



A Publication  
of Reliable Methods  
for the Preparation  
of Organic Compounds

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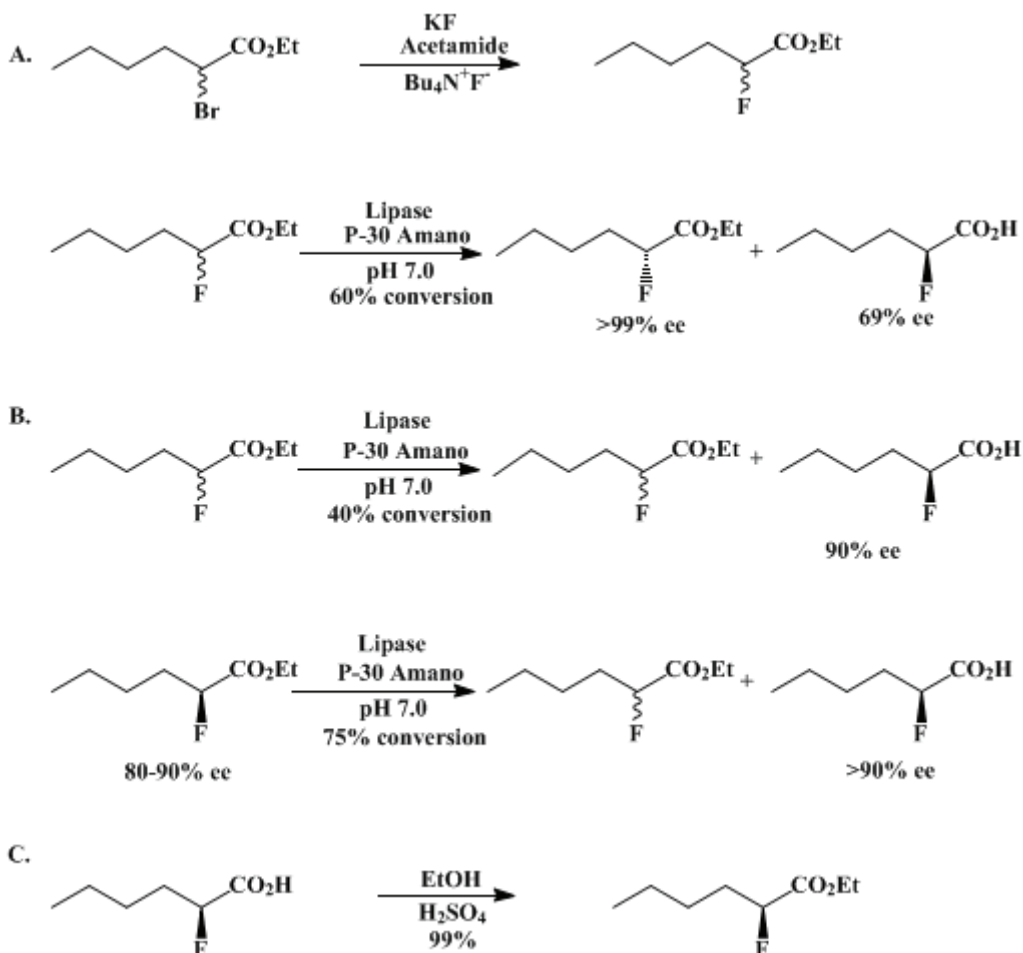
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*These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

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## ENANTIOMERICALLY PURE ETHYL (*R*)- AND (*S*)- 2-FLUOROHEXANOATE BY ENZYME-CATALYZED KINETIC RESOLUTION

[Hexanoic acid, 2-fluoro-, ethyl ester, (*R*)- and (*S*)-]



Submitted by P. Kalaritis and R. W. Regenye<sup>1</sup>.

Checked by Ronan Guevel and Leo A. Paquette.

### 1. Procedure

For preparation of ethyl 2-fluorohexanoate (Note 1), a 1-L flask equipped with a mechanical stirrer, thermometer, condenser and a gas adapter is charged under an atmosphere of argon with 38.5 g of acetamide and 80 g (0.36 mol) of ethyl 2-bromohexanoate (Note 2). The mixture is heated to 80°C until solution is effected and 38.6 g (0.65 mol) of potassium fluoride (Note 3) is added to it followed by 2.7 mL of tetra-*n*-butylammonium fluoride (Note 4). The resulting mixture is heated at 140°C with rapid stirring for 4–5 (Note 5). The reaction mixture is allowed to cool to 90°C and then is poured into 600 mL of ice. The reaction flask is rinsed with 100 mL of water and 100 mL of dichloromethane, which are added to the ice mixture. The aqueous phase is extracted with dichloromethane (4 × 200 mL). The combined organic layers are dried over anhydrous sodium sulfate and filtered. The dichloromethane solution is then cooled to 5°C and treated under an atmosphere of argon with 15 mL of bromine (Note 6). The reaction is judged complete after ca. 3 hr. It is quenched by adding 200 mL of saturated sodium thiosulfate solution. The two phases are separated and the organic phase is successively partitioned with

saturated aqueous sodium bicarbonate solution (2 × 150 mL) and then with 200 mL of brine. It is finally dried over anhydrous sodium sulfate and concentrated to an oil at 40°C / 7 mm (Note 7). Vacuum distillation at 36–37°C / 0.8–0.9 mm affords 26.2–31.4 g (45–54% yield) of pure ethyl 2-fluorohexanoate as a colorless liquid (Note 8).

Method A. *Enantiomerically pure ethyl (R)-2-fluorohexanoate (60% hydrolysis)*. A 1-L Morton flask equipped with a mechanical stirrer, a glass baffle, an electrode connected to a pH control unit, and an addition tube connected to a syringe pump is charged with 300 mL of 0.05 M aqueous phosphate buffer (pH 7.0) (Fisher), 300 mL of deionized water, and 70 g (0.43 mol) of ethyl 2-fluorohexanoate. The resulting mixture is stirred for several minutes and the pH is adjusted to 7.0 with the addition of a few drops of 0.1 N sodium hydroxide solution. Then 0.43 g of Pseudomonas lipase enzyme (P-30, Amano International Enzyme Co., Inc., Troy, VA) is added and the hydrolysis is allowed to proceed at 5°C with stirring (reaction time ca. 2 hr). The pH is kept constant at 7.0 by adding 0.1 N sodium hydroxide solution via the syringe pump, which is activated by the pH control unit. The hydrolysis is discontinued when 260 mL of 1.0 N sodium hydroxide solution has been added (60% conversion, (Note 9)). The mixture is extracted with diethyl ether (5 × 300 mL). The combined organic layers are dried over anhydrous potassium carbonate, filtered, and concentrated at 40°C / 70 mm. Vacuum distillation at 36–38°C / 0.7–0.8 mm gives 24.0 g (34% yield, 85% of theory, (Note 10)) of pure ethyl (R)-2-fluorohexanoate, which is 97.5–99% enantiomerically pure,  $[\alpha]_D^{25} + 13.0$  to  $+ 13.2^\circ$  (CHCl<sub>3</sub>, *c* 1.3) (Note 9). The aqueous layer is acidified to pH 2 with 3 N hydrochloric acid and extracted with diethyl ether (3 × 500 mL). The combined organic layers are dried over anhydrous sodium sulfate, filtered, and concentrated at 40°C / 70 mm. The residue is distilled at 71–72°C / 0.7 mm to give 30.9 g (53% yield; 89% of theory) of (S)-2-fluorohexanoic acid, which is 53–68% enantiomerically pure (Note 11)  $[\alpha]_D^{25} - 6.8$  to  $- 8.7^\circ$  (CHCl<sub>3</sub>, *c* 1.3).

Method B. *Enantiomerically pure ethyl (S)-2-fluorohexanoate*. A 1-L, three-necked flask equipped with a mechanical stirrer, a glass baffle, an electrode connected to a pH control unit, and an addition tube connected to a syringe pump is charged with 300 mL of deionized water, 300 mL of 0.05 M phosphate buffer (pH 7.0) (Fisher), and 80 g (0.49 mol) of racemic ethyl 2-fluorohexanoate. The pH is adjusted to 7.0 with a few drops of 1 N aqueous sodium hydroxide solution, and 23 mg of Pseudomonas lipase enzyme (P-30, Amano International) is added to the mixture. The hydrolysis is allowed to proceed at 5–10°C with stirring. The pH is maintained at 7.0 by adding adequate 1 N aqueous sodium hydroxide solution via the syringe pump. The hydrolysis is discontinued when 197 mL (40% conversion) of 1 N aqueous sodium hydroxide solution has been added (total reaction time: 2.5 hr). The reaction mixture is immediately transferred to an extractor containing 750 mL of ethyl ether. The mixture is agitated for 5 min and the two phases are separated. The aqueous phase is extracted with ethyl ether (3 × 400 mL). The combined organic layers are dried over anhydrous potassium carbonate, filtered, and concentrated at 30°C/70 mm to afford 47.2 g (98% of theory) of optically active ethyl (R)-2-fluorohexanoate. The aqueous phase is transferred back into the extractor and carefully acidified to pH 2.0 with concentrated hydrochloric acid. It is subsequently extracted with diethyl ether (4 × 500 mL). The combined organic layers are dried over anhydrous sodium sulfate and concentrated at 30°C/70 mm to provide 26.1 g (39% yield; 98% of theory) of (S)-2-fluorohexanoic acid (81–86% ee).

OPTICAL PURITY ENHANCEMENT. A 1-L, three-necked flask equipped as described above is charged with 28.4 g (0.175 mol) of ethyl (S)-2-fluorohexanoate (81% ee) (Note 12), 300 mL of deionized water and 300 mL of 0.05 M phosphate buffer (pH 7.0). The pH is adjusted to 7.0 with a few drops of 1 N aqueous sodium hydroxide solution and 36 mg of Pseudomonas lipase enzyme (P-30, Amano International) is added to the mixture. The hydrolysis is allowed to proceed at 5°C. The pH is kept at 7.0 by adding adequate 1 N aqueous sodium hydroxide solution via the syringe pump. The hydrolysis is discontinued when 131.3 mL (75% conversion) of 1 N aqueous sodium hydroxide solution has been added (total reaction time: 4 hr). The mixture is quickly extracted with ethyl ether (3 × 500 mL). The combined organic layers are dried over anhydrous potassium carbonate and concentrated at 35°C/70 mm to provide 5.66 g of nearly racemic ethyl 2-fluorohexanoate. The aqueous phase is acidified to pH 2.0 with concentrated hydrochloric acid and extracted with ethyl ether (4 × 500 mL). The combined organic layers are dried over anhydrous sodium sulfate and concentrated at 35°C/70 mm to give 16.8 g (71% yield; 95.5% of theory) of (S)-2-fluorohexanoic acid. This acid is distilled at 67°C/0.4–0.5 mm to give 14.2 g of enantiomerically pure (S)-2-fluorohexanoic acid as a colorless oil:  $[\alpha]$

$n_D$  -13.8° (CHCl<sub>3</sub>, *c* 1.7) (Note 11) and (Note 13).

Method C. *Esterification of (S)-2-fluorohexanoic acid*. A 250-mL flask is charged with 13.8 g of (*S*)-2-fluorohexanoic acid, 200 mL of ethanol, and 2 mL of concentrated sulfuric acid. The solution is heated at reflux for 4 hr. Most of the ethanol is distilled slowly at atmospheric pressure and the residue is dissolved in 200 mL of dichloromethane after allowing it to cool to 23°C. The solution is partitioned with 200 mL of saturated aqueous sodium bicarbonate solution and the aqueous layer is back-extracted with 100 mL of dichloromethane. The combined organic layers are washed with 100 mL of brine, dried over anhydrous potassium carbonate, and concentrated at 30°C/70 mm to afford 15.6 g (93% yield) of enantiomerically pure (Note 11) ethyl (*S*)-2-fluorohexanoate as a colorless liquid:  $[\alpha]_D^{25}$  -13.8° (CHCl<sub>3</sub>, *c* 1.0), chemical purity 100% (GC analysis).

## 2. Notes

1. This procedure was originally used by P. Rosen, G. Holland, and R. J. Karasiewicz at Hoffmann-La Roche. A similar procedure has appeared in the literature.<sup>2</sup>
2. Ethyl 2-bromohexanoate was purchased from Aldrich Chemical Company, Inc.
3. Potassium fluoride was purchased from Fluka and was ground to a fine powder prior to use.
4. Tetra-*n*-butylammonium fluoride was purchased from Aldrich Chemical Company, Inc.
5. The progress of the reaction was monitored by gas chromatography on an OV-17 column at 100–250°C (20°/min).
6. Bromine was added dropwise keeping the temperature below 10°C at all times. The progress of the reaction was monitored by gas chromatography as described in (Note 4). Bromine was added to brominate the  $\alpha,\beta$ -unsaturated ester that was present as a product in the crude material. This procedure simplified the isolation of the ethyl 2-fluorohexanoate by distillation.
7. Some yellow solids appeared on removing the solvent; they were filtered prior to distillation.
8. The purity of ethyl 2-fluorohexanoate was determined by gas chromatography as described above. The reaction yield varied from 42 to 70%.
9. Percent conversion is based on the amount of base added.
10. Percent theoretical yield is based on percent conversion.
11. The enantiomeric excess (% ee) of these compounds was determined by the submitters as follows. The ester and acids were first reduced to the corresponding alcohols with DIBAL and LAH, respectively. The alcohols were then allowed to react with 100% excess of (*S*)-(+)- $\alpha$ -methoxy- $\alpha$ -trifluoromethylphenylacetyl chloride (Mosher's reagent) in (1 : 1) pyridine–carbon tetrachloride for 18 hr. The diastereomeric ratio of these derivatives was finally determined by isothermal gas chromatography on a capillary OV-17 column at 160°C.
12. This ester was prepared from the optically active (*S*)-2-fluorohexanoic acid isolated above, by the esterification method described in this procedure.
13. The checkers have noted that the 2-fluorohexanoic acid crystallizes when allowed to stand at room temperature. This material can be recrystallized from pentane at low temperature. The crystals liquify on standing in the open air at room temperature.

## 3. Discussion

In recent years there has been an increasing interest in the use of enzymes and microorganisms to produce optically active compounds by means of either a kinetic resolution or stereospecific chemical transformations (e.g., reductions, oxidations, epoxidations, hydroxylations).<sup>3</sup> Hydrolases in general have been used to effect kinetic resolutions of racemic esters and alcohols via their corresponding esters.<sup>4</sup> Lipases, a subclass of hydrolases, are commercially available and relatively inexpensive. As a result, they constitute a very attractive class of catalysts for effecting kinetic resolutions, some of which might be difficult by other means.

Lipase P-30 Amano (ex *Pseudomonas fluorescens*) has been found to be synthetically useful in catalyzing very effectively kinetic resolutions of both racemic alcohols and racemic acids via their corresponding esters. This property is seldom observed with other enzymes and, therefore, makes this particular enzyme of greater synthetic utility. The enzyme can tolerate high concentrations of substrates and their hydrolysis products. The rates of the hydrolyses have usually been fast and the enantiomeric

excesses achieved high. In most cases, the hydrolyses have been carried out in water and in the absence of cosolvents. These resolutions can be easily accomplished in multikilogram scale. A wide variety of substrates have been resolved enantioselectively with this lipase.<sup>5</sup>

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## References and Notes

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## Appendix

### Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

brine

ETHYL (R)- AND (S)- 2-FLUOROHEXANOATE

Hexanoic acid, 2-fluoro-, ethyl ester, (R)- and (S)-

[ethanol](#) (64-17-5)

[potassium carbonate](#) (584-08-7)

[sulfuric acid](#) (7664-93-9)

[hydrochloric acid](#) (7647-01-0)

Acetamide (60-35-5)

ethyl ether,  
diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

sodium thiosulfate (7772-98-7)

Pentane (109-66-0)

dichloromethane (75-09-2)

potassium fluoride (7789-23-3)

argon (7440-37-1)

tetra-n-butylammonium fluoride (429-41-4)

Ethyl 2-fluorohexanoate (17841-31-5)

ethyl 2-bromohexanoate (615-96-3)

ethyl (R)-2-fluorohexanoate (124439-29-8)

ethyl (S)-2-fluorohexanoate (124439-31-2)

(S)-2-fluorohexanoic acid (113776-26-4)

2-Fluorohexanoic acid

(S)-(+)- $\alpha$ -methoxy- $\alpha$ -trifluoromethylphenylacetyl chloride (20445-33-4)