Pergamon

Tetrahedron Letters 41 (2000) 9859–9863

TETRAHEDRON LETTERS

Convenient route to both enantiomers of chiral 5-hydroxypyrrolidin-2-one and 5-hydroxy-1,5-dihydropyrrol-2-one: reverse enantioselectivity in lipase-catalyzed kinetic resolution

Kunihiko Takabe,[a,*] Masahisa Suzuki,[a] Toshiki Nishi,[a] Masaomi Hiyoshi,[a] Yasuaki Takamori,[b] Hidemi Yoda[a] and Nobuyuki Mase[a]

[a]*Department of Molecular Science, Faculty of Engineering, Shizuoka University, 3-5-1 Johoku, Hamamatsu 432-8561, Japan*

[b]*Iwata Chemical Co., Ltd., Nakaizumi, Iwata 438-0078, Japan*

Received 28 August 2000; accepted 29 September 2000

Abstract

High enantioselectivity was achieved in the lipase-catalyzed kinetic resolution of 5-hydroxypyrrolidin-2-one and 5-hydroxy-1,5-dihydropyrrol-2-one derivatives. Lipase PS and Novozym 435 were the successful catalysts ($E=>1000$). The acetylation of the *N*-protected 5-hydroxy-1,5-dihydropyrrol-2-one derivative gave the (*R*)-acetate with high enantioselectivity, while, without *N*-protection, the (*S*)-acetate was obtained.

Chiral 5-hydroxypyrrolidin-2-one and 5-hydroxy-1,5-dihydropyrrol-2-one derivatives are valuable building blocks for the asymmetric synthesis of natural products.[1] Enantioselective reduction of succinimide derivatives is an effective method to lead to chiral 3,4-disubstituted-5-hydroxypyrrolidin-2-one derivatives, in which bicyclic derivatives give rise to moderate to high enantioselectivities, whereas monocyclic derivatives show moderate enantioselectivities (Fig. 1).[2,3] Kinetic resolution of 5-hydroxypyrrolidin-2-one and 5-hydroxy-1,5-dihy-

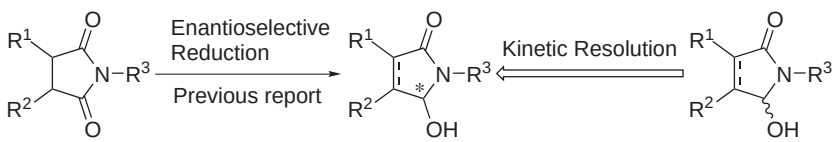


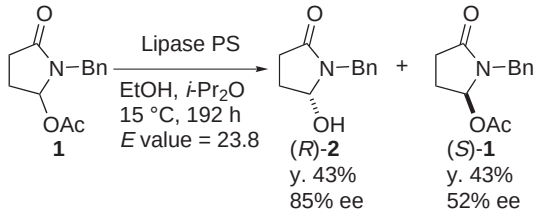
Figure 1. Enantioselective reaction to 5-hydroxylactam

* Corresponding author. Tel/fax: +81-53-478-1148; e-mail: tcktaka@ipc.shizuoka.ac.jp

0040-4039/00/$ - see front matter
PII: S0040-4039(00)01745-7

dropyrrol-2-one derivatives is a more practical method. Recently, we reported the first asymmetric synthesis of (*R*)-(−)-5-hydroxy-3-methyl-1,5-dihydropyrrol-2-one (jatropham), which is an antitumor alkaloid, using kinetic resolution of the racemic jatropham.[4] We report[5] herein highly enantioselective kinetic resolution of 5-hydroxypyrrolidin-2-one and 5-hydroxy-1,5-dihydropyrrol-2-one derivatives catalyzed by lipase[6] (Fig. 1).

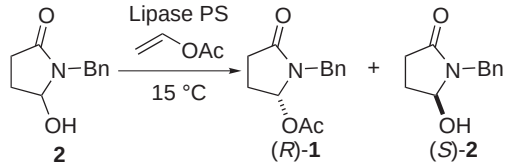
Lipase PS (Amano, *Pseudomonas cepacia*) catalyzed transesterification of 5-acetoxy-1-benzylpyrrolidin-2-one **1** to give the (*R*)-hydroxylactam **2** and the recovered (*S*)-acetate **1** in a good enantiomeric ratio of $E^{7}=23.8$ after 192 hours stirring (Scheme 1).



Scheme 1. Lipase PS-catalyzed transesterification of 5-acetoxy-1-benzylpyrrolidin-2-one **1**

The enantioselectivity was increased to $E=41.9$ in the acetylation[8] of 1-benzyl-5-hydroxypyrrolidin-2-one **2** with vinyl acetate in 1,4-dioxane solution after 48 hours (Table 1, entry 3). Furthermore, we found that the recovered 5-hydroxylactam (*S*)-**2** was stable without racemization after 10 days, while the acetate (*R*)-**1** was easily racemized after a few days at room temperature.[9]

Table 1
Enantioselective acetylation of 1-benzyl-5-hydroxypyrrolidin-2-one **2**



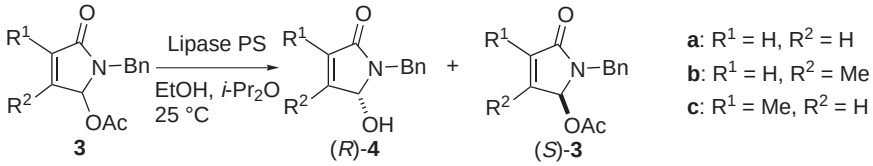
Entry	Solvent	Time (h)	Acetate **1**		Alcohol **2**		*E* value
			Yield (%)	Ee[a] (%)	Yield (%)	Ee[a] (%)	
1	–	72	40	51	40	99	4.2
2	*i*-Pr_2O	120	26	83	51	48	14.3
3	1,4-Dioxane	48	49	88	47	99	41.9

[a] Determined by chiral HPLC using Chiralcel OD (flow rate: 0.5 mL/min, eluent: hexane/*i*-PrOH = 80/20).

High enantioselectivity was observed in the monocyclic succinimide derivatives above. Next, we examined the kinetic resolution of maleimide and citraconimide derivatives. Results are shown in Table 2. The transesterification of the 5-acetoxylactam **3a** proceeded to give the (*R*)-alcohol **4** and the recovered (*S*)-acetate **3** in a high enantiomeric ratio of $E=>501$ (entry 1). The 4-methyl-5-acetoxylactam **3b** did not react with ethanol, whereas the 3-methyl-5-acetoxylactam **3c** gave the (*R*)-alcohol **2** with high enantioselectivity (entries 2 and 3).

Although high enantioselectivity was obtained in the transesterification of **3**, the reactivity was relatively low. On the other hand, enhanced reactivity was observed in the acetylation of the 5-hydroxylactam **5a–c** with vinyl acetate as shown in Table 3. The reaction of the 1-benzyl-5-hydroxylactam **5a** in the presence of lipase PS gave the (*R*)-acetate **6a** and the recovered (*S*)-alcohol **5a** with extremely high enantioselectivity ($E = >1057$, entry 1). Novozym 435 (Novo Nordisk, *Candida antarctica*) was also a practical catalyst for the kinetic resolution ($E = >752$, entry 2). The 1-allyl-5-hydroxylactam **5b** was effectively resolved under similar conditions (entries 3 and 4). Interestingly, reverse enantioselectivity was observed in the reaction of the 5-hydroxylactam **5c** (R = H, entries 5–6); thus, the enantioselectivity depends upon *N*-protection. These resolved compounds are stable at room temperature, and racemization was not observed.

Table 2
Enantioselective transesterification of the 5-acetoxylactam **3**



Entry	Substrate	Time (h)	Alcohol **4**		Acetate **3**		*E* value
			Yield (%)	Ee (%)[a]	Yield (%)	Ee (%)[a]	
1	**3a**	72	45	>99	49	90	>501
2	**3b**	480	Trace	–	99	–	–
3	**3c**	120	26	>99	62	43	>280

[a] Determined by chiral HPLC using Chiralpak AS (flow rate: 0.3–1.0 mL/min, eluent: hexane/EtOH = 90/10-98/2).

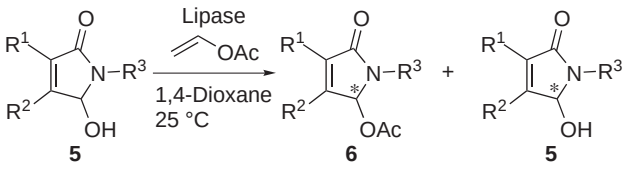
This approach is even successful with the citraconimide derivatives **5d–g**. The (*R*)-1-benzyl-4-methyl-5-acetoxylactam **6d** (98% ee) was obtained but in 20% conversion after prolonged reaction time (entry 7). This low reactivity was due to the steric interaction of the 4-methyl group. In the case of the 1-benzyl-3-methyl-5-acetoxylactam **5e** the acetylation smoothly proceeded to give the (*R*)-acetate **6e** (>99% ee) and the recovered (*S*)-alcohol **5e** (>99% ee) (entry 8). Reverse enantioselectivity was also observed in the acetylation of **5g** without *N*-protection in the presence of Lipase PL (Meito, *Alcaligenes* sp.) ($R^3 = H$, entry 10).

In conclusion, we have discovered that racemic hydroxylactams are easily resolved by lipase, and that enantioselectivities depended upon the presence or absence of *N*-protection. Although the mechanism of the enantioselectivity is not clear at this stage, probably, a hydrogen bonding between the amide-hydrogen and the hydrogen acceptor near the reaction site plays an important role in leading to the reverse enantioselectivity.

Acknowledgements

Thanks to Amano Pharmaceutical Co., Ltd, Novo Nordisk Bioindustry Co., Ltd., and Meito Sangyo Co., Ltd. for a generous gift of some enzymes. This work was partially supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan.

Table 3
Enantioselective acetylation of the 5-hydroxylactam **5**



a: R^1 = H, R^2 = H, R^3 = Bn
b: R^1 = H, R^2 = H, R^3 = Allyl
c: R^1 = H, R^2 = H, R^3 = H
d: R^1 = H, R^2 = Me, R^3 = Bn
e: R^1 = Me, R^2 = H, R^3 = Bn
f: R^1 = Me, R^2 = H, R^3 = Ally
g: R^1 = Me, R^2 = H, R^3 = H

Entry	Substrate	R^3	Lipase	Time (h)	Yield **6** (ee)[a] (%)	Config.	Yield **5** (ee)[a] (%)	Config.	*E* value
1	**5a**	Bn	Lipase PS	24	50 (>99)	*R*	48 (>99)	*S*	>1057
2	**5a**	Bn	Novozym 435	20	49 (>99)	*R*	48 (>99)	*S*	>752
3	**5b**	Allyl	Lipase PS	6	42 (96)	*R*	50 (70)	*S*	102
4	**5b**	Allyl	Novozym 435	20	48 (81)	*R*	47 (93)	*S*	21.2
5	**5c**	H	Lipase PL	5	49 (75)	*S*	32 (>99)	*R*	14.9
6	**5c**	H	Novozym 435	20	43 (75)	*S*	44 (99)	*R*	12.3
7	**5d**	Bn	Lipase PS	240	20 (98)	*R*	67 (38)	*S*	126
8	**5e**	Bn	Novozym 435	20	49 (>99)	*R*	48 (>99)	*S*	>752
9	**5f**	Allyl	Novozym 435	20	46 (79)	*R*	48 (81)	*S*	16.0
10	**5g**	H	Lipase PL	6	53 (50)	*S*	35 (98)	*R*	5.1

[a] Determined by chiral HPLC using Chiralpak AS (flow rate: 0.5–1.0 mL/min, eluent: hexane/EtOH = 80/20-98/2).

References

1. (a) Dijkink, J.; Cintrat, J.-C.; Speckamp, W. N.; Hiemstra, H. *Tetrahedron Lett*. **1999**, *40*, 5919–5922. (b) Yoda, H.; Kitayama, H.; Katagiri, T.; Takabe, K. *Tetrahedron* **1992**, *48*, 3313–3322. (c) Koot, W.-J.; Ginkel, R. v.; Kranenburg, M.; Hiemstra, H.; Louwrier, S.; Moolenaar, M. J.; Speckamp, W. N. *Tetrahedron Lett*. **1991**, *32*, 401–404. (d) Klaver, W. J.; Hiemstra, H.; Speckamp, W. N. *J. Am. Chem. Soc*. **1989**, *111*, 2588–2595.
2. (a) Ostendorf, M.; Romagnoli, R.; Pereiro, I. C.; Roos, E. C.; Moolenaar, M. J.; Speckamp, W. N.; Hiemstra, H. *Tetrahedron: Asymmetry* **1997**, *8*, 1773–1789. (b) Kang, J.; Lee, J. W.; Kim, J. I.; Pyun, C. *Tetrahedron Lett*. **1995**, *36*, 4265–4268. (c) Matsuki, K.; Inoue, H.; Ishida, A.; Takeda, M.; Nakagawa, M.; Hino, T. *Chem. Pharm. Bull*. **1994**, *42*, 9–18. (d) Romagnoli, R.; Roos, E. C.; Hiemstra, H.; Moolenaar, M. J.; Speckamp, W. N.; Kaptein, B.; Schoemaker, H. E. *Tetrahedron Lett*. **1994**, *35*, 1087–1090.
3. We tried to achieve high stereoselectivity in the enantioselective reduction of *N*-benzylmaleimide to the 5-hydroxy-1,5-dihydropyrrol-2-one derivative with BINAL-H; however, low enantioselectivity was observed.
4. Mase, N.; Nishi, T.; Takamori, Y.; Yoda, H.; Takabe, K. *Tetrahedron*: *Asymmetry* **1999**, *10*, 4469–4471.
5. A part of this work was presented at the 5th International Kyoto Conference on New Aspects of Organic Chemistry (Kyoto, 12 November, 1991) and the 4th Symposium on Biotransformation of Organic Compounds (Otsu, 22 January, 1992).
6. (a) Drauz, K.; Waldmann, H. *Enzyme Catalysis in Organic Synthesis*; VCH: Weinheim, 1995. (b) Wong, C.-H.; Whitesides, G. M. *Enzymes in Synthetic Organic Chemistry*; Pergamon: Oxford, 1994. (c) Drueckhammer, D. G.; Hennen, W. J.; Pederson, R. L.; Carlos, F.; Barbas, I.; Gautheron, C. M.; Krach, T.; Wong, C.-H. *Synthesis* **1991**, 499–525. (d) Chen, C.-S.; Sih, C. J. *Angew. Chem., Int. Ed. Engl*. **1989**, *28*, 695–707.
7. Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc*. **1982**, *104*, 7294–7299.
8. Typical procedure: a solution of imide derivatives **1** (50 mg) and lipase (50 mg) in vinyl acetate (500 mg) was stirred for an appropriate time; then, lipase was removed through filtration, and concentrated to give a crude, which was purified by column chromatography (silica gel, eluent: hexane–AcOEt) to give the acetate **2** and the recovered alcohol **1**.
9. Recently, Feringa and Kellogg reported that lipase-catalyzed esterification and transesterification of 1-acetoxy maleic anhydride and 1-acetoxymaleimide derivatives gave the chiral 1,5-diacetoxylactone and 1,5-diacetoxylactam with >99% enantioselectivity and 100% yield due to spontaneous racemization of 5-hydroxylactone and 5-hydroxylactam. van der Deen, H.; Cuiper, A. D.; Hof, R. P.; van Oeveren, A.; Feringa, B. L.; Kellogg, R. M. *J. Am. Chem. Soc*. **1996**, *118*, 3801–3803.