

# Studies in Zinc-Carbenoid Mediated Chain Extensions and $\beta$ -Proline Derivative Formations via Activated Imines in the Presence of $\gamma$ -Keto Esters

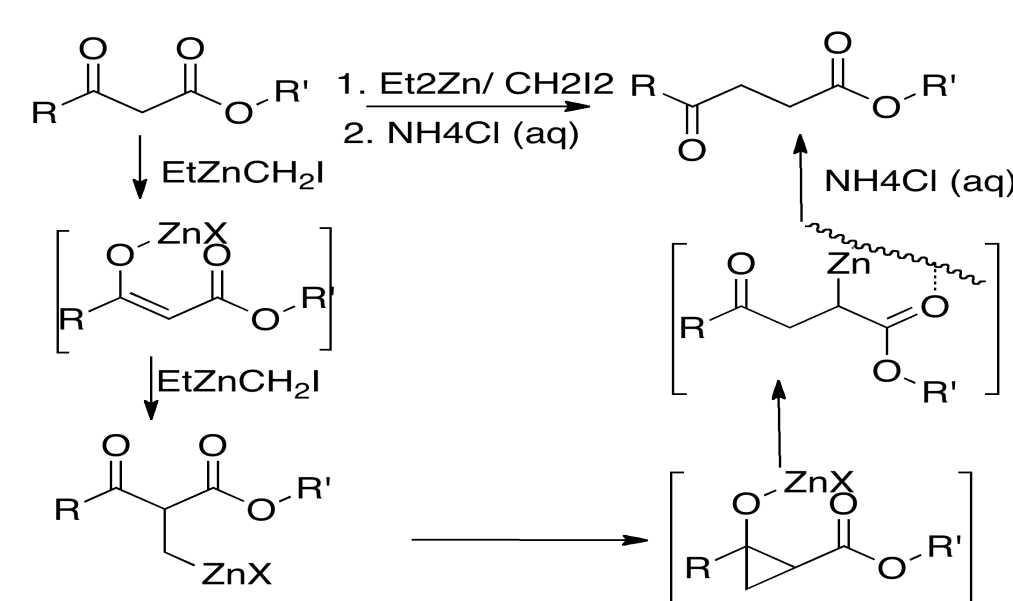


Victoria Curtin and Charles Zercher

Department of Chemistry, University of New Hampshire, Durham, NH 03824

## Introduction

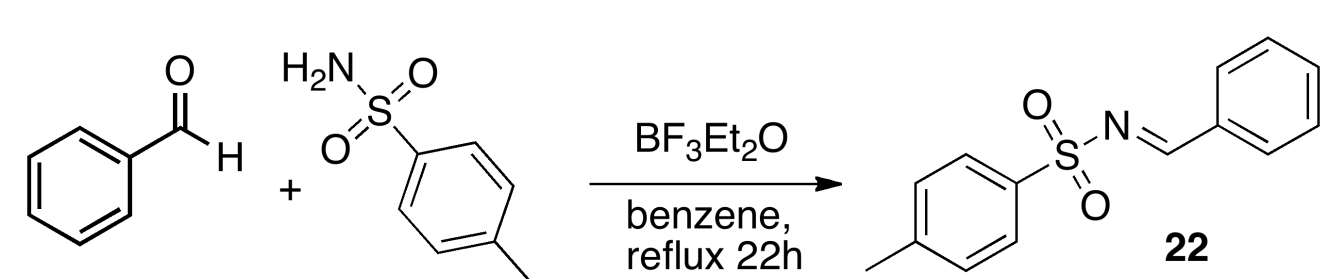
The discovery of the zinc-mediated homologation reaction, in 1997, facilitates the synthesis of a  $\gamma$ -keto ester formation from a  $\beta$ -keto ester and contributes to the chain homologation.<sup>2</sup> A wide range of  $\beta$ -keto esters have been used in this procedure, all yielding a corresponding  $\gamma$ -keto ester in an efficient one-pot reaction. Subsequent studies determined that the homologation reaction was applicable to analogous  $\beta$ -keto substrates.<sup>3</sup> With few exceptions, homologation of these  $\beta$ -keto substrates proceeds cleanly and rapidly (within 30-60 minutes) to provide good yields of the analogous  $\gamma$ -keto substrates.



**Scheme 1-** Proposed homologation mechanism of  $\beta$ -keto esters<sup>3</sup>

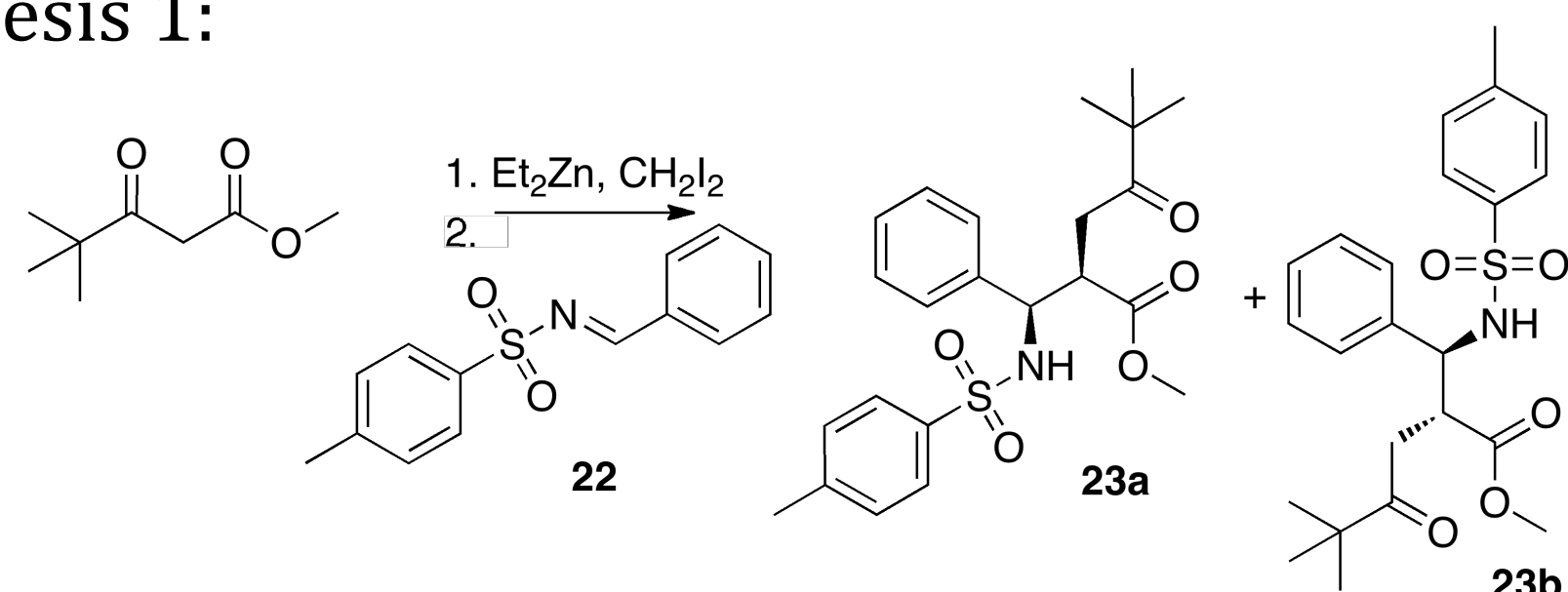
Development of  $\beta$ -proline derivatives is beneficial and desirable for medicinal as well as synthetic purposes because their alternate structural organization could make pharmaceutical drug production and many reactions more feasible. Proteases will not process  $\beta$ -amino acids, therefore  $\beta$ -proline-containing substances are more resistant to degradation in pharmaceutical application. A zinc carbenoid-initiated chain extension reaction provides access to an organometallic intermediate, which is used to capture activated imines and result in the formation of  $\beta$ -amino acids. Deprotection of the amine results in cyclization, which upon treatment with a reducing agent generates the  $\beta$ -proline derivative.

## Methodology



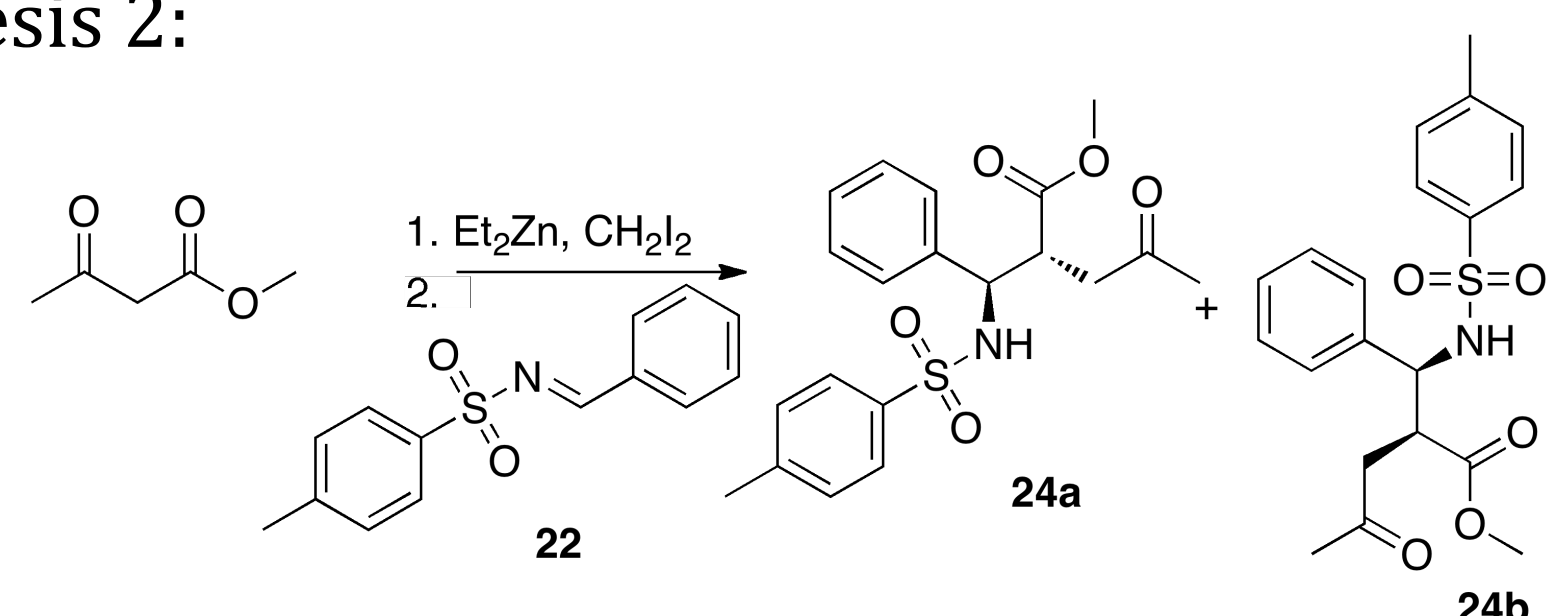
**Scheme 2-** Synthesis of (*N*)-benzylidene-4-methylbenzenesulfonamide (**22**)

### Synthesis 1:



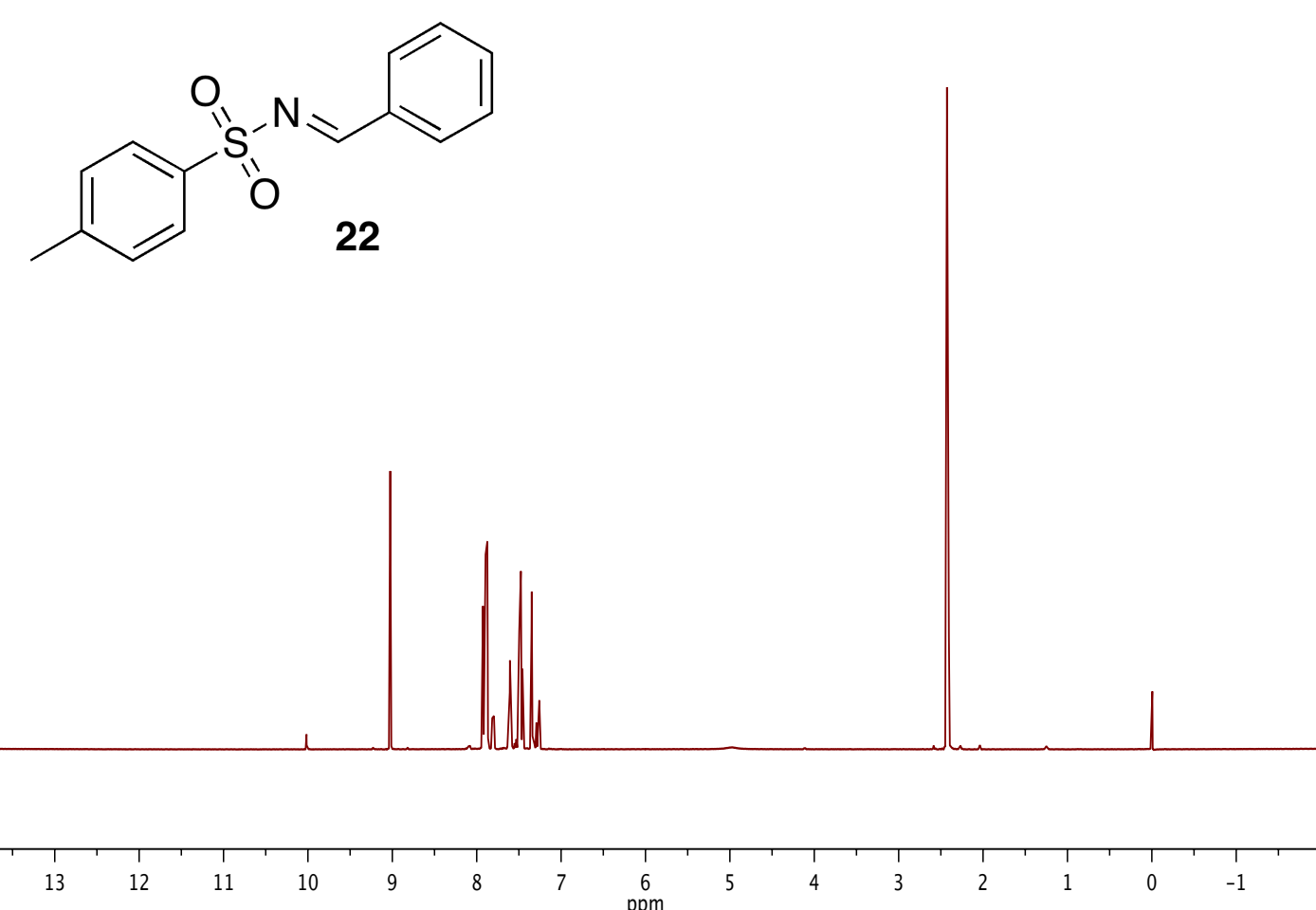
**Scheme 3-** Synthesis of methyl-5,5-dimethyl-2-((4-methylphenylsulfonamido)(phenyl)methyl)-4-oxohexanoate (**23**)

### Synthesis 2:

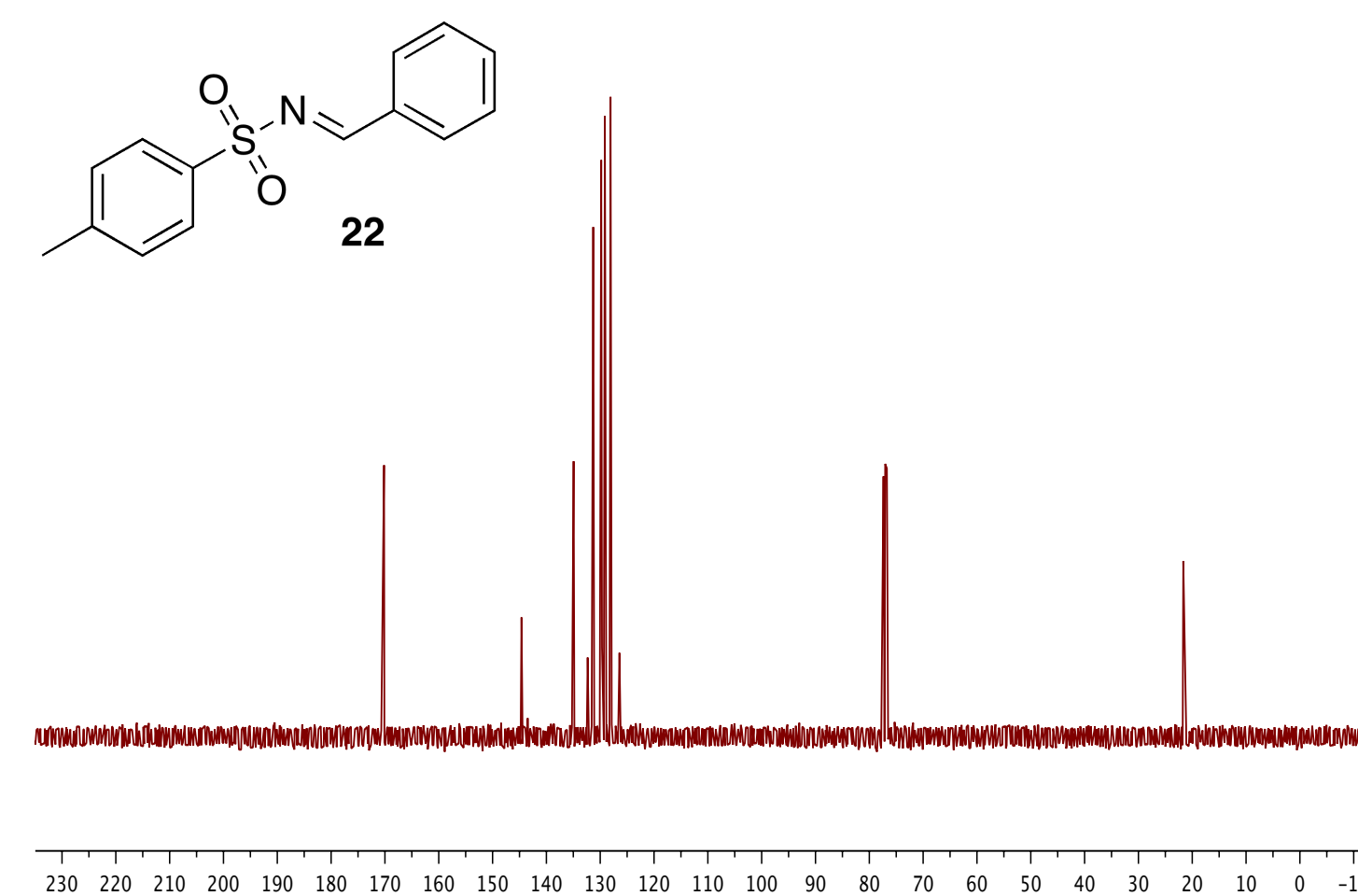


**Scheme 4-** Synthesis of methyl-2-((4-methylphenylsulfonamido)(phenyl)methyl)-4-oxopentanoate (**24**)

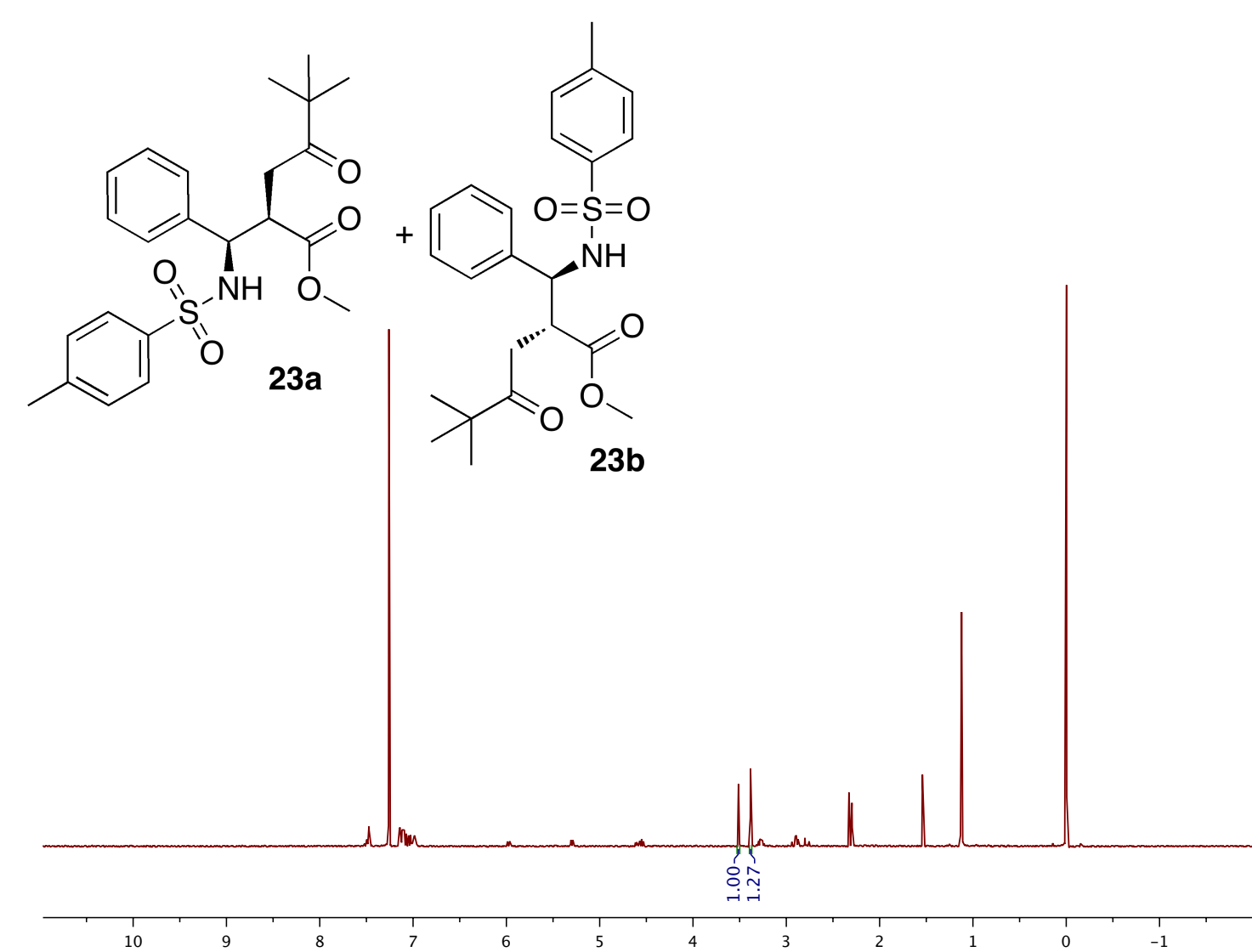
## Results



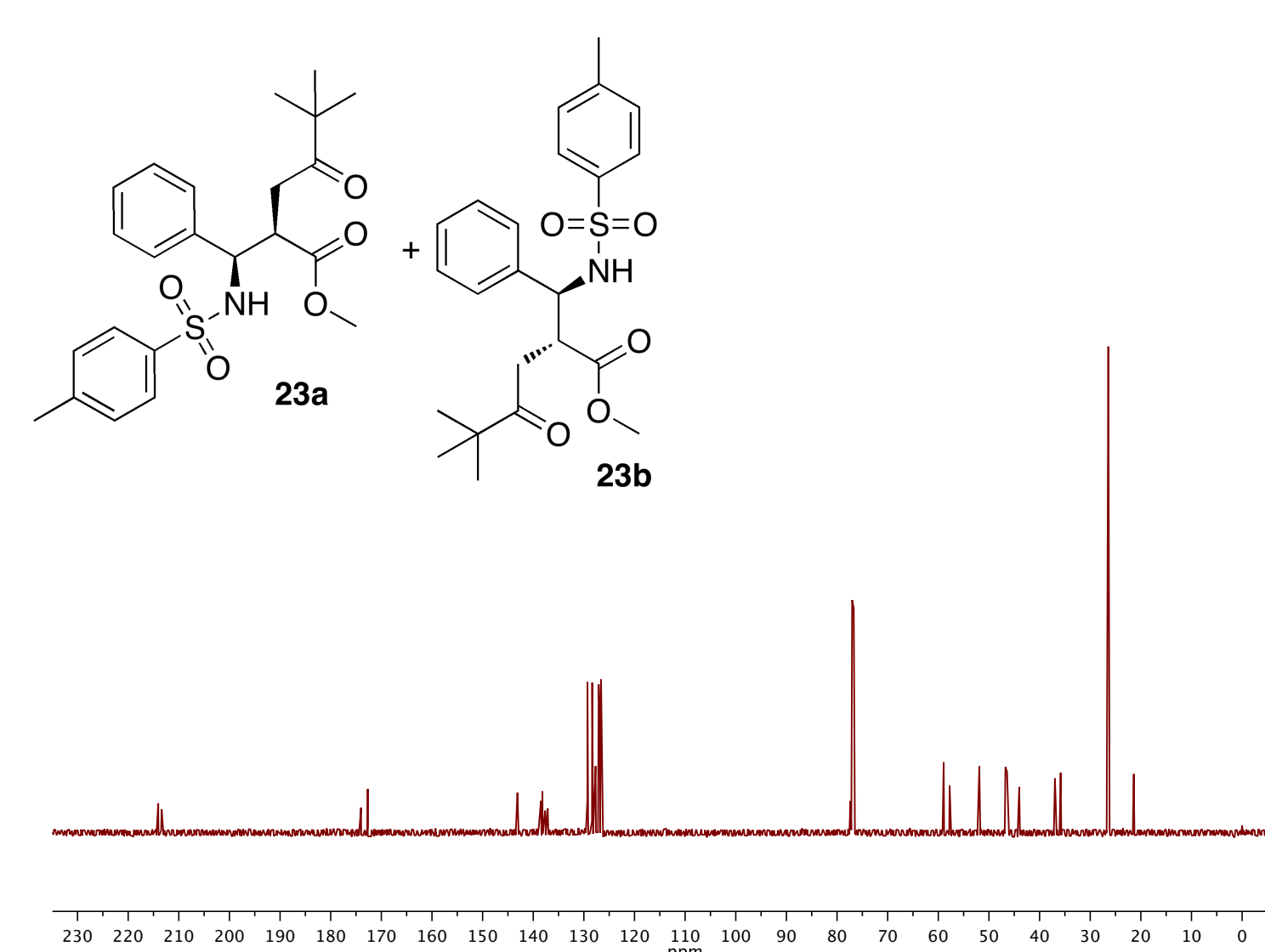
**Figure 1:** <sup>1</sup>H NMR of *N*-benzylidene-4-methylbenzenesulfonamide (**23**)



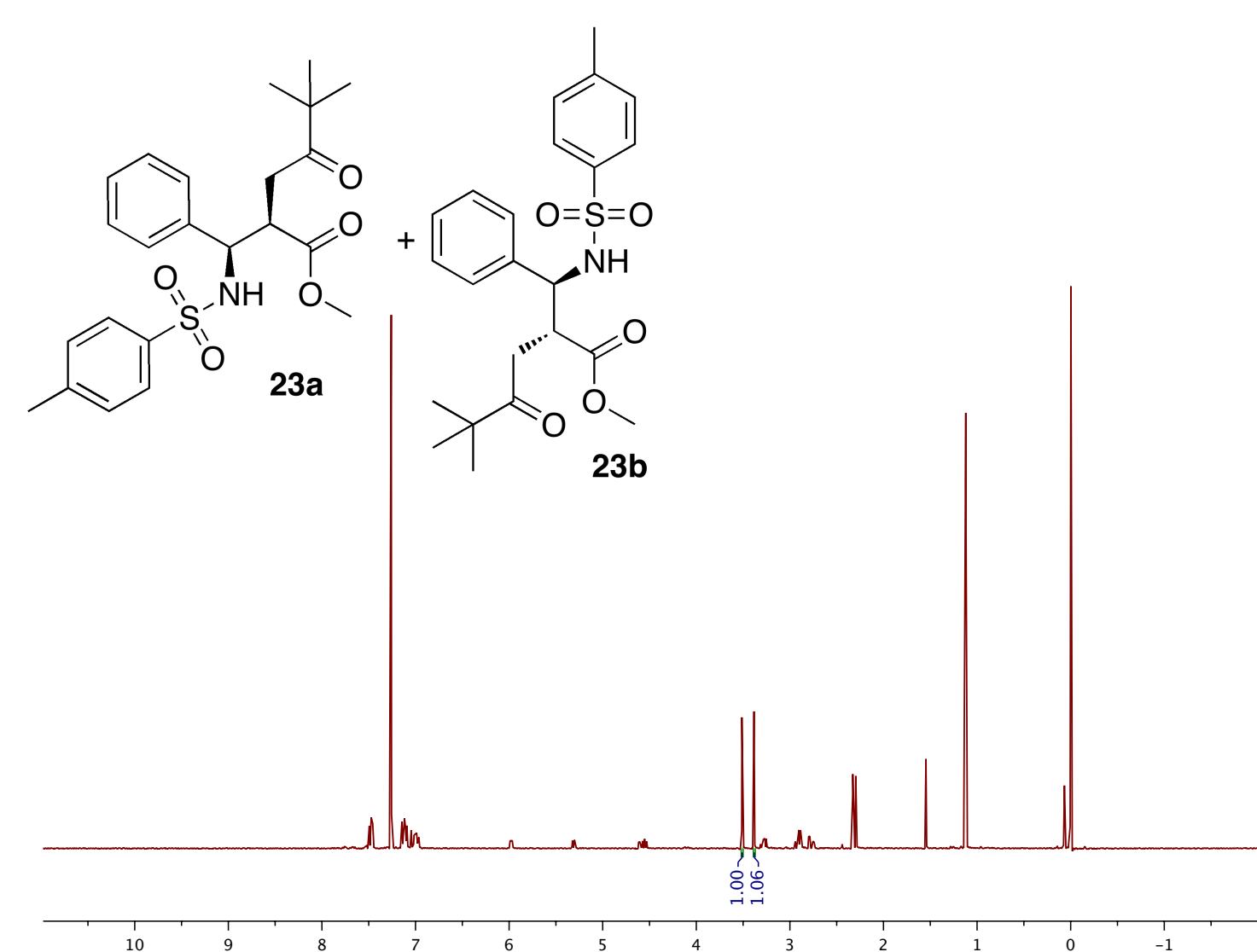
**Figure 1:** <sup>13</sup>C NMR of *N*-benzylidene-4-methylbenzenesulfonamide (**23**)



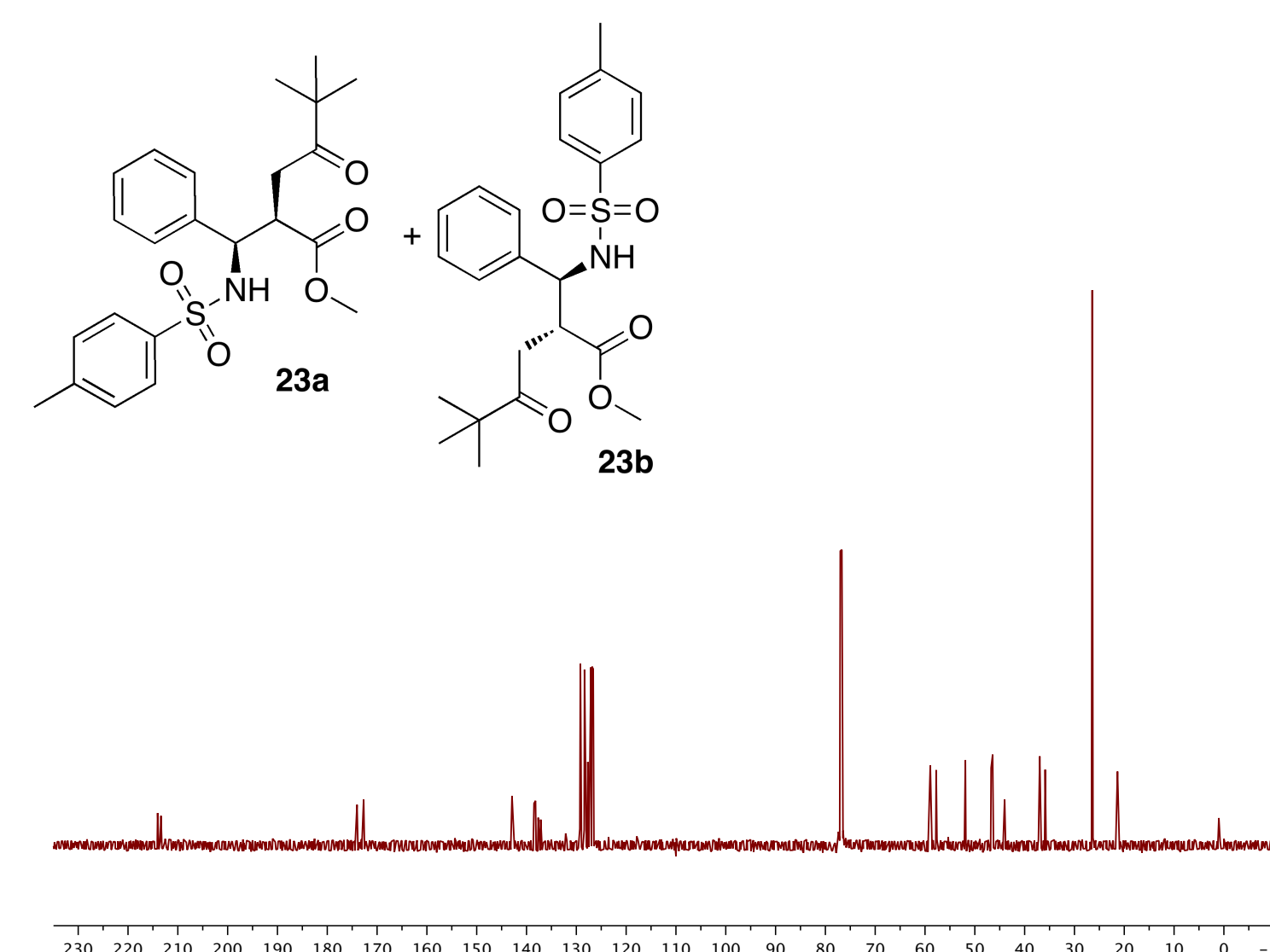
**Figure 2:** <sup>1</sup>H NMR of methyl-5,5-dimethyl-2-((4-methylphenylsulfonamido)(phenyl)methyl)-4-oxohexanoate (**23**) after 48 hours



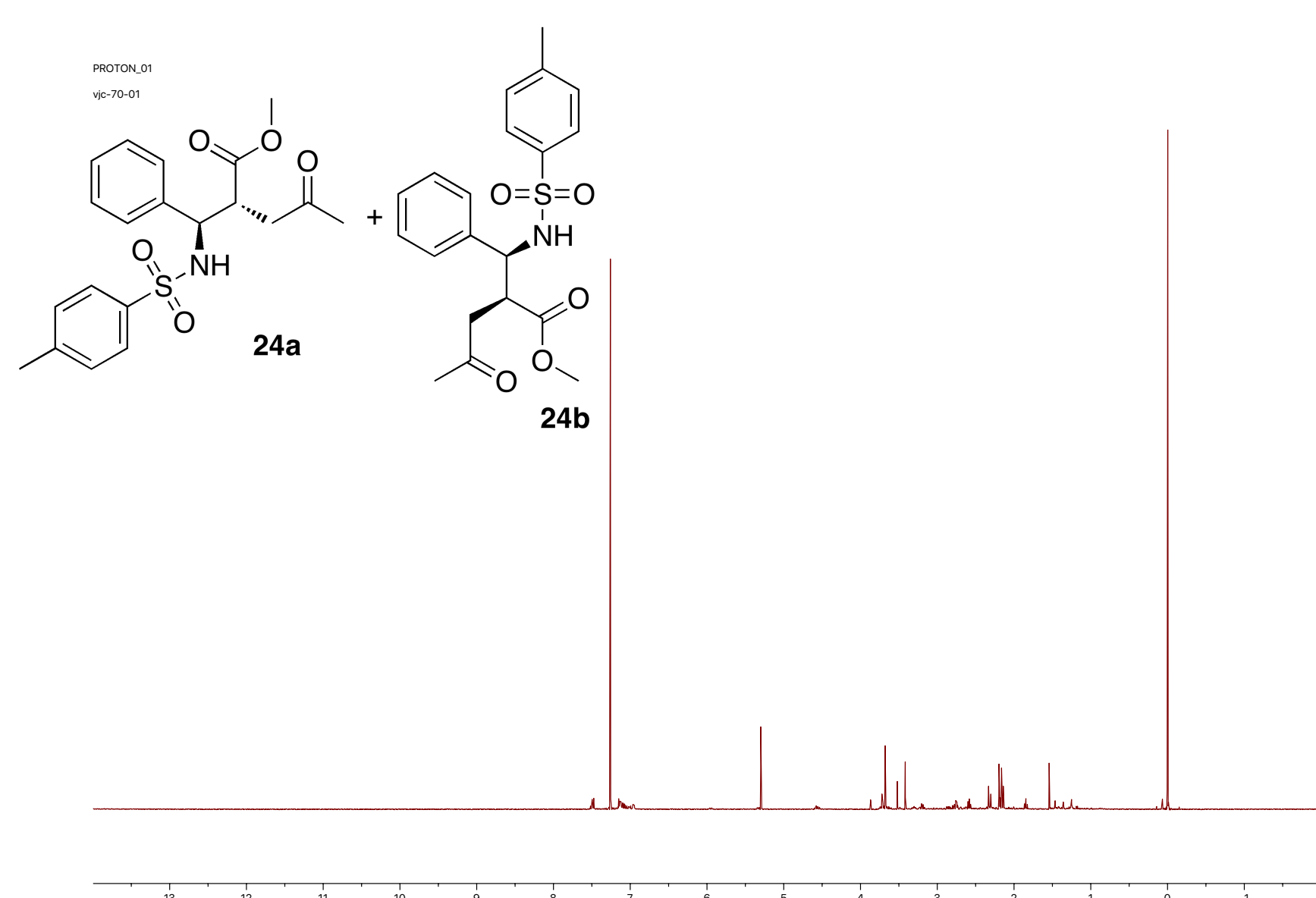
**Figure 3:** <sup>13</sup>C NMR of methyl-5,5-dimethyl-2-((4-methylphenylsulfonamido)(phenyl)methyl)-4-oxohexanoate (**23**) after 48 hours



**Figure 4:** <sup>1</sup>H NMR of methyl-5,5-dimethyl-2-((4-methylphenylsulfonamido)(phenyl)methyl)-4-oxohexanoate (**23**) after 1 1/2 hours

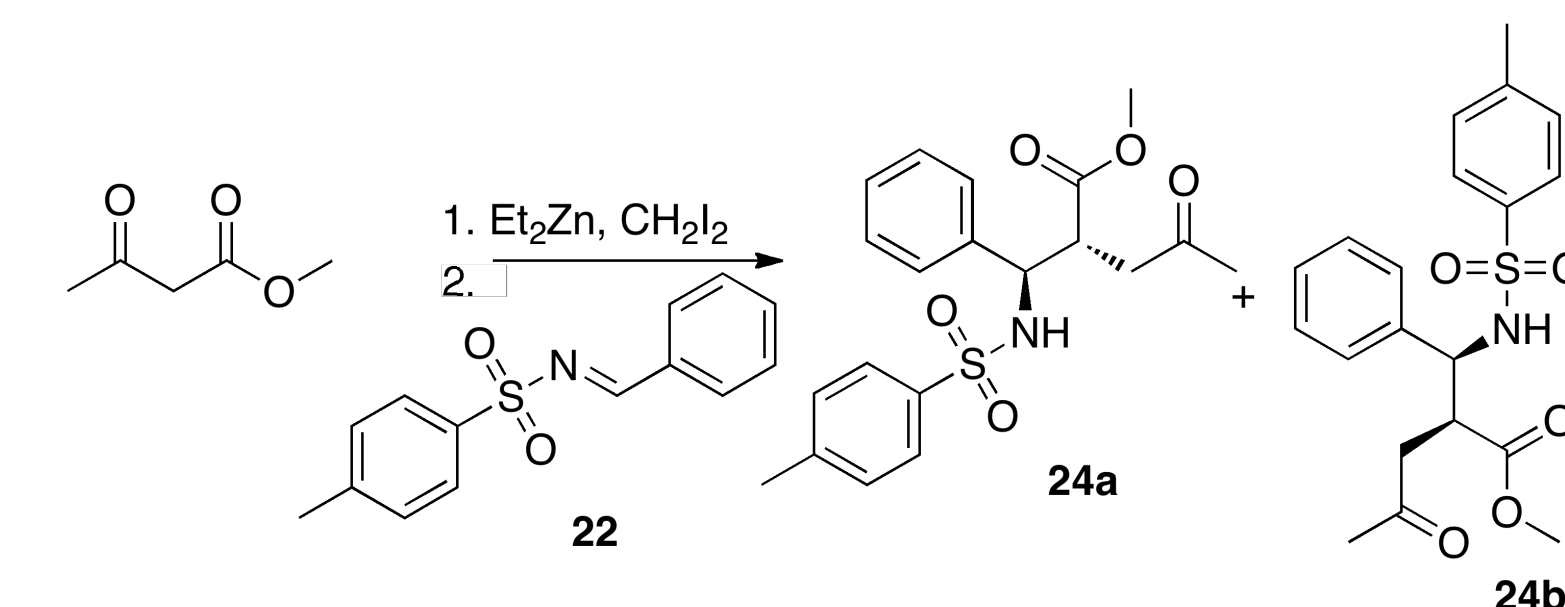


**Figure 5:** <sup>13</sup>C NMR of methyl-5,5-dimethyl-2-((4-methylphenylsulfonamido)(phenyl)methyl)-4-oxohexanoate (**23**) after 1 1/2 hours

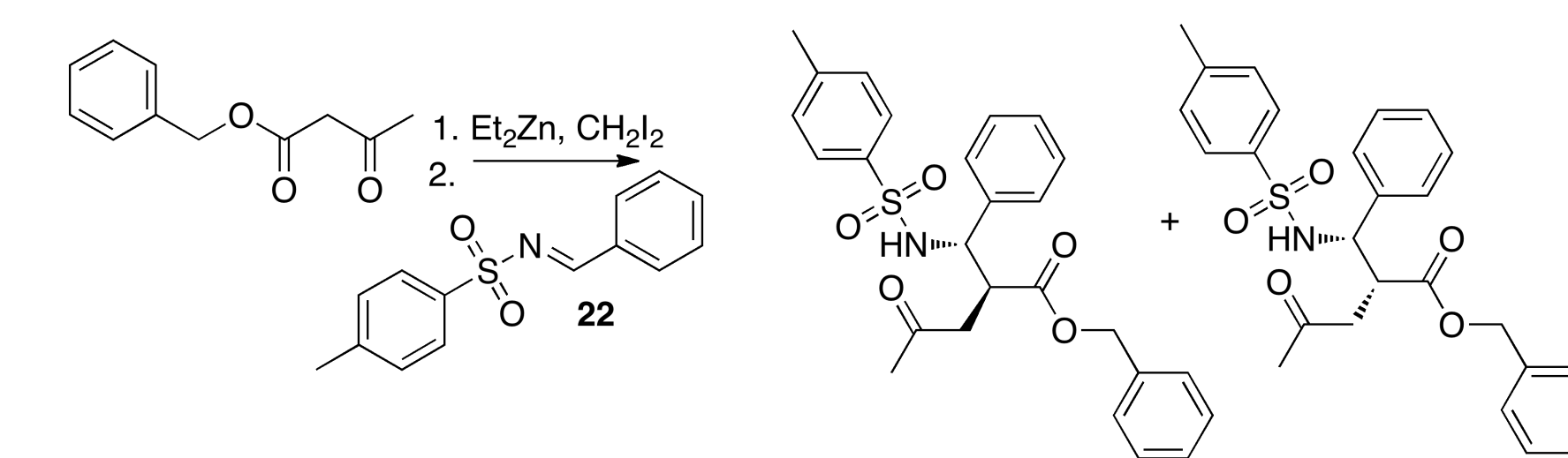


**Figure 6:** Crude <sup>1</sup>H NMR of methyl-2-((4-methylphenylsulfonamido)(phenyl)methyl)-4-oxopentanoate (**24**) after 1 1/2 hours

## Future Work



**Scheme 4-** Synthesis of methyl-2-((4-methylphenylsulfonamido)(phenyl)methyl)-4-oxopentanoate (**24**)



**Scheme 5-** Synthesis of benzyl-2-((4-methylphenylsulfonamido)(phenyl)methyl)-4-oxopentanoate

## Conclusions

The  $\beta$ -amino acid derivative, methyl 5,5-dimethyl-2-((4-methylphenylsulfonamido)(phenyl)methyl)-4-oxohexanoate (**23**), was successfully synthesized via a zinc carbenoid-initiated chain extension reaction. The product was formed in a good yield (91%) and with a diastereomeric ratio of 1:1 in a short reaction time (~1 1/2 hours).

Benzyl-2-((4-methylphenylsulfonamido)(phenyl)methyl)-4-oxopentanoate was likely synthesized, but further purification techniques need to be optimized in order to fully isolate the compound for characterization.

## Acknowledgements

I would like to thank Dr. Zercher for allowing me the opportunity to conduct this research as well as taking the time to meet with me to go over the results obtained. I would also like to give a special thanks to Nick Arnista, the graduate student in the Zercher research group, for mentoring me and answering the many questions I had along the way. As well as my friends and family for their constant support and encouragement. Finally, I would like to thank the UNH Chemistry department for making this research possible.

## References

1. Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron Lett.* **1996**, 3353-3354.
2. Brogan, J. B.; Zercher, C. K. *J. Org. Chem.* **1997**, 62, 6444-6446.
3. Mower, M.P. Bachelor of Science Thesis, University of New Hampshire, **2012**.
4. Bala, K. I. Master of Science Thesis, University of New Hampshire, **2016**.
5. Eger, W. A.; Zercher, C.K.; Williams, C.M. *J. Org. Chem.* **2010**, 75, 7322-7331. <https://scholars.unh.edu/cgi/viewcontent.cgi?article=2071&context=thesis>
6. Alken, K.S.; Eger, W.A.; Williams, C.M.; Spencer, C.M.; Zercher, C.K. *J. Org. Chem.* **2012**, 77(14), 5942-5955.
7. Lai, S.; Zercher, C.K.; Jasinski, J.P.; Reid, S.N.; Staples, R.J. *Org. Lett.* **2001**, 3(26), 4169-4171.
8. Figure 2f from: Irimia R, Gottschling M (2016) Taxonomic Revision of *Rocheffortia* Sw. (Ehretiaceae, Boraginales). *Biodiversity Data Journal* 4: e7720. <https://doi.org/10.3897/BDJ.4.e7720>
9. Guizzetti, S.; Benaglia, M.; Pignataro, L.; Puglisi, A. *Tetrahedron Lett.* **2006**, 17, 2754.
10. Bhagavan, N.V.; Ha, C. *Essentials of Medical Biochemistry*, **2015**, 2.
11. Proline Derivatives. <https://www.sigmaaldrich.com/technicaldocuments/articles/chemfiles/proline-derivatives.html> (accessed Nov 11, 2018).
12. Vignola, N.; List, B. *J. Am. Chem. Soc.* **2003**, 125, 450. (b) Dalako, P.I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, 43, 5138.
13. Jacobine, A.M.; Puchlopek, A.L.A.; Zercher, C.K.; Briggs, J.B.; Jasinski, J.P.; Butcher, R.J. *Tetrahedron Lett.* **2012**, 68, 7799-7805.
14. Lu, K.; Kwon, O.; Brummond, K.M.; Davis, M.M. *Organic Synth.* **2009**, 86, 212-224.