Convenient Enzymatic Resolution of Alcohols Using Highly Reactive, Nonharmful Acyl Donors, 1-Ethoxyvinyl Esters

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1-Ethoxyvinyl esters **3**, a new type of acyl donors for enzymatic resolution of racemic alcohols, were disclosed to be superior to the contemporary major reagents, vinyl esters **1** and isopropenyl esters **2**. Three features of **3** are noticeable: (1) **3** generates ethyl acetate as a single coproduct, which does not affect any enzymes, while acetaldehyde liberated from **1** deactivates some kinds of lipases. (2) The reactivity of **3** was not less than that of **1** and much higher than that of **2**, and the optical purity of the products was as high as that of **1** and **2**. Especially, it was generally observed that **3** showed higher reactivity than **1** for reactions using *Candida rugosa* lipases, one of the most commonly employed lipases, having liberal applicability to substrates but sensitive to acetaldehyde. Twelve examples of the kinetic resolution of racemic secondary alcohols (**5** and **10**) and one desymmetrization of *meso*-alcohol **7** were presented employing the acetate **3a** or the octanoate **3b** and four types of lipases. (3) A one-pot procedure for the preparation of **3** from the corresponding carboxylic acid and the subsequent enzymatic resolution of alcohols, which has not been reported using **1** or **2**, was elucidated. The chemical and optical yields of the products by this procedure were similar to those obtained using isolated **3**.

Introduction

As well as hydrolysis of esters catalyzed by lipases and esterases, transesterifications of alcohols with acylating reagents (acyl donors) catalyzed by the same enzymes in organic media have been established as efficient asymmetric syntheses in this decade.[1] Important progress in this method can be mainly attributed to the development of effective acyl donors. Among diverse reagents involving 2-haloethyl esters,[2a] cyanomethyl esters,[2b] oxime esters,[2c−g] acid anhydrides,[2h,i] vinyl esters **1**,[3] and isopropenyl esters **2**,[3] currently **1** is the best reagent and employed to a major extent. This is because **1** has realized an irreversible system by generating neutral volatile acetaldehyde as a single coproduct and thereby produced optically active compounds in high optical as well as chemical yields in short reaction periods. However, acetaldehyde is known to deactivate some kinds of enzymes [e.g., lipases from *Candida rugosa* and *Geotrichum candidum*] through, for example, formation of Schiff bases with ϵ-amino groups of lysine residues, which limits the reliable use of **1**.[4] Although immobilization of the enzyme on a support was reported to overcome this problem,[4a] this technique seems to become laborious when one surveys a suitable catalyst from a variety of readily available enzymes. On the other hand, isopropenyl esters **2** are the second most often employed reagents, which also feature an irreversible system generating nonharmful acetone as a coproduct; however, they are generally less reactive than **1**.[3f] Therefore, use of an alternative, highly reactive acyl donor which does not produce any enzyme inhibitors must become the best method facilitating the use of enzymes without any modification.

Recently we briefly communicated that 1-ethoxyvinyl acetate (**3a**)[5] is such a reagent suitable for this requirement, providing high chemical and optical yields of the products with release of nonharmful volatile ethyl acetate as a single coproduct (Scheme 1).[6,7]

We have further evaluated the advantages of **3** over **1** and **2**, *i.e.*, general applicability to enzymatic esterification of alcohols, higher reactivity for reactions using lipases from *C. rugosa*, and a novel one-pot procedure for the preparation of **3** and the subsequent enzymatic resolution of alcohols, which has not been reported using **1** or **2**. In this paper, we present full details of these results in addition to those of our previous communication.

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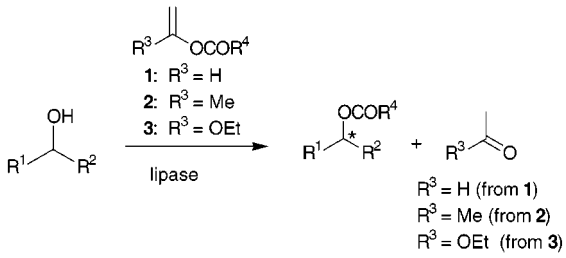
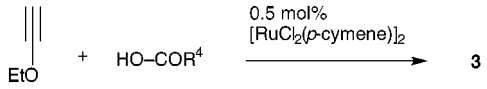
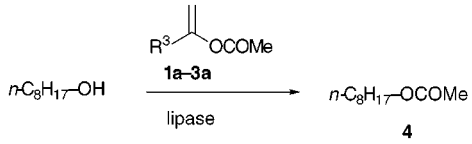
Scheme 1



Scheme 2



Scheme 3



Results and Discussion

Applicability, Reactivity, and Stereoselectivity of 1-Ethoxyvinyl Esters 3 Compared with Those of Vinyl Esters 1 and Isopropenyl Esters 2. 1-Ethoxyvinyl esters **3** are readily available by the addition of the corresponding carboxylic acids to ethoxyacetylene in the presence of a catalytic amount (≤0.5 mol % equiv) of $[RuCl_2(p\text{-cymene})]_2$ in high yields,[8] easy to handle, and, in most cases, storable in a freezer over a year without any significant decomposition (Scheme 2).

At first, general applicability and reactivity of the acetate **3a** for the enzymatic reactions were examined by esterification of 1-octanol, comparing with those of corresponding **1a** and **2a** (Scheme 3 and Figure 1). As shown in Figure 1a, **3a** showed reactivity almost equal to that of **1a** and approximately 4 times higher reactivity than **2a** for the reaction using lipase PS (from *Pseudomonas cepacia*). Similar reactivity of **3a** to **1a** was also observed for the reactions using lipases AK (from *Pseudomonas fluorescens*) and CAL-B (from *Candida antarctica*) (Figure 1b,c). Interestingly, the reactions of **3a** using lipases AY and CRL (both from *C. rugosa*) were about 2−3 times faster than those of **1a** (Figure 1d,e). In all reactions of **3a**, the alcohol was completely converted to the corresponding acetate **4**. Thus, excellent applicability of the new acyl donor **3a** to the enzymatic reactions was disclosed.

We next compared **1a** and **3a** on the kinetic resolution of a racemic secondary alcohol **5** using lipase AY. The results summarized in Table 1 reveal two advantages of **3a**: First, **3a** was much more reactive than **1a**; *viz.*, reaction using **3a** reached 50% conversion after 2.5 h, while the similar reaction using **1a** took 120 h to reach 30% conversion. The *E* values[9] for both reactions were equal (runs 1 and 3). Second, a striking contrast between **1a** and **3a** was observed about the reproducibility of recovered lipases: the recovered lipase from run 1 retained similar reactivity with even higher enantioselectivity (run 2), whereas the lipase recovered from run 3 completely lost its reactivity (run 4).

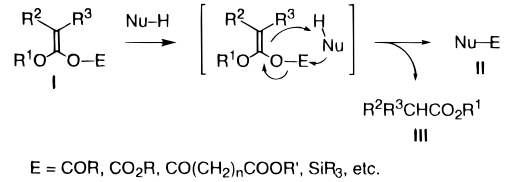
Comparison of three acetyl donors, **1a**, **2a**, and **3a**, on desymmetrization of a *meso*-diol (**7**) employing lipase AY was also studied under the same reaction conditions (Table 2). It is obvious that the relative reactivity was in the order **3a** > **1a** > **2a**, and **3a** afforded the best chemical and optical yields of the product (−)-**8**, although the differences were small.

The kinetic resolution of various types of racemic secondary alcohols **10** by **3a** or the octanoate **3b** was investigated employing lipases PS, PS-D (PS immobilized on diatomaceous earth), AK, and CAL-B (Table 3). In every run, the reaction proceeded within a reasonable period *using only a slight excess amount (0.7 equiv) of* ***3***. After the conversion reached about 50%, the reaction mixture was filtered, and the filtrate was concentrated. Purification by SiO_2 chromatography gave the unreacted alcohol **10** and the ester **11** (method A).[10] The *E* values of these reactions were good to excellent and were by no means inferior to the reported values using **1a**.

One-Pot Procedure for the Preparation of Ethoxyvinyl Esters 3 from Carboxylic Acids and Subsequent Enzymatic Resolution of Racemic Alcohols. In the previous section, we used **3** purified by distillation or chromatography (method A). On the other hand, one-pot operation for the preparation and subsequent enzymatic reaction of **3** (method B) also provided the same products with retention of the high reactivity and enantioselectivity (Scheme 4).

A typical procedure is presented for the resolution of **10a** by **3a**: According to the standard preparation of **3**,[8] a solution of acetic acid (1.6 mmol, 0.8 equiv compared to **10a**) in *i*-Pr_2O (0.8 mL) was added to a mixture of ethoxyacetylene (2.1 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (6 μmol) in *i*-Pr_2O (2.2 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h and at room temperature for 1 h and then was added to a mixture of (±)-**10a** (2.0 mmol) and lipase PS-D (80 mg) in *i*-Pr_2O (2.9 mL). The whole mixture was stirred at 30 °C for 6 h. Usual workup and purification gave (*S*)-**10a** (45%, >99% ee) and (*R*)-**11a** (46%, 96% ee) (Table 4, run 1). This method was similarly applied to the resolution of **10a** by lipase AK and **3a** and that of **10g** by CAL-B and **3b** to give (*S*)-

(5) We have disclosed various types of very mild and convenient reactions utilizing the ketene acetal reagents **I**. Thus, the reactions with nucleophiles (Nu-H) proceed in inert solvents at room-to-moderate temperature to give the products **II** accompanied by formation of volatile esters **III** as the only coproducts. Simple concentration of the reaction mixture gives pure **II** in high yields. For reviews, see: Kita, Y.; Tamura, O.; Tamura, Y. *J. Synth. Org. Chem. Jpn.* **1986**, *44*, 1118−1133. Kita, Y.; Shibata, N. *Synlett* **1996**, 289−296.



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(10) A blank experiment of run 1 was run without the lipase (other conditions are the same), resulting in only 5% conversion after 7 d.

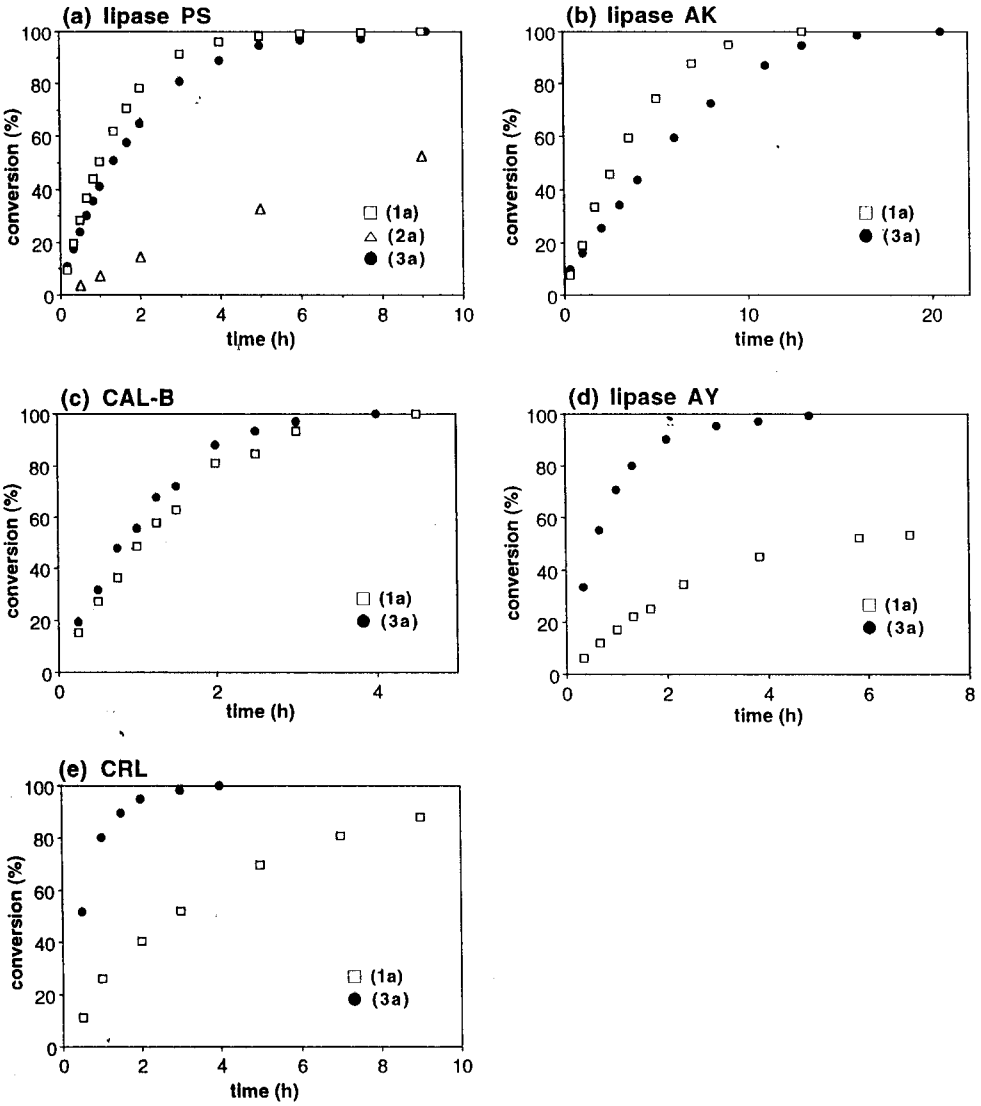

Figure 1. Time course of the reaction of 1-octanol (0.77 mmol) with the acetyl donor **1a**, **2a**, or **3a** catalyzed by (a) lipase PS, (b) lipase AK, (c) CAL-B, (d) lipase AY, and (e) CRL. Reaction conditions: for (a), lipase PS (50 mg), acyl donor (1.5 mmol), *i*-Pr_2O (20 mL), 30 °C; for (b), lipase AK (15 mg), acyl donor (1.5 mmol), *i*-Pr_2O (20 mL), 30 °C; for (c), CAL-B (5 mg), acyl donor (1.5 mmol), *i*-Pr_2O (20 mL), 30 °C; for (d), lipase AY (500 mg), acyl donor (2.3 mmol), *i*-Pr_2O-H_2O (1000:1, 20 mL), 30 °C; for (e), CRL (500 mg), acyl donor (1.5 mmol), *i*-Pr_2O-H_2O (1000:1, 20 mL), 30 °C.

10a,**g** and (*R*)-**11a**,**h** in high chemical and optical yields (runs 2 and 3). In Table 4, a comparison of methods A and B is also given to show no particular difference in terms of the reaction time and chemical and optical yields of the products.

Conclusions

1-Ethoxyvinyl esters **3**, readily prepared and easy-to-handle acylating donors, feature reactivity similar to and enantioselectivity at least as high as those of **1** and **2** for enzymatic resolution of a wide range of alcohols. Especially, 2−3 times higher reactivity of **3** than **1** was generally observed from the reactions using *C. rugosa* lipases. It is worth mentioning that *C. rugosa* lipases have often been employed in recent years due to their liberal applicability to bulky substrates despite their sensitivity to acetaldehyde.[1b,12] Considering that **3** produces a nonharmful coproduct, ethyl acetate, in addition to its native high reactivity, use of **3** for enzymatic esterification reactions should enhance their practical efficacy.

On the other hand, selection of the acyl moiety of an acyl donor is well-known to be crucial to improve chemical and optical yields[13] and also the stability of the products.[14] However, reported examples were limited to commercially available **1** involving linear aliphatic acyl groups and a few simple unsaturated acyl groups.[13,15,16]

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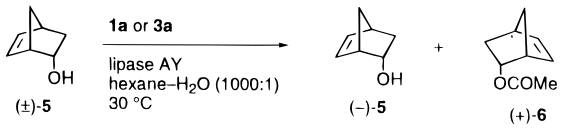
(14) For an example, see: Akai S.; Naka T.; Takebe Y.; Kita Y. *Tetrahedron Lett.* **1997**, *38*, 4243−4246.

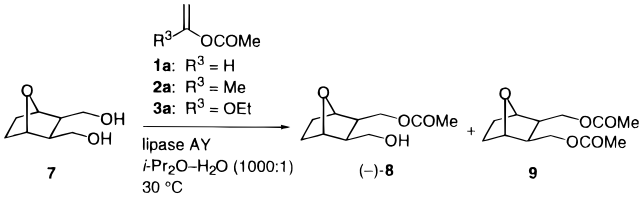
Table 1. Kinetic Resolution of (±)-5 Using 1a or 3a Catalyzed by Lipase AY



run	acyl donor	reaction time	conversion (%)	ee (%)[a] (−)-**5**	ee (%)[a] (+)-**6**	*E* value
1	**3a**	2.5 h	52	78	72	14
2[b]	**3a**	12 h	51	81	79	21
3	**1a**	120 h	31	40	81	14
4[c]	**1a**	11 d	≤10			

[a] Determined by HPLC using Daicel CHIRALCEL OD (hexane−*i*-PrOH) after conversion to the corresponding 3,5-dinitrobenzoate. Conversion of **6** to the 3,5-dinitrobenzoate was run by alkaline hydrolysis followed by esterification. [b] The enzyme recovered from run 1 was reused after drying (<0.1 mmHg, room temperature, 2 d). [c] The enzyme recovered from run 3 was reused after drying (same as footnote *b*).

Table 2. Desymmetrization of 7 Using 1a−3a Catalyzed by Lipase AY



run	acyl donor	reaction time (h)	(−)-**8** isolated yield (%)	(−)-**8** ee (%)[a]	yield of **9** (%)
1	**3a**	7	75	86	13
2	**1a**	31	74	84	14
3	**2a**	170	70	78	18

[a] Determined by ^{1}H NMR analysis with Eu(hfc)$_3$.

We believe the present procedures (methods A and B) offer not only a convenient screening protocol of a wide range of acyl moieties[14] but also extensive application of tailor-made and/or unstable **3** for rarely developed new variants of enzyme-catalyzed asymmetric synthesis.[17]

Experimental Section

General Method. GLC analyses were carried out using a column (2 m × 3 mm) filled with 5% PEG-20M or a G-100 column (40 m × 1.2 mm, Chemical Inspection and Testing Institute, Japan). ^{1}H NMR spectra were measured at 200−300 MHz with TMS as an internal standard. IR spectra were recorded by diffuse reflectance measurement of samples dispersed in KBr powder or as a $CHCl_3$ solution. Chiral HPLC analyses were carried out using a Daicel CHIRALCEL OD column (250 mm × 4.6 mm, eluent: hexane−*i*-PrOH). Column chromatographic purification was done using silica gel 60 (70−230 mesh, Merck Co., Ltd.) or silica gel BW-300 (200−400 mesh, Fuji Silysia Chemical Co., Ltd., Japan). Lipases PS (from *P. cepacia*), PS-D (PS immobilized on diatomaceous earth), AK (from *P. fluorescens)*, and AY (from *C. rugosa*) were gifts from Amano Pharmaceutical Co., Ltd., Japan. CAL-B (CHIRAZYME L_2, from *C. antarctica*, fraction B) was a gift from Roche Diagnostics. CRL (LIPASE type VII, from *C. rugosa*) was purchased from Aldrich. Enzymes were dried (1 mmHg, room temperature, overnight) prior to use. Yields refer to isolated material of ≥95% purity as determined by ^{1}H NMR. All the products (**5**, **6**, **8**, **9**, **10**, and **11**), except for **11i**, are known and well identified by spectroscopic data.

1-Ethoxyvinyl acetate (3a) was prepared by the reported method.[8]

1-Ethoxyvinyl octanoate (3b) was prepared from octanoic acid (1.08 g, 7.5 mmol), ethoxyacetylene (840 mg, 12 mmol), and $[RuCl_2(p\text{-cymene})]_2$ (14 mg, 23 μmol) in *i*-Pr_2O (30 mL) similarly to the reported procedure.[8] The crude product was purified by distillation under reduced pressure to give 1.09 g (68%) of pure **3b** as a colorless oil: bp 65−67 °C (0.6 mmHg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t, J = 7.0 Hz), 1.27−1.45 (11H, m), 1.60−1.75 (2H, m), 2.42 (2H, t, J = 7.5 Hz), 3.76 (1H, d, J = 3.5 Hz), 3.81 (1H, d, J = 3.5 Hz), 3.87 (2H, q, J = 7.0 Hz); IR ($CHCl_3$) 1767, 1674 cm^{-1}. Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.29; H, 10.35. Found: C, 67.16; H, 10.14.

Lipase-Catalyzed Esterification of 1-Octanol by 1a−3a for Comparison of Their Reactivity. General Procedure. A mixture of 1-octanol (0.77 mmol) and an acyl donor (**1a**−**3a**) in a solvent was stirred at 30 °C for 10 min, to which was added a lipase. The reaction mixture was stirred at the same temperature, and the conversion was determined by GLC using a G-100 column. The results are shown in Figure 1. The reaction conditions for each run are listed in the caption.

Kinetic Resolution of (±)-*endo*-Bicyclo[2.2.1]hept-5-en-2-ol (5). To a solution of (±)-**5** (165 mg, 1.5 mmol) in hexane−H_2O (1000:1, 5 mL) were added lipase AY (165 mg) and an acyl donor (**1a** or **3a**) (1.5 mmol). The reaction mixture was stirred at 30 °C for the time shown in Table 1 and filtered through a Celite pad. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography (hexanes−Et_2O, 1:1) to give (−)-**5** (76 mg, 46% for run 1, and 90 mg, 55% for run 3) as colorless oil and (+)-**6** (90 mg, 55% for run 1, and 55 mg, 24% for run 3). The optical purities of (−)-**5** and (+)-**6** and their determination method are shown in Table 1.

(1*S*,2*S*,4*S*)-Bicyclo[2.2.1]hept-5-en-2-ol (5): 78% ee, $[\alpha]^{22}_D$ −113 ($CHCl_3$, *c* 1.7) {lit.[18] $[\alpha]^{20}_D$ +162 ($CHCl_3$, *c* 19) for >97% ee of the (1*R*,2*R*,4*R*)-isomer}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.70−0.82 (1H, m), 1.05−1.37 (3H, m), 2.00−2.18 (1H, m), 2.83 (1H, br s), 3.13 (1H, br s), 4.40−4.50 (1H, m), 6.05−6.08 (1H, m), 6.40−6.47 (1H, m); IR ($CHCl_3$) 3550 cm^{-1}.

(1*R*,2*R*,4*R*)-Bicyclo[2.2.1]hept-5-en-2-yl Acetate (6): ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.85−0.93 (1H, m), 1.15−1.40 (3H, m), 1.40−1.52 (1H, m), 1.98 (3H, s), 2.02−2.20 (1H, m), 2.84 (1H, br s), 3.13 (1H, br s), 5.20−5.32 (1H, m), 5.90−6.00 (1H, m), 6.30−6.40 (1H, m); IR (KBr) 1725 cm^{-1}.

Desymmetrization of *cis-exo*-2,3-Bis(hydroxymethyl)-7-oxabicyclo[2.2.1]heptane (7). To a solution **7** (158 mg, 1.0 mmol) in *i*-Pr_2O−H_2O (1000:1, 10 mL) were added lipase AY (300 mg) and an acyl donor (**1a**−**3a**) (5.0 mmol). The reaction mixture was stirred at 30 °C for the time shown Table 2 and filtered through a Celite pad. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography (hexanes−EtOAc, 2:1) to give (−)-**8** and **9**. The yields of **8** and **9** and optical purity of **8** are shown in Table 2.

(2*R*,3*S*)-2-[(Acetyloxy)methyl]-3-(hydroxymethyl)-7-oxabicyclo[2.2.1]heptane (8): 86% ee, $[\alpha]^{22}_D$ −10.8 (EtOAc, *c* 0.24) {lit.[19] $[\alpha]^{20}_D$ −14.6 (EtOAc, *c* 0.2) for 96.5% ee of the

(15) Examples of the preparation of some specified vinyl esters and their use for enzymatic reaction have been reported. However, preparation of the vinyl esters was run by transesterification between large amounts of vinyl acetate and the carboxylic acids under strong basic conditions in moderate-to-high yields (59−90%). Enzymatic reactions were carried out after purification of the vinyl esters. See: Lobell, M.; Schneider, M. P. *Tetrahedron: Asymmetry* **1993**, *4*, 1027−1030; *Synthesis* **1994**, 375−377. A similar preparation of vinyl esters was also reported by the use of catalytic amounts of $Hg(OAc)_2$ and 100% H_2SO_4. See: Swern, D.; Jordan, E. F., Jr. *Organic Syntheses*; Wiley: New York, 1963, Collect. Vol. 4, pp 977−980.

(16) For the preparation of functionalized isopropenyl esters, see: Kita, Y.; Maeda, H.; Takahashi, F.; Fukui, S. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2639−2649.

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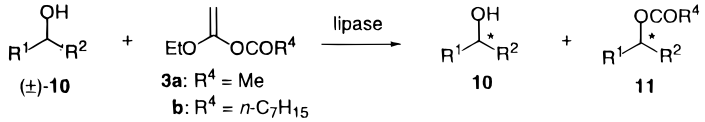
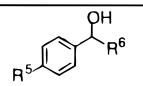
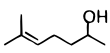
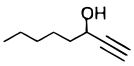
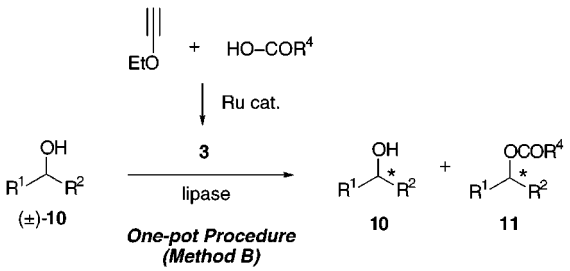
Table 3. Lipase-Catalyzed Kinetic Resolution of (±)-10 Using 3a,b (Method A)



run	(±)-10				3	lipase, mg/mmol solvent	reaction time (h)	conversion (%)	ee (%)[a] 10[b]	ee (%)[a] 11[c]	E value [lit. value using 1a]
1		**10a**	R^5 = H	R^6 = Me	**3a**	PS, 40 *i*-Pr_2O	11	51	(*S*)-**10a** >99	(*R*)-**11a** 96	>390 [>684 [3d]]
2		**10a**			**3a**	PS-D, 40 *i*-Pr_2O	4.5	51	(*S*)-**10a** 97	(*R*)-**11a** >99	>300
3		**10a**			**3a**	AK, 40 *i*-Pr_2O	6	51	(*S*)-**10a** 97	(*R*)-**11a** 94	136
4		**10b**	OMe	Me	**3a**	PS, 40 *i*-Pr_2O	56	58	(*S*)-**10b** >99	(*R*)-**11b** 72	44 [20 [3d]]
5		**10c**	Cl	Me	**3a**	PS, 40 *i*-Pr_2O	21	52	(*S*)-**10c** >99	(*R*)-**11c** 91	>110
6		**10d**	H	Et	**3a**	PS, 80 *i*-Pr_2O	25	48	(*S*)-**10d** 91	(*R*)-**11d** >99	>630 [>280 [3d]]
7		**10e**	H	CH_2Cl	**3a**	PS, 80 *i*-Pr_2O	96	53	(*R*)-**10e** >99	(*S*)-**11e** 89	>93 [98 [3f]]
8		**10f**			**3a**	PS, 40 *i*-Pr_2O	7	48	(*S*)-**10f** 91	(*R*)-**11f** >99	>640 [>747 [3d]]
9		**10g**			**3a**	PS, 40 *t*-BuOMe	20	50	(*S*)-**10g** 83[d]	(*R*)-**11g** 82[d]	27 [28 [11]]
10		**10g**			**3b**	CAL-B, 40 *i*-Pr_2O	5	50	(*S*)-**10g** 95[d]	(*R*)-**11h** 96[d]	183
11		**10h**			**3b**	CAL-B, 10 *i*-Pr_2O	10	51	(*S*)-**10h** >99[d]	(*R*)-**11i** 95[d]	>206

[a] Determined by HPLC using Daicel CHIRALCEL OD (hexane−*i*-PrOH). [b] The absolute configuration was determined by comparison of the specific rotation of the recovered **10** with that of an authentic sample. [c] Determined after saponification of **11** to corresponding **10**. [d] Determined after conversion to the corresponding 3,5-dinitrobenzoate. Conversion of **11g,h** to the 3,5-dinitrobenzoate was run by saponification followed by esterification.

Scheme 4



(2*R*,3*S*)-form}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.48−1.58 (2H, m), 2.06 (3H, s), 2.00−2.25 (2H, m), 3.50−3.70 (2H, m), 3.92−4.20 (2H, m), 4.38−4.52 (2H, m); IR (KBr) 1740 cm^{-1}.

(2*R*,3*S*)-2,3-Bis[(acetyloxy)methyl]-7-oxabicyclo[2.2.1]-heptane (9): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50−1.56 (2H, m), 1.72−1.83 (2H, m), 2.07 (6H, s), 2.18−2.28 (2H, m), 3.90−4.03 (2H, m), 4.07−4.18 (2H, m), 4.40−4.46 (2H, m); IR (KBr) 1732 cm^{-1}.

Lipase-Catalyzed Kinetic Resolutions of (±)-10a. Typical Procedure for Method A. A mixture of (±)-**10a** (246 mg, 2.0 mmol), **3a** (182 mg, 1.4 mmol), and lipase PS (80 mg) in *i*-Pr_2O (6.0 mL) was stirred at 30 °C for 5.5 h. The lipase powder was filtered off through a Celite pad, and the filtrate was concentrated in vacuo. The crude product was purified by chromatography (hexanes−Et_2O, 3:1) to give (*S*)-**10a** (117 mg, 48%, >99% ee) and (*R*)-**11a** (155 mg, 47%, 96% ee). The reaction conditions, the conversion, and the optical purity of the products **10** and **11** for other cases are summarized in Table 3. The optical purity and the absolute configuration of the products were determined as shown in the footnotes of Table 3.

(*S*)-1-Phenylethanol (10a): $[\alpha]^{22}_D$ −58.8 (c-C_5H_{10}, *c* 1.1) {lit.[20] $[\alpha]_D$ −49.7 (c-C_5H_{10}, *c* 2.0) for 91% ee}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.49 (3H, d, *J* = 6.0 Hz), 1.90 (1H, br s), 4.89 (1H, q, *J* = 6.0 Hz), 7.25−7.37 (5H, m); IR (KBr) 3358 cm^{-1}.

(*R*)-1-Phenylethyl Acetate (11a): ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.53 (3H, d, *J* = 6.5 Hz), 2.07 (3H, s), 5.88 (1H, q, *J* = 6.5 Hz), 7.27−7.36 (5H, m); IR (KBr) 1732 cm^{-1}.

(*S*)-1-(4-Methoxyphenyl)ethanol (10b): $[\alpha]^{22}_D$ −52.5 ($CHCl_3$, *c* 0.7) {lit.[21] $[\alpha]^{21}_D$ +47.2 ($CHCl_3$, *c* 0.9−1.1) for 89% ee of the (*R*)-form}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.49 (3H, d, *J* = 6.5 Hz), 1.75 (1H, br s), 3.81 (3H, s), 4.86 (1H, q, *J* = 6.5 Hz), 6.86−6.91 (2H, m), 7.26−7.33 (2H, m); IR (KBr) 3382 cm^{-1}.

(*R*)-1-(4-Methoxyphenyl)ethyl Acetate (11b): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.52 (3H, d, *J* = 6.5 Hz), 2.05 (3H, s), 3.80 (3H, s), 5.85 (1H, q, *J* = 6.5 Hz), 6.85−6.92 (2H, m), 7.25−7.33 (2H, m); IR (KBr) 1734 cm^{-1}.

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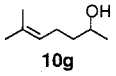
(21) Hayashi, T.; Matsumoto, Y.; Ito, Y. *J. Am. Chem. Soc.* **1989**, *111*, 3426−3428.

Table 4. Kinetic Resolution of (±)-10 by a One-Pot Procedure (Method B)[a]

run	(±)-10	3	lipase, mg/mmol solvent	method	reaction time (h)	isolated yield, ee[b] 10	11[d]	E value
1	 **10a**	**3a** (R^4 = Me)	PS-D, 40 *i*-Pr_2O	B [A	6 4.5	(*S*)-**10a** 45%, >99% ee 47%, 97% ee	(*R*)-**11a** 46%, 96% ee 46%, >99% ee	>259 >300]
2	**10a**	**3a**	AK, 40 *i*-Pr_2O	B [A	6 4.5	(*S*)-**10a** 43%, 94% ee 43%, 97% ee	(*R*)-**11a** 45%, 97% ee 50%, 94% ee	235 136]
3	 **10g**	**3b** (R^4 = *n*-C_7H_{15})	CAL-B, 15 *i*-Pr_2O	B [A	3 5	(*S*)-**10g** 49%, 84% ee[c] 50%, 95% ee[c]	(*R*)-**11h** 33%, 97% ee[c] 45%, 96% ee[c]	175 183]

[a] Results by method A are cited from Table 1. [b] The ee value for **10** was determined by HPLC using Daicel CHIRALCEL OD (hexane−*i*-PrOH). The ee value for **11** was determined after saponification of **11** into corresponding **10** otherwise noted. [c] Th ee value was determined after conversion to the corresponding 3,5-dinitrobenzoate. Conversion of **11h** to the 3,5-dinitrobenzoate was run by saponification followed by esterification.

(*S*)-1-(4-Chlorophenyl)ethanol (10c): $[\alpha]^{22}_D$ −49.6 (Et_2O, *c* 1.8) {lit.[21] $[\alpha]^{21}_D$ +46.1 (Et_2O, *c* 0.9−1.1) for 91% ee of the (*R*)-form}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.48 (3H, d, J = 6.5 Hz), 1.81 (1H, d, J = 3.5 Hz), 4.89 (1H, dd, J = 6.5, 3.5 Hz), 7.31 (4H, s); IR (KBr) 3329 cm^{-1}.

(*R*)-1-(4-Chlorophenyl)ethyl Acetate (11c): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.51 (3H, d, J = 6.5 Hz), 2.06 (3H, s), 5.83 (1H, q, J = 6.5 Hz), 7.29−7.35 (4H, m); IR (KBr) 1740 cm^{-1}.

(*S*)-1-Phenyl-1-propanol (10d): $[\alpha]^{22}_D$ −43.9 ($CHCl_3$, *c* 1.7) {lit.[20] $[\alpha]_D$ −47.6 ($CHCl_3$, *c* 6.1) for 98% ee}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.93 (3H, t, J = 7.5 Hz), 1.70−1.90 (3H, m), 4.55−4.68 (1H, m), 7.20−7.40 (5H, m); IR (KBr) 3354 cm^{-1}.

(*R*)-1-Phenyl-1-propyl Acetate (11d): ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.88 (3H, t, J = 7.5 Hz), 1.78−1.95 (2H, m), 2.08 (3H, s), 5.66 (1H, t, J = 7.5 Hz), 7.30−7.34 (5H, m); IR (KBr) 1736 cm^{-1}.

(*R*)-2-Chloro-1-phenylethanol (10e): $[\alpha]^{22}_D$ −58.9 (c-C_6H_{12}, *c* 1.3) {lit.[22] $[\alpha]_D$ +53.3 (c-C_6H_{12}, *c* 2) for the (*S*)-form}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.65 (1H, d, J = 3.0 Hz), 3.60−3.80 (2H, m), 4.86−4.96 (1H, m), 7.26−7.43 (5H, m); IR (KBr) 3320 cm^{-1}.

(*S*)-2-Chloro-1-phenylethyl Acetate (11e): ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.14 (3H, s), 3.60−3.90 (2H, m), 5.96 (1H, dd, J = 7.5, 5.0 Hz), 7.37 (5H, s); IR (KBr) 1748 cm^{-1}.

(*S*)-1-Indanol (10f): $[\alpha]^{22}_D$ +30.8 ($CHCl_3$, *c* 0.8) {lit.[23] $[\alpha]_D$ +24.4 ($CHCl_3$, *c* 2) for 71% ee}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.70 (1H, d, J = 7.0 Hz), 1.87−2.03 (1H, m), 2.42−2.58 (1H, m), 2.75−2.90 (1H, m), 3.00−3.12 (1H, m), 5.21−5.30 (1H, m), 7.21−7.45 (4H, m); IR (KBr) 3339 cm^{-1}.

(*R*)-1-Indanyl Acetate (11f): ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.00−2.43 (1H, m), 2.06 (3H, s), 2.43−2.54 (1H, m), 2.82−2.93 (1H, m), 3.05−3.15 (1H, m), 6.20 (1H, dd, J = 4.0, 7.0 Hz), 7.12−7.43 (4H, m); IR (KBr) 1734 cm^{-1}.

(*S*)-6-Methyl-5-hepten-2-ol (10g): $[\alpha]^{22}_D$ +14.0 (EtOH, *c* 0.7) {lit.[11] $[\alpha]_D$ +16.6 (EtOH, *c* 1.0) for 99.9% ee}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.19 (3H, d, J = 7.0 Hz), 1.38−1.60 (2H, m), 1.63 (3H, s), 1.69 (3H, s), 1.90−2.20 (2H, m), 3.70−3.85 (1H, m), 5.05−5.20 (1H, m); IR ($CHCl_3$) 3611 cm^{-1}.

(*R*)-6-Methyl-5-hepten-2-yl Acetate (11g): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.21 (3H, d, J = 5.0 Hz), 1.40−1.70 (2H, m), 1.60 (3H, s), 1.68 (3H, s), 1.90−2.10 (2H, m), 2.03 (3H, s), 4.80−4.95 (1H, m), 5.00−5.12 (1H, m); IR ($CHCl_3$) 1724 cm^{-1}.

(*R*)-6-Methyl-5-hepten-2-yl Octanoate (11h): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t, J = 6.0 Hz), 1.20−1.40 (11H, m) 1.40−1.75 (10H, m), 2.00 (2H, q, J = 7.0 Hz), 2.26 (2H, t, J = 7.0 Hz), 4.80−4.95 (1H, m), 5.00−5.10 (1H, m); IR ($CHCl_3$) 1720 cm^{-1}.

(*S*)-1-Octyn-3-ol (10h): $[\alpha]^{24}_D$ −6.0 (pentane, *c* 1.0) {lit.[24] $[\alpha]^{20}_D$ −3.57 (pentane, *c* 5.39) for 21% ee}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (3H, t, J = 6.5 Hz), 1.30−1.80 (9H, m), 2.47 (1H, d, J = 2.0 Hz), 4.30−4.40 (1H, m); IR ($CHCl_3$) 3300 cm^{-1}.

(*R*)-1-Octyn-3-yl Octanoate (11i): $[\alpha]^{24}_D$ −36.9 (pentane, *c* 1.1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t, J = 7.0 Hz), 0.90 (3H, t, J = 6.5 Hz), 1.30−1.80 (18H, m), 2.33 (2H, t, J = 7.5 Hz), 2.44 (1H, d, J = 2.0 Hz), 5.36 (1H, td, J = 6.5, 2.0 Hz); IR ($CHCl_3$) 1732 cm^{-1}. Anal. Calcd for $C_{16}H_{28}O_2$: C, 76.14; H, 11.18. Found: C, 76.12; H, 11.13.

Lipase-Catalyzed Kinetic Resolution of (±)-10a by a One-Pot Procedure. Typical Procedure for Method B. To an ice-cooled solution of ethoxyacetylene (168 mg, 2.1 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (3.9 mg, 6.4 μmol) in anhydrous *i*-Pr_2O (2.2 mL) was added dropwise a solution of acetic acid (96 mg, 1.6 mmol) in anhydrous *i*-Pr_2O (0.8 mL). The reaction mixture was stirred at 0 °C for 0.5 h, warmed to room temperature, and stirred for an additional 1 h. This mixture was added to a mixture of (±)-**10a** (244 mg, 2.0 mmol) and lipase PS-D (80 mg) in anhydrous *i*-Pr_2O (2.9 mL). The remainder of the procedure is the same as described in method A to give (*S*)-**10a** (109 mg, 45%, >99% ee) and (*R*)-**11a** (152 mg, 46%, 96% ee). The reaction conditions, isolated yields, and optical purity of the products **10** and **11** for other cases are summarized in Table 4. All products obtained by this method are identical, except for the optical purity, with the compounds obtained by method A. **10a** (run 1), $[\alpha]^{24}_D$ −54.1 (c-C_5H_{10}, *c* 1.8); **10a** (run 2), $[\alpha]^{23}_D$ −50.3 (c-C_5H_{10}, *c* 1.9); **10g** (run 3); $[\alpha]^{22}_D$ +13.1 (EtOH, *c* 1.0).

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