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Reverse enantioselectivity in the lipase-catalyzed desymmetrization of prochiral 2-carbamoylmethyl-1,3-propanediol derivatives

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Abstract

Enantioselective acetylation of 2-carbamoylmethyl-1,3-propanediol derivatives was catalyzed effectively by lipase PS to give monoacetates with high enantioselectivity: The enantioselectivity depended on the 2-carbamoylmethyl groups. The reaction of *N*-monoalkylcarbamoylmethyl-1,3-propanediol afforded the monoacetate with the (*S*)-configuration, whereas *N*,*N*-dialkylcarbamoylmethyl-1,3-propanediol gave the monoacetate with the (*R*)-configuration.

Asymmetric desymmetrization of *meso*-compounds or prochiral 1,3-propanediols and diacetates in the presence of lipase[1] has become a practical approach for the preparation of chiral compounds due to its high specificity and reproducibility.[1,2] Most previous approaches in the asymmetric desymmetrization of the 1,3-propanediols refer to specific substrates; R^1 = alkyl, alkenyl, alkynyl, aryl, benzyloxy, and acetoxy groups (Fig. 1).[1,2] Investigation of the desymmetrization of a prochiral 1,3-propanediol incorporating a functional group should provide a

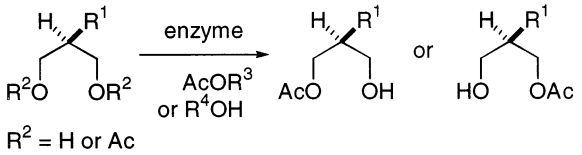

Figure 1. Asymmetric desymmetrization of 1,3-propanediols and diacetates

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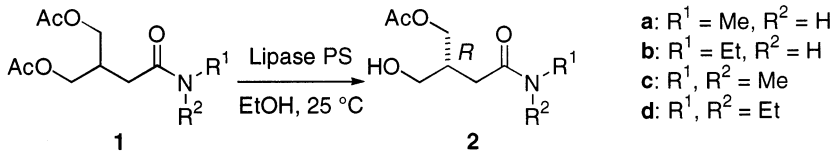
new strategy for enantiomerically enriched compound synthesis. We report herein the asymmetric desymmetrization of the 2-carbamoylmethyl-1,3-propanediol and the corresponding diacetate.

Enantioselective lipase PS (Amano, *Pseudomonas cepacia*)-catalyzed transesterification of the diacetate[3] **1** was investigated.[4] Results are shown in Table 1. The transesterification of *N*-monoalkylcarbamoyl-diacetates **1a**,**b** afforded (*R*)-monoacetates **2a**,**b** with 90 and 95% ee, respectively (entries 1 and 2), whereas *N*,*N*-dialkylcarbamoyl-diacetates **1c**,**d** did not react after 168 h stirring (entries 1 and 2). The absolute configuration of **2a**,**b** was determined to be (*R*) by comparison of the value of the specific rotation of 4-(phenylsulfanylmethyl)dihydrofuran-2-one.[5]

The enantioselective acetylation of the 2-carbamoylmethyl-1,3-propanediols **3** was examined as shown in Table 2.[6] *N*-Monomethylcarbamoyl-diol **3a** gave the (*S*)-monoacetate **2a** with >99%

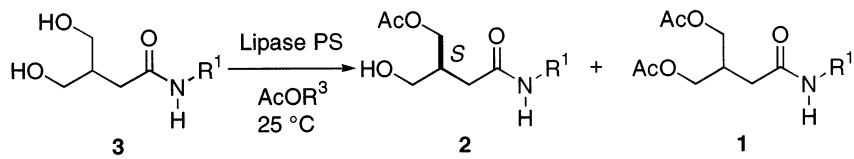
Table 1
Enantioselective transesterification of 2-carbamoylmethyl-1,3-diacetates



Entry	Substrate	Time (h)	Yield (%)	Ee (%)[a]	Config.
1	**1a**	67	35	90	*R*
2	**1b**	55	45	95	*R*
3	**1c**	168	No reaction	–	–
4	**1d**	168	No reaction	–	–

[a] Determined by HPLC analysis using Chiralpak AS (flow rate: 0.8 mL/min, eluent: hexane/2-propanol = 70/30).

Table 2
Enantioselective acetylation of *N*-monoalkylcarbamoylmethyl-1,3-propanediols **3**



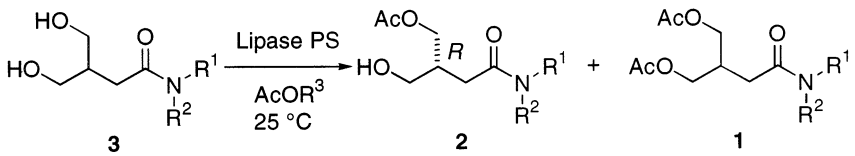
Entry	Substrate	R^3	Time (h)	Monoacetate **2**			Diacetate **1**
				Yield (%)	Ee (%)[a]	Config.	Yield (%)
1	**3a**	Vinyl	24	30	80	*S*	38
2	**3a**	Phenyl	12	26	>99	*S*	37
3	**3a**	Phenyl[b]	24	55	88	*S*	25
4	**3b**	Phenyl	3	43	94	*S*	20

[a] Determined by HPLC analysis using Chiralpak AS (flow rate: 0.8 mL/min, eluent: hexane/2-propanol = 70/30).
[b] *i*-Pr_2O was used as a solvent.

ee in the presence of phenyl acetate (entry 2). The reaction of *N*-monoethylcarbamoyl-diol **3b** also gave the (*S*)-monoacetate **2b** with 94% ee (entry 4).

Next, we examined the reaction of *N*,*N*-dialkylcarbamoyl-diols **3c**,**d** as shown in Table 3. The reaction of *N*,*N*-dimethylcarbamoyl-diol **3c** gave the monoacetate (*R*)-**2c** in 42% yield with 97% enantiomeric excess (entry 1). It was noted that the absolute configuration of the monoacetate **2c** was (*R*); thus, the pro-(*S*) hydroxy group was preferentially acetylated in the case of *N*-monoalkylcarbamoyl-diol **3a**,**b** (Table 2), while the pro-(*R*) hydroxy group was more reactive in the case of *N*,*N*-dialkylcarbamoyl-diol **3c**,**d** (Table 3).[7] Similarly, *N*,*N*-diethylcarbamoyl-diol **3d** also afforded the monoacetate (*R*)-**2d** with 96% ee (entry 4).

Table 3
Enantioselective acetylation of *N*,*N*-dialkylcarbamoylmethyl-1,3-propanediols **3**



3 **2** **1**

c: R^1, R^2 = Me
d: R^1, R^2 = Et

Entry	Substrate	R^3	Time (h)	Monoacetate **2**			Diacetate **1**
				Yield (%)	Ee (%)[a]	Config.	Yield (%)
1	**3c**	Vinyl	5	42	97	*R*	5
2	**3c**	Phenyl	14	77	96	*R*	Trace
3	**3c**	Phenyl[b]	48	66	95	*R*	10
4	**3d**	Vinyl[b]	74	52	96	*R*	27
5	**3d**	Phenyl	68	43	84	*R*	16

[a] Determined by HPLC analysis using Chiralpak AS (flow rate: 0.5–0.8 mL/min, eluent: hexane/2-propanol = 80/20–90/10).
[b] *i*-Pr_2O was used as a solvent.

Among the studies on structure–enantioselectivity relationships,[8] the mechanism of the expression of enantioselectivity[9] in the present case is not clear at this stage. We propose here the importance of hydrogen bonding between the enzyme and substrate. In a plausible mechanism shown in Fig. 2, the *N*-monoalkylcarbamoyl group in **3a**,**b** would hydrogen bond with an amide group in the lipase; thus, the pro-(*S*) hydroxy group is stereoselectively acetylated (Fig. 2, Type I). On the other hand, in the reaction of *N*,*N*-dialkylcarbamoyl-diols **3c**,**d** the *N*,*N*-dialkylcarbamoyl group is more likely located at the hydrophobic site in the active-site model for the lipase (Fig. 2, Type II); therefore, the pro-(*R*) hydroxy group is discriminated to give the (*R*)-monoacetate **2c**,**d**.

In conclusion, we have shown a high level of asymmetric desymmetrization in the reaction of 1,3-propanediols and diacetates bearing a carbamoyl group. This present reaction should provide a new strategy for asymmetric desymmetrization of 1,3-propanediols and diacetates, and these monoacetates **2** could potentially become a new chiral building block for the synthesis of natural products.

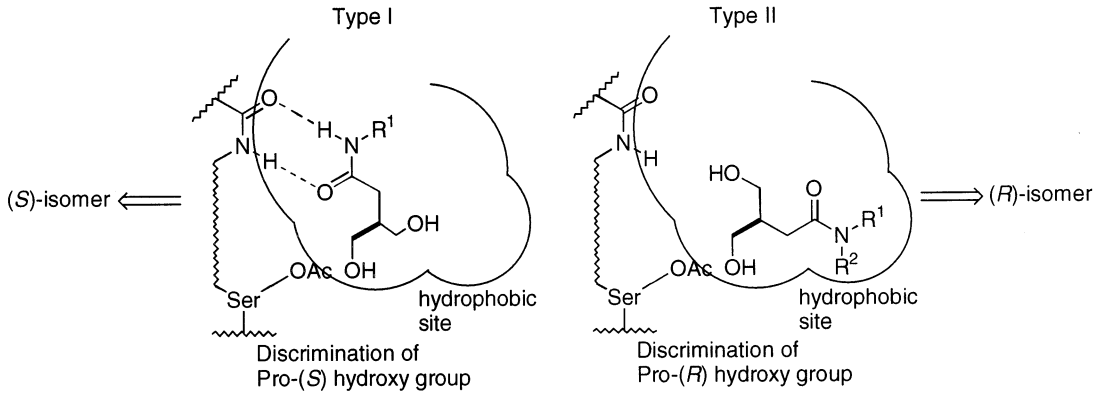


Figure 2. Proposed active-site model for lipase

Acknowledgements

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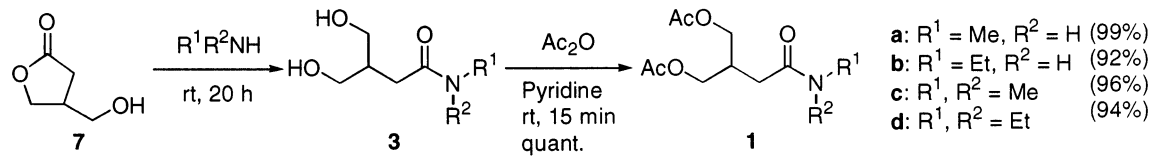
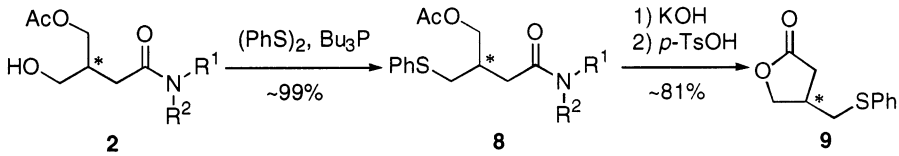
3. 2-Carbamoylmethyl-1,3-propanediols **3** and diacetates **1** were prepared by amidation of 4-hydroxymethyldihydrofuran-2-one **7** and subsequent acetylation (Scheme 1).



Scheme 1. Preparation of 2-carbamoylmethyl-1,3-propanediols **3** and diacetates **1**

4. We also examined the enantioselective hydrolysis of 2-carbamoylmethyl-diacetates **1** in a buffer solution; however, low conversion (18–49%) and enantioselectivities (11–20% ee) were observed after prolonged reaction time (4–7 days).

5. 4-(Phenylsulfanylmethyl)dihydrofuran-2-one **9** was prepared in two steps as shown in Scheme 2. The lactone **9** with (*R*)-configuration shows a positive value of the optical rotation (lit. (*R*)-isomer: $[\alpha]_D^{23} = +15.8$ (*c* 0.985, $CHCl_3$, 99% ee)); see, Takabe, K.; Hiyoshi, H.; Sawada, H.; Tanaka, M.; Miyazaki, A.; Yamada, T.; Katagiri, T.; Yoda, H. *Tetrahedron: Asymmetry* **1992**, *3*, 1399–1400.



Scheme 2. Preparation of 4-(phenylsulfanylmethyl)dihydrofuran-2-one **9**

6. Typical procedure: A solution of 2-carbamoylmethyl-1,3-propanediols **3** (1.0 g) and lipase PS (0.050 g) in acetate (2 equivalents) was stirred at 25°C for an appropriate time; then, lipase PS was removed by filtration, and concentrated to give a crude oil, which was purified by column chromatography (silica gel, eluent: hexane–AcOEt) to give the monoacetate **2** and the diacetate **1**.
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