The effect on enantioselectivity in a Diels-Alder reaction involving menthyl acrylate and cyclopentadiene

John Huynh and Stephen G. Newman
Department of Chemistry, University of Ottawa

Introduction

The isolation of enantiopure compounds is critical in the pharmaceutical industry. Chiral auxiliaries are incorporated into the reaction to control the stereochemistry of the desired product. Chiral auxiliaries are not commonly used because they are extremely costly to synthesize and wasteful.

The purpose of the project is to synthesize an effective chiral auxiliary and develop a feasible method to isolate the chiral auxiliary so that it could be recycled. Previous experiments performed indicate that acrylates are effective chiral auxiliaries. Menthyl acrylate will be used as the chiral auxiliary and will undergo a Diels-Alder reaction with cyclopentadiene (shown in Scheme 1).

It is hypothesized that the Diels-Alder reaction would yield a higher proportion of one enantiomer in the acid product over the other.

Methodology

Prepare the menthyl acrylate product from a reaction involving (-)-menthol and acryloyl chloride.

↓

Prepare cyclopentadiene through the pyrolysis of dicyclopentadiene.

↓

Immediately following the synthesis of cyclopentadiene, it is mixed with menthyl acrylate. An ester product is formed through a Diels-Alder reaction.

↓

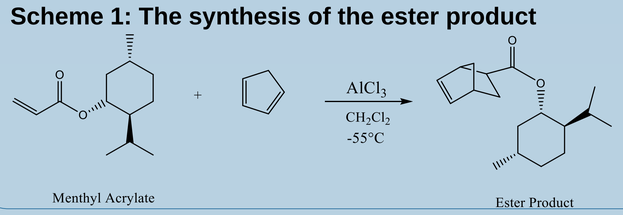
Add potassium hydroxide to the ester product. This cleaves the ester bond through. The reaction is Shown in Scheme 2.

↓

Isolate the menthyl acrylate and the acid product through liquid-liquid extraction and flash column chromatography.

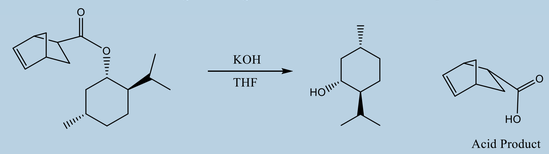
Reaction Schematics

Scheme 1: The synthesis of the ester product



Menthyl Acrylate — Ester Product

Scheme 2: The hydrolysis of the ester product



Ester Product — (-)-menthol Chiral Auxiliary — Acid Product

Results

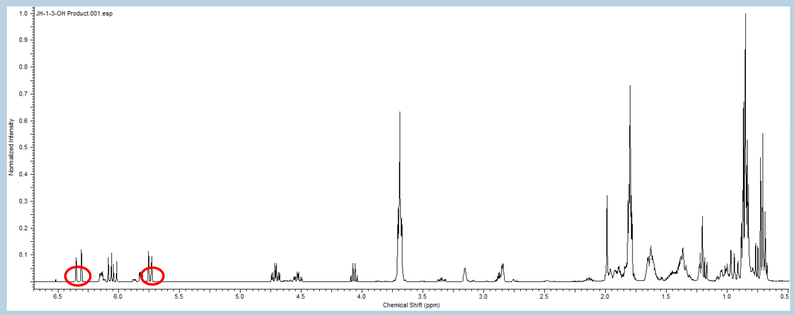


Figure 1. The H-NMR data obtained for the isolated (-)-menthol after the ester product was cleaved. The target peaks that correspond to (-)-menthol are circled in red. A percent yield of approximately 17% of (-)-menthol was isolated.

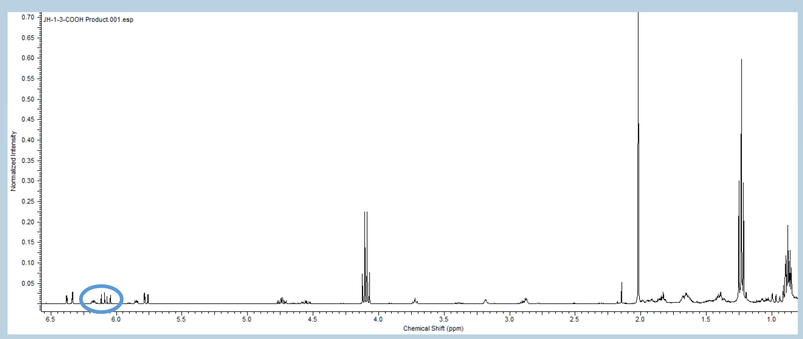


Figure 2. The H-NMR data obtained for the acid product after the ester product was cleaved and extraction. The target peaks that correspond to the acid product are circled in blue. A percent yield of approximately 8% of the acid product was obtained.

Discussion

From the NMR data, the chiral auxiliary menthyl acrylate was successfully synthesized and reacted with the cyclopentadiene. The target peaks of menthyl acrylate are present as well as the target peak for the acid product

Although the ester product was successfully synthesized, the separation of the menthyl acrylate and acid product was unsuccessful. Both NMR displayed very similar peaks implying the products were not separated. We think that the hydrolysis of the ester product was unsuccessful.

To conclude, the hypothesis was partially correct. The Diels-Alder reaction between the menthyl acrylate product and cyclopentadiene is feasible with a low yield. But we were unable to separate the chiral acrylate from the acid product.

Future Studies

The reaction would need to be repeated in order to determine whether it is feasible to separate the menthyl acrylate from the acid product and under different conditions in order to improve the yield.

If the (-)-menthol (chiral auxiliary) can be isolated from the product, the next step would be to incorporate a flow reactor in order to better control the reaction.

References

[1] Oppolzer, Kurth, Reichlin, and Moffatt. (1981). A reinvestigation of asymmetric induction in Diels-Alder reactions to chiral acrylates. *Tetraheron Letters.* Vol.22, No.27, pp 2545-2548.
[2] Hedin-Dahlstrom, Shoravi, Wikman, Nicholls, (2004). Stereoselective reduction of menthone by molecularly imprinted polymers. *Tetrahedron: Assymetry*. 2431-2436
[3] Partridge, Chadha and Uskokivic. (1985) Assymetric hydroboration of 5-substituted cyclopentadienes: synthesis of methyl (1R, 5R)-5-hydoxy-2-cyclopentene-1-acetate. *Organic Syntheses.* Vol 7, p.339-348

Acknowledgements

This research was funded by UROP and performed in the Centre of Catalysis Research and Innovation.

Centre for Catalysis Research and Innovation
Centre de recherche et d'innovation en catalyse

I would like to thank Dr. Newman and the members of the Newman group for their efforts.

John Huynh, jhuyn064@uottawa.ca