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Asymmetric Synthesis of DEHP

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Background

Di(2-ethylhexyl) phthalate (DEHP) is a plasticizer found in polyvinylchloride (PVC), dialysis and catheter tubing, toys, food packaging, and hydraulic fluid, among other sources [1]. Like other phthalate esters, DEHP is classified as both a peroxisome proliferator chemical (PCC) [2] and endocrine disrupting chemical (EDC) [1] and has been seen to increase the occurrence of liver tumors as well as cause developmental changes to the male reproductive tract in mice. Studies have suggested DEHP and its metabolites are able to induce these changes in gene expression through multiple nuclear receptors including PPARα and CAR [2]. Given that biological response often varies greatly between different isomers of the same compounds, it is likely the toxicity of DEHP and its metabolites could vary between the enantiomeric forms.

Methods

The enzymatic resolution of 2-ethyl-1-hexanol was monitored by GC-FID. The progress of each reaction was monitored by TLC, and column chromatography was used to purify all intermediates and products. ^{1}H NMR was used to confirm the identity of the MEHP and DEHP products.

Discussion

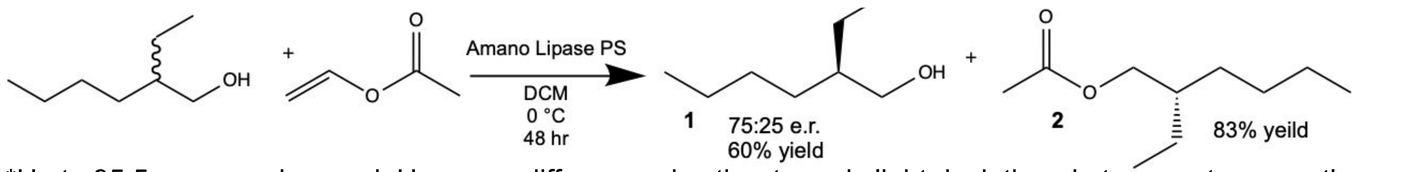
Goals of this Research

This research aims to synthesize the three enantiomers of DEHP: R,R; R,S; and S,S. Once this is accomplished, the metabolites of each enantiomer can be synthesized and their binding to PPARα can be compared.

Accomplishments

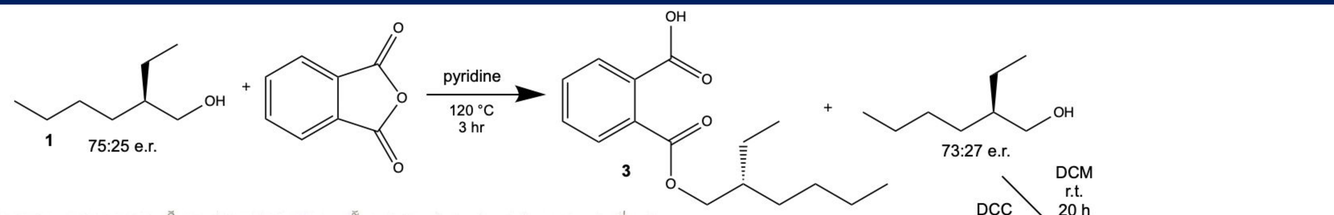
(R,R)-DEHP (approximately 75:25 e.r.) and (S)-MEHP (83:17 e.r.) were synthesized. It was demonstrated that the enzymatic resolution protocol used can yield R-alcohol in higher enantiomeric purity if the reaction conditions are monitored more closely.

Enzymatic Resolution of 2-ethyl-1-hexanol



*Up to 95:5 e.r. was observed. However, differences in stir rate and slight deviations in temperature greatly decreased the reaction rate in some trials.

Synthesis of (R)-MEHP (3) and (R,R)- DEHP (4)



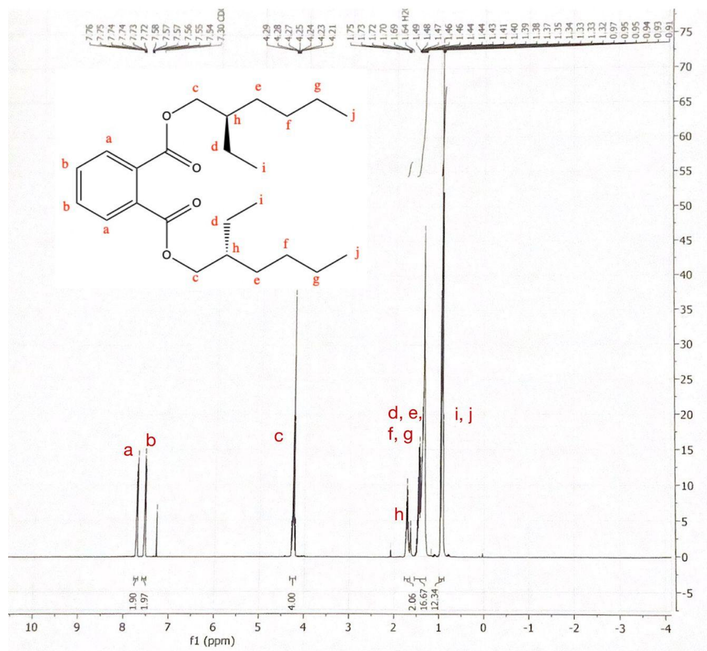
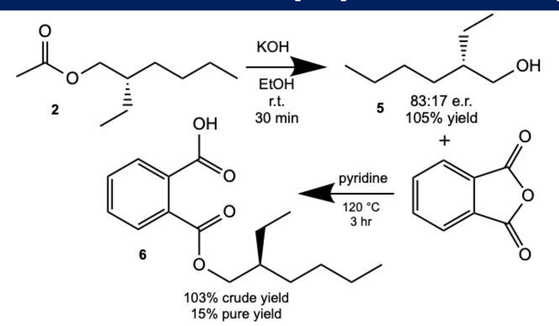


Figure 1 ^{1}H NMR of (4) after purification.

Synthesis of (S)-MEHP (6)



Future Work

A more efficient method for recovering (S)-2-ethyl-1-hexanol in higher enantiomeric purity is needed to complete the synthesis of all enantiomers of DEHP. Reduction of 2-ethyl-2-hexenal to 2-ethyl-1-hexanol by baker's yeast has been shown to be highly enantioselective [3] and will be carried out in the next phase of this project.

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References

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