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Enzyme-catalyzed Asymmetrization of 2,2-Disubstituted 1,3-Propanediols Using 1-Ethoxyvinyl Esters

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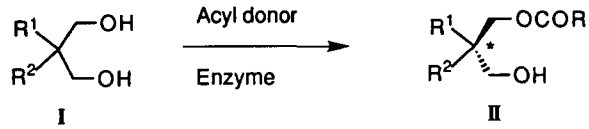
Abstract: The lipase-catalyzed asymmetrization of the prochiral 2,2-disubstituted 1,3-propanediols **1, 6,** and **9** was studied using various types of 1-ethoxyvinyl esters **2**. Among them, the use of the benzoate **2f** provided good chemical and optical yields of the products **3, 7,** and **10** bearing chiral quaternary carbon centers which are fairly stable against racemization. © 1997 Elsevier Science Ltd.

The synthetic importance as well as chemical interest for the construction of optically active quaternary carbon centers have widely been recognized.[1] Among the increasing number of novel methods for this topic, the enzymatic differentiation of the prochiral hydroxyl groups of the 2,2-disubstituted 1,3-propanediols **I** leading to the chiral compounds **II** must be attractive (Scheme 1). However, this approach has rarely been reported,[2-5] although many successful examples are known for the similar asymmetrization of 2-monosubstituted 1,3-propanediols (**I** where R^2 = H).[6] This seems to be due to the low reactivity of the sterically congested substrates **I** and the easy racemization of the products **II** through acyl group migration.



I **II**

Scheme 1

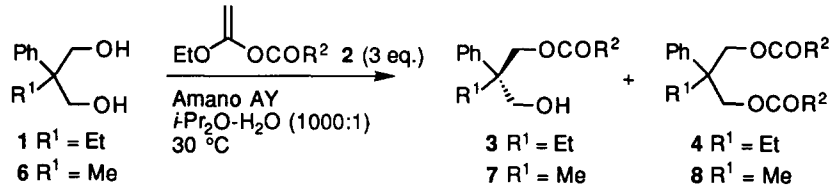
Very recently, we have disclosed a novel enzymatic resolution of the alcohols using the 1-ethoxyvinyl ester (EVE) as an acyl donor.[7] In contrast to the well known method using vinyl esters, our method features the formation of ethyl acetate as a single side-product which does not disturb the enzymatic reactions, therefore, it allows the reliable use of a variety of enzymes.[8] It also shows comparative to or higher reactivity than the usual method and its asymmetric efficiency is similarly high. We now demonstrate additional advantages of our method in the above mentioned enzymatic asymmetrization of prochiral 2,2-disubstituted 1,3-propanediols **I**, in which ready availability of EVEs having various kinds of acyl groups and their high reactivity led us to overcome these problems.

At first, we attempted the reaction of the diol **1** with ethoxyvinyl acetate **2a** (3 equiv.) in the presence of several lipases (Amano PS, AK, AY, PPL, Toyobo LIP) in hexane or *i*-Pr_2O at 30 °C. However, the maximum ee of the desired monoacetate **3a** was 27% which was obtained using Amano AY (from *Candida rugosa*) in *i*-Pr_2O (Run 1 in Table 1).

We then investigated other acyl group donors **2b-i** instead of **2a**. The reagents **2b-i** were prepared in good yields by the addition of the corresponding carboxylic acid to ethoxyacetylene catalyzed by [$RuCl_2$(*p*-

cymene)]$_2$.[9] Similar reactions of **1** with **2b-i** were carried out in the presence of Amano AY in *i*-Pr_2O, and the results are summarized in Table 1.

Table 1. Lipase-catalyzed asymmetrization of the 1,3-diols **1** and **6** using various types of **2**

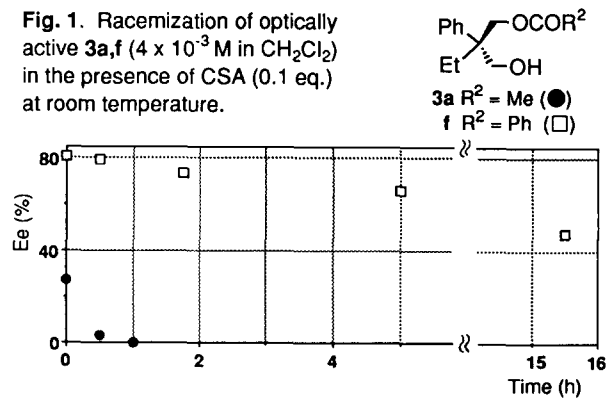


Run	Diol	2, R^2 =	Reaction time	Monoester 3,7			Diester 4,8	
					Isolated yield, %[a]	Ee, %[b]		Isolated yield, %[a]
1	**1**	**a** Me	4 d	**3a**	66	27	**4a**	--
2	**1**	**b** CH_2Cl	7 d	**b**	36	1[c]	**b**	64
3	**1**	**c** C_3H_7	5 h	**c**	86	63	**c**	14
4	**1**	**d** C_7H_{15}	4 d	**d**	85	36	**d**	12
5	**1**	**e** $C_{11}H_{23}$	21 d	**e**	78	0[c]	**e**	--
6	**1**	**f** C_6H_5	6 h	**f**	90	81	**f**	--
7	**1**	**f** C_6H_5	18 h	**f**	39	91	**f**	61
8	**1**	**g** 4-MeO-C_6H_4	8.5 d	**g**	50	69	**g**	33
9	**1**	**h** 4-NO_2-C_6H_4	13 d	**h**	64	53	**h**	d
10	**1**	**i** 2,6-diMe-C_6H_3	30 d	**i**	<5	--	**i**	--
11	**6**	**a** Me	8 d	**7a**	46	1	**8a**	ca.10
12	**6**	**f** C_6H_5	3 d	**f**	71	84	**f**	26

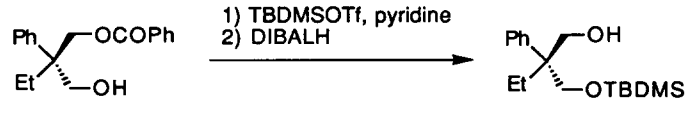
a, Purified by SiO_2-column chromatography. b, Determined by Daisel CHIRALCEL OD (hexane-*i*-PrOH). c, Determined after transformation into **5** by a method similar to that shown in Scheme 2. d, Not determined.

Several aspects are noteworthy. First, the benzoate **2f** was the most effective in terms of high chemical and optical yields as well as high reactivity (Run 6).[10] A prolonged reaction gave a slightly better ee of **3f**, although its yield was decreased (Run 7). Second, the other aroyl reagent, *p*-methoxybenzoate **2g** (Run 8), was in the second best class along with the aliphatic butyryl reagent **2c** (Run 3). These effective results of the aroyl donors **2f,g** are outstanding because the successful use of benzoyl donors for the enzymatic reactions have been reported in limited cases.[11] Moreover, the product **3f** having a benzoyl group was found to be relatively stable against the racemization compared to the acetate **3a**. A comparison of the stability of these two products under acidic conditions [0.1 equiv. of camphor sulfonic acid (CSA), CH_2Cl_2, room temperature] is shown in Fig. 1.[12]

Fig. 1. Racemization of optically active **3a,f** (4×10^{-3} M in CH_2Cl_2) in the presence of CSA (0.1 eq.) at room temperature.



A preliminary transformation of the functional group of **3f** into the silyl ether **5** was attained without loss of its optical purity (Scheme 2).



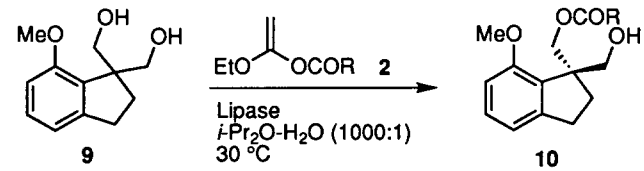
3f (85% ee) **5** (69%, 84% ee)

Scheme 2

Similarly, asymmetrization of **6** using **2f** and Amano AY gave the chiral product **7f** in 71% yield with 84% ee,[10] while a similar reaction using **2a** was not satisfactory (Table 1; Runs 11 and 12).

This method was also applied to the more hindered diol **9** (Table 2). The use of the benzoate **2f** gave 72% ee **10f** in 50% isolated yield (Run 3), while the use of **2a** or **2c** was again insufficient (Runs 1,2). A better result (82% yield, 71% ee) was obtained using a similar lipase MY (Meito Sangyo) obtained from *Candida rugosa* (Run 4). The product **10f** {71% ee, $[\alpha]_D^{24}$ -39.9 (c 0.4, $CHCl_3$)} was converted to the carboxylic acid **11** (59% yield). An enantiomerically pure **11** was obtained through formation of a crystalline salt **12** with (*S*)-1-phenethylamine followed by recrystallization from EtOH (Scheme 3). In contrast to the cases of **3f** and **7f**, the absolute stereochemistry of the chiral center of **10f** was disclosed to be *R*, because the X-ray crystallographic analysis of **12** unambiguously showed that the chiral center of **11** was *S*.

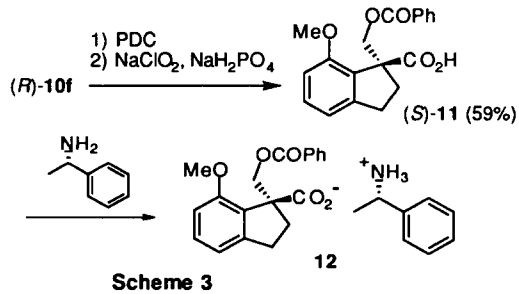
Table 2. Lipase-catalyzed asymmetrization of the 1,3-diol **9**.



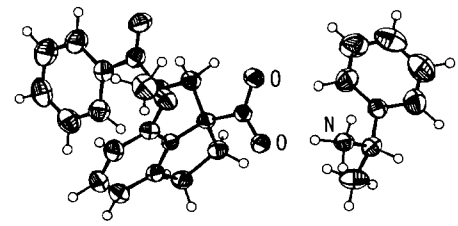
9 **10**

Run	Lipase	**2**, R =	Reaction time	**10**		
					Isolated yield, %[a]	Ee, %[b]
1	Amano AY	**a** Me	25 d	**a**	41	10
2	Amano AY	**c** C_3H_7	25 d	**c**	37	10
3	Amano AY	**f** C_6H_5	4 d	**f**	50	72
4	Lipase MY[c]	**f** C_6H_5	4 d	**f**	82	71
5	Lipase OF[c]	**f** C_6H_5	4 d	**f**	67	58

a, Purified by SiO_2-column chromatography. b, Determined by Daisel CHIRALCEL OD (hexane-*i*-PrOH). c, From Meito Sangyo.



Scheme 3



The X-Ray crystallographic structure of the salt **12**.

In this research, the screening of the acyl group of the EVEs provided a promising access for asymmetrization of the prochiral 2,2-disubstituted 1,3-propanediols featuring high asymmetric efficiency and reduced racemization of the products. Since various types of EVEs are easily available from the corresponding carboxylic acid,[9] our method is believed to become a readily operative and highly effective methodology for the enzymatic resolution of a variety of alcohols.

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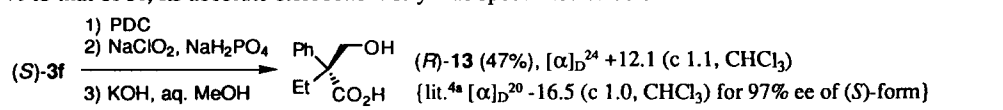
2. Just before completion of this paper, the first example of the asymmetrization of prochiral 2,2-disubstituted 1,3-propanediols was reported using isopropenyl acetate. See, Fadel, A.; Arzel, P. *Tetrahedron: Asym.* **1997**, *8*, 283-291.
3. Other enzymatic asymmetrizations of molecules having prochiral quaternary carbons have been limited to the hydrolysis of 2,2-disubstituted malonates,[1,4] hydrolysis of the diesters of 2,2-disubstituted 1,3-propanediols,[5] and the resolution of 2,2-disubstituted 1,3-diones.[1] The process of Scheme 1 is advantageous because it can be run in organic solvents.
4. Recent examples, see; a) Fadel, A.; Garcia-Argote, S. *Tetrahedron: Asym.* **1996**, *7*, 1159-1166 and references cited therein; b) Hallinan, K. O.; Honda, T. *Tetrahedron* **1995**, *51*, 12211-12216.
5. Suemune, H.; Harabe, T.; Xie, Z.-F.; Sakai, K. *Chem. Pharm. Bull.* **1988**, 36, 4337-4344; For the related hydrolysis of 2,2-disubstituted 1,3-propanediyl diesters, see, Prasad, K.; Estermann, H.; Chen, C.-P.; Repic, O.; Hardtmann, G. E. *Tetrahedron: Asym.* **1990**, *1*, 421-424; Seu, Y.-B.; Kho, Y.-H. *Tetrahedron Lett.* **1992**, *33*, 7015-7016; Ito, T.; Ohara, H.; Takagi, Y.; Kanda, N.; Uneyama, K. *ibid.* **1993**, *34*, 4215-4218.
6. Reviews: Faber, K.; Riva, S. *Synthesis* **1992**, 895-910; Santaniello, E.: Ferraboschi, P.; Grisenti, P.; Manzocchi, A. *Chem. Rev.* **1992**, *92*, 1071-1140; Theil, F. *ibid.* **1995**, *95*, 2203-2227; Nakamura, K.; Hirose, Y. *J. Synth. Org. Chem., Jpn.* **1995**, *53*, 668-677.
7. Kita, Y.; Takebe, Y.; Murata, K.; Naka, T.; Akai, S. *Tetrahedron Lett.* **1996**, *37*, 7369-7372.
8. A very similar concept using 1-ethoxyvinyl acetate for the enzymatic resolution of alcohols was also very recently reported. See, Schudok, M.; Kretzschmar, G. *Tetrahedron Lett.* **1997**, *38*, 387-388.
9. Kita, Y.; Maeda, H.; Omori, K.; Okuno, T.; Tamura, Y. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2999-3005; Shibata, N.; Matsugi, M.; Kawano, N.; Fukui, S.; Fujimori, C.; Gotanda, K.; Murata, K.; Kita, Y. *Tetrahedron: Asym.* **1997**, *8*, 303-310.
10. Specific rotations for some selected products: **3a** (27% ee), $[\alpha]_D^{24}$ -2.13 (c 1.1, $CHCl_3$); **3f** (81% ee), $[\alpha]_D^{24}$ -14.1 (c 0.8, $CHCl_3$); **7f** (84% ee), $[\alpha]_D^{24}$ -0.62 (c 0.7, $CHCl_3$). The absolute stereochemistry of **3f** was determined to be *S* by its derivation to the known carboxylic acid **13** and the comparison of its specific rotation with that of the reported compound.[4a] Based on the similarity of the specific rotation of **7f** to that of **3f**, its absolute stereochemistry was speculated to be *S*.



11. For the use of resolution of a racemic alcohol, see; Tamazaki, Y.; Hosono, K. *Tetrahedron Lett.* **1990**, *31*, 3895-3896. Other examples are on the use for the site selective acylation of sugars. See, Holla, E. W. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 220-221; Panza, L.; Brasca, S.; Riva, S.; Russo, G. *Tetrahedron: Asym.* **1993**, *4*, 931-932.
12. Under basic conditions (pyridine/room temperature/1 d, imidazole/DMF/room temperature/1 d), **3a** and **3f** did not change at all.

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