



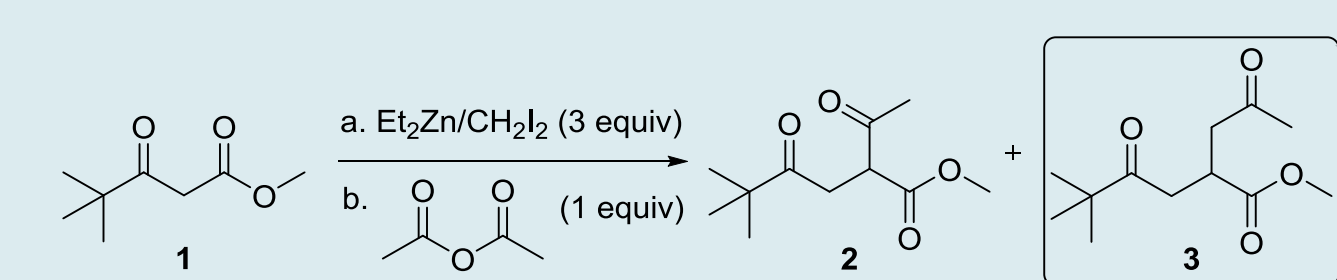
# The Double Chain Extension

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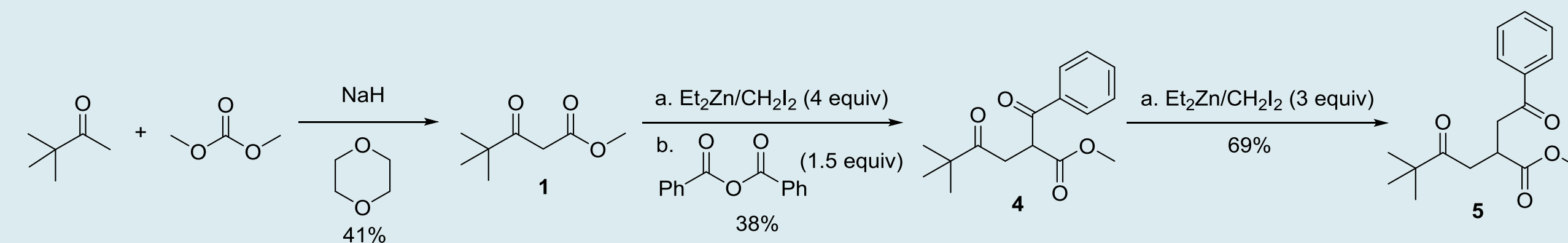
## Introduction<sup>1</sup>

One area of current research in the Zercher group has been directed toward the development of tandem chain extension-acylation reactions.<sup>2</sup> The scope of this reaction includes  $\beta$ -keto esters and  $\beta$ -keto imides using various anhydrides or in a few cases activated carboxylic acids. During the investigation of a tandem chain extension-acylation reaction of methyl pivaloylacetate (**1**), the desired product **2**, was formed along with a minor byproduct (**3**). Compound **3** was formed by the further homologation of compound **2** when produced in the presence of excess zinc-carbenoid. This minor product sparked interest in the development of a double chain extension protocol, which could be optimized to produce compounds similar to compound **3** instead of the acylated product **2**.

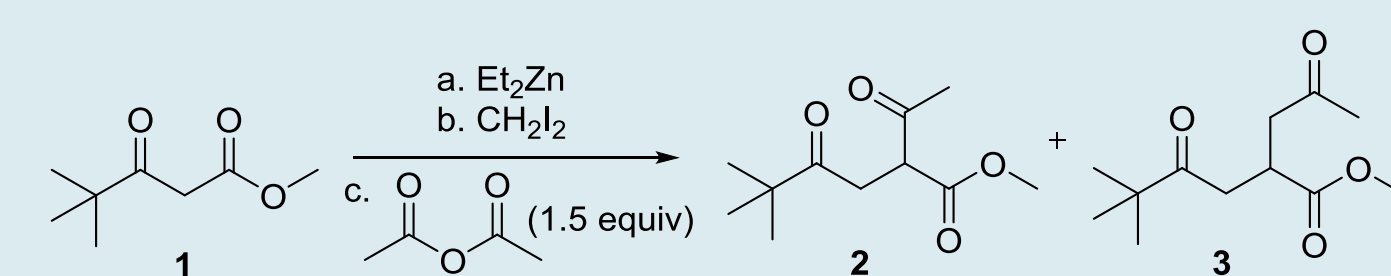


## Results and Discussion

The Double Chain Extension was first attempted on methyl pivaloylacetate **1** with benzoic anhydride. The result was acylated product **4**, which was subjected to zinc carbenoid to afford double chain extended compound **5**.



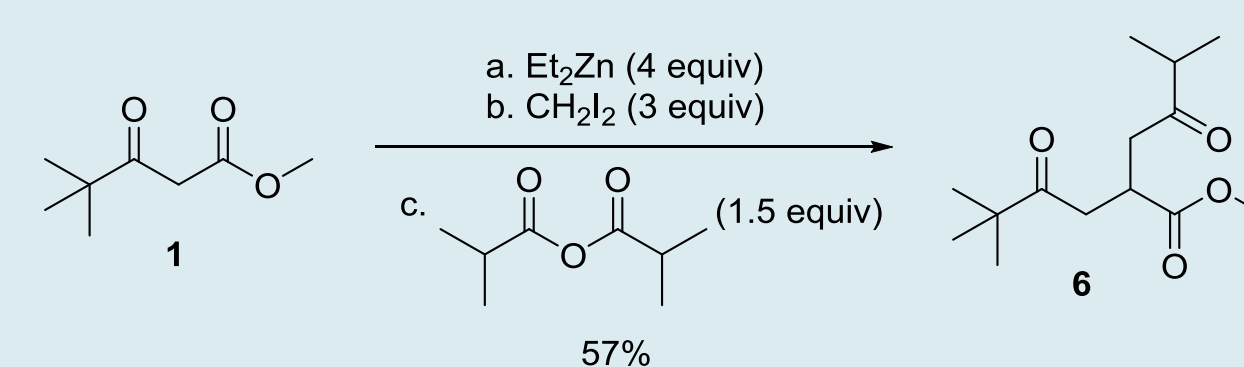
In a second attempt at a one-pot double chain extension, the less bulky acetic anhydride was used to afford a mixture of compounds **2** and **3**.



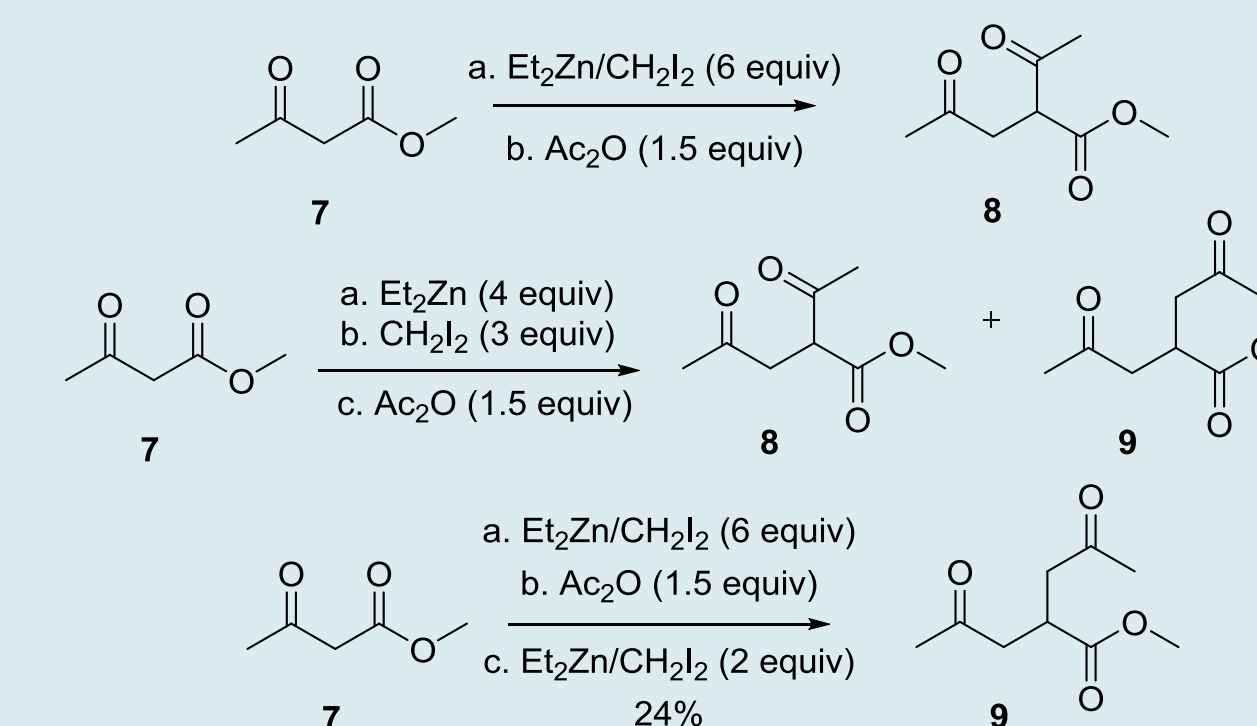
This reaction was optimized by varying the stoichiometry to push the reaction towards the double chain extended product **3**.

Method	Equivalents of Et <sub>2</sub> Zn	Equivalents of CH <sub>2</sub> I <sub>2</sub>	Approximate Ratio of 2:3	Yield (%)
A	4	4	1:0.9	26
B	6	6	1:3.8	63
C	4	3	1:1.6	21

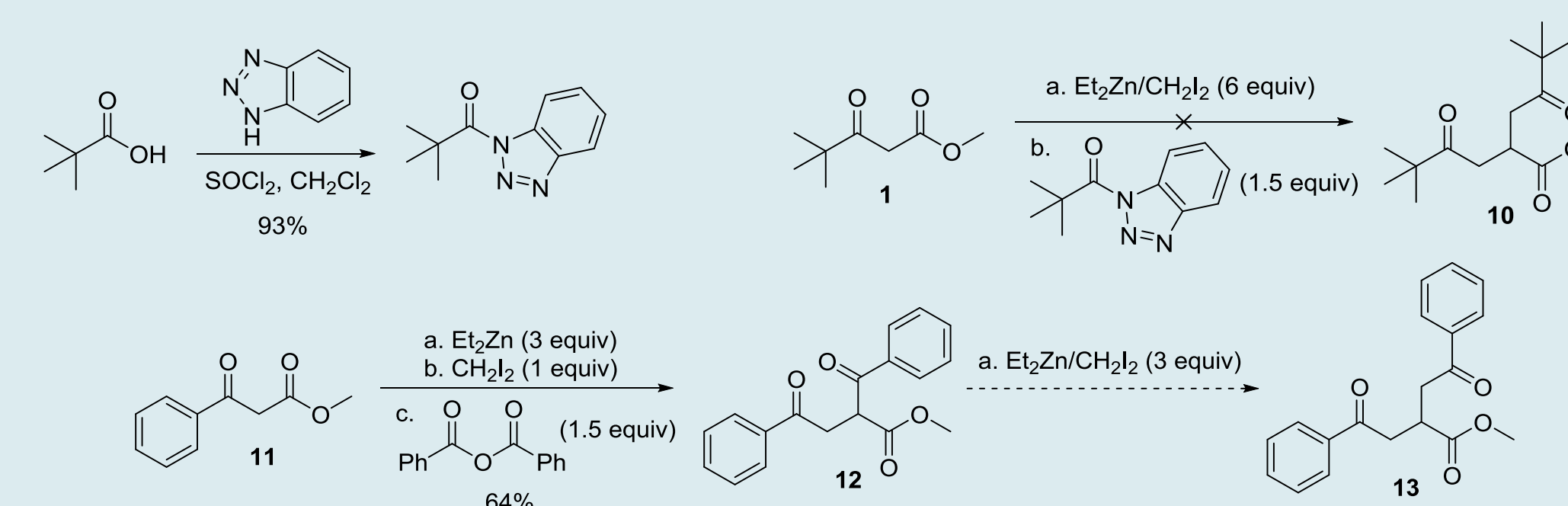
A double chain extension was then performed using the slightly bulkier isobutyric anhydride in a one-pot synthesis of compound **6**.



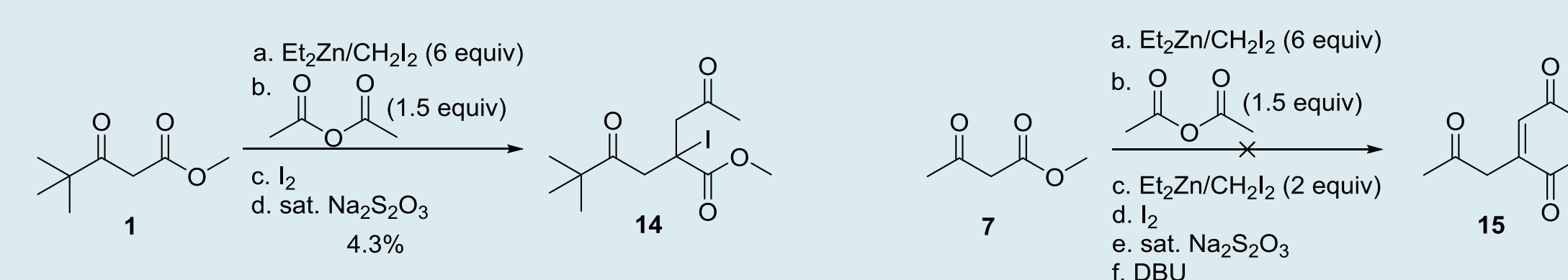
The next goal in the scope of this reaction was to obtain symmetric double chain extended products. This was first attempted with methyl acetoacetate **7** in a series of reactions of varying stoichiometric quantities to eventually afford the double chain extended product **9** after difficult separation on a flash column.



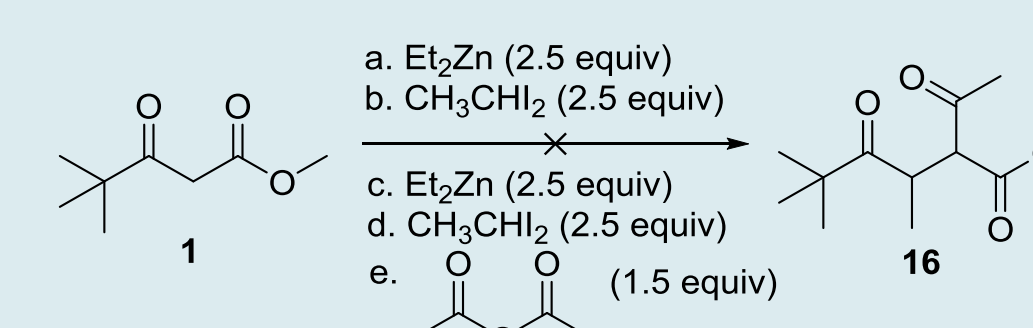
Attempted syntheses of symmetric double chain extended compounds **10** and **13** have proven unsuccessful and will require further investigation.



Iodination at the  $\alpha$ -position of the double chain extended product was then studied in compound **14**, which led to the attempted tandem chain extension acylation chain extension iodination elimination (TCACIE).<sup>3</sup>



Adding functionality at the  $\beta$  position was shown using substituted carbenoid, although the acylation and double chain extension are still being pursued.<sup>4</sup>

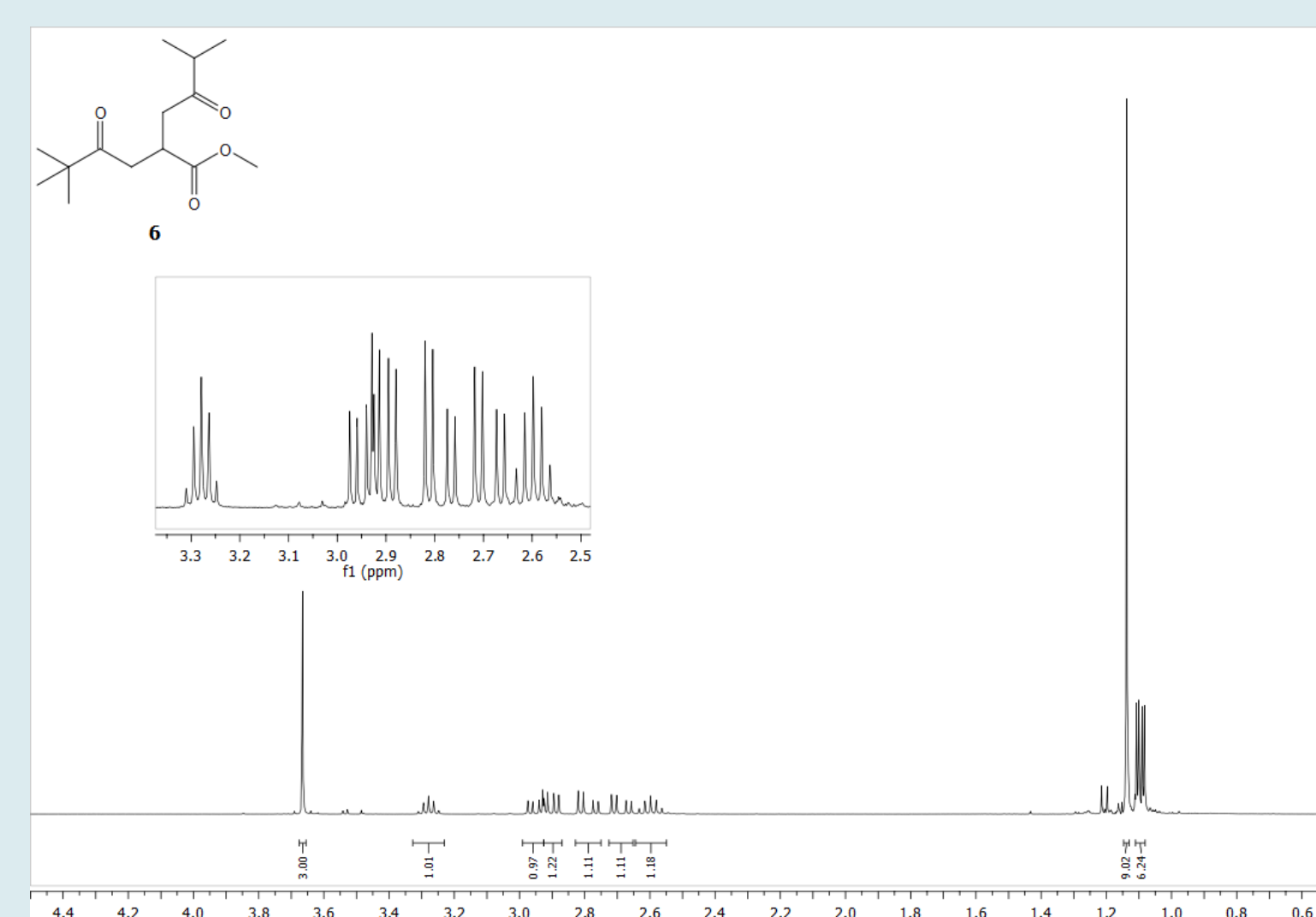
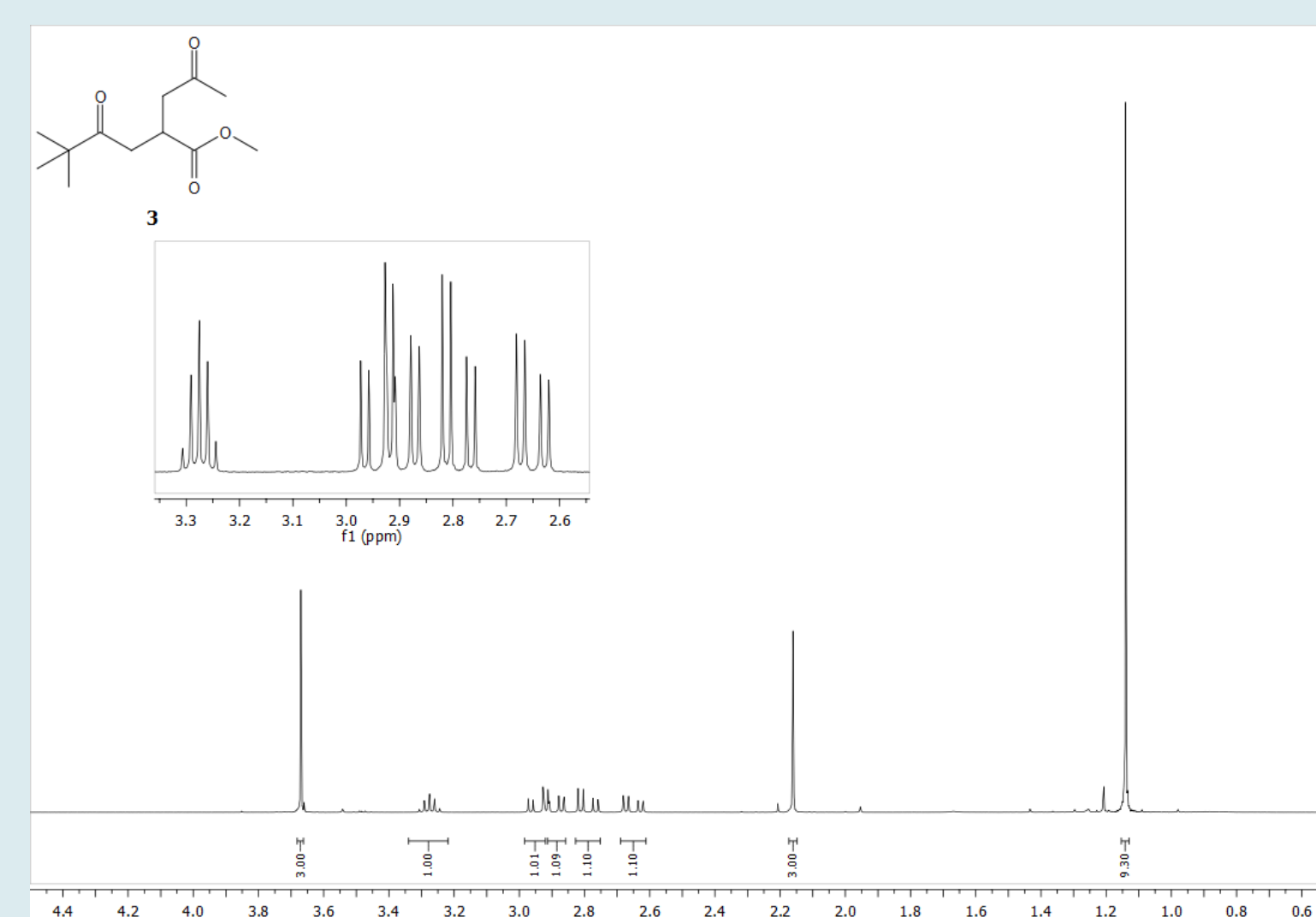
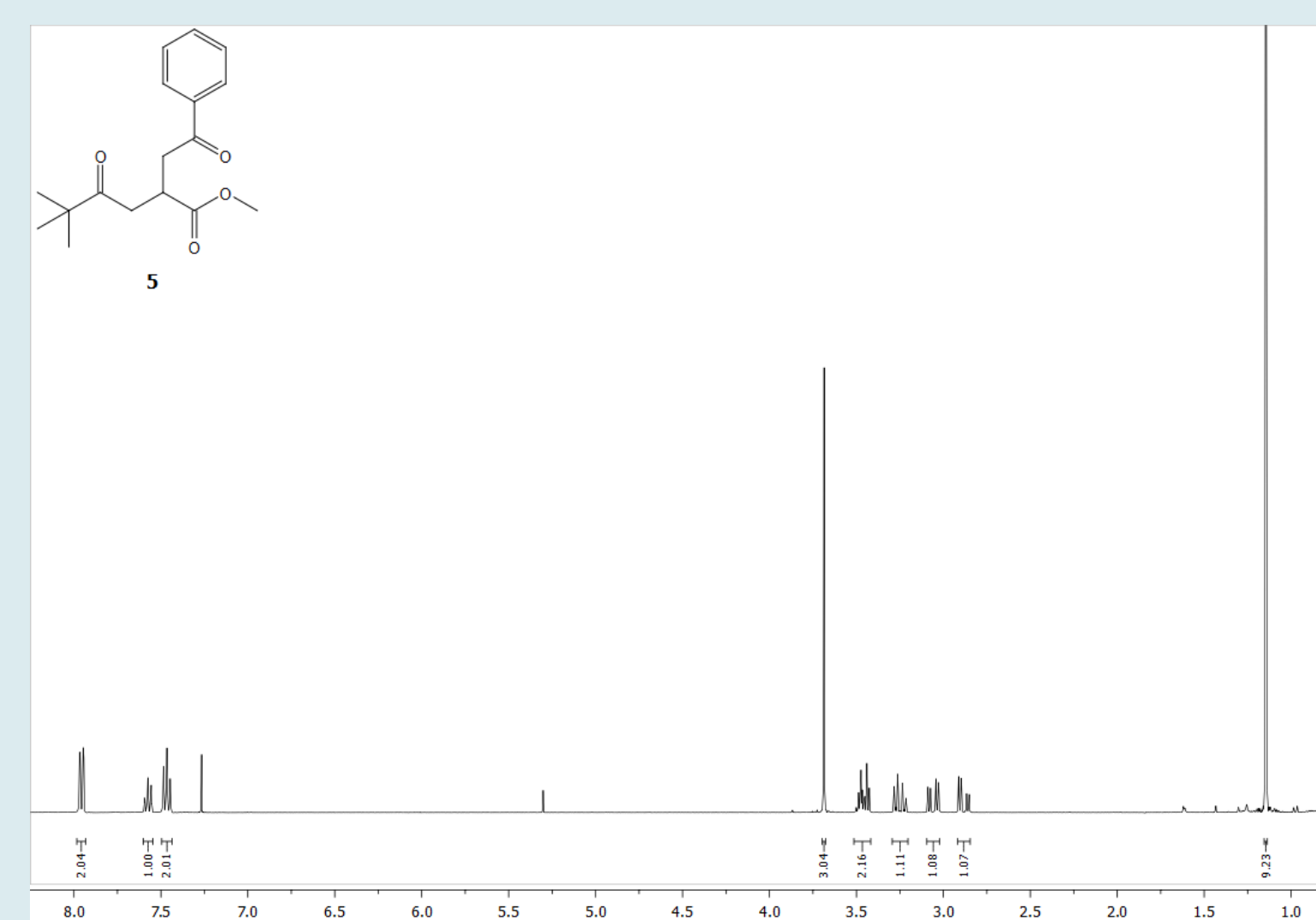
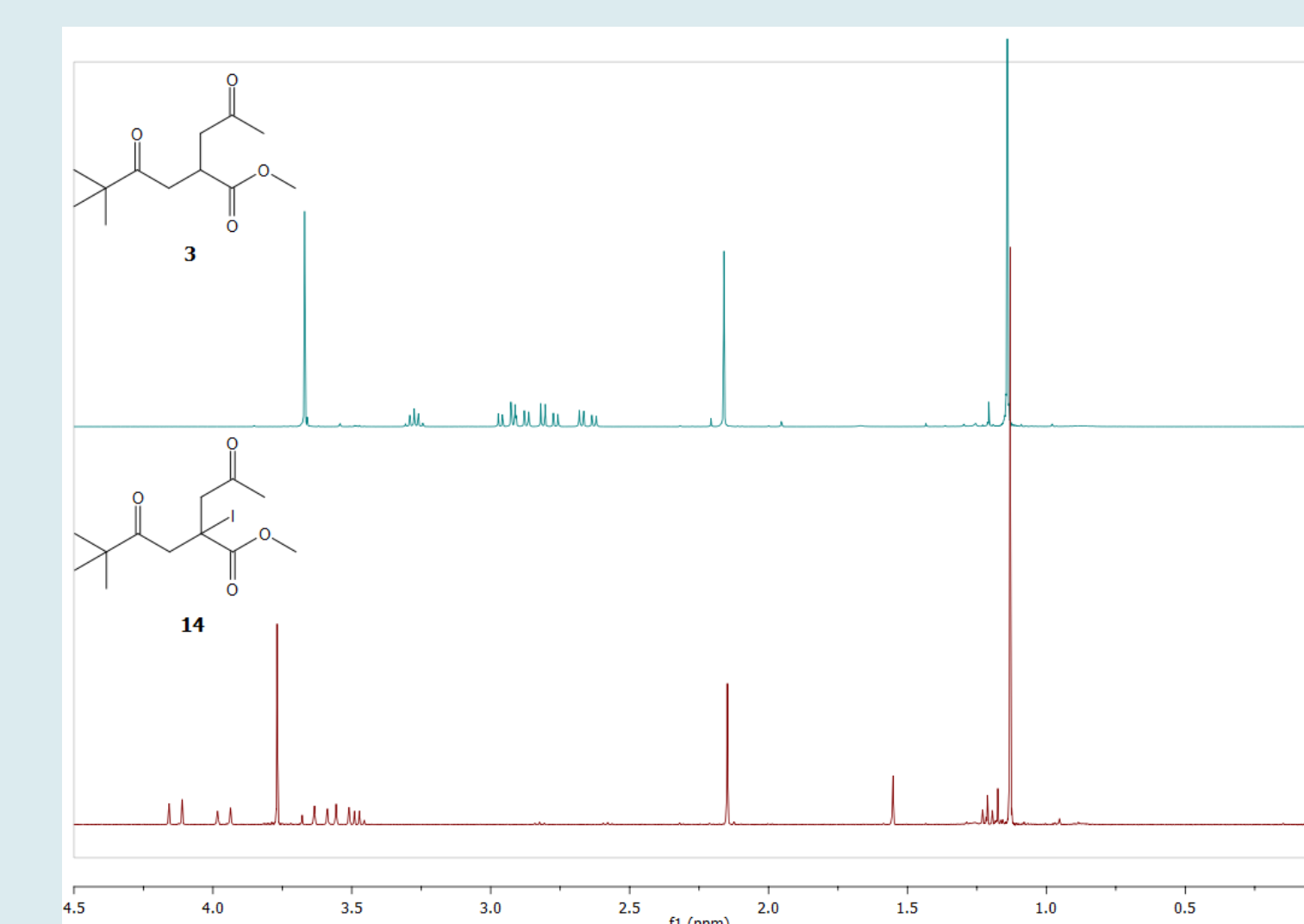
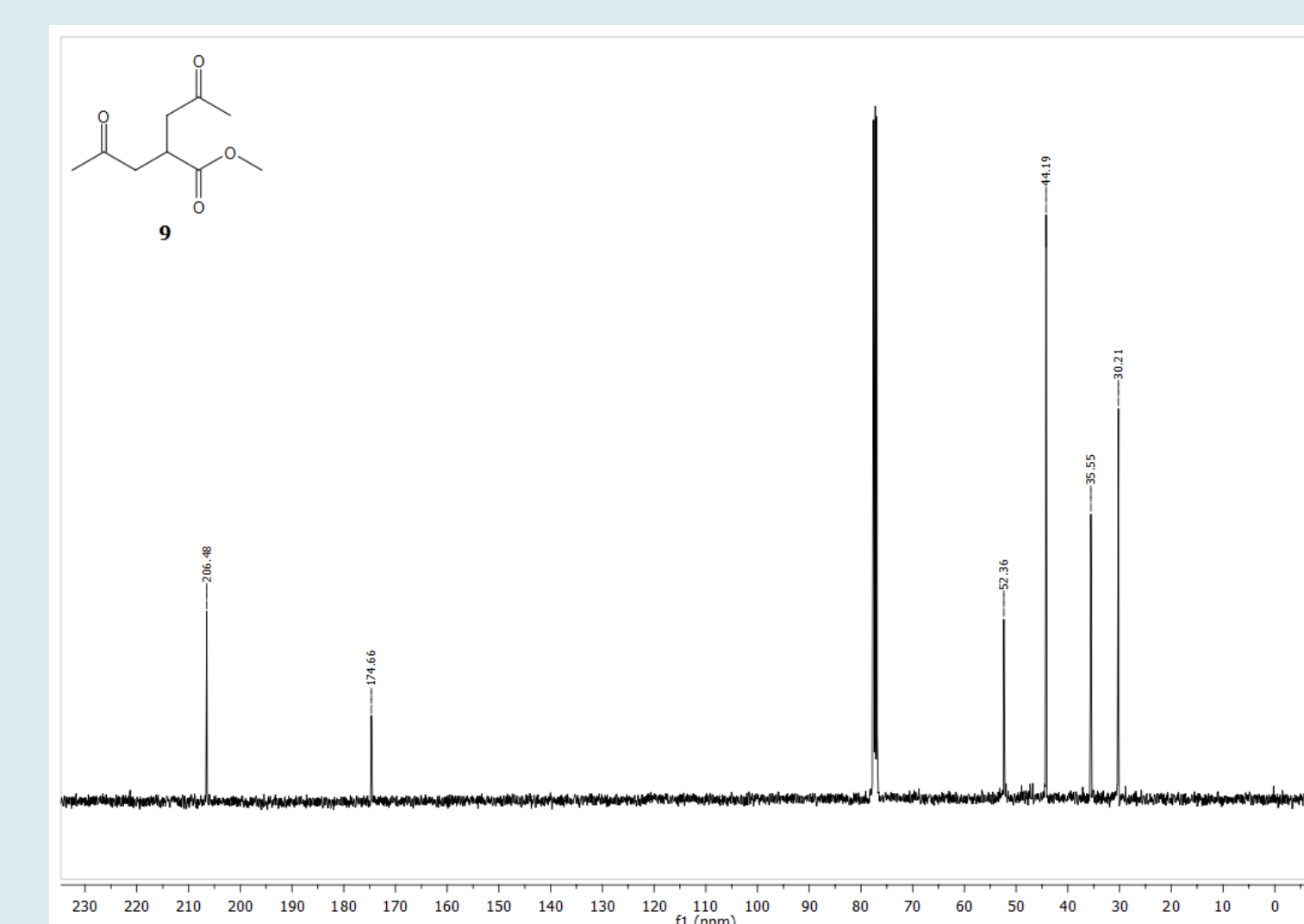
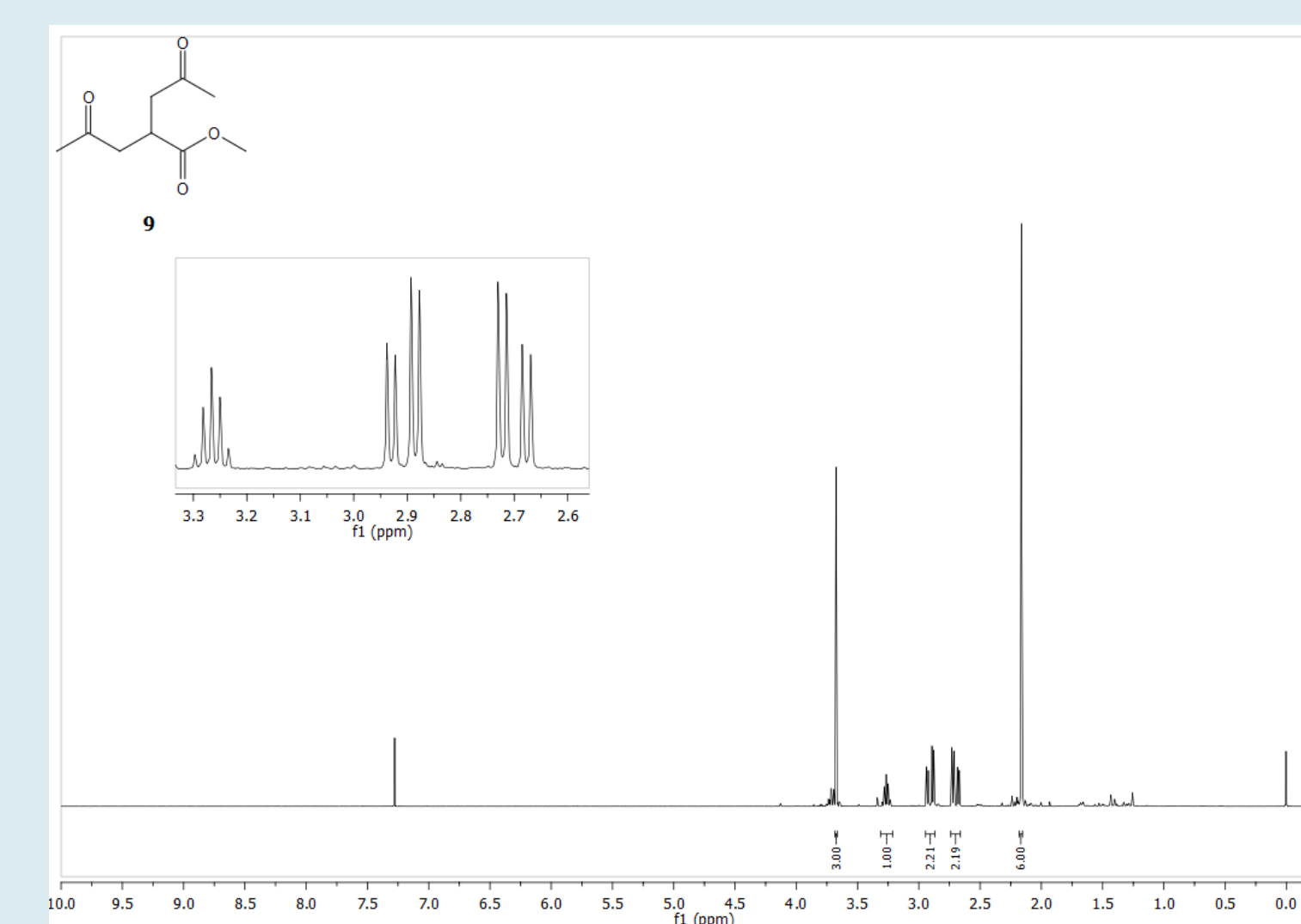
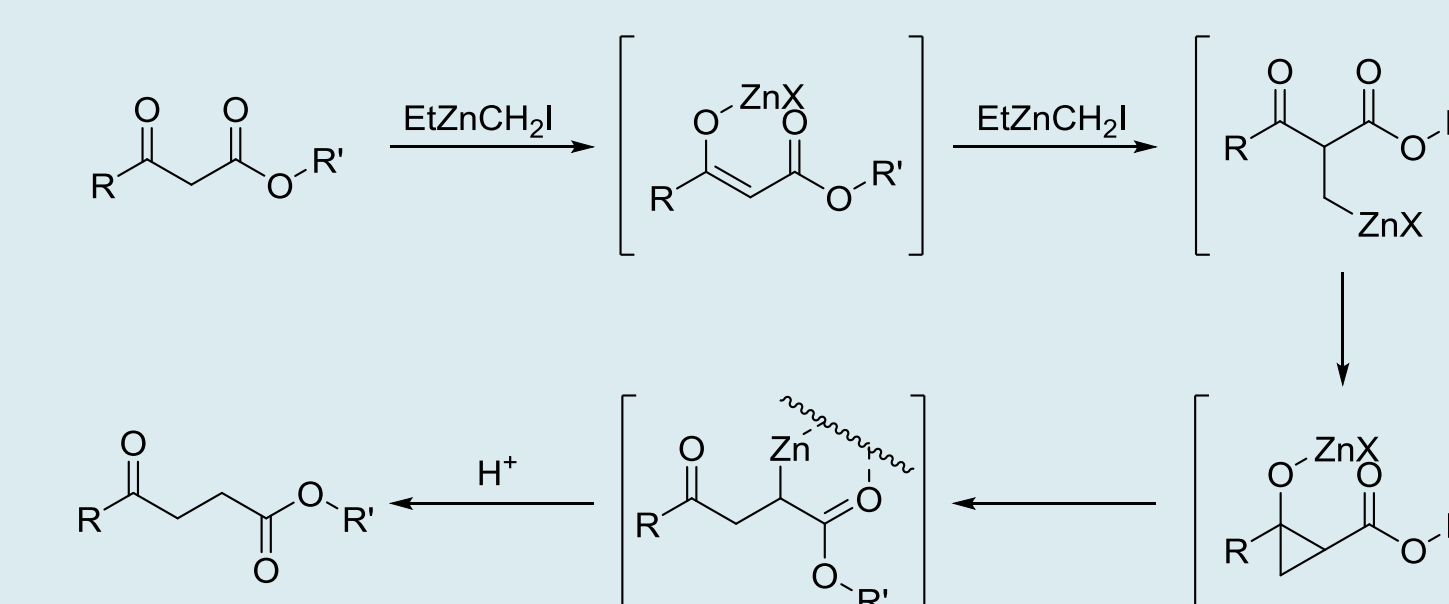


## Conclusion

Zinc carbenoid-mediated chain extension of  $\alpha$ -acylated  $\gamma$ -keto esters provides a facile approach to synthesizing 1,5-diketones.

## Acknowledgements

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