Problem of the Month:

December 2020

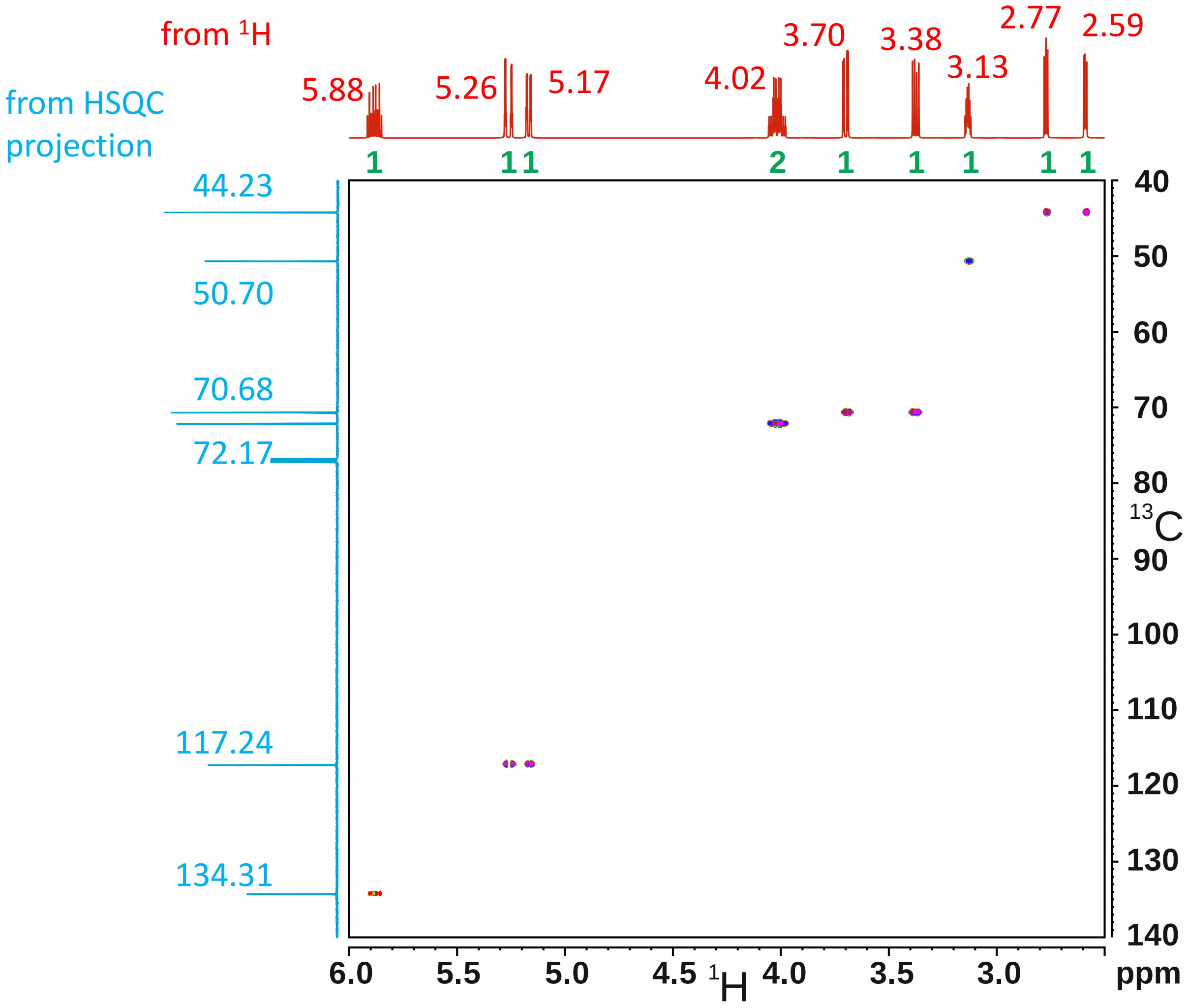
Solution

The following description will guide you through the analysis of the December example. An animated version may be found here!

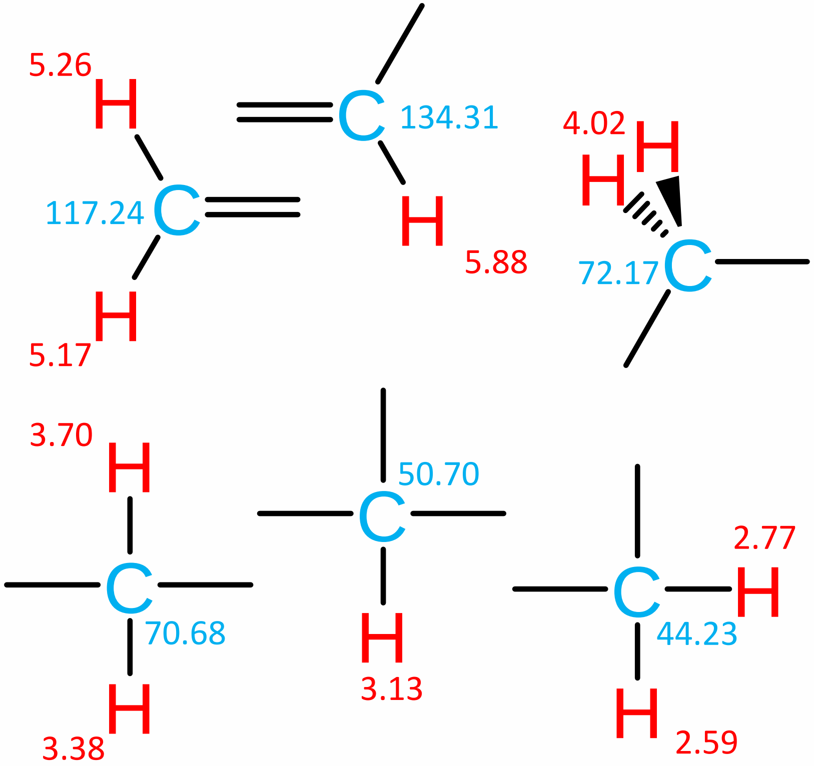
If available, in most cases the HSQC is an ideal point to start a structure elucidation.

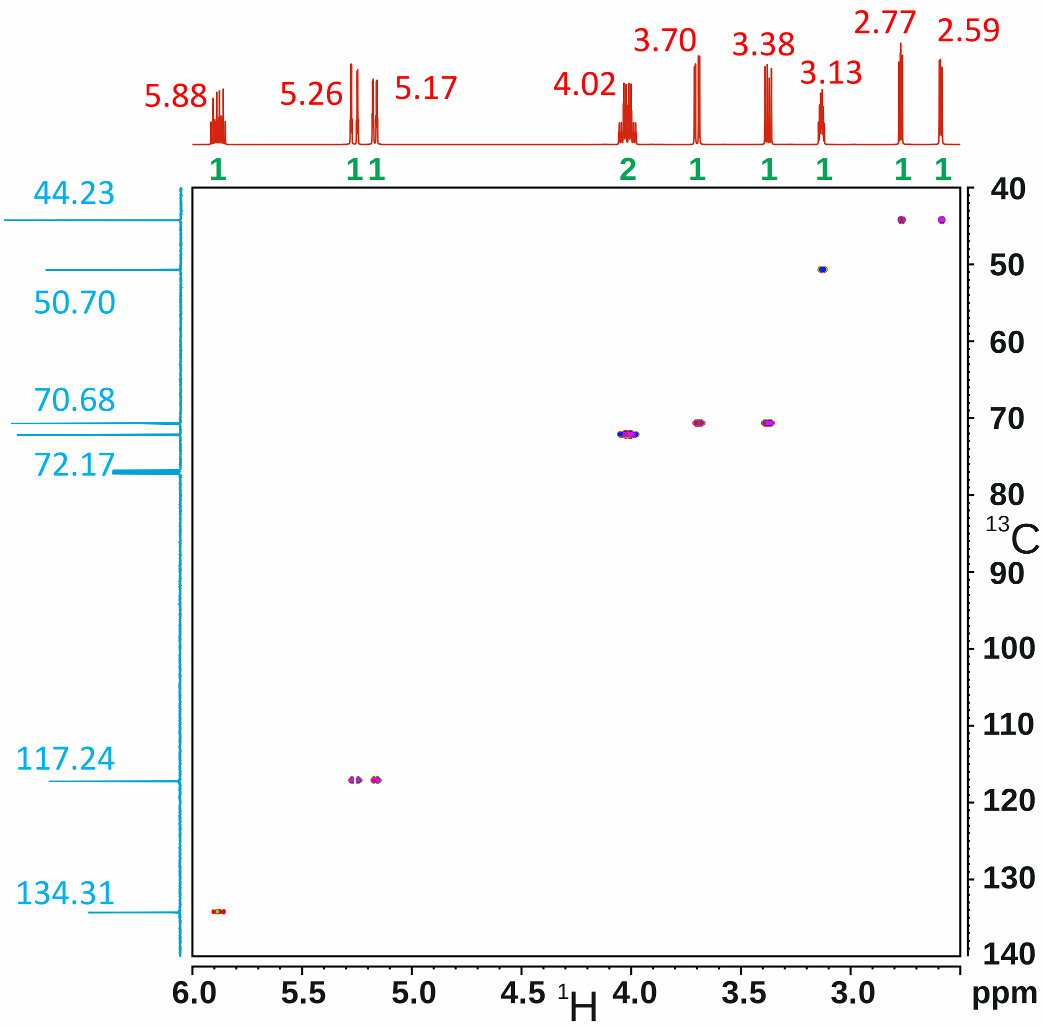
The evaluation of an HSQC is a bit like picking out the right Lego bricks from the big box.

As a first step we extract the chemical shifts from the one-dimensional spectra, and the integrals from the proton spectrum.



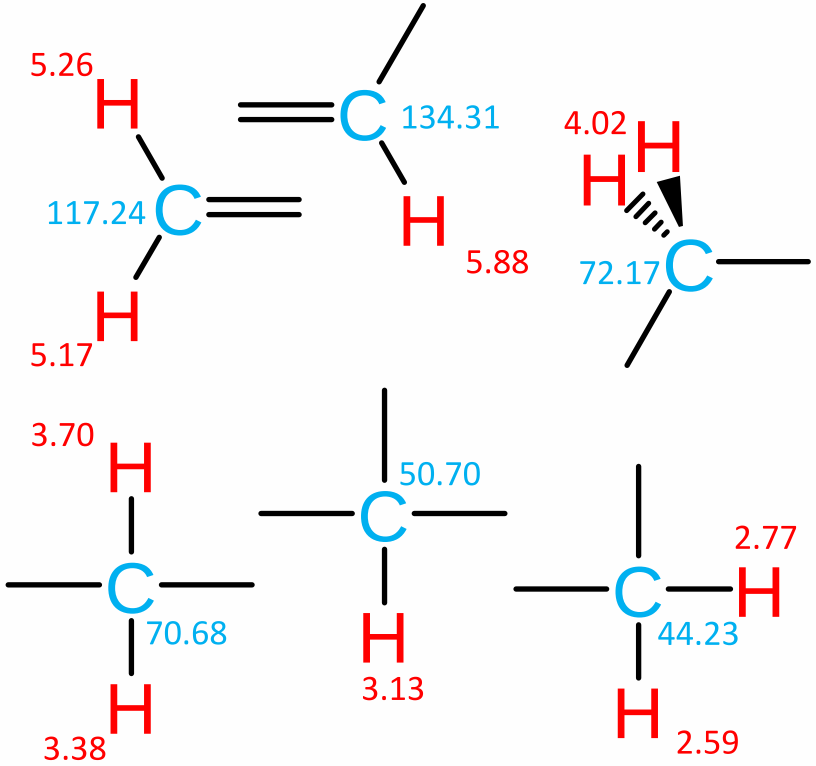
And finally, several building blocks containing sp^2 and sp^3 hybridized carbons can be identified.

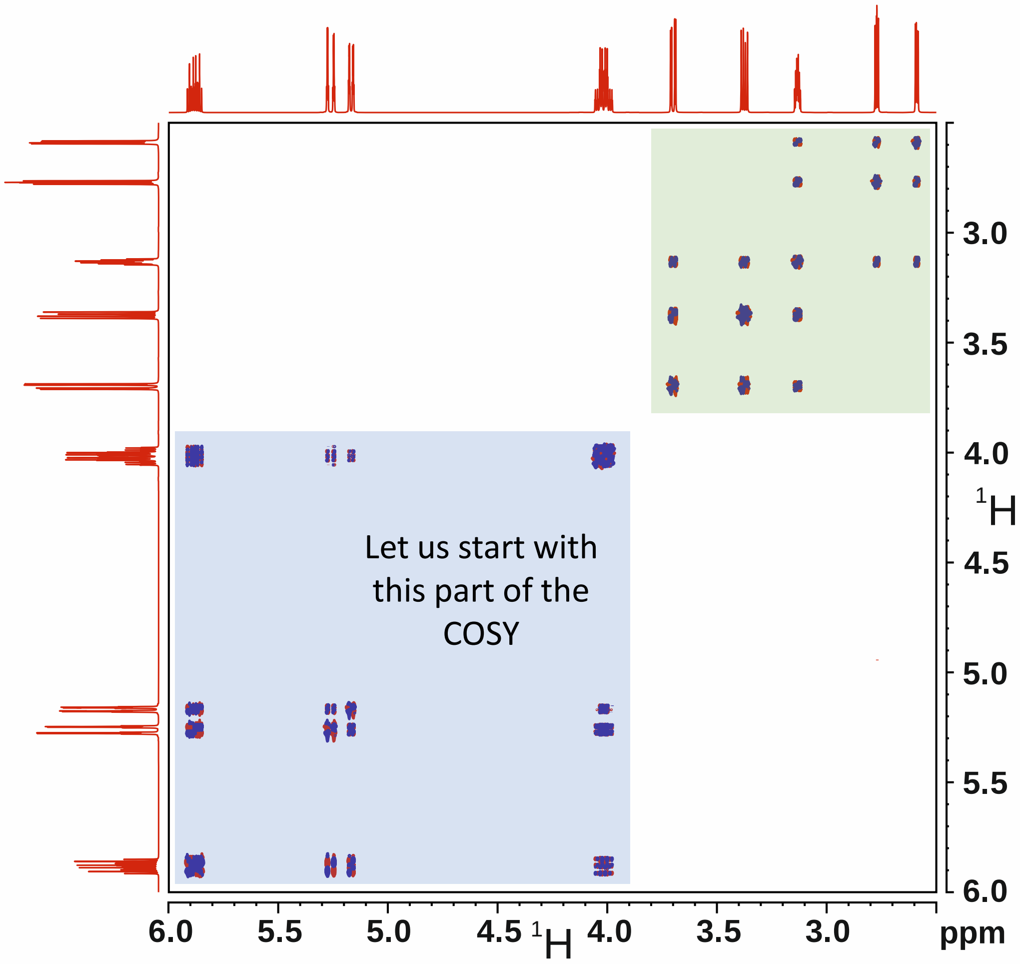




To connect the structural fragments into the right order, we need the COSY.

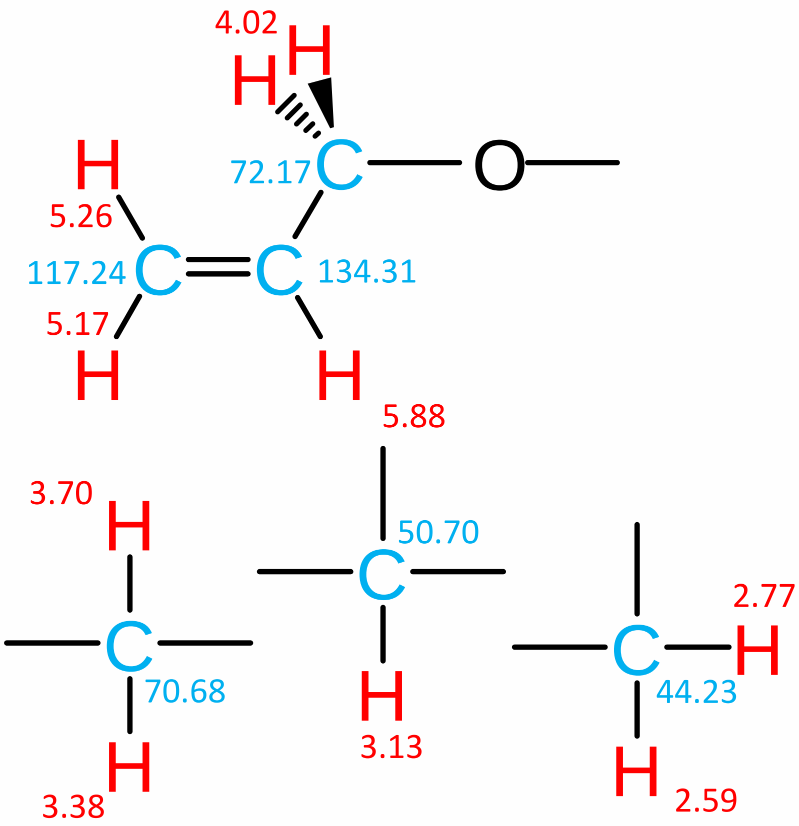
Fortunately, two substructures may be constructed completely independently of each other.

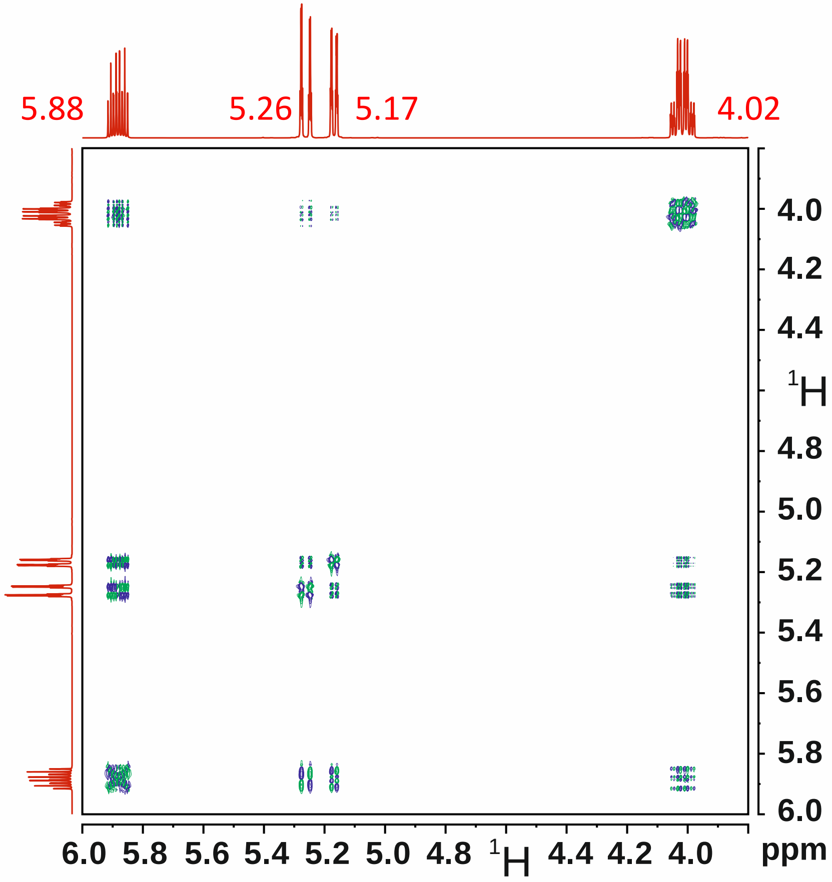




Let us start with this part of the COSY

According to the COSY no other CH_n group can be attached to this allyl group. The only choice from the molecular formula is an oxygen atom.





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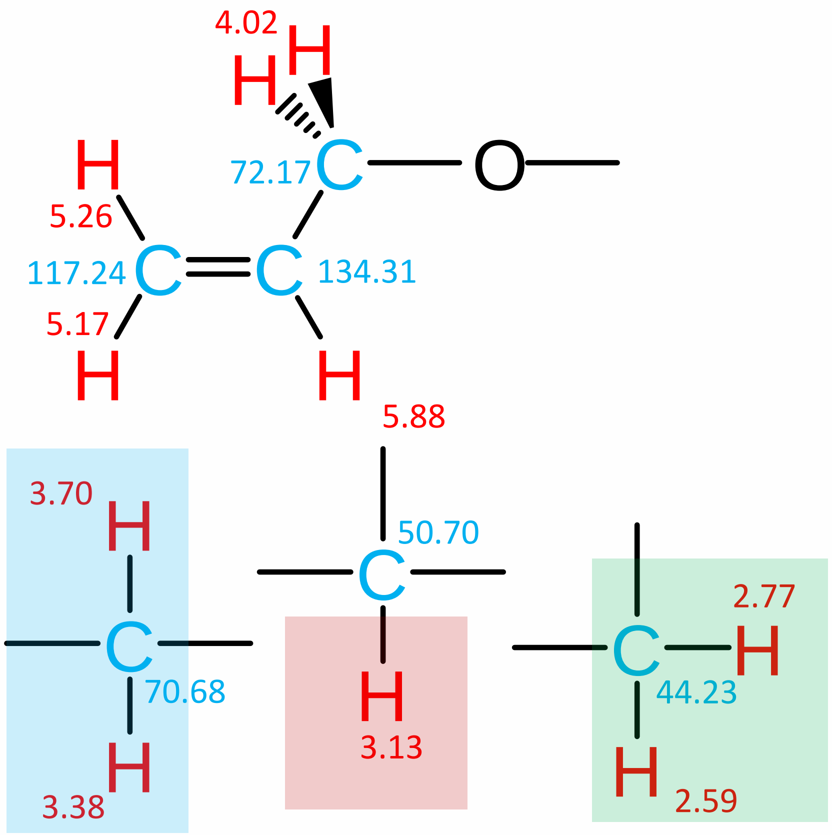
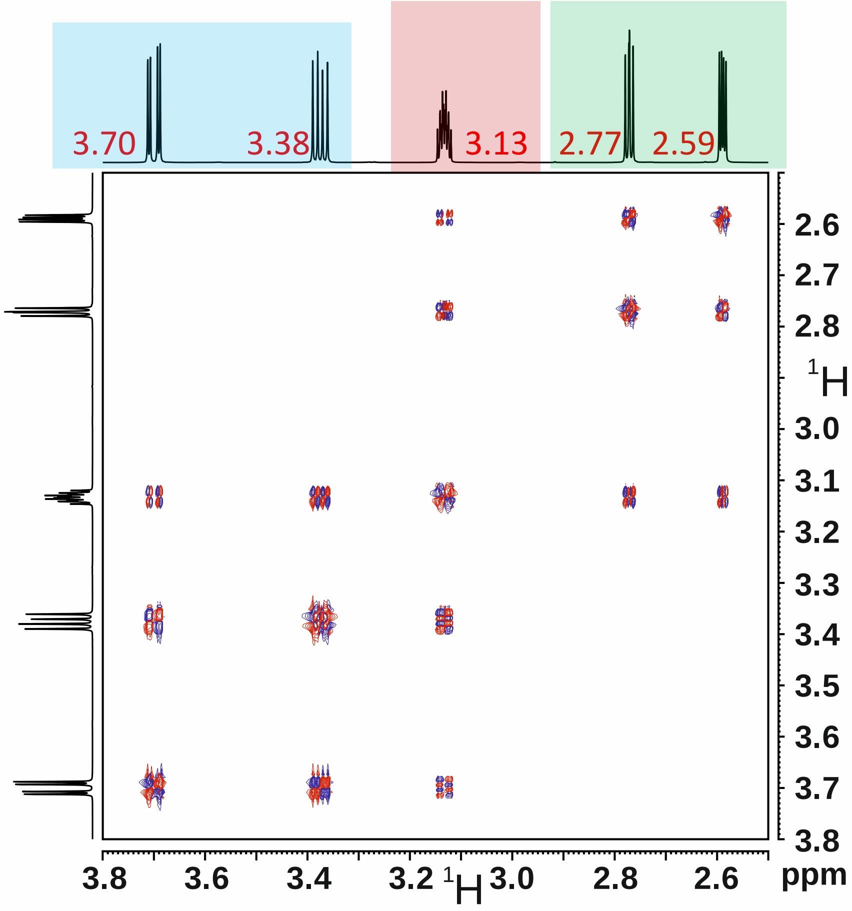
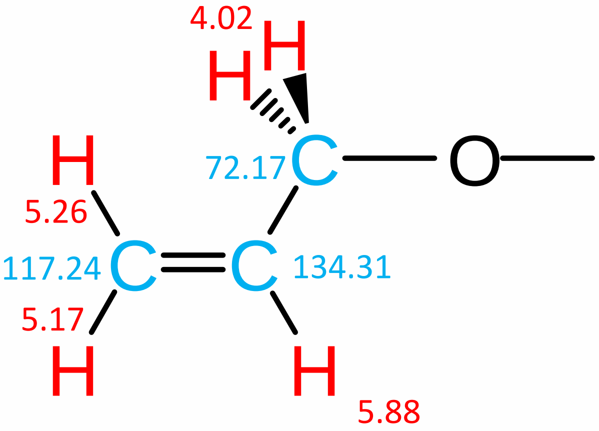
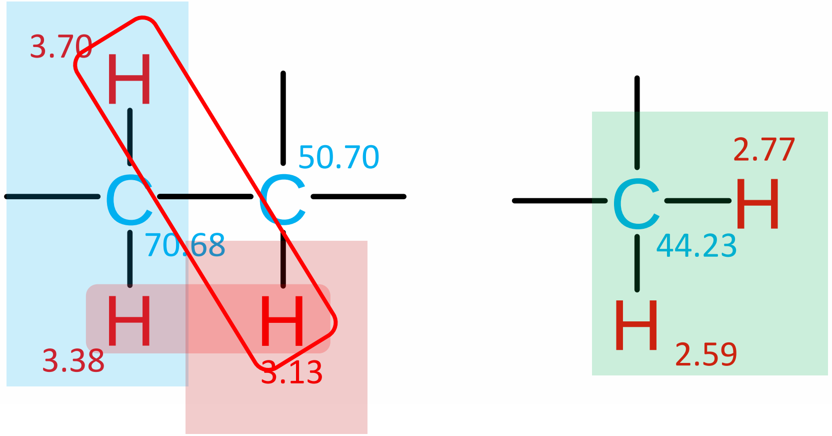
To connect the remaining three structural fragments we need the high-field part of the COSY. Different colours are used to label the protons within the fragments.

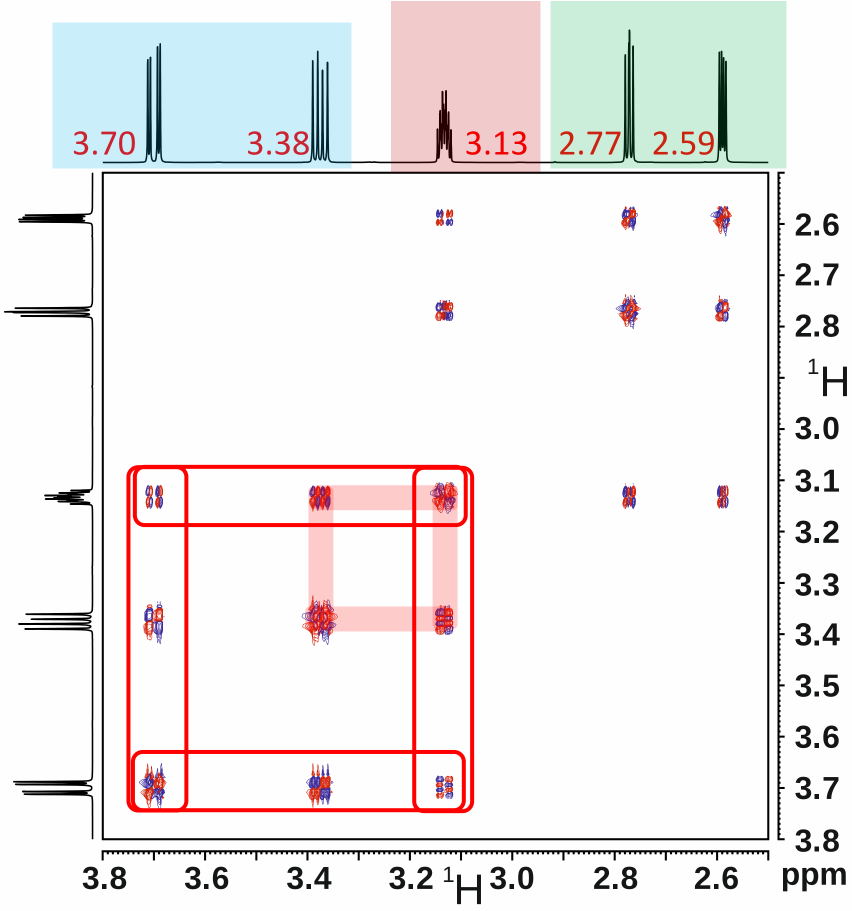




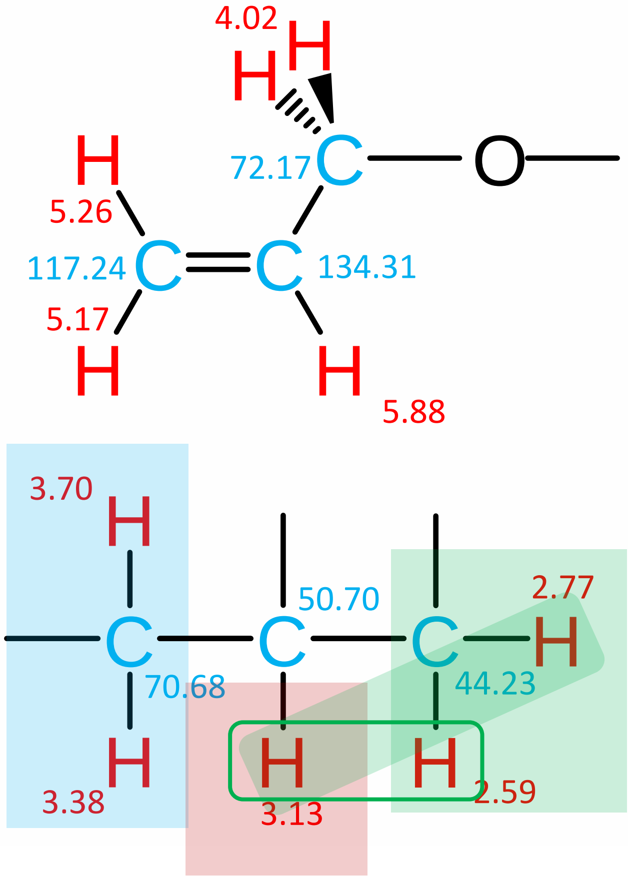
We see one correlation between the protons at 3.13 and 3.38 ppm and a second correlation between the protons at 3.13 and 3.70 ppm. Both correlations tell us about the same connectivity.

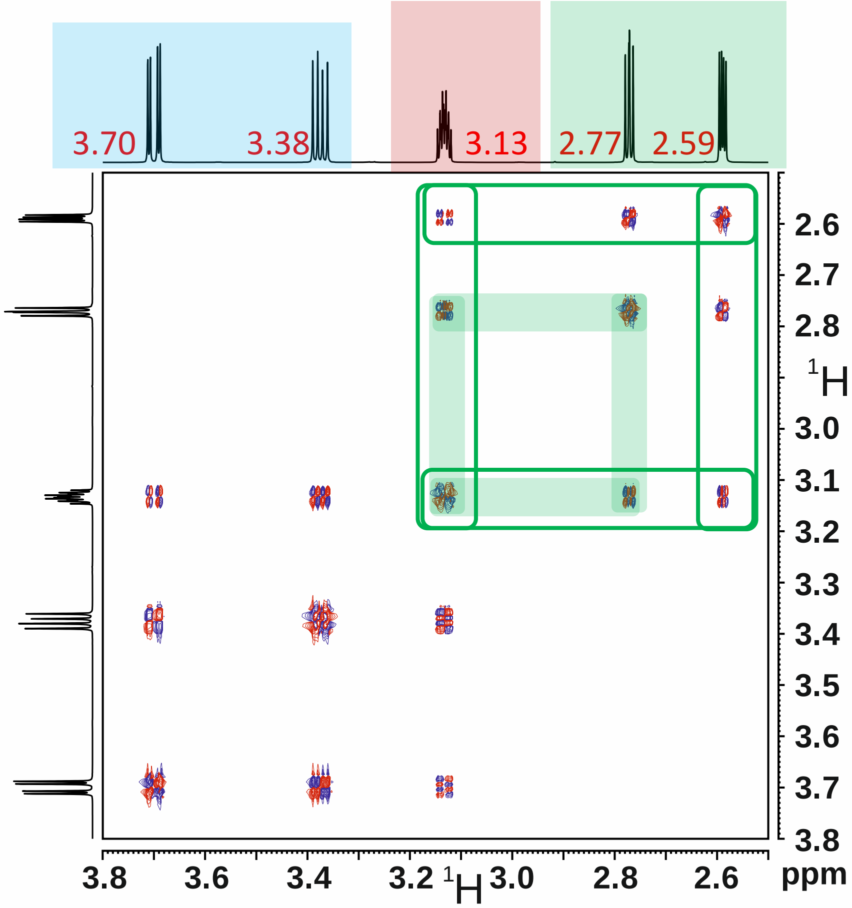




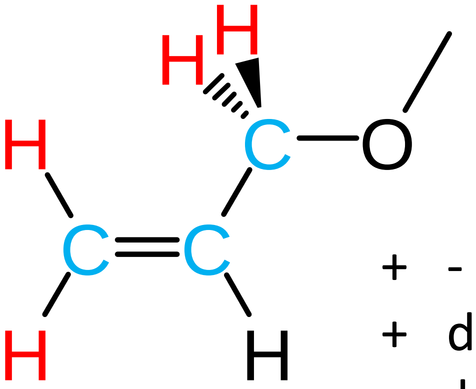


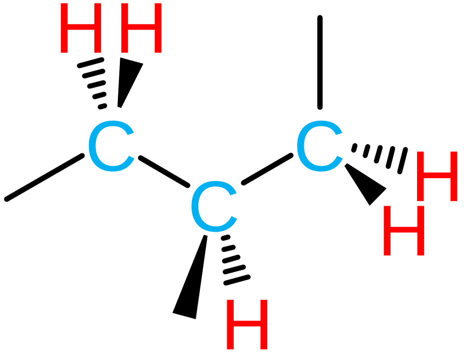
We see another correlation between the protons at 3.13 and 2.77 ppm and between the protons at 3.13 and 2.59 ppm. Once again both correlations tell us about the same connectivity.





Now we have four building blocks.





\+ - O -

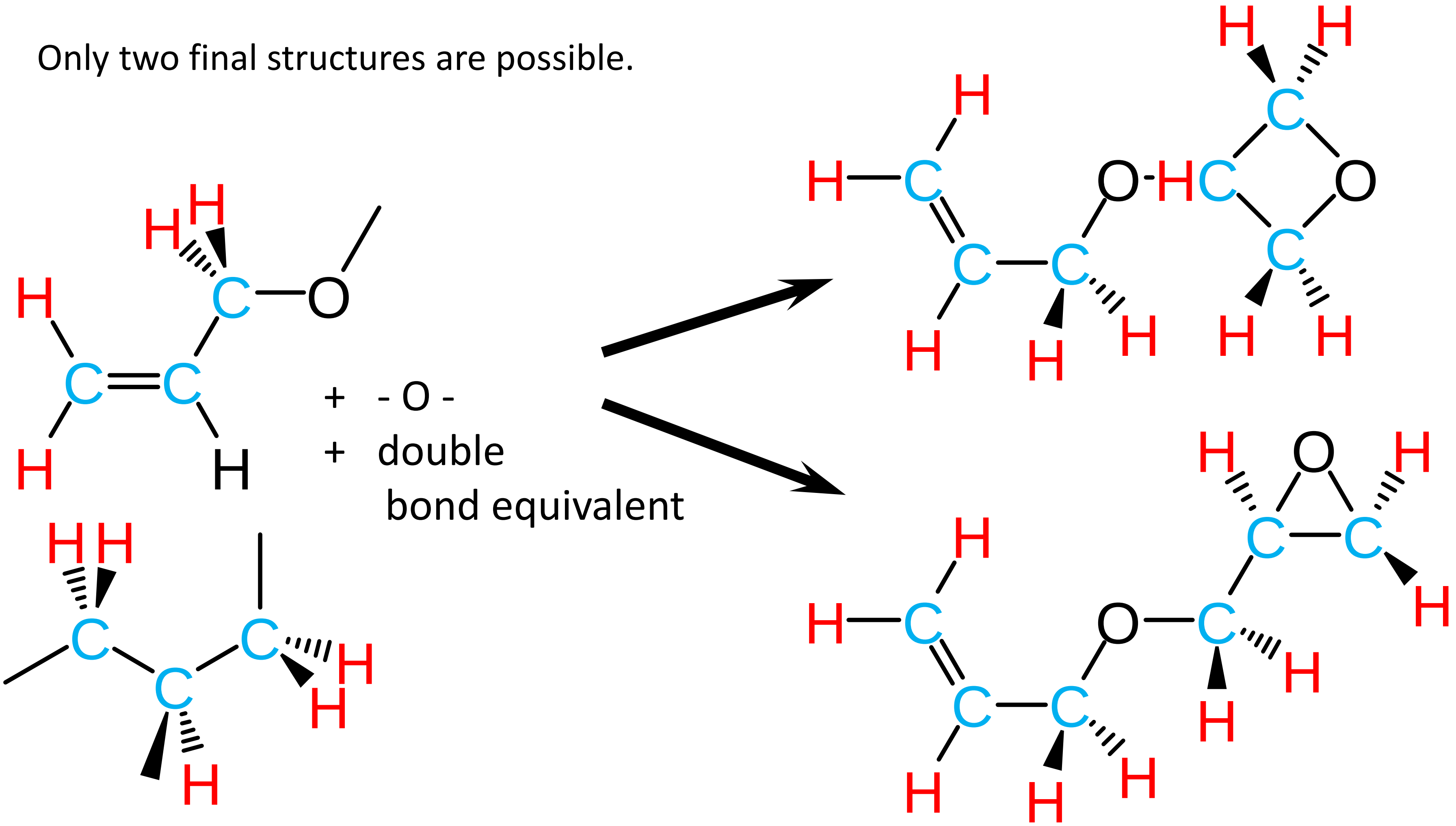
\+ double bond equivalent

1. The two substructures just deduced

2. From the molecular formula, the remaining fragment must contain:

- One double bond equivalent and
- One oxygen atom

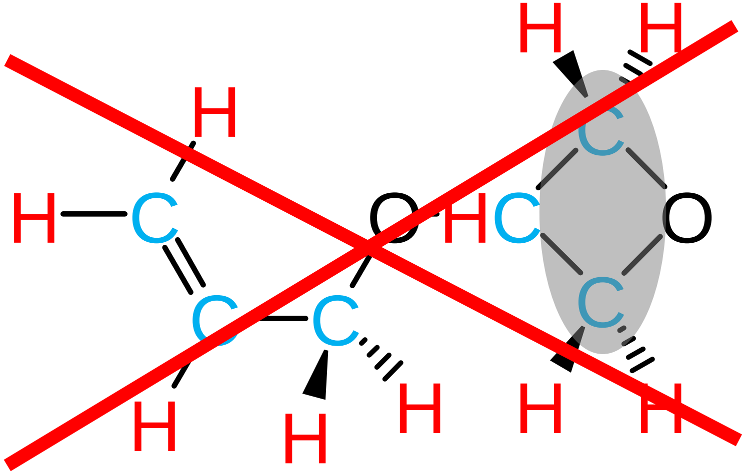
Only two final structures are possible.



\+ - O -

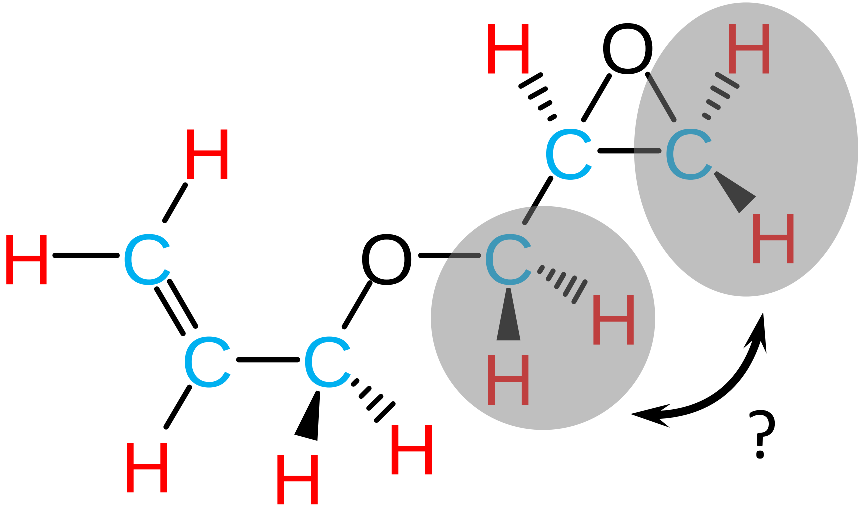
\+ double bond equivalent

Only two final structures are possible.



In the case of the upper structure we would expect *five carbon signals only* due to partial symmetry.

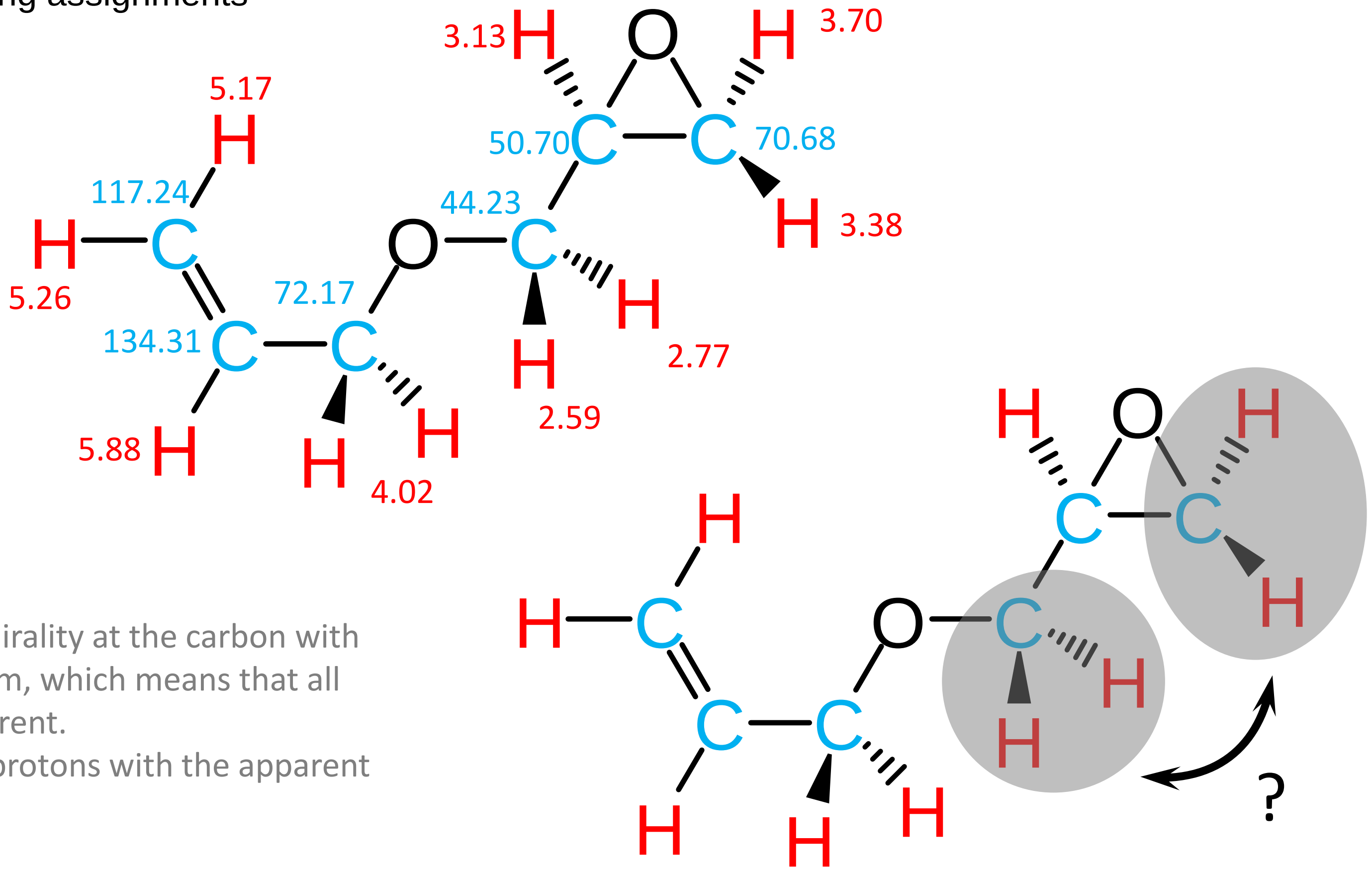
But our happiness is not complete. So far we cannot determine the assignment of the two methylene groups beyond any doubt.



For further work, let’s intentionally start with the wrong assignment in order to determine how to get the correct assignment.

Solution structure

(with some intentionally wrong assignments



Please note the center of chirality at the carbon with a chemical shift of 50.70 ppm, which means that all protons are chemically different.
This is equally valid for the protons with the apparent chemical shift of 4.02 ppm.

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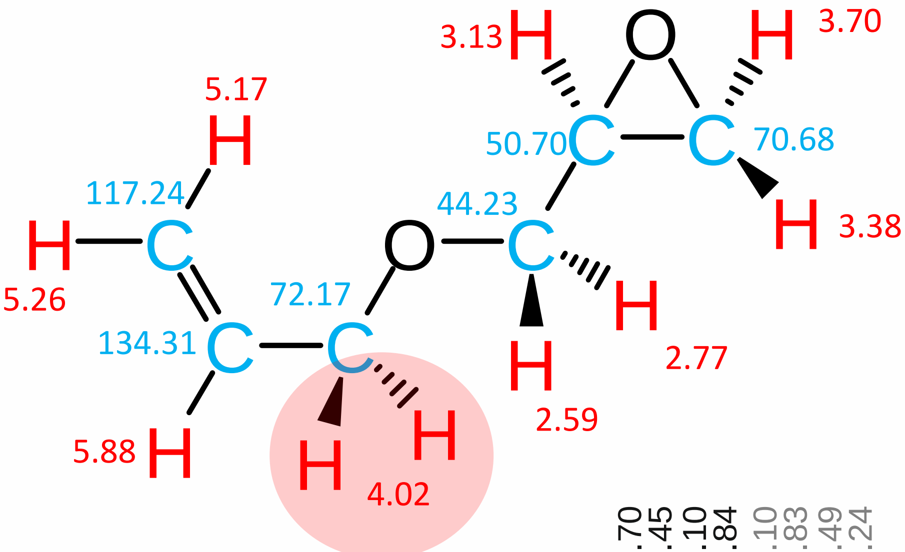
The analysis of the homonuclear coupling constants and the correct assignment

A basic consideration about the multiplet structure

Due to the center of chirality there are no equivalent protons in this molecule. As a result, every coupling pattern without any exception - completely independent of its apparent structure - can only be a doublet, a doublet of doublets, a doublet of doublets of doublets, ...

Each multiplet consists of 2, 4, 8, or generally 2^n lines of equal intensity. Deviations from this general rule can only be explained by overlapping lines.



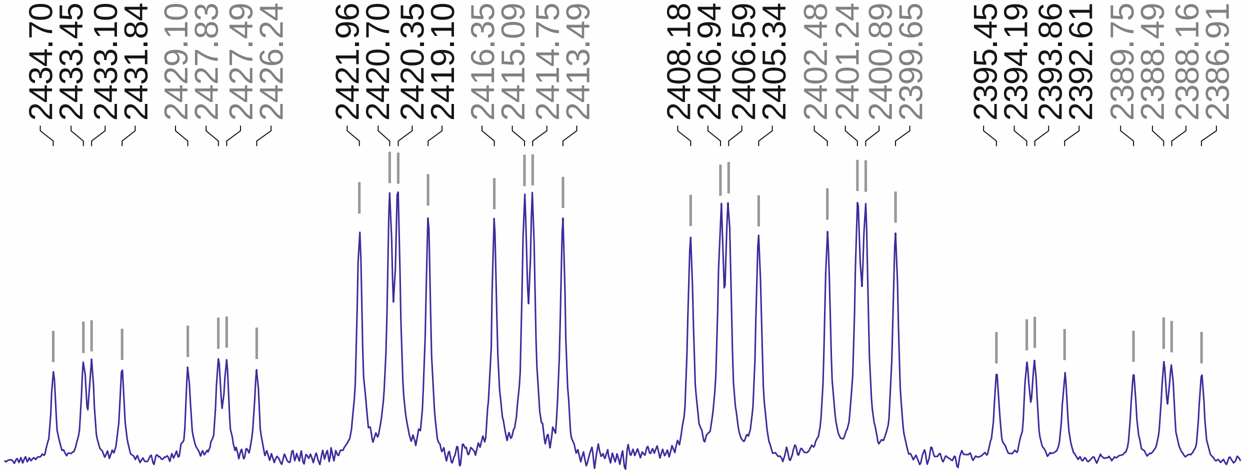
The multiplet comes from these protons.

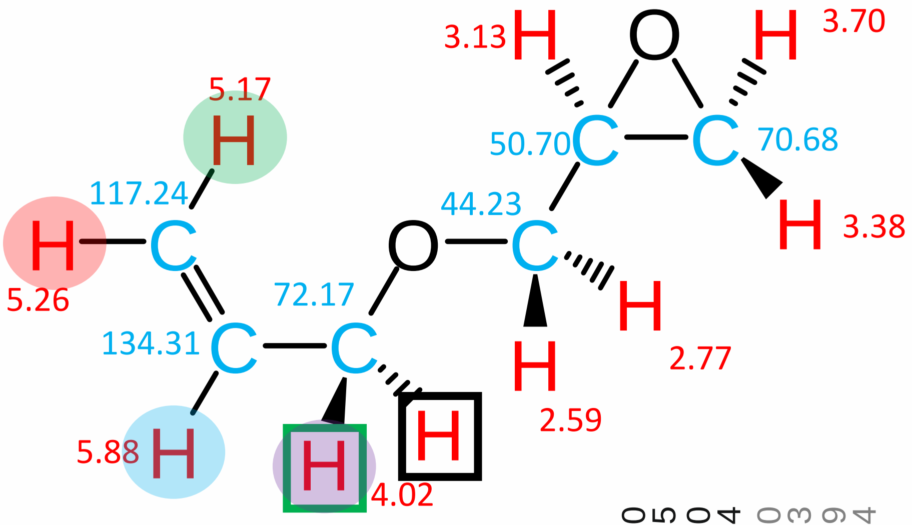
But …

There is a perfect quartet (with the same fine structure for each of the four lines) visible at about 4 ppm.

That‘s not possible! (see the explanation just given)

What might be the real structure of this complicated multiplet?



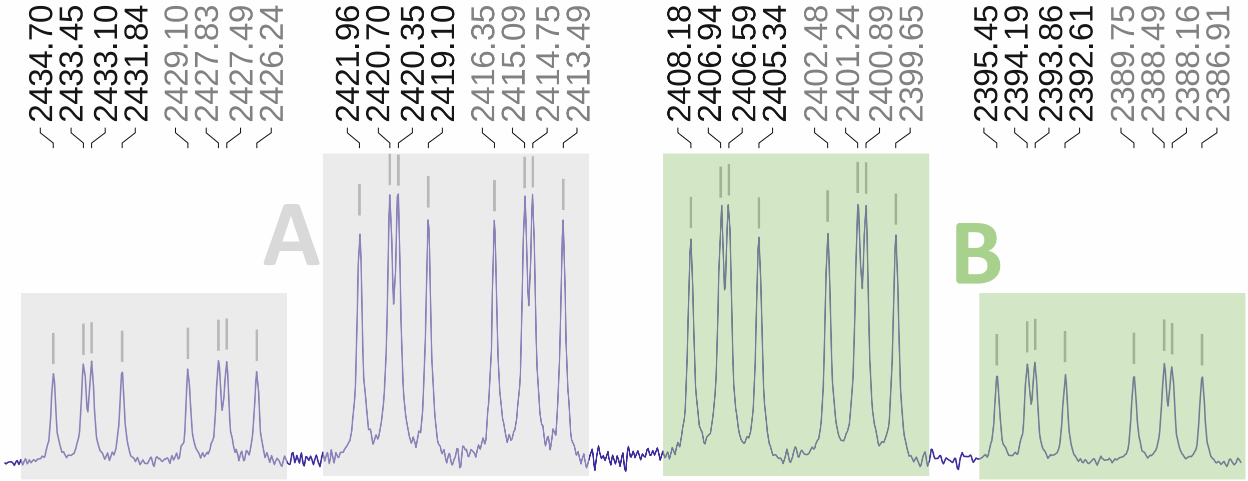


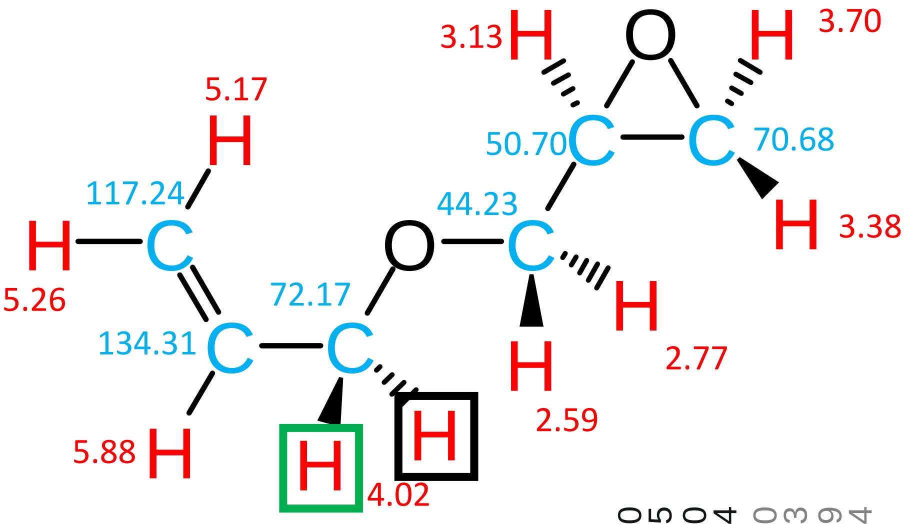
The protons labelled in black and green are chemically different. We expect different chemical shifts for these protons.

The signal of the black labelled proton should appear as a doublet (about 12 Hz) of doublets (about 7 Hz) of doublets (about 1 Hz) of doublets (about 1 Hz)

The same is true for the green labelled proton

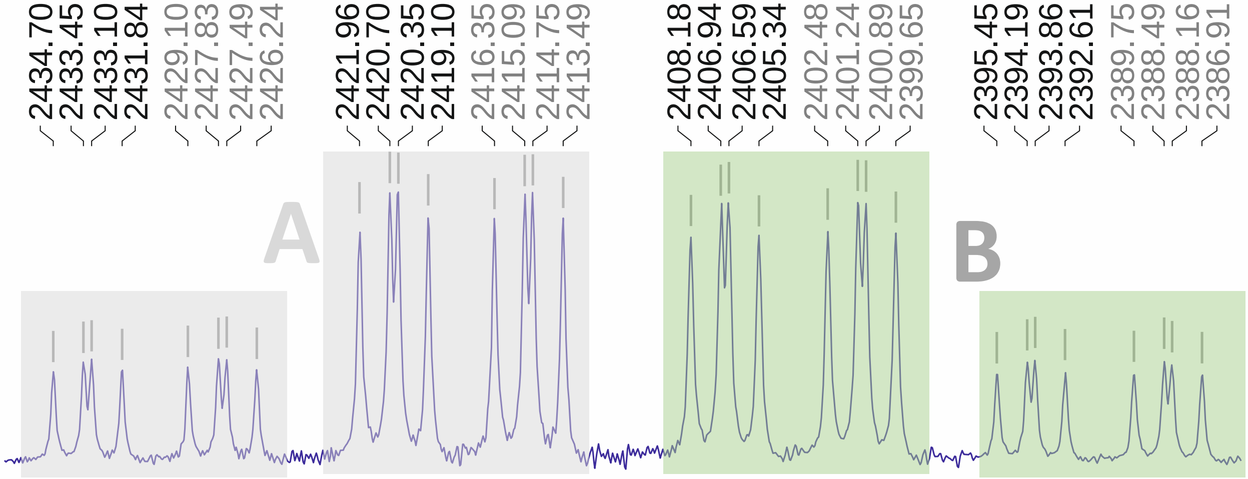
Apparently the chemical shifts of the black and the green labelled proton are not too different, which means, we expect an **AB** system as base structure for these both protons.



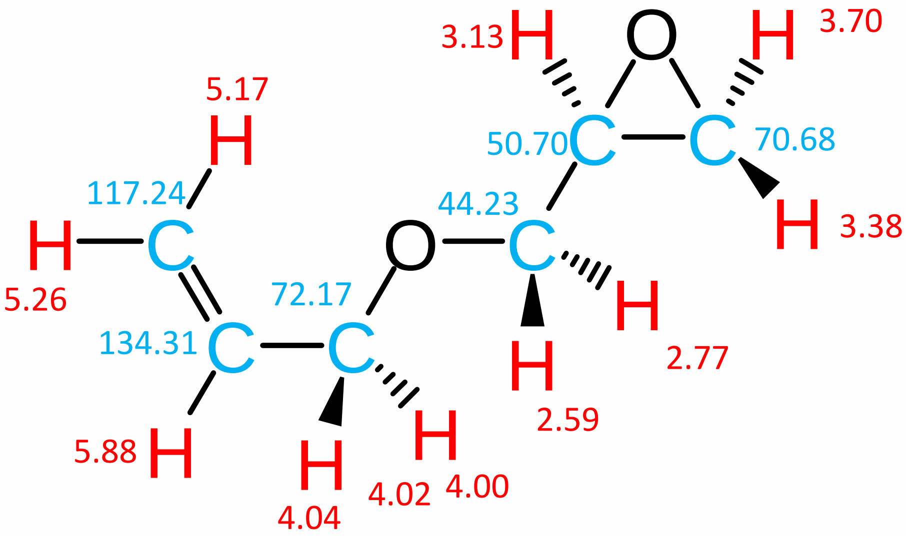


Let us start to analyze the B part first according to the *first order rules*.
Of course, we introduce some errors using this method.

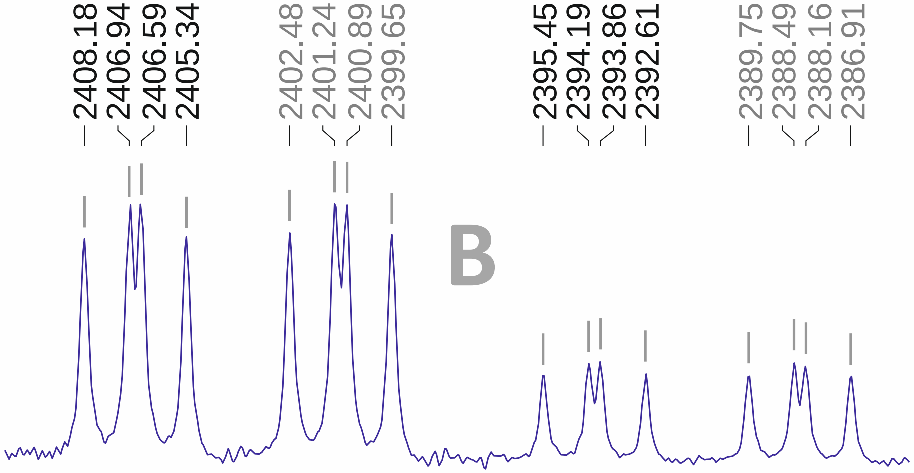
We can recalculate the chemical shifts of both geminal protons according to the *AB rules*, as soon as we know the coupling constant between both protons.



And finally, having all chemical shifts and coupling constants, we can calculate the whole spin system and estimate the error made by using the *first order rules*.

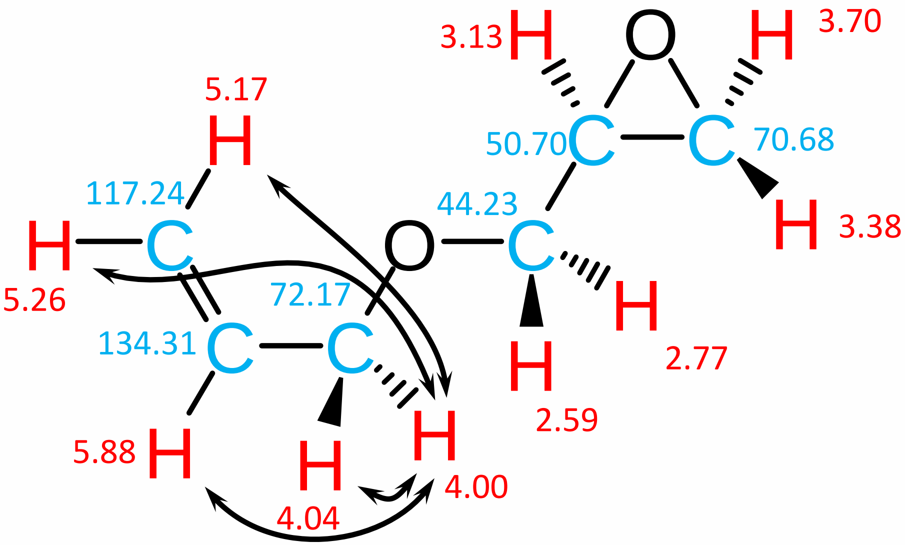


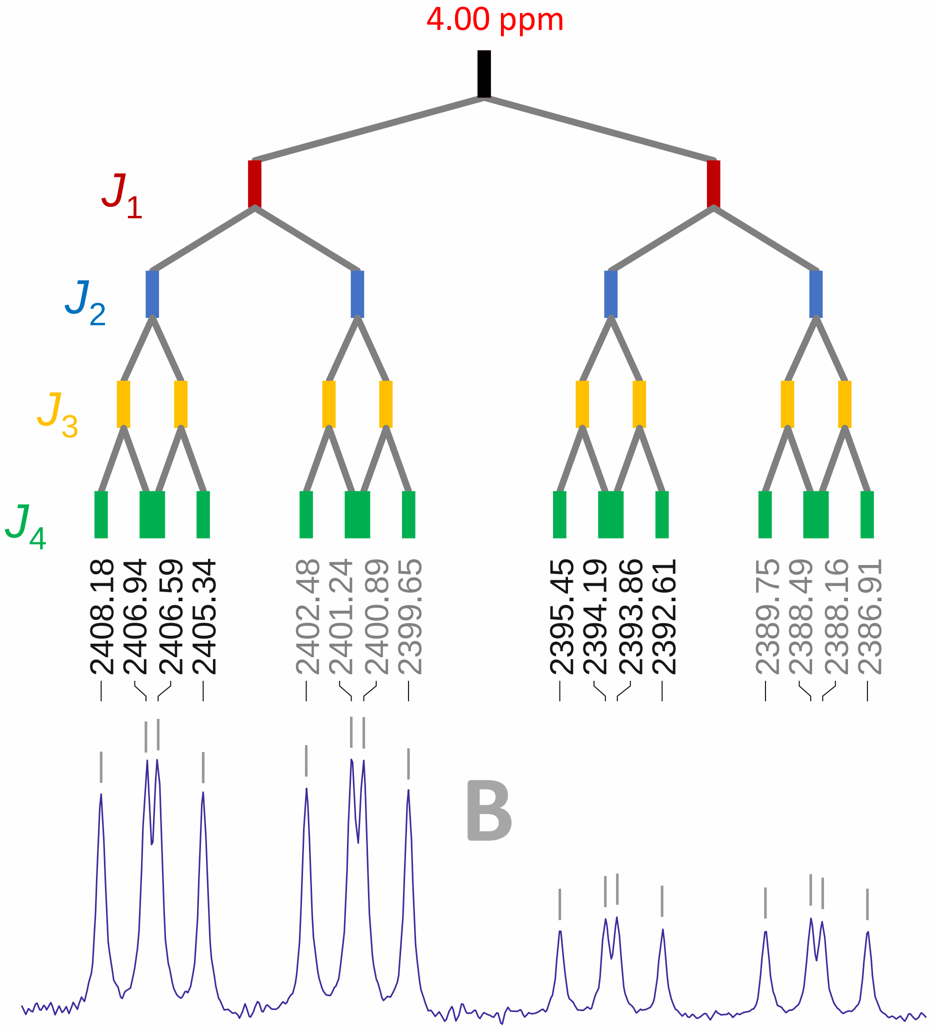
$$\left(\delta_B = \frac{(2408.18\ Hz + 2386.91\ Hz)}{2} \;/\; 600.13\ \text{MHz} \right)$$



The calculation of the chemical shifts for the AB protons according to *first order rules* gives 4.00 and 4.04 ppm respectively.

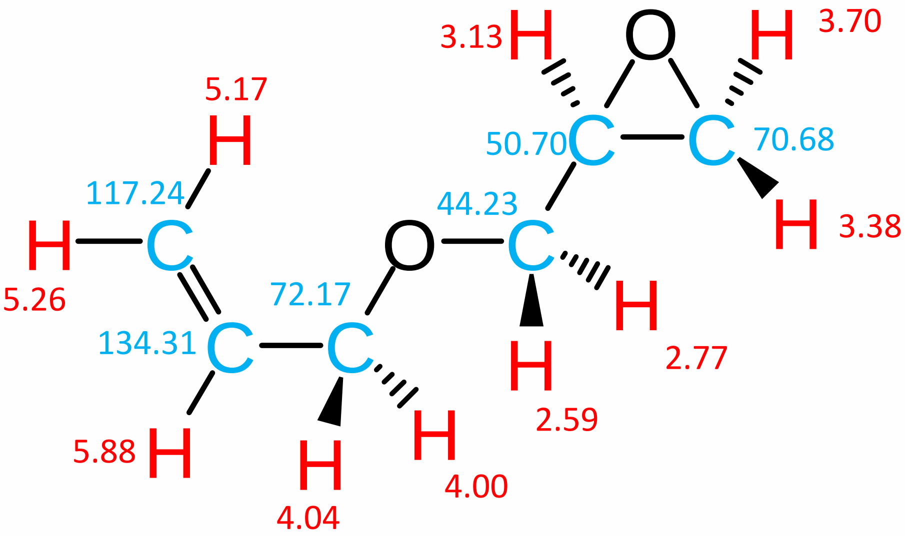
Remember: These values have to be recalculated, as soon as the coupling constant between these protons is known.





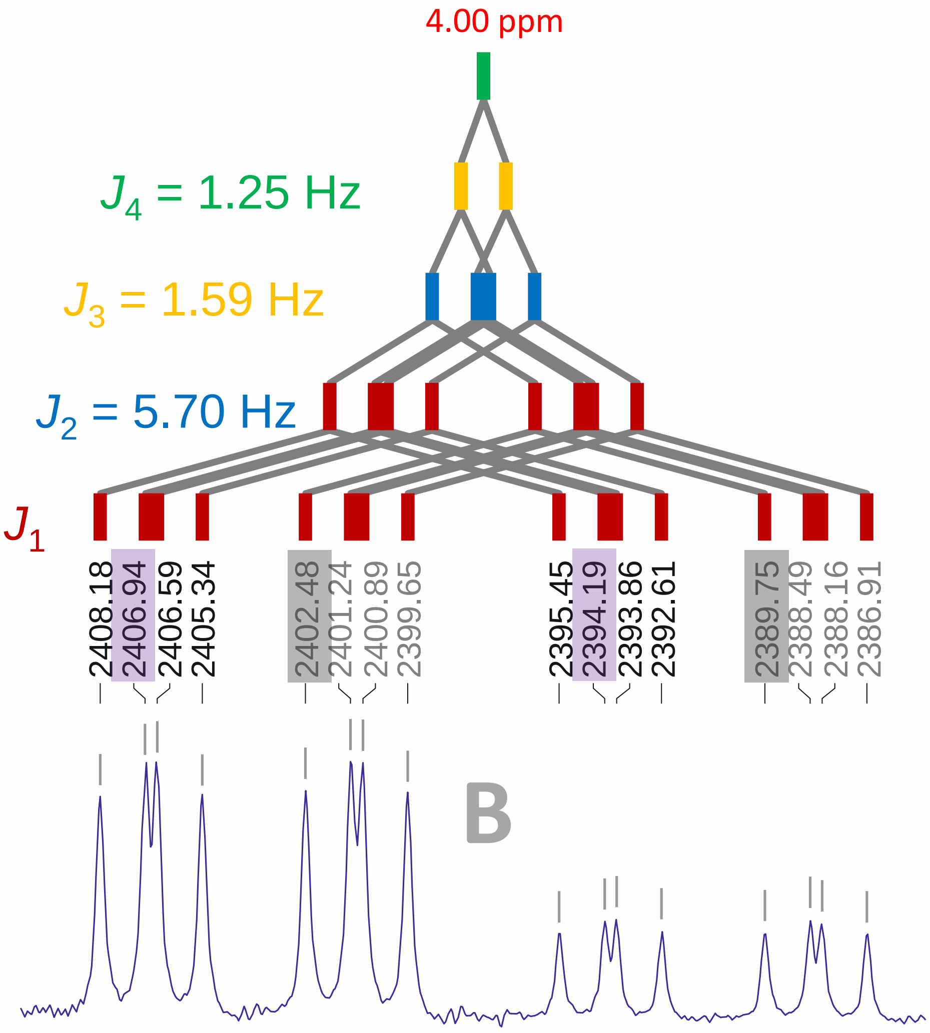
Multiplet **B** is a doublet of doublets of doublets of doublets.

The easiest way to start the analysis (as mentioned before according to *first order rules*) is to extract the smallest doublet coupling constant first.



For the largest coupling, the average over all 8 frequency differences this time is

$$J_1 = 12.74 \text{ Hz}$$

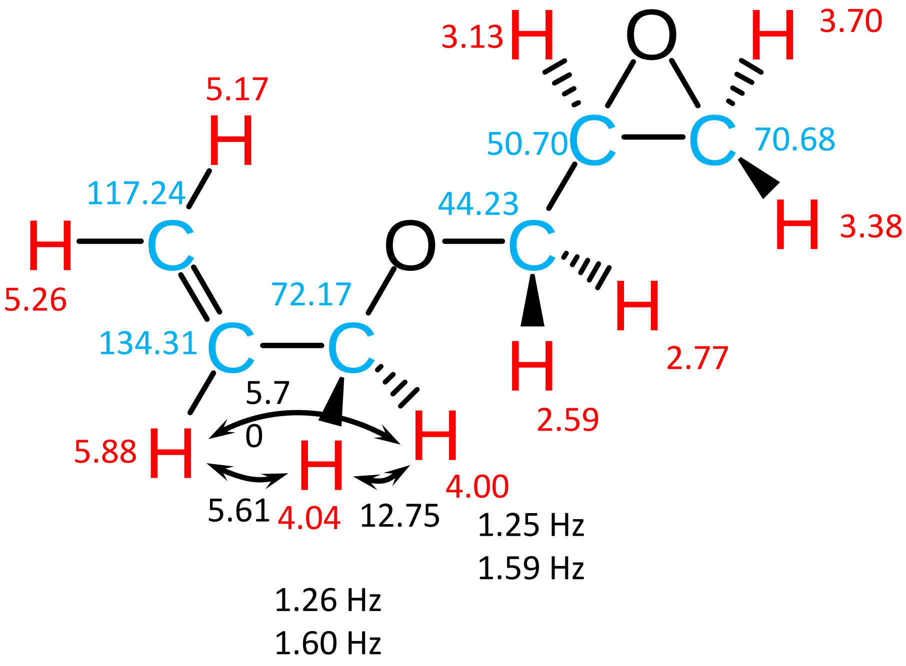


Of course, it is not necessary to draw the coupling tree again and again.

After some time, you should have found a simple rule. If all lines are well separated, which results in 2^n lines and you label all lines with consecutive integer numbers, then you always get a valid coupling constant if you select two lines and the difference of the indices of these two lines is a power of 2.

As an example, between the lines 3 and 11 you can measure a coupling constant, because $11 – 3$ is 2^3. Another valid coupling constant might be measured between the lines 3 and 4 ($4 – 3 = 2^0$), whereas measuring between the lines 6 and 3 returns nonsense.

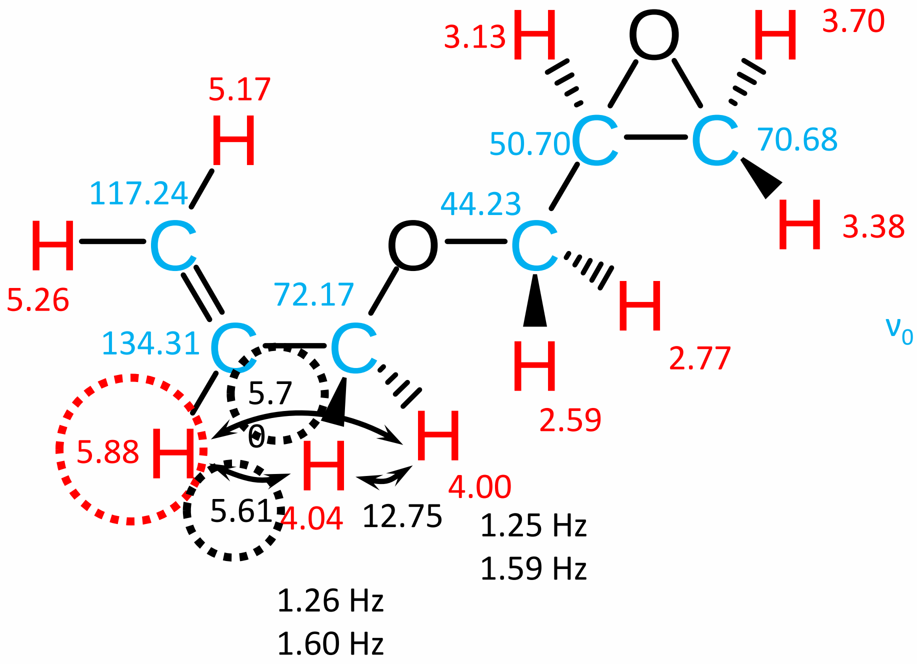
In the case of overlapping lines pattern recognition is a little bit more challenging.

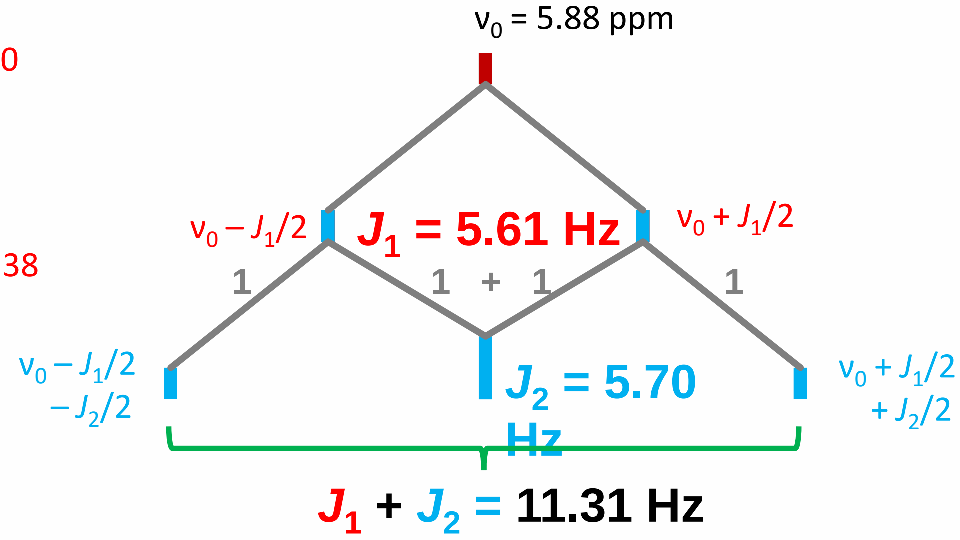


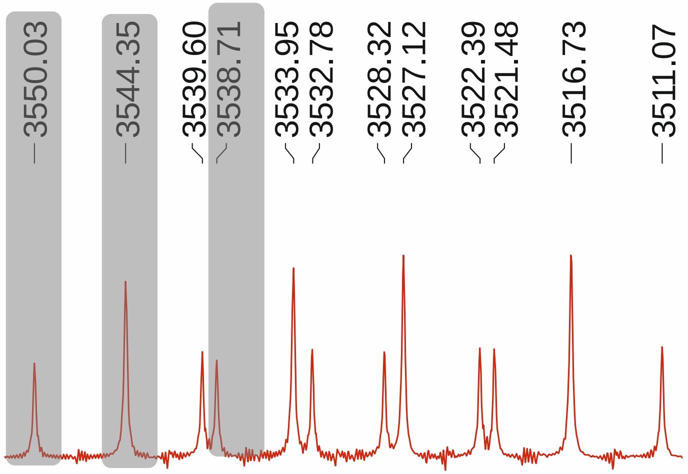
Repeating the whole procedure with the **A** part of the multiplet finally we end up with 8 coupling constants.

Some of them are easily to assign to be geminal or vicinal coupling constants.

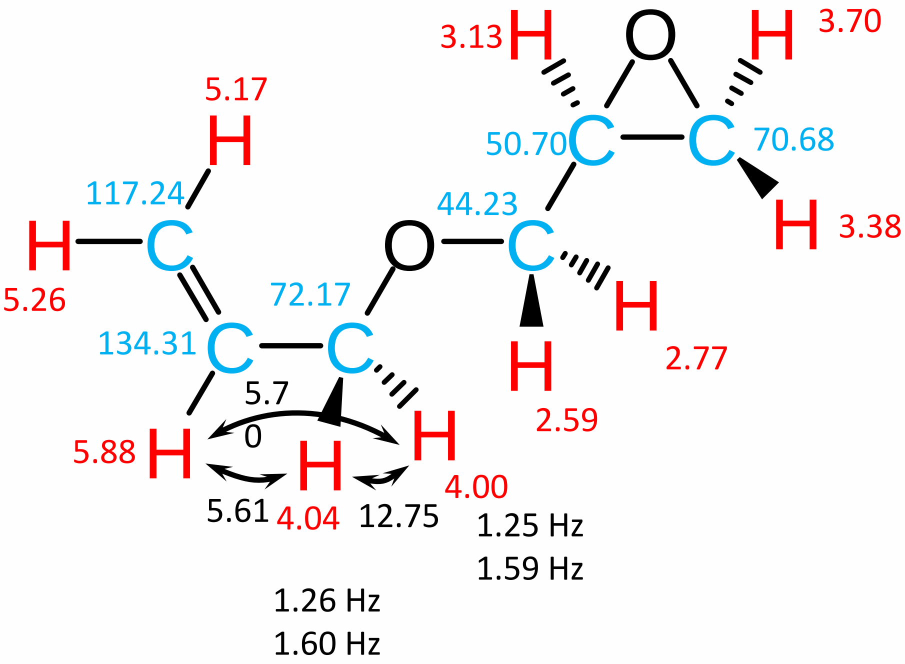
Some of the coupling constants remain unassigned for the moment. Of course this must be long range coupling constants to the olefinic protons at the end of the molecule.

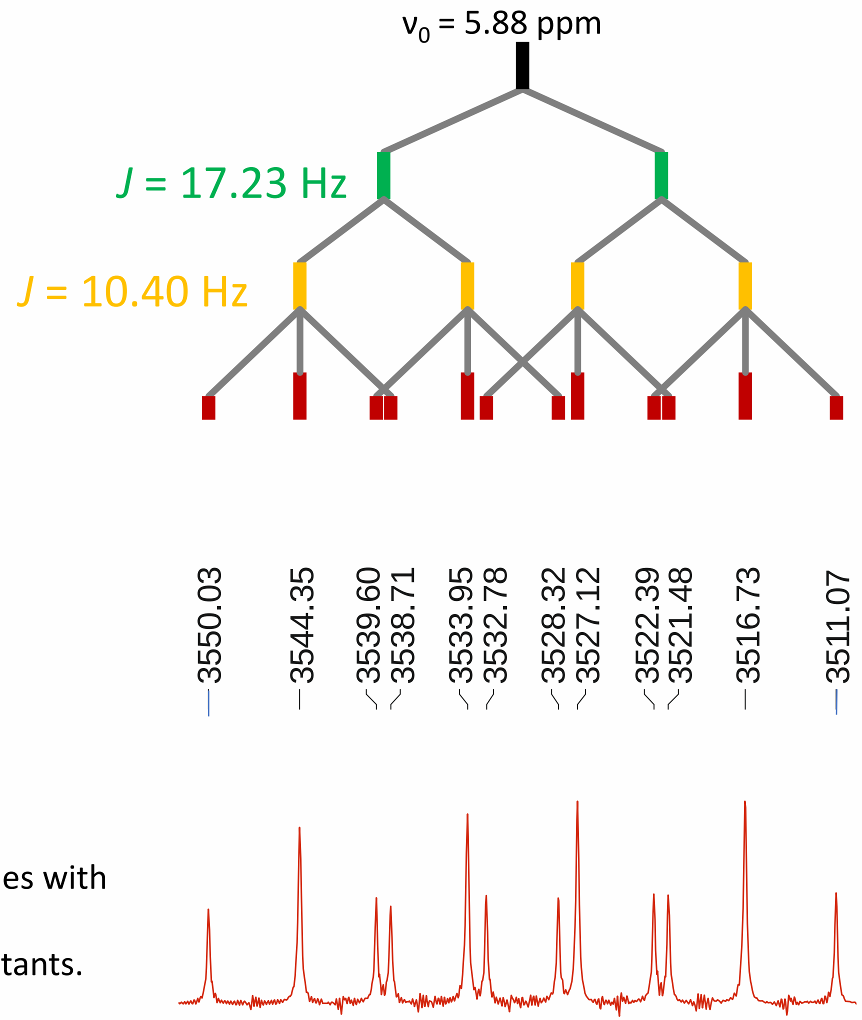






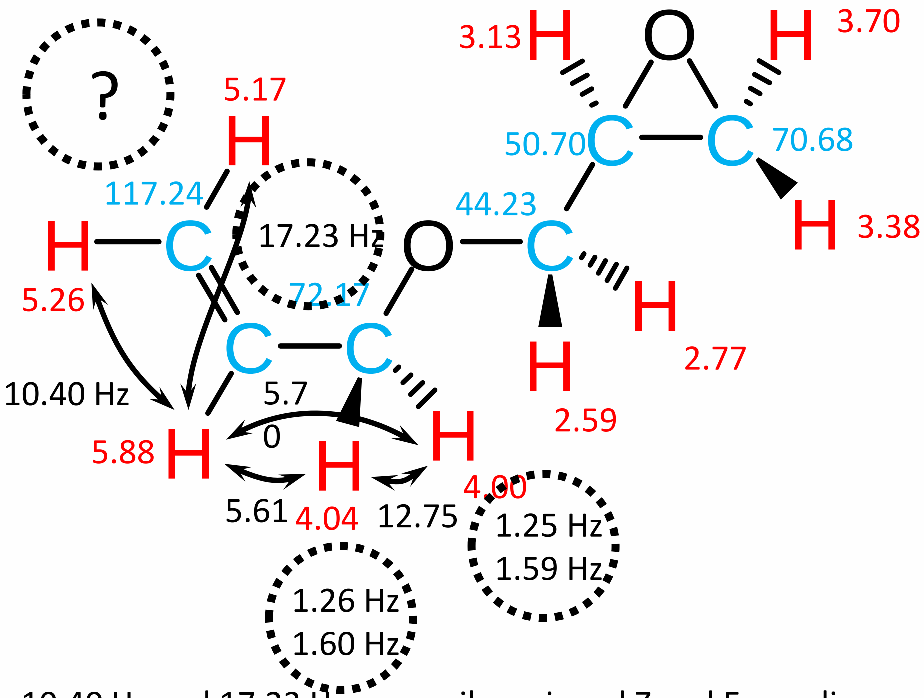
The multiplet of the olefinic methine proton with a chemical shift of 5.88 ppm seems to show a triplet substructure.
Of course this has to be a doublet of doublets with two very similar coupling constants. If we measure the sum of these coupling constants from the real multiplet, we get 11.32 Hz, which is very close to the expected value.

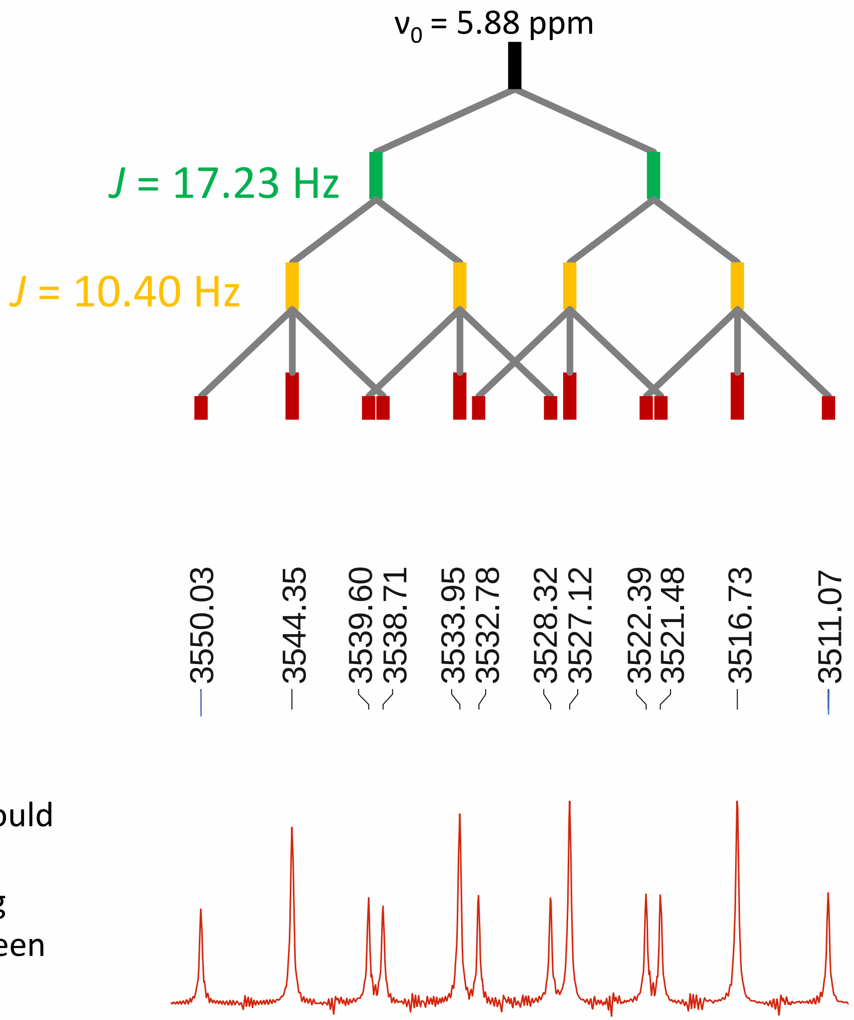




The pseudo triplet structure is visible within the multiplet four times.

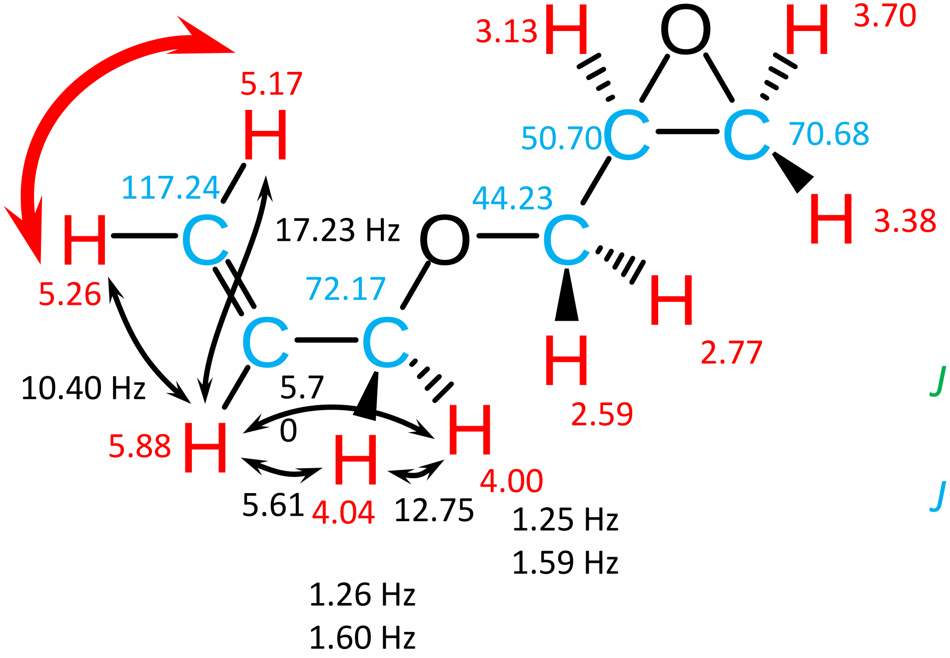
After collapsing the four pseudo triplets we end up with four lines with identical intensity, which are clearly a doublet of doublets.
From this doublet of doublets we can extract two coupling constants.

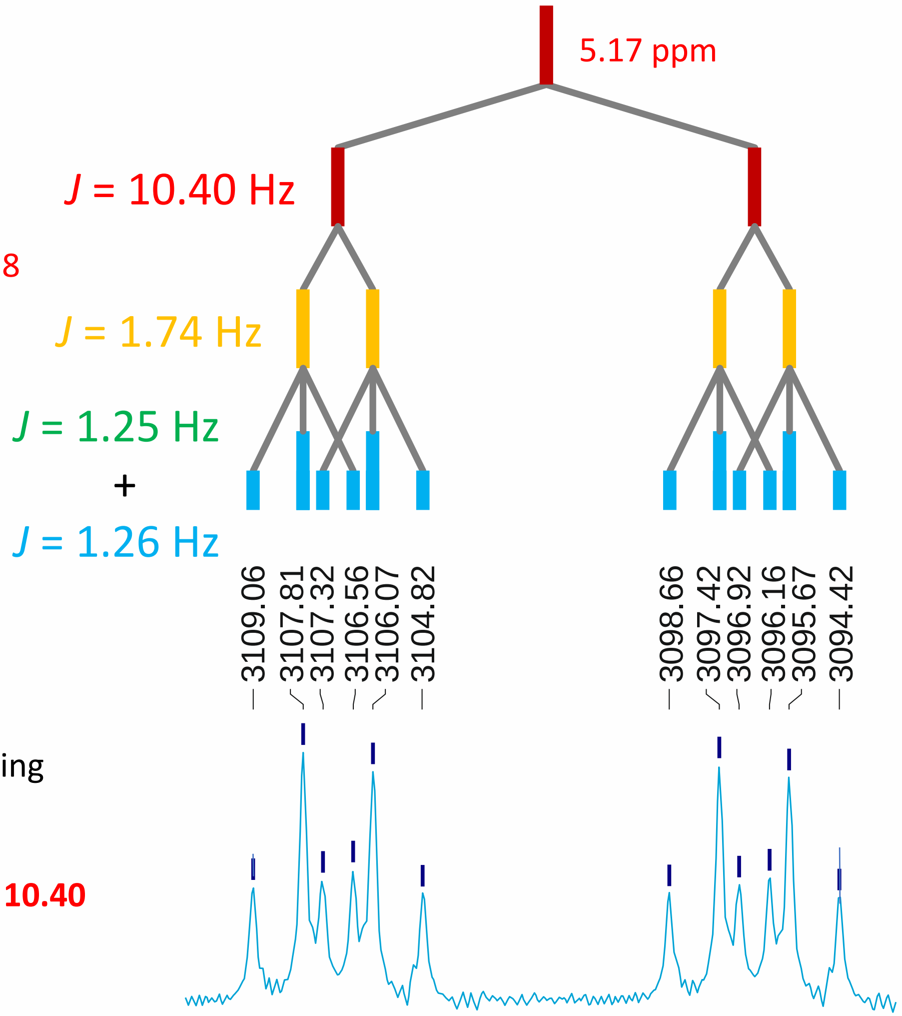




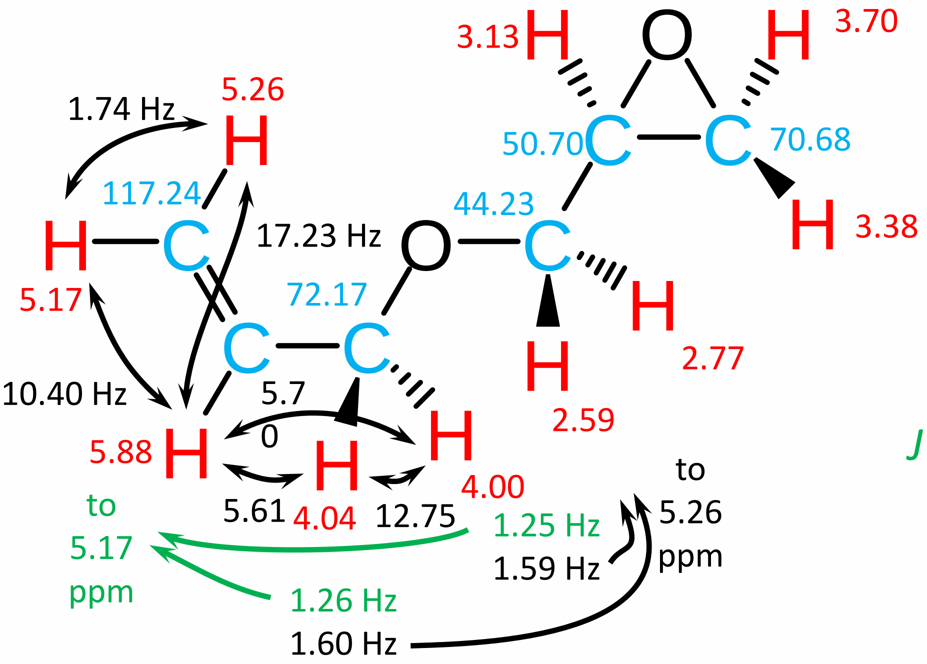
10.40 Hz and 17.23 Hz are easily assigned Z and E coupling constants.

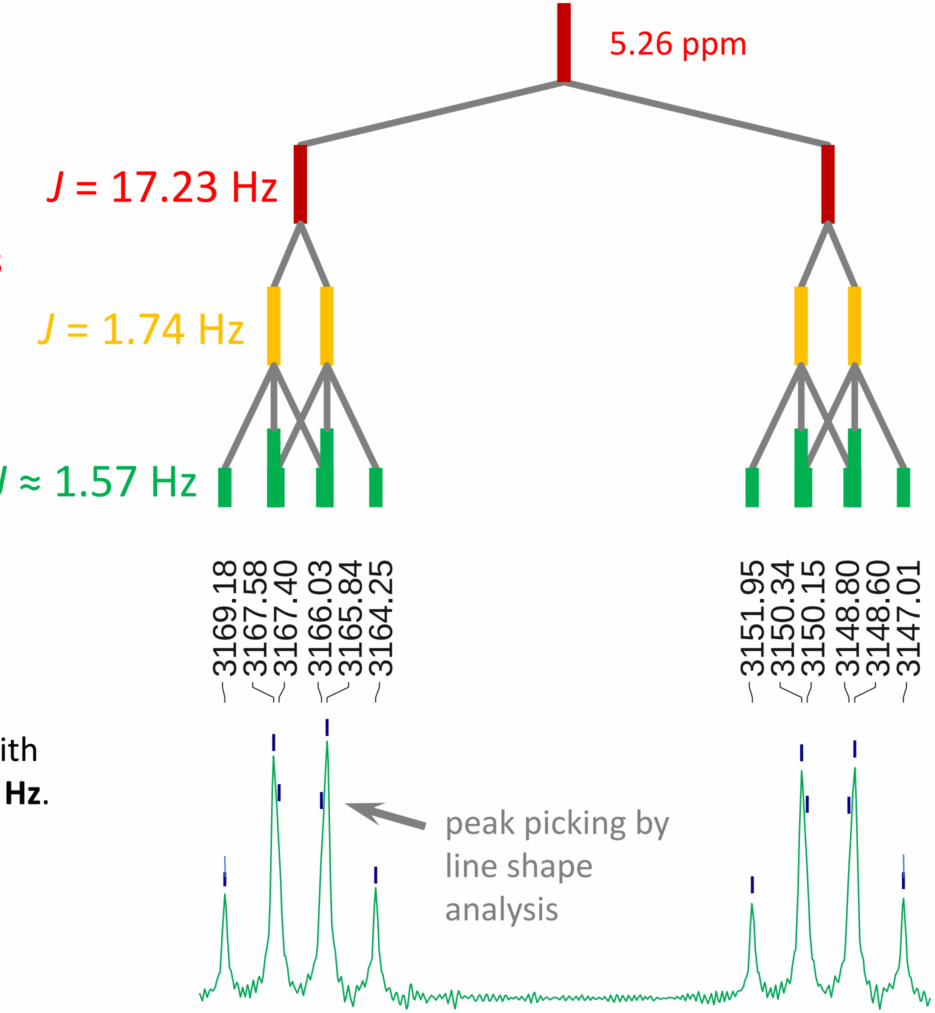
The multiplet of the proton with a chemical shift of 5.17 ppm should be a **dddd**, containing a geminal coupling constant (?) to the neighbour proton with a chemical shift of 5.26 ppm, the coupling constant of **17.23 Hz** and two long rang coupling constants between **1.25 Hz** and **1.60 Hz**. Let us check.





Analyzing the multiplet at 5.17 ppm we get the geminal coupling constant of **1.74 Hz**, the already known long-range coupling constants of **1,25 Hz** and **1.26 Hz** from the methylene group resulting in a pseudo triplet and finally a coupling constant of **10.40 Hz**, which clearly is a E coupling constant.
We have to reverse the assignment of two olefinic protons!

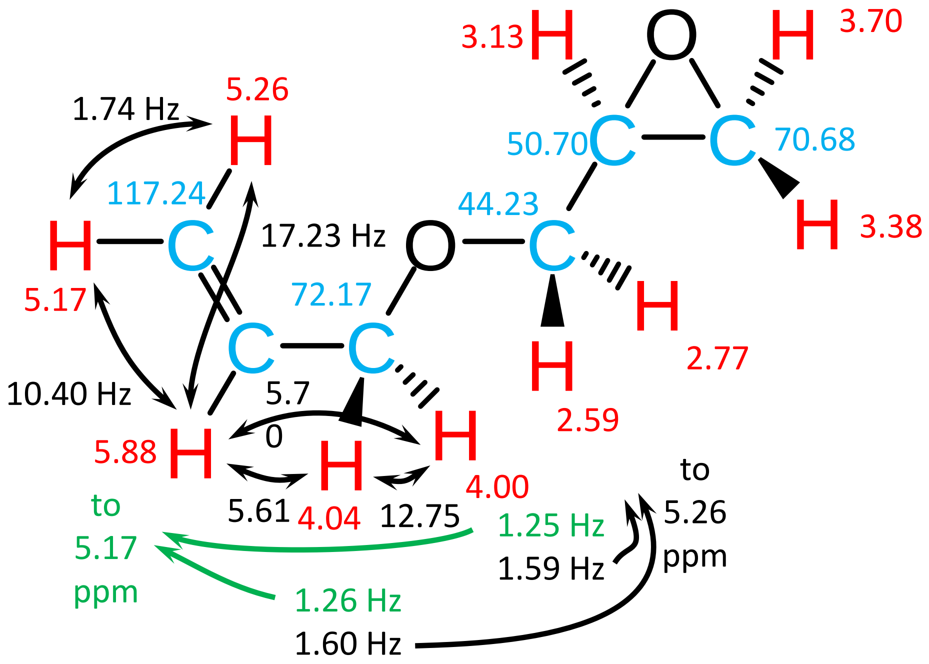




peak picking by line shape analysis

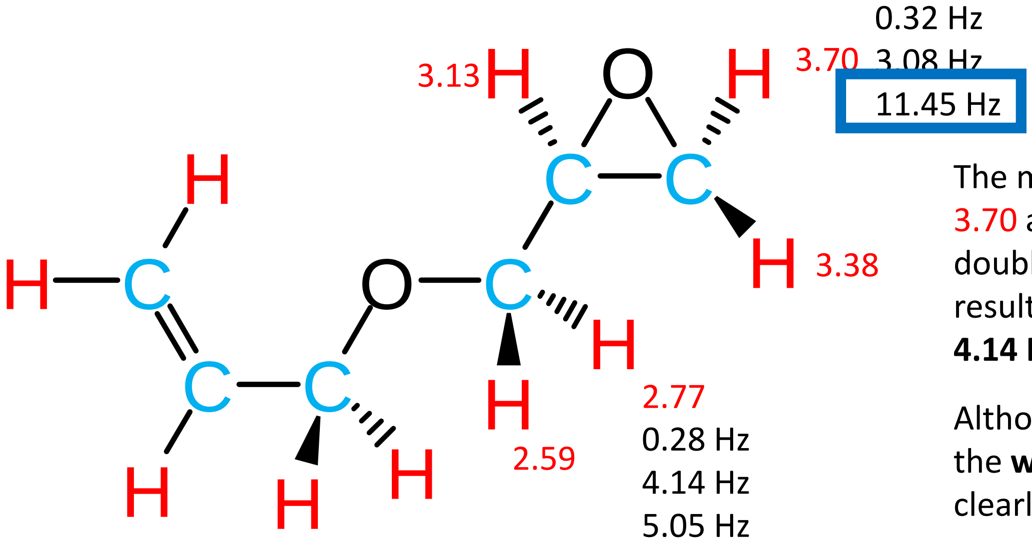
Finally, for the proton at 5.26 Hz we should observe a **dddd** with the coupling constants of **1.74 Hz**, **17.23 Hz**, **1.59 Hz** and **1.60 Hz**. Because of the nearly identical values of **1.59 Hz** and **1.60 Hz**, these couplings would appear as a pseudo triplet.

Let us try.



The allyl part of the ether is now fully analyzed.

For the sake of clarity, it is now useful to remove all pieces of information collected so far, except for the chemical shifts of the protons in the glycidyl part.



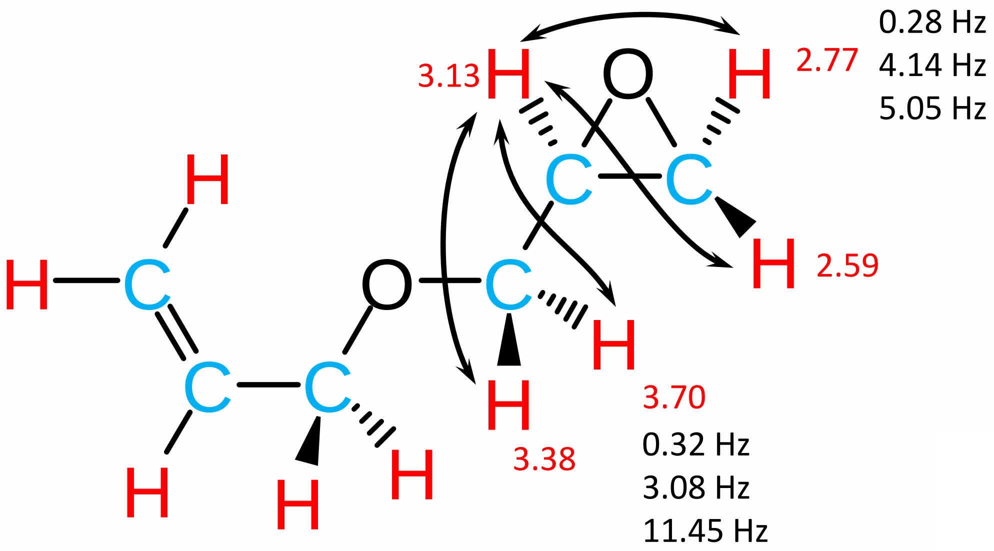
The multiplets of the protons with chemical shifts of 3.70 and 2.77 ppm, respectively, are cleary doublets of doublet of doublets. Extracting the coupling constants results in **0,32 Hz** / **3.08 Hz** / **11.45 Hz** and **0.28 Hz** / **4.14 Hz** / **5.05 Hz**, respectively.

Although the coupling partners are, as yet, unknown, the **wrong assignment of the methylene groups** is clearly visible.

The coupling constant between two geminal protons arranged at an almost ideal tetrahedral angle should be 10 ... 14 Hz. We expect near tetrahedral geometry for the methylene next to the linear ether linkage, but not for the methylene that is part of the epoxide ring (ring strain).

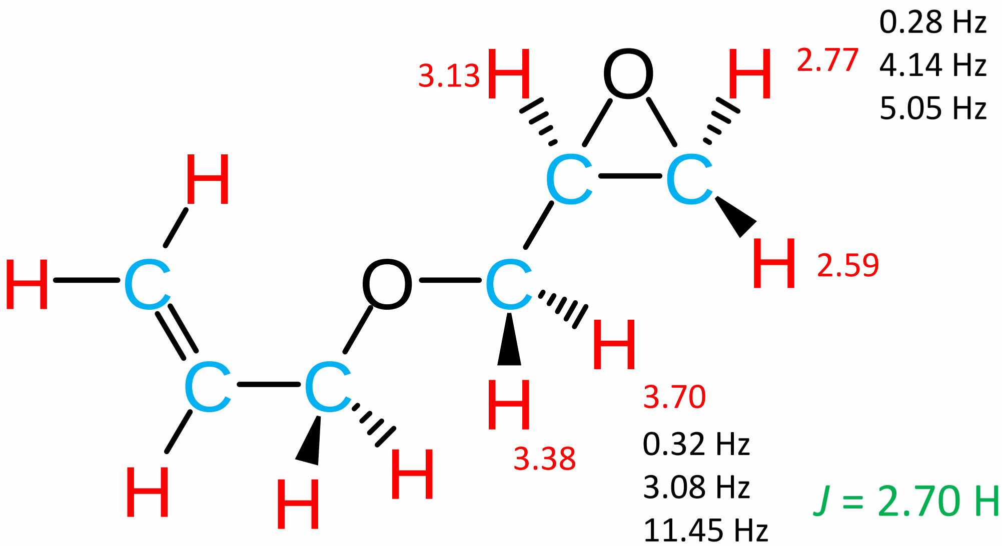
Such a coupling constant is part of the multiplet of the proton with the chemical shift of 3.70 ppm, but not of the multiplet seen at 2.77 ppm.

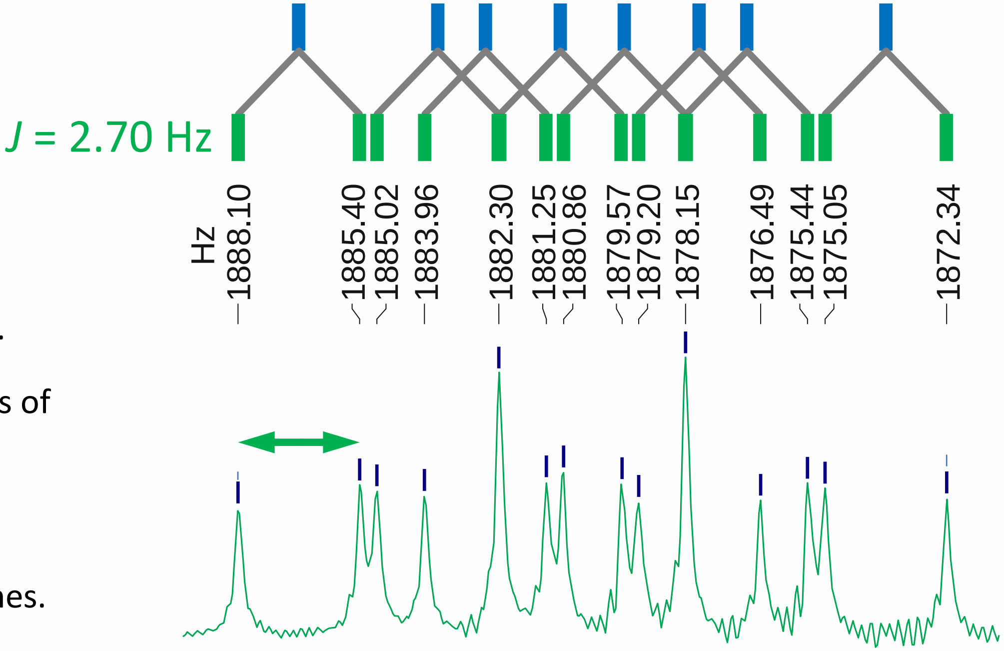
Let us reverse the assignment of both methylene groups (of course including the carbon signals not shown here).



The proton with the chemical shift of 3.13 ppm should appear as a **doublet of doublets of doublets of doublets**. The values of all four vicinal coupling constants should be of comparable size.
There are only 14 of 16 lines visibles. Two pairs of lines are superimposed by chance.

How do we extract all four coupling constants?



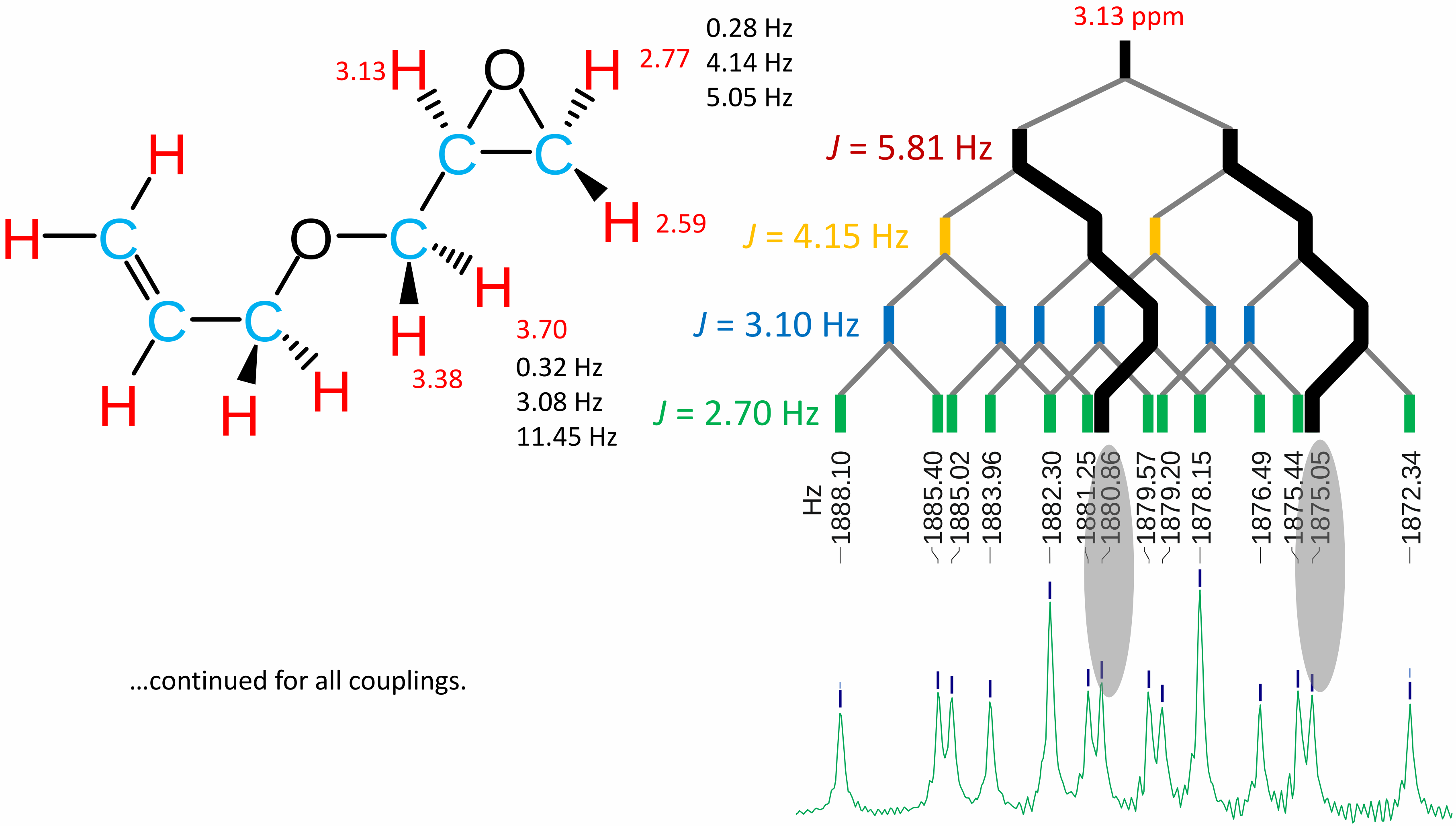


The first coupling constant of 2.70 Hz is easy to extract.

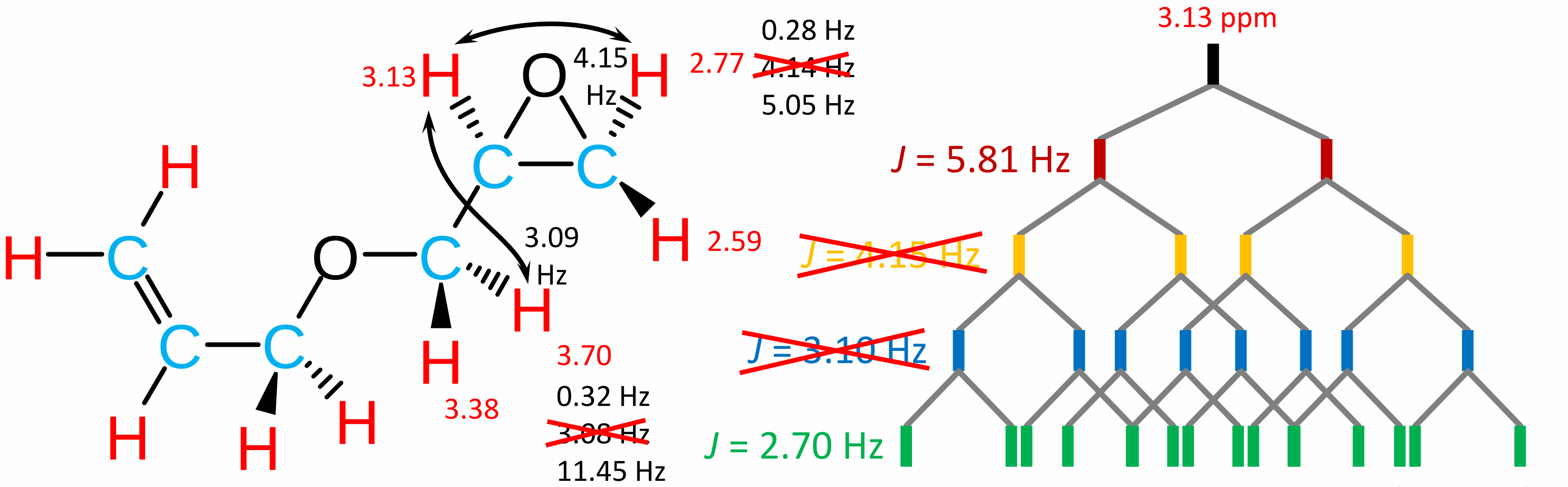
Now we have to look for alltogether seven further pairs of lines with a frequency difference of 2.70 Hz.

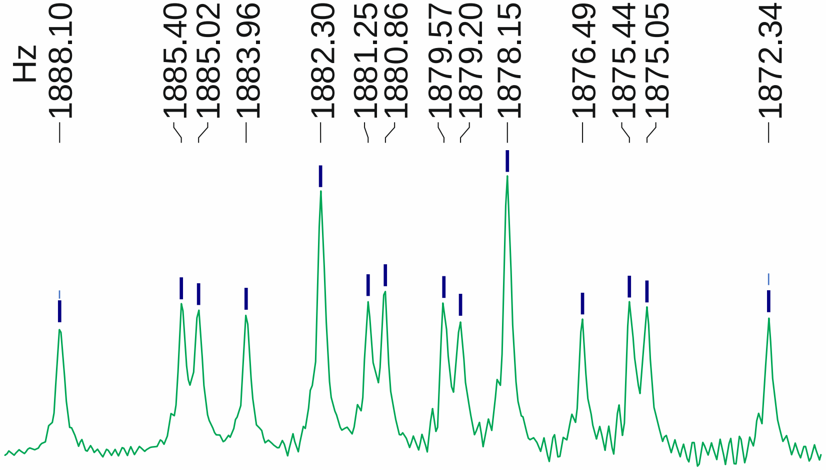
Let us do this boring job.

And we don‘t forget the multiplets with overlapping lines.



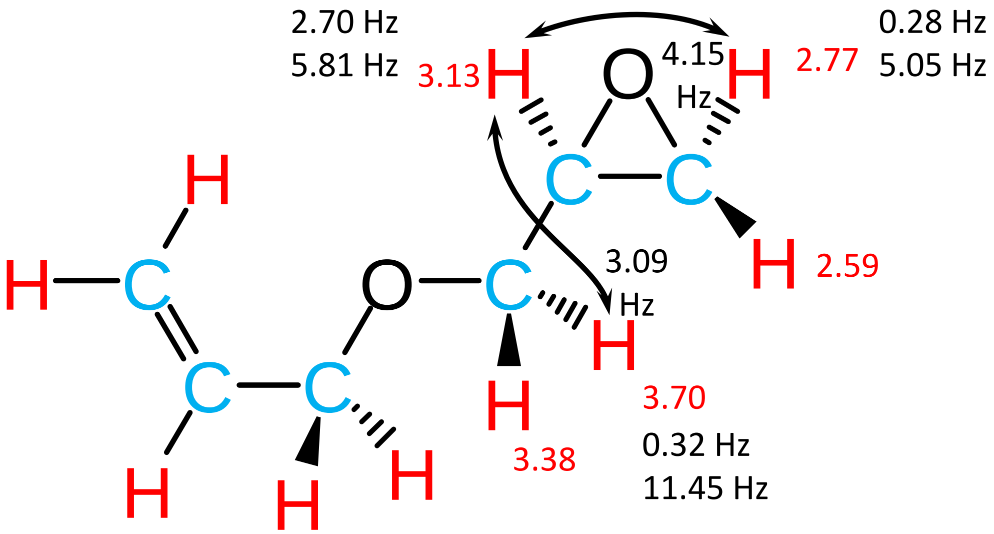
…continued for all couplings.



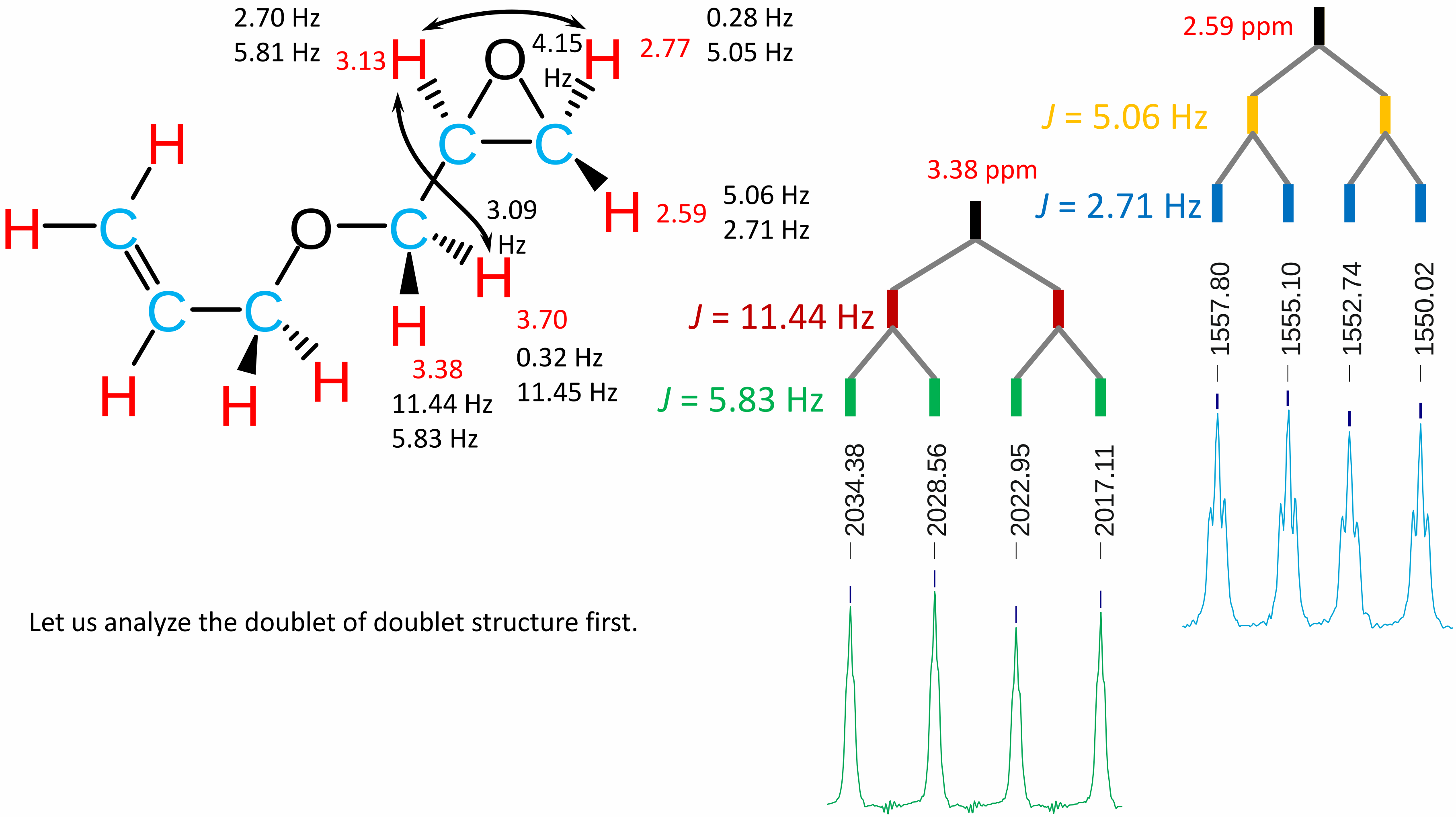


Now we can assign two coupling constants unambiguously.

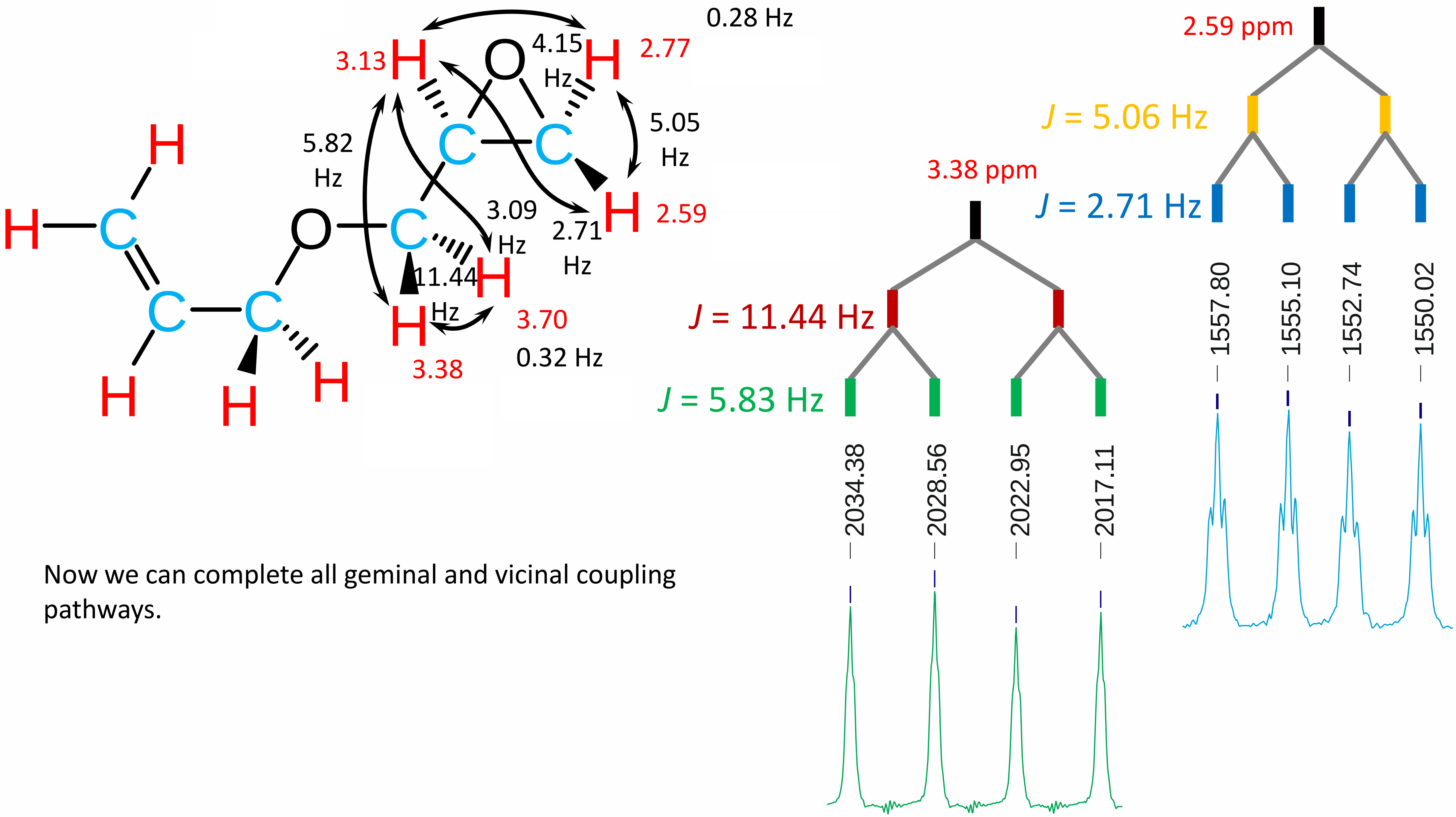
The couplings constants of 2.70 Hz and 5.81 Hz remain unassigned so far.



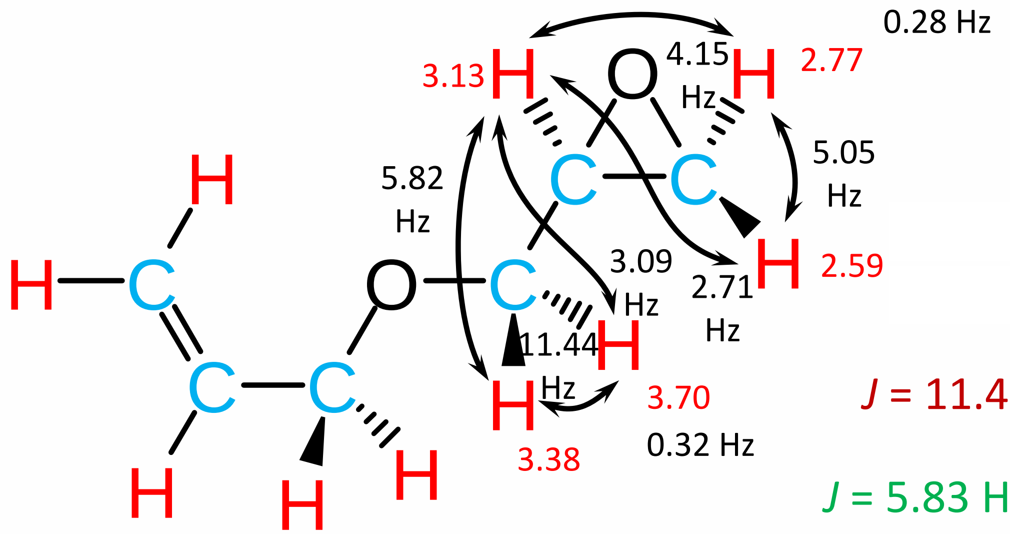
The multiplets of the protons with the chemical shifts of 3.38 ppm and 2.77 ppm, respectively, look like doublets of doublets with some additional fine splitting.

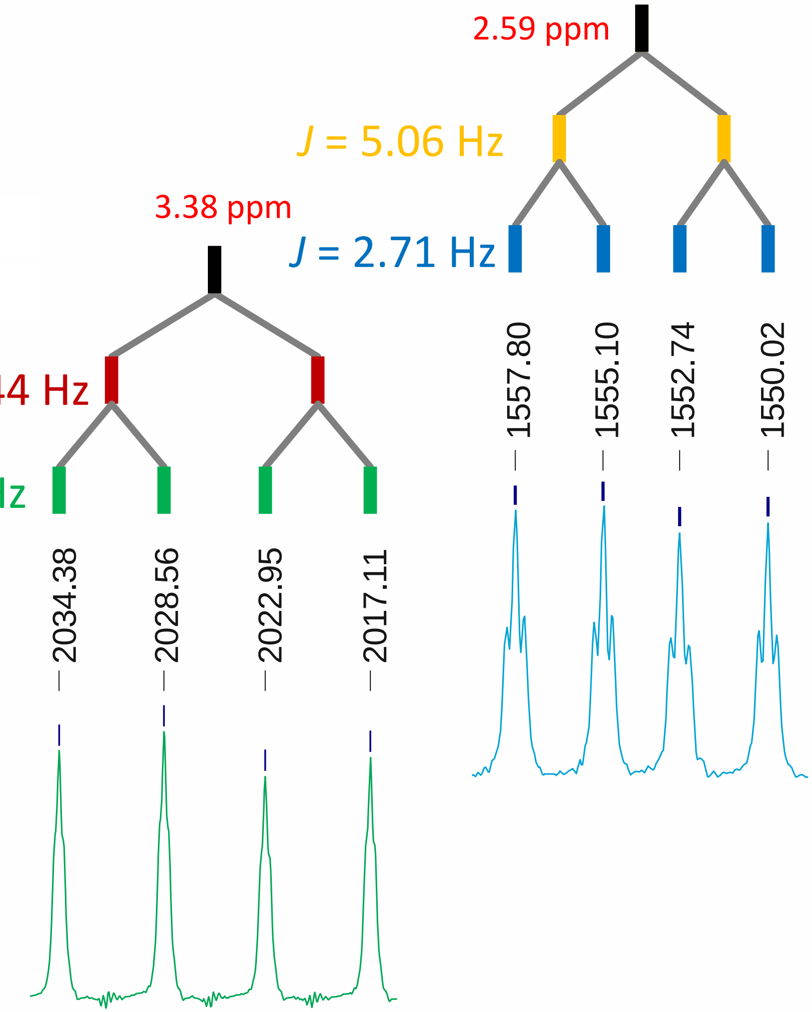


Let us analyze the doublet of doublet structure first.



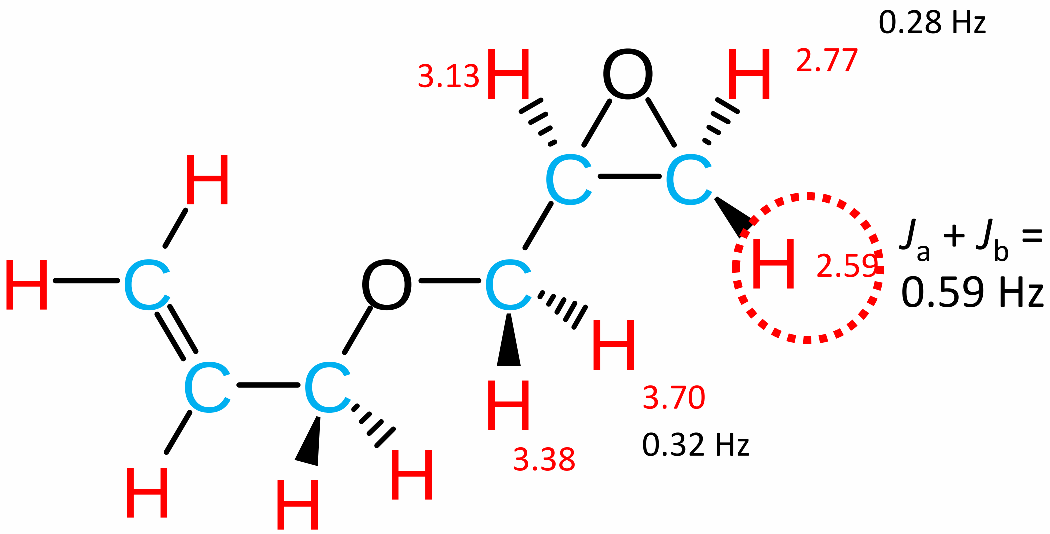
Now we can complete all geminal and vicinal coupling pathways.





Analyzing the fine splitting of these both multiplett will allow the analysis of the four bond coupling constants. We already found two such coupling constants but don‘t know the coupling pathway so far.

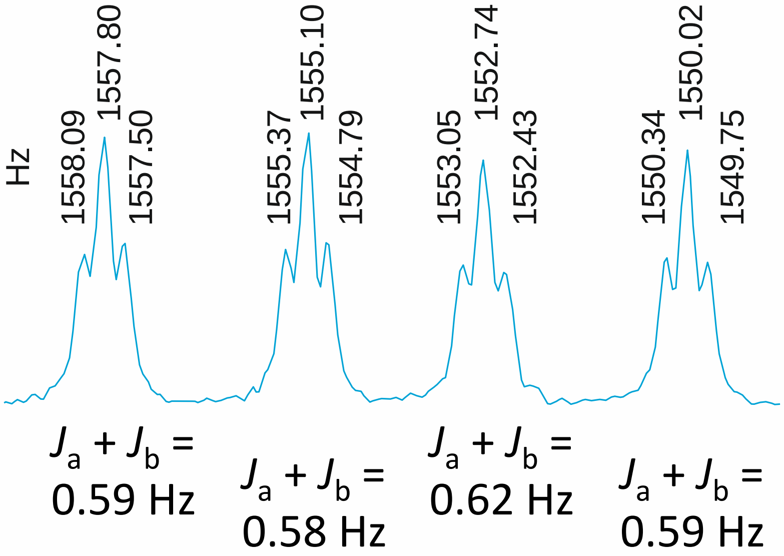
For clarity let us delete all geminal and vicinal coupling pathways deduced so far.

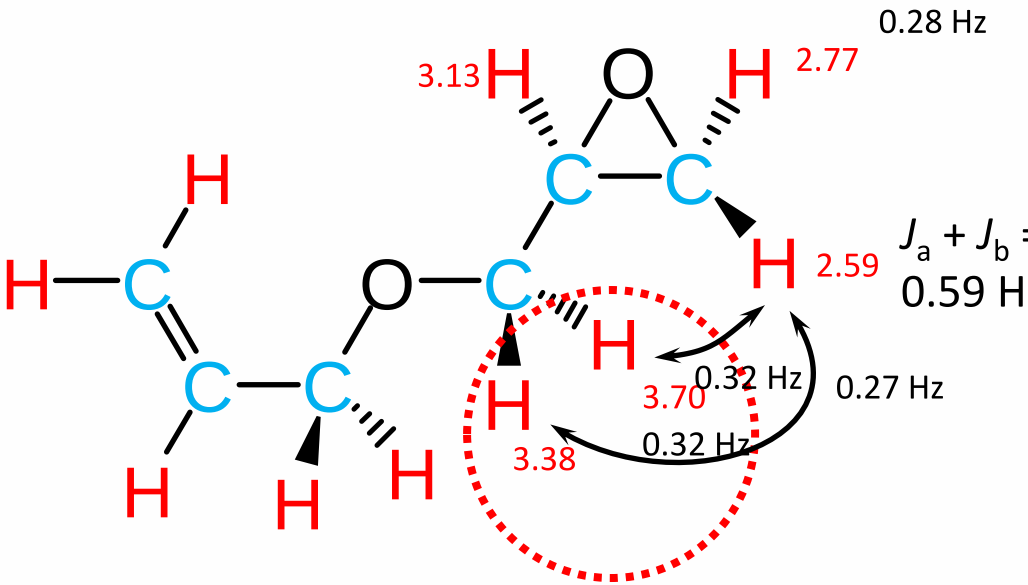


Let us visit the multiplet at 2.59 ppm first. The fine structure seems to be a triplet, but due to the lack of two equivalent protons anywhere in the molecule, this has to be a doublet of doublets.

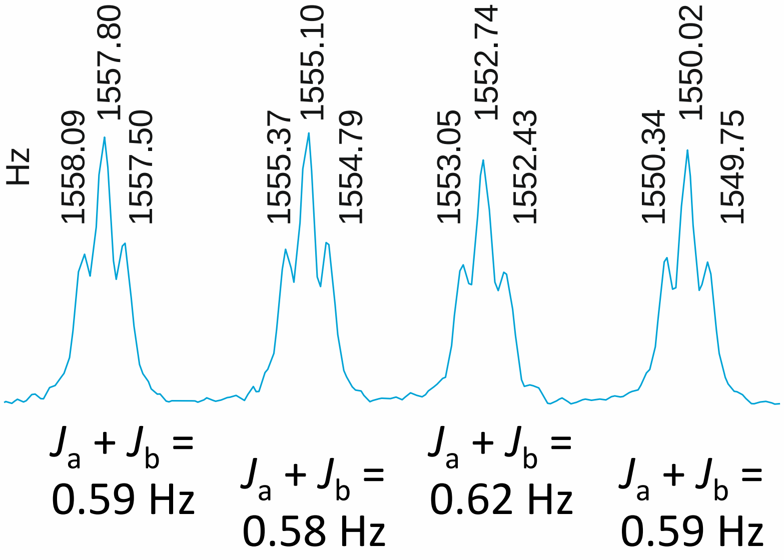
We are not able to get the coupling constants of both doublets separately, but we can measure the sum of both doublet coupling constants.

2.59 ppm





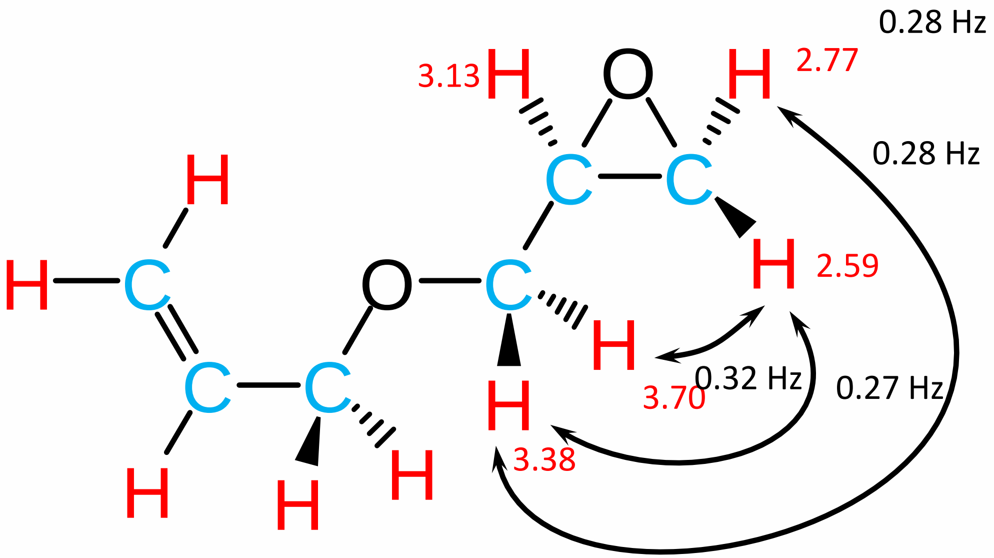
2.59 ppm



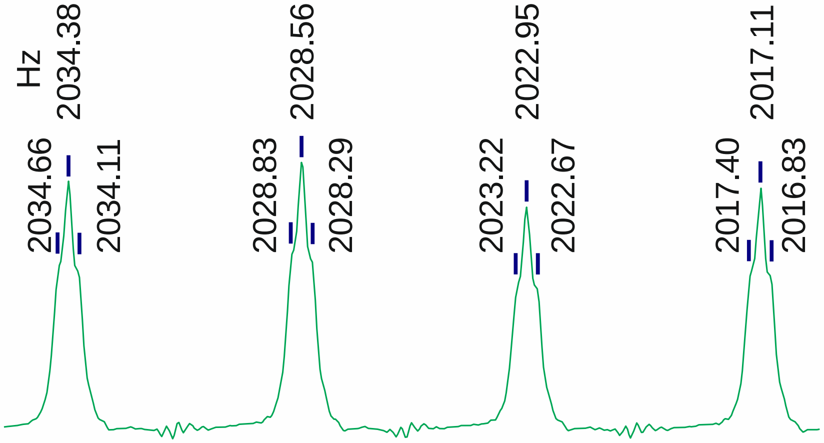
There are two protons four bonds away.

One coupling constant (0.32 Hz) is already known from the analysis of another multiplet earlier done.

As a result the second doublet coupling constant is 0.27 Hz.

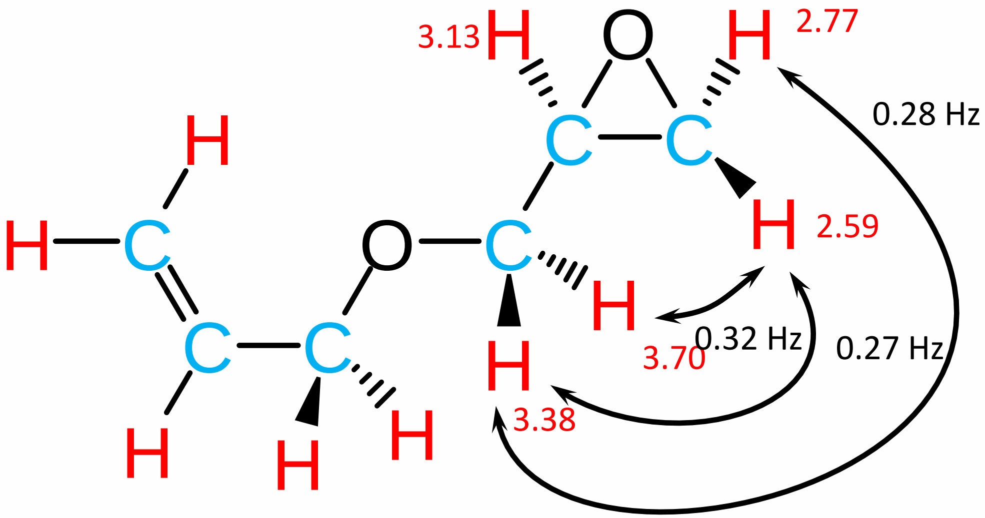


3.38 ppm

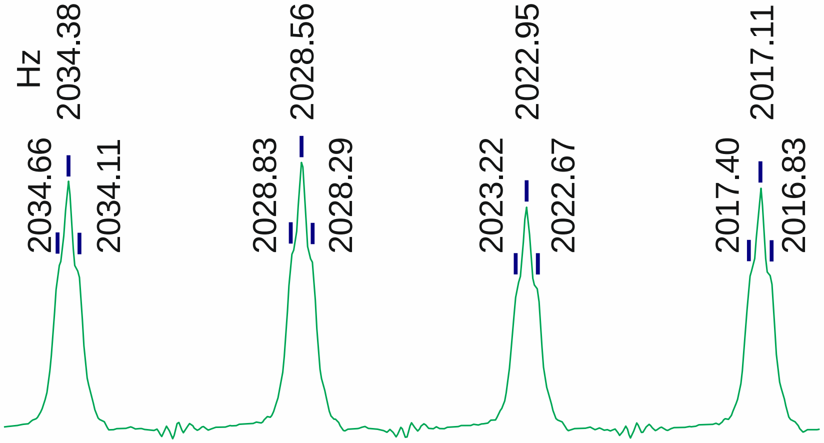


Let us try a prediction.
One coupling constant is unassigned so far (0.28 Hz) and only one proton multiplet (3.38 ppm) not analyzed in detail so far.

The coupling constant of 0.28 Hz has to be part of the fine structure inside the multiplet structure of the proton at 3.38 ppm. There is no other choice.



3.38 ppm



$J_a + J_b =$ 0.55 Hz

$J_a + J_b =$ 0.54 Hz

$J_a + J_b =$ 0.55 Hz

$J_a + J_b =$ 0.57 Hz

The fine structure of the multiplet once again is a pseutriplett and in fact a doublet of doublets. The sum of both doublet coupling constants should be 0.55 Hz(0.27 Hz + 0.28 Hz)

Let us try …

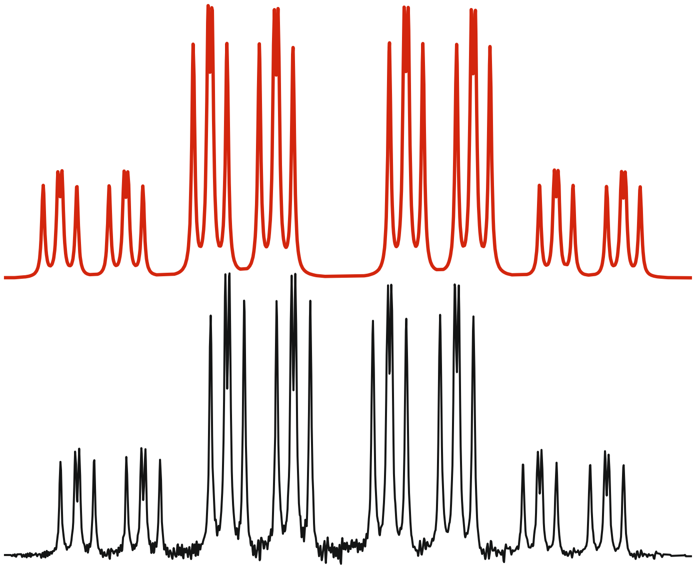
Everything finished now?

Almost.

We had determined the chemical shifts of the methylene group protons as part of the allyl group according to first order rules.

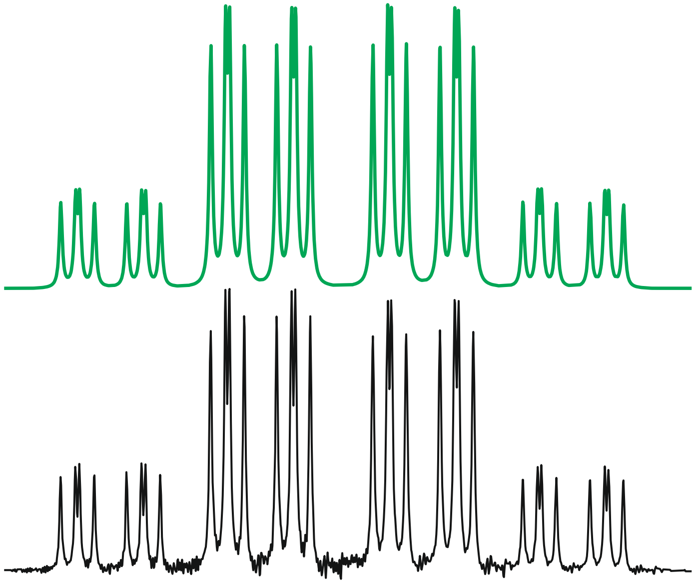
How erroneous are the values determined in this way?

Using first order rules we get two chemical shifts of 4.0393 ppm and 3.9951 ppm, respectively. Four digits are necessary here as you will see.
The result – only one multiplet of the whole spectrum is shown here – is good, but not perfect.



Experimental proton multiplet at about 4 ppm

If we take the analytical solution for an AB system (see nearly any textbook) to calculate the chemical shifts of 4.0366 ppm and 3.9978 ppm, respectively, we get perfect coincidence between measurement and simulation.
Please note the very small differences between first order and AB calculation.



Experimental proton multiplet at about 4 ppm

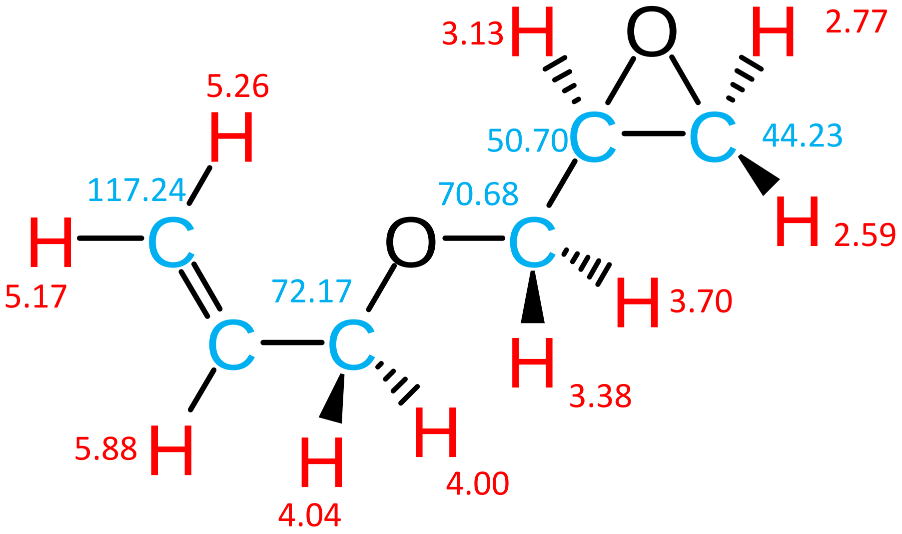
Summary

To summarize all pieces of information extracted from the NMR spectra of this molecule in one slide doesn‘t seem to be a good idea.

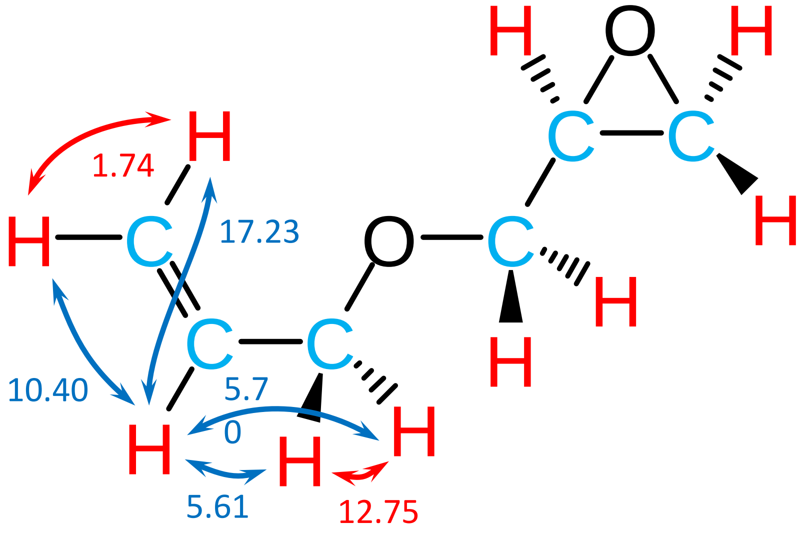
Even the distribution of all values over 5 slides results in a “just about acceptable” information density.

All chemical shifts [ppm]

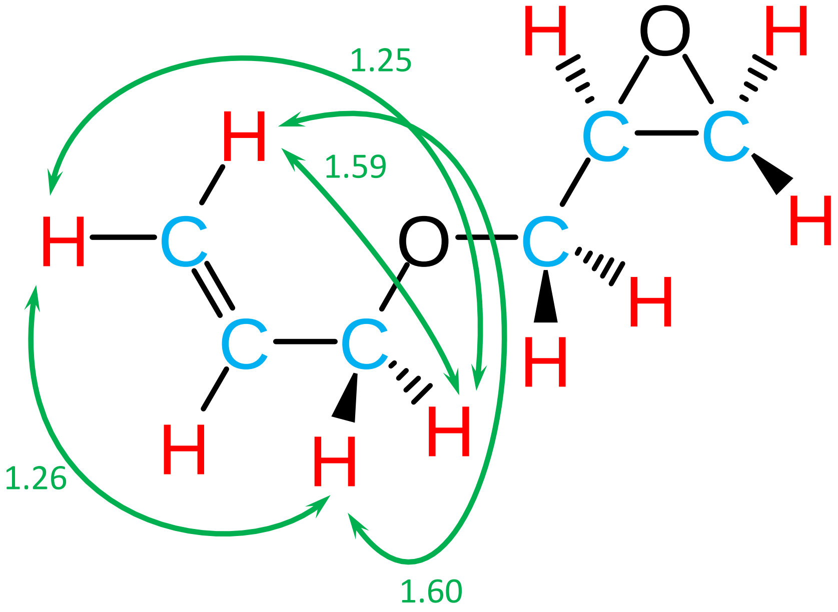
(The assignment of the methylene proton chemical shifts might be reversed in each case)



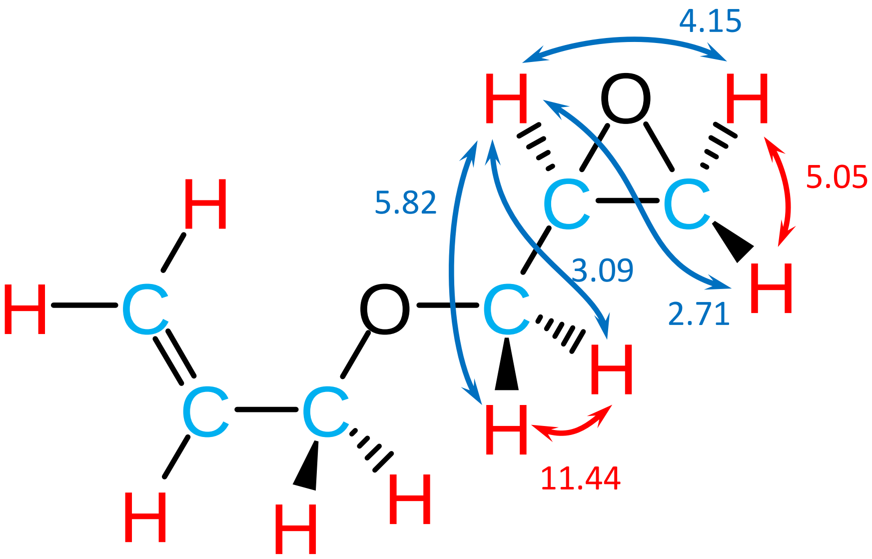
Geminal and vicinal coupling constants in the allylic part of the molecule [Hz]



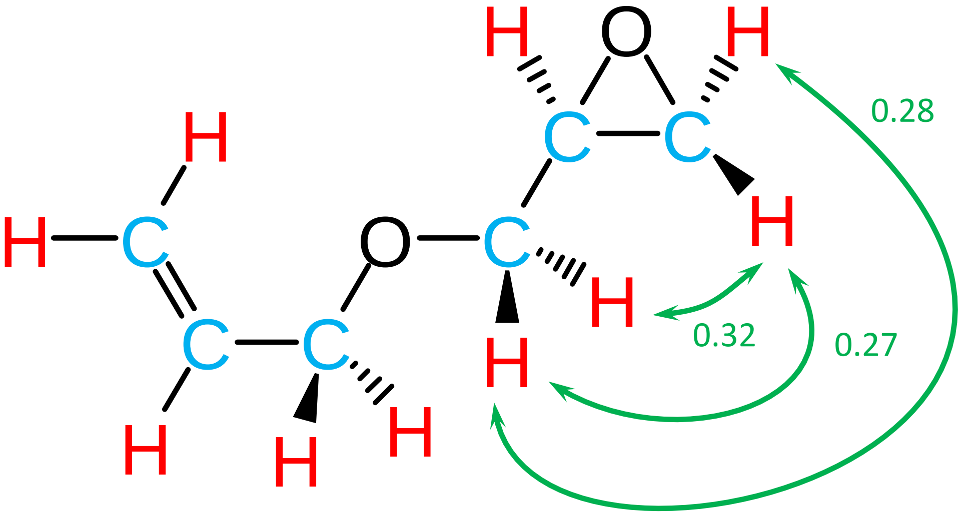
Four bond coupling constants in the allylic part of the molecule [Hz]



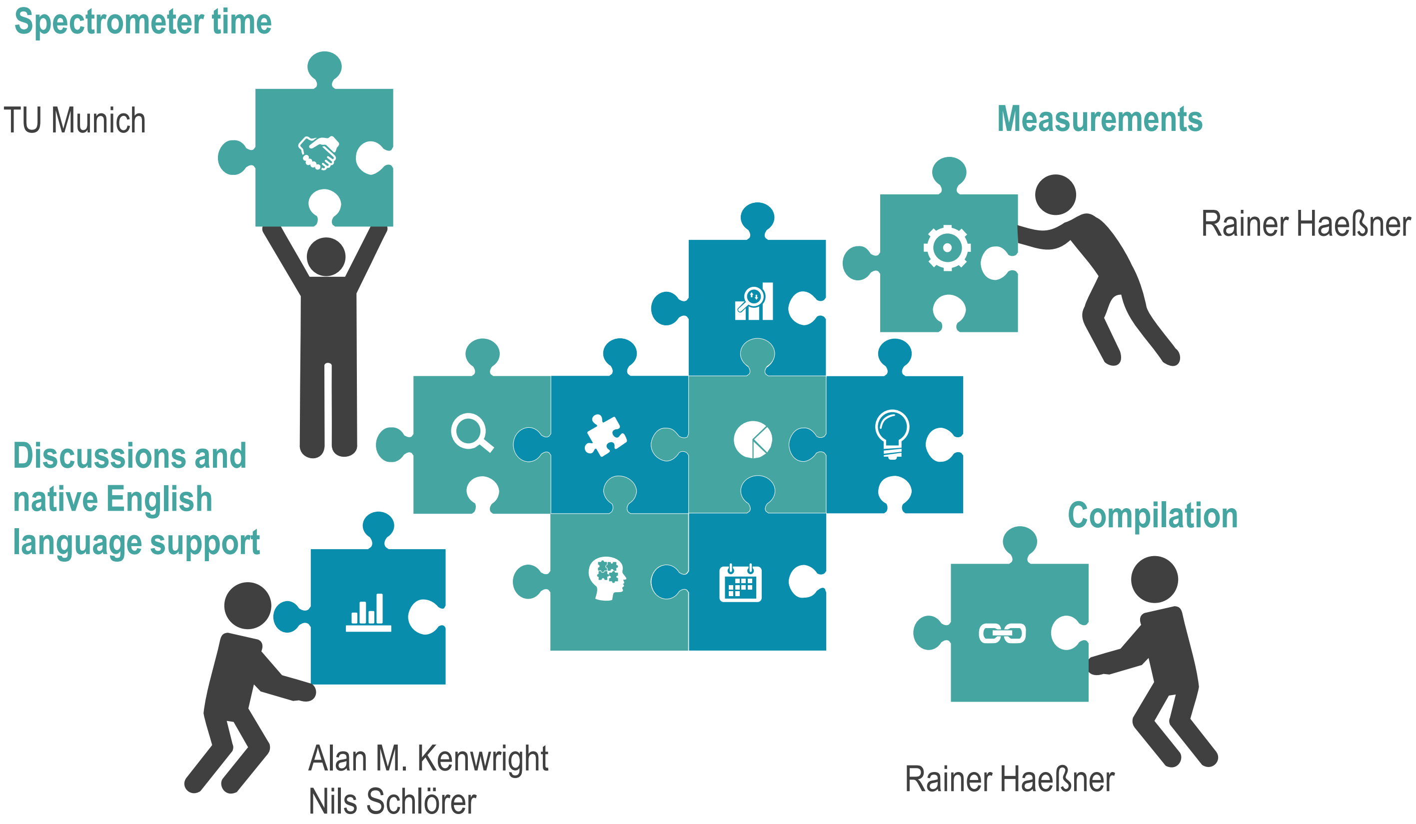
Geminal and vicinal coupling constants in the epoxy part of the molecule [Hz]



Four bond coupling constants in the epoxy part of the molecule [Hz]



Contributions



Spectrometer time

TU Munich

Measurements

Rainer Haeßner

Discussions and native English language support

Alan M. Kenwright
Nils Schlörer

Compilation

Rainer Haeßner