

Telescoped Reaction: Insights into the mechanism of step A using NMR

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**working with I. Clegg¹, C.M. Gordon², F. Susanne², D. Smith³ and
acknowledgements to several other colleagues**

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Where did the work take place ?



Once upon a time in 2007 ...

Objectives:

- Reaction Mechanism
- Kinetic Modelling
- Reaction Optimisation and Scale up

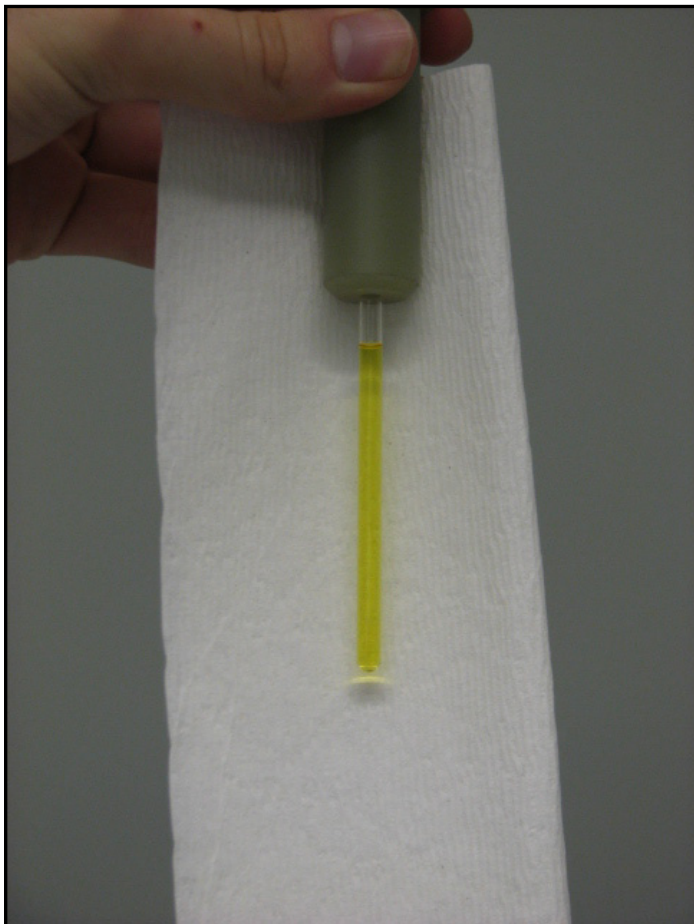


Questions:

- Why does the reaction stall?
- Mass balance, are we detecting all major products?
- Reactive species?

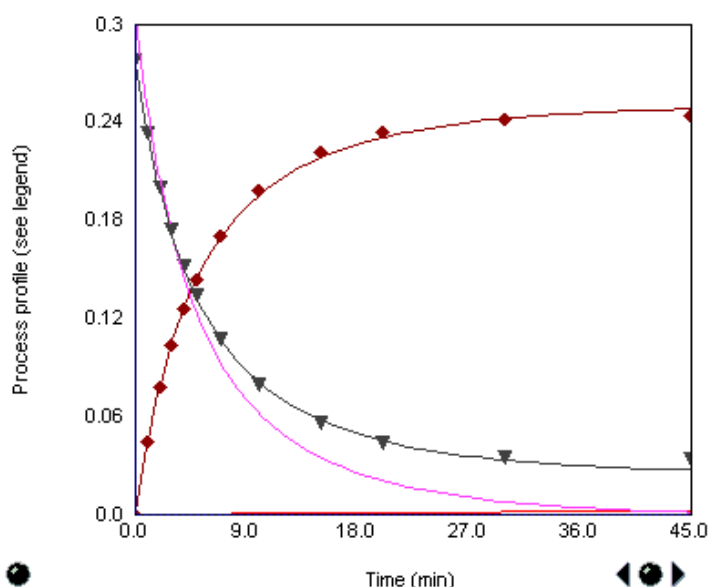
NMR?

Tube NMR



Reaction Optimisation and Scale Up

Yield and cost



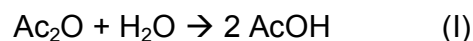
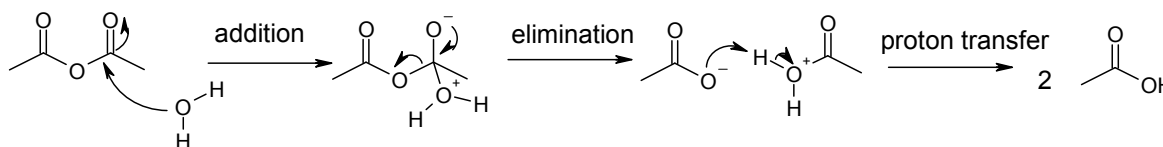
Plug Flow Reactor



High Quality Quantitative
NMR data!

94% yield

Can we do kinetic modelling with NMR data only?



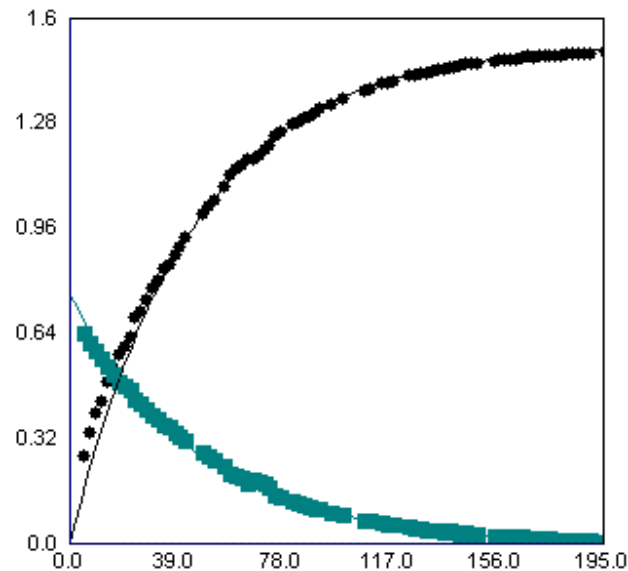
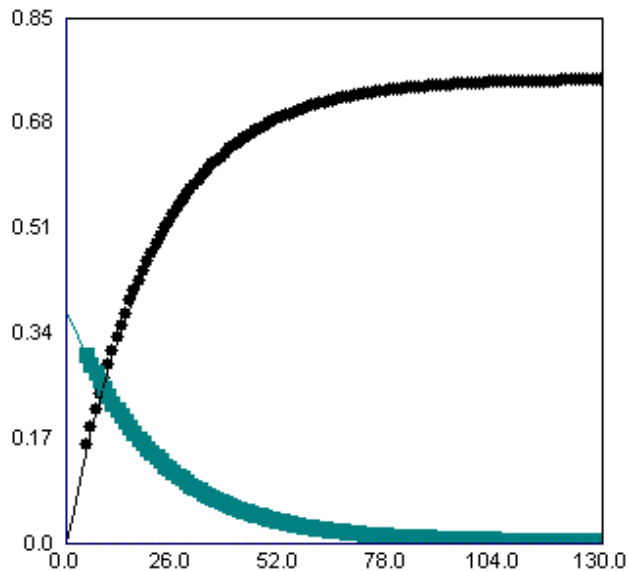
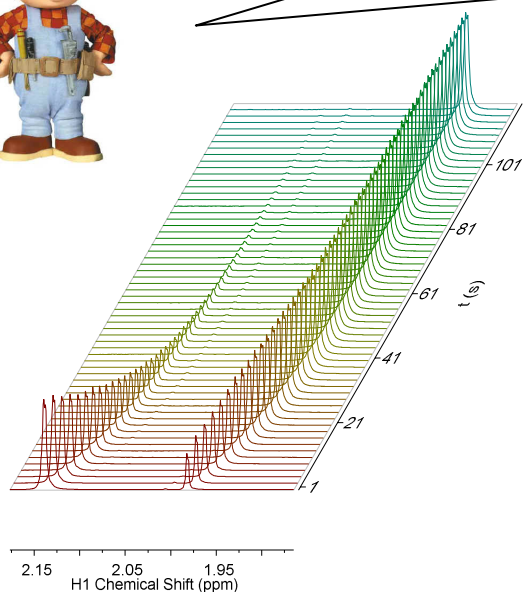
$$-d[\text{Ac}_2\text{O}]/dt = k[\text{Ac}_2\text{O}][\text{H}_2\text{O}] = A.e^{-E_a/RT} \cdot [\text{Ac}_2\text{O}][\text{H}_2\text{O}] \quad (\text{II})$$

$$k = A.e^{-E_a/RT} \quad (\text{III})$$

M	t_0	Temperature (°C)		D ₂ O	Acetic Anhydride		Acquisition	
		Bath	Spectrometer		Mass (mg)	$[\text{I}](\text{M})$	Pad (min)	Total (h)
1	~5	24.8	25	750	78.0	0.91	1	1
2	~5	14.8	15	750	78.0	0.91	2	3
3	5' 5"	5	5	750	77.7	0.91	10	10
4	4'15"	24.5	25	750	38.5	0.47	1	2
5	4'19"	24.9	25	750	19.2	0.24	2	4

Yes, We Can!

POSTER!



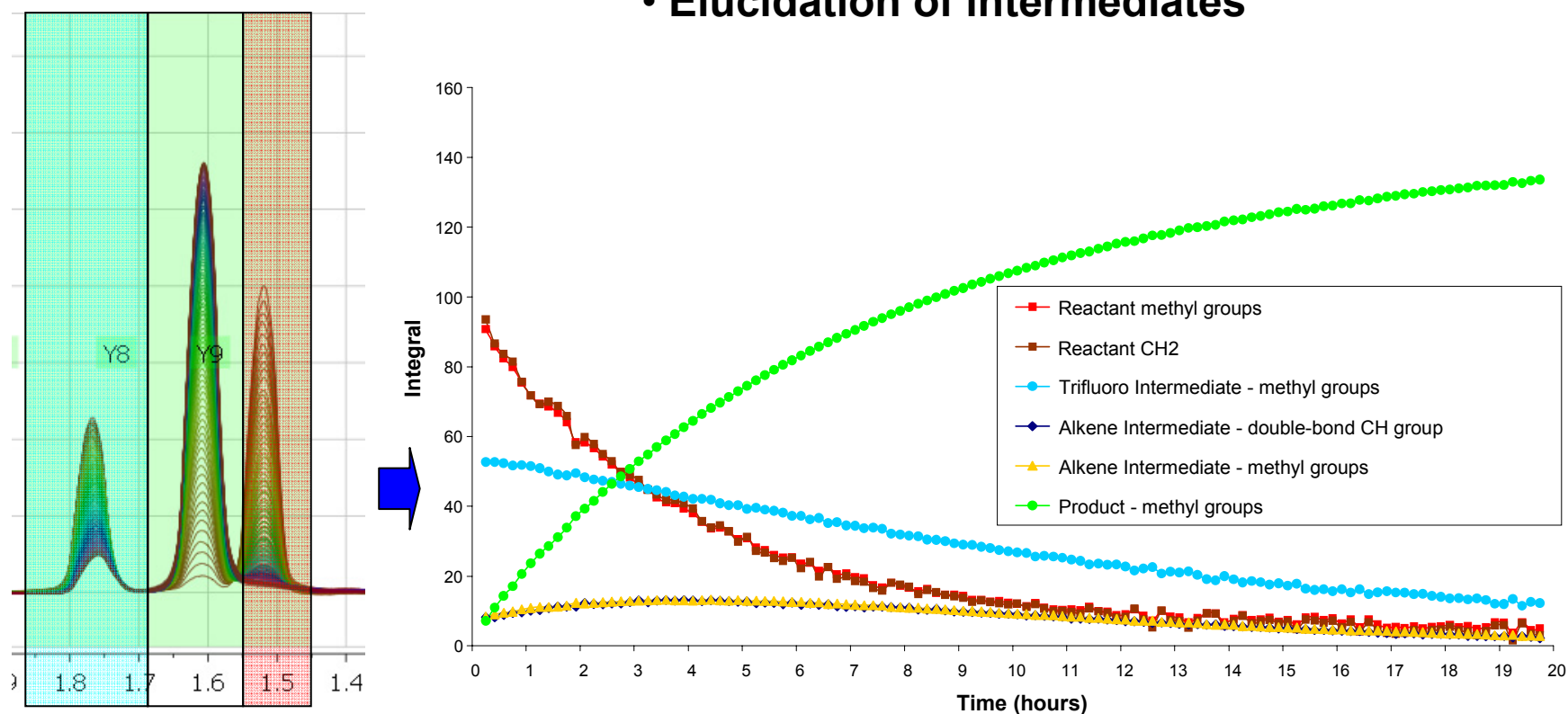
0.5 M 25 °C

1 M 15 °C

	Activation energy (kcal/g mol)	$\ln(A)$ (L/(g.mol.s))
→ This work	11.4	7.81
S. P. Asprey et Al	10.9	7.66
Glasser and Williams (1971)	10.8	7.95
Cleland and Wilhelms (1956)	10.6	7.80
Eldridge and Piret (1950)	10.3	7.53

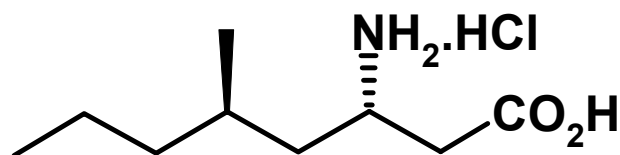
Other Applications:

- In situ yield determination
- Elucidation of intermediates



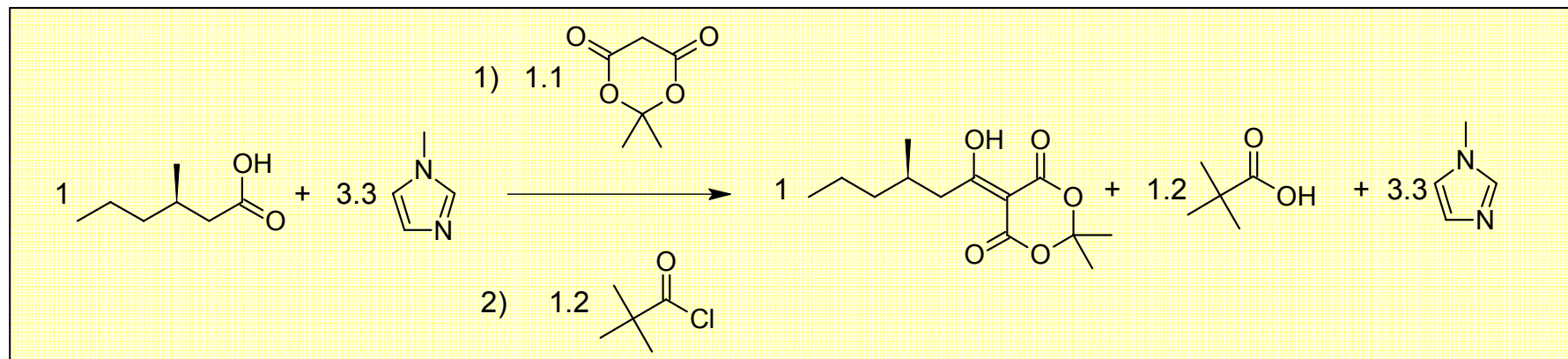
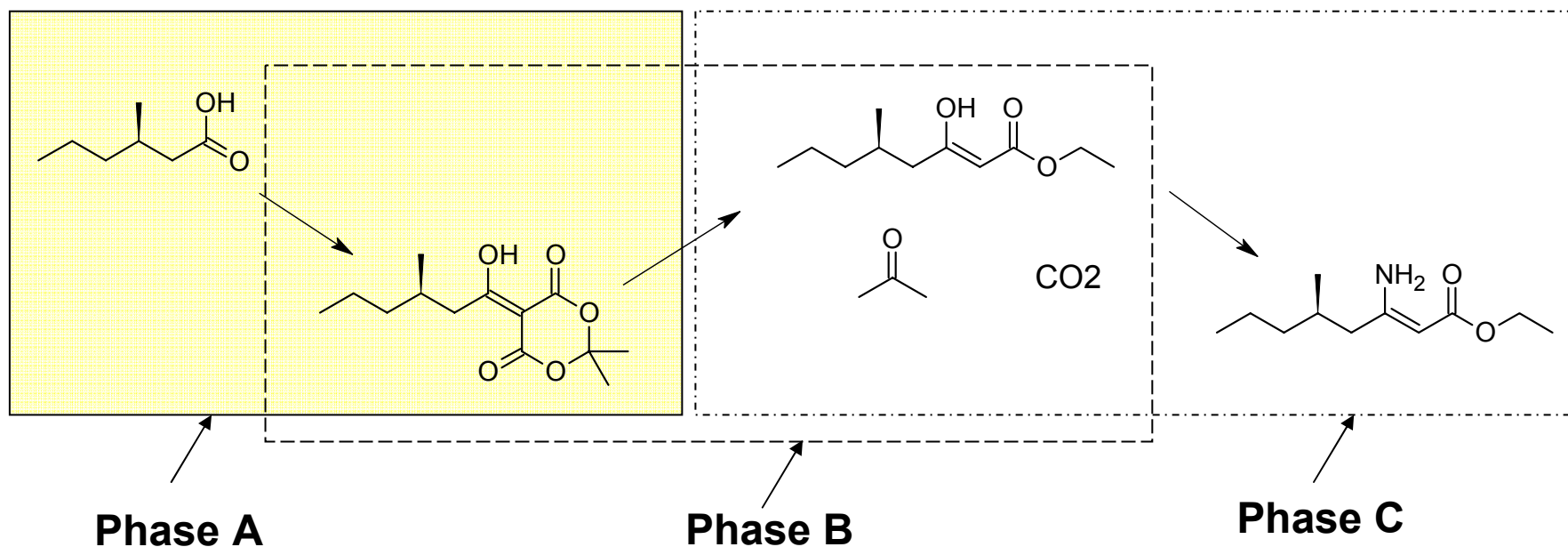
The target molecule (discontinued project)

- Generic Name: Imagabalin Hydrochloride
- Therapeutic Class/Indication: CNS ($\alpha 2\delta$)/General Anxiety Disorder (GAD)
- Anticipated Commercial Volume: High (>50 MT)
- Cost of API critical: lowest possible cost at launch:
 - **Telescope as much as possible and minimise the number of isolations**



Reaction

Ian Clegg, David Smith, Charlie Gordon



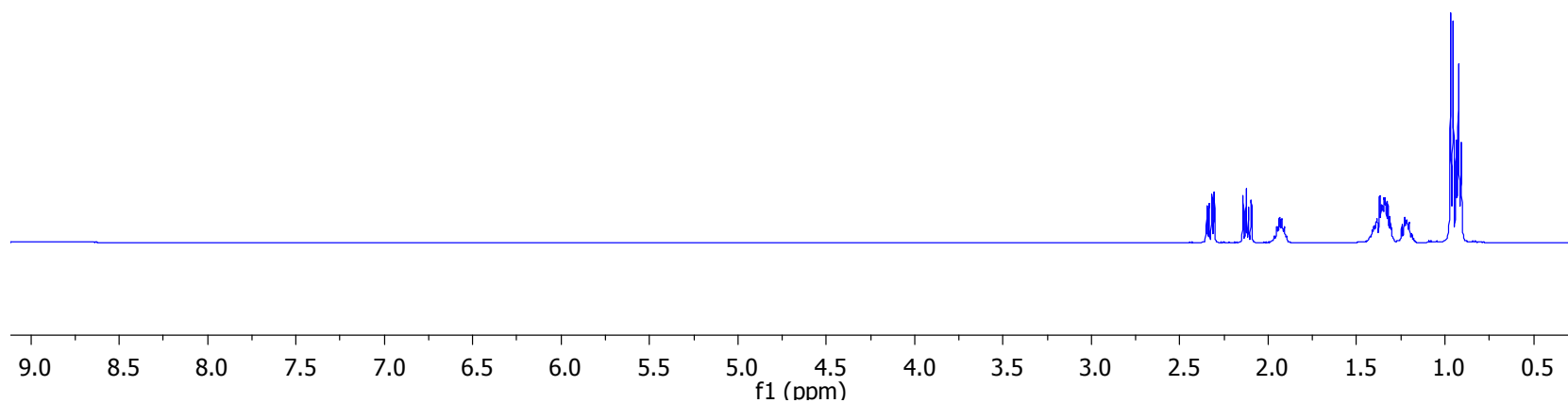
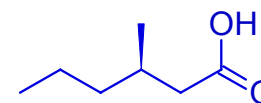
Objective:

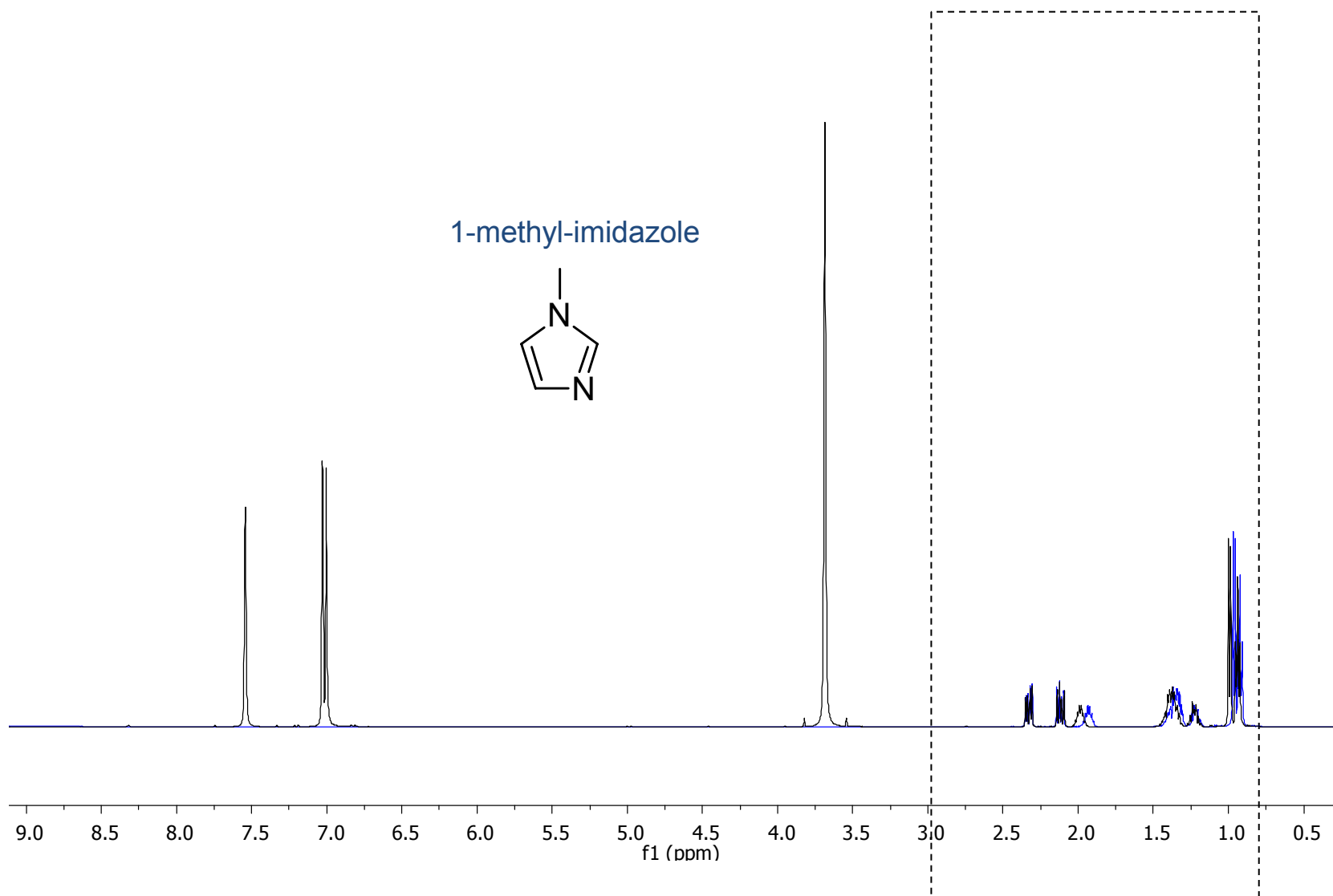
- **Reaction understanding**
 - Identification/confirmation of intermediates (unstable)
 - Insights into the mechanism
- **No chromophore → difficult analytics**

Feasibility of NMR Study:

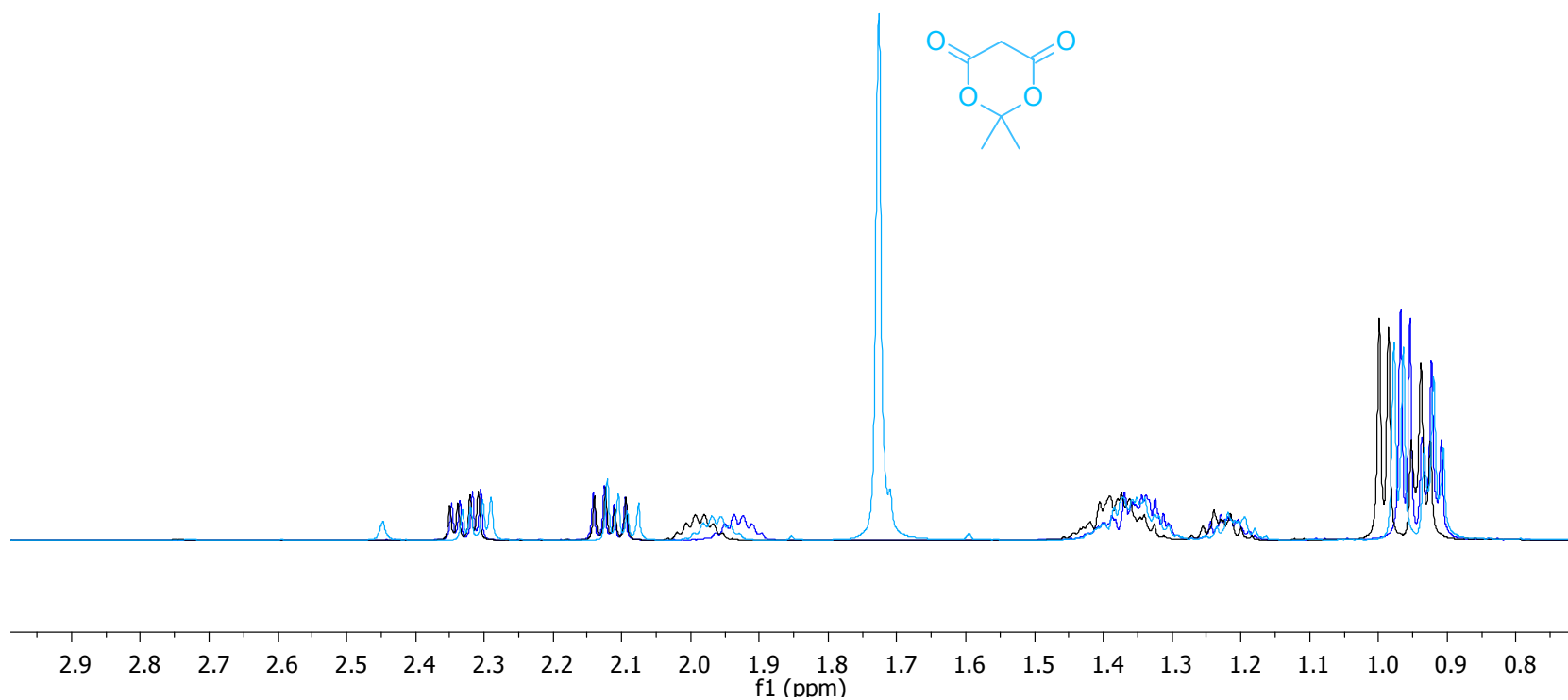
- **Monophasic system.**
- **Reaction completion relatively slow.**
- **Ambient temperature**
- **Clean reaction**
- **Safe**

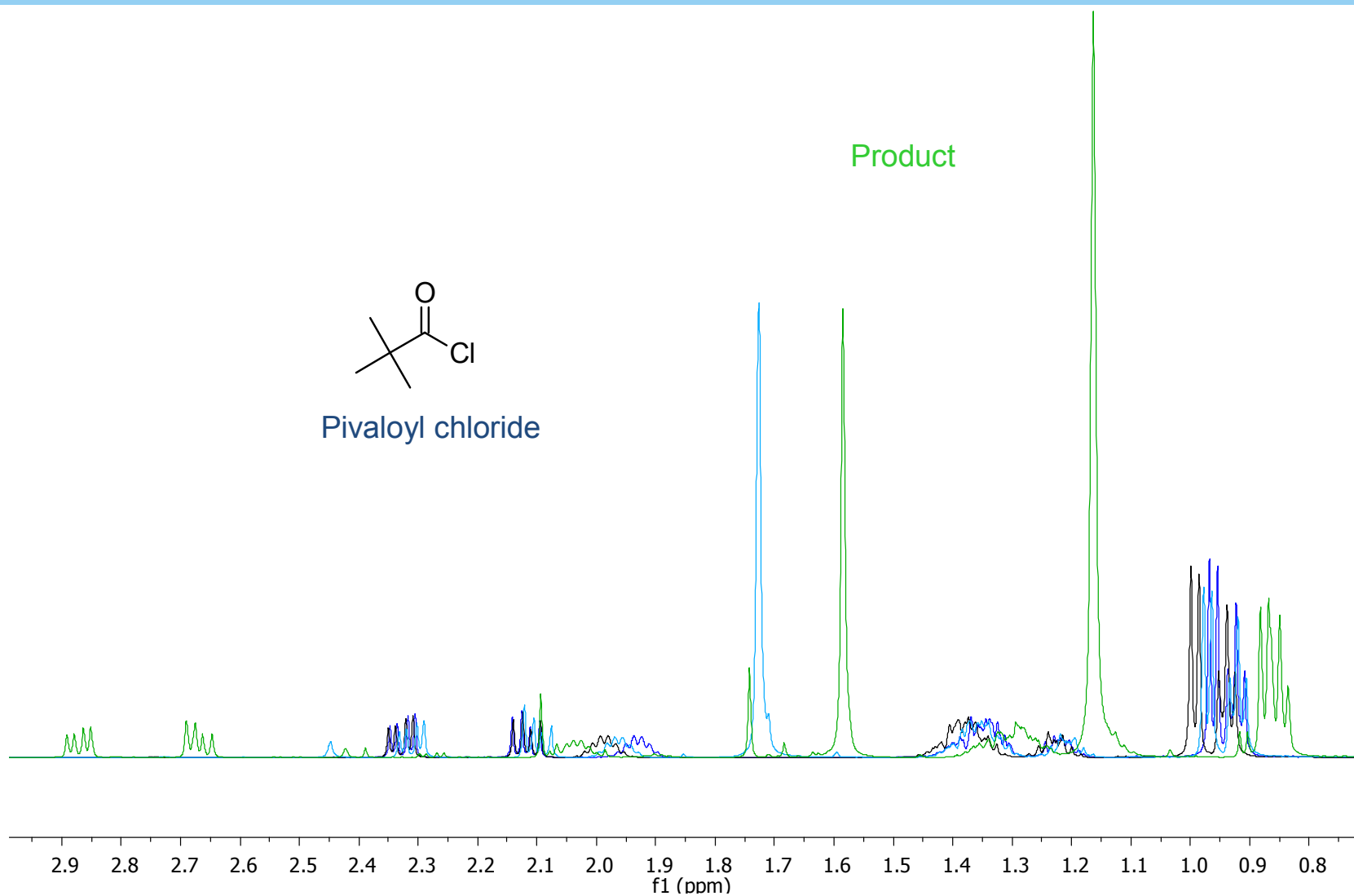
Starting Material



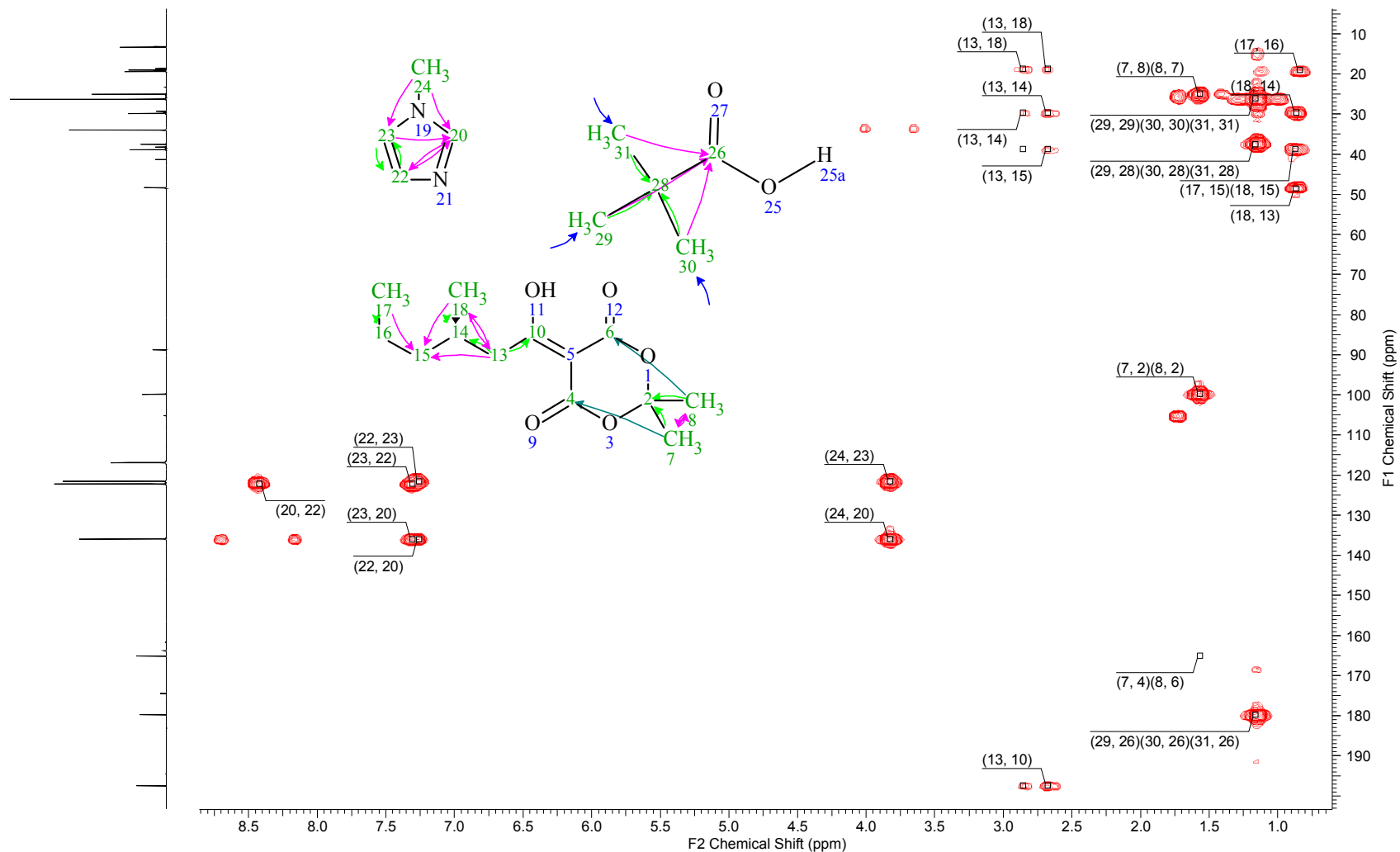


Meldrum's acid

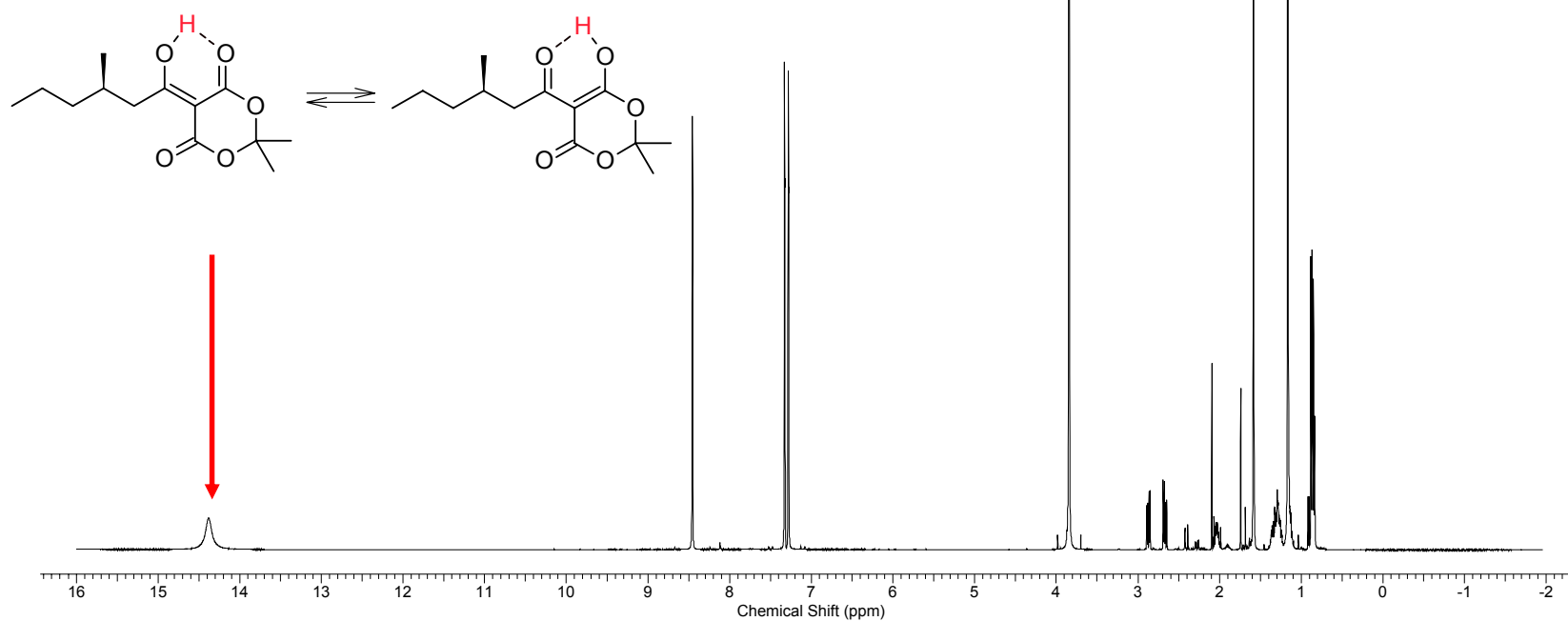




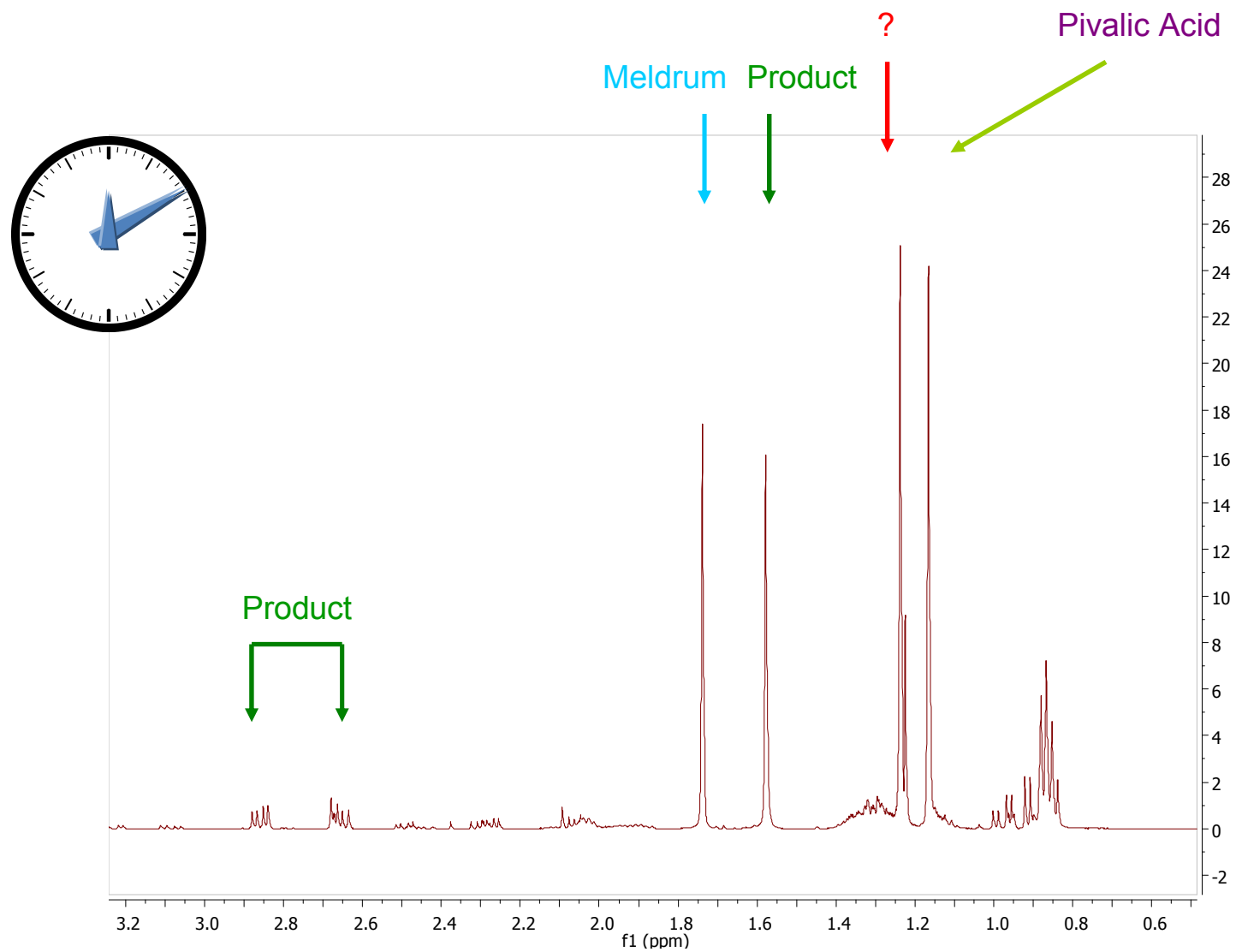
HMBC

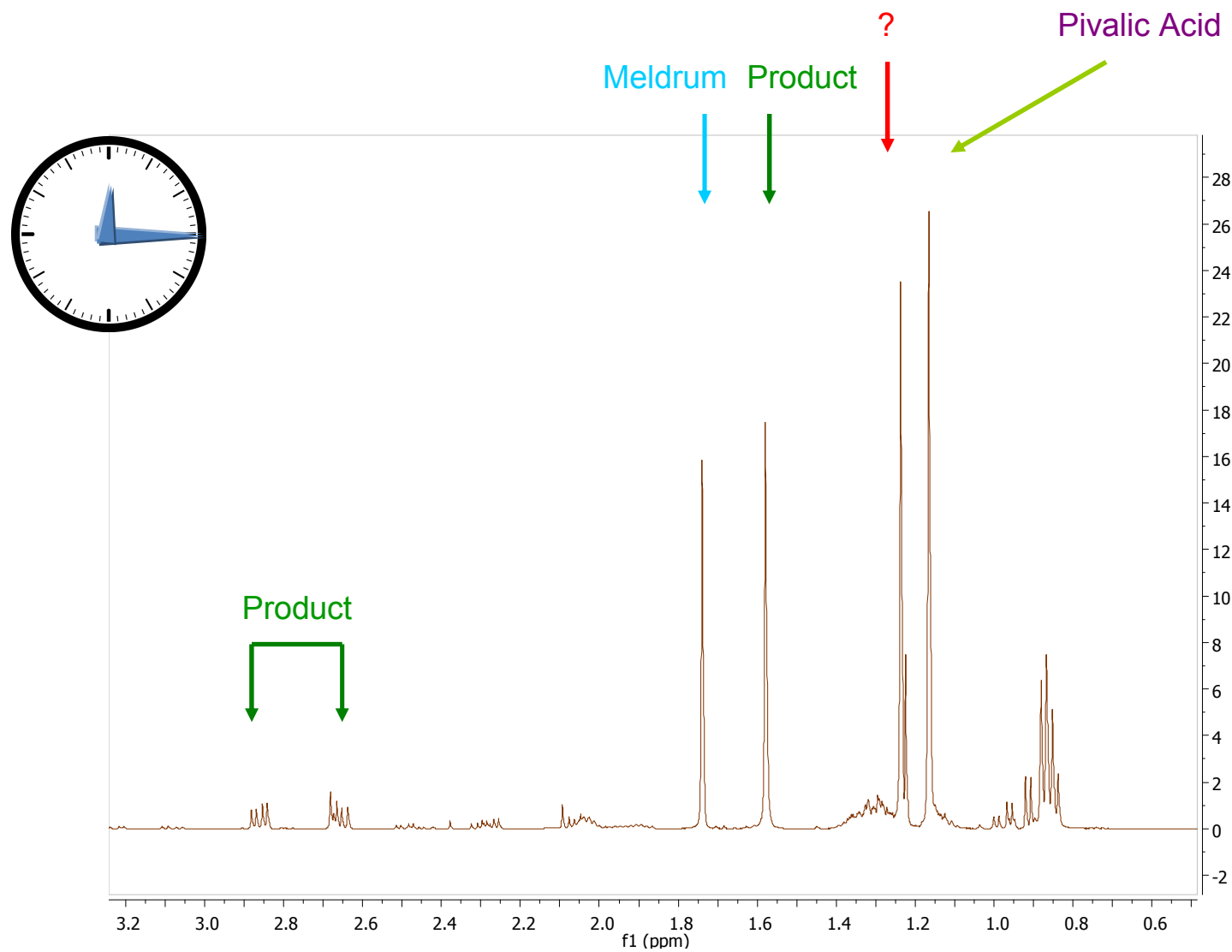


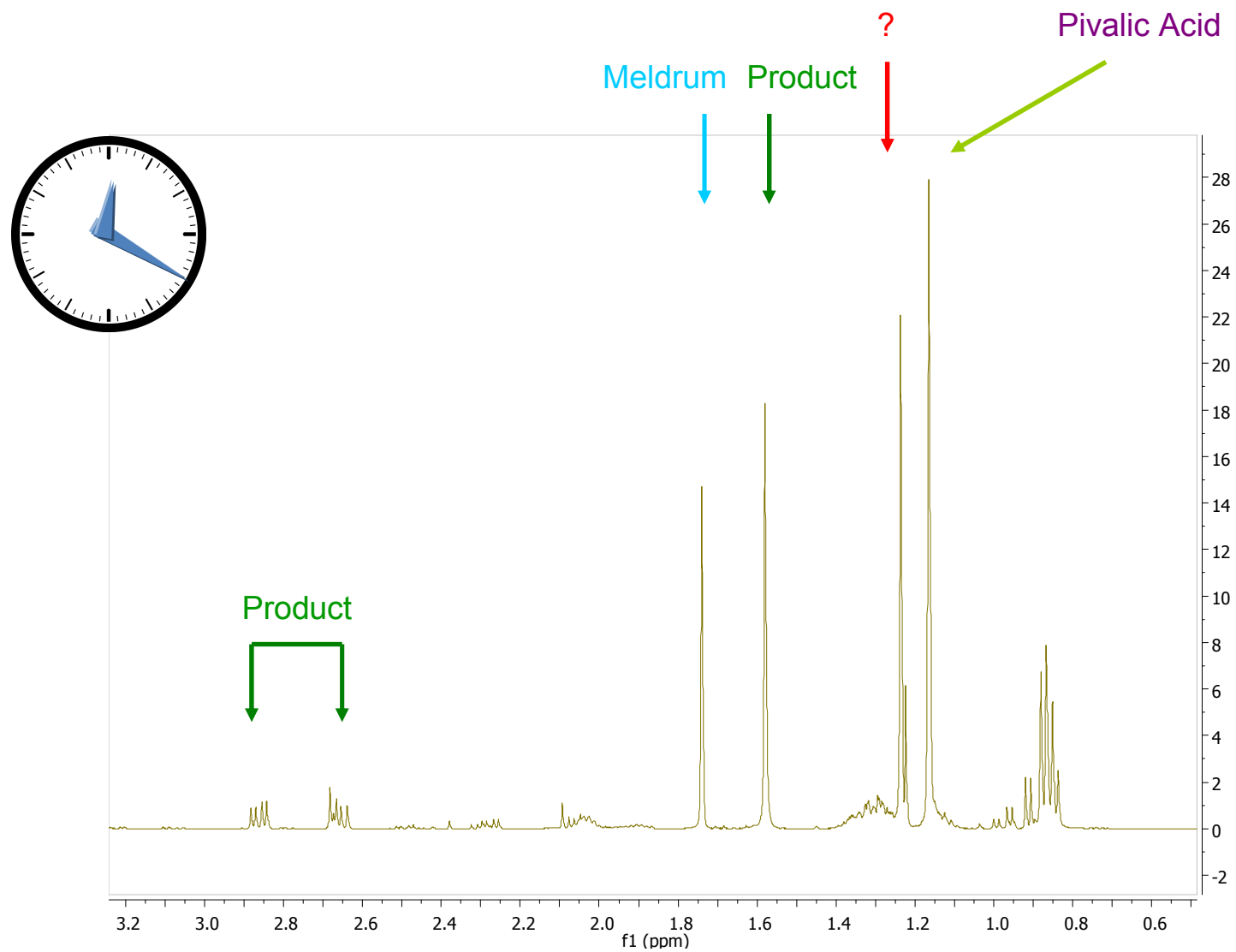
Resonance Assisted Hydrogen Bond

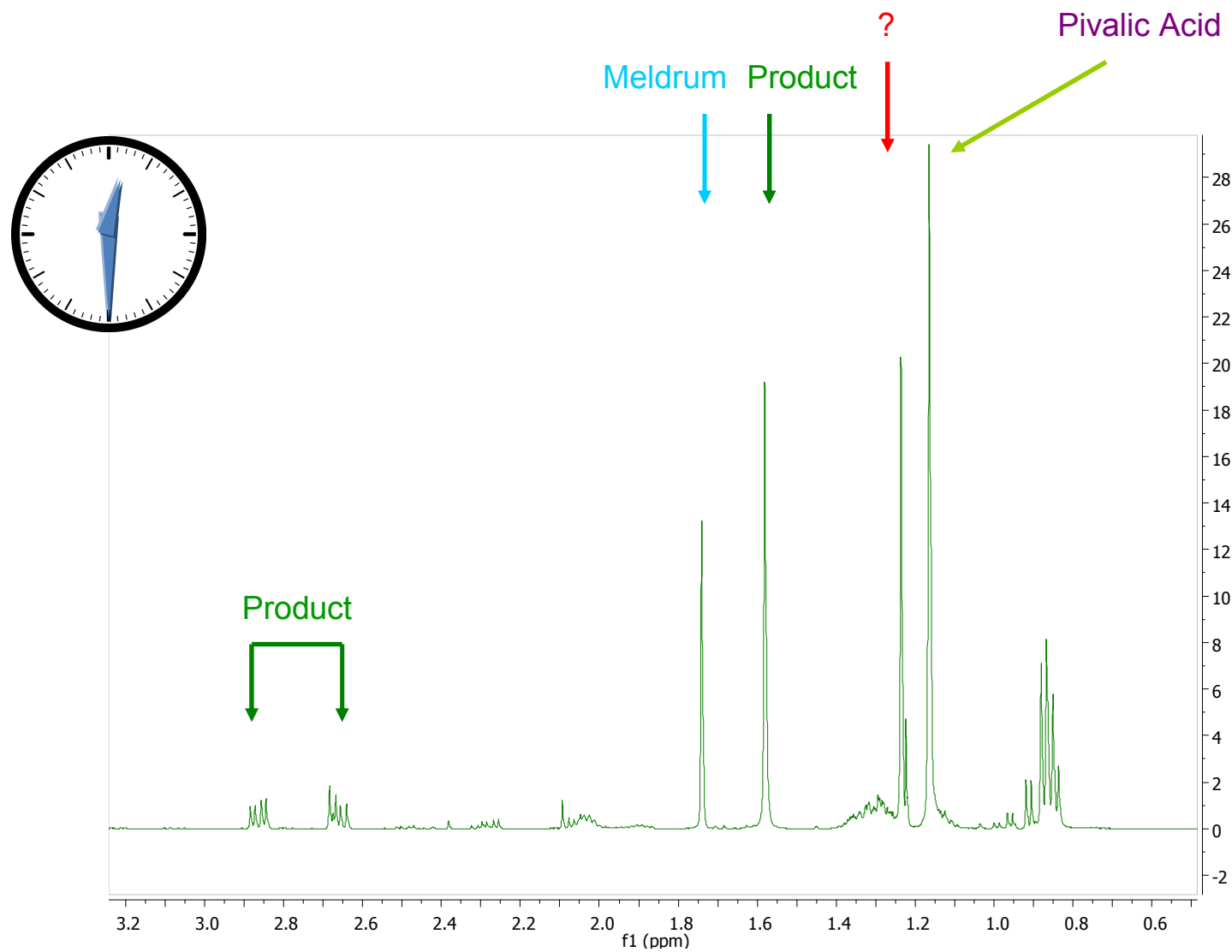


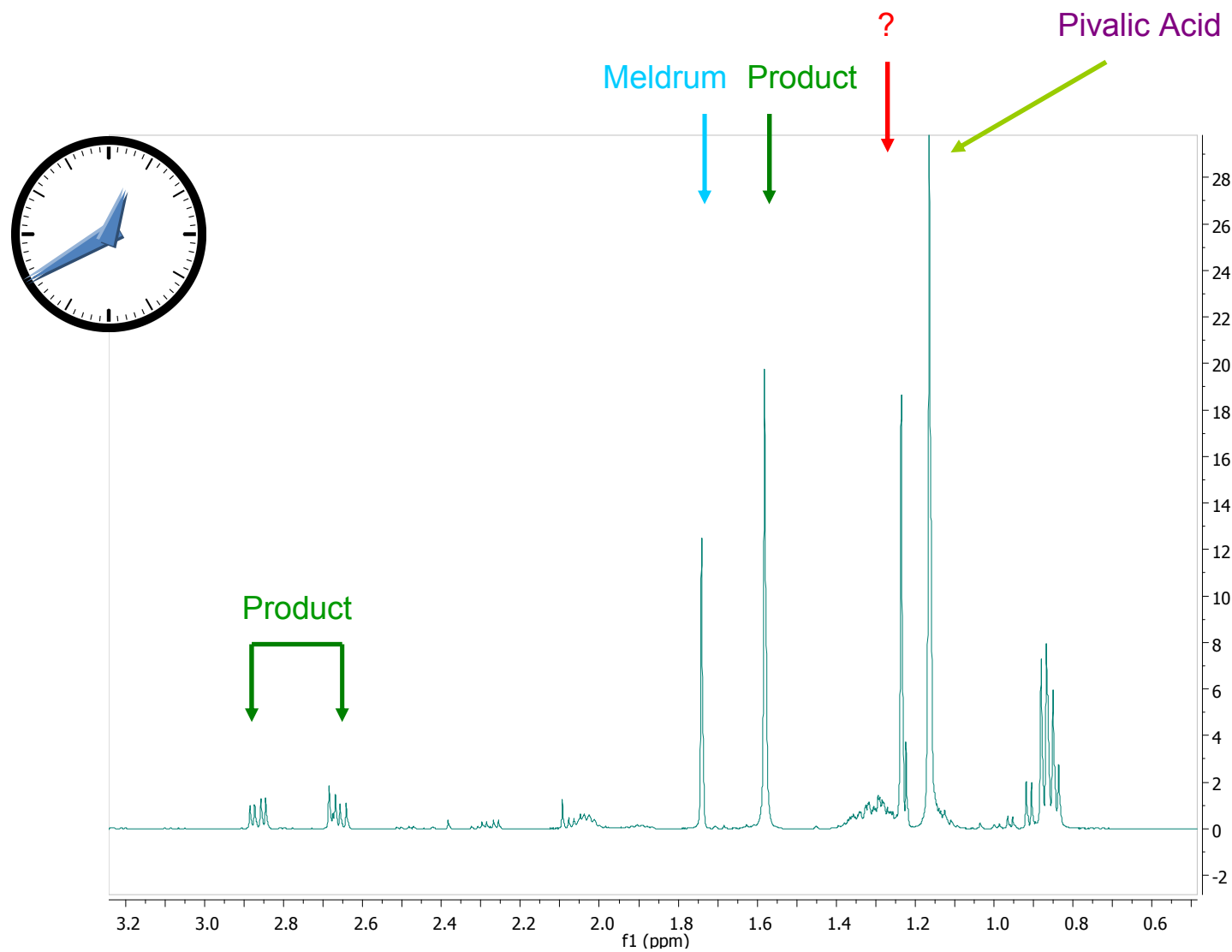
- Bertolasi, V.; Gilli, P.; Ferretti, V.; Gilli, G. *J. Chem. Soc., Perkin Trans. 2* **1997**, 5, 945.
- Schiøtt, B.; Iversen, B. B.; Hellerup Madsen, G. K.; Bruice, T. C. *J. Am. Chem. Soc.* **1998**, 120, 12117.
- Perrin, C. L.; Nielson, J. B. *Annu. Rev. Phys. Chem.* **1997**, 48, 511.

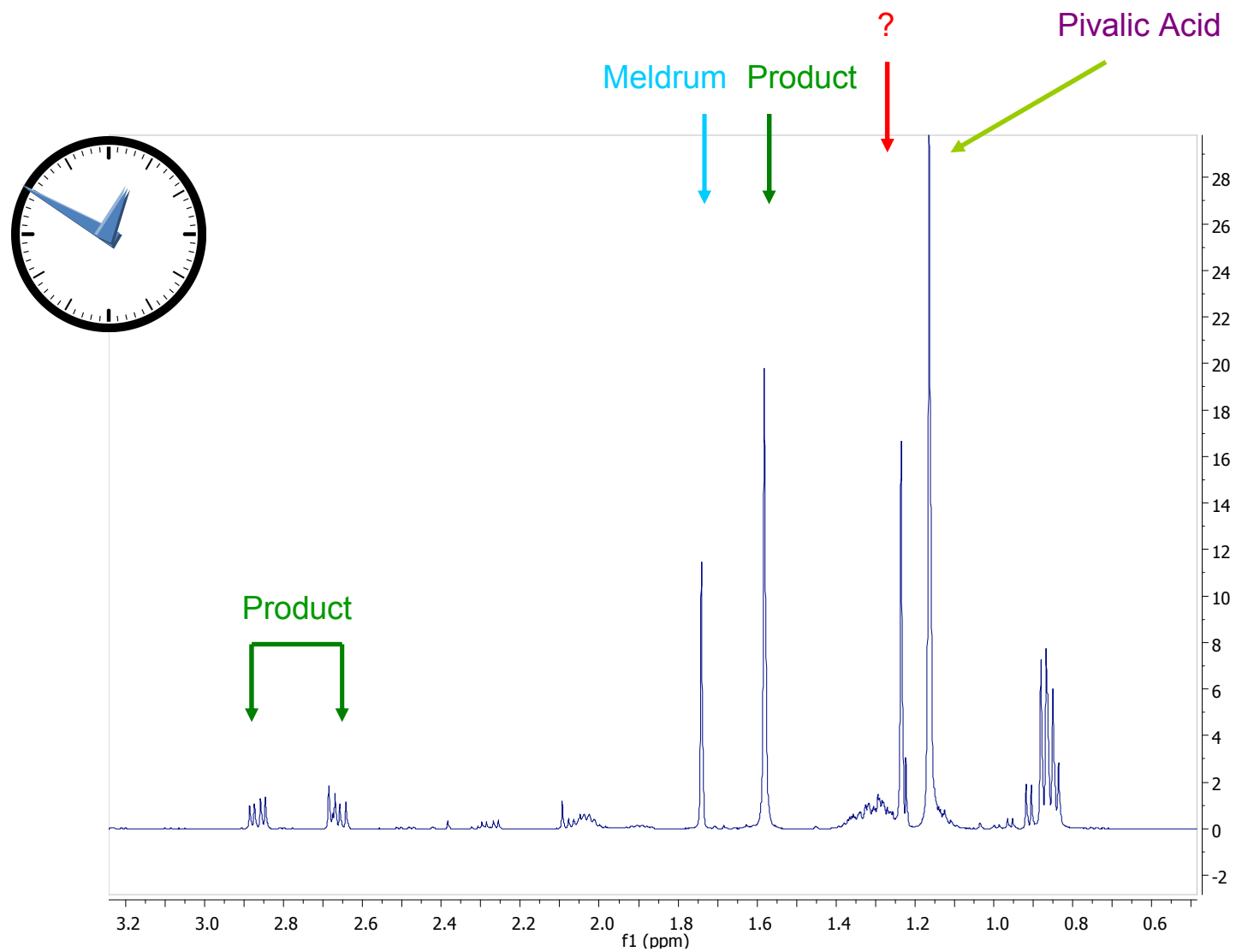


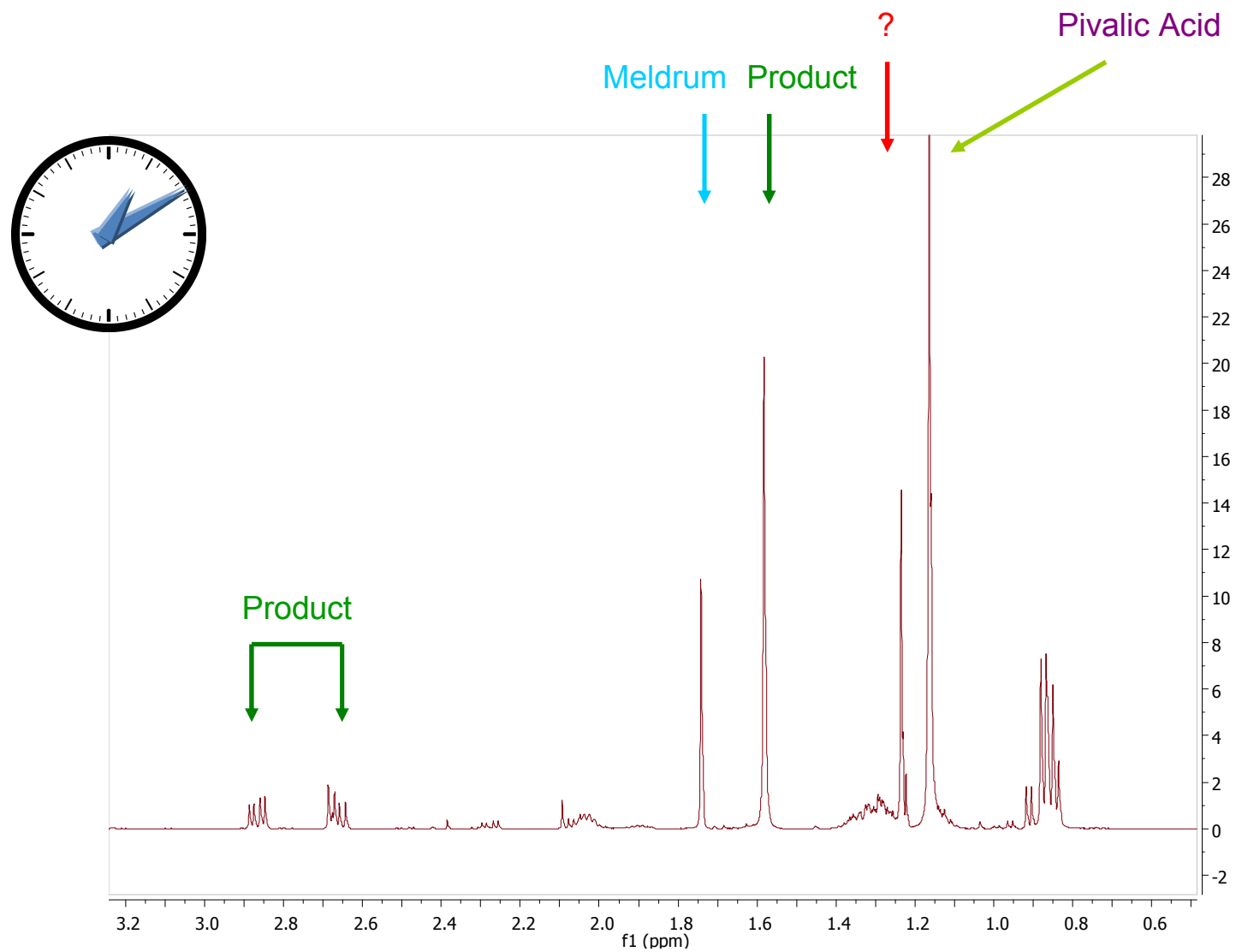


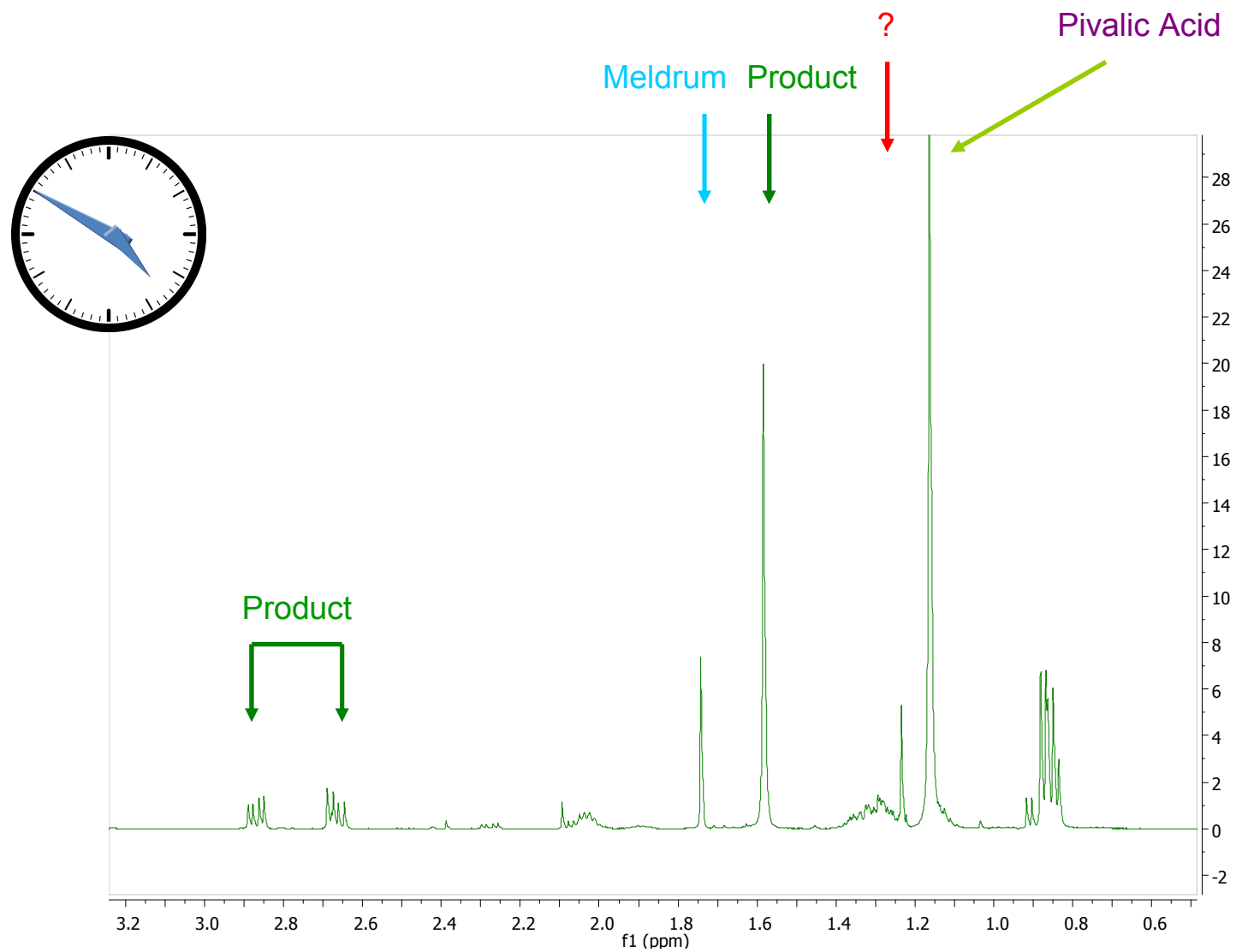


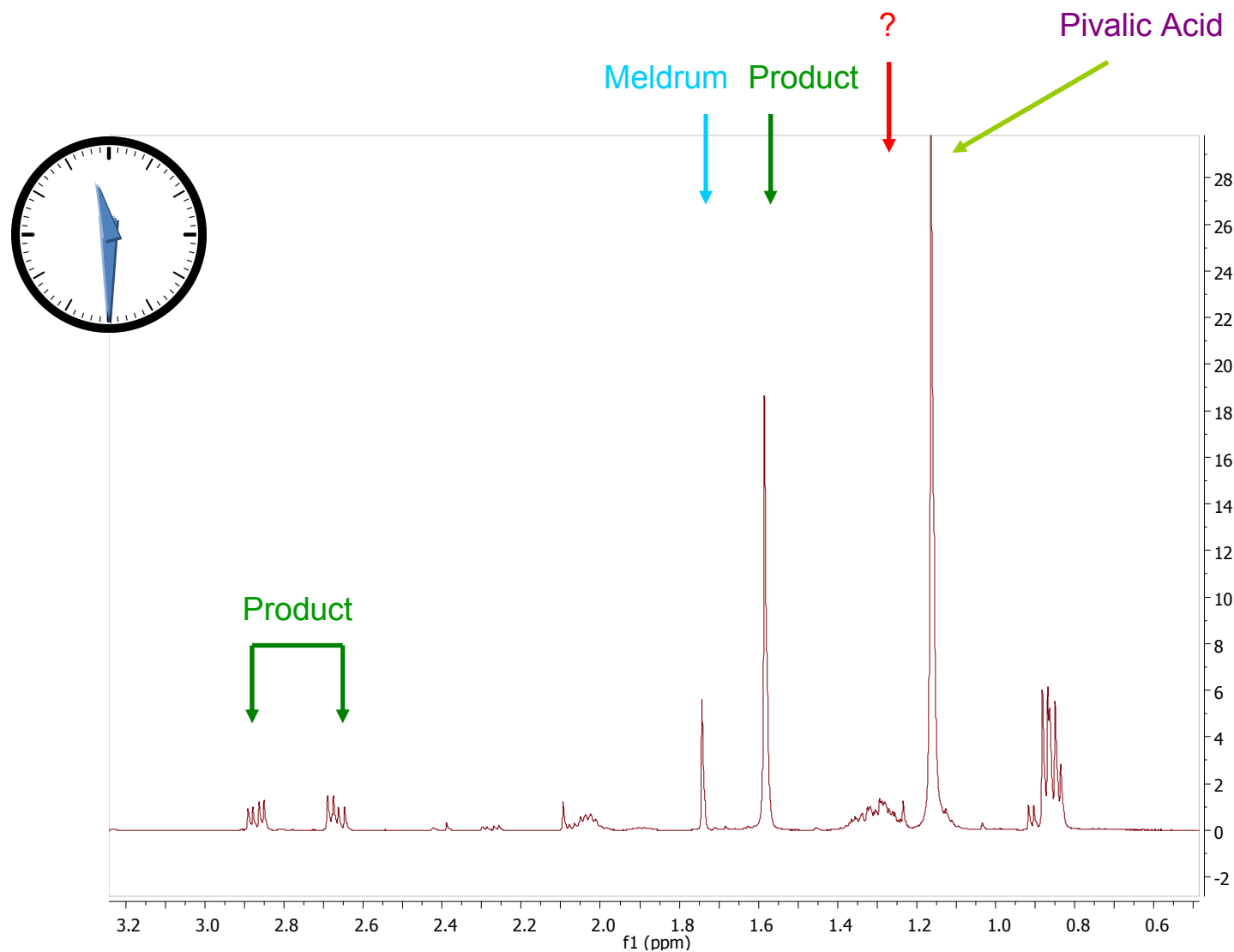




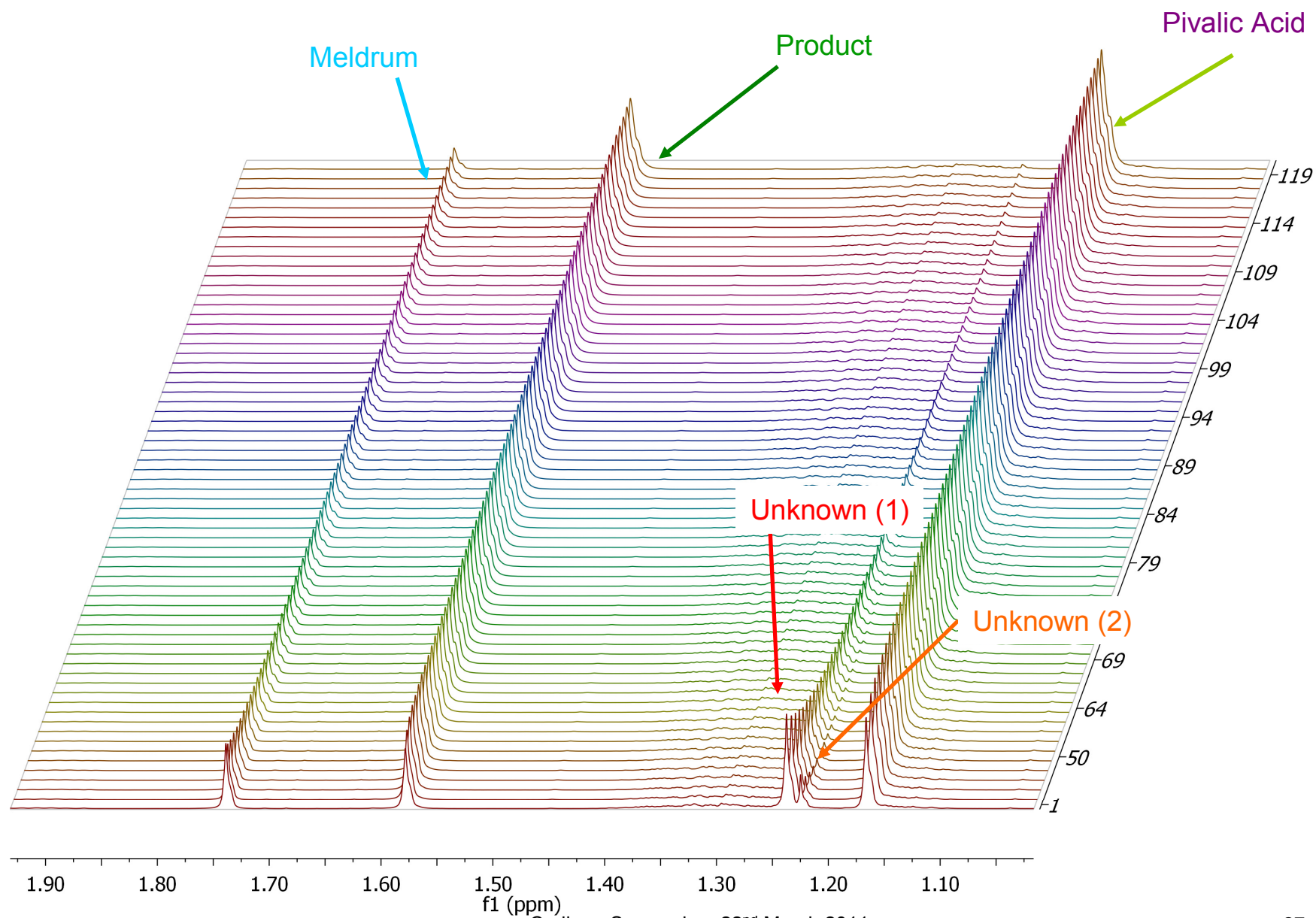




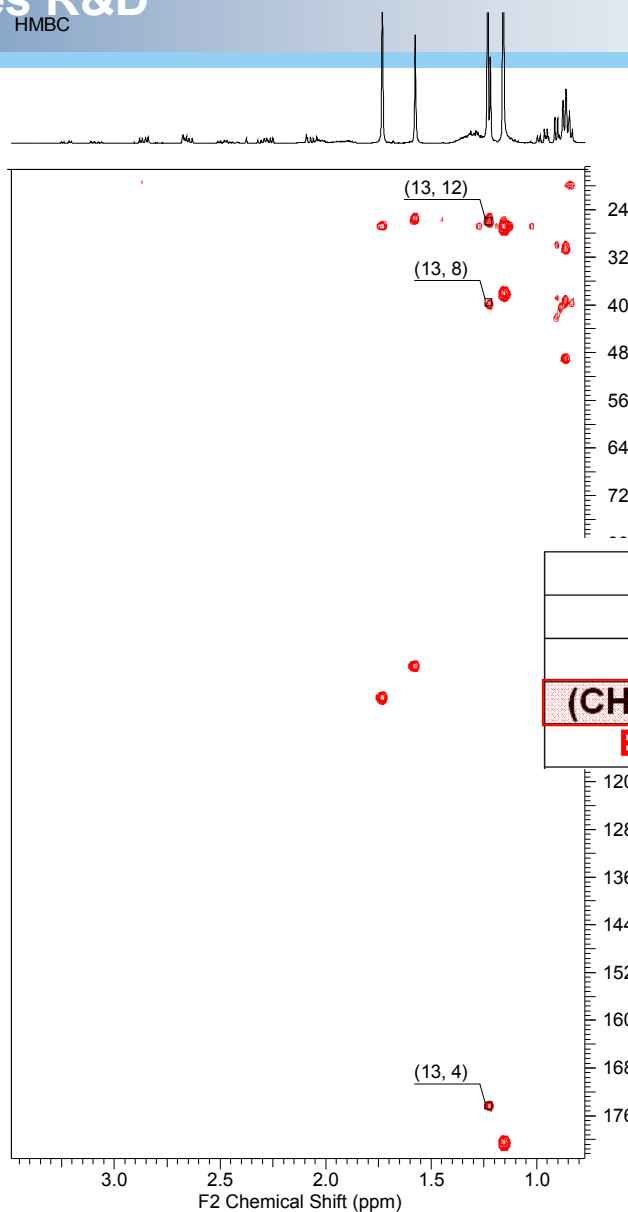
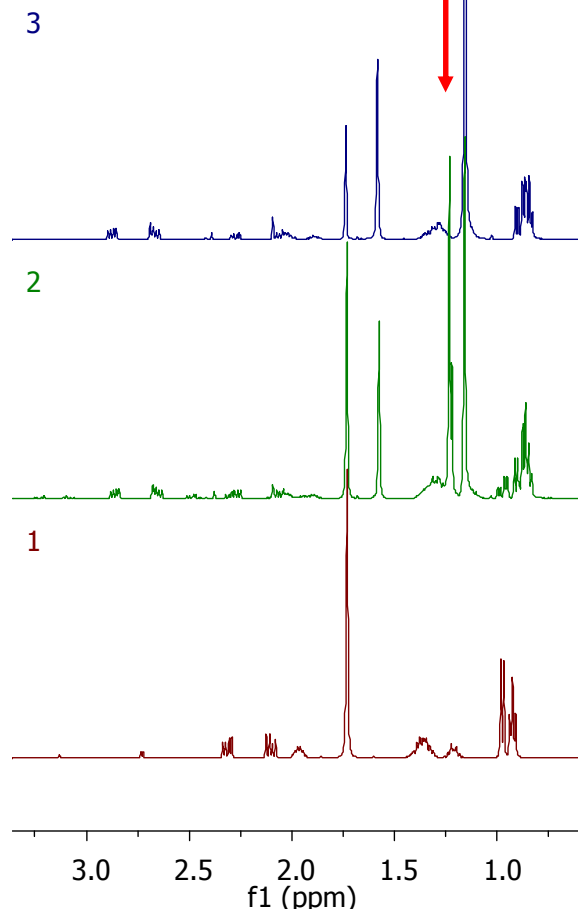




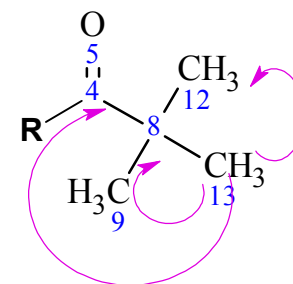
<http://www.youtube.com/watch?v=bpwbU2UntB4>



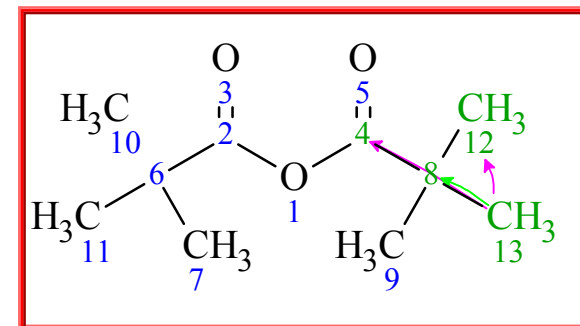
- Reaction tf = 10 h
- Reaction t0 = 10 min
- Before Piv-Cl



Unknown 1

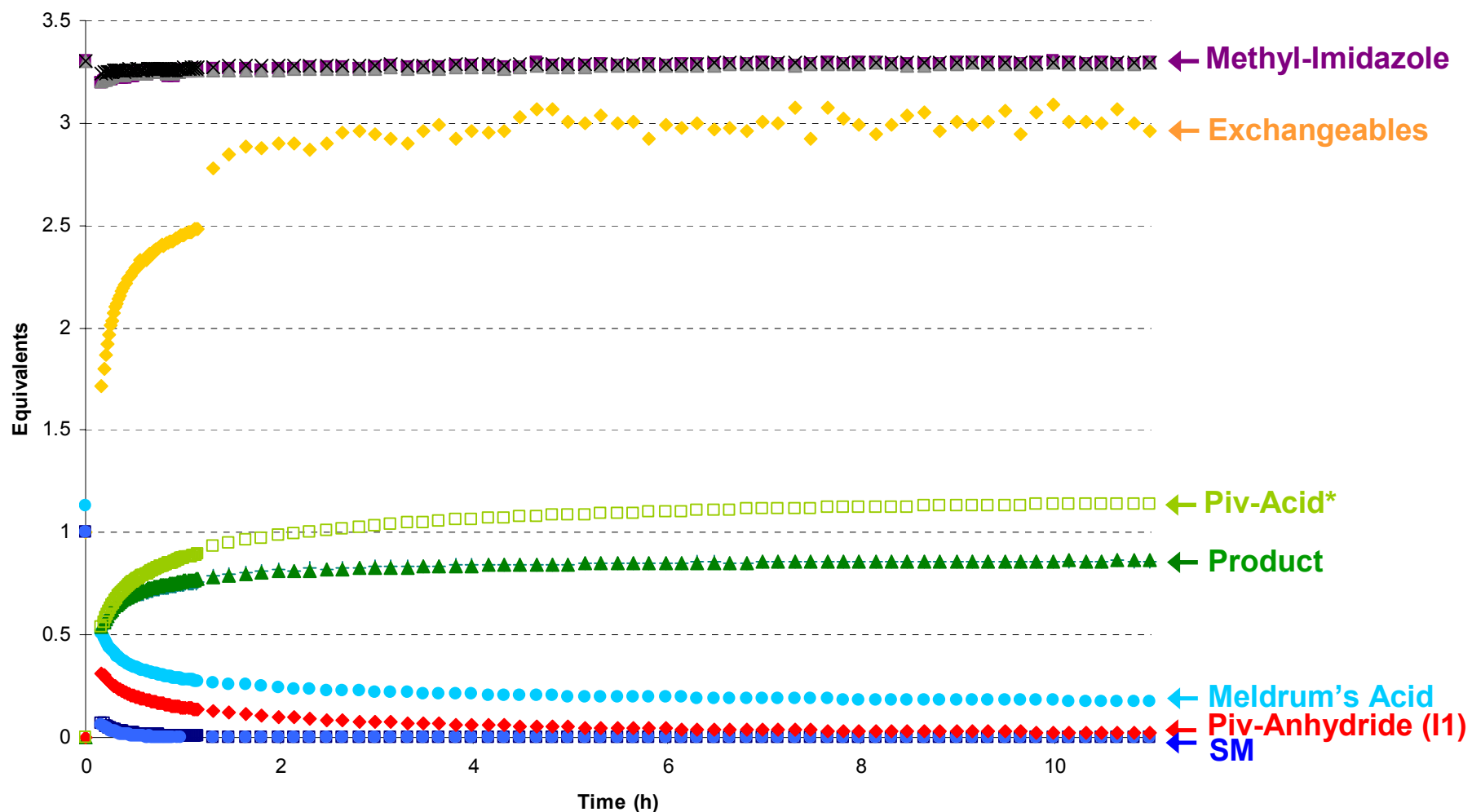


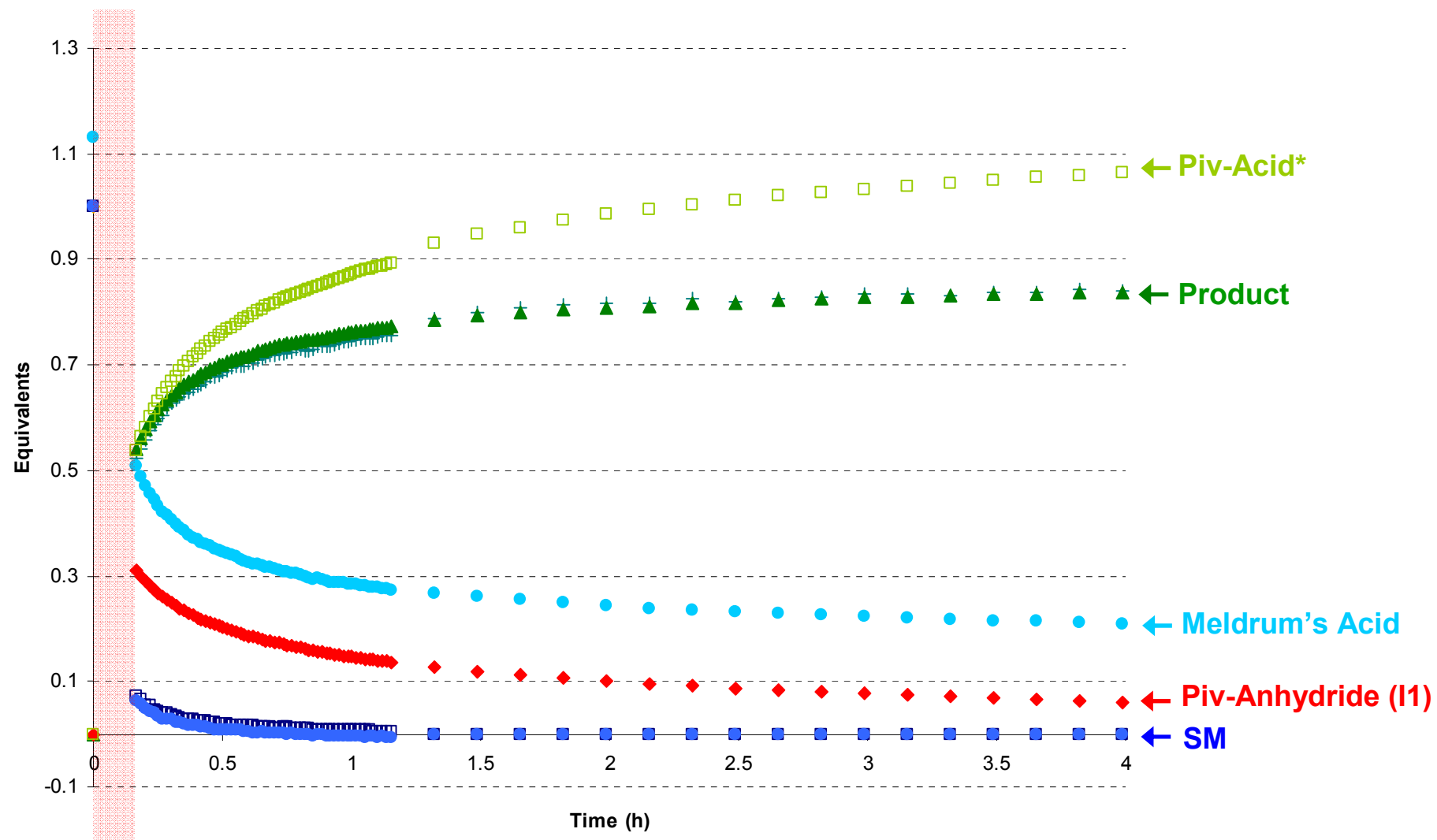
R	CH ₃	C	CO
Cl	27	50	182
OH	27	39	182
(CH ₃) ₃ CCOO	27	41	175
Exp. 1	26	40	174



Piv-Anhydride = 11

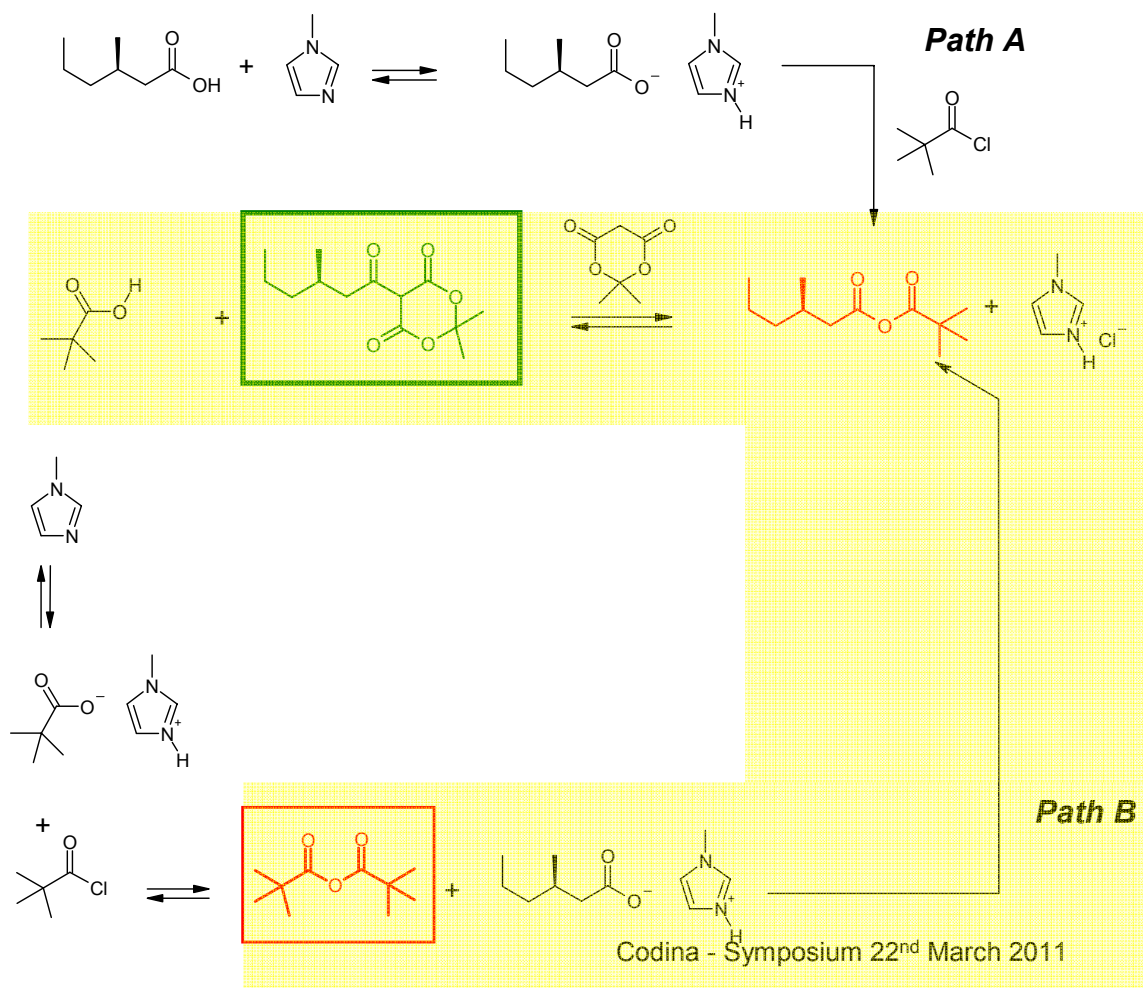
Quantitative Reaction Profile



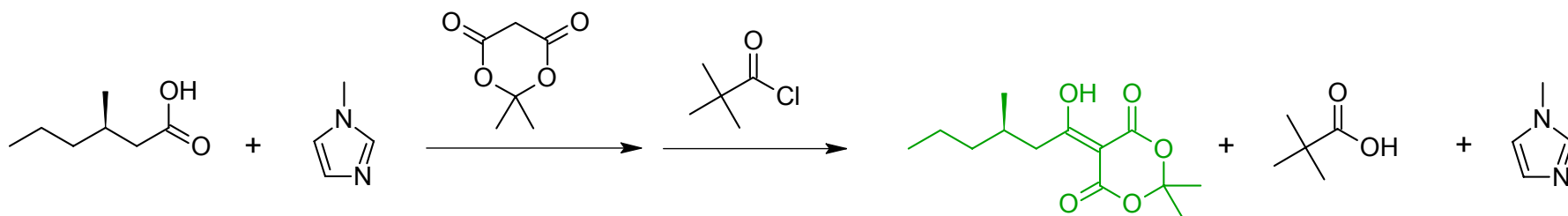


Understanding the mechanism:

- ^1H NMR and IR data indicate the major intermediate is pivalic anhydride
- The reaction is not dose controlled. Therefore 2 pathways.

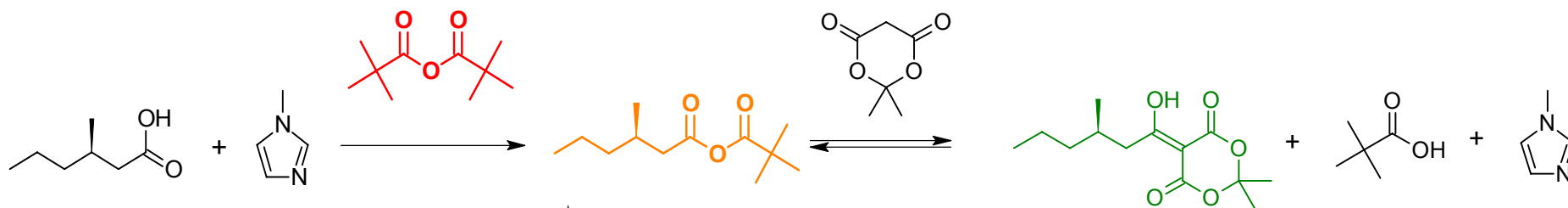


R1



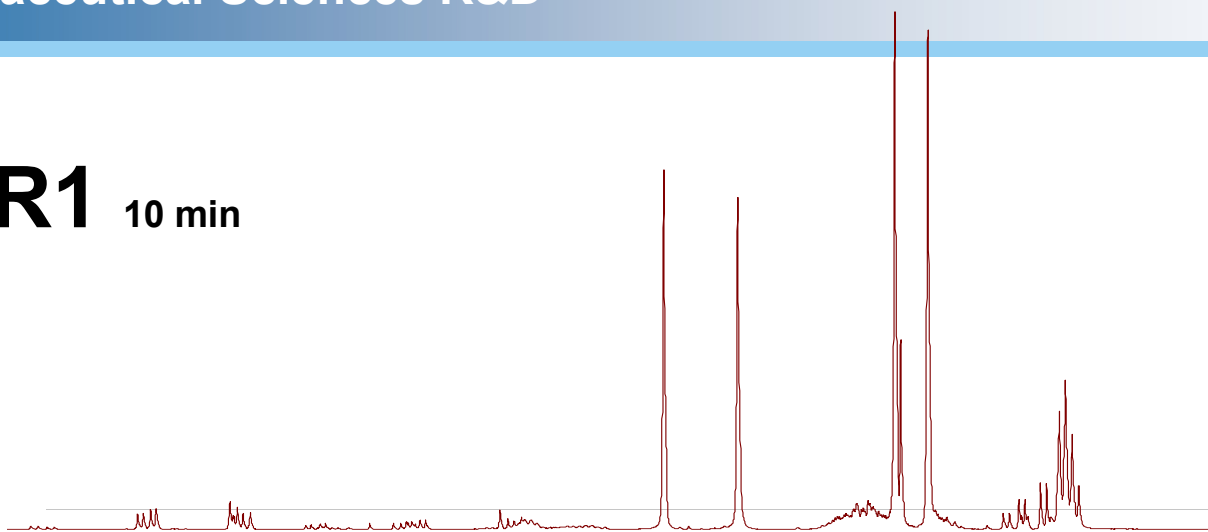
R2A

R2B

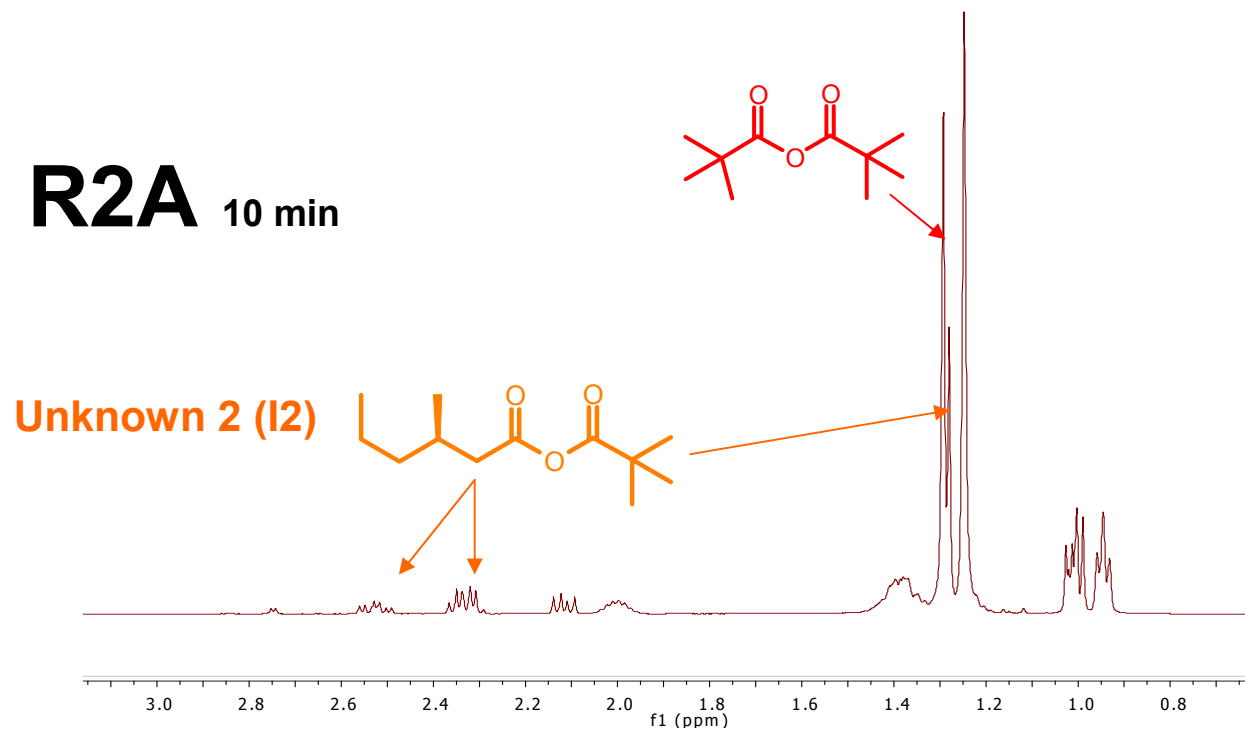


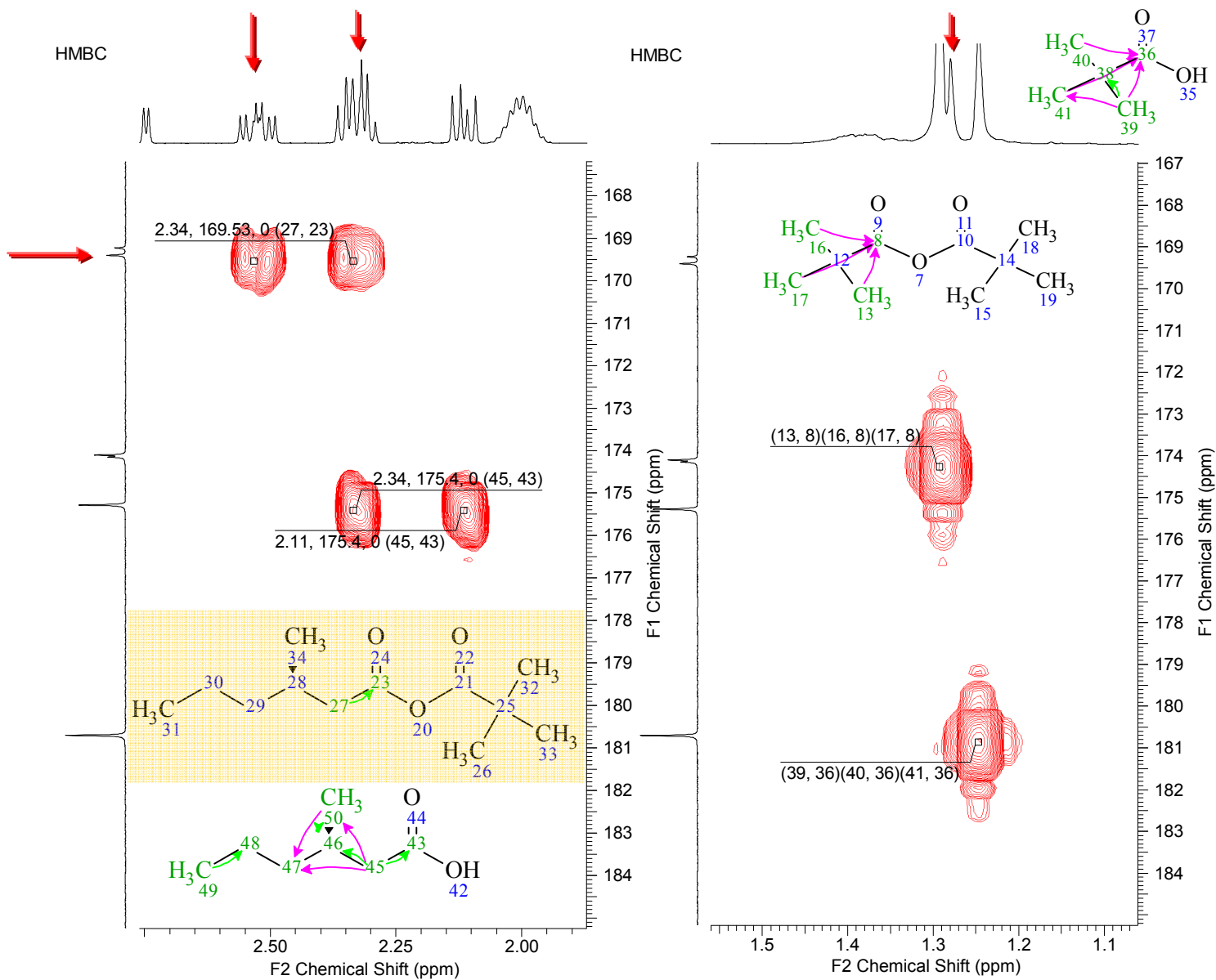
Dosed controlled

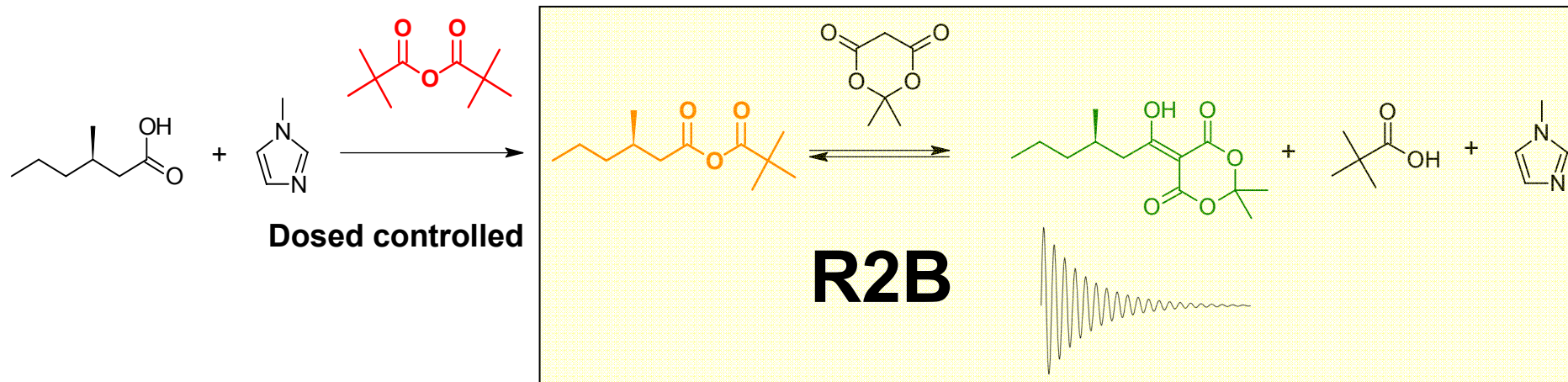
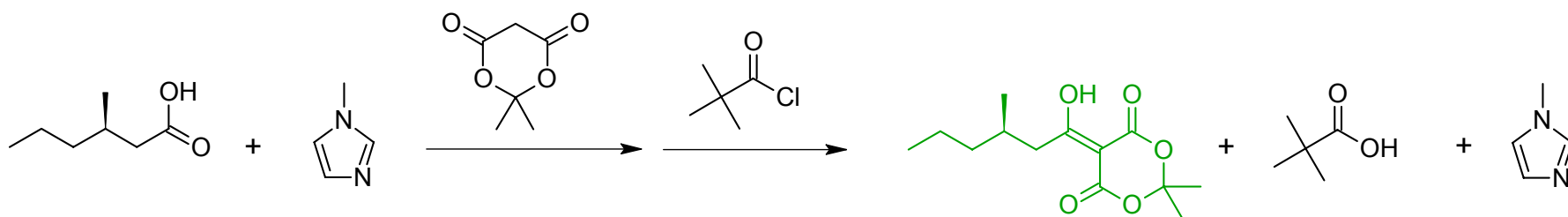
R1 10 min

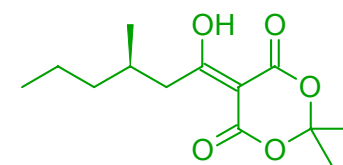
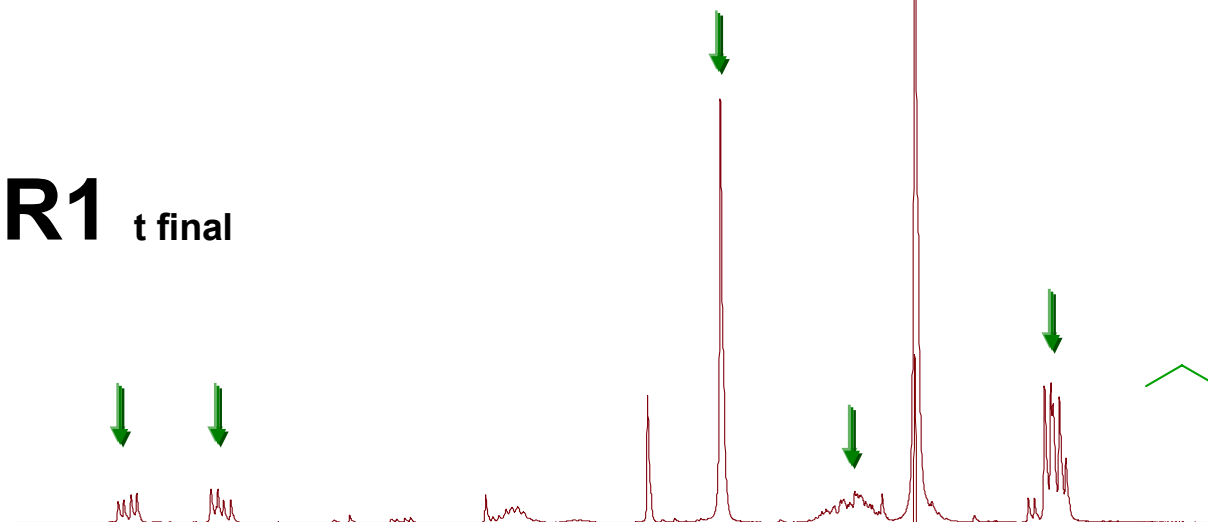
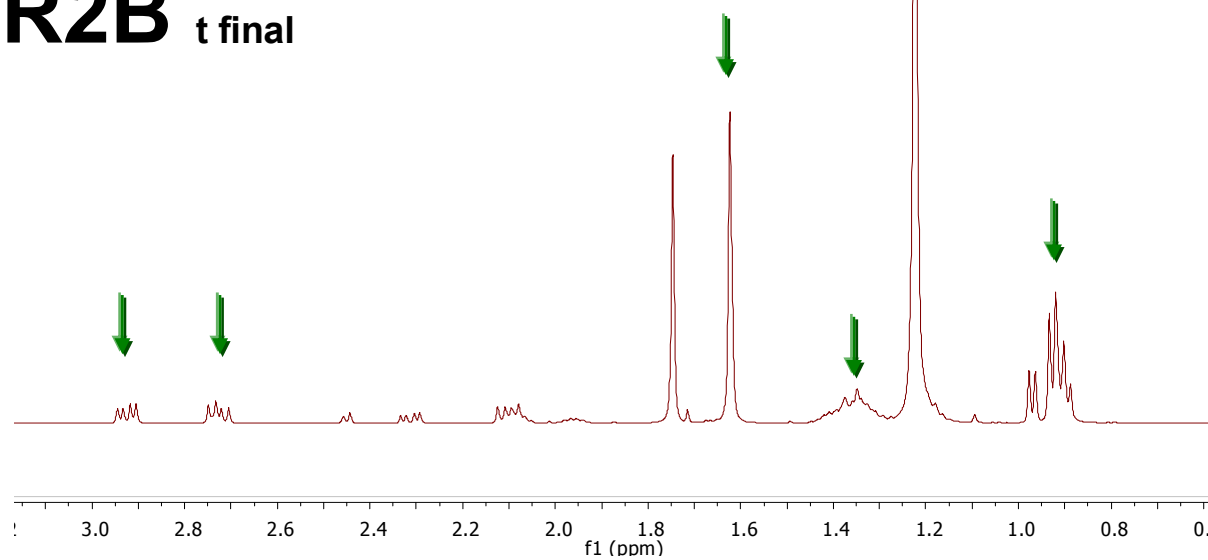


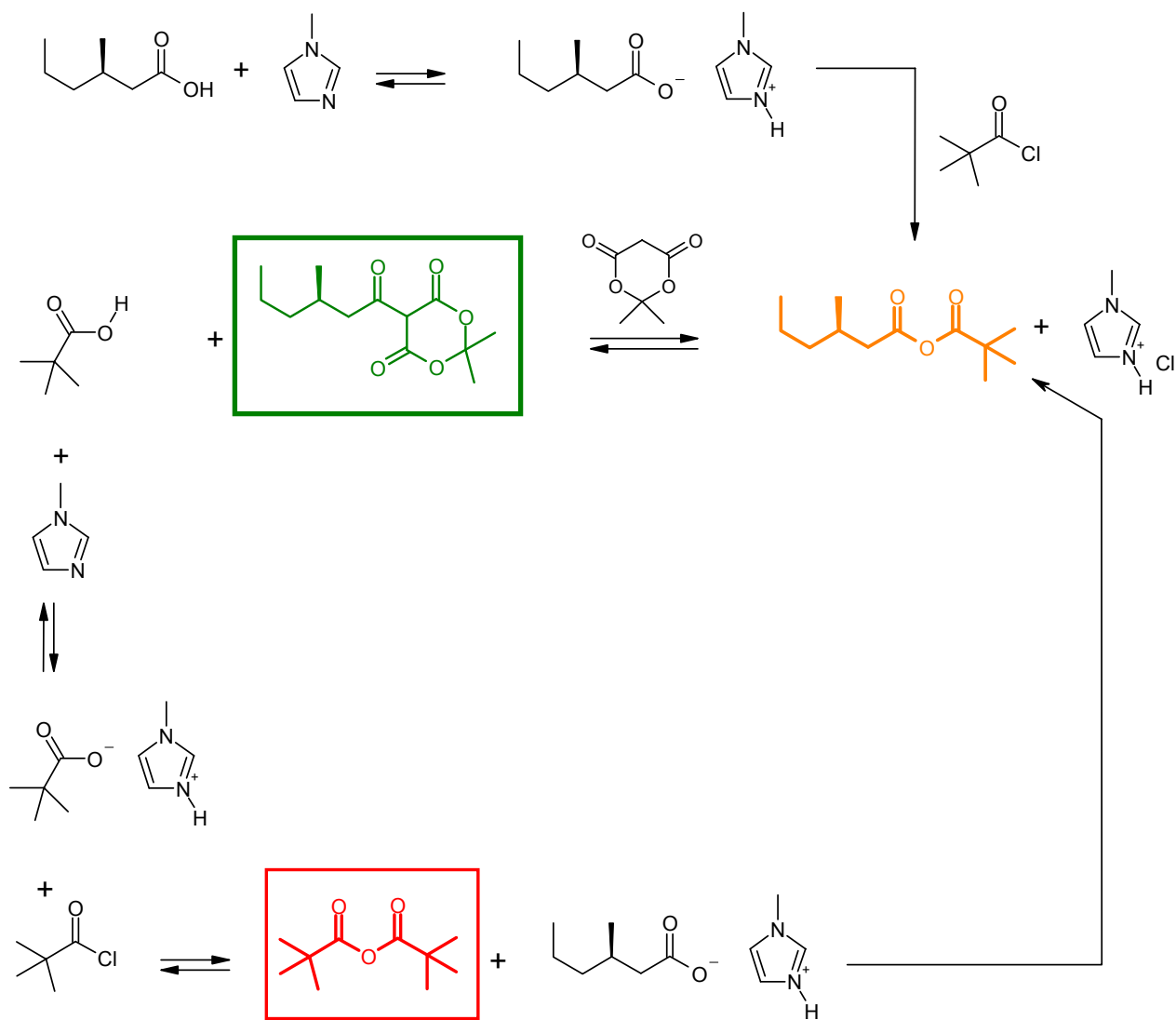
R2A 10 min



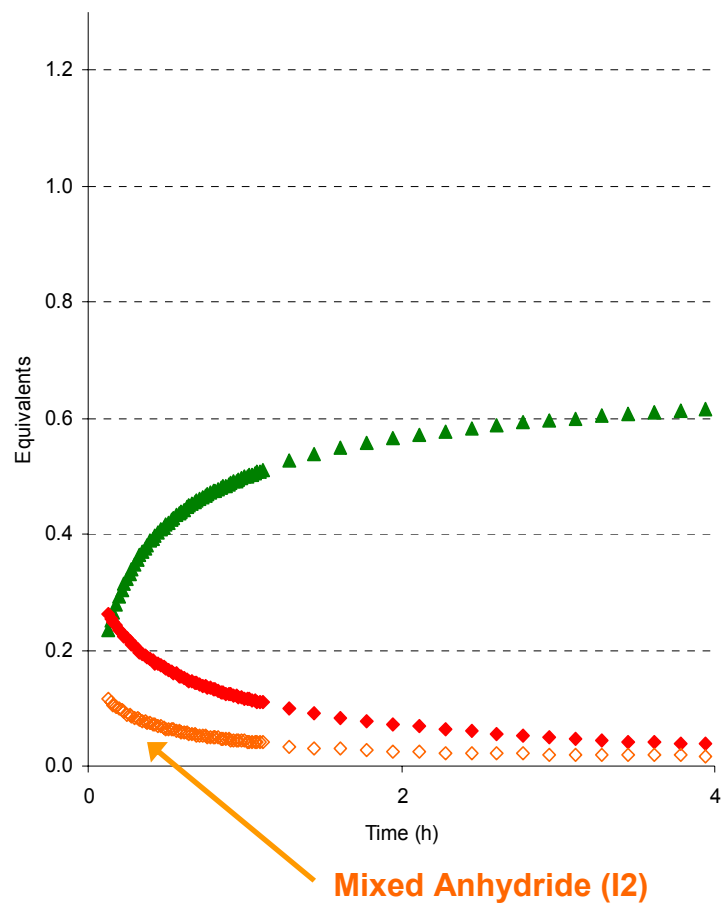




R1 t final**R2B** t final



R2B



R1

