Exp 5
Working with chiral molecules: A resolution of racemic mixture and 'design your own' synthesis

Intended learning outcomes

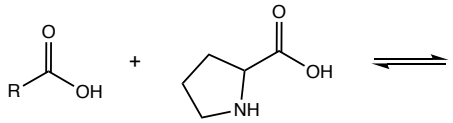
By the end of this experiment you should able to:

- Understand the concept of chirality and its importance in designing molecules
- Recognize and understand various methods to achieve enantiomeric enrichment
- Preform chiral resolution
- Research and design a synthetic route
- Purify, analyze and identify the products of a reaction

Before we start

Answer the following questions:

1. Define chirality
2. Define chiral resolution. What is the fundamental principle behind chiral resolution?
3. Complete the following proton transfer reaction, including arrow-pushing.



Overview

This experiment has two parts:

1. **Part a**: Resolution of a chiral starting material

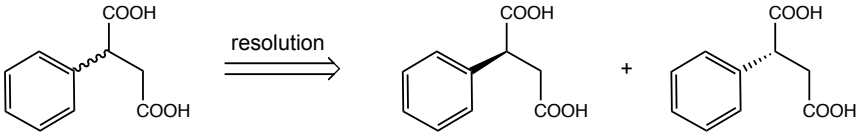


Figure 1. Chiral resolution of phenylsuccinic acid

In this part you will start with a racemic mixture of phenylsuccinic acid and preform a resolution. The resolution is based on forming a salt with the amino acid L-proline[1]. Because proline is added in enantiomerically pure form, two diastereomers of the salt are formed. In this case, one diastereomers is less soluble than the other and therefore you will be able to

[1] For historic reasons, amino acids enantiomers are designated as L- and D. L-proline has S-configuration

isolate it by filtration. Once the salt is isolated, it is possible to liberate the phenylsuccinic acid by adding excess of HCl and pushing the equilibrium towards the free phenylsuccinic acid.

2. **Part b**: This part is an open-end experiment. This means that you are going on a synthetic quest and it is up to you to create your own pathway.

Here is your assignment:

You now have enantiomerically pure diacid that will serve as a starting material. Your task is to selectively convert only one of the carboxylic acid groups into an ester (We will refer to this product as a mono-ester)

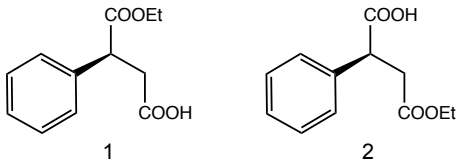


Figure 2. Two possible mono ethyl esters

It is not important which carboxylic acid group would be converted to an ester and what is the alkyl group you choose for your esters. Your goal is to find a way to synthesize it selectively and efficiently. Selectivity will be defined as the ratio between the two possible mono-esters. For example, the ratio between mono-ethyl esters 1 and 2. Efficiency will be defined as the overall yield.

The following alcohols will be available in the lab: 1-propanol, isobutyl alcohol, benzyl alcohol 1-phenyl-1-propanol.

Prelab assignment

You will need to submit a proposal during the first lab section that will be reviewed by your TAs. Your proposal should be typed and chemical structures must be created with a 'chemical structure editor' such as ChemDraw, ChemSketch, Chemdoodle, etc.

1. *Design:* Research the literature and come up with a synthetic plan to create a mono-ester of your choice with high efficiency and selectivity. This may require multiple steps.
2. *Justification:* Explain why do you believe your proposal will achieve high selectivity and efficiency. Be aware that references will add credibility to your argument. Don't add a reference without summarizing the facts that you relay on.

After your TA will approve the plan, you will need to write a detailed procedure and prepare a prelab for the next steps.

Resolution of phenylsuccinic acid

Procedure

Preheat a hotplate to ~70^{O}C. Transfer racemic phenylsuccinic acid (1.94 g, 0.01 mmol) into a 125 mL Erlenmeyer flask with a magnetic stir bar. Add isopropanol (50 mL) and stir until the compound dissolves. Add L-proline (1.15 g, 0.01 mol) and heat the mixture at ~70^{O}C for 30 minutes. Cool to the solution to form a precipitate. Filter the solid with 2 pieces of #2 filter paper and wash with acetone (2x7 mL).

Recovery of the free acid:

The solid material is added into ice-cold 6N HCl (8 mL) and the solution is stirred for 5 minutes. The solution is filtered and the precipitate is washed with ice-cold water (1-2 ml). The solid is recrystallized from water (7 ml). Dry the compound and then determine its specific rotation ($[\alpha]_D$).