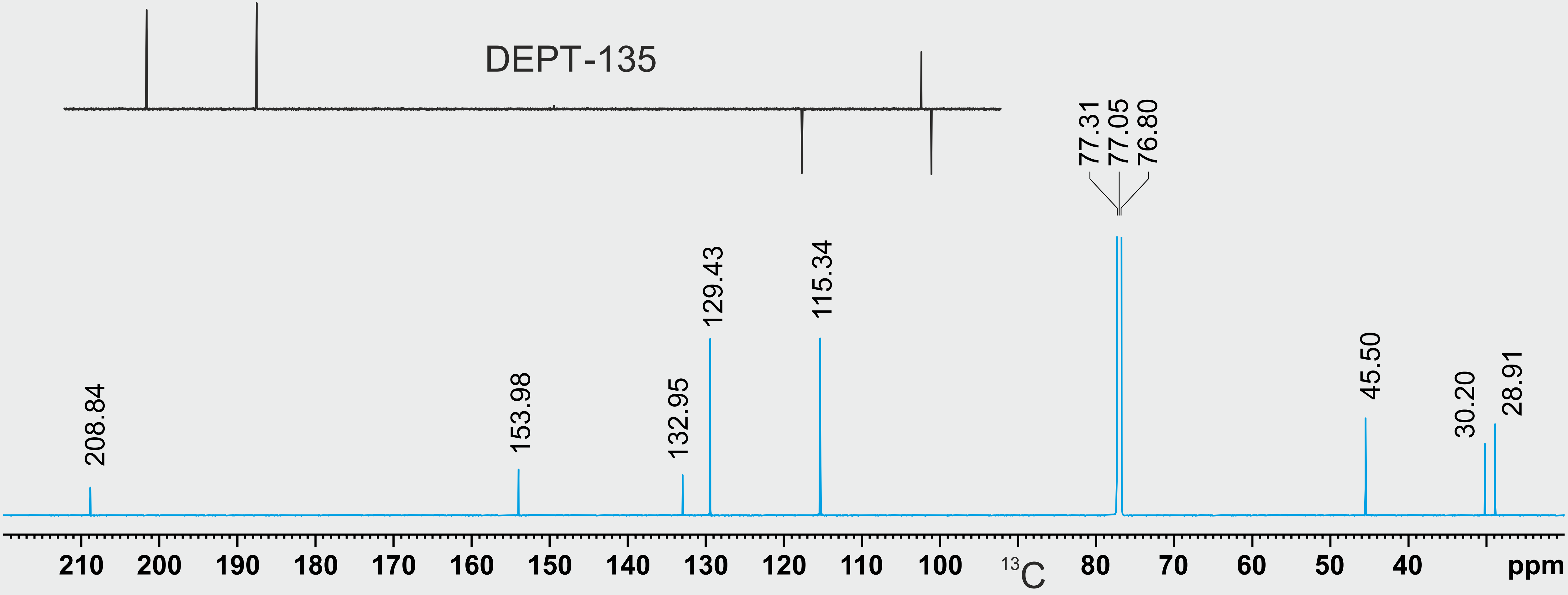
Exercise plus Solution – Quick overview

It is recommended to use this version only for a quick overview of the NMR challenge. All animations of the PowerPoint version are missing, under certain circumstances quality deficiencies may also occur.

The higher quality PowerPoint files are freely available for download at any time.



Problem of the month

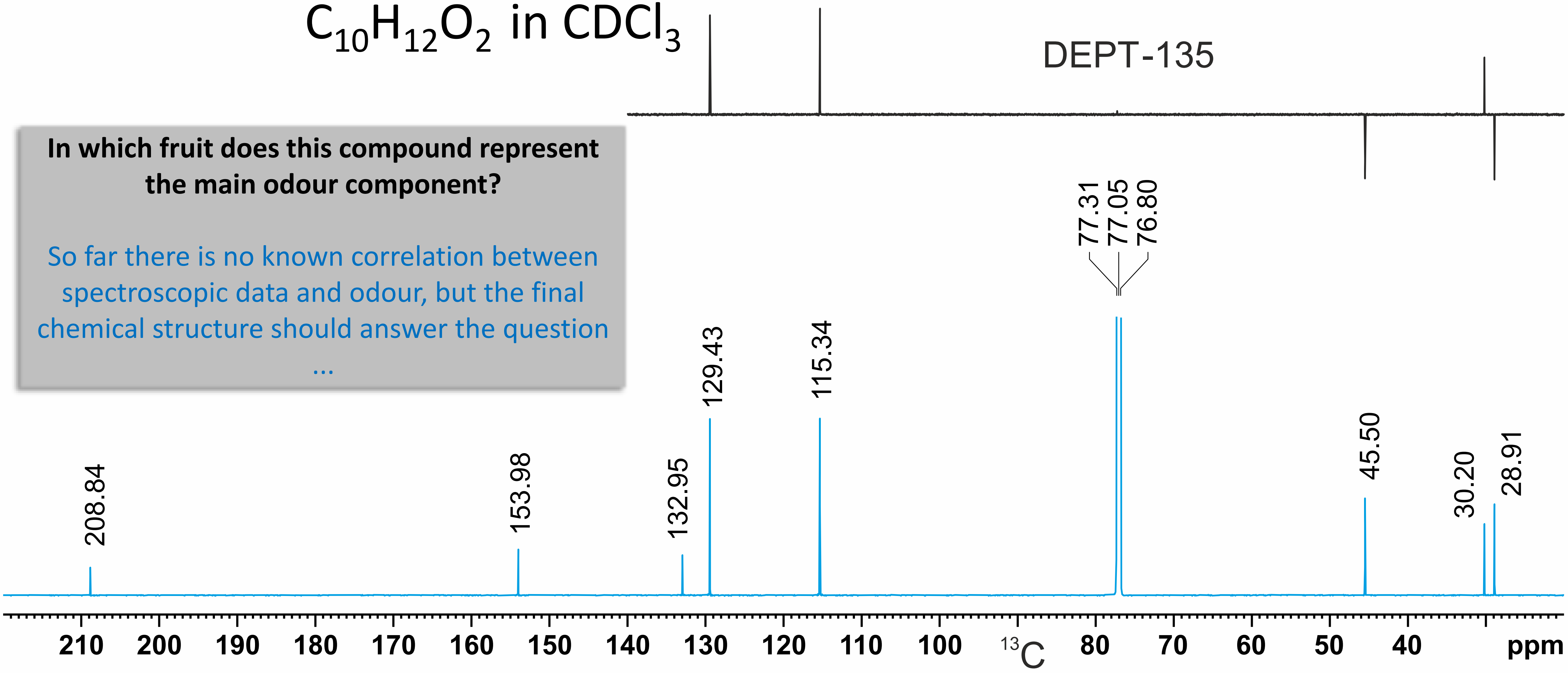
November 2022

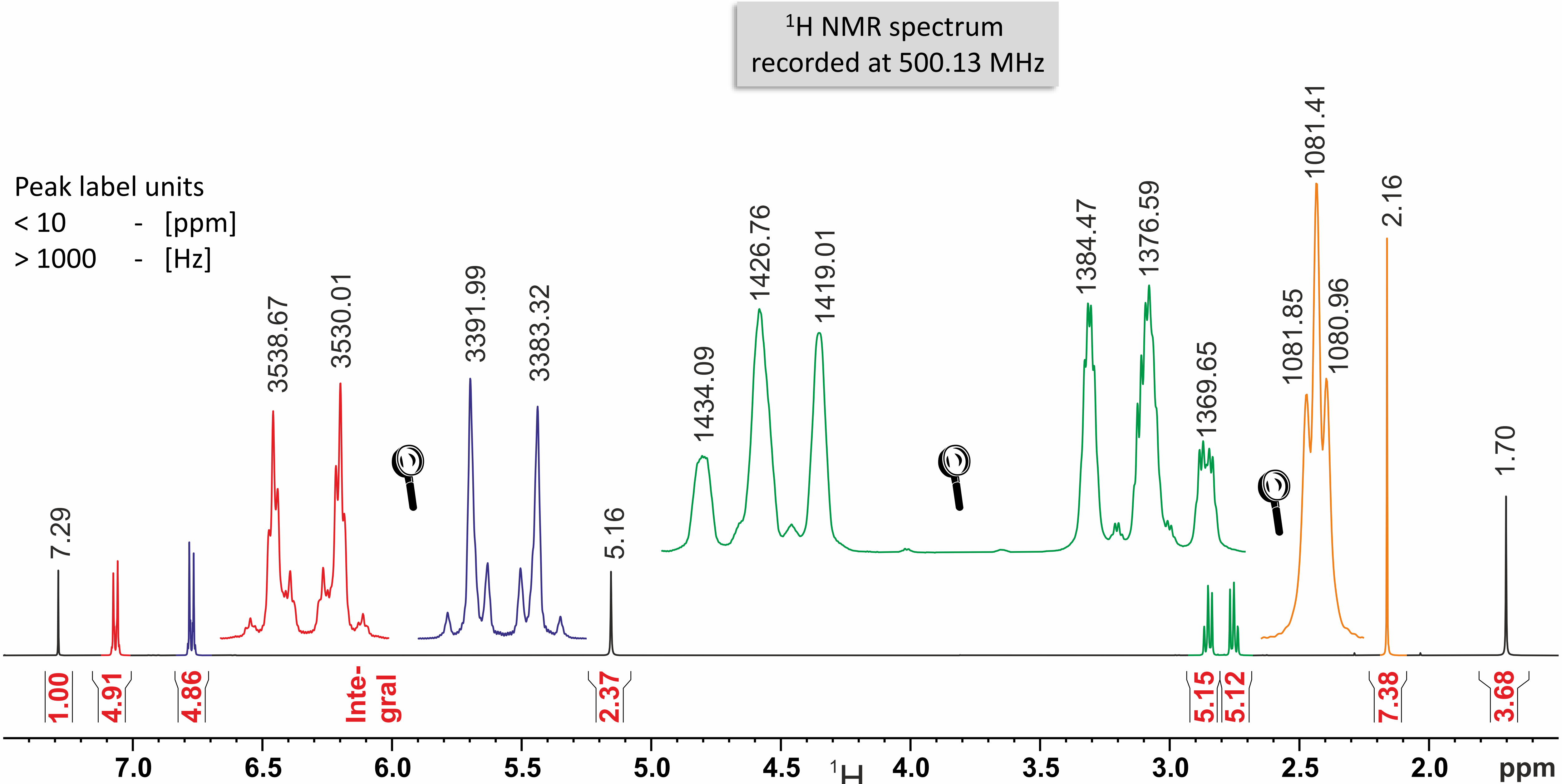
$C_{10}H_{12}O_2$ in $CDCl_3$

$^{13}C\{^1H\}$ NMR spectrum
recorded at 125.83{500.36} MHz

In which fruit does this compound represent the main odour component?

So far there is no known correlation between spectroscopic data and odour, but the final chemical structure should answer the question …

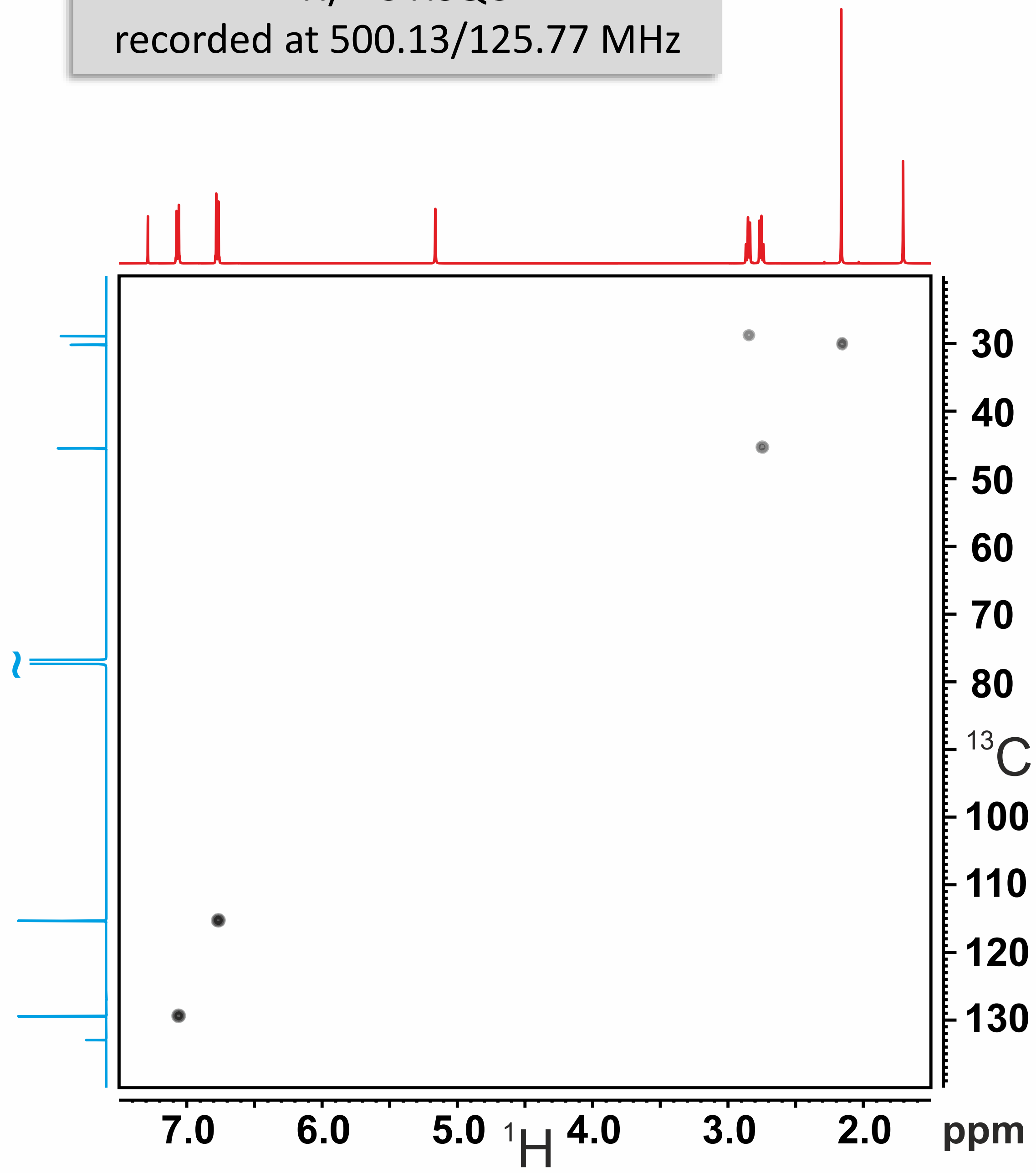




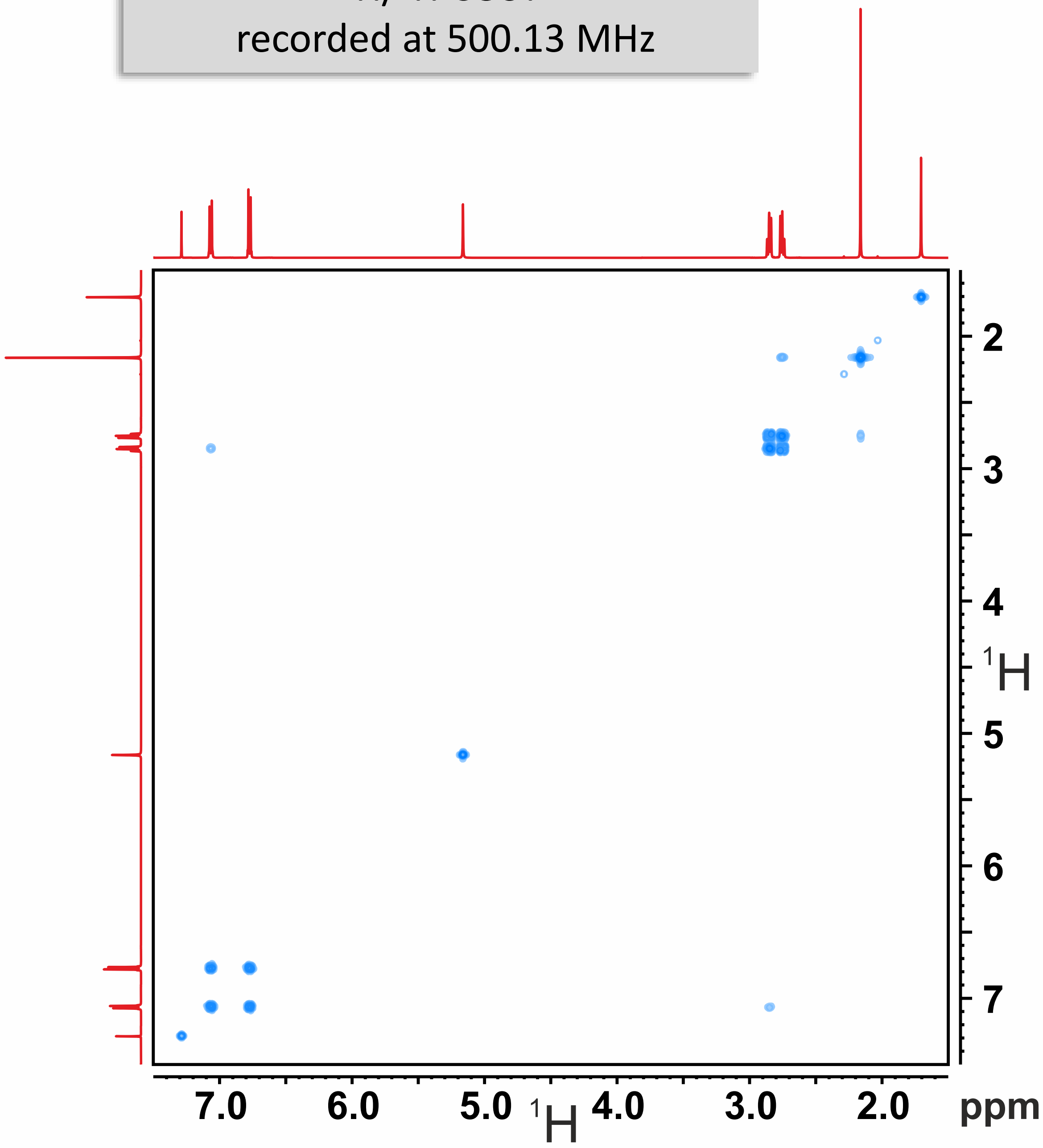
^{1}H NMR spectrum
recorded at 500.13 MHz

Peak label units
< 10 - [ppm]
> 1000 - [Hz]

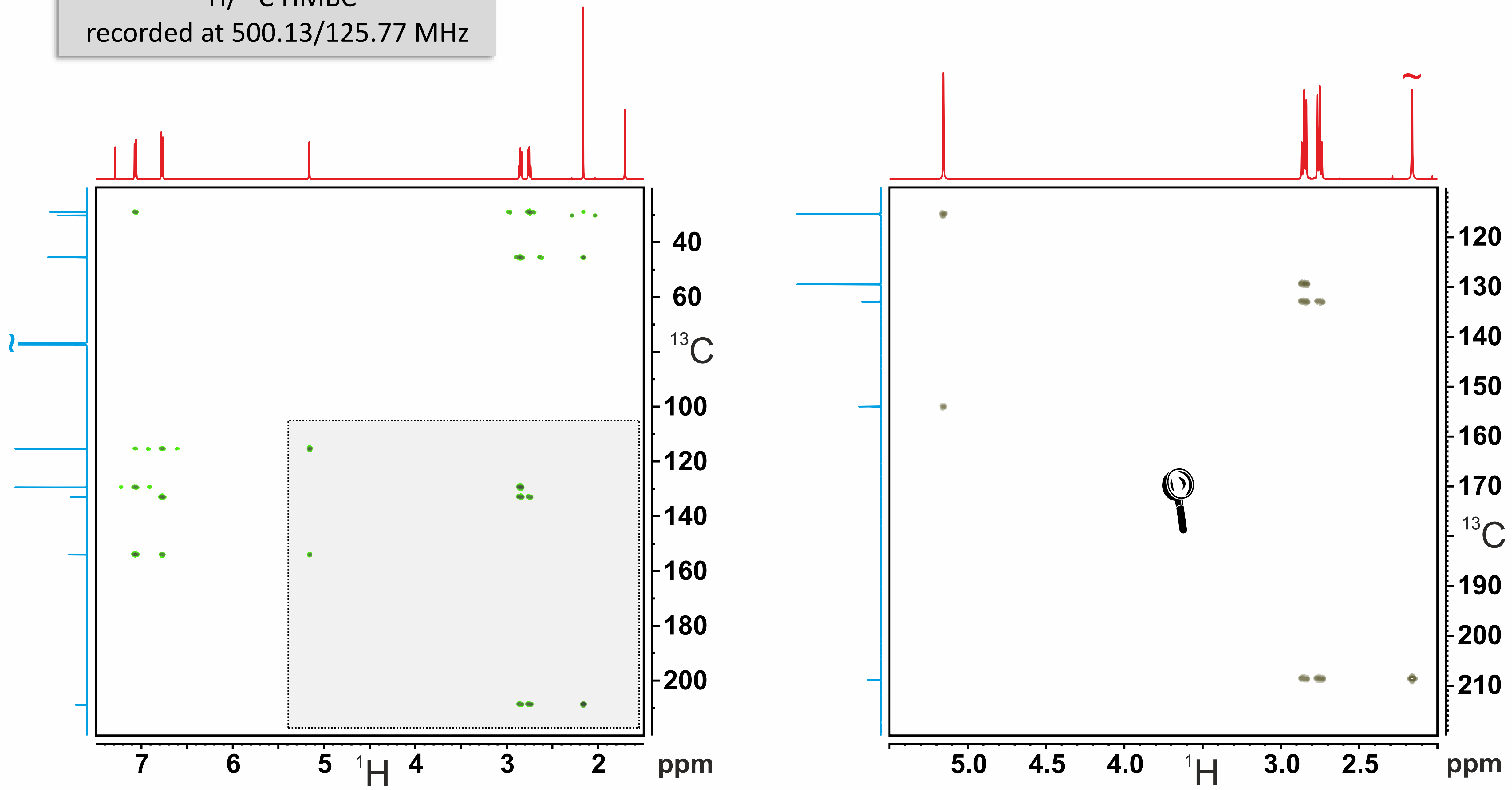
$^1H/^{13}C$ HSQC
recorded at 500.13/125.77 MHz



$^1H/^1H$ COSY
recorded at 500.13 MHz



$^1H/^{13}C$ HMBC
recorded at 500.13/125.77 MHz



5 DBE

Basic considerations

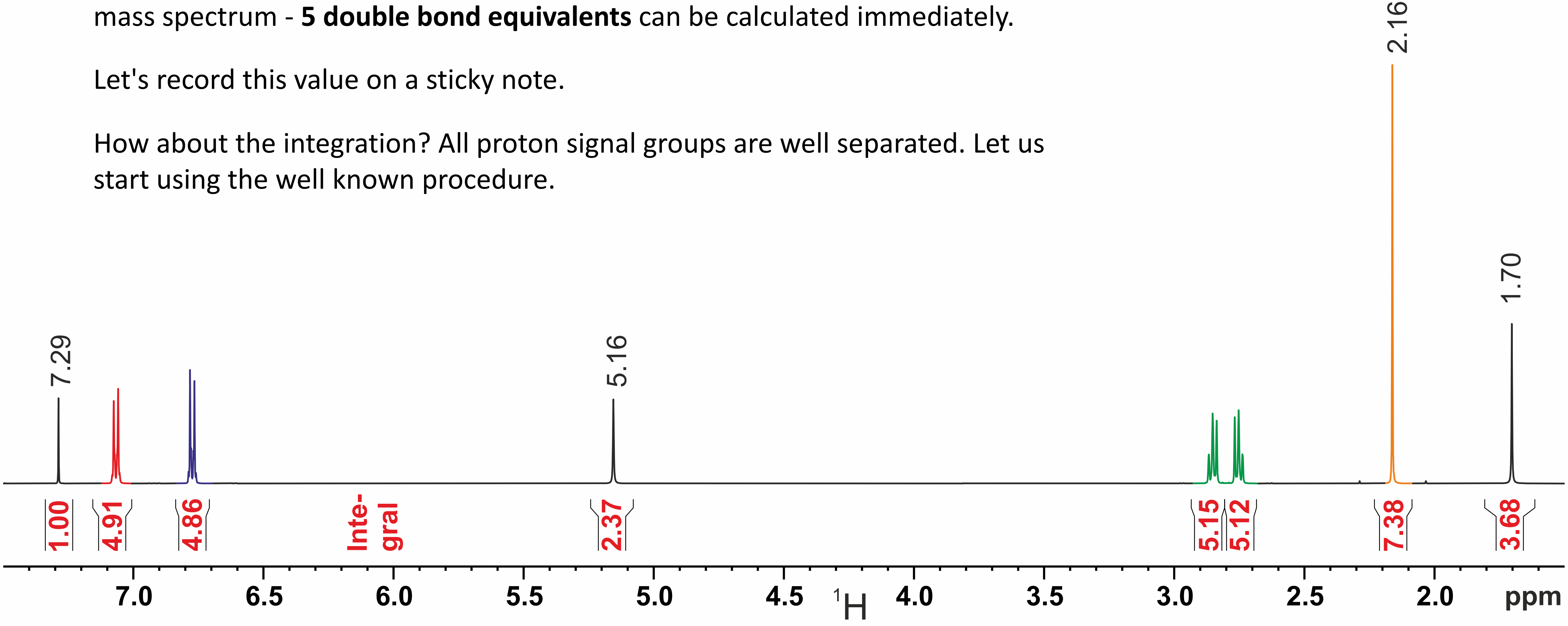
Double bond equivalents, integration

$C_{10}H_{12}O_2$ in $CDCl_3$

Because the molecular formula is known - for example from a high-resolution mass spectrum - **5 double bond equivalents** can be calculated immediately.

Let's record this value on a sticky note.

How about the integration? All proton signal groups are well separated. Let us start using the well known procedure.



5 DBE

Basic considerations

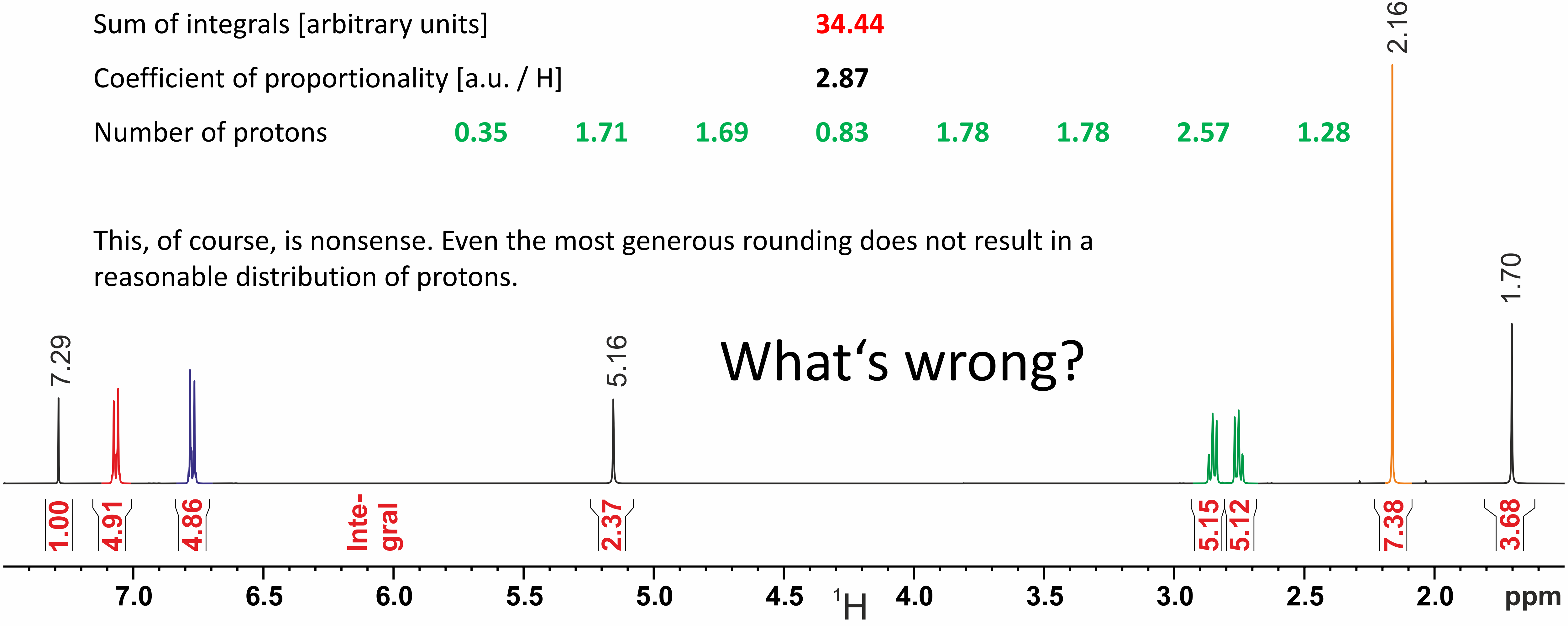
Double bond equivalents, integration

$C_{10}H_{12}O_2$ in $CDCl_3$

Integrals [arbitrary units]	1.00	4.91	4.86	2.37	5.12	5.12	7.38	3.68
Sum of integrals [arbitrary units]				34.44				
Coefficient of proportionality [a.u. / H]				2.87				
Number of protons	0.35	1.71	1.69	0.83	1.78	1.78	2.57	1.28

This, of course, is nonsense. Even the most generous rounding does not result in a reasonable distribution of protons.

What‘s wrong?



5 DBE

Basic considerations

Double bond equivalents, integration

$C_{10}H_{12}O_2$ in $CDCl_3$

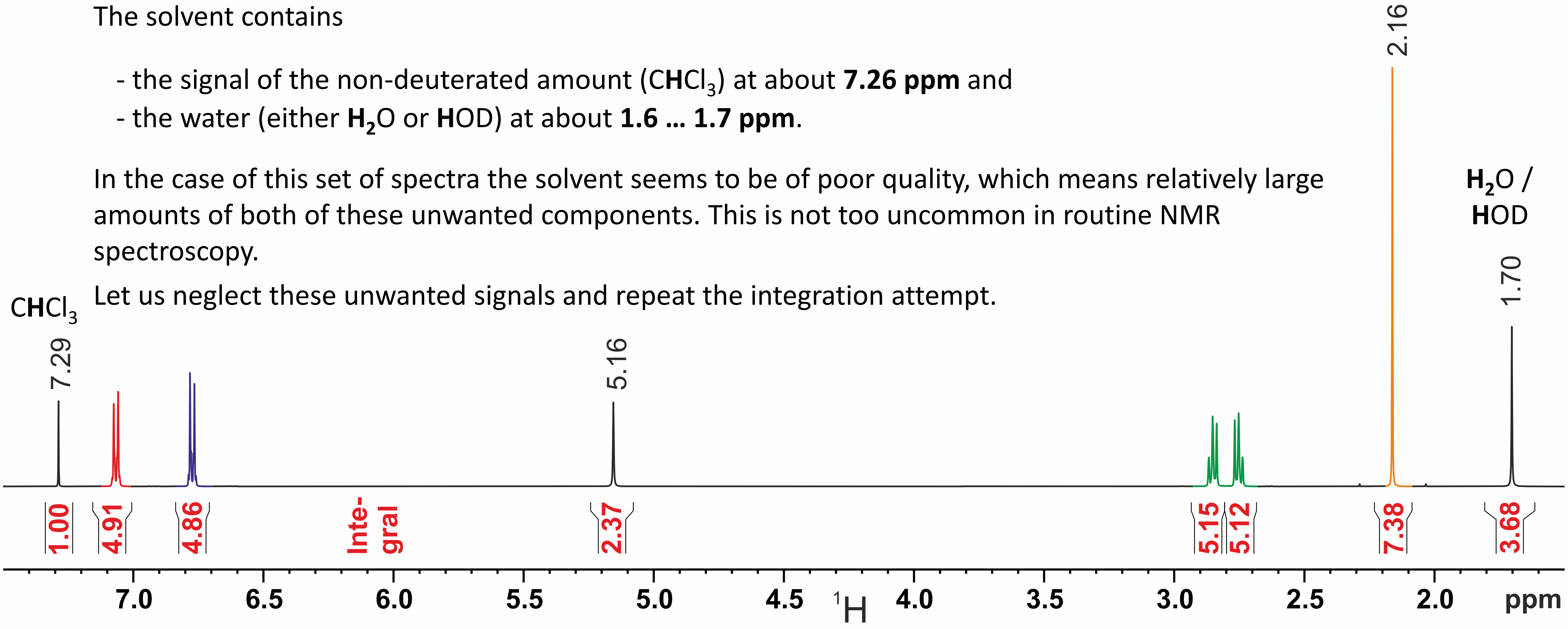
Please note the solvent.

The solvent contains

- the signal of the non-deuterated amount ($C\mathbf{H}Cl_3$) at about **7.26 ppm** and
- the water (either $\mathbf{H_2}O$ or **H**OD) at about **1.6 … 1.7 ppm**.

In the case of this set of spectra the solvent seems to be of poor quality, which means relatively large amounts of both of these unwanted components. This is not too uncommon in routine NMR spectroscopy.

Let us neglect these unwanted signals and repeat the integration attempt.



5 DBE

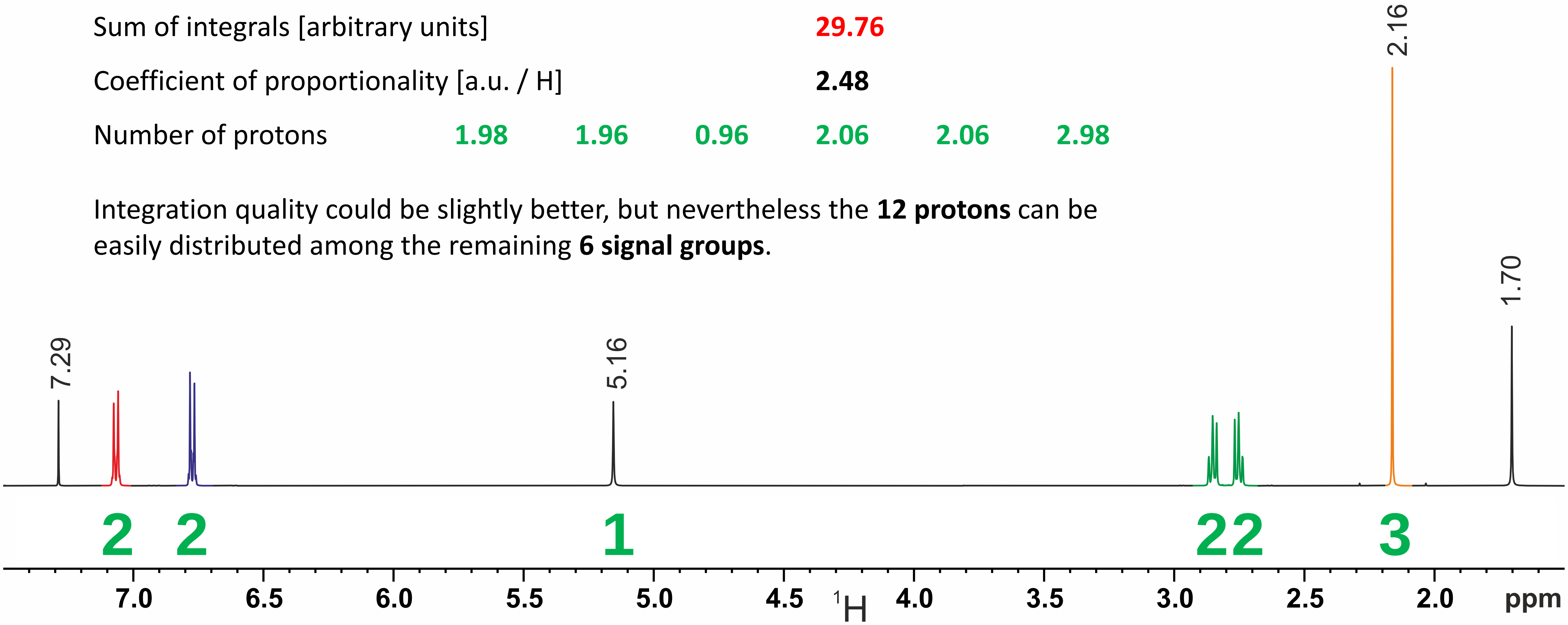
Basic considerations

Double bond equivalents, integration

$C_{10}H_{12}O_2$ in $CDCl_3$

Integrals [arbitrary units]	**4.91**	**4.86**	**2.37**	**5.12**	**5.12**	**7.38**
Sum of integrals [arbitrary units]				**29.76**		
Coefficient of proportionality [a.u. / H]				**2.48**		
Number of protons	**1.98**	**1.96**	**0.96**	**2.06**	**2.06**	**2.98**

Integration quality could be slightly better, but nevertheless the **12 protons** can be easily distributed among the remaining **6 signal groups**.



5 DBE

Basic considerations

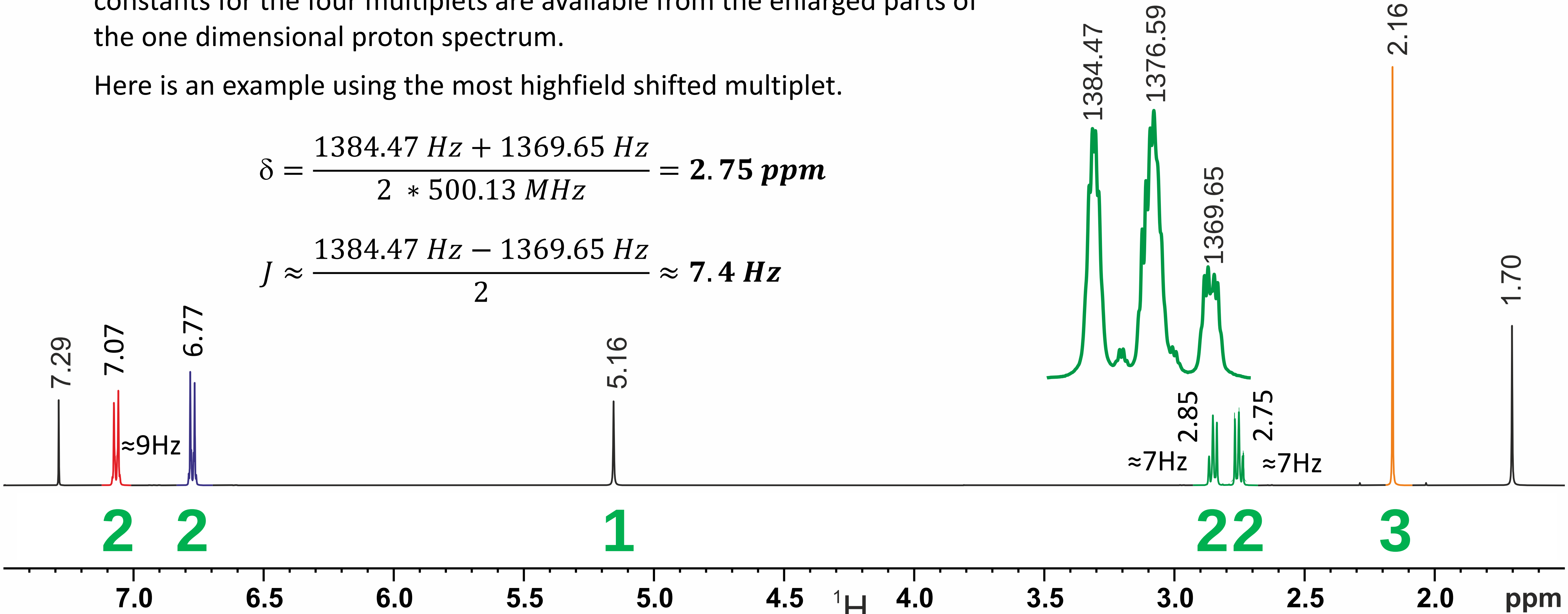
Double bond equivalents, integration

Some more details about the chemical shifts and the estimated coupling constants for the four multiplets are available from the enlarged parts of the one dimensional proton spectrum.

Here is an example using the most highfield shifted multiplet.

$$\delta = \frac{1384.47\ Hz + 1369.65\ Hz}{2\ *\ 500.13\ MHz} = \mathbf{2.75\ ppm}$$

$$J \approx \frac{1384.47\ Hz - 1369.65\ Hz}{2} \approx \mathbf{7.4\ Hz}$$



2.16 **3**

2.75 **2**

2.85 **2**

5 DBE

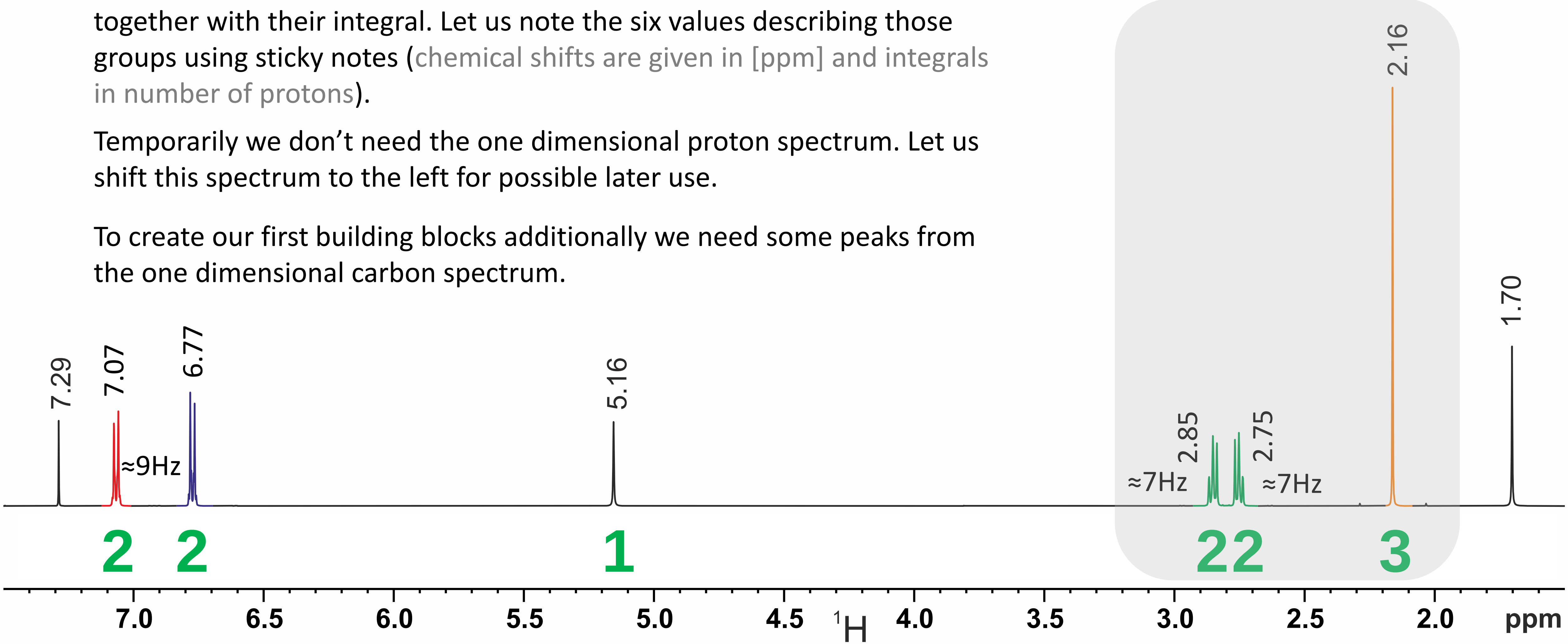
Basic considerations

Double bond equivalents, integration

During the next steps we need the three signal groups **below 3 ppm** together with their integral. Let us note the six values describing those groups using sticky notes (chemical shifts are given in [ppm] and integrals in number of protons).

Temporarily we don't need the one dimensional proton spectrum. Let us shift this spectrum to the left for possible later use.

To create our first building blocks additionally we need some peaks from the one dimensional carbon spectrum.



Basic considerations

Carbon signals

28.91

30.20

45.50

2.16 **3**

2.75 **2**

2.85 **2**

5 DBE

From the one dimensional carbon spectrum we need the three most highfield-shifted signals.

In the DEPT you already see, that the signals at 45.50 ppm and 28.91 ppm belong to CH_2 groups, whereas the signal at 30.20 ppm belongs to a methyl group. Although we didn’t evaluate the HSQC until now this coincides perfectly with the proton integrals.

^{13}C

^{1}H

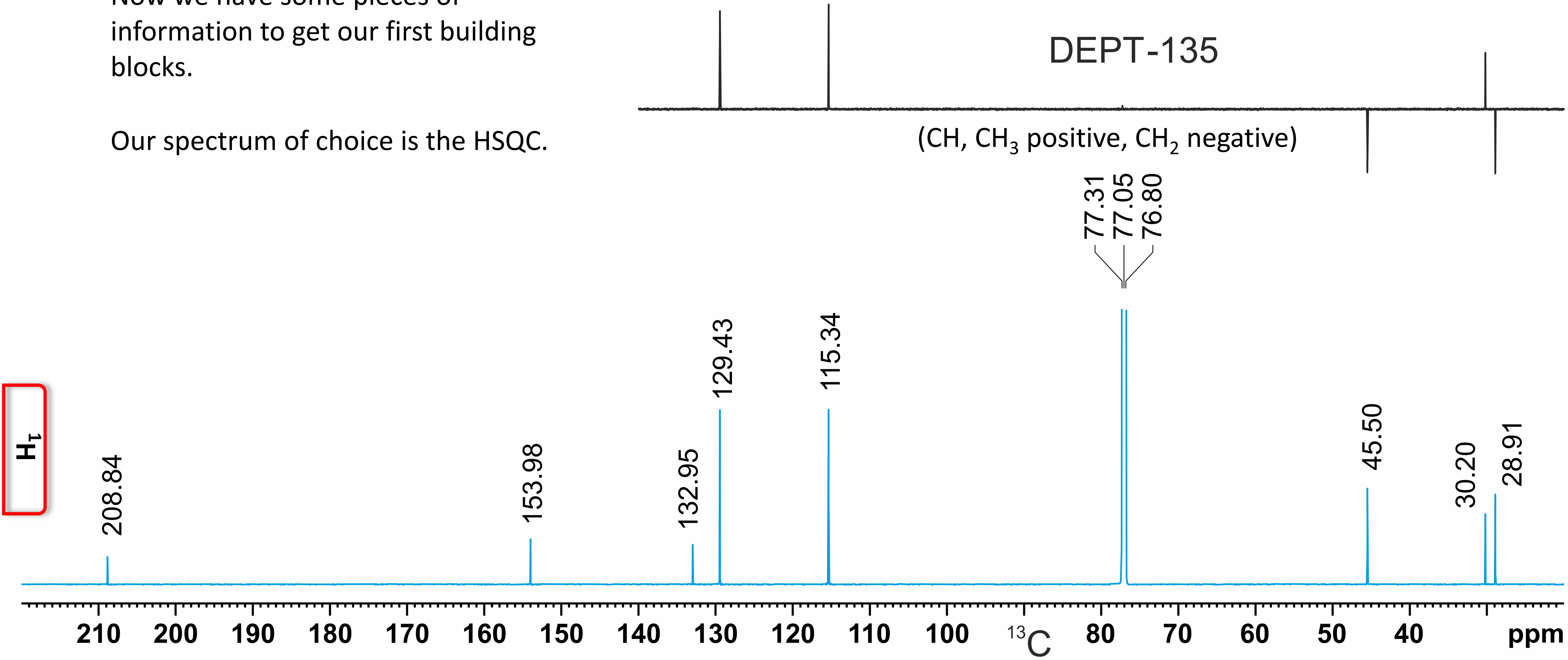
HSQC

28.91 | 30.20 | 45.50 | 2.16 **3** | 2.75 **2** | 2.85 **2** | 5 DBE

Building blocks

Now we have some pieces of information to get our first building blocks.

Our spectrum of choice is the HSQC.

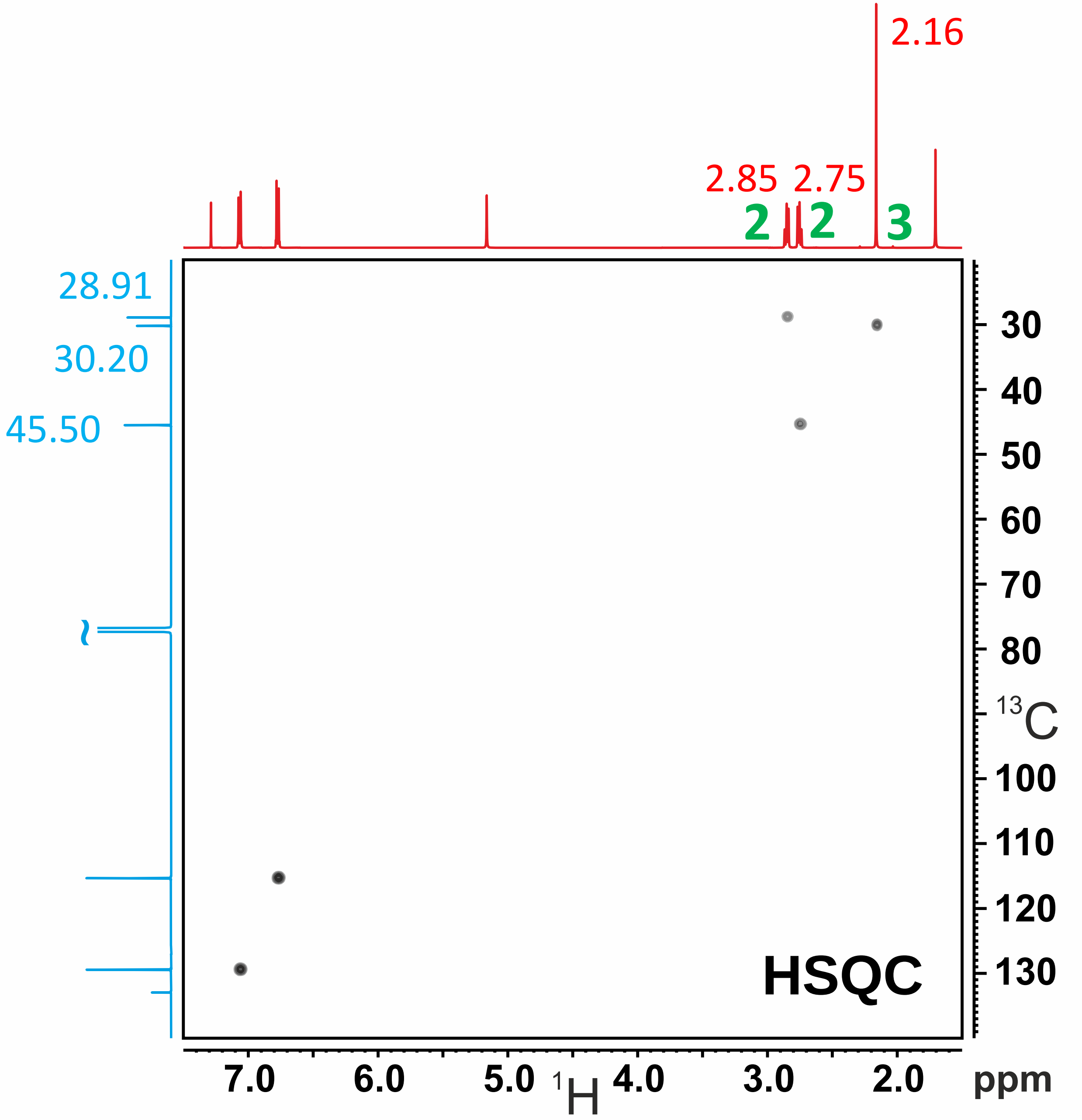


^1H

28.91 30.20 45.50 2.16 **3** 2.75 **2** 2.85 **2** 5 DBE

Building blocks

The HSQC provides us with structural fragments. To get their chemical shifts we need the collected data from the one-dimensional spectra.



^{13}C

^{1}H

5 DBE

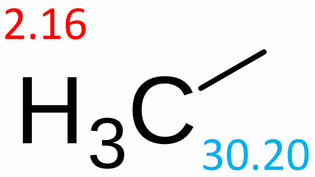
Building blocks

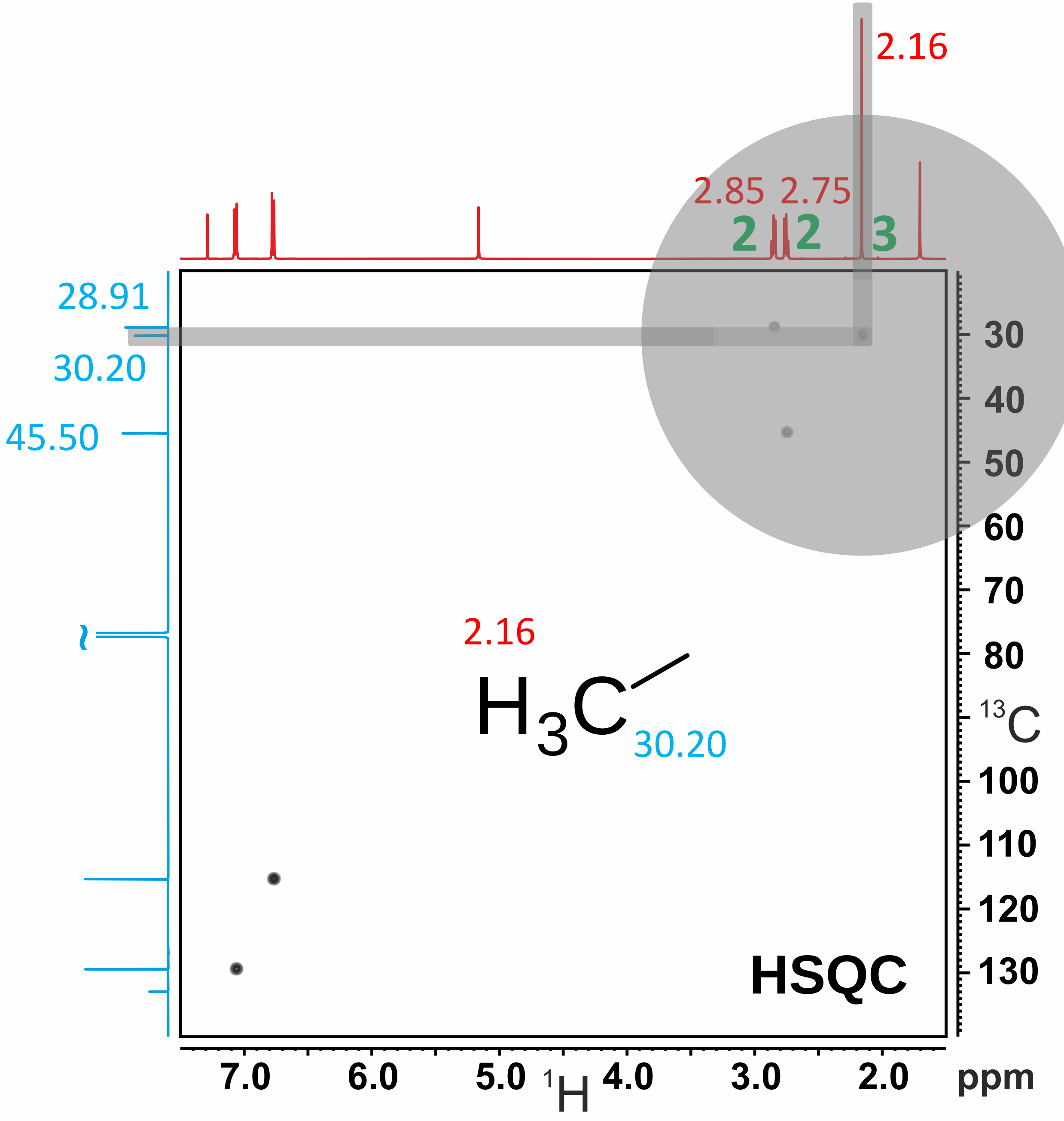
The three cross peaks in the upper right area of the HSQC are clearly due to CH_n fragments with sp^3 hybridized carbon.

Let’s extract the three parts of the final molecule one after the other.

^{13}C

^{1}H





5 DBE

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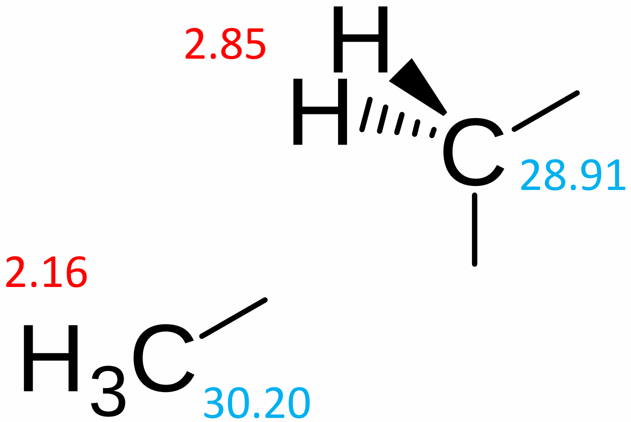

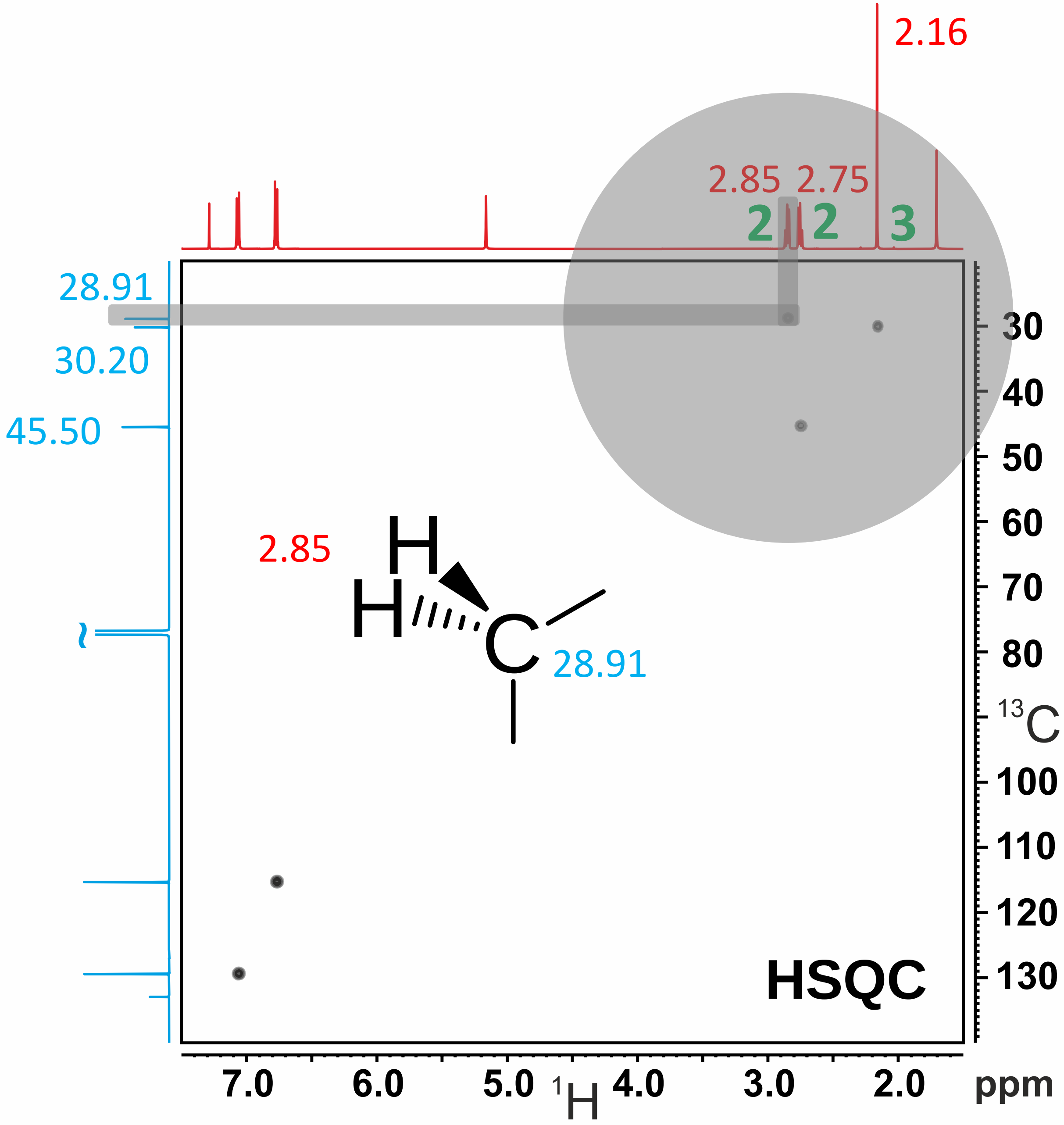

5 DBE

Building blocks

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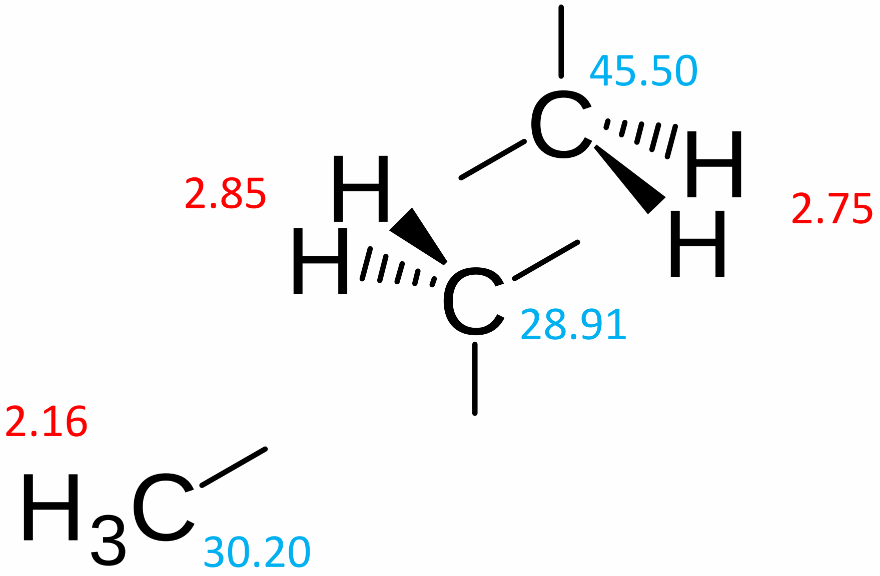
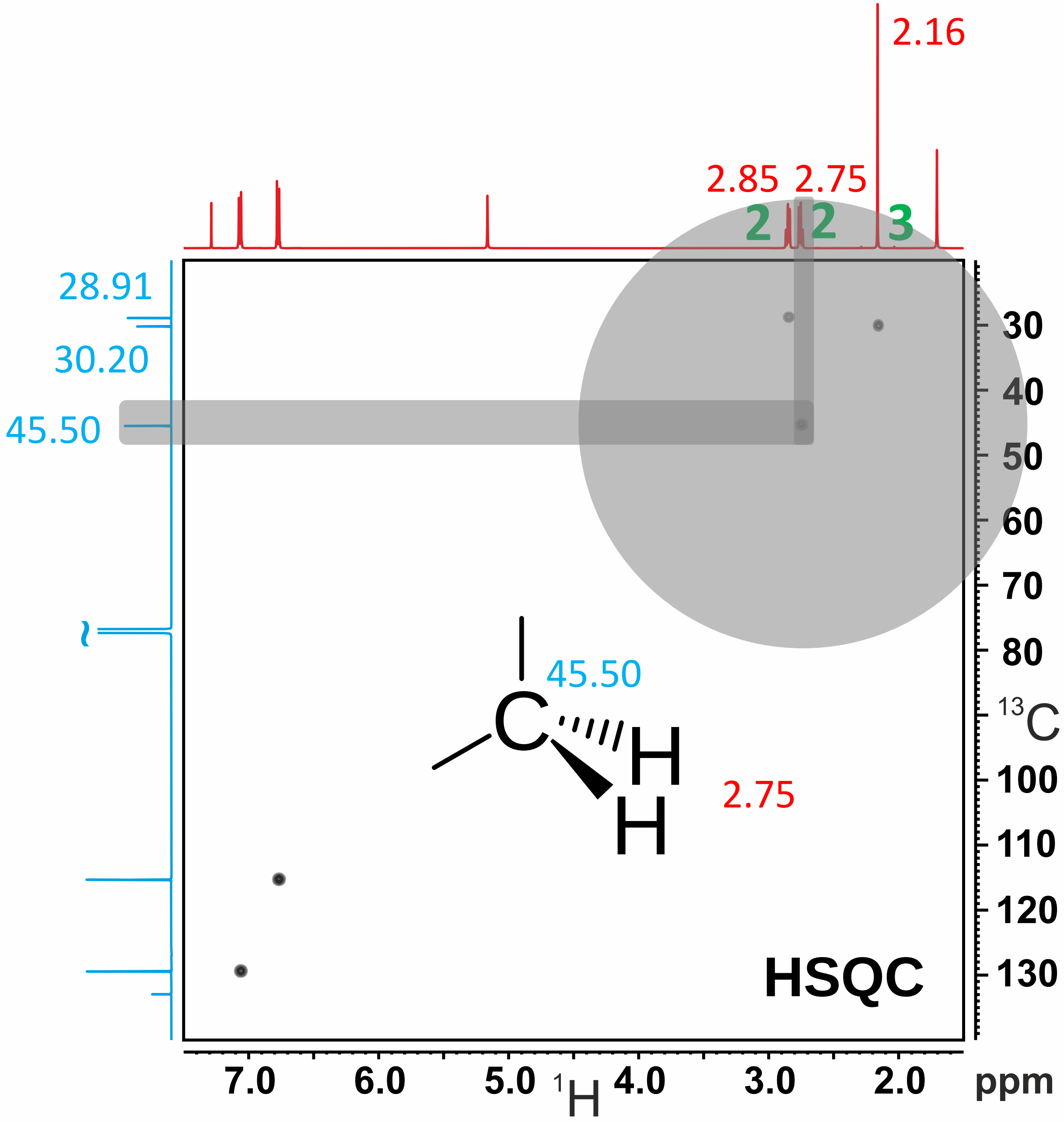
^{1}H





5 DBE

Building blocks

Connectivity

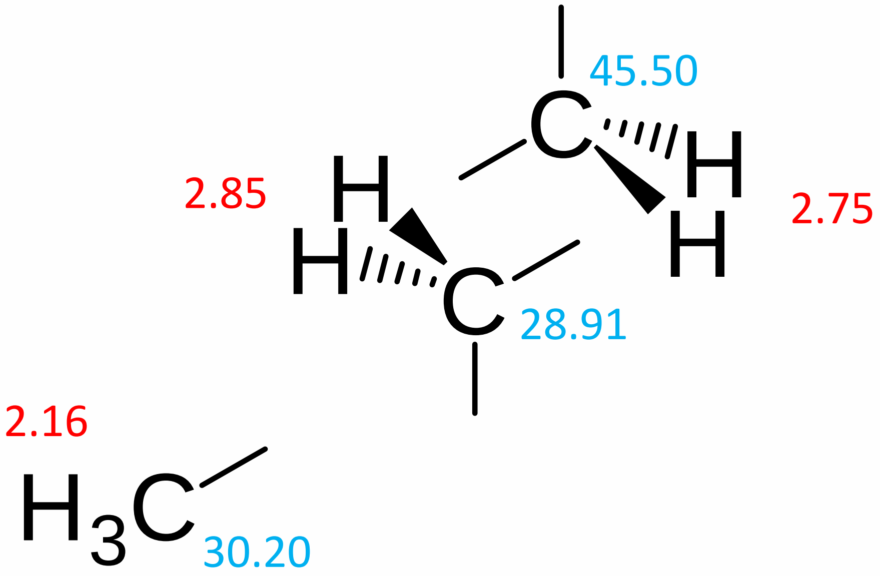
HMBC

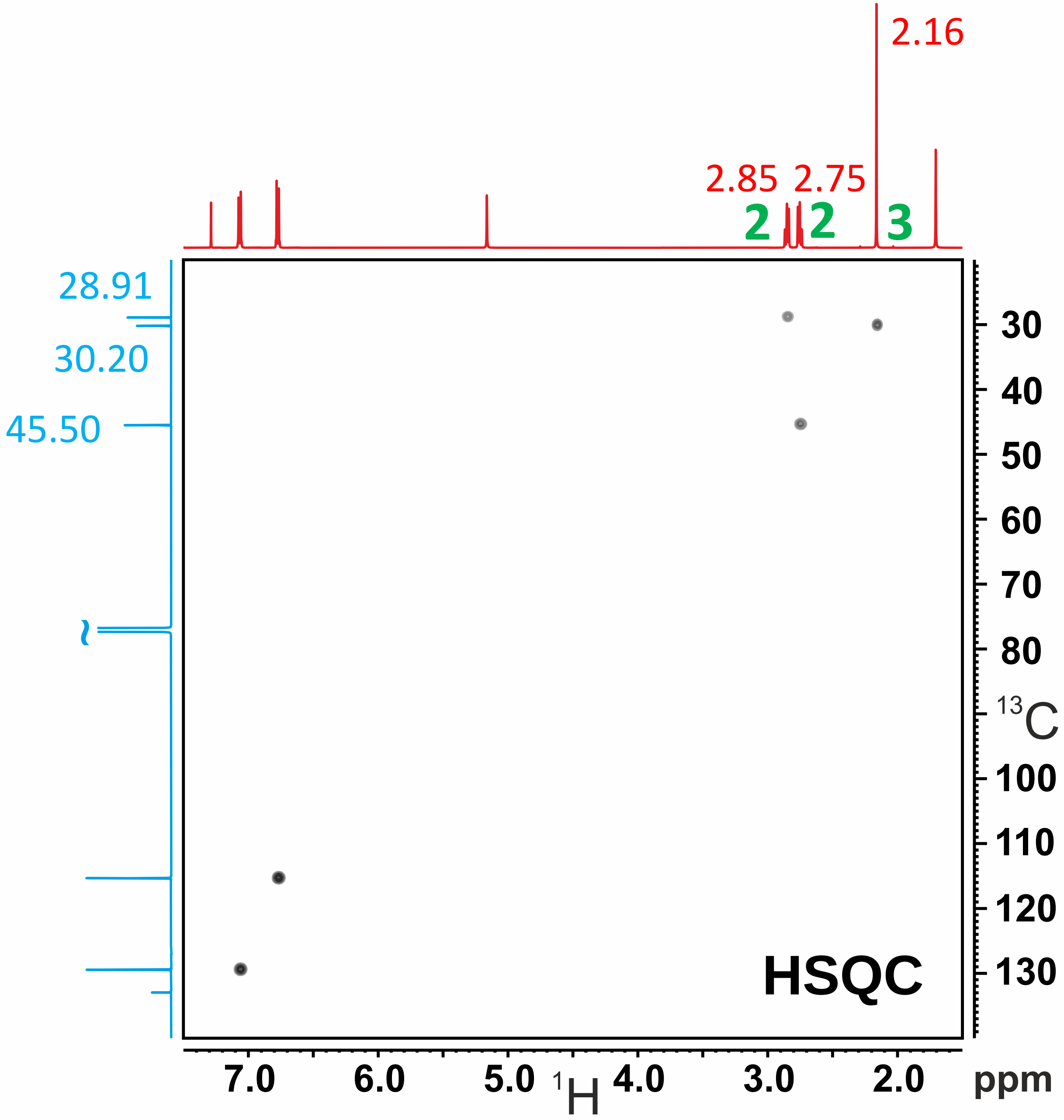
^{13}C

^{1}H

We now have the first three fragments to build our molecule. But is there any connectivity between these fragments? The HSQC provides us the building blocks only.

One possibility to get connectivities is the HMBC. Let’s try.





HSQC

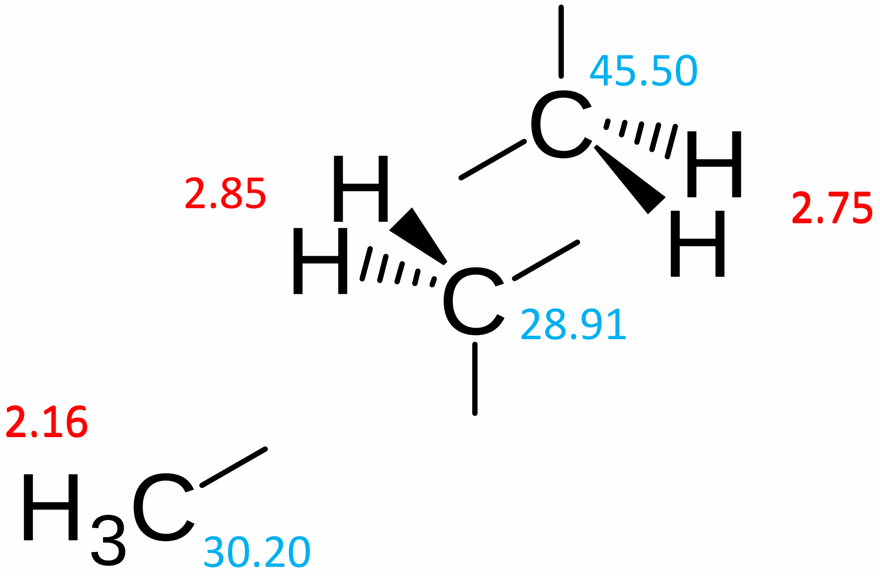
5 DBE

Building blocks

Connectivity

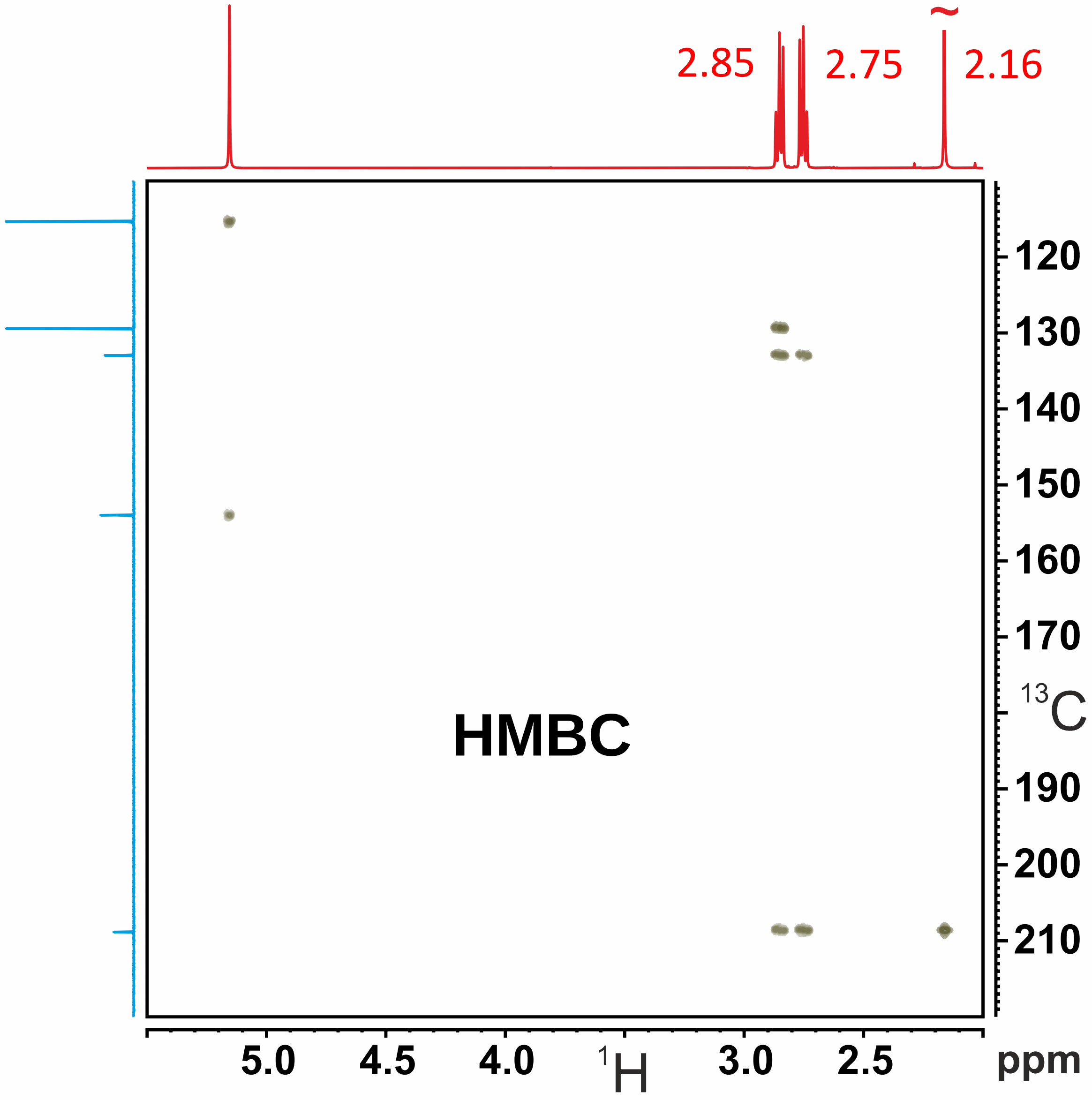
This subset of the HMBC is sufficient and makes the evaluation of this HMBC rich of cross peaks easier.
Very often it is a real challenge to find the really helpful HMBC cross peaks out of the huge number of available signals.

We already know three of the proton signals.



^{13}C

^{1}H



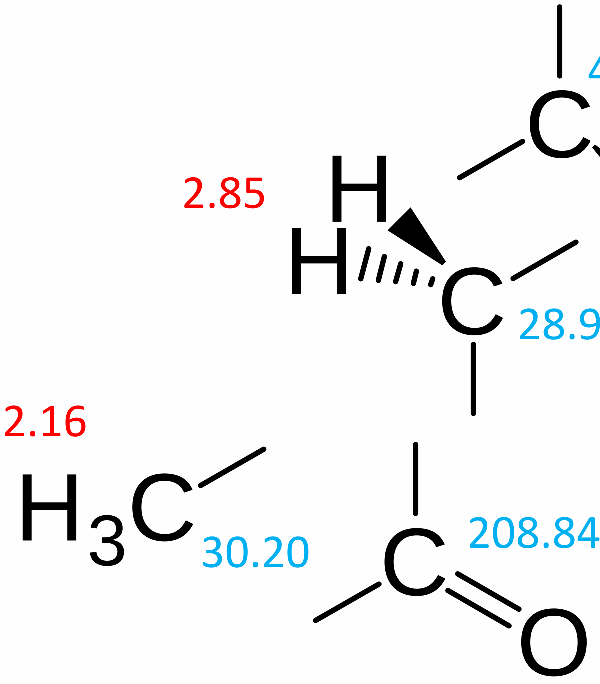
5 DBE

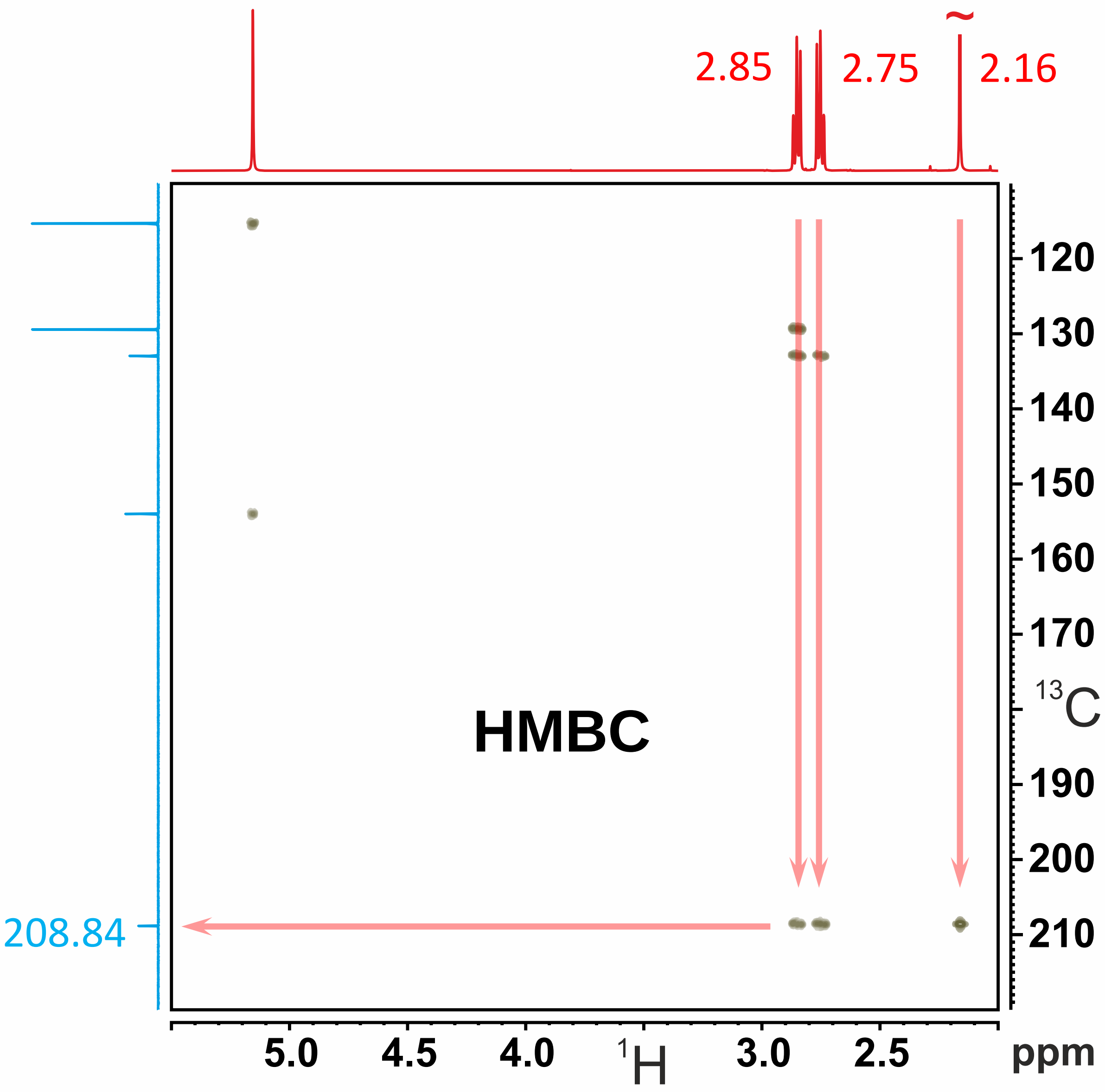
Building blocks

Connectivity

In the lower right corner of the HMBC there are three cross peaks showing a correlation of all three proton signals with the same carbon atom at 208.84 ppm (the exact value is extracted from the one dimensional carbon spectrum).

This, of course, is a carbonyl group.





HSQC

^{13}C

^{1}H

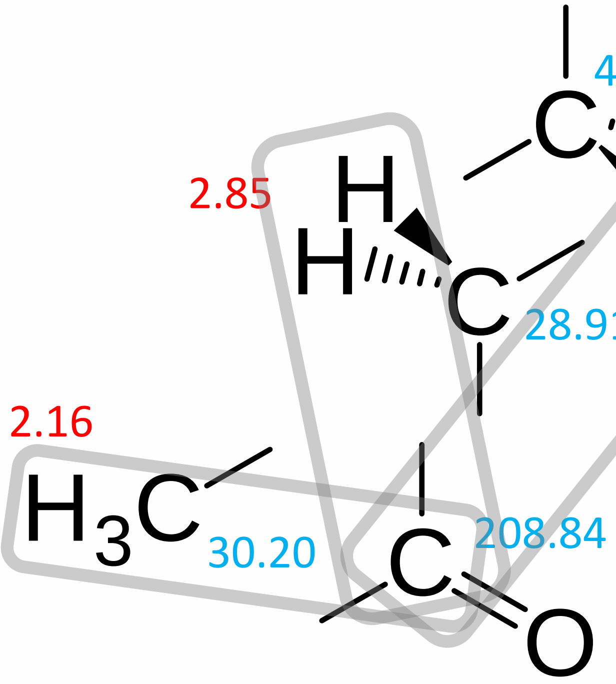
5 DBE

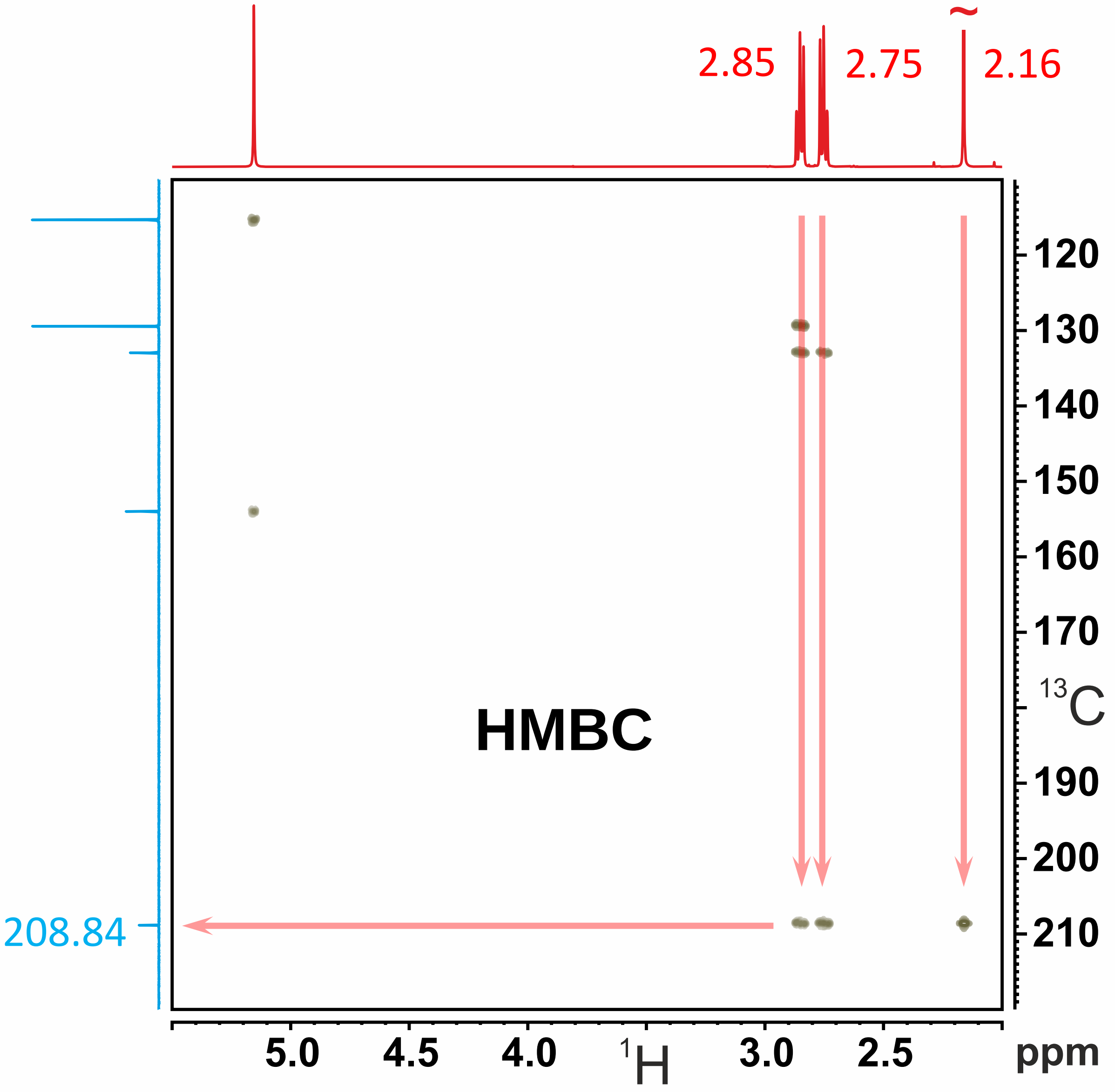
Building blocks

Connectivity

The carbon atom of the carbonyl group is two or three bonds away from each of the three proton groups.

It is easy to create a substructure to explain the neighbourhoods 208.84 ppm/2.16 ppm and 208.84 ppm/2.85 ppm (via two bonds).





HSQC

^{13}C

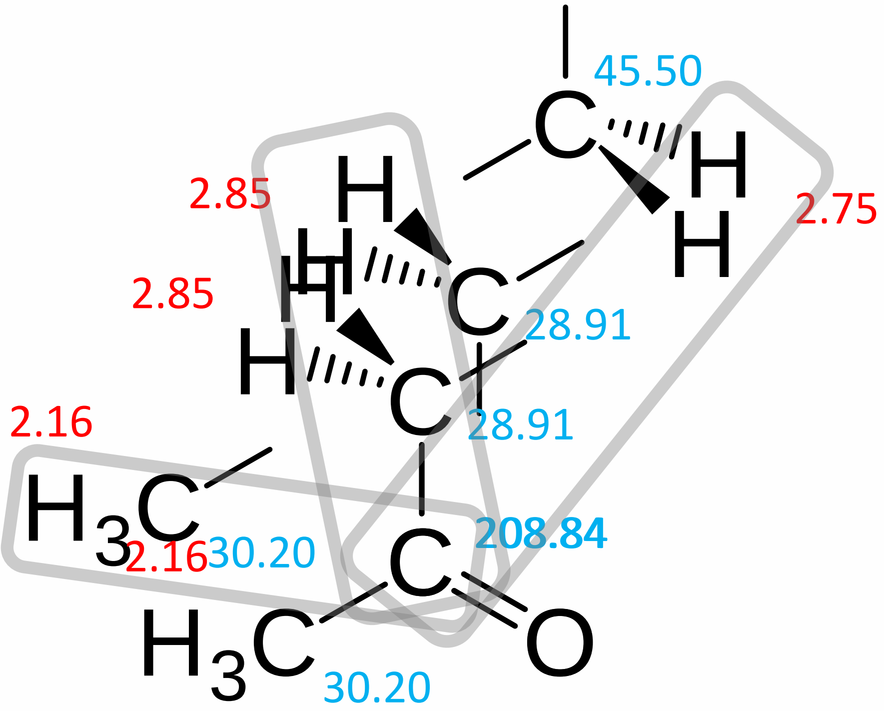
^{1}H

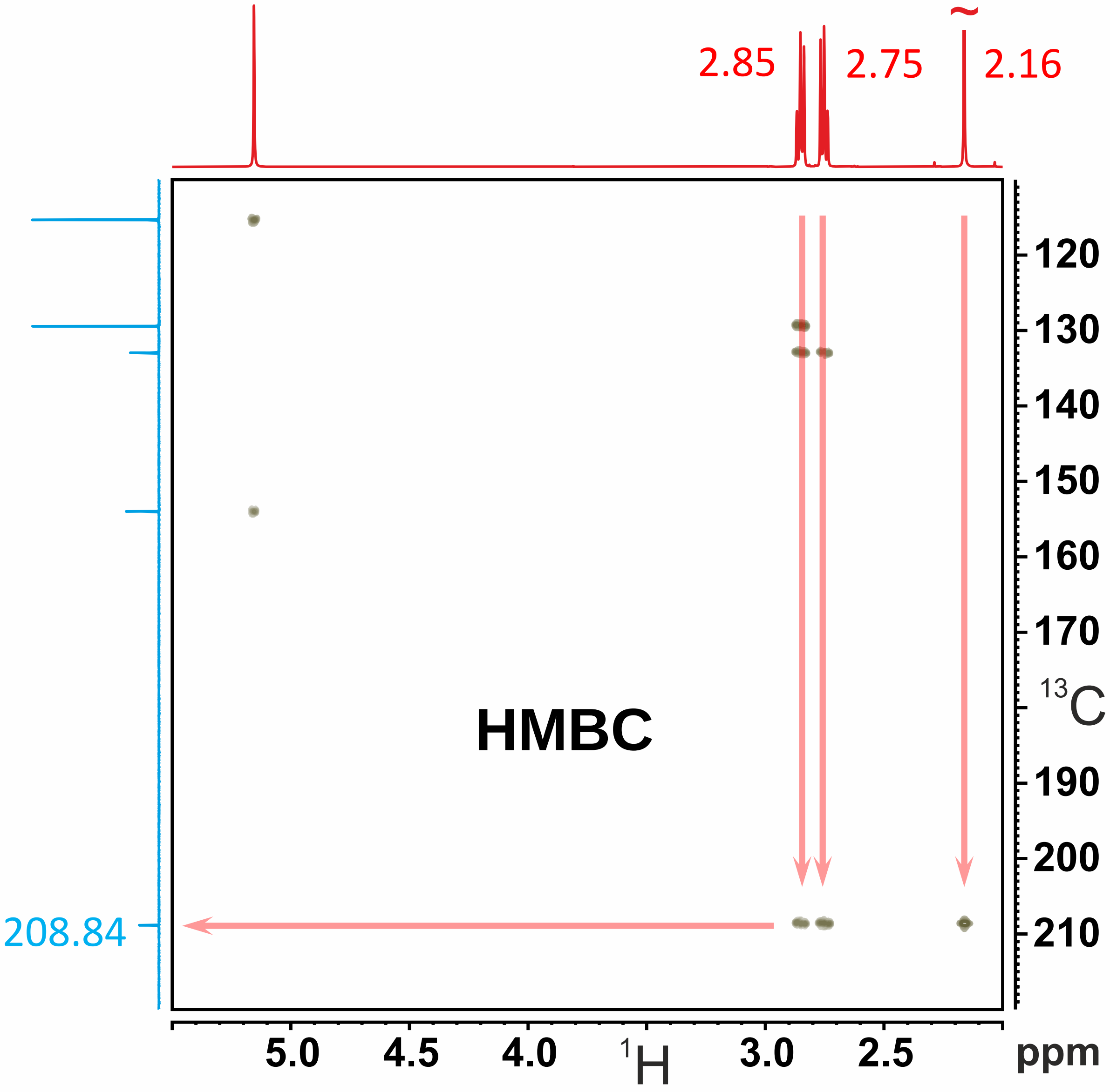
5 DBE

Building blocks

Connectivity

There are no more open (free) bond at the carbonyl group. But if we join both methylene groups, the distance between the carbon at 208.84 ppm and the proton at 2.75 ppm is three bonds, which is totally fine to explain an HMBC peak.





HSQC

5 DBE

Building blocks

Connectivity

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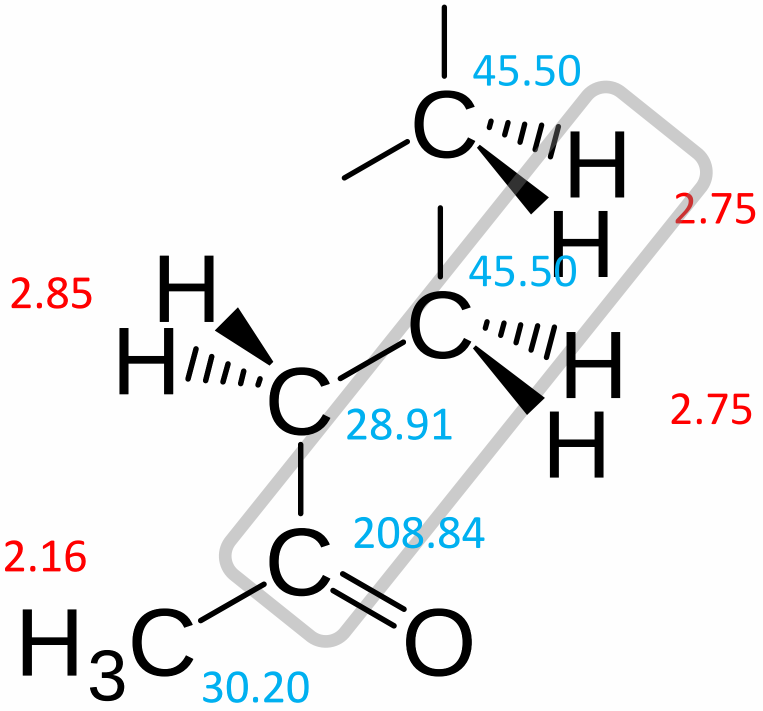
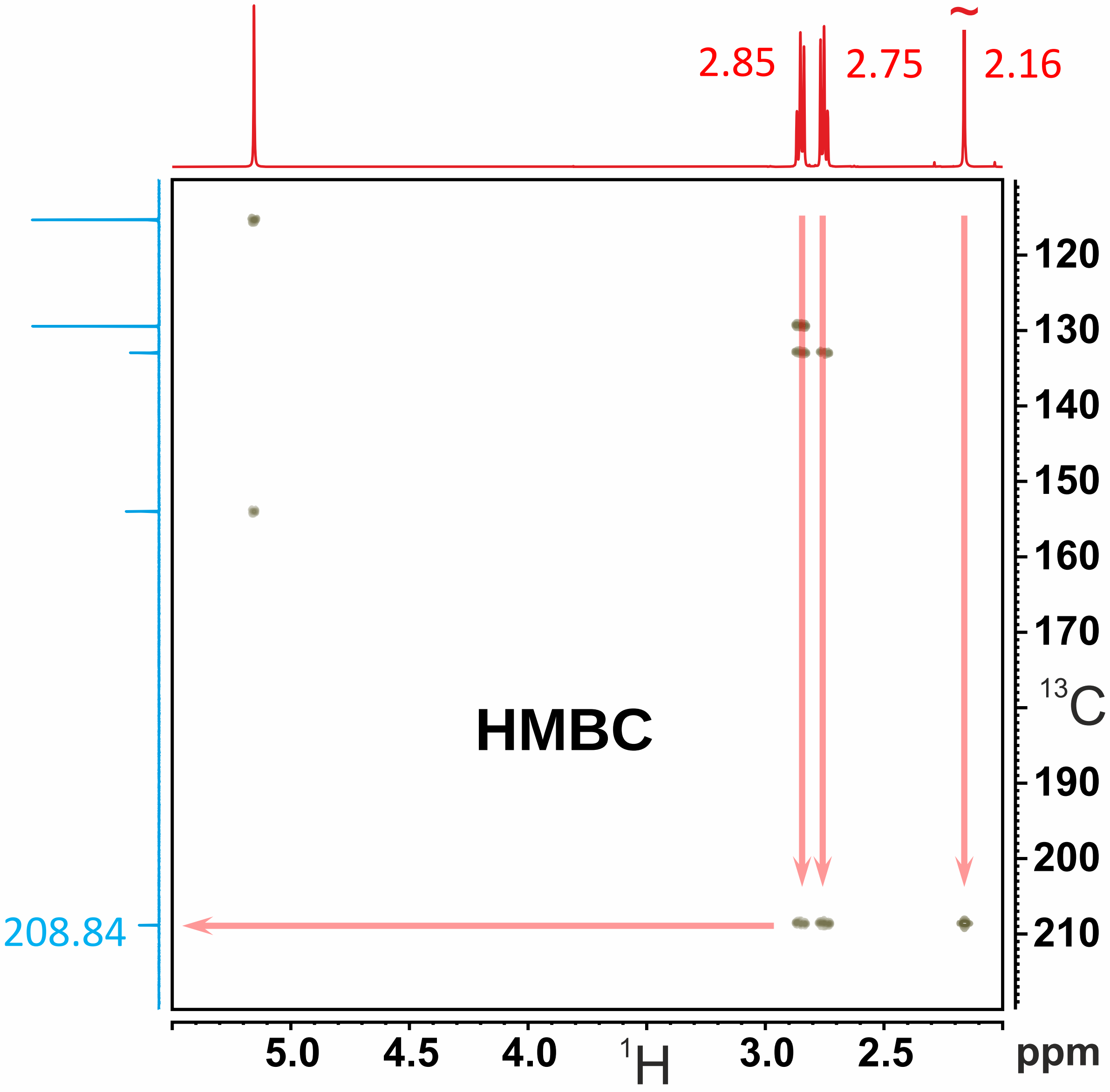
^{13}C

^{1}H





HSQC

4 DBE

Building blocks

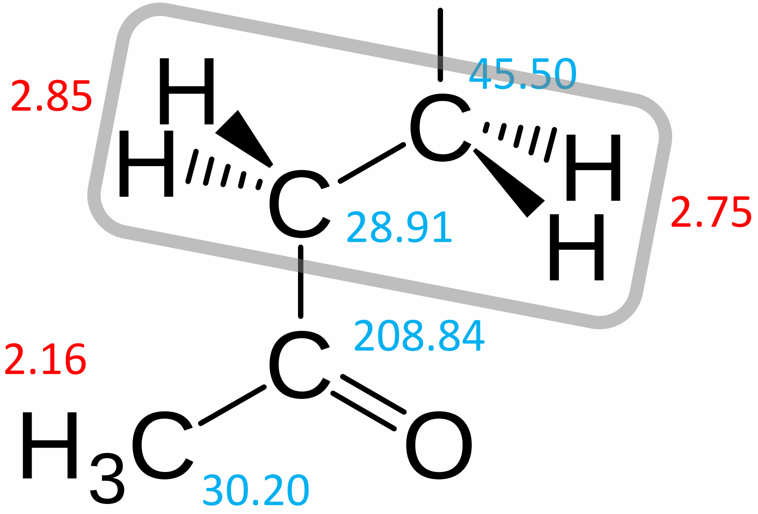
Connectivity

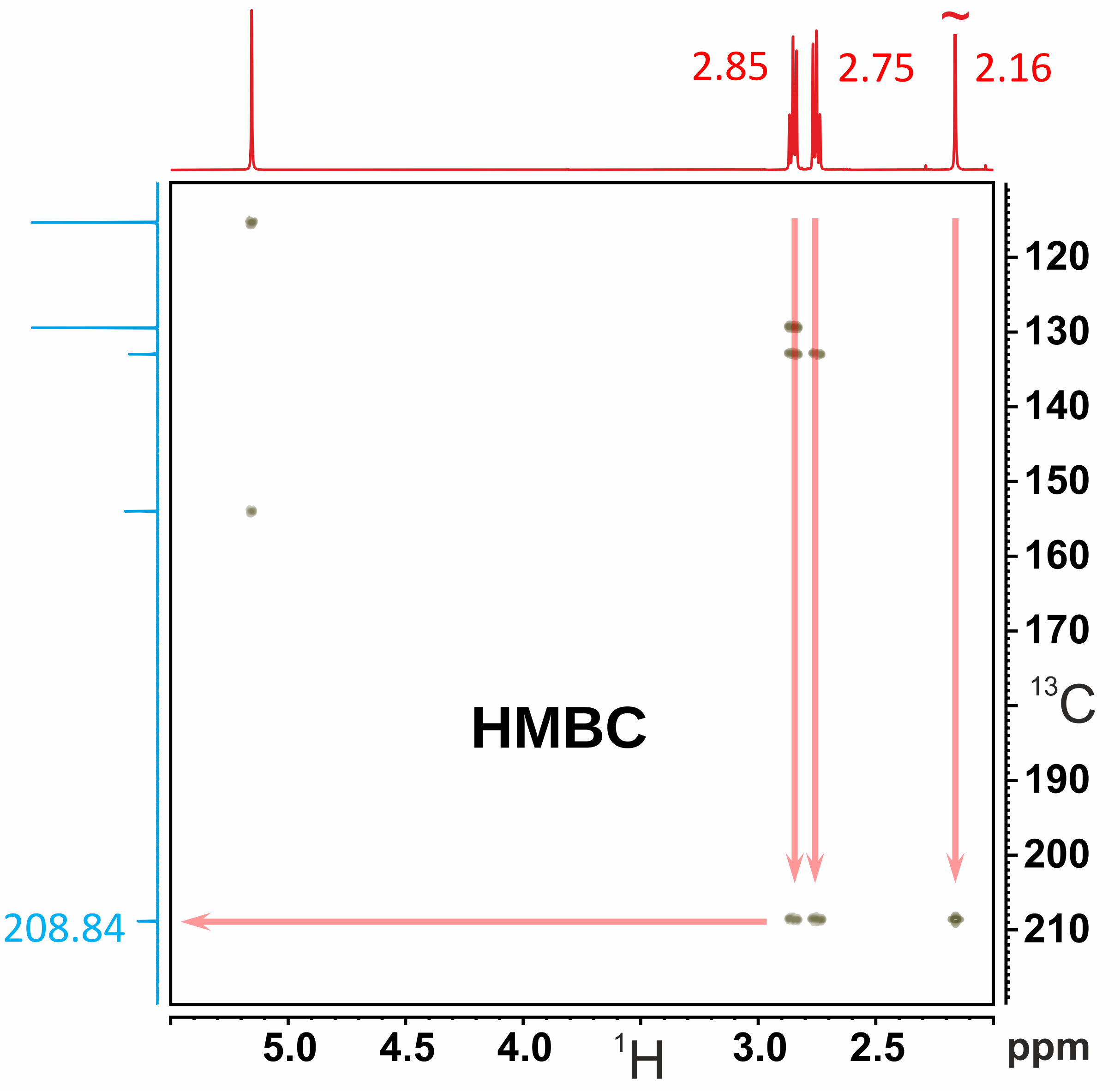
The carbonyl group contains one double bond equivalent. Now there are **four remaining double bond** equivalents to be assigned.

The connectivity of two methylene groups should be visible in the COSY.
Let’s check.

^{13}C

^{1}H





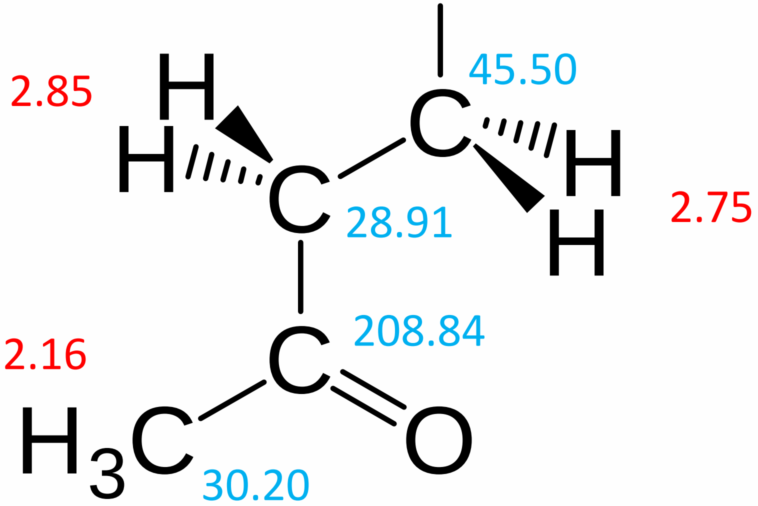
HSQC

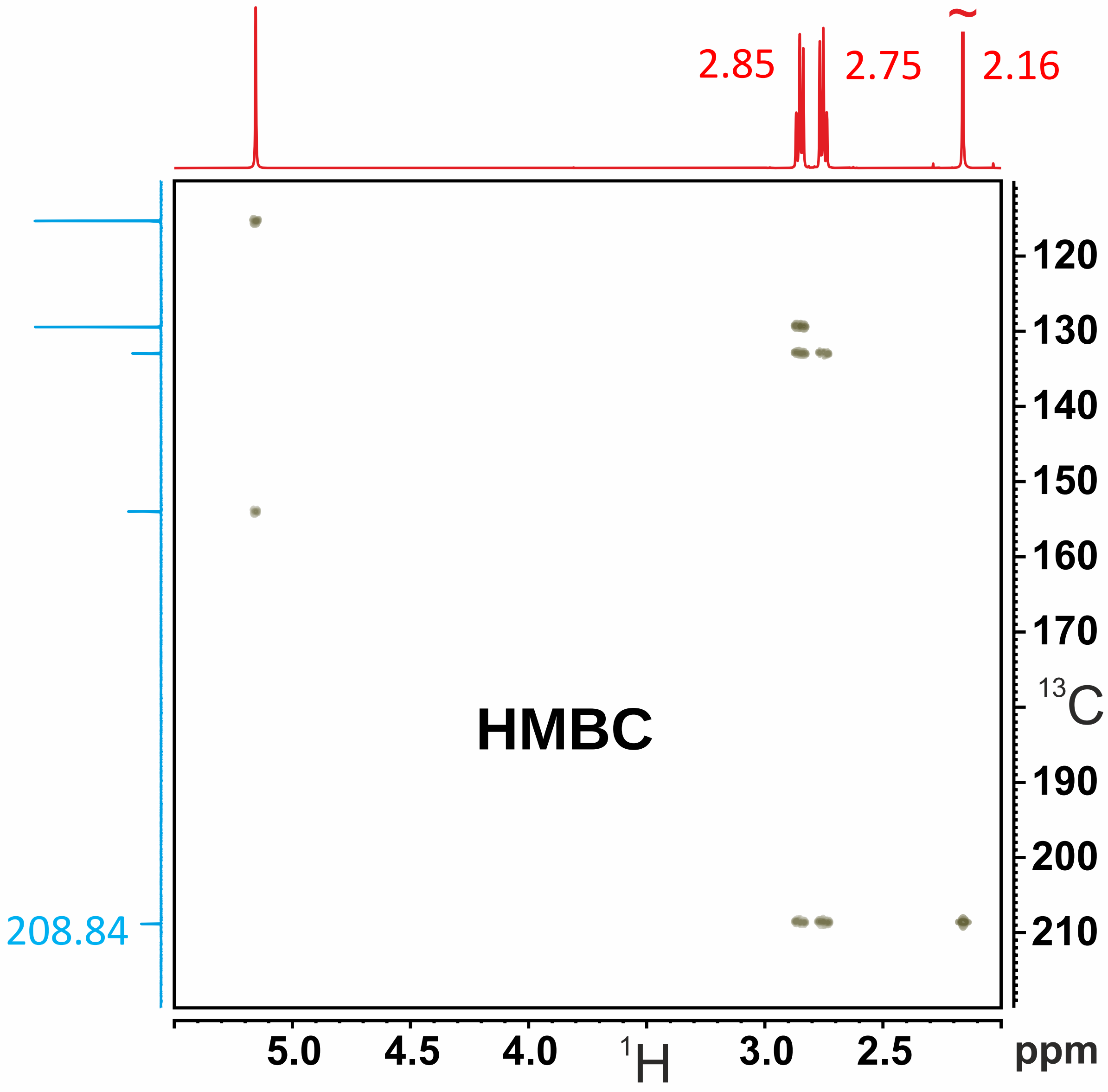
4 DBE

Building blocks

Connectivity

Let’s label the pseudo projections with the three signal groups of interest.





^{13}C

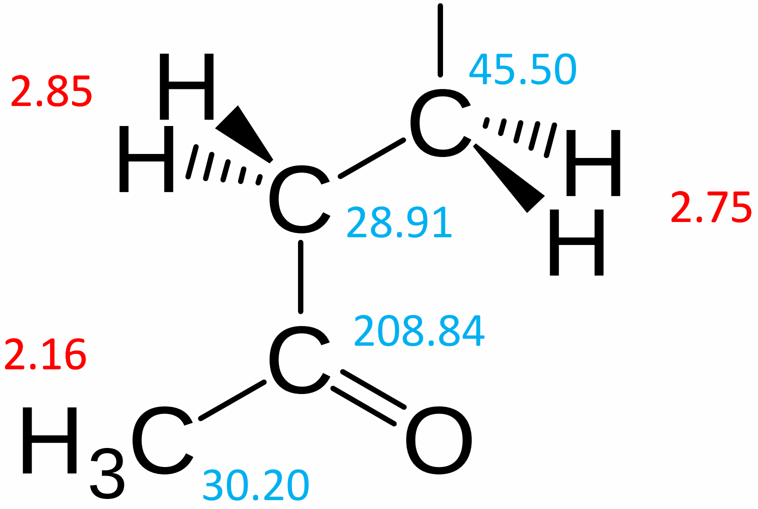
^{1}H

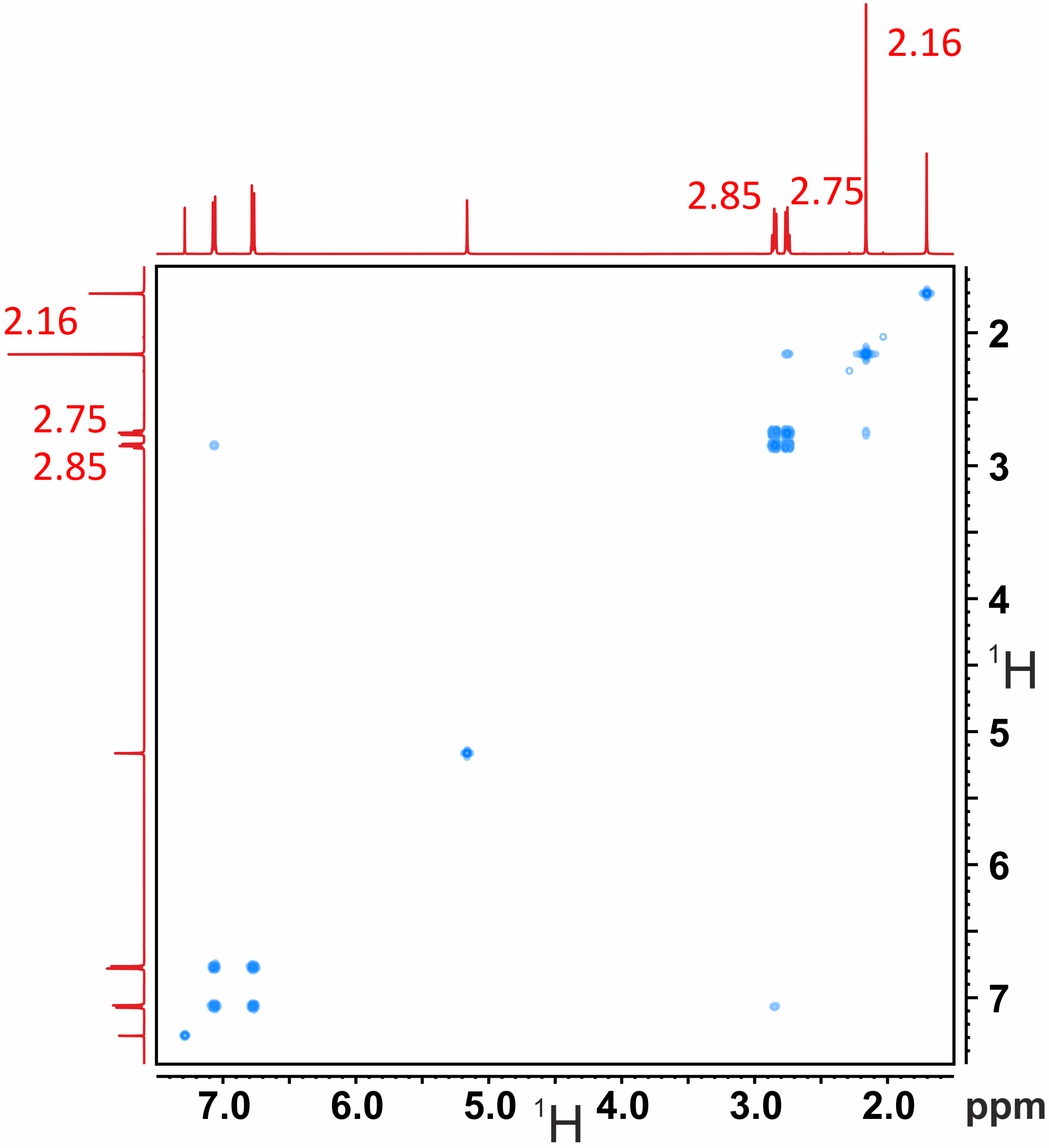
4 DBE

Building blocks

Connectivity

Although the chemical shifts of the two methylene groups are similar, the connectivity between both groups is clearly visible in the COSY.





4 DBE

HSQC

HMBC

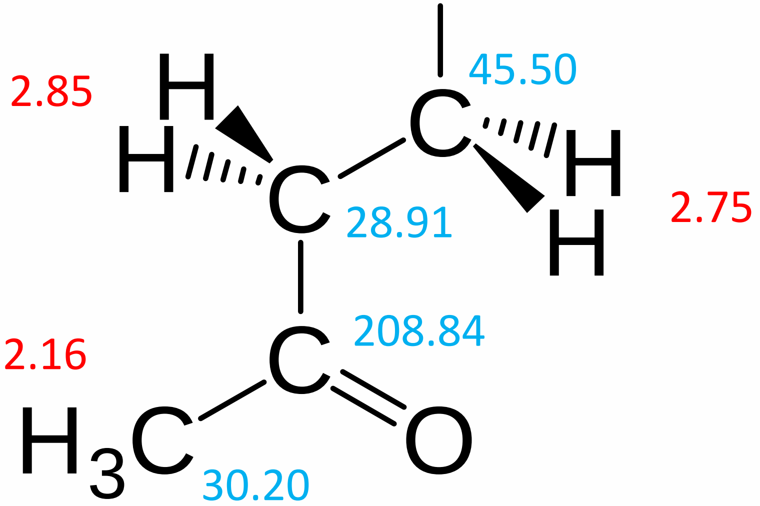
^{13}C

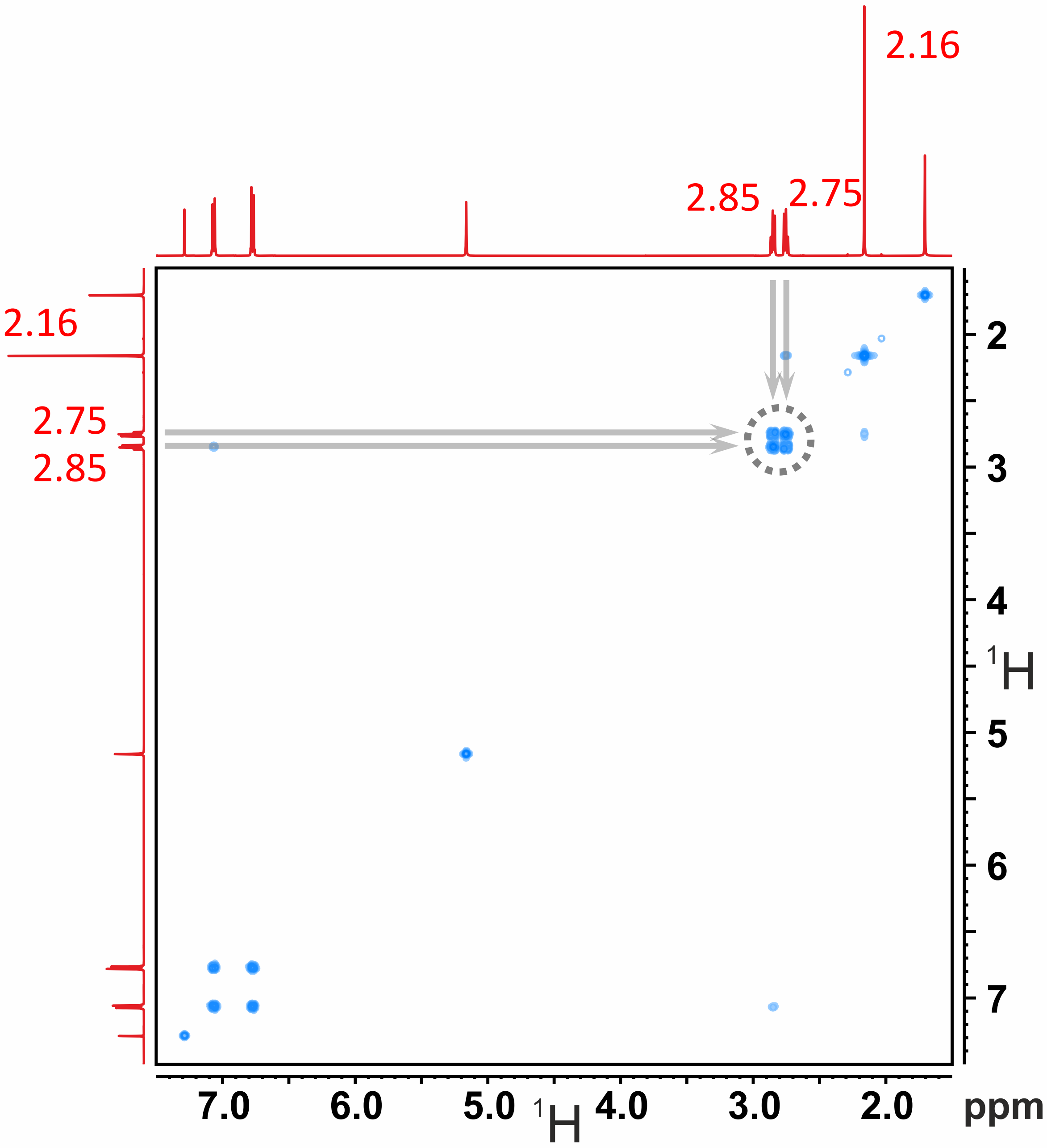
^{1}H

Building blocks

Connectivity

But there is another really unexpected correlation visible.





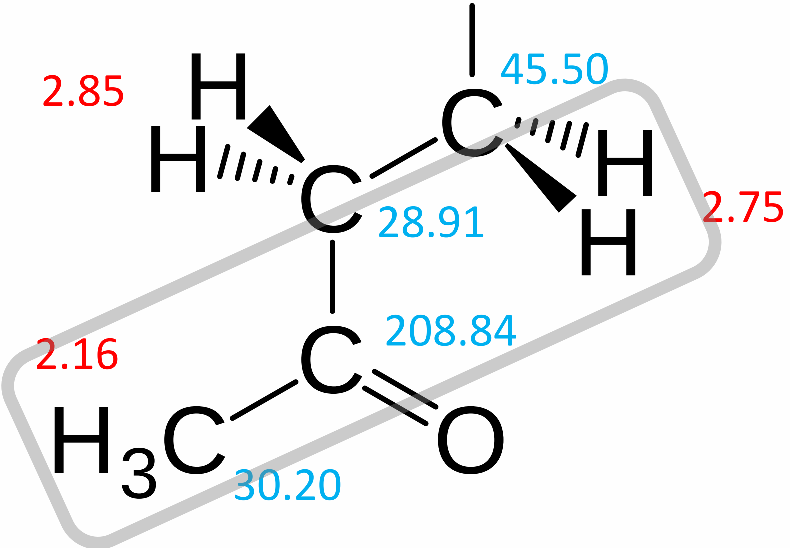
4 DBE

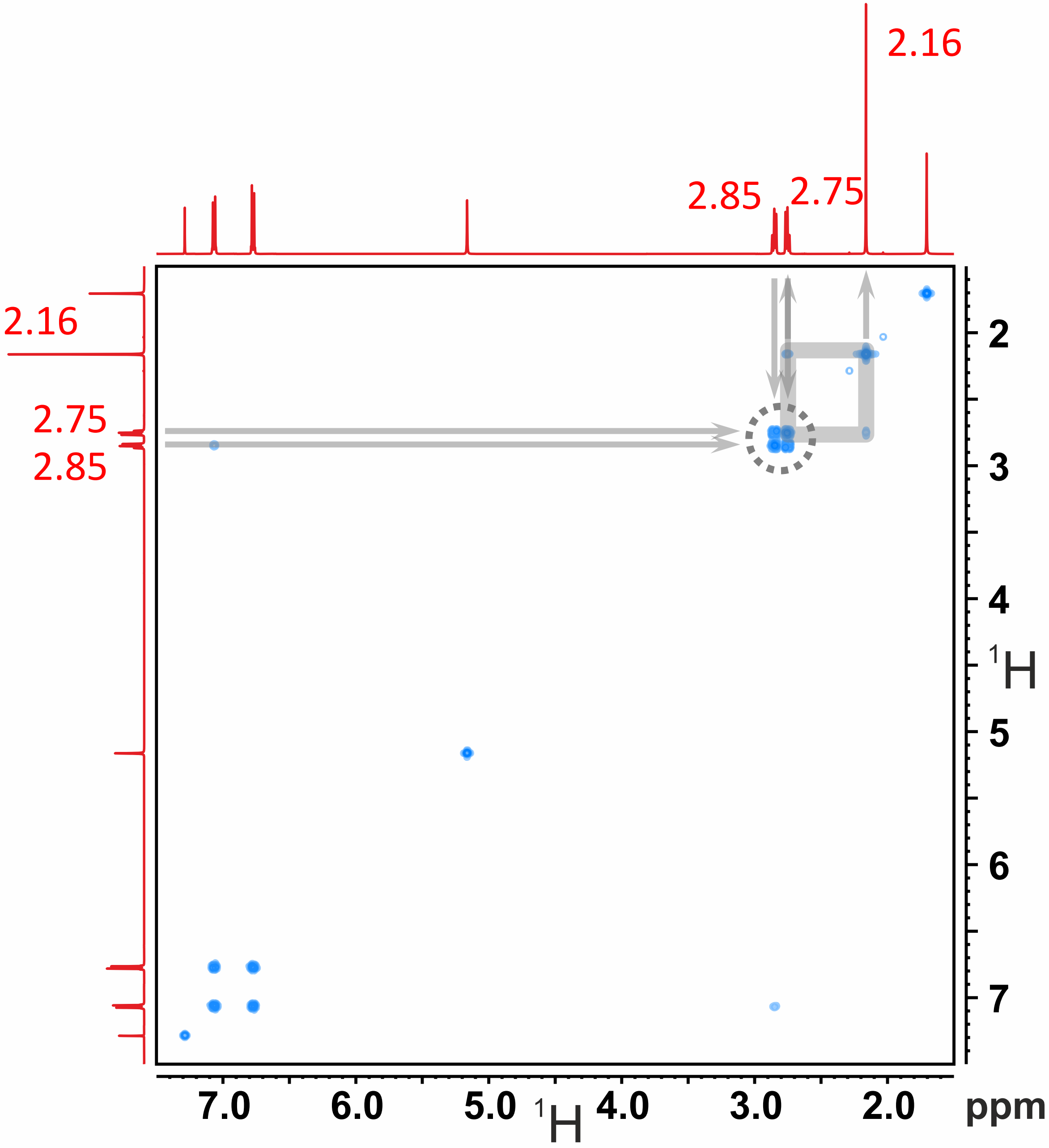
Building blocks

Connectivity

Using our temporary structure, this cross peak would be the result of a coupling pathway across **five single bonds**. Such coupling pathways are really very, very rare.

Even across four single bonds coupling is not visible very often, but apparently we have such a case in our compound. If we swap both methylene groups, the coupling distance reduces to four bonds.





HSQC

HMBC

^{13}C

^{1}H

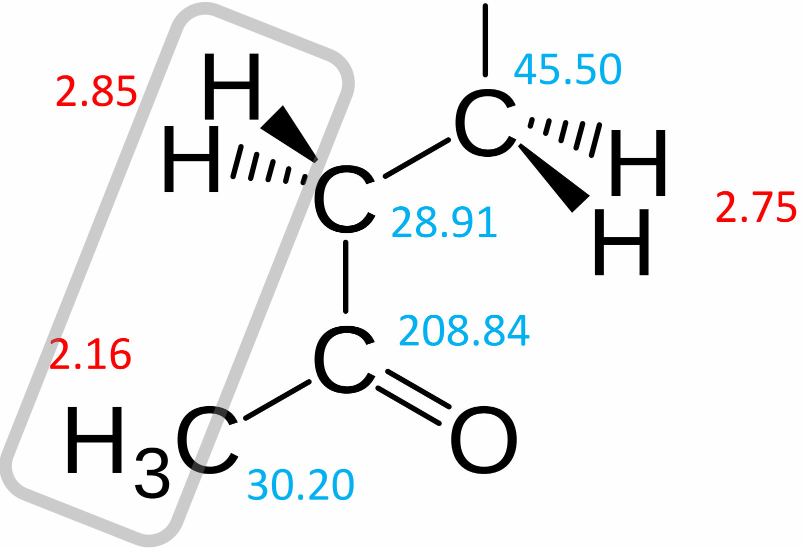
4 DBE

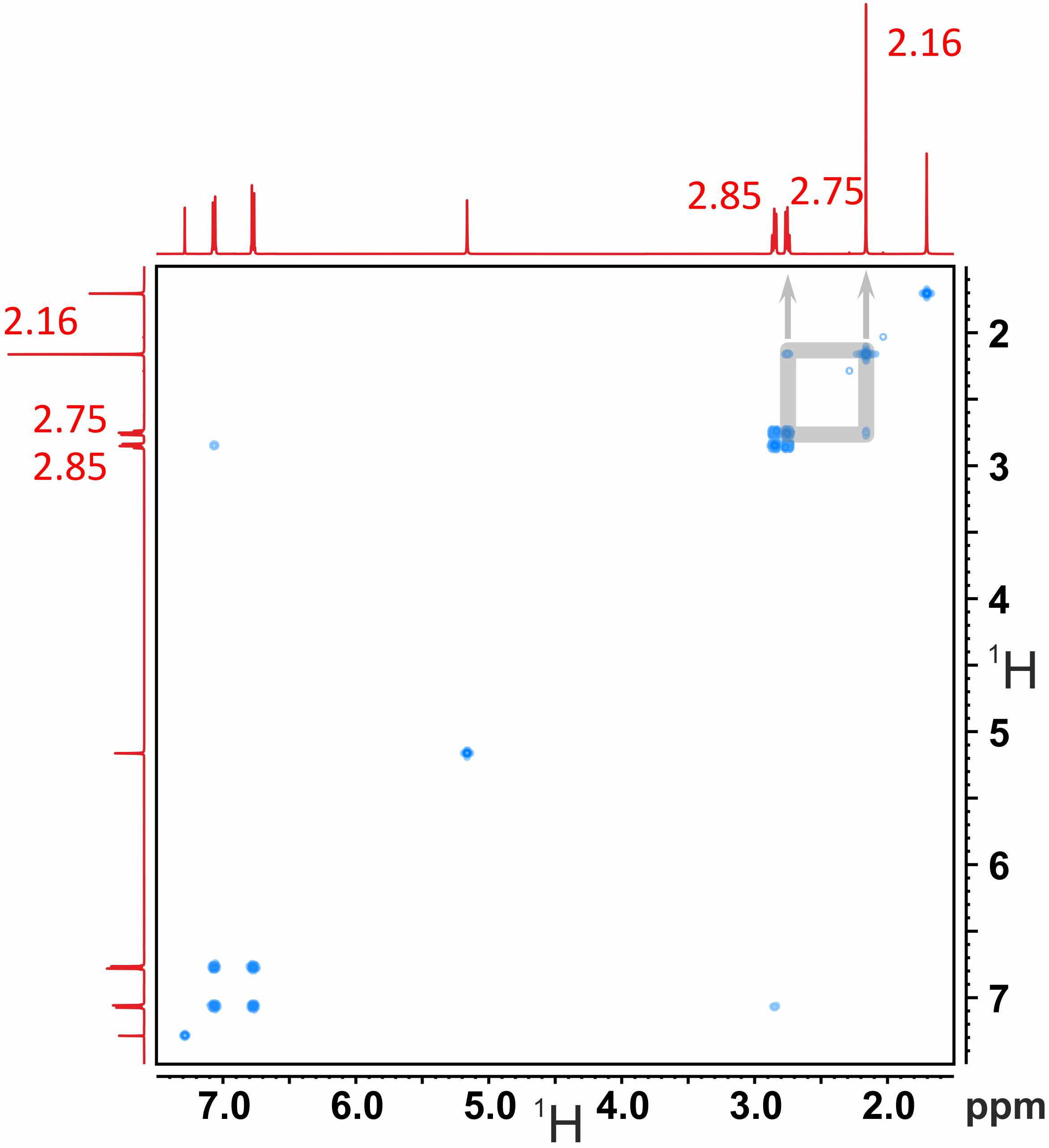
Building blocks

Connectivity

Now we have four single bonds between the coupling nuclei.

But if there is a coupling, our methyl signal should be a triplet?





HSQC

HMBC

^{13}C

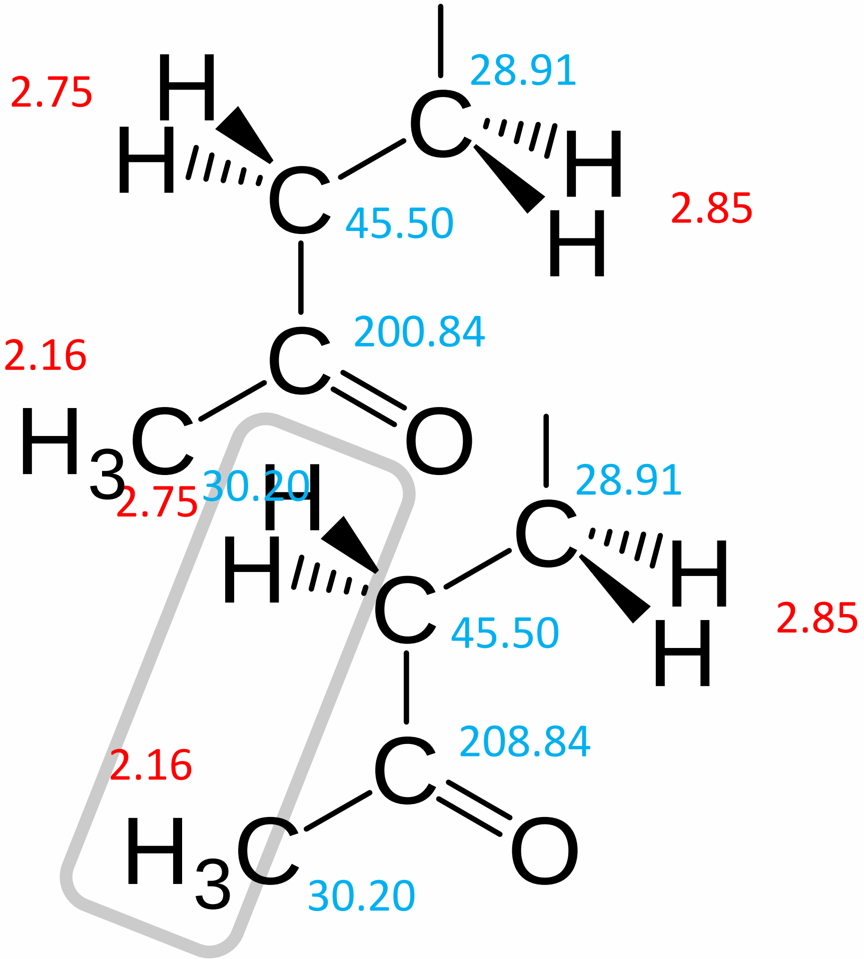
^{1}H

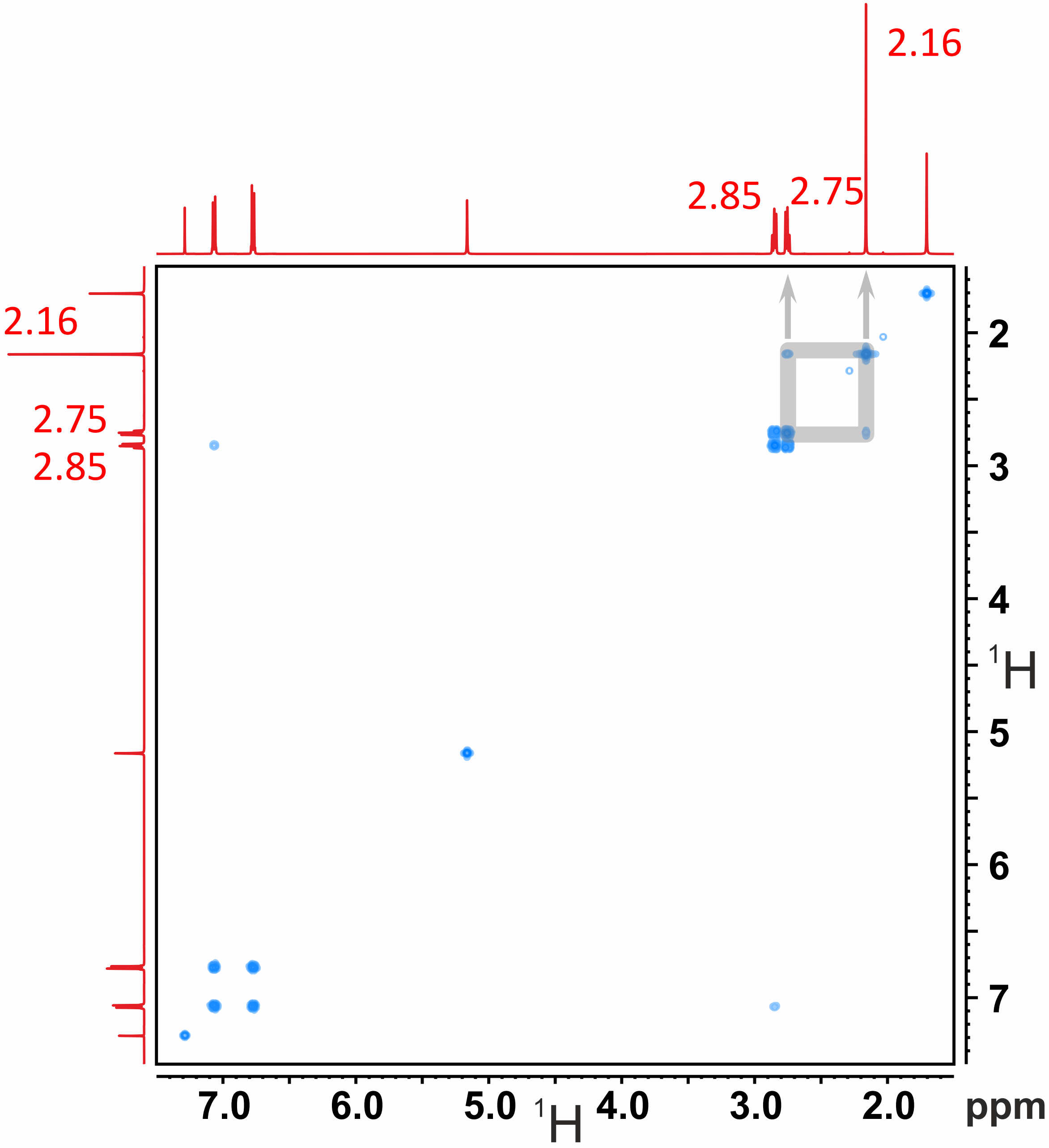
4 DBE

Building blocks

Connectivity

Indeed! The methyl protons show a triplet with a four bond coupling constant of 0.45 Hz.





HSQC

HMBC

COSY

^{13}C

Building blocks

Connectivity

7.07 2

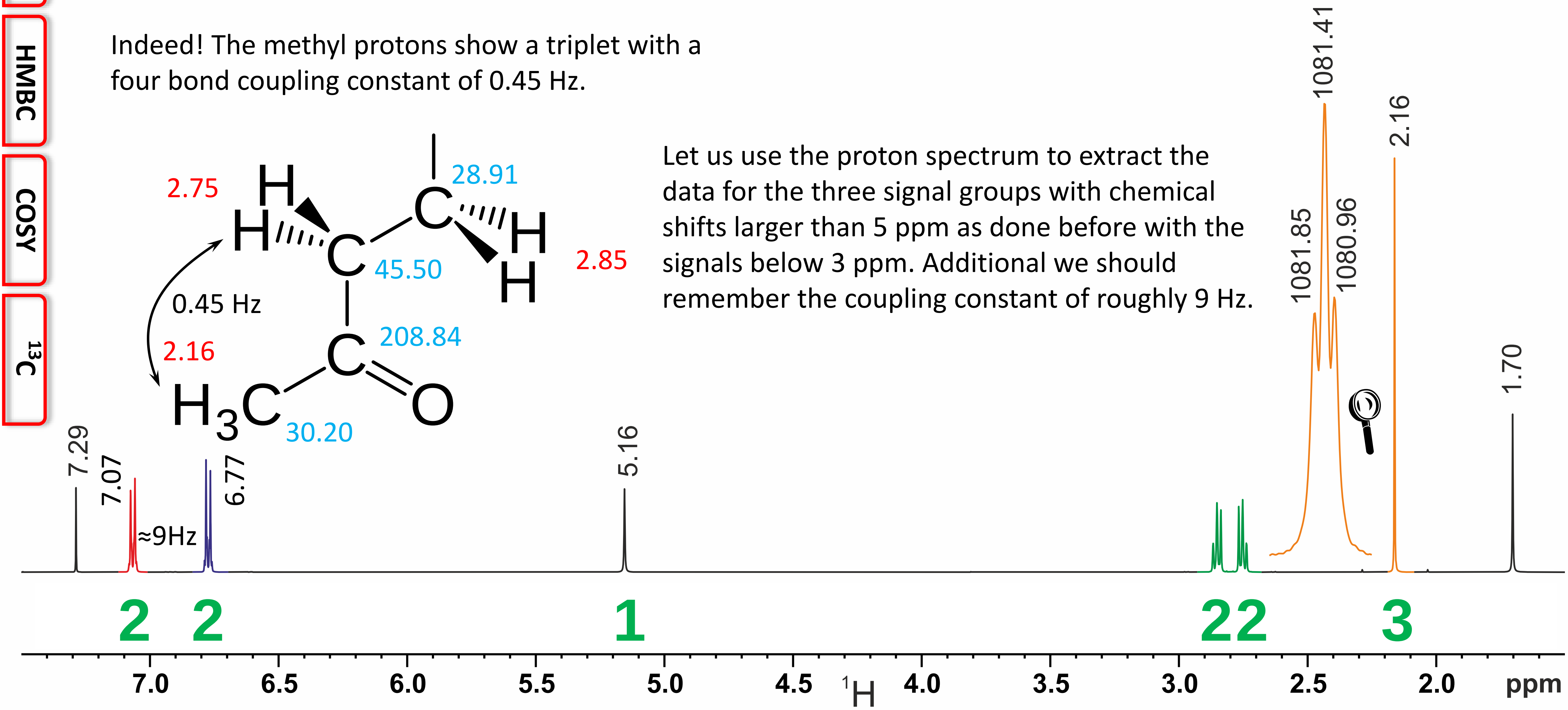
≈9Hz

6.77 2

5.16 1

4 DBE

Indeed! The methyl protons show a triplet with a four bond coupling constant of 0.45 Hz.



Let us use the proton spectrum to extract the data for the three signal groups with chemical shifts larger than 5 ppm as done before with the signals below 3 ppm. Additional we should remember the coupling constant of roughly 9 Hz.

HSQC

HMBC

COSY

^{13}C

7.07 2

≈9Hz

6.77 2

5.16 1

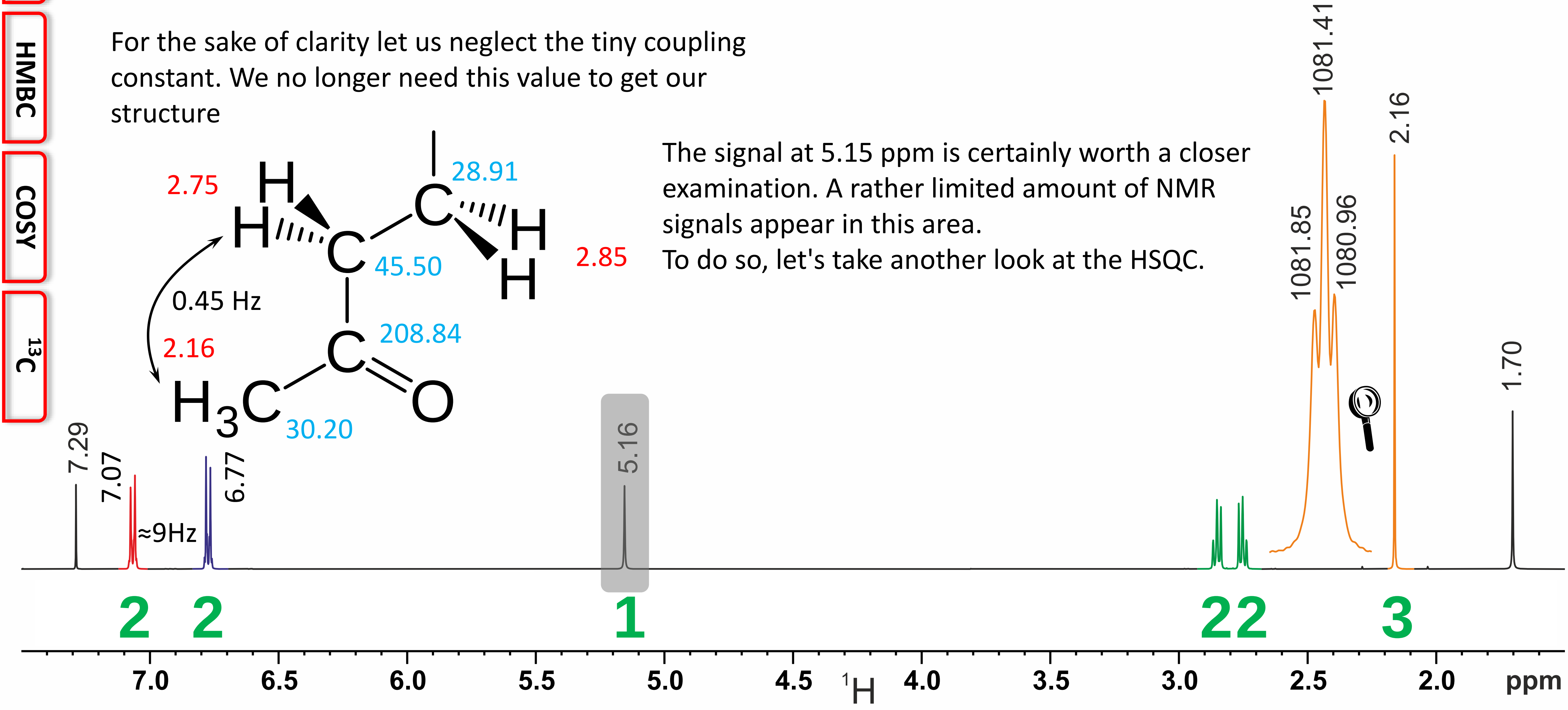
4 DBE

Building blocks

One more substituent

For the sake of clarity let us neglect the tiny coupling constant. We no longer need this value to get our structure

The signal at 5.15 ppm is certainly worth a closer examination. A rather limited amount of NMR signals appear in this area.
To do so, let's take another look at the HSQC.



HSQC

HMBC

COSY

^{13}C

Building blocks

One more substituent

7.07 **2**

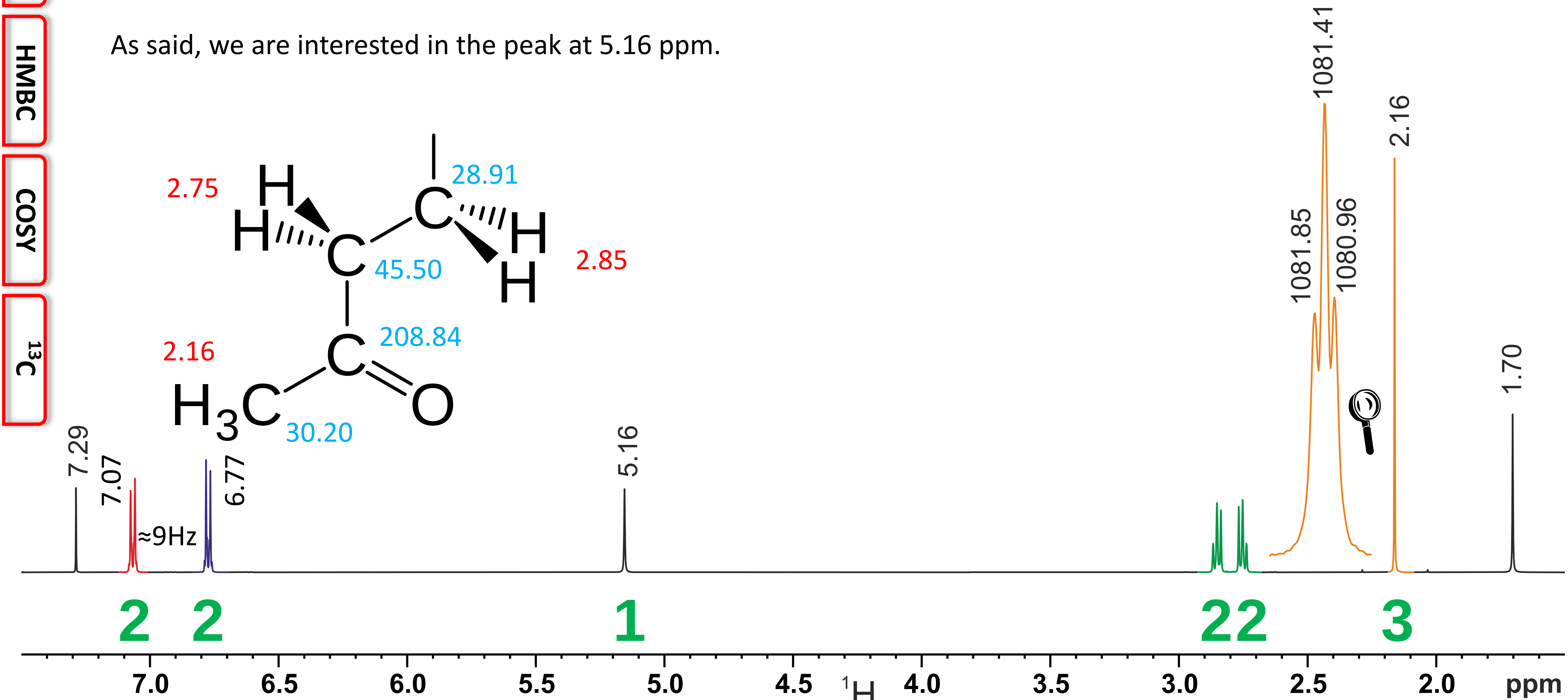
≈9Hz

6.77 **2**

5.15 **1**

4 DBE

As said, we are interested in the peak at 5.16 ppm.



Building blocks

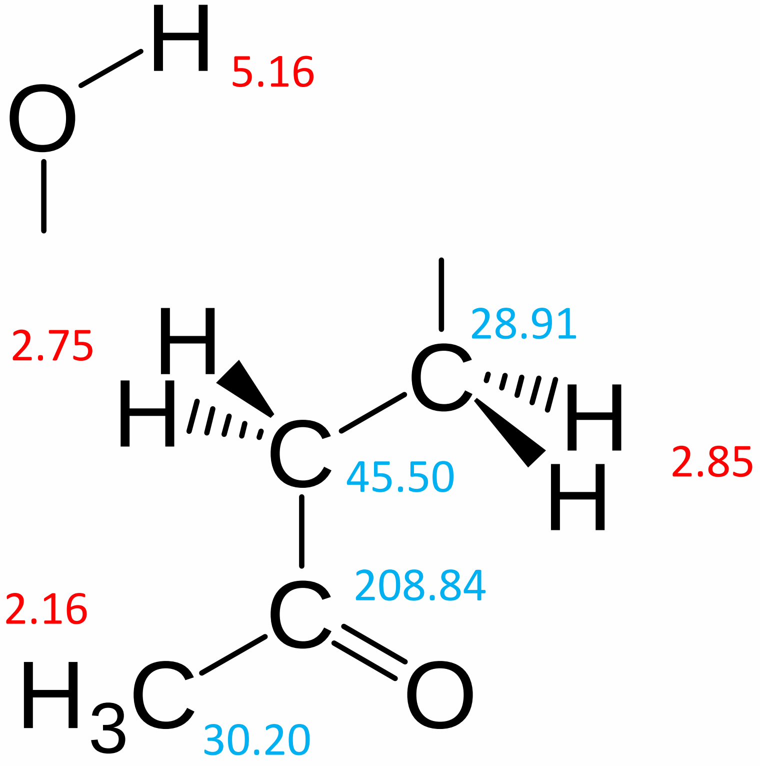
One more substituent

HMBC

COSY

^{13}C

^{1}H



There is no cross peak at all with the proton signal at 5.16 ppm.

Because the molecular formula contains only H, C and O this means, this signal belongs to an OH group.

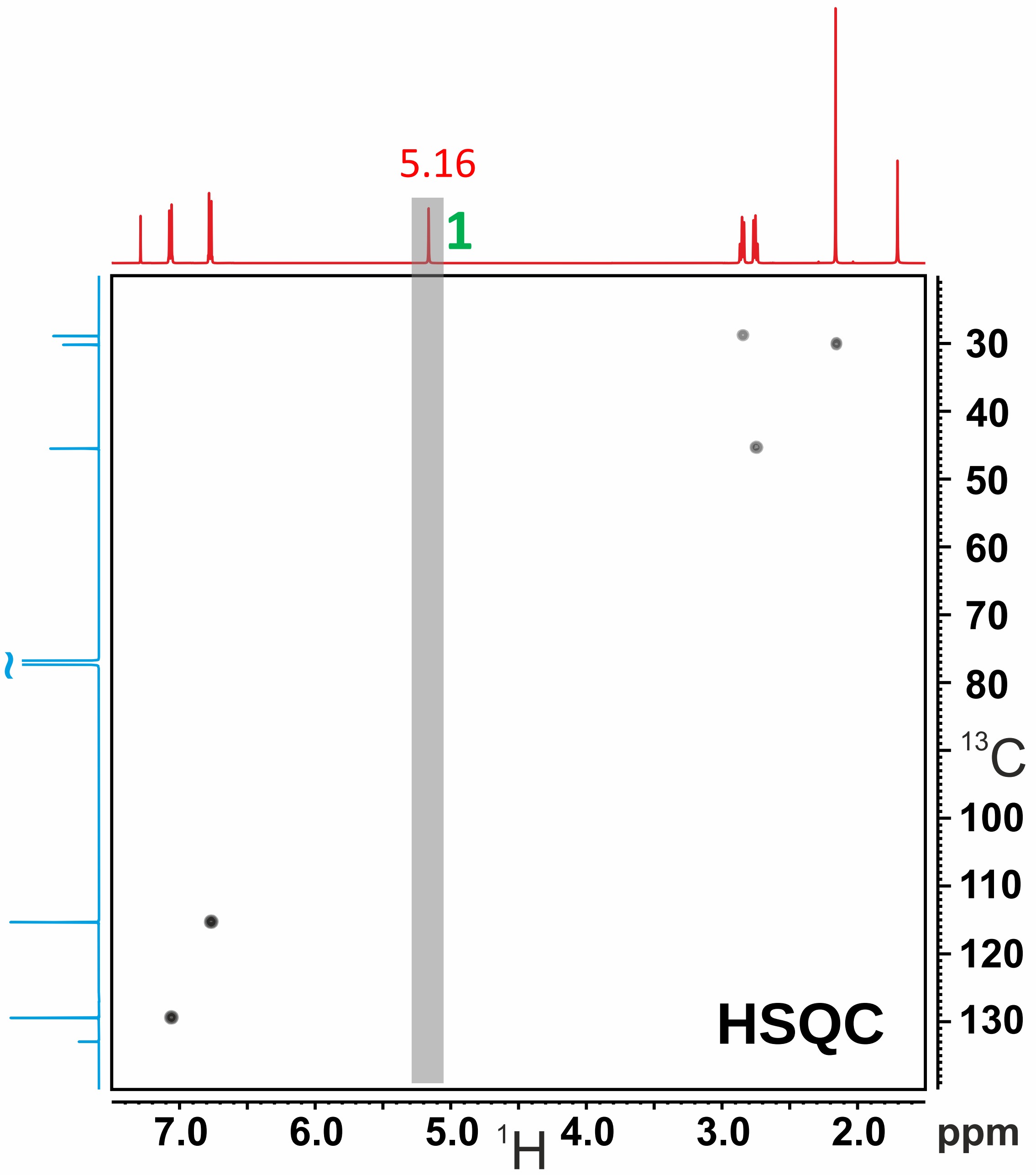
7.07 2

≈9Hz

6.77 2

5.16 1

4 DBE



7.07 **2**

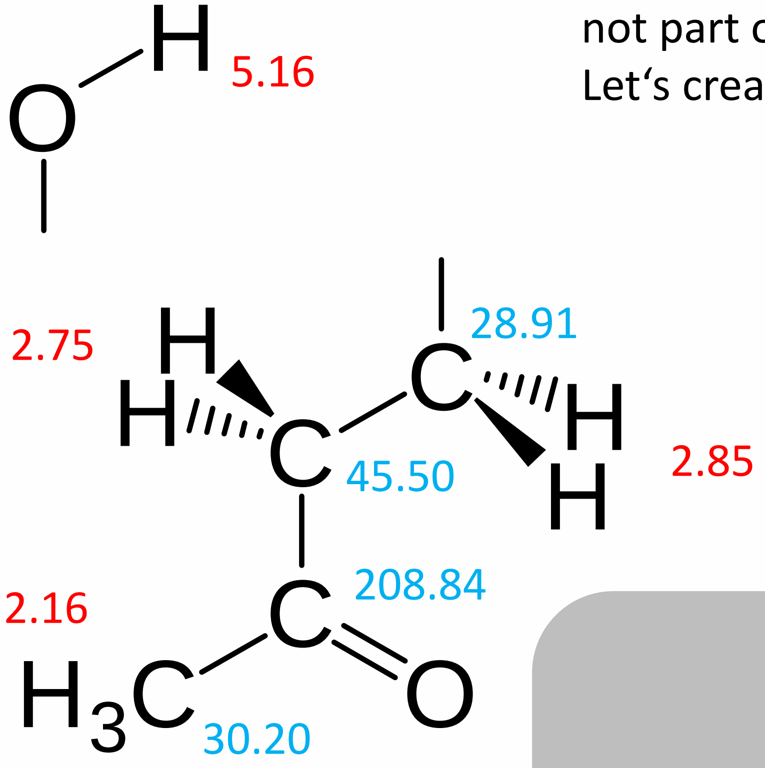
≈9Hz

6.77 **2**

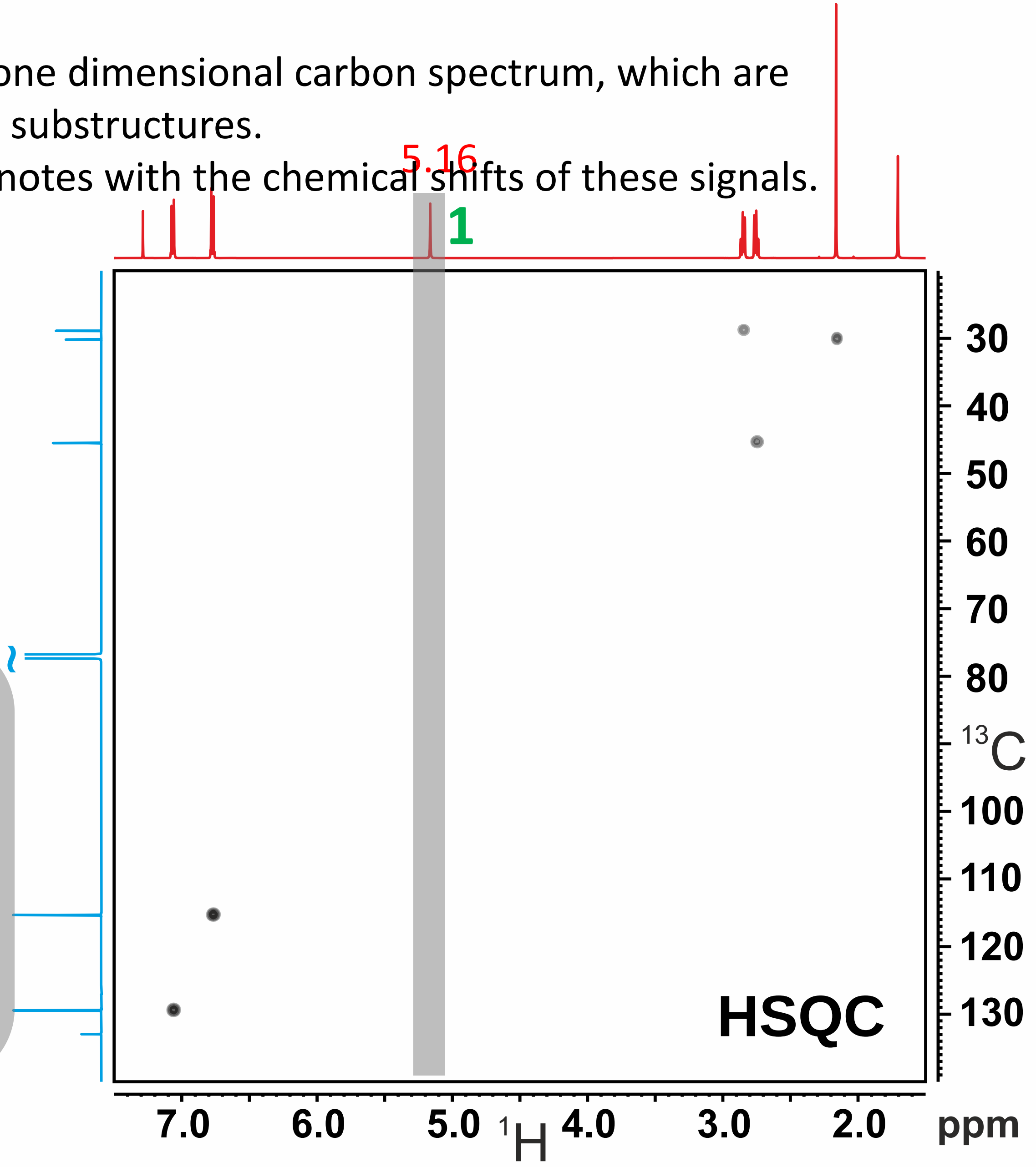
4 DBE

Building blocks

One more substituent



There are four signals in the one dimensional carbon spectrum, which are not part of the already found substructures.
Let‘s create four more sticky notes with the chemical shifts of these signals.



There is no cross peak at all with the proton signal at 5.16 ppm.

Because the molecular formula contains only H, C and O this means, this signal belongs to an OH group.

HMBC

COSY

^{13}C

^{1}H

HSQC

HMBC

COSY

^1H

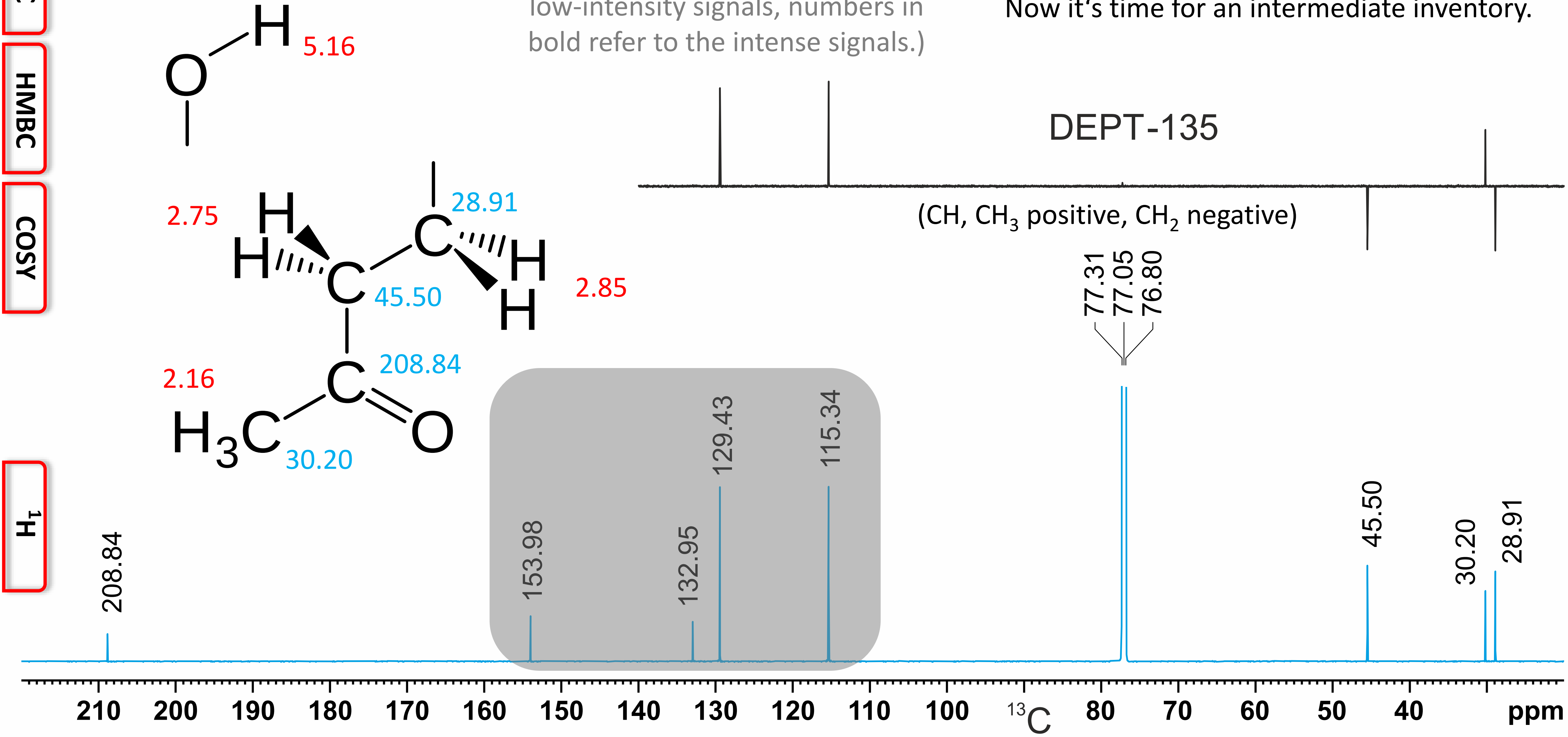
153.98 *132.95* **129.43** **115.34** 7.07 **2** ≈9Hz 6.77 **2** 4 DBE

Building blocks

One more substituent

(Numbers in italics refer to the low-intensity signals, numbers in bold refer to the intense signals.)

Now it‘s time for an intermediate inventory.



HSQC

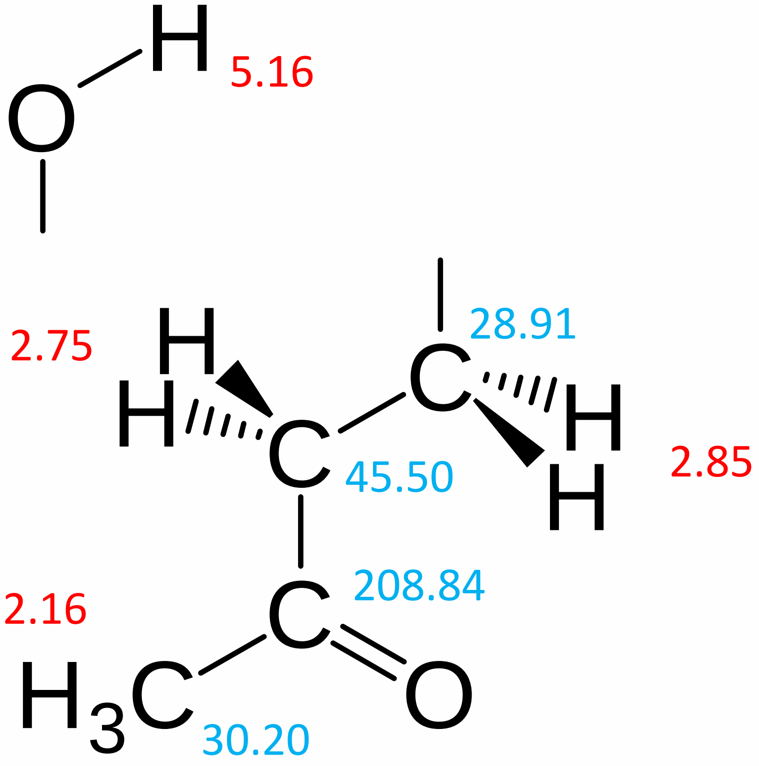
HMBC

COSY

^1H

Building blocks

One more substituent



153.98

132.95

129.43

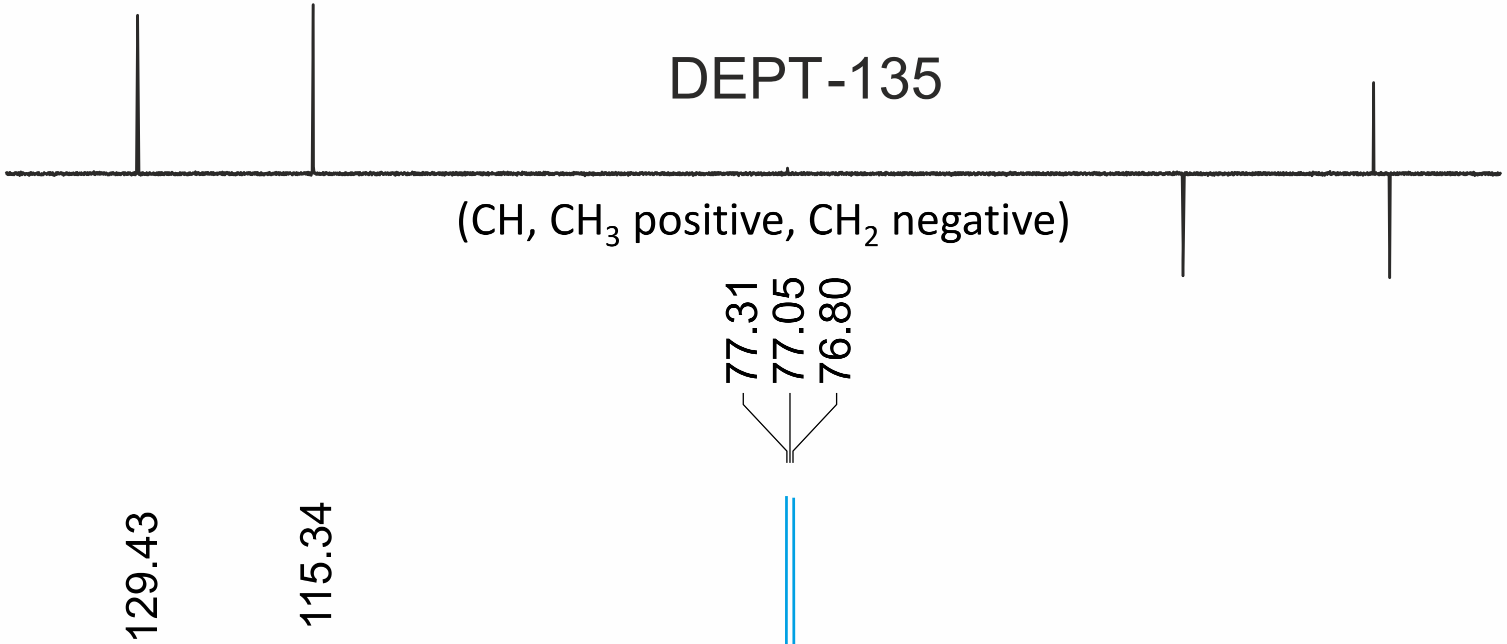
115.34

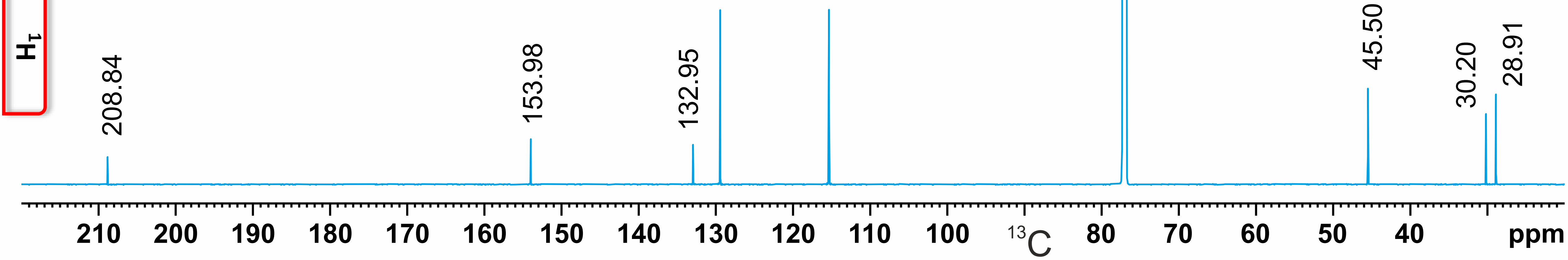
7.07 **2**

≈9Hz

6.77 **2**

4 DBE



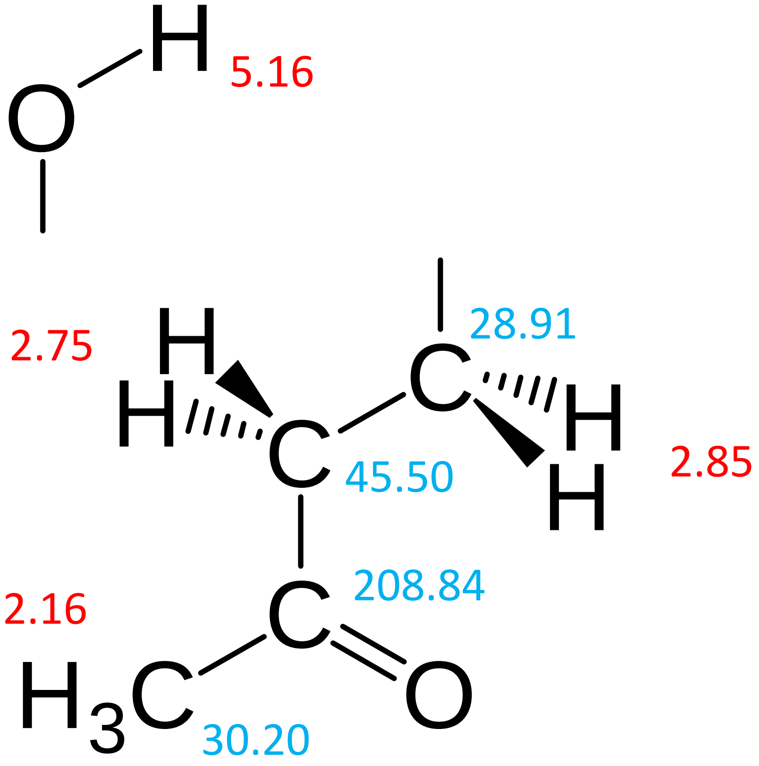


HSQC
HMBC
COSY
^{13}C
^{1}H

153.98 | 132.95 | 129.43 | 115.34 | 7.07 **2** | ≈9Hz | 6.77 **2** | 4 DBE

Building blocks

The missing link



Our molecular formula is $\mathbf{C_{10}H_{12}O_2}$.

We found two fragments. Together their molecular formula is $\mathbf{C_4H_8O_2}$.

missing: C_6H_4

What else do we know?

- The missing fragment contains 4 double bond equivalents.
- We have **only two proton signal groups for four protons**. The chemical shift is typical for protons bound to sp^2 hybridized carbon atoms.
- We have **four carbon signals but six carbon atoms**.

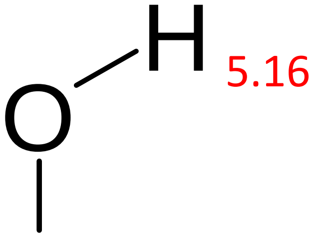
Clearly there is some kind of **symmetry**.

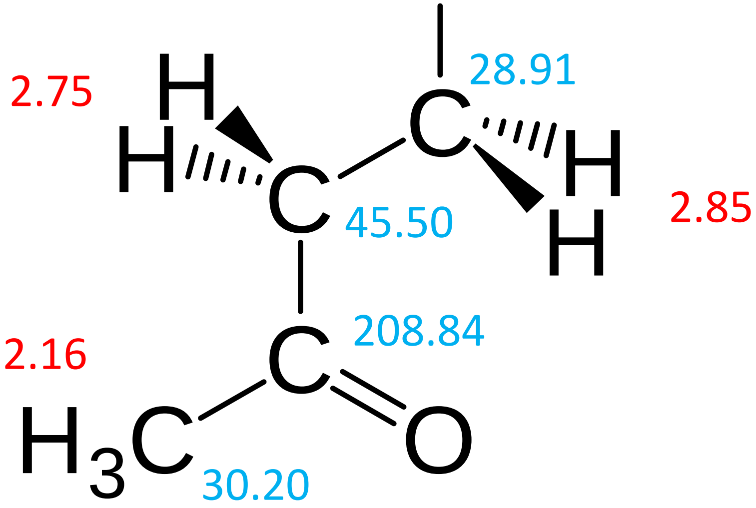
Maybe there are exotic solutions to fulfill all these conditions.
But one possible structure stands out. What about benzene, substituted in the 1 and 4 positions? Two possible substituents have already been identified.

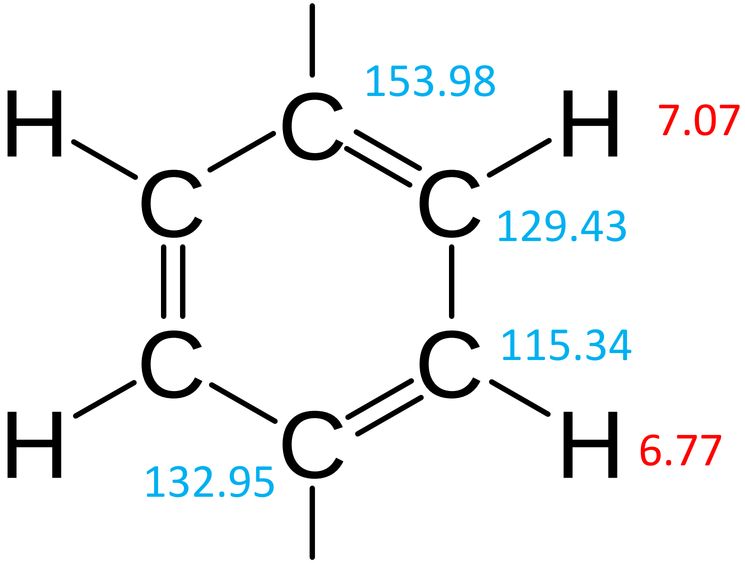
153.98 132.95 129.43 115.34 7.07 2 ≈9Hz 6.77 2 4 DBE

Building blocks

The missing link







And the signal assignments fell from sky?

They didn‘t, of course. And even more, they might be wrong. But first let‘s finalize our molecule. The explanation for the assignment will be given afterwards.

Maybe there are exotic solutions to fulfill all these conditions. But one possible structure stands out. What about benzene, substituted in the 1 and 4 positions? Two possible substituents have already been identified.

HSQC

HMBC

COSY

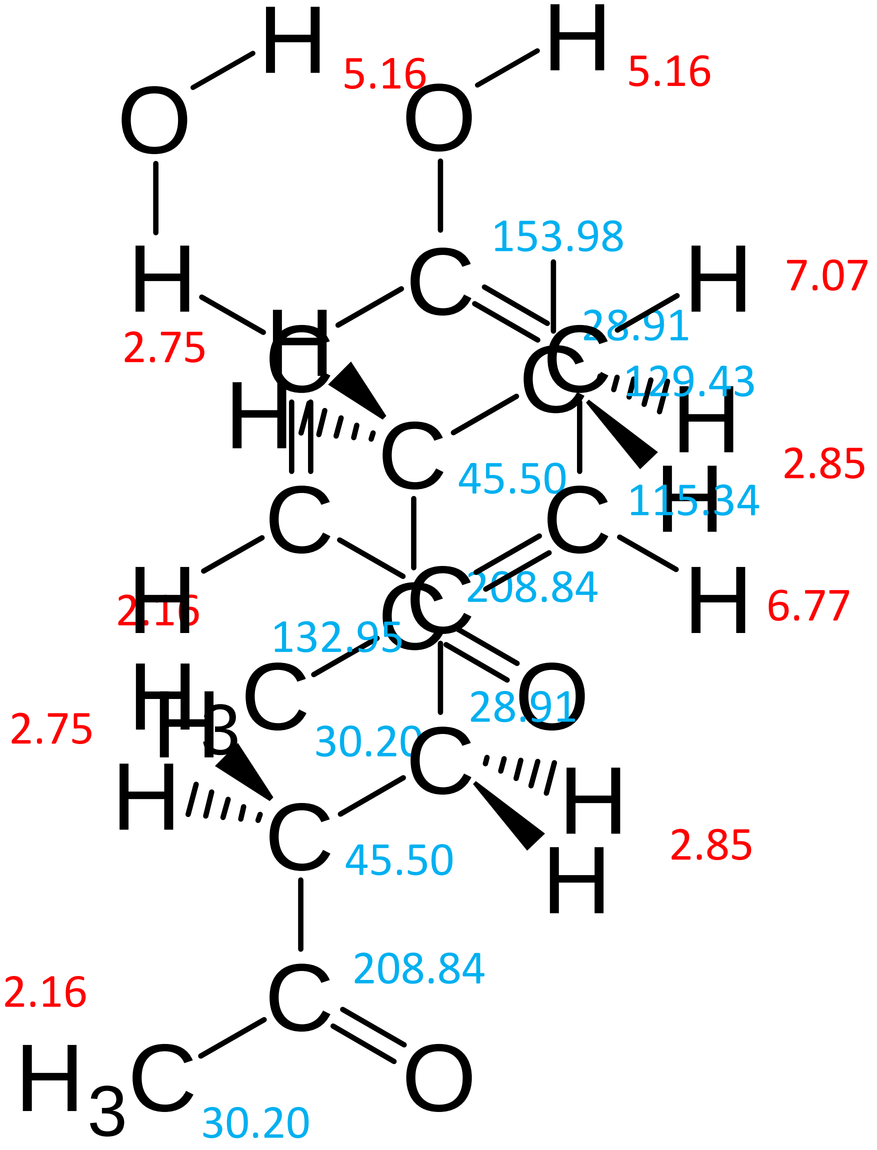
^{13}C

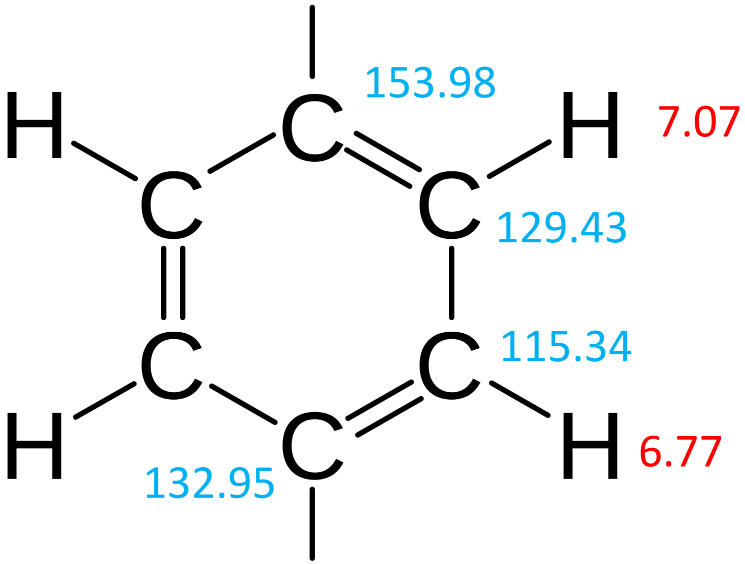
^{1}H

153.98 132.95 129.43 115.34 7.07 **2** ≈9Hz 6.77 **2** 4 DBE

Building blocks

The missing link





Now that we know the final structure with some signal assignment fallen from the sky, let's take another look at the HSQC.

HSQC

HMBC

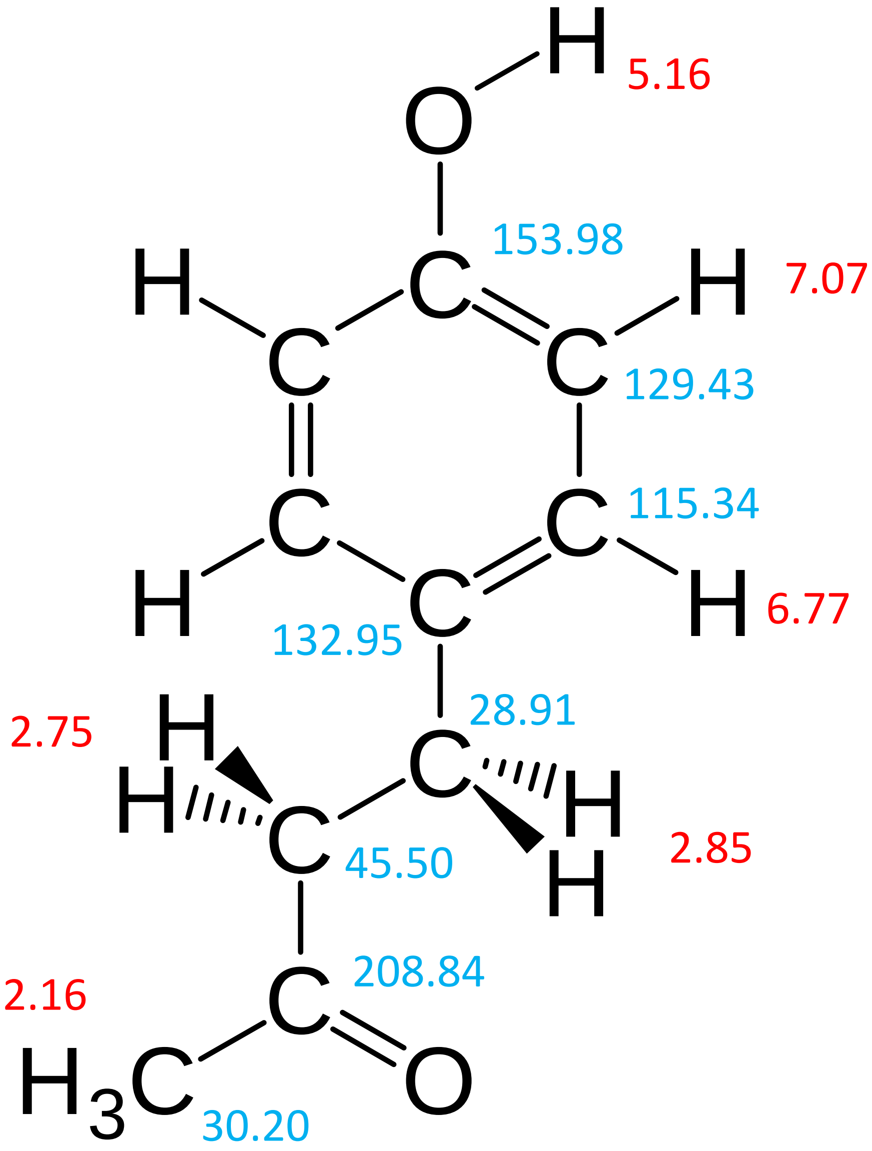
COSY

^{13}C

^{1}H

Signal assignment

153.98 | 132.95 | 129.43 | 115.34 | 7.07 **2** | ≈9Hz | 6.77 **2** | 4 DBE



For both pseudo projections we need the chemical shifts corresponding to these cross peaks

Signal assignment

153.98 | 132.95 | 129.43 | 115.34 | 7.07 **2** | 6.77 **2** | 4 DBE

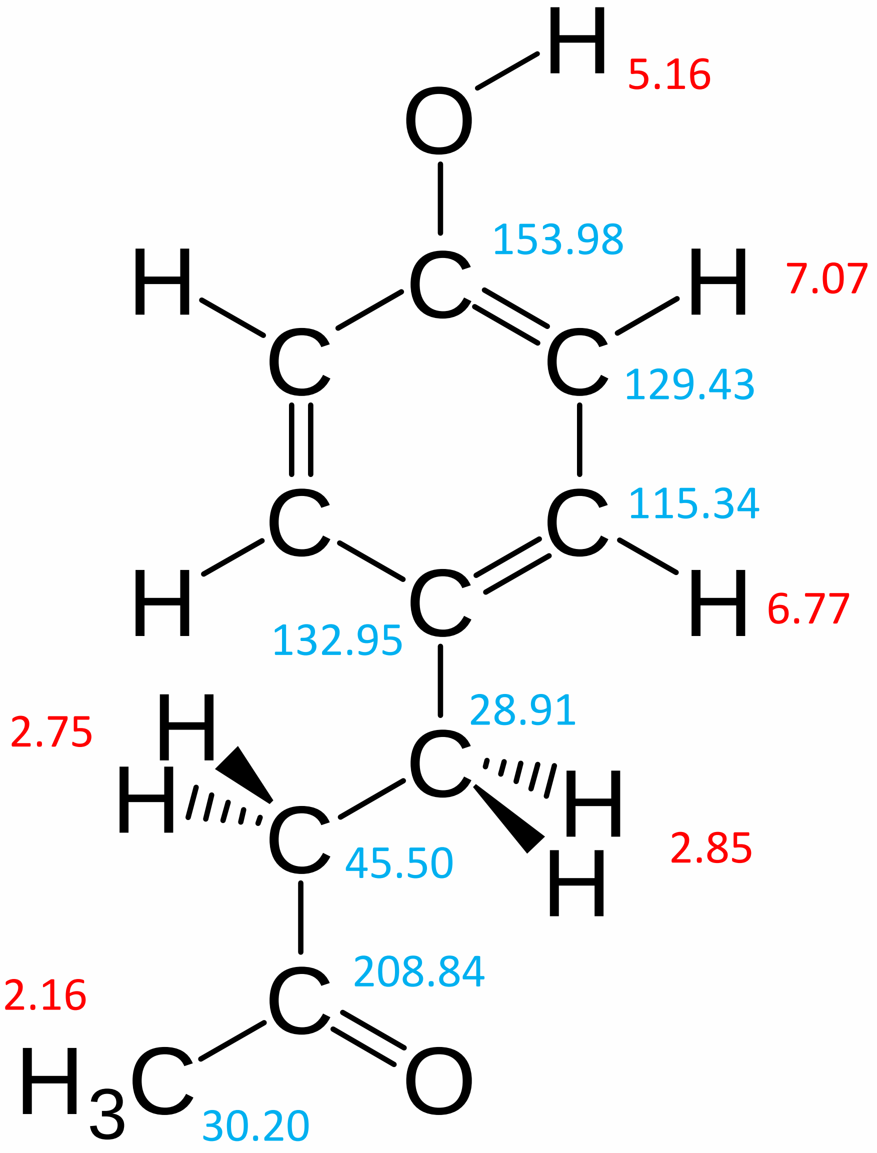
≈9Hz

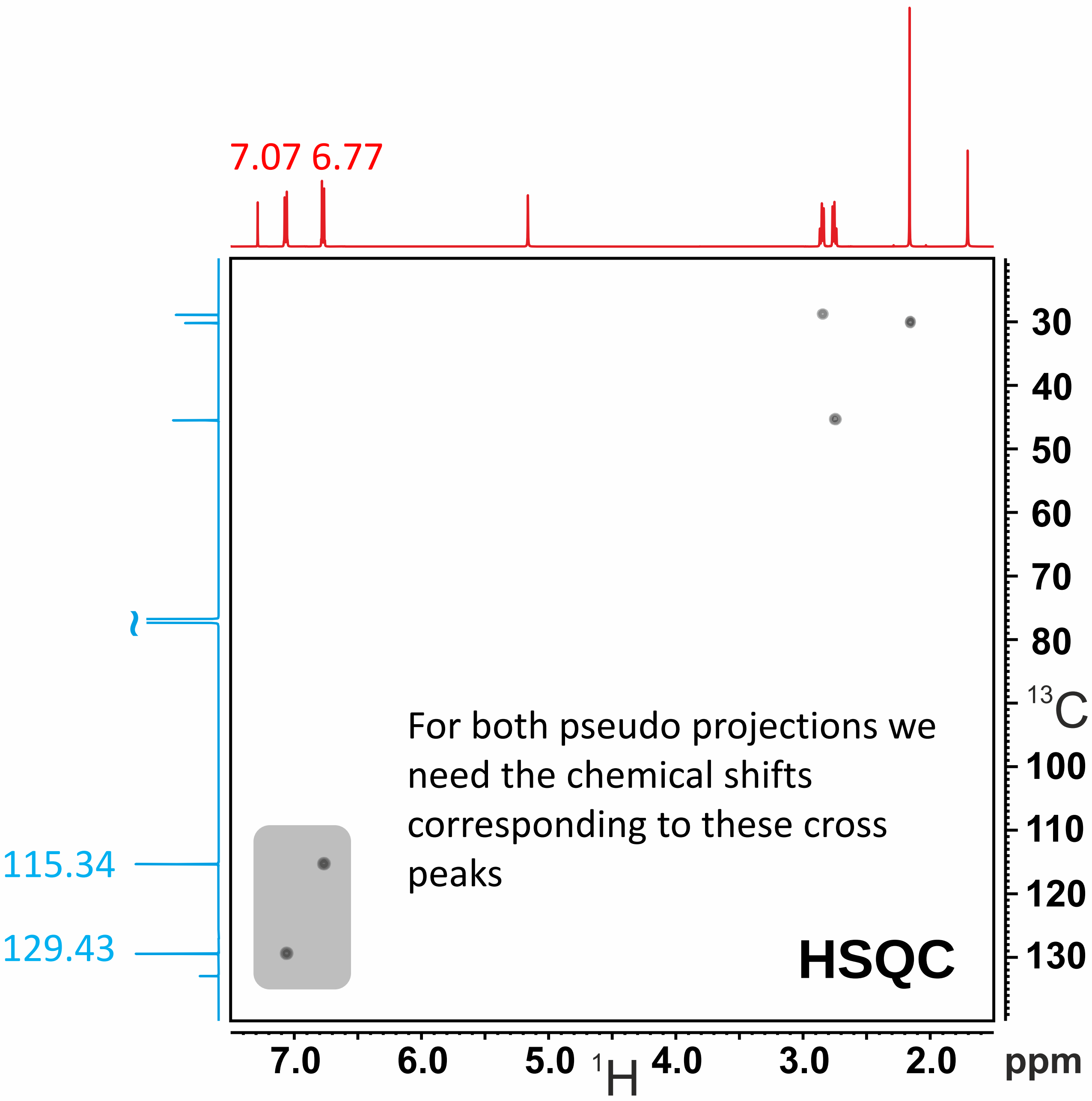
HMBC

COSY

^{13}C

^{1}H





For both pseudo projections we need the chemical shifts corresponding to these cross peaks

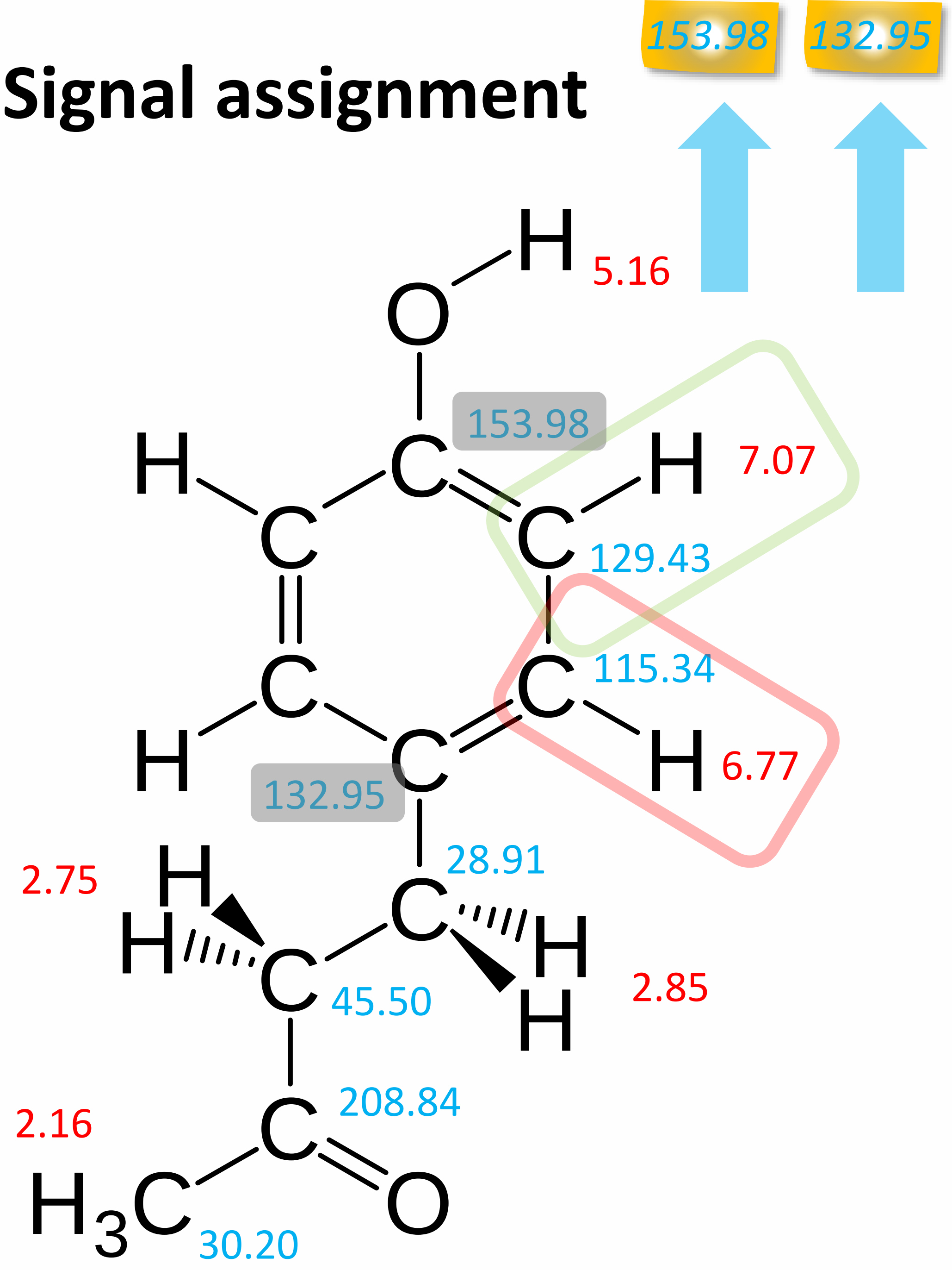
Signal assignment

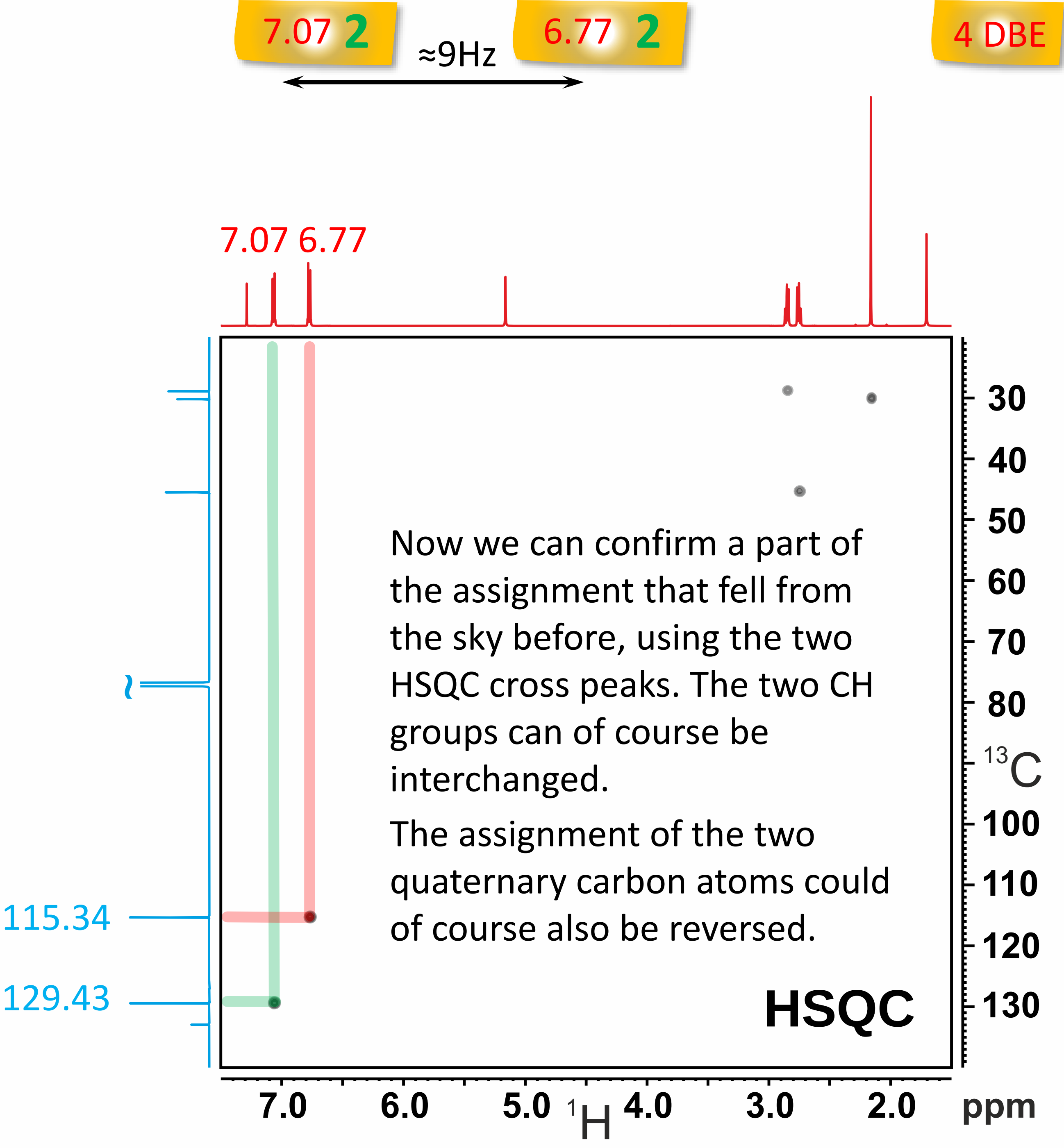
HMBC

COSY

^{13}C

^{1}H





Now we can confirm a part of the assignment that fell from the sky before, using the two HSQC cross peaks. The two CH groups can of course be interchanged.

The assignment of the two quaternary carbon atoms could of course also be reversed.

Signal assignment

153.98 132.95

7.07 **2** ≈9Hz 6.77 **2**

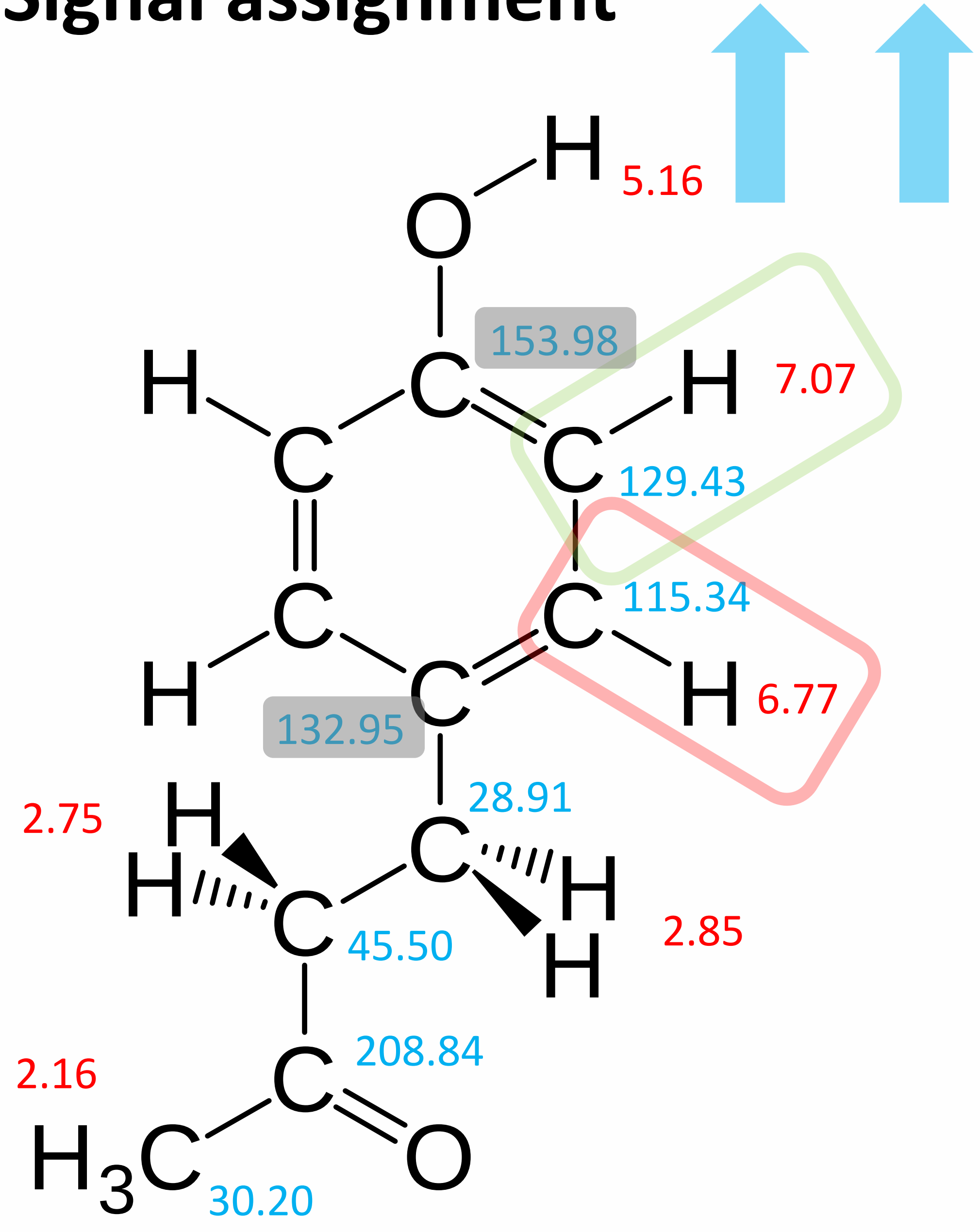
4 DBE

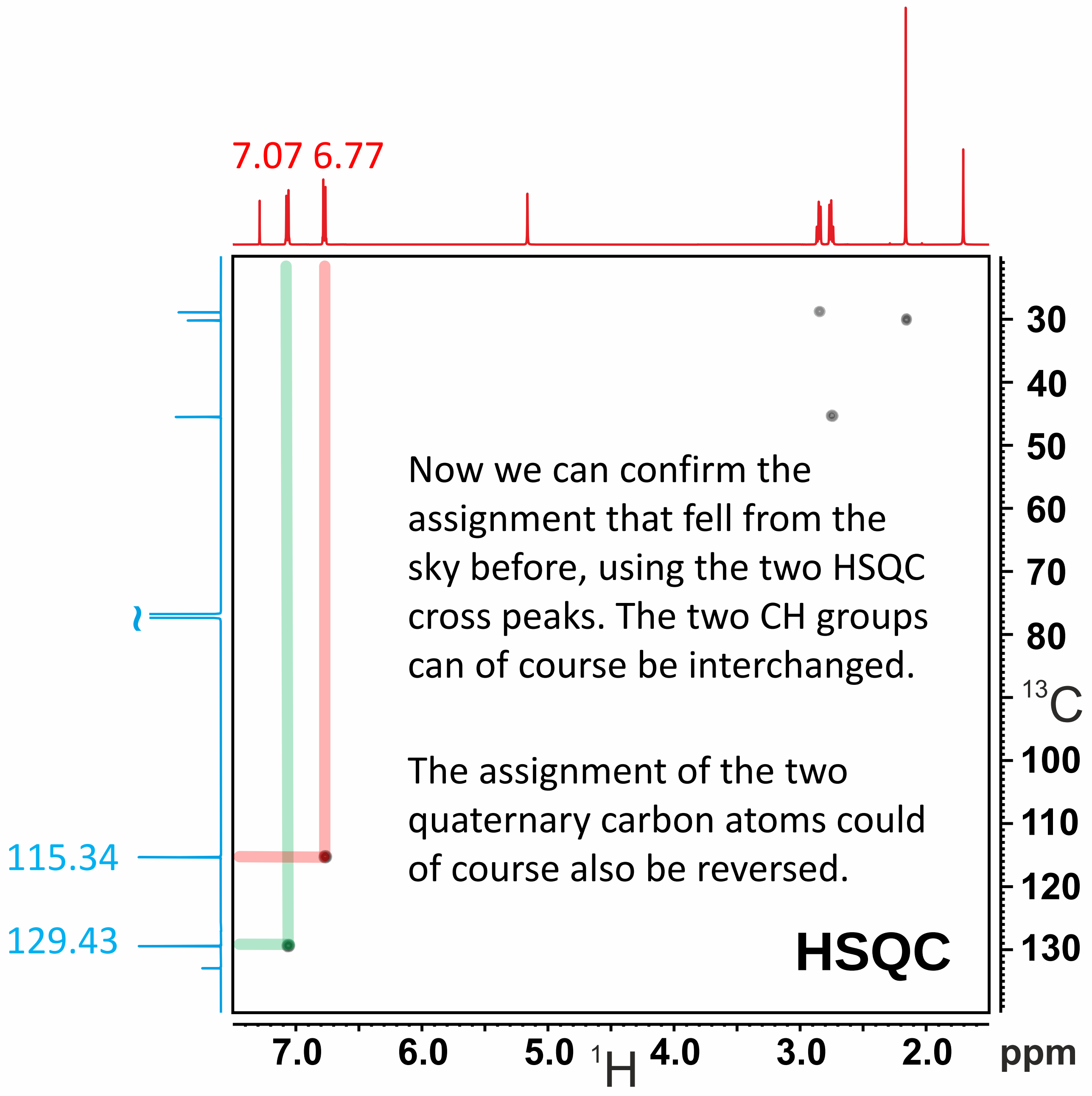
HMBC

COSY

^{13}C

^{1}H





Now we can confirm the assignment that fell from the sky before, using the two HSQC cross peaks. The two CH groups can of course be interchanged.

The assignment of the two quaternary carbon atoms could of course also be reversed.

HSQC

HMBC

COSY

^{13}C

^{1}H

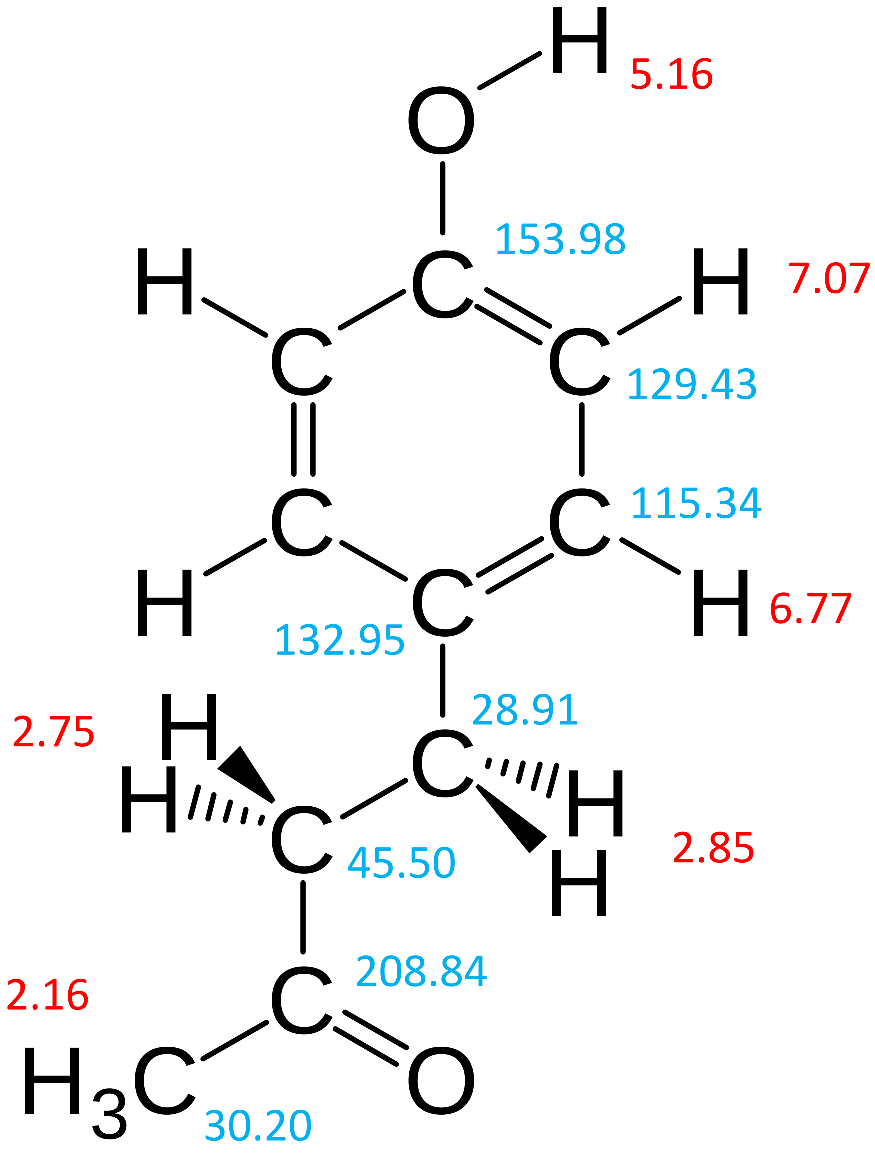
7.07 **2**

≈9Hz

6.77 **2**

4 DBE

Signal assignment



There is a last argument supporting our six membered aromatic ring.

The protons of the aromatic ring form a non-trivial AA'XX' spin system. Nevertheless, there is a dominant vicinal coupling constant.

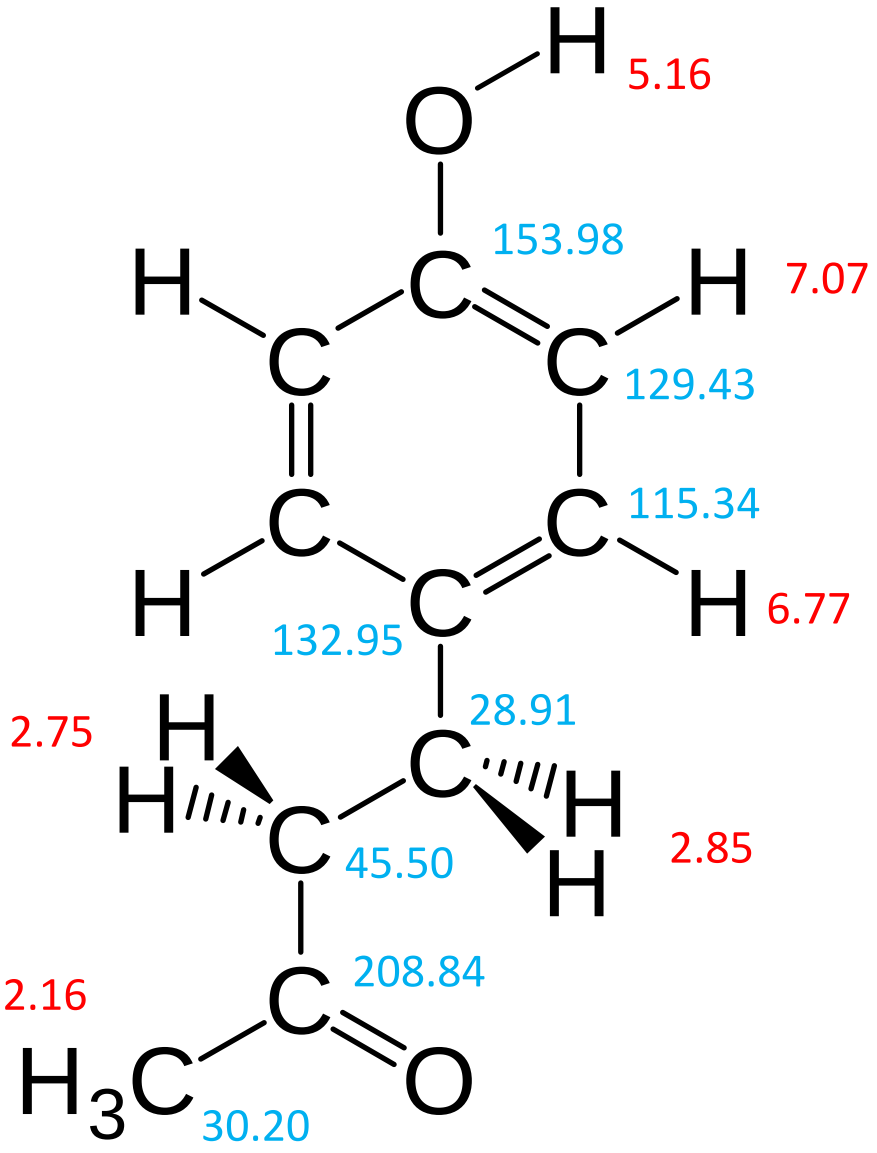
The protons with chemical shifts of 6.77 ppm and 7.07 ppm are in the Z-position to each other. The coupling constant should be about 8 ... 10 Hz.

We have extracted a value of approximately this size from the multiplets of the two protons.

And, of course, there is a cross peak in the COSY between the two proton signals mentioned above.

HSQC
HMBC
COSY
^{13}C
^{1}H

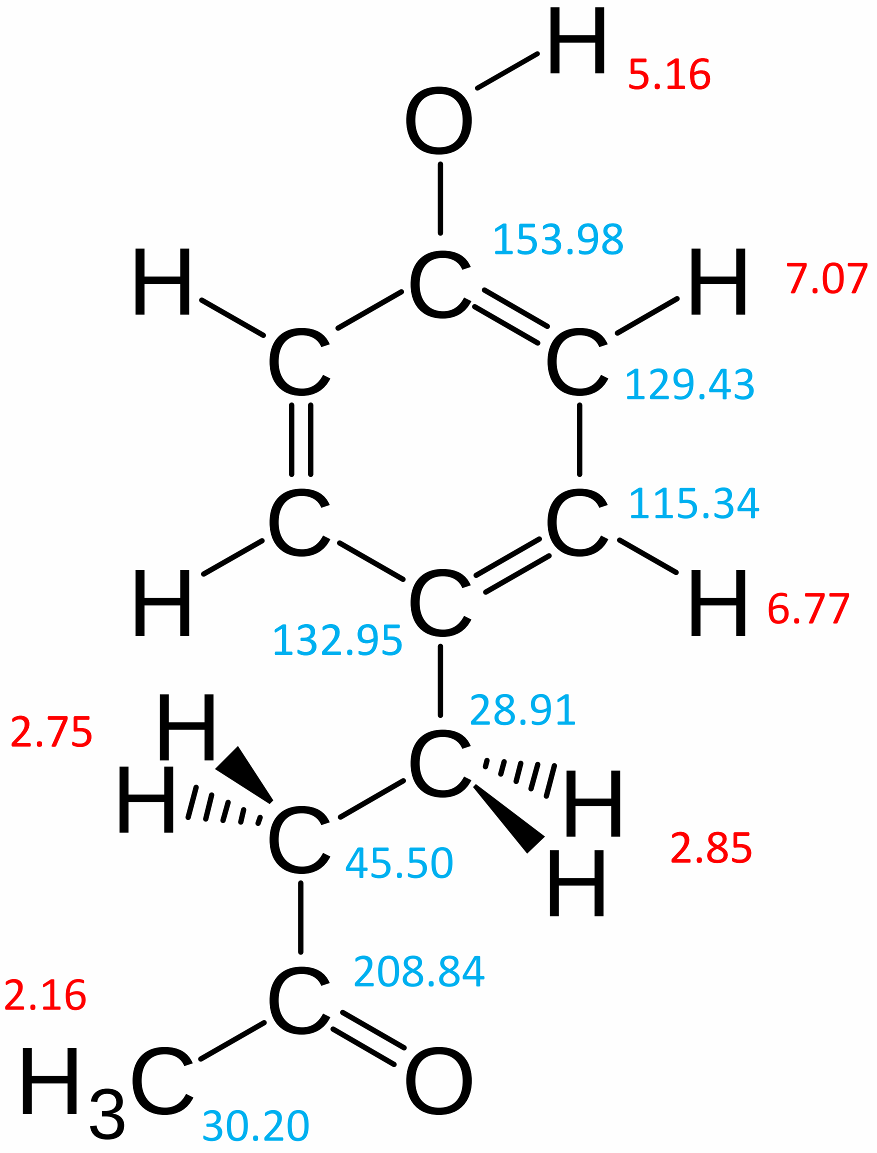
Signal assignment

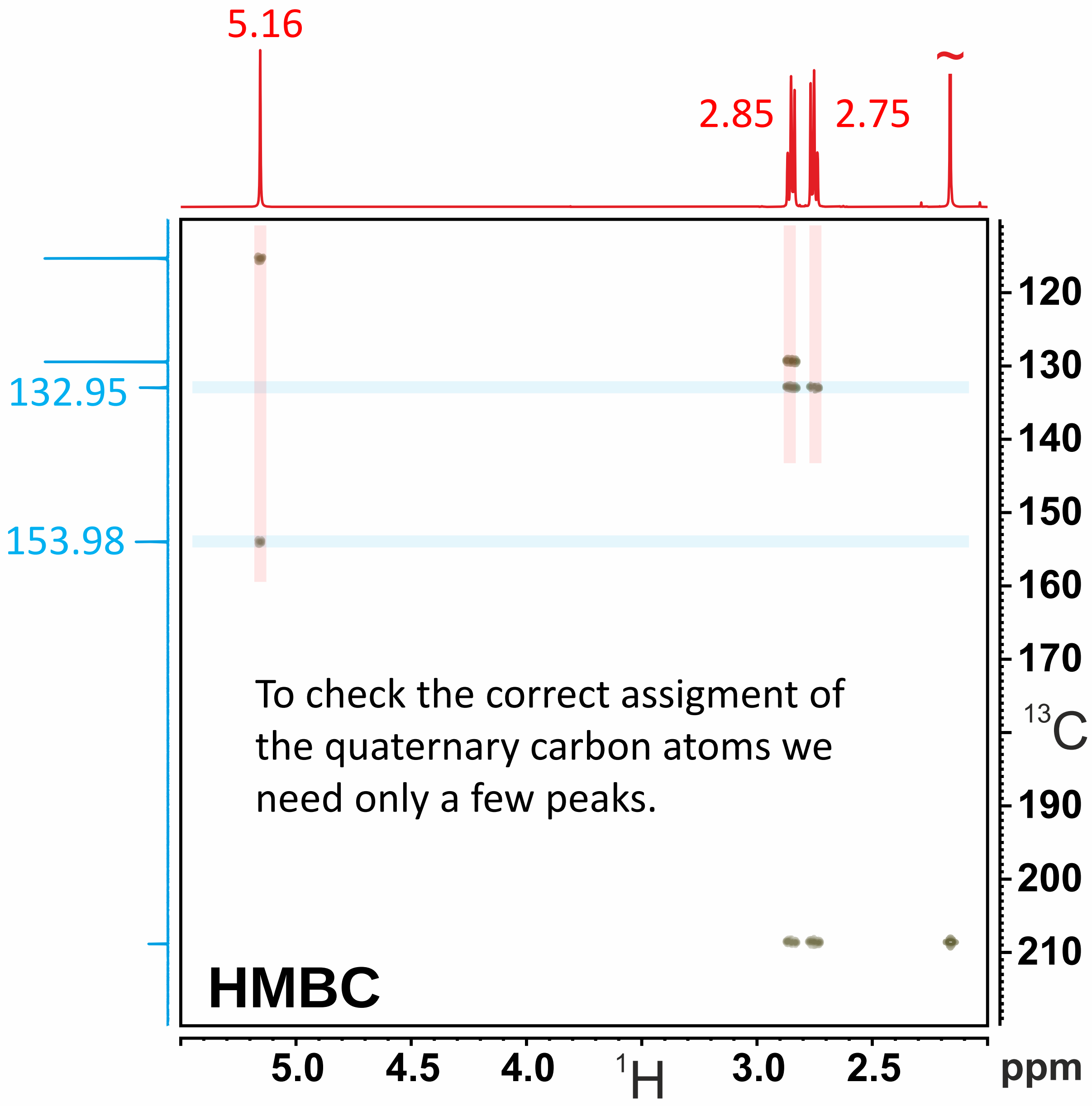


A good possibility to check the assignments made for the atoms of the six membered aromatic ring is the HMBC.

HSQC
COSY
^{13}C
^{1}H

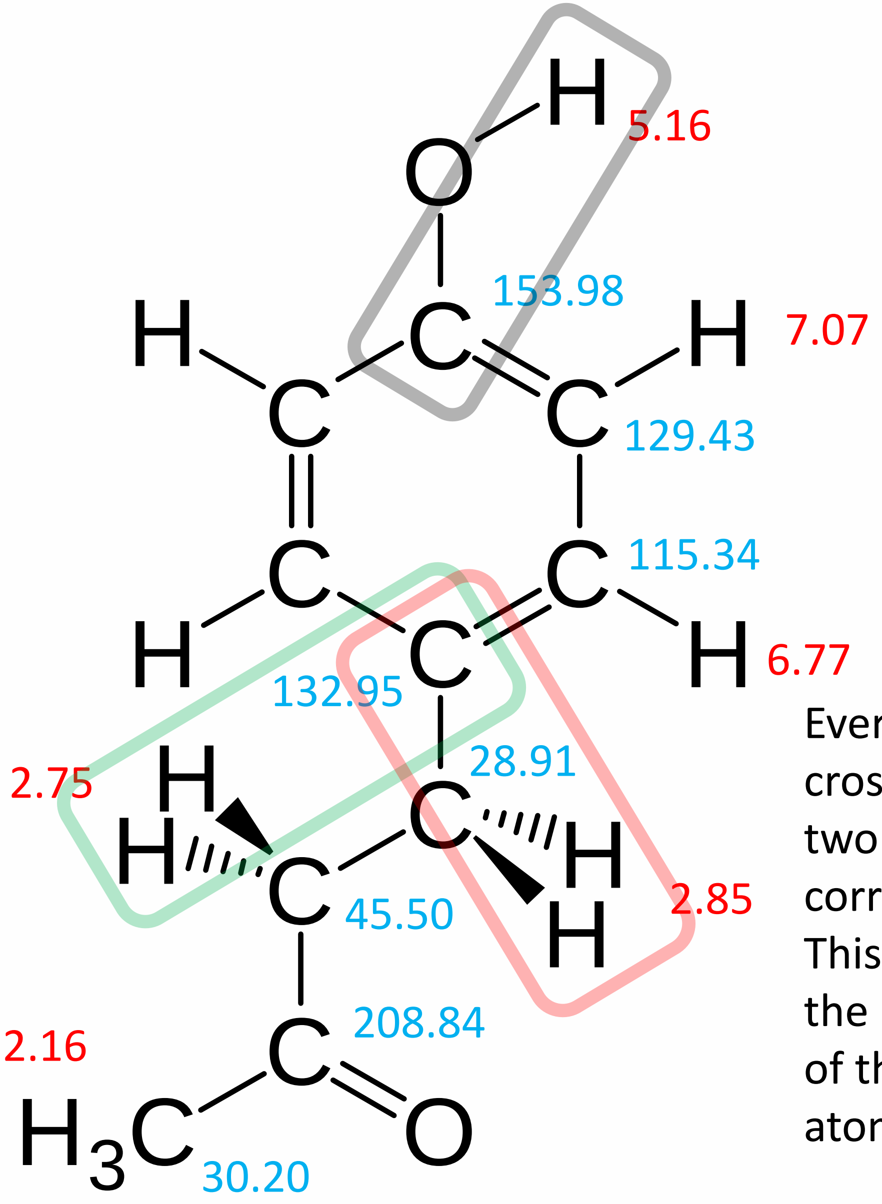
Signal assignment



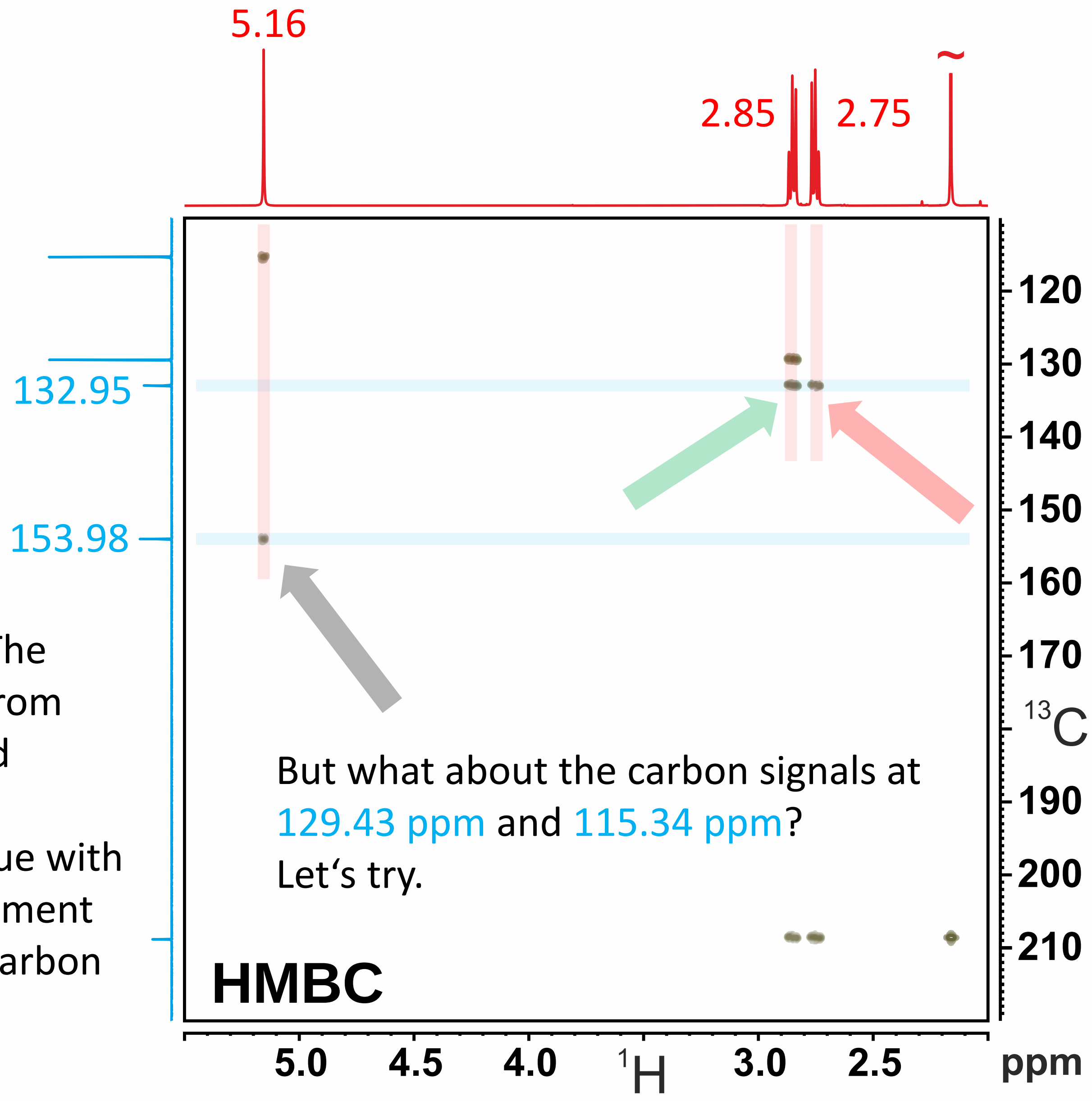


To check the correct assigment of the quaternary carbon atoms we need only a few peaks.

Signal assignment



Everything is fine. The cross peaks come from two and three bond correlations.
This wouldn‘t be true with the opposite assignment of the quaternary carbon atoms.



But what about the carbon signals at 129.43 ppm and 115.34 ppm?
Let‘s try.

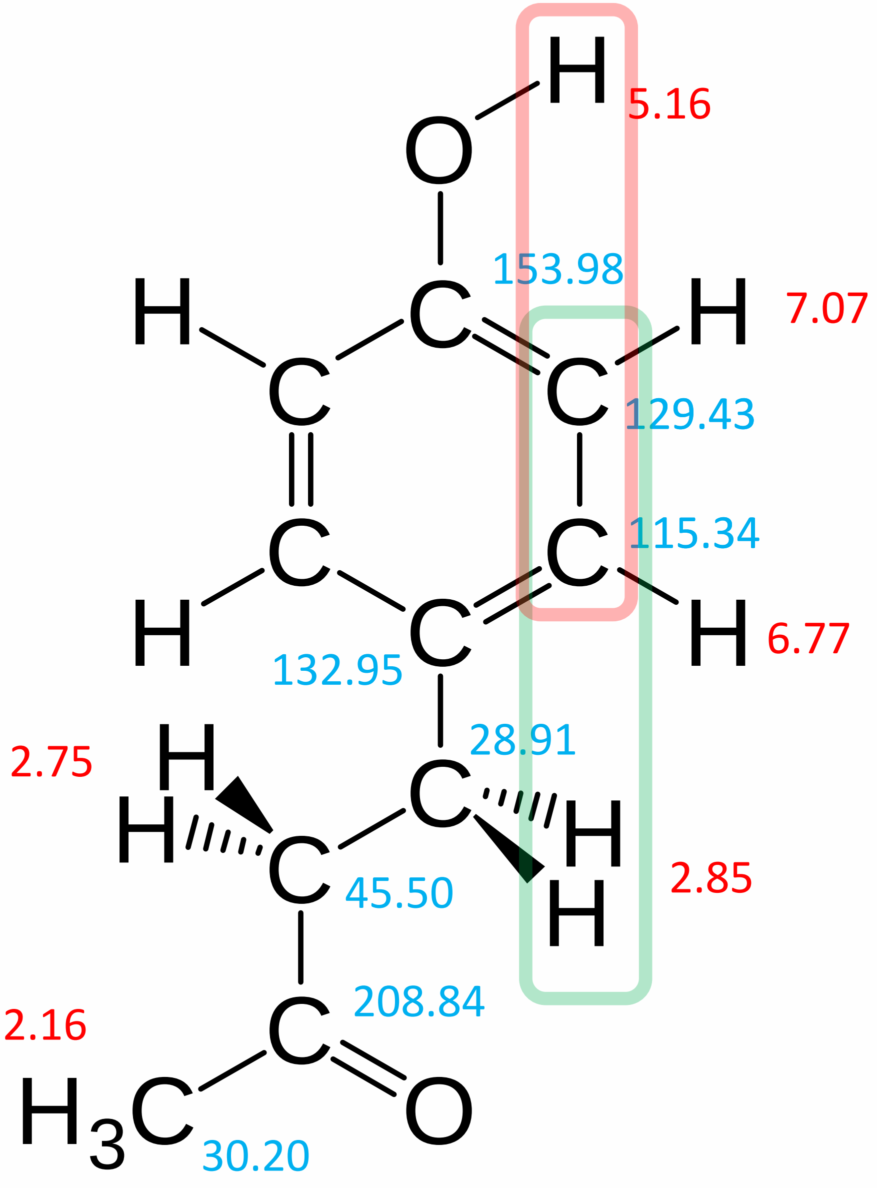
HSQC

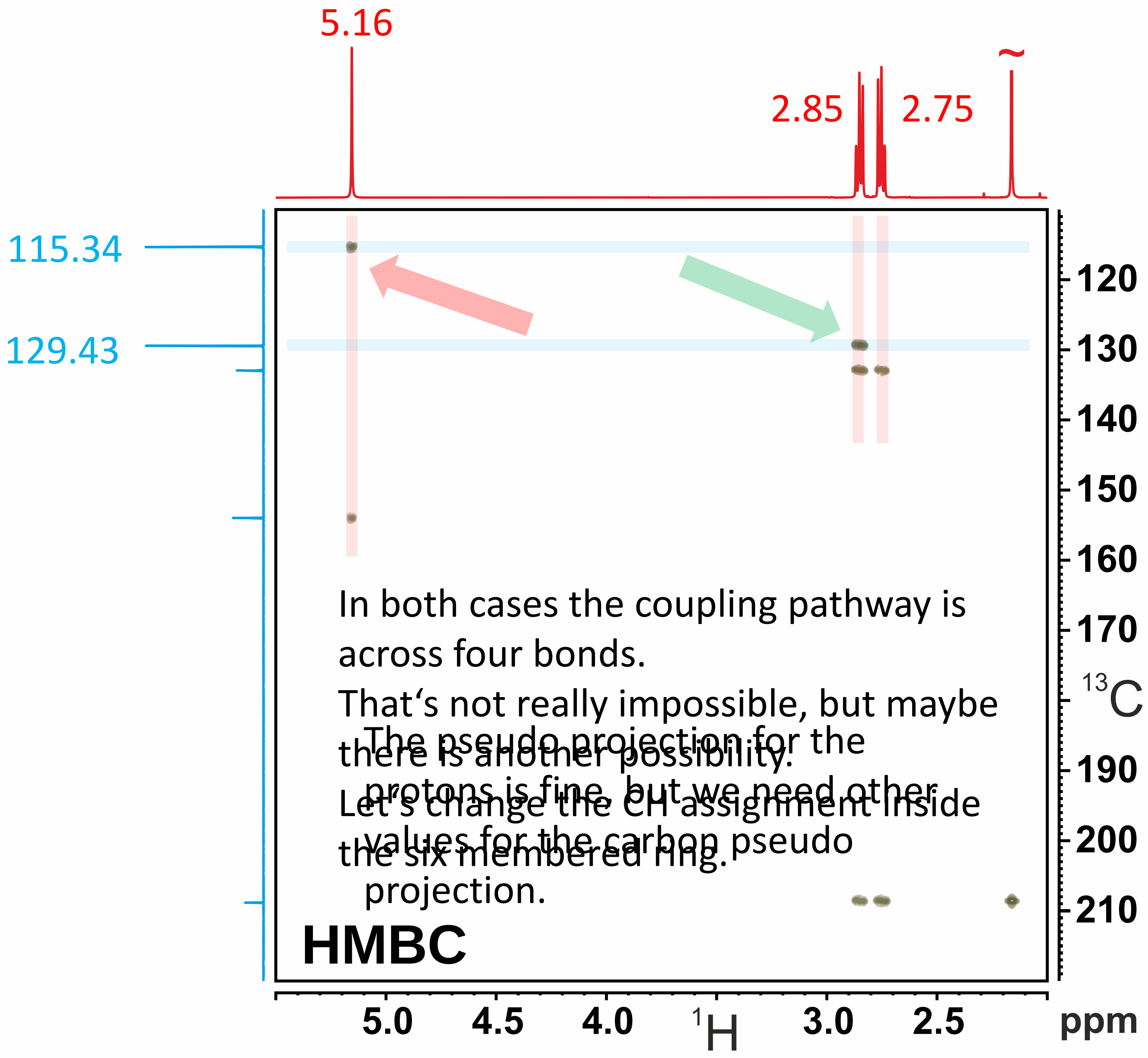
COSY

^{13}C

^{1}H

Building blocks





In both cases the coupling pathway is across four bonds.

That‘s not really impossible, but maybe there is another possibility.

Let‘s change the CH assignment inside the six membered ring.

The pseudo projection for the protons is fine, but we need other values for the carbon pseudo projection.

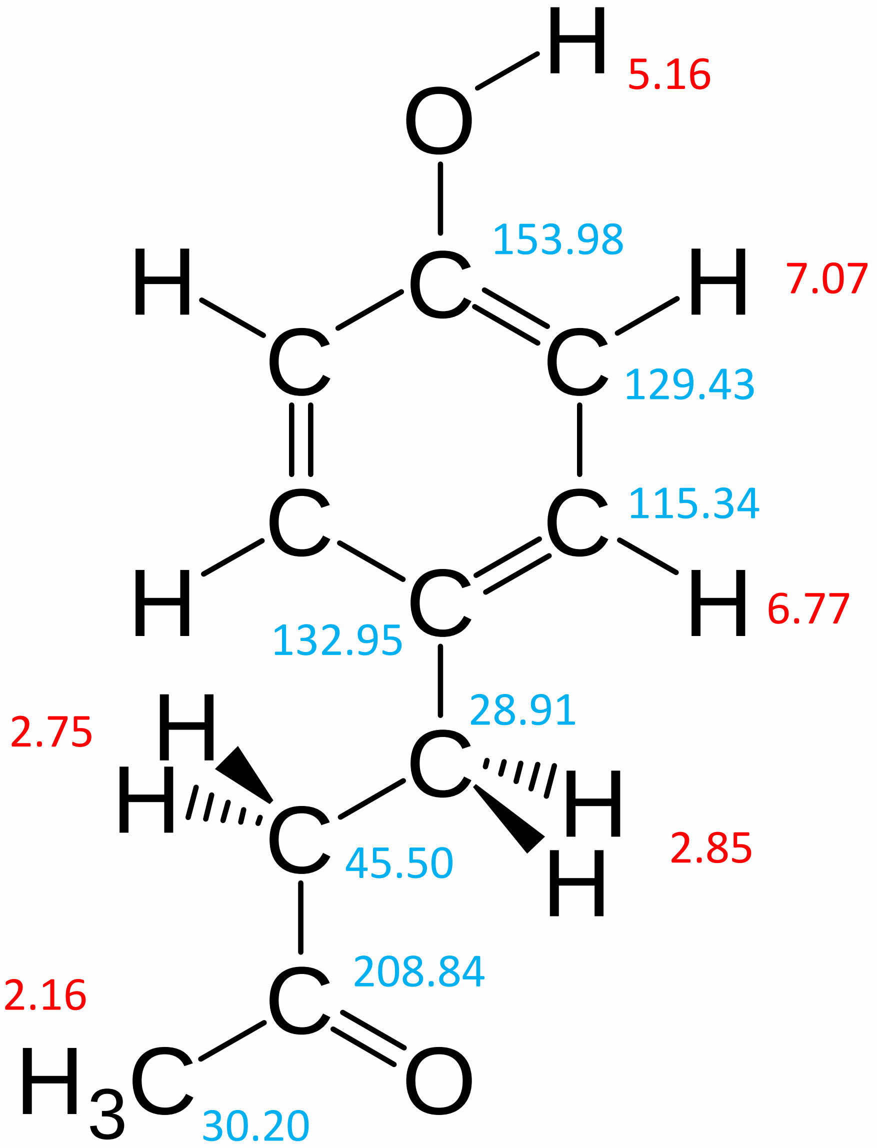
HSQC

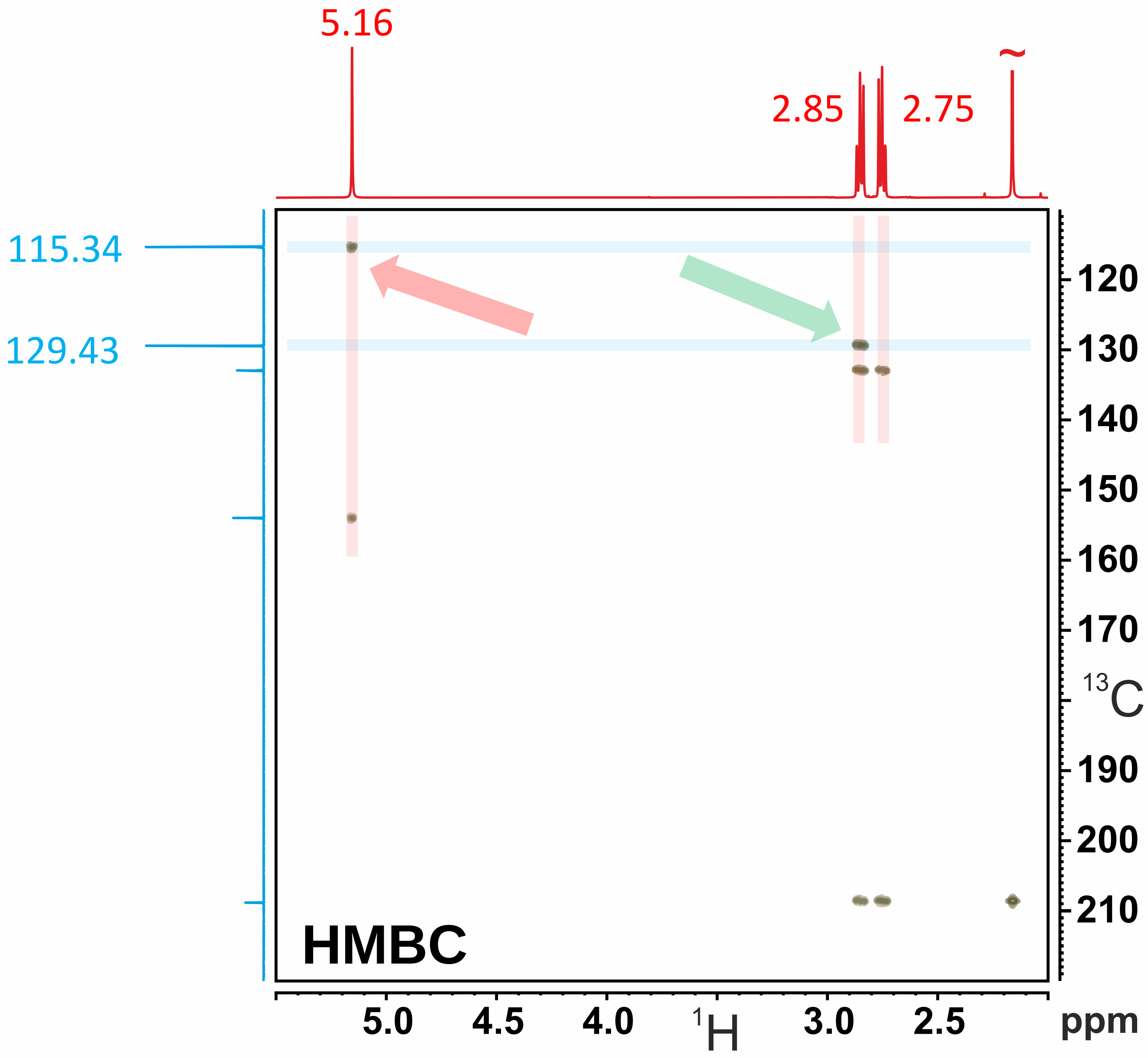
COSY

^{13}C

^{1}H

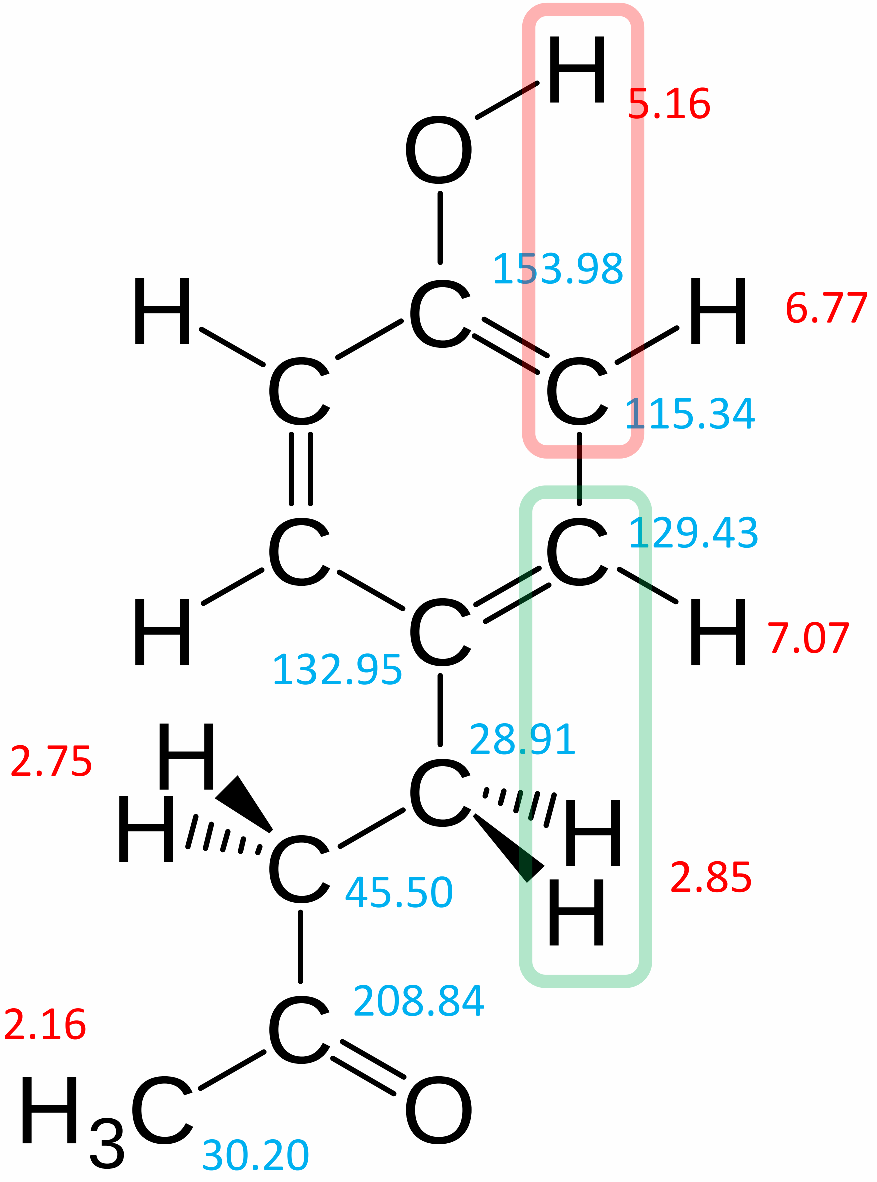
Signal assignment

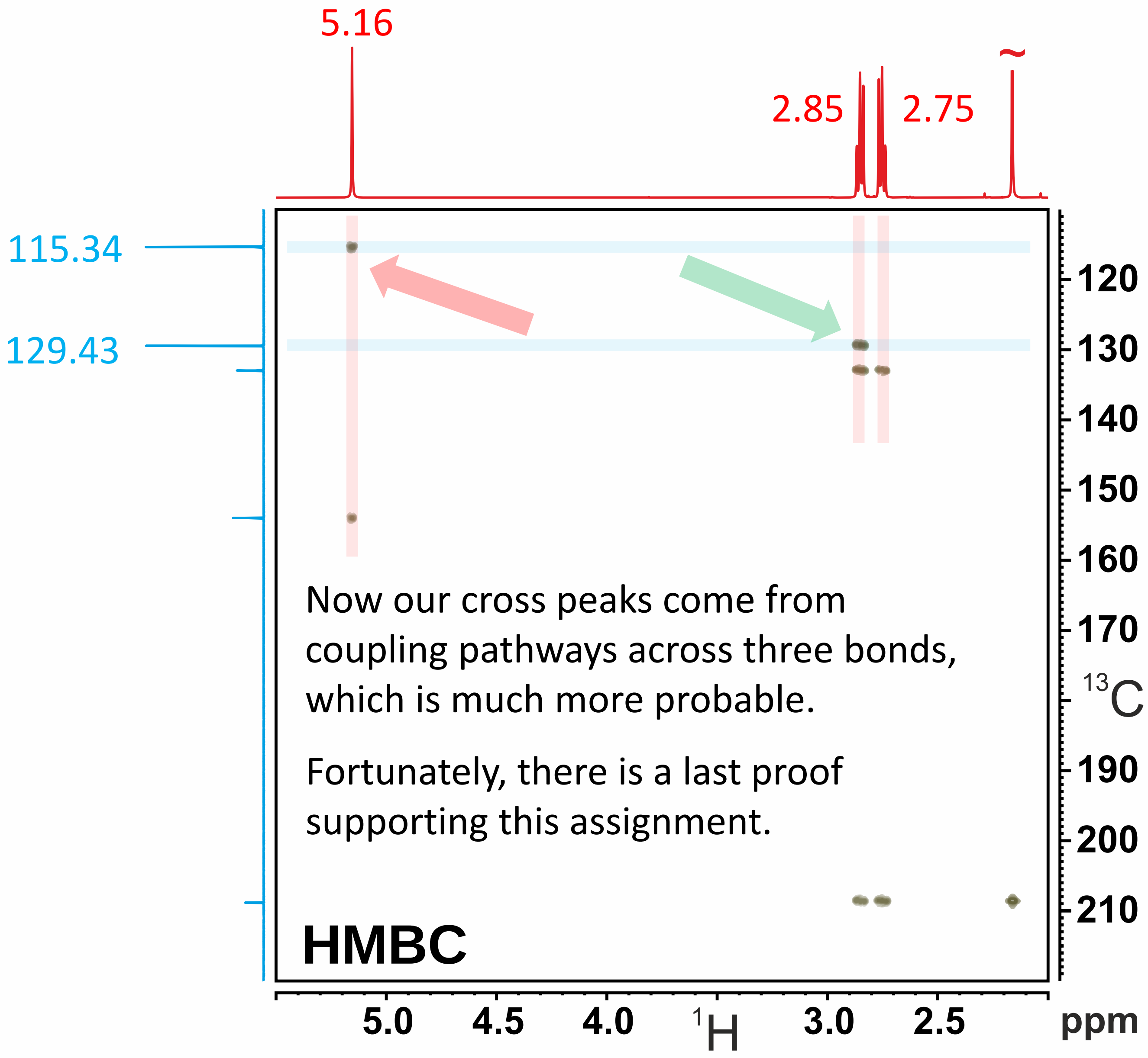




HSQC
COSY
^{13}C
^{1}H

Signal assignment



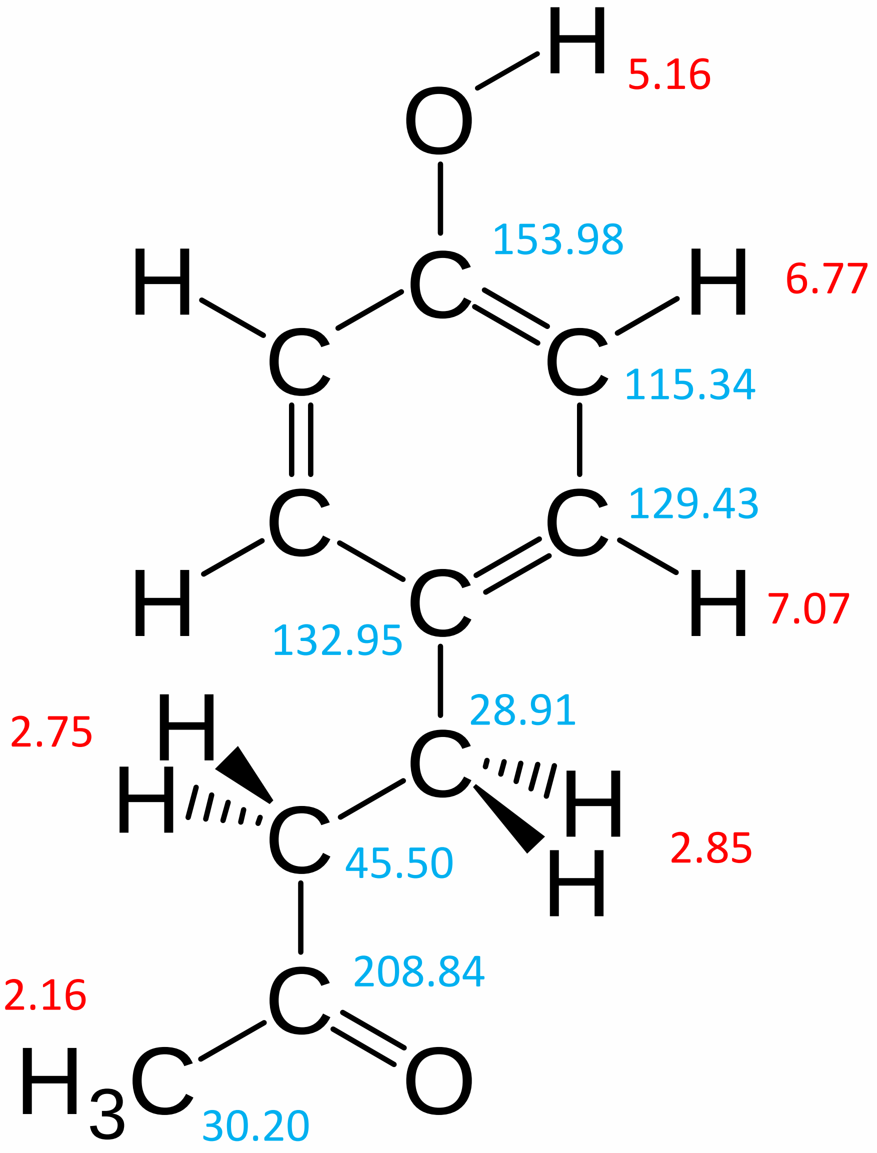


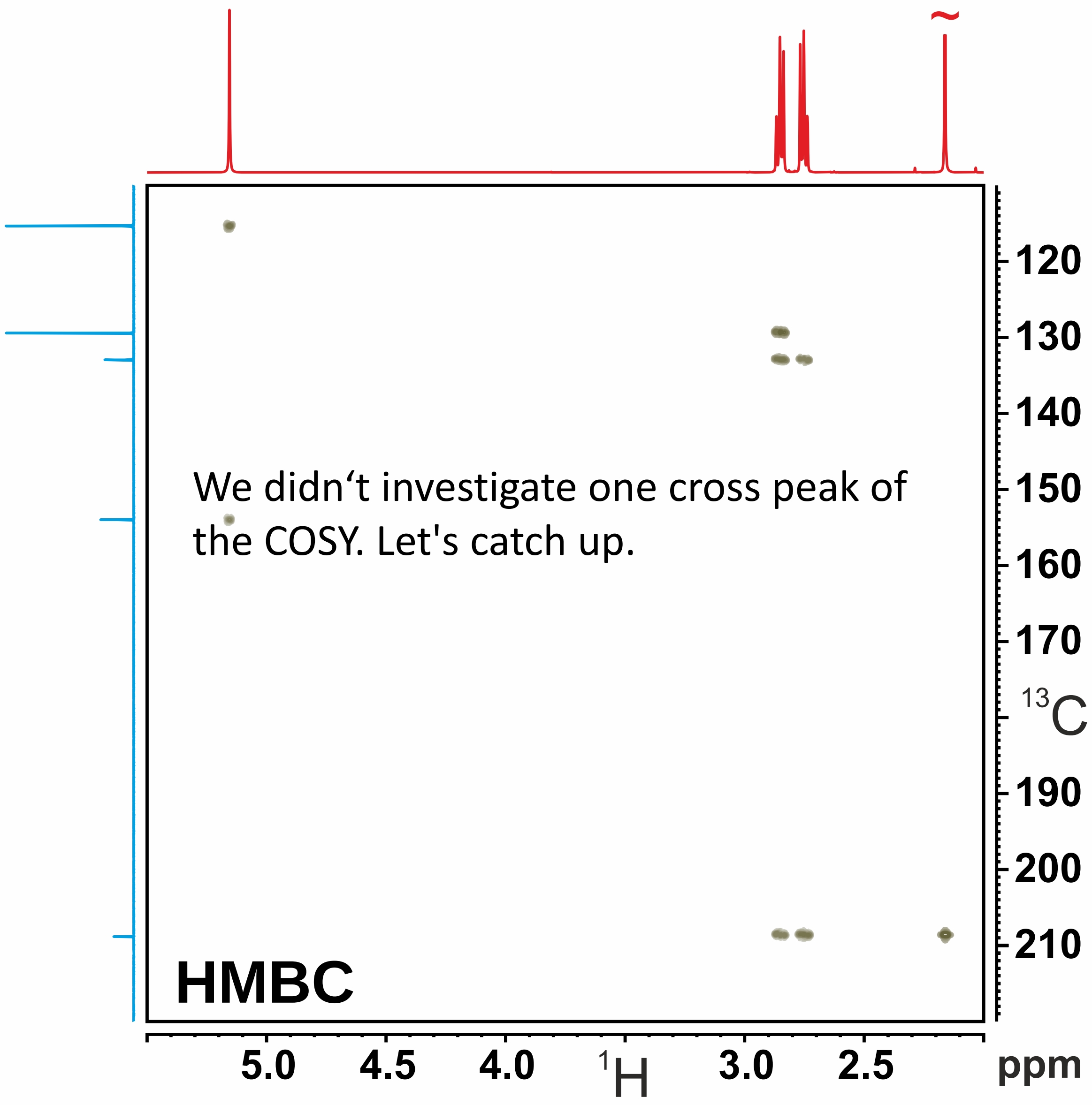
Now our cross peaks come from coupling pathways across three bonds, which is much more probable.

Fortunately, there is a last proof supporting this assignment.

HSQC
COSY
^{13}C
^{1}H

Signal assignment





We didn‘t investigate one cross peak of the COSY. Let's catch up.

HSQC

HMBC

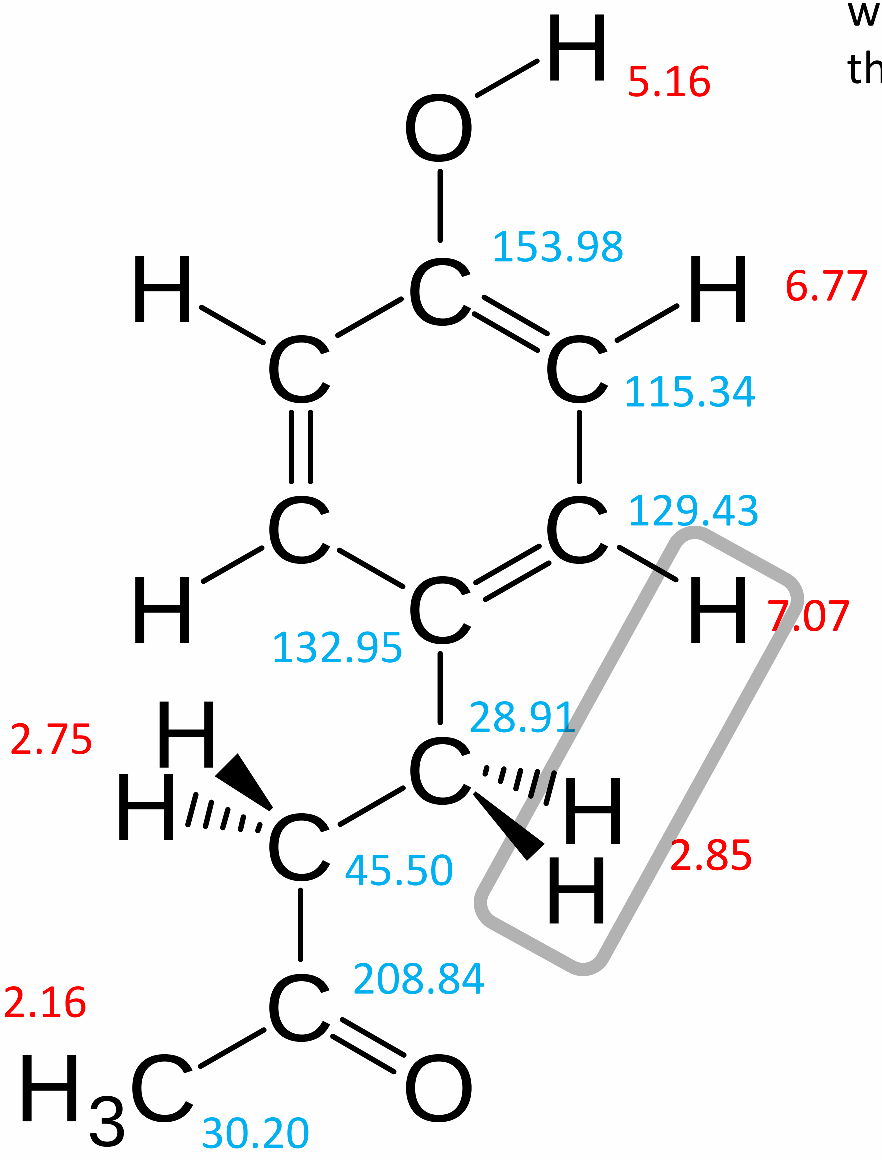
^{13}C

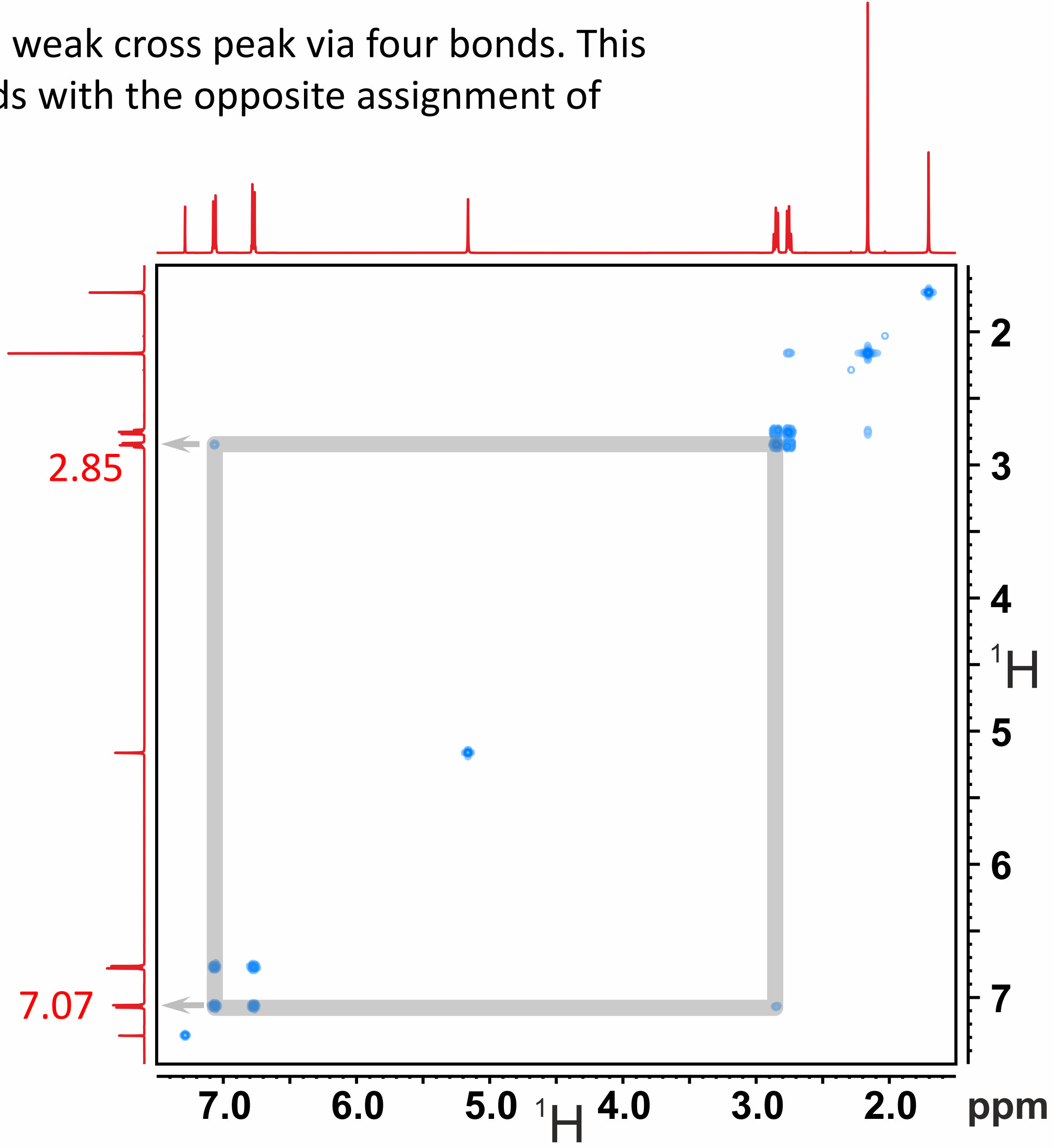
^{1}H

Building blocks

We have to label two signals groups only.

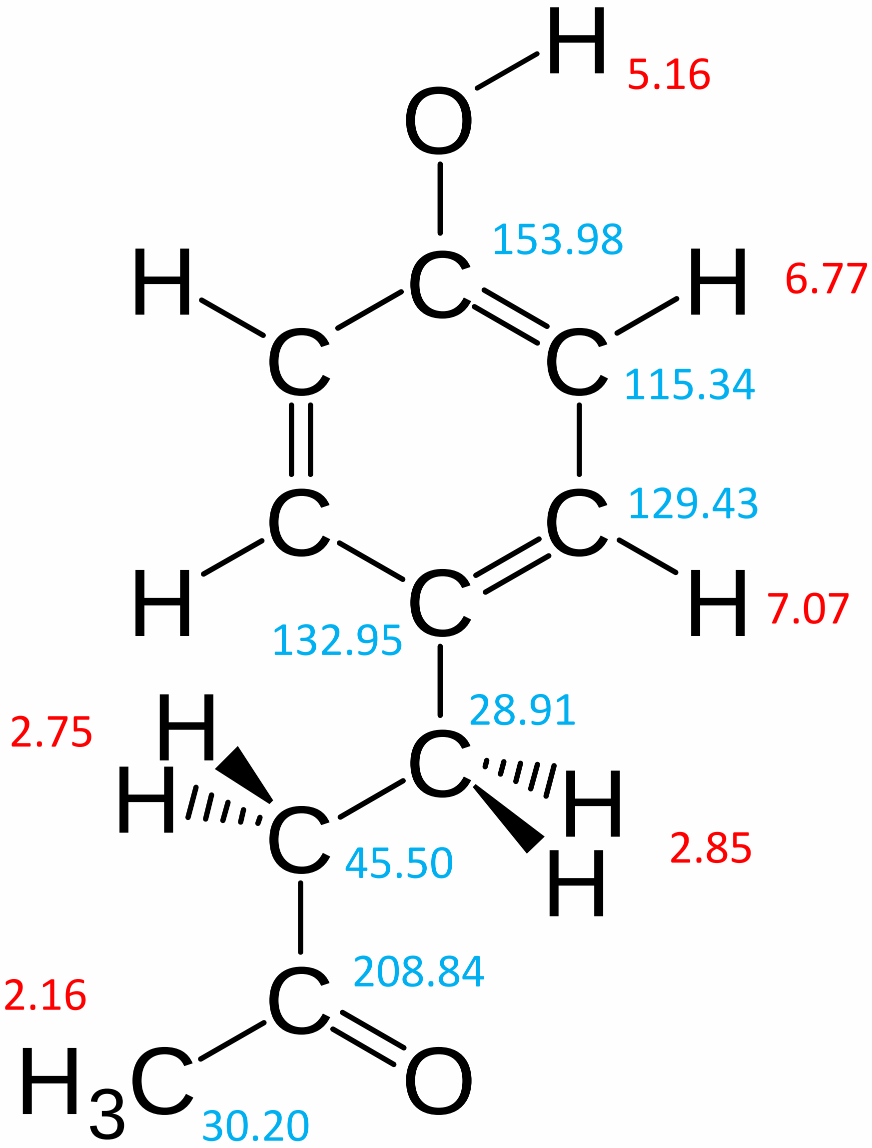
And now there is a weak cross peak via four bonds. This would be five bonds with the opposite assignment of the CH groups.





HSQC
HMBC
^{13}C
^{1}H

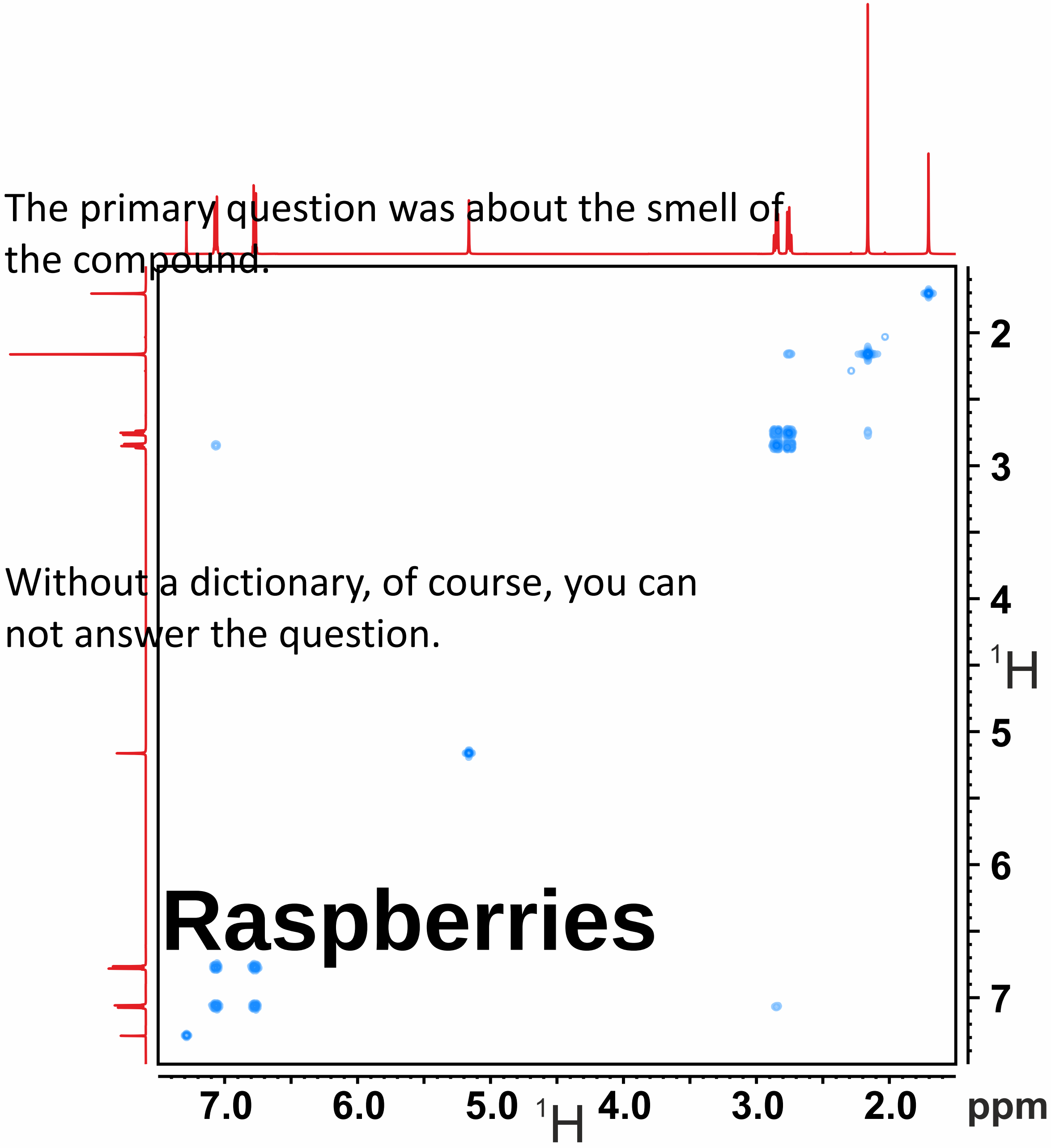
Final solution



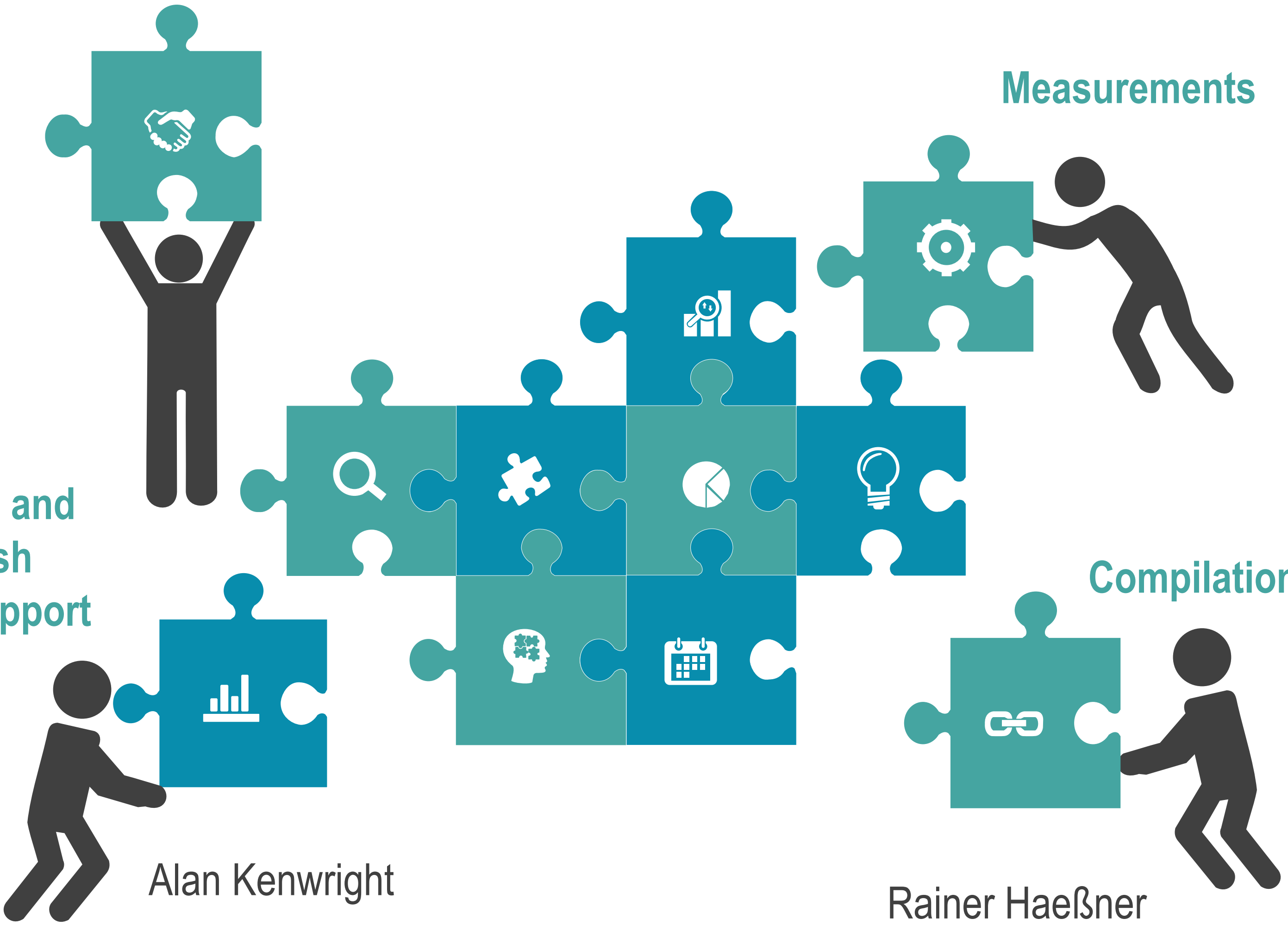
The primary question was about the smell of the compound.

Without a dictionary, of course, you can not answer the question.

Raspberries



Contributions



Spectrometer time

TU Munich

Measurements

Thomas Geisberger

Discussions and native English language support

Alan Kenwright

Compilation

Rainer Haeßner

[More exercises …](#)