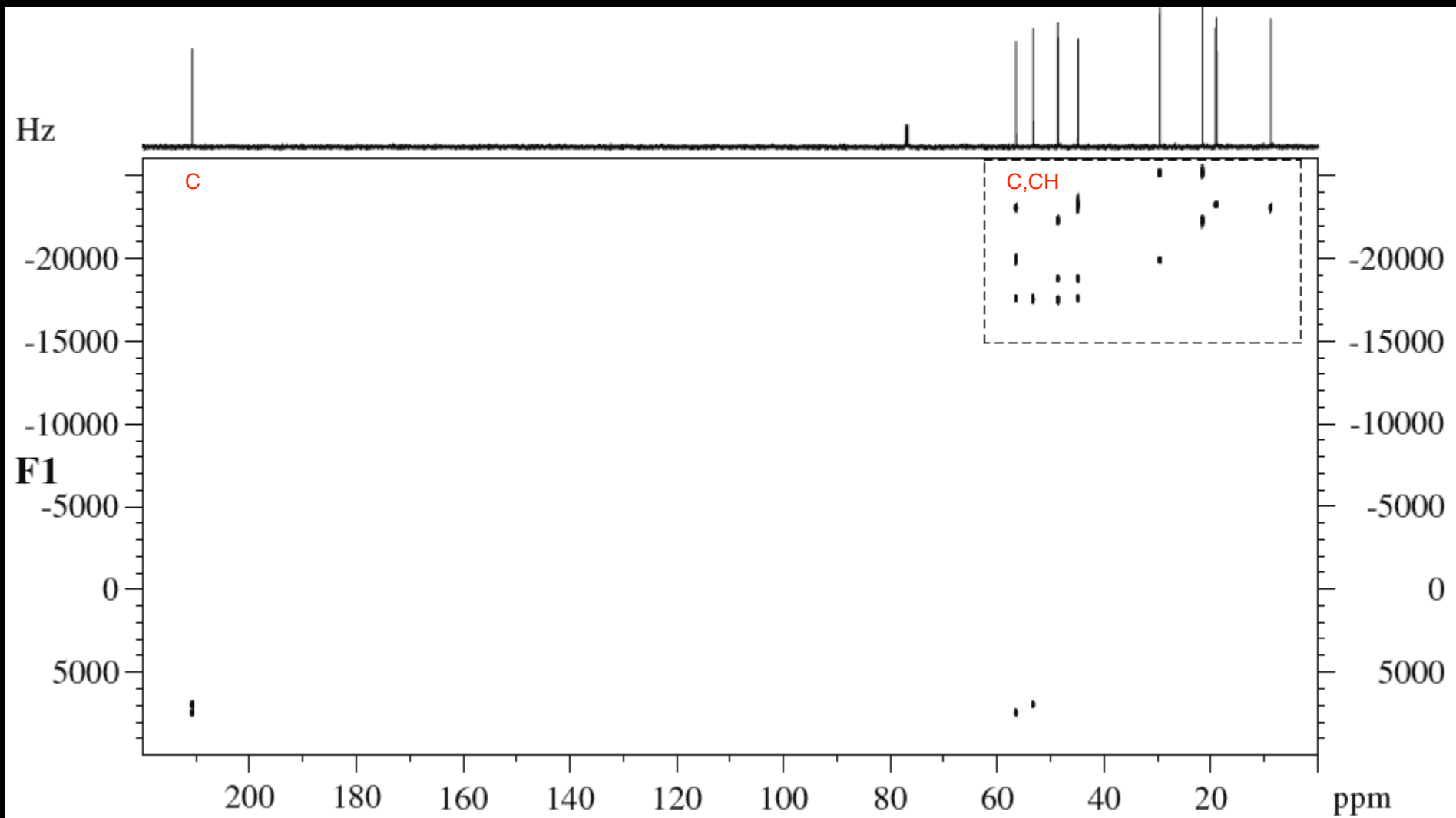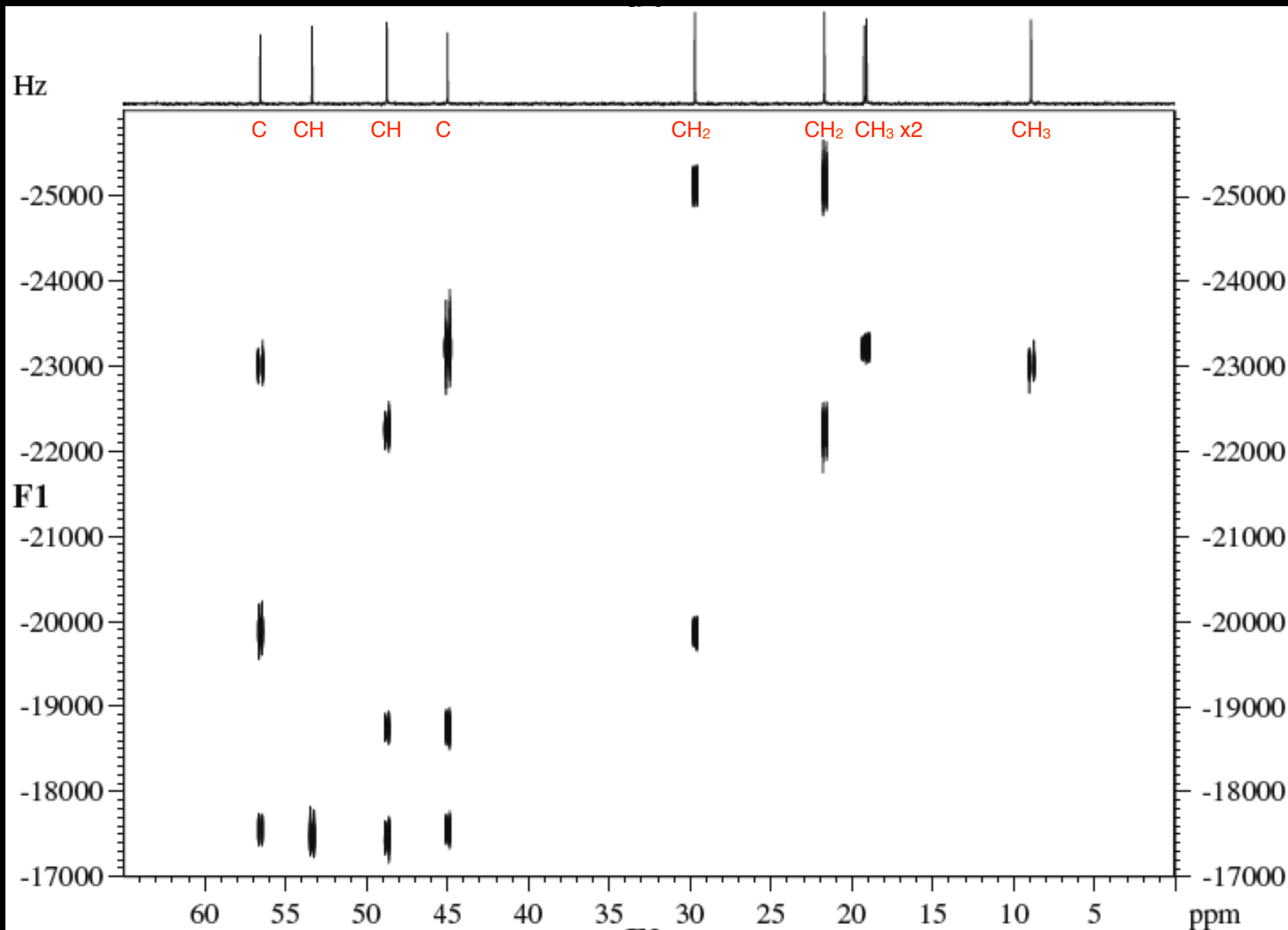
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MASS

Peaks labeled: 41, 55, 69, 83, 95, 110, 123, 151, 230, 232

% of Base Peak (y-axis), m/z (x-axis)

^{13}C/DEPT NMR 150.9 MHz

Inset: 20.0, 19.9, 19.8 ppm

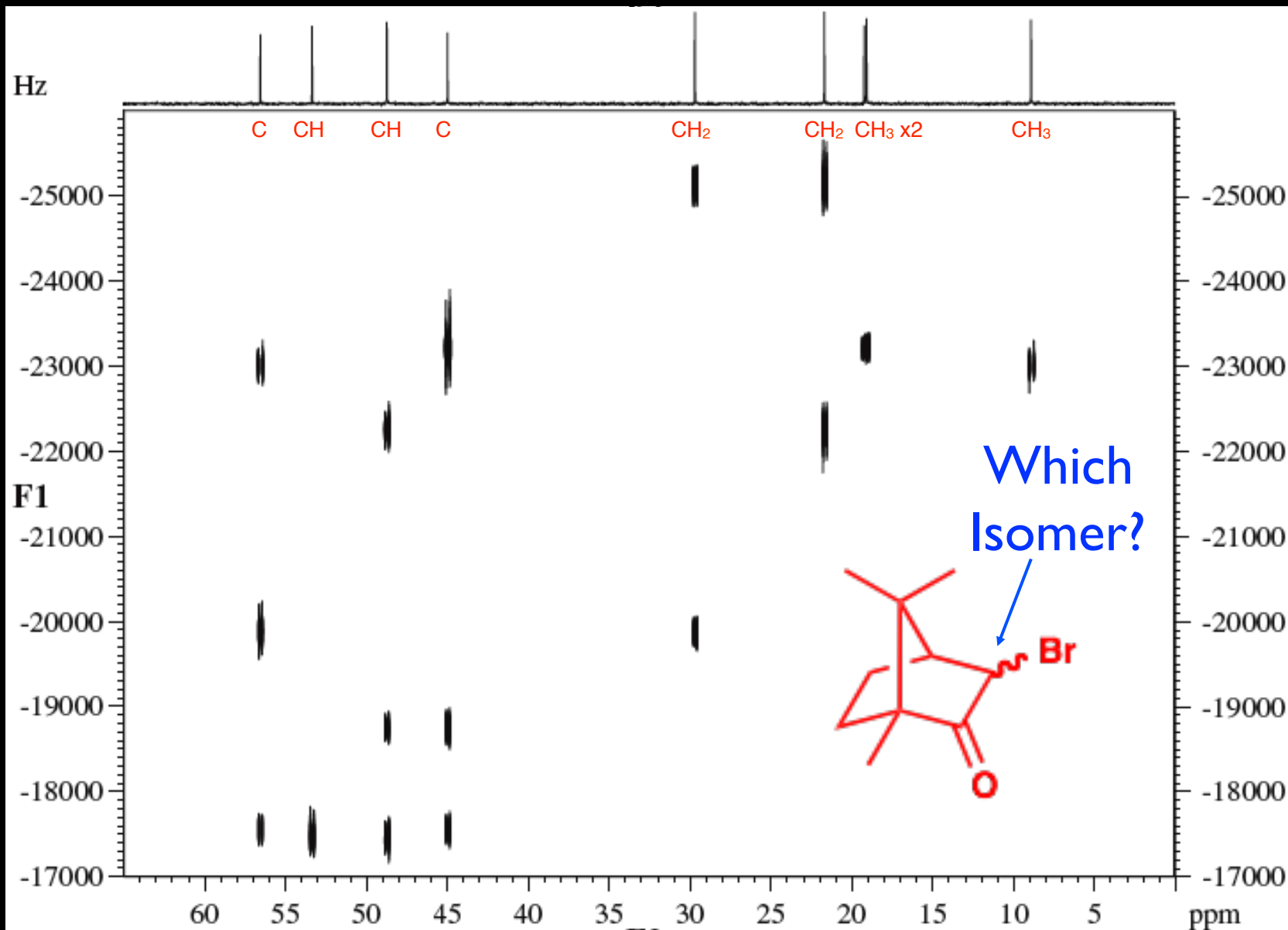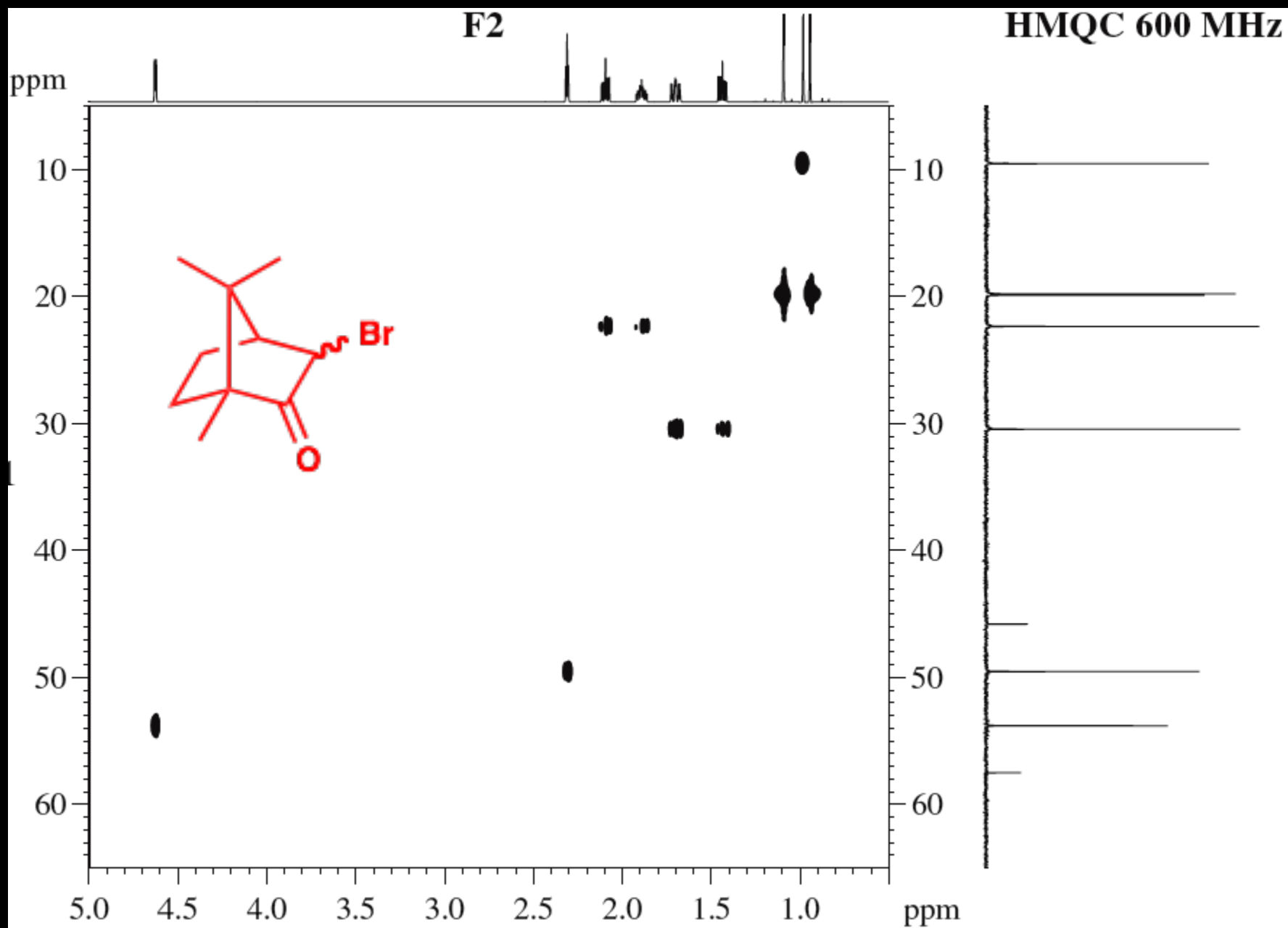x-axis: 200, 180, 160, 140, 120, 100, 80, 60, 40, 20 ppm

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