Pergamon

Tetrahedron Letters, Vol. 38, No. 11, pp. 1987-1990, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00255-4

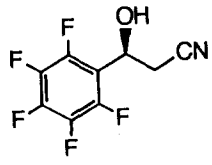
Lipase-Catalyzed Efficient Kinetic Resolution of 3-Hydroxy-3-(pentafluorophenyl)propionitrile

Takashi Sakai,* Tetsuo Takayama, Takafumi Ohkawa, Osamu Yoshio, Tadashi Ema, and Masanori Utaka*

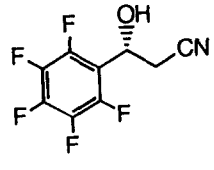
Department of Applied Chemistry, Faculty of Engineering, Okayama University, Tsushima, Okayama 700, Japan

Abstract: Efficient kinetic resolution of racemic 3-hydroxy-3-(pentafluorophenyl)- propionitrile (±)-**1** by a lipase-catalyzed transesterification gave optically pure (*S*)-3-hydroxy-3-(pentafluorophenyl)-propionitrile (*S*)-**1** and (*R*)-(+)-3-acetoxy-3-(penta-fluorophenyl)propionitrile (*R*)-**1** [>99% ee, respectively, E = 1057], the former of which was further transformed into (*S*)-(-)-3-amino-1-(pentafluorophenyl)-1-propanol (*S*)-**7** in four steps. © 1997 Elsevier Science Ltd. All rights reserved.

Optically active 3-hydroxy-3-phenylpropionitrile[1] and its reduction product, 3-amino-1-phenyl-1-propanol,[2] have been known as useful chiral building blocks for the synthesis of biologically active compounds such as Norfluoxetine, Fluoxetine and Tomoxetine[3] which have recently attracted much attention in view of their potent antidepressant activities. In this paper we report an efficient preparative method for the pentafluorophenyl analogs, (*S*)- and (*R*)-3-hydroxy-3-(pentafluorophenyl)propionitrile (*S*)-**1** and (*R*)-**1**, with high enantiomeric purities by the lipase-catalyzed kinetic resolution[4] of the racemic hydroxy nitrile (±)-**1** and its acetate (±)-**2**. The selectivity in the resolution was found to be dramatically enhanced[5] as compared with that of the non-fluorinated compound. The prepared compound (*S*)-**1** was further transformed into its amino alcohol derivative (*S*)-**7**. These newly prepared fluorinated compounds, (*S*)-**1**, (*R*)-**1** and (*S*)-**7**, would be useful not only for the synthesis of fluorinated mimics of the biologically active compounds but also as fluorinated chiral ligands utillized in asymmetric synthesis. We have been interested in the potentiality of molecular recognition of the pentafluorophenyl moiety in the vicinity of a chiral center.[6]



(*S*)-**1**



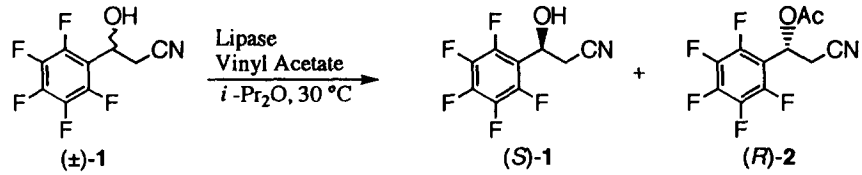
(*R*)-**1**

For the preparation of (±)-**1**,[7] we initially utilized the reaction conditions for the non-fluorinated analog[3] of **1** which was easily prepared from benzaldehyde and acetonitrile [*n*-BuLi, THF, −60 °C]. However, the fluorinated compound (±)-**1** was obtained from pentafluorobenzaldehyde in only 10% yield in similar conditions and contaminated with many unidentified by-products. After optimization of the reaction conditions, the reaction temperature was found to be a definitive factor and was carefully controlled at −100 °C. Thus, to a cooled (−50 °C) solution of *n*-BuLi (1.2 equiv.) in THF was added acetonitrile (1.2 equiv.). The

resulting cloudy suspension was further cooled to −100 °C and stirred for 30 min. Then, a THF solution of pentafluorobenzaldehyde (1.0 equiv.) and ZnI_2[8] (0.02 equiv.) was added quickly and stirred for an additional 30 min at that temperature. The usual work-up followed by chromatographic purification gave (±)-**1** as white crystals (60% yield; mp 86–88 °C, AcOEt–hexane).

The lipase-catalyzed kinetic resolutions were carried out both by the transesterification of alcohol (±)-**1** with vinyl acetate (Table 1) and by the hydrolysis of the acetate (±)-**2**[9] (Table 2). Both procedures gave optically pure enantiomers, respectively. Table 1[10] shows that TOYOBO LIP[11] exhibited ideal results: both enantiomers of alcohol (*S*)-**1**[12] and acetate (*R*)-**2**[13] ($[\alpha]^{24}_D$ = +32.9 (*c* 1.00, $CHCl_3$)) have >99% ee with E = 1057.[14] Significantly, (*S*)-**1** showed a very small value of the optical rotation ($[\alpha]_D \approx 0$ in some different solvents) which, thus, could not be used for the assignment of the absolute configuration.

Table 1

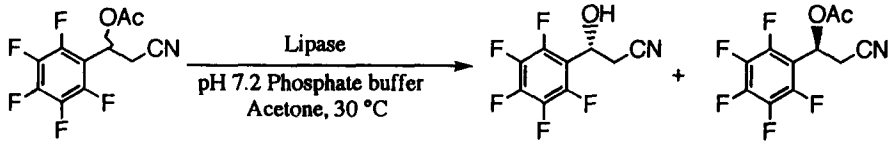


(±)-**1** (*S*)-**1** (*R*)-**2**

			(*S*)-**1**	(*R*)-**2**		
Entry	Lipase	Time (h)	% Yield (% ee)[a]	% Yield (% ee)[b]	Conv.	*E*
1	TOYOBO LIP[c]	19	42 (>99)	45 (>99)	0.50	>1057
2	Amano PS[d]	67	53 (61)	39 (73)	0.45	12

a) Determined by ^{1}H NMR (500 MHz) analysis of the MTPA ester. b) Determined by ^{1}H NMR (500 MHz) analysis with 50% mol of Eu(hfc)$_3$. c) *Pseudomonas sp.* lipase immobilized on Hyflo Super-Cel. d) *Pseudomonas cepacia.*

Table 2



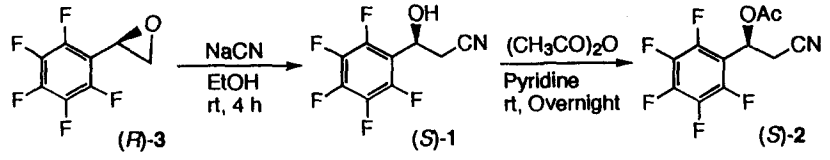
(±)-**2** (*R*)-**1** (*S*)-**2**

			(*R*)-**1**	(*S*)-**2**		
Entry	Lipase	Time (h)	% Yield (% ee)[a]	% Yield (% ee)[b]	Conv.	*E*
1	Amano PS	84	25 (93)	68 (30)	0.24	37
2	Amano AK[c]	112	40 (93)	37 (82)	0.47	70
3	Amano A6[d]	12	8.3 (10)	53 (0.2)	0.20	1.2
4	Amano AY[e]	96	58 (70)	29 (71)	0.50	12
5	TOYOBO LIP	25	41 (>98)	52 (>99)	0.50	>1057

a) Determined by ^{1}H NMR (500 MHz) analysis of the MTPA ester. b) Determined by ^{1}H NMR (500 MHz) analysis with 50% mol of Eu(hfc)$_3$. c) *Pseudomonas fluorescens.* d) *Aspergillus niger.* e) *Candida rugosa.*

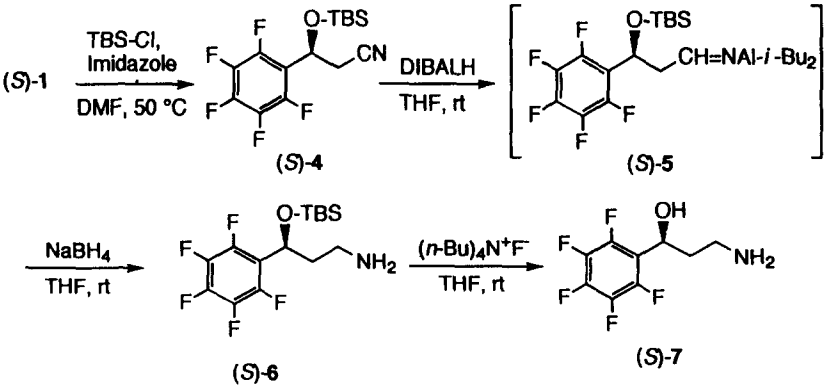
In the results of the hydrolytic resolution (Table 2[15]), TOYOBO LIP also showed outstanding superiority to give (*R*)-**1** (>98% ee) and (*S*)-**2** (>99% ee, $[\alpha]^{25}_{D}$ = -33.7 (*c* 0.6, $CHCl_3$) (*E* = 1057[11]). It should be noted here that a fluorinated substrate such as (±)-**2** much improved the selectivity as compared with the non-fluorinated analog which had been reported to be resolved by use of Amano P with only *E* = 8.[16] We examined the resolution of the non-fluorinated analog with TOYOBO LIP and also obtained a low, but slightly improved, selectivity (*E* = 16). The contrastive results with the fluorinated substrate suggest that the highly hydrophobic pentafluorophenyl group may be suitably taken into the hydrophobic pocket of the enzyme to give the much improved selectivity. The R/S selectivity is the same as that of the non-fluorinated compound and obeys the empirical rules.[17]

For the determination of the absolute configurations of the thus-prepared enantiomerically pure **1** and **2**, compounds (*S*)-**1** and (*S*)-**2** were prepared independently from commercially available (*R*)-pentafluorostyrene oxide **3**[18] as shown in Scheme 1. Reaction of (*R*)-**3** with NaCN in EtOH in the usual manner[19] gave alcohol (*S*)-**1** (64% yield), which was then esterified to give acetate (*S*)-**2** (93% yield) ($[\alpha]^{20}_{D}$ = -36.6 (*c* 2.40, $CHCl_3$)) and the optical rotation was compared with that obtained from the lipase-catalyzed resolution.



Scheme 1

Finally, (*S*)-**1** thus prepared by the lipase-catalyzed resolution was transformed into the corresponding amino alcohol (*S*)-**7** as shown in Scheme 2. Protection of the hydroxyl group of (*S*)-**1** with TBS-Cl[20] in DMF-Py at 50 °C (68% yield) followed by the reaction with DIBALH[21] in THF, and subsequent *in situ* reduction of the intermediate imine (*S*)-**5** with $NaBH_4$ gave a TBS ether of amino alcohol (*S*)-**6** (22% yield in two steps, mp 61-63 °C, $[\alpha]^{21}_{D}$ = -50.0 (*c* 2.00, $CHCl_3$)). Deprotection of the TBS group with $(n\text{-}Bu)_4N^+F^-$ gave the desired (*S*)-**7** (48% yield). Synthetic utilization of optically active **1**, **2** and (*S*)-**7** is now under active investigation.



Scheme 2

Acknowledgment:
This work was partially supported by a Grant-in-Aid for Scientific Research (B, No. 07455362; C, No. 06650985) from the Ministry of Education, Science and Culture of Japan. We are grateful to Amano Pharmaceutical Co., Ltd., TOYOBO Co., Ltd. and Sumitomo Chemical Co., Ltd. for kind supply of the lipases and to the SC-NMR laboratory of Okayama University for ^{19}F NMR (188 MHz) and ^{1}H NMR (500 and 200 MHz) analyses.

References and Notes

1. Lipase-catalyzed kinetic resolution of 3-hydroxy-3-phenylpropionitrile: a) Itoh, T.; Takagi, Y. *Chem. Lett.* **1989**, 1505. b) Itoh, T.; Takagi, Y.; Nishiyama, S. *J. Org. Chem.* **1991**, *56*, 1521. Related aliphatic 3-hydroxy nitrile: c) Itoh, T.; Takagi, Y. *J. Synth. Org. Chem.* **1994**, *52*, 59. d) Itoh, T.; Takagi, Y.; Murakami, T.; Hiyama, Y.; Tsukube, H. *J. Org. Chem.* **1996**, *61*, 2158 and the literature cited therein.
2. a) Schneider, M. P.; Goergens, U. *Tetrahedron: Asymm.* **1992**, *3*, 525. b) Fülöp, F.; Lázár, L.; Bernáth, G.; Sillanpää, R.; Pihlaja, K. *Tetrahedron* **1993**, *49*, 2115 and the literature cited therein.
3. Koenig, T. M.; Mitchell, D. *Tetrahedron Lett.* **1994**, *35*, 1339.
4. Recent reviews for examples: a) Santaniello, E.; Ferraboschi, P.; Grisenti, P.; Manzocchi, A. *Chem. Rev.* **1992**, *92*, 1071. b) Faber, K.; Riva, S. *Synthesis* **1992**, 895.
5. Examples of efficient applications to fluorinated substrates. a) 2,2,2-Trifluoromethyl-1-(naphtyl)ethanol: Kato. K.; Katayama, M.; Gautam, R. K.; Fujii, S.; Kimoto, H. *Biosci. Biotech. Biochem.* **1995**, *59*, 271. 1,1,1-Trifluoro-2-alkanols: b) Hamada, H.; Shiromoto, M.; Funahashi, M.; Ito, T.; Nakamura, K. *J. Org. Chem.* **1996**, *61*, 2332. c) Yonezawa, T.; Sakamoto, Y.; Nogawa, K.; Yamasaki, T.; Kitazume, Y. *Chem. Lett.* **1996**, 855.
6. Sakai, T.; Kubo, K.; Kashino, S.; Uneyama, K. *Tetrahedron: Asymm.* **1996**, *7*, 1883.
7. Preparation from pentafluorobenzaldehyde and Bu_3SnCH_2CN: Noltes, J. G.; Creemers, H. M. J. C.; Van der Kerk, G. J. M. *J. Organomet. Chem.* **1968**, *11*, 21.
8. Rawal, V. H.; Rao, J. A.; Cava, M. P. *Tetrahedron Lett.* **1985**, *26*, 4275.
9. Prepared by the addition of acetic anhydride before quenching the reaction and an additional stirring of the reaction mixture overnight at room temperature.
10. A mixture of (±)-**1** (150 mg), lipase (300 mg) and vinyl acetate (127 mg) in *i*-Pr_2O (7.5 mL) (distilled from sodium) was stirred for the indicated time at 30 °C.
11. TOYOBOLIP was suitably utilized in the resolution of the fluorinated substrate (see reference 5a).
12. (*S*)-**1**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.93 (dd, *J* = 6.5, 6.6 Hz, 1H, CH_2CN), 3.13 (dd, *J* = 7.7, 7.8 Hz, 1H, CH_2CN), 5.44 (t, *J* = 7.3 Hz, 1H, CH(OH)); ^{19}F NMR (200 MHz, $CDCl_3$) δ 81.23-81.68 (m, 2F), (t, *J* = 22.3Hz, 1F), 98.70-99.18 (m, 2F); IR (KBr) 3411 (OH), 2958 (CH), 2267 (CN).
13. (*R*)-**2**: $[\alpha]^{24}_D$ = + 32.9 (*c* 1.80, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ2.51 (s, 3H, CH_2CO), 2.99 (dd, *J* = 7.1, 7.1 Hz, 1H, CH_2CN), 3.18 (dd, *J* = 7.7, 7.6 Hz, 1H, CH_2CN), 6.25 (t, *J* = 7.3 Hz, 1H, CH(OH)); ^{19}F NMR (200 MHz, $CDCl_3$) δ 81.40-81.82 (m, 2F), 90.87 (t, *J* = 22.3Hz, 1F), 100.28–100.72 (m, 2F); IR (neat) 2993 (CH), 2258 (CN), 1751 (C=O).
14. Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294.
15. A mixture of (±)-**2** (100 mg), lipase (entry 1–4: 100 mg, entry 5: 200 mg) and a phosphate buffer (pH 7.2, 5.0 mL), acetone (0.5 mL) was stirred for the indicated time at 30 °C.
16. The selectivity was enhanced by use of phenylthioacetate as an acyl moiety (see references 1a and 1b).
17. a) Weissfloch, A. N. E.; Kazlauskas, R. J. *J. Org. Chem.* **1995**, *60*, 6959. b) Burgess, K.; Jennings, L. D. *J. Am. Chem. Soc.*, **1991**, *113*, 6129.
18. Purchased from Tokyo Kasei Co. Ltd., Tokyo, Japan.
19. Behrens, C. H.; Ko, S. Y.; Sharpless, K. B.; F. Walker, F. J. *J. Org. Chem.* **1985**, *50*, 5687.
20. Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
21. Hayashi, M. *Tetrahedron* **1994**, *50*, 2821.

(*Received in Japan* 14 *January* 1997; *accepted* 7 *February* 1997)