Note

A Simple Preparation of
(*R*)-2-Hydroxy-4-phenyl-
butanoic Acid†

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(*R*)-2-Hydroxy-4-phenylbutanoic acid (**1a**) is an important intermediate for the synthesis of angiotensin-converting enzyme inhibitors, for example, enalapril.¹⁾ Several methods for the chemical or biochemical optical resolution of readily available ($\pm$)-**1a** itself,^{2,3)} corresponding esters^{4,5)} or corresponding cyanohydrin⁶⁾ have been reported. Recent success in the lipase-catalyzed enantioselective acylation of 2-hydroxyhexadecanoic acid⁷⁾ prompted us to extend the reaction to the kinetic resolution of ($\pm$)-**1a**.

In the present case, the substrate was treated with hexanoic anhydride as the acylating agent in the presence of lipase PS (Amano, from *Pseudomonas*). Because only unreacted **1a** is insoluble in hexane, in which hexanoic anhydride, hexanoic acid and acylated product **2a** are soluble, separation of the desired **1a** is quite easy after the reaction. Thus, the addition of hexane to the crude reaction mixture leads to the separation of (*R*)-**1a** as practically pure crystals. At first, three kinds of solvent which dissolved ($\pm$)-**1a** sufficiently were compared for their effect on the rate and selectivity of the lipase-catalyzed reaction. Among them, diethyl ether proved the best to realize a smooth and highly enantioselective acylation process (see the experimental section). When the substrate (10% in diethyl ether) was treated with a total 1.0 equivalent of the

anhydride for 30 hr at 20–25°C, (*R*)-**1a** (>99% *e.e.*) was recovered in a 39% yield by a simple crystallization from hexane, as well as (*S*)-2-hexanoyloxy-4-phenylbutanoic acid (**2a**) of 66% *e.e.* The *E*(*S*) value⁸⁾ [*E*(*S*) = ln[(1 – *c*)(1 – *e.e.*)]/ln[(1 – *c*)(1 + *e.e.*)] = 27] quoted here shows the high efficiency of this reaction. In addition, the lipase that was recovered after the reaction could be re-used with high retention of its activity. Finally, this reaction worked well for 20 g of the substrate.

Experimental

Enzymatic acylation of ($\pm$)-2-hydroxy-4-phenylbutanoic acid (1a**).** To a solution of ($\pm$)-**1a** (2.00 g) in diethyl ether (20 ml) was added lipase PS (2.00 g) and hexanoic anhydride (1.44 g, 0.6 eq.), and the mixture was stirred at 20–25°C for 20 hr. Another portion of the anhydride (0.96 g, 0.4 eq.) was then added, and the mixture was further stirred for 10 hr. The mixture was next filtered, and the residue was washed with ethyl acetate. The conversion was 60% by the GLC analysis (15% BDS, 2 m; at 195°C + 5°C/min) of a small portion after methylating with diazomethane. The residue (recovered lipase) was dried *in vacuo* over phosphorus pentoxide for 2 hr and stored in a desiccator until required for further use. The filtrate and washings were combined and concentrated *in vacuo*. The residue was mixed with hexane (40 ml) and vigorously stirred while ice-cooling for 30 min. The crystalline material was then collected by filtration, washed with ice-cooled hexane and dried *in vacuo* to give 782 mg (39%) of (*R*)-**1a**, mp 115–116°C, [α]_D²³ –8.82° (*c* 1.02, ethanol) [an authentic specimen³⁾: [α]_D²² –8.75° (*c* 1.04, ethanol)]. IR $\nu_{\max}$ cm^{–1} (KBr) 3480, 3300–2400, 1730, 1600, 1500, 1240, 1175, 1100, 1080, 740, 695. NMR (400 MHz, CDCl₃) δ : 1.97–2.08 (1H, m), 2.15–2.24 (1H, m), 2.75–2.87 (2H, m), 4.27 (1H, dd, *J* = 3.9, 7.8 Hz), 7.19–7.31 (5H, m). OH signals were not observed because of broadening. The IR and NMR spectra of the material were identical with those of an authentic specimen. *Anal.* Found: C, 66.64; H, 6.59. Calcd. for C₁₀H₁₂O₃: C, 66.65; H, 6.71%. A small portion of this was converted to (*R*)-**1b**, [α]_D²³ –30.7° (*c* 1.30, CHCl₃). HPLC analysis (Daicel chiralcel OJ column, 4.6 mm × 250 mm, hexane/2-propanol = 9:1, 0.5 ml/min) *t*_R: 24.2 min (99.7%), 27.2 min (0.3%). Therefore, the *e.e.* was determined to be over 99%.

The mother liquor was combined after collecting (*R*)-**1a** and then concentrated *in vacuo*. A small portion was stirred with aqueous pyridine to destroy the remaining anhydride. After acidifying, the mixture was extracted with ether, and a small portion of the extract was treated with ethereal diazomethane. The product was purified by silica gel column chromatography to give (*S*)-**2b**, [α]_D²⁴ –4.68° (*c*

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2.14, CHCl_3) [a specimen prepared from authentic (R)-**1a**³]: $[\alpha]_D^{24} + 7.11^\circ$ (*c* 2.01, CHCl_3). Its *e.e.* was therefore estimated to be 66%.

In the case of reusing lipase PS (2.00 g): (R)-**1a**, 840 mg (42%), mp 115–116°C, $[\alpha]_D^{22} - 8.29^\circ$ (*c* 1.03, ethanol); (R)-**1b**, $[\alpha]_D^{24} - 28.7^\circ$ (*c* 1.61, CHCl_3), 95% *e.e.* by HPLC analysis.

In the case of using 20 g of the substrate: (R)-**1a**, 7.25 g (36%), mp 115–116°C, $[\alpha]_D^{25} - 8.49^\circ$ (*c* 1.01, ethanol); (R)-**1b**, $[\alpha]_D^{27} - 30.8^\circ$ (*c* 1.52, CHCl_3), >99% *e.e.* by HPLC analysis.

Comparison among solvents. The experiments were carried out as already described by using the substrate (100 mg), lipase PS (100 mg), the anhydride (72 mg) and each solvent (1 ml) for 20 hr at 20–25°C. The results are shown below.

Diethyl ether: Conversion, 56%; (R)-**1a**, 27.2 mg (27%), mp 115–116°C, $[\alpha]_D^{23} - 8.52^\circ$ (*c* 1.05, ethanol). Its *e.e.* was estimated to be 97% by a comparison of its specific rotation with the known figure.

Ethyl acetate: Conversion, 48%; (R)-**1a**, 31.8 mg (32%), mp 110–112°C, $[\alpha]_D^{25} - 4.42^\circ$ (*c* 1.04, ethanol), 51% *e.e.*

Dichloromethane: Conversion, 35%; (R)-**1a**, 60.0 mg (60%), mp 103–104°C, $[\alpha]_D^{25} - 0.3^\circ$ (*c* 1.02, ethanol), 3%

e.e.

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References

- 1) H. Urbach and R. Henning, *Tetrahedron Lett.*, **25**, 1143 (1984).
- 2) D. Biquard, *Ann. Chim. Phys.*, **20**, 97 (1933).
- 3) JP 01,308,244 (Kuraray Co.); [*Chem. Abstr.*, **112**, 55241r (1990)].
- 4) JP 01,225,499 (Toray Industries Inc.); [*Chem. Abstr.*, **112**, 137582s (1990)].
- 5) P. Kalaritis, R. W. Regenye, J. J. Partridge and D. L. Coffen, *J. Org. Chem.*, **55**, 812 (1990).
- 6) Y.-F. Wang, S. T. Chen, K. K. C. Liu and C.-H. Wong, *Tetrahedron Lett.*, **30**, 1917 (1989).
- 7) T. Sugai and H. Ohta, *Agric. Biol. Chem.*, **54**, 3337 (1990).
- 8) C.-S. Chen, Y. Fujimoto, G. Girdaukas and C. J. Sih, *J. Am. Chem. Soc.*, **104**, 7294 (1982).