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# Simple Preparation of Optically Pure Bis(trifluoromethyl)-alkanediols through Lipase-Catalyzed Reaction

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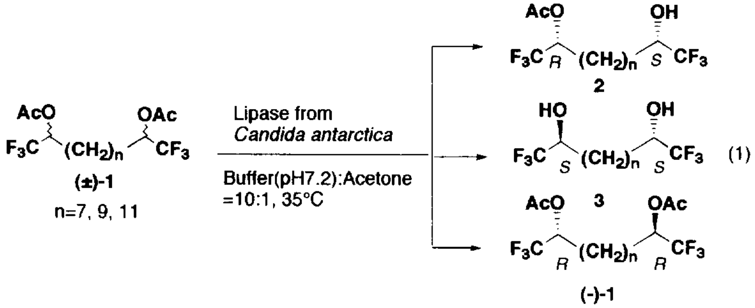
**Abstract**: Enantioselective hydrolysis of diacetate of bis(trifluoromethyl)alkanediols has been demonstrated. *Candida antarctica* lipase was chosen from among commercial enzymes as the one most able to enantioselectively hydrolyze the acetyl group giving optically pure diols and diacetate. Copyright © 1996 Elsevier Science Ltd

Antiferroelectric liquid crystal (AFLCs) compounds, which possess a chiral 1,1,1-trifluoromethyl-2-alkanol moiety, are known to be important high-speed switching devices.[1] Kusumoto and his colleagues recently reported the synthesis of unique dimeric AFLCs molecules which contain optically active bis(trifluoromethyl)alkanediols **3** as chiral core units.[2] The reported means for preparing optically pure **3**, however, required a nuisance resolution process using HPLC on chiral phase because enantiomeric excess of the starting compound, commercial (*S*)-3,3,3-trifluoro-1,2-epoxypropane, was only 75%.[3] We recently found that *Candida antarctica* lipase (CAL) catalyzed trans-esterification of racemic 1,1,1-trifluoro-2-alkanols with perfect enantioselectivity.[4] In this report, we describe a simple method for preparing optically pure **3** through CAL catalyzed hydrolysis of corresponding diacetate (±)-**1** (Eq. 1).



We initially attempted trans-esterification of diol **3** in hexane using vinyl acetate as an acyl donor.[5] Trans-esterification, however, did not take place when the reaction was carried out using **3a** as a model substrate. Fortunately, hydrolysis reaction of (±)-**1a** proceeded smoothly to provide monoacetate **2a** and diol **3a**. Addition of acetone was effective for increasing reaction rate. Lipase-catalyzed hydrolysis reactions were thus

Table. Lipase-catalyzed hydrolysis of diacetate (±)-**1** [a)]

| Entry | Substrate | n | Time (h) | %Yield of **2**[b] | %Yield of **3**<br>(optical purity ) | %Yield of (-)-**1**<br>(optical purity) |
|---|---|---|---|---|---|---|
| 1 | (±)-**1 a** | 7 | 140 | 49 | 20 (>99%ee)[c] | 20 (>99%ee)[c] |
| 2 | (±)-**1 b** | 9 | 47 | 39 | 25 (>99%ee)[c] | 24 (>99%ee)[c] |
| 3 | (±)-**1 c** | 11 | 30 | 39 | 25 (>99%ee)[c] | 20 (>99%ee)[c] |

a) Reaction was carried out at 35℃ in a mixed solvent of 10:1 (v/v) of 0.1 M phosphate buffer (pH 7.2) and acetone.
b) Because the corresponding diacetate **1** is a *meso* form, %ee has not yet been determined. c) No isomer was detected by capillary GC analysis.

carried out in a mixed solvent of 0.1M phosphate buffer (pH7.2) and acetone (10:1) at 35℃ using 10 wt% of CAL. The products, (*R,S*)-monoacetate **2** and (*S,S*)-diol **3**, and the remaining substrate (*R,R*)-**1** were isolated through silica gel flash column chromatography. The optical purity was determined by capillary GC analysis using a chiral phase (Chiraldex G-Ta) as corresponding diacetate **1**.[6] *Perfect enantioselectivity* was recorded when substrate **1a** (n=3), **1b** (n=7), or **1c** (n=11) was subjected to the reaction (Entries 1-3 in the Table). The lipase-catalyzed reaction can be used in a large scale preparation, the present method therefore affords a valuable means of preparing optically pure bis(trifluoromethyl)alkanediols. Key compounds for making ferroelectric liquid crystals were thus obtained easily. Further study of the scope and limitations of this reaction will make it even more beneficial.

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## References and Notes

1) (a) Clark, N. A.; Lagerwal, S. T. *Springer Ser. Chem. Phys.*, **1980**, *11(Liq. Cryst. One- and Two-Dimens. Order)*, 222-227. (b) Skarp, K.; Handschy, M. A. *Mol. Cryst. Liq. Cryst.*, **1988**, *165*, 439-509. (c) Nohira, H. *J. Synth. Org. Chem., Jpn.* **1991**, *49*, 467-474. (d) "Future Liquid Crystal Display and Its Materials," ed. by Fukuda, A., CMC, Tokyo (1992). and references cited therein.

2) Suzuki, Y.; Isozaki, T.; Kusumoto, T.; Hiyama, T. *Chem. Lett.* **1995**, 719-720; Dimeric liquid crystals prepared from alkanediols, **3**, with odd number of n exhibited only $SmC_A^*$ phase, while liquid crystals prepared from **3** with even number of n exhibited $SmC^*$ and SmA phase.

3) Preparation of 96%ee of (trifluoromethyl)oxirane was reported recently through enantioselective reduction of 1,1,1-trifluoro-3-chloro-2-propanone by chlorodisiopinocamphenylborane: Ramachandran, P. V.; Gong, B.; Brown, H. C. *J. Org.Chem.* **1995**, *60*, 41-46.

4) Hamada, H.; Shiromoto, M.; Funahashi, M.; Itoh, T.; Nakamura, K. *J. Org.Chem.* **1996**, *61*, 2332-2336.

5) CAL has the highest acylation efficiency of 1,1,1-trifluoro-2-alkanols among 25 types of commercial enzymes. For preparing optically active 1,1,1-trifluoro-2-nonanol, the trans-esterification method gave the product with better %ee than hydrolysis of the corresponding acetate in 0.1 M phosphate buffer at pH7.2, though the hydrolysis reaction proceeded more speedily than trans-esterification. See ref.4. We re-examined CAL-catalyzed hydrolysis of 1,1,1-trifluoro-2-nonyl acetate under the present mixed solvent system, and found that hydrolyzed alcohol formed in an optically pure state with good yield. The mixed solvent system seemed effective to suppress non-enzymatic hydrolysis reaction of the acetate. Therefore, perfect resolution of 1,1,1-trifluoro-2-alkanols was achieved by both hydrolysis- and trans-esterification methods using CAL.

6) Retention times on GC analyses of diacetate **1** are summarized as follows: Chiraldex G-Ta, ϕ 0.25 mm x 20 m, Carrier gas: He 40 ml/min. Temp: 150 ℃, Inlet pressure: 1.35 Kg/cm$^2$, Amount 400 ng, Detection: FID; **1a**: $Rt_{(R,R)}$ =3.5 min., $Rt_{(R,S)}$ =3.7 min., $Rt_{(S,S)}$ =3.9 min., **1b**: $Rt_{(R,R)}$ =8.0 min., $Rt_{(R,S)}$ =8.5 min., $Rt_{(S,S)}$ =9.1 min. **1c**: $Rt_{(R,R)}$ = 20.5 min., $Rt_{(R,S)}$ =21.7 min., $Rt_{(S,S)}$ = 23.1 min. Assignment was carried out by comparing the authentic samples derived from commercial 75%ee of (*S*)-3,3,3-trifluoro-1,2-epoxypropane.

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