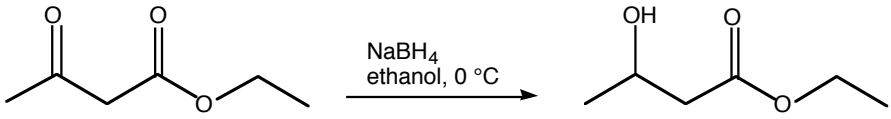
Chiral Compounds and Green Chemistry: Reduction of a ketone by sodium borohydride and baker's yeast

PROCEDURES:

METHOD 1: Reduction of Ethyl Acetoacetate with Sodium Borohydride

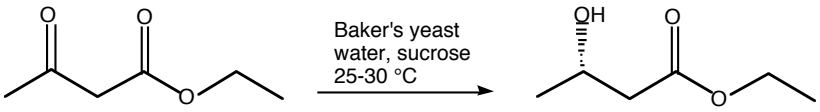


Add sodium borohydride (1.5 g, 40 mmol, MW 37.83) to ethanol (25 mL) in a 100-mL round-bottomed flask, and cool the resulting mixture to 0-3 °C. To this mixture add a solution of the ethyl acetoacetate (5.0 g, 38 mmol, MW 130.14) in ethanol (15 mL), and stir the resulting solution at 0 °C for 15 minutes, then at room temperature for 15 minutes.

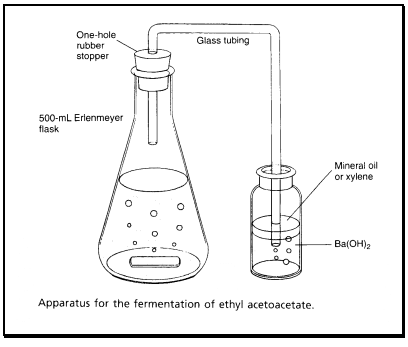
Evaporate the solvents on a rotary evaporator, and suspend the resulting white solid in dichloromethane (30 mL). Add 1 M hydrochloric acid (30-45mL: as needed to dissolve solids) drop-wise to quench the reaction. (**CAUTION:** The addition of HCl will cause frothing and will release hydrogen gas.) Add the hydrochloric acid slowly and while the flask is on ice. Separate any organic layer. Extract the aqueous layer two times with dichloromethane (20 mL). Combine the organic layers and dry using magnesium sulfate. Filter off the magnesium sulfate and evaporate the solvent using a rotary evaporator with a water bath temperature no higher than 30 °C. Record the actual yield. Run an IR of the sample. Bottle, label and turn in the sample to Dr. R. *The ^{1}H NMR spectrum, ^{13}C NMR spectrum, IR spectrum, and the observed rotation of the product will be provided. Interpret the spectra, and calculate the specific rotation and percent yield. The published literature value for the specific rotation of (+)-ethyl 3-hydroxybutanoate is $[\alpha]_D^{25} = +43.5°$.*

CAUTION: As with any hydride reaction, hydrogen gas is evolved during the course of the reaction. Hydrogen must be kept away from ignition sources to avoid explosions.

METHOD 2: Chiral Reduction of Ethyl Acetoacetate with Baker's Yeast



Fermentation Apparatus. Equip a 500-mL Erlenmeyer flask with a magnetic stirring bar and a one-hole rubber stopper with a tube leading to a container with a solution of barium hydroxide or lime water (calcium hydroxide). Protect the barium hydroxide from air by adding some mineral oil or xylene to form a layer above the barium hydroxide. A precipitate will form, indicating that carbon dioxide is being evolved during the course of the reaction. Oxygen from the atmosphere is excluded through the use of the trap.



Apparatus for the fermentation of ethyl acetoacetate.

Add 100 mL of tap water, 30 g of sucrose, and about ~3.5 g (one package) of dry baker's yeast to the flask. Add these materials, while stirring, in the order indicated. Attach the trap to the fermentation flask. Stir this mixture for about 1 hour, preferably in a warm location. Add 4.0 grams of ethyl acetoacetate and stir the fermenting mixture vigorously at room temperature. Set aside and let stand until the next laboratory period.

After this time, prepare a second solution of 30 g sucrose in 100-mL tap water. Add this solution, along with 3.5 g (one package) of dry baker's yeast to the fermenting mixture, warm to ~30-40 °C with stirring and with the trap attached. Set aside and let stand until the next laboratory period.

Place about 6 g of Filter Aid or Celite in a beaker with about 20 mL of water. Stir the mixture vigorously and then pour the contents into a large Büchner funnel (with filter paper) while applying a gentle vacuum, as in a vacuum filtration. Be careful not to let the Filter Aid dry completely. This procedure will cause a thin layer of Filter Aid to be deposited on the filter paper. Discard the water that passes through this filter. Decant as much of the clear supernatant fluid as possible and pass it through this filter, using very gentle suction. Filter the residue through the same filter. The extremely tiny yeast particles are trapped in the pores of the Filter Aid.

Wash the residue with ~20-30mL of water, allowing the water to pass into the flask containing the filtered reaction mixture. Add ~30 g of sodium chloride and stir the mixture vigorously for 5 minutes. Divide the aqueous solution into two equal portaions. Extract each portion two times with 15-mL portions of diethyl ether using a 250-mL separatory funnel. Be careful not to shake the separatory funnel too vigorously to prevent the formation of emulsions. If an emulsion should develop, drain the aqueous solution from the separatory funnel up to the level of the emulsion. Add 2-3 mL of water to the separatory funnel and swirl the mixture to break up the emulsion. Drain the remaining water from the separatory funnel.

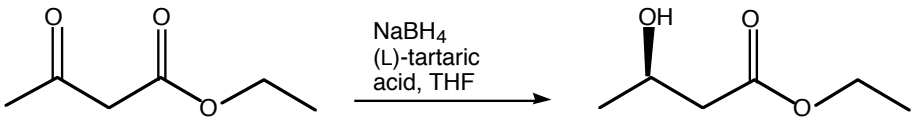
Dry the combined ether extracts with anhydrous magnesium sulfate. Evaporate the ether using the rotary evaporator. You should recover about ~2 mL of liquid.

Using a 5.75" Pasteur pipette, prepare a microscale column with neutral alumina as the absorbent and dichloromethane as the eluent. (See pages 160-165 of your laboratory guide for background.) Place a small piece of cotton in the pipette and carefully push it to the bottom. The cotton should allow liquid to freely move through the column. Fill the pipette with approximately 1.5" of alumina then loosely place a small cotton plug at the top. Add dichloromethane (2 mL) to the column allowing it to drain through the alumina until the solvent surface is just above the alumina surface. This fraction of dichloromethane can be properly discarded. Transfer the product to the wet column. Allow the mixture to flow through the column until the solvent level just reaches the alumina. Add dichloromethane (2 mL) to the column and again allow the mixture to pass through the column as before. A dropper bulb may be used to force the liquid material through the chromatography column. Repeat with another portion of the solvent (2 mL) to elute the product from the column. Use a rotary evaporator to remove the solvent.

Record the actual yield. Run an IR of the sample. Bottle, label and turn in the sample to Dr. R.

The ^{1}H NMR spectrum, ^{13}C NMR spectrum, IR spectrum, and the observed rotation of the product will be provided. Interpret the spectra, and calculate the specific rotation and percent yield. The published literature value for the specific rotation of (+)-ethyl 3-hydroxybutanoate is $[\alpha]_D^{25} = +43.5°$.

METHOD 3: Chiral Reduction of Ethyl Acetoacetate by Sodium Borohydride and (L)-Tartaric Acid



Place a magnetic stir bar in a 50-mL round-bottomed flask and add approximately 15 mL of tetrahydrofuran (THF). Add sodium borohydride (0.50 g, 13 mmol, MW 37.83) to the flask and begin stirring. To the suspension, add (L)-tartaric acid (2.0 g, 13 mmol, MW 150.09) and stir for 15 minutes. Cool the flask on an ice bath and add ethyl acetoacetate (0.44 g, 3.4 mmol, MW 130.14). Remove the flask from the ice bath and stir for 1 hour.

Quench the reaction in a fume hood with 15 mL of 1 M hydrochloric acid. Recall that addition of the acid will cause violent frothing and the formation of hydrogen gas. The acid should be added drop-wise while the flask is on an ice bath and the reaction is stirring. After adding the HCl, remove the flask from the ice bath and stir the solution for 10 minutes.

Extract the solution with ethyl acetate (2 x 30 mL). If your separatory funnel is not large enough to allow sufficient mixing of the aqueous wash with your organic layer, you may need to separate the extracts into two portions. Wash the extracts with saturated aqueous sodium bicarbonate solution (40 mL) and separate the layers. Wash the organic layer with saturated aqueous sodium chloride solution (40 mL) and again separate the layers. Aqueous layers should be kept until you are certain the product is in the organic layer. Dry the organic layer with magnesium sulfate. Filter off the magnesium sulfate using gravity filtration. Use a rotary evaporator to remove the solvent.

Using a 5.75" Pasteur pipette, prepare a microscale column with neutral alumina as the absorbent and dichloromethane as the eluent. (See pages 160-165 of your laboratory guide for background.) Place a small piece of cotton in the pipette and carefully push it to the bottom. The cotton should allow liquid to freely move through the column. Fill the pipette with approximately 1.5" of alumina then loosely place a small cotton plug at the top. Add dichloromethane (2 mL) to the column allowing it to drain through the alumina until the solvent surface is just above the alumina surface. This fraction of dichloromethane can be properly discarded. Transfer the product to the wet column. Allow the mixture to flow through the column until the solvent level just reaches the alumina. Add dichloromethane (2 mL) to the column and again allow the mixture to pass through the column as before. A dropper bulb may be used to force the liquid material through the chromatography column. Repeat with another portion of the solvent (2 mL) to elute the product from the column. Use a rotary evaporator to remove the solvent.

Record the actual yield. Run an IR of the sample. Bottle, label and turn in the sample to Dr. R.

The ^{1}H NMR spectrum, ^{13}C NMR spectrum, IR spectrum, and the observed rotation of the product will be provided. Interpret the spectra, and calculate the specific rotation and percent yield. The published literature value for the specific rotation of (-)-ethyl 3-hydroxybutanoate is $[\alpha]_D^{25}$ = -43.5°.

FINAL LAB REPORT

The final report is to be typed with molecular structures drawn using a template or electronically with ISIS Draw, Marvin or similar structural drawing software program for each reaction. The report must follow the general format of the attached publication. Answer the following questions on a separate paper to turn in. Answers do not need to be typed but must be legible. Copies of Lab Notebook pages for each method are to be attached to the typed report.

1) Compare and contrast the sodium borohydride/tartaric acid reduction with the yeast reduction. Which process is more "green"? Briefly explain the reasons for your choice. Include an evaluation of all waste (including aqueous), chemical yields, yield of a single enantiomer, safety, and energy efficiency.

2) What methods of chemical characterization can you use to characterize the presence of an enantiomerically pure compound? Do the ^{1}H NMR and ^{13}C NMR spectra of racemic mixtures look the same as those of an enantiomerically pure compound found in the mixture? Optical rotations? IR?