than the reactants. The S-C bond length was calculated to be 1.91 Å for the tetrahedral intermediate. The O-protonated formamide was found to be 24.5 kcal mol^{-1} more stable than the N-protonated species at the MP2/6-31G* level of calculation. No stable tetrahedral intermediate was found for the N-protonated formamide–HS^- reaction; rather, the NH_3 was such a good leaving group that geometry optimization of tetrahedral H3N-C(H)-(SH)O immediately led to the formation of a stable hydrogen-bonded complex of H_3N-HSCHO. This is analogous to the study of water-catalyzed proton transfer in the tetrahedral intermediate of HO^-/formamide by Weiner et al.[9], in which, as soon as the water proton had migrated to the NH_2 group, the C-N bond spontaneously lengthened. Finally, the reaction of the O-protonated formamide with HS^- led to a stable tetrahedral intermediate with a MP2/6-31G* energy that was 146 kcal mol^{-1} more stable than the reactants. The S-C bond length of this intermediate was 1.96 Å. In addition, geometry optimizations with S-C constraints of 1.96, 2.16, and 2.50 Å showed a smooth potential and did not detect any barrier to the formation of this intermediate.

It is generally agreed[22] that protonation of amides occurs preferentially at the oxygen, not nitrogen, atom. The above results, in conjunction with the previously mentioned results for the unprotonated carbonyl compounds, are consistent with a mechanism in which O-protonation of the carbonyl substrate precedes or accompanies attack by the hydrosulfide anion during a nucleophilic addition. The above considerations lead us to speculate that in the thiol protease enzyme papain, where it appears that the active site sulfhydryl is anionic and the histidine cationic,[23] the sulfhydryl attack may be preceded or accompanied by proton transfer from the imidazole ring of histidine-159 (His) to the substrate rather than following it, as appears to be the case in the serine proteases. Based on the pK_a of an amide group, preprotonation of the substrate in papain is more likely on the oxygen, but it is not clear if His can accomplish this or if there is an alternative acid. Preprotonation of the oxygen would make an "oxy anion hole"—with NH groups pointing toward the carbonyl group—an unfavorable structural element. Alternatively, protonation of the amide nitrogen, unfavorable per se, might be possible if the enzyme distorts the amide group from planarity[24] or if protonation is accompanied by concerted RS^- attack. Given our energy estimates, mechanism a, attack by RS^- preceding protonation, is the least likely mechanism to describe the reaction.

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Registry No. HS^-, 15035-72-0; H_2NCHO, 75-12-7; HCHO, 50-00-0; HO^-, 14280-30-9; $HCOS^-$, 37619-01-5; H_2COH^+, 18682-95-6; H_2NC-[H]OH^+, 50785-80-3.

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Lipase-Catalyzed Irreversible Transesterifications Using Enol Esters as Acylating Reagents: Preparative Enantio- and Regioselective Syntheses of Alcohols, Glycerol Derivatives, Sugars, and Organometallics

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Abstract: Isopropenyl and vinyl esters have been found to be useful for lipase-catalyzed stereoselective acylation of a number of hydroxy compounds including glycerol and serinol derivatives, ferrocenylethanol, sugars, and other alcohols. The reactions are faster, more selective, and easier to optimize than other transesterifications using alkyl esters as acylating reagents. The alcohol freed from the transesterification rapidly tautomerizes to volatile acetaldehyde or acetone, making the process *irreversible* and simpler for product isolation. The process is particularly useful for synthesis of certain chiral compounds, such as ferrocenyl ethyl esters and acyl sugars, which are difficult to prepare in aqueous solution. Compared to hydrolysis, transesterifications are about 10^2–10^4 times slower with normal alkyl esters as acylating reagents and about 10 times slower with the enol esters as acylating reagents. In some cases, transesterifications are less selective than hydrolyses.

Hydrolytic enzymes such as lipases, esterases, and proteases have been extensively used as catalysts in enantioselective syntheses.[1] Because of their relatively high stability in organic media, they can also be used in organic solvents for certain types of transformations which are difficult to do in water.[2] The most common reactions are esterase- and lipase-catalyzed stereoselective esterifications and transesterifications.[2-7] The reactions, however,

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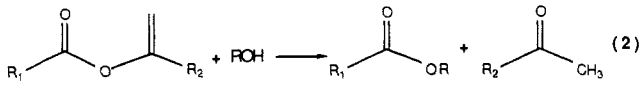
0002-7863/88/1510-7200$01.50/0

are very slow compared to hydrolyses,[7] and the products produced very often have to be separated from other byproducts (particularly the alcohol generated from the acylating reagent). Further, due to the reversible nature of these reactions and the same stereoselectivity of the enzyme catalysis in both directions, the optical purity of the desired product obtained decreases as the reverse reaction proceeds. This situation is illustrated in eq 1 where a

$$\text{(D,L) ROH} + \text{R'COOR''} \rightleftharpoons \underset{\text{(major)}}{\text{(D) - R'COOR}} + \underset{\text{(major)}}{\text{(L) - ROH}} + \text{R''OH} \quad (1)$$

$$\text{(L) - R'COOR (minor)} + \text{(D) - ROH (minor)}$$

racemic alcohol is to be resolved via an enzymatic esterification (R″ = H) or transesterification. As shown in the equation, if the D isomer is a better substrate than the L isomer for the enzyme, accumulation of the D ester and the unreacted L alcohol will be observed. In the reverse reaction, however, the D ester is a better substrate converted to D alcohol. The enantiomeric excesses of both the D ester and the L alcohol will, therefore, decrease progressively as the extent of the reverse reaction increases. This problem has been clearly illustrated in the kinetic resolution of menthol.[3] The same situation can be seen in the enantioselective esterification or transesterification of meso compounds. To overcome these problems we have developed an irreversible procedure for acylation of polyols using enol esters as acylating reagents and lipases as catalysts.[8] The enol freed on transesterification rapidly tautomerizes to the corresponding volatile aldehyde or ketone preventing the back reactions. We report here the extension of such reactions to lipase-catalyzed stereoselective syntheses of several optically active esters (eq 2) including chiral glycerol and



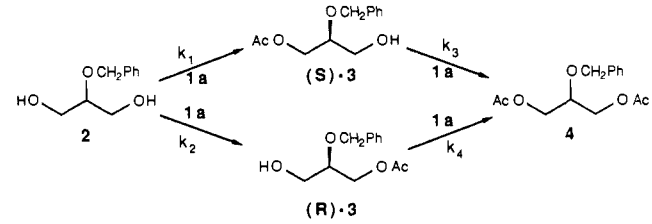
(2)

	R_1	R_2	
1a	CH_3·	CH_3	isopropenyl acetate
1b	$CH_3(CH_2)_3$·	CH_3	isopropenyl valerate
1c	CH_3·	H	vinyl acetate
1d	CH_3CH_2·	H	vinyl propionate
1e	$CH_3(CH_2)_3$·	H	vinyl valerate

serinol derivatives, organometallics, sugars, and other chiral alcohols. Some of the esters (e.g., acyl sugars) prepared in this study can only be obtained in nearly anhydrous solvents because of thermodynamic reasons or because of the lack of appropriate esterases for use to obtain such esters via hydrolysis (e.g., (*S*)-**3** and (*R*)-**6**). In the case of kinetic resolution of ferrocenylethanol (**17a**), the (*R*)-propionate ester (**17b**) obtained in toluene is stable toward solvolysis, while in ethanol or water it decomposes to ferrocenylethyl ethyl ether or **17a**. We also explore the structural effect of different enol esters on the rate and stereoselectivity of the enzymatic transformations and discuss the advantages and disadvantages of such irreversible processes as compared to hydrolyses and other commonly used transesterification reactions.

Results and Discussion

Transesterification of Symmetrically Prochiral Diols. Chiral 3-*O*-acetyl-2-*O*-benzylglycerol, (*R*)- or (*S*)-**3**, and 3-*O*-acetyl-2-*N*-(benzyloxycarbonyl)serinol, (*R*)- or (*S*)-**6**, are considered to be useful building blocks for the preparation of enantiomerically pure, biologically active molecules such as phospholipids,[9] PAF (platelet-activating factor),[10] phospholipase A2 inhibitors,[11] sphingoglycolipids,[12] and many others.[13] To prepare these chiral synthons, the prochiral diols 2-*O*-benzylglycerol (**2**) and 2-*N*-(benzyloxycarbonyl)serinol (**5**) were chosen as substrates, respectively. Thus, a solution of **2** (3 mmol) and isopropenyl acetate (**1a**) (12 mmol) in 6 mL of chloroform was mixed with 12 mg of the lipase from *Pseudomonas* (PSL) species at 28 °C with stirring. After 24 h, the amounts of diacetate, monoacetate, and diol were quantitatively determined to be 10.0:82.6:7.4. The products were separated by column chromatography on silica gel to afford 538 mg (80%) of monoacetate (*S*)-**3**, the optical purity



For PSL: $\alpha = 5.6 = k_1/k_2$, $E_1 = 0.033 = k_3/(k_1 + k_2)$, $E_2 = 0.2 = k_4/(k_1 + k_2)$

of which was determined to be 75.5% by ^{1}H NMR spectroscopy in the presence of tris[3-[(heptafluoropropyl)hydroxymethylene]-(+)-camphorato]europium(III) derivative (Eu(hfc)$_3$). We expected that the monoacetates produced in the transesterification reaction would undergo further acetylation to yield the diacetate **4** and that the enzyme would show the same stereochemical preference in the second step (i.e. $k_4 > k_3$), as in the hydrolysis of *meso*-diacetate compounds,[14] so that the optical purity of (*S*)-**3** could be enhanced by increasing the conversion. As predicted, when the reaction was terminated at 71.5% conversion,[15] the optical purity of monoacetate (*S*)-**3**[16] obtained was 96% (the isolated chemical yield was 53%). The kinetics of these irreversible reactions can be treated as that in hydrolysis, and the equations developed by Sih et al.[14] for use in prediction of ee vs conversion in hydrolysis should be applicable here. Indeed, the kinetic constants for the transesterification of **2** using PSL were determined[14] to be $\alpha = k_1/k_2 = 5.6$, $E_1 = k_3/(k_1 + k_2) = 0.02$, and $E_2 = k_4/(k_1 + k_2) = 0.33$.

To determine the absolute stereochemistry of the monoacetate, it was converted to 2,2-dimethyl-1,3-dioxane-4-methanol (glycerol acetonide)[10] which has the *R* configuration based on rotation, indicating that the monoacetate obtained has the *S* configuration. It has been reported that (*R*)-**3** can be prepared from 2-*O*-benzylglycerol diacetate via a lipoprotein lipase-catalyzed hydrolysis.[16] The same enantioselectivity in the hydrolysis of **4** was observed with PSL, and (*R*)-**3** was obtained in 52% yield with 71% ee.[17] These two irreversible enzymatic processes thus provide a new route to (*R*)- and (*S*)-**3**.

On the other hand, diol **5** (1 mmol) and vinyl valerate (**1e**) (4 mmol) in 22.5 mL of tetrahydrofuran (THF) was incubated with 900 mg of the lipase from porcine pancreas (PPL) at 28 °C with

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(12) Kojke, K.; Numata, M.; Sugikoto, M.; Nakahara, Y.; Ogawa, T. *Carbohydr. Res.* **1986**, 113 and references cited.

(13) Review: Jurczak, J.; Pikul, S.; Bauer, T. *Tetrahedron* **1986**, *42*, 447.

(14) Wang, Y. F.; Chen, C. S.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1984**, *106*, 3695. Wang, Y. F.; Sih, C. J. *Tetrahedron Lett.* **1985**, *25*, 4999. To determine the constants, the diols, monoesters, and diesters were determined by GC analysis at certain degrees of conversion. The enantiomeric compositions of monoesters were determined by NMR analysis as described in the text.

(15) A 50% conversion corresponds to the hydrolysis of one acetate group.

(16) The reported rotations of (*R*)-**3** are not in agreement with our values. The rotation of (*R*)-**3** prepared through a lipoprotein lipase-catalyzed hydrolysis of **4** was $[\alpha]^{20}_D$ −13.2° (*c* 3, EtOH); 91% ee (Breitgoff, D.; Laumen, K.; Schneider, M. P. *J. Chem. Soc., Chem. Commun.* **1986**, 1523). On the basis of the rotation of the enantiomer we prepared, this specific rotation corresponds to 77% ee. Another reported value was $[\alpha]^{25}_D$ +15.0° (*c* 2, $CHCl_3$) or −12.3° (*c* 1.8, EtOH): Kerscher, V.; Kreiser, W. *Tetrahedron Lett.* **1987**, *28*, 531.

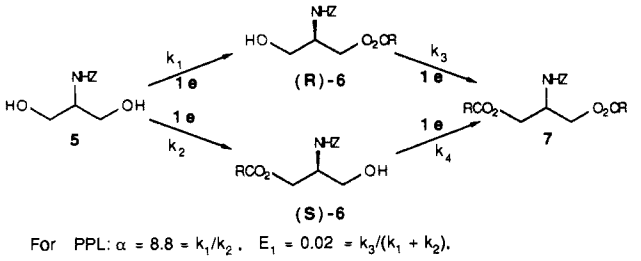
(17) When (*S*)-**3** (91% ee) was suspended in phosphate buffer (0.1 M, pH 7) at 28 °C without enzyme, the optical purity was found to decrease 2.0–2.5%/h.

Table I. Lipase-Catalyzed Transesterifications with Enol Esters as Acylating Agents

entry	substrate	enz	enol ester	% conversion	% ee alcohol (config)	% ee ester (config)
1	**2**	PSL	**1a**	72		96 (*S*)
2	**5**	PPL	**1e**	60		97 (*R*)
3	**8a**	PSL	**1a**	32	29 (*S*)	67 (*R*)
4	**8b**[a]	PSL	H_2O	50	92 (*R*)	
5	**8a**	PSL	**1b**	25	21 (*S*)	64 (*R*)
6	**8a**	ChE	**1a**	33	22 (*S*)	54 (*R*)
7	**8a**	CCL	**1a**	21	14 (*S*)	50 (*R*)
8	**9a**	PPL	**1d**	43		54 (*S*)
9	**9a**	PPL	**1e**	45		39 (*S*)
10	**9a**	PSL	**1d**	50		18 (*S*)
11	**10a**	PPL	**1d**	40		33 (*S*)
12	**10a**	PPL	**1c**	40		42 (*S*)
13	**10b**[a]	PPL	H_2O	30	82 (*S*)	
14	**10a**	PPL	**1c**	80	65 (*R*)	
15	**10a**	PPL	**1e**	40		30 (*S*)
16	**10a**	ChE	**1a**	31	5 (*R*)	10 (*S*)
17	**11a**	PSL	**1c**	30		70 (*R*)
18	**11b**[a]	PSL	H_2O	60	94 (*R*)	
19	**12a**	CCL	**1e**	30		37 (*R*)
20	**13a**	PPL	**1c**	37	56 (*S*)	98 (*R*)
21	**13a**	PPL	**1c**	58	>98 (*S*)	71 (*R*)
22	**14a**	PPL	**1c**	27	37 (*S*)	98 (*R*)
23	**14a**	PPL	**1c**	62	>98 (*S*)	61 (*R*)
24	**15**	CCL	**1c**			
25	**16**	CCL	**1c**			
26	**17a**	PPL	**1d**	40		84 (*R*)
27	**17a**	PPL	**1d**	60	84 (*S*)	
28	**18a**	CCL	**1c**	30		>98[b]
29	**19a**	PN[c]	**1a**	100		90[b,c]
30	**19b**	PN[c]	**1a**	100		70[b,c]

[a] The obtained optically active ester was used as substrate in hydrolysis in 0.1 M phosphate buffer (pH 7) at 28 °C. The pH was controlled at 7.0 during the reaction by addition of 1 N NaOH. Monitoring of the reaction progress and isolation of the products were the same as that in transesterification reactions. [b] Regioselectivity was indicated. The byproduct was mainly the unreacted substrate. [c] PN: protease N from *Bacillus subtilis* obtained from Amano. Kim, M. J.; Hennen, W. J.; Sweers, H. M.; Wong, C.-H. *J. Am. Chem. Soc.*, in press.

stirring. After 60% conversion (11 h), the reaction was terminated and the monoacetate **6** was isolated in 77% yield. To determine



For PPL: $\alpha = 8.8 = k_1/k_2$. $E_1 = 0.02 = k_3/(k_1 + k_2)$. $E_2 = 0.35 = k_4/(k_1 + k_2)$

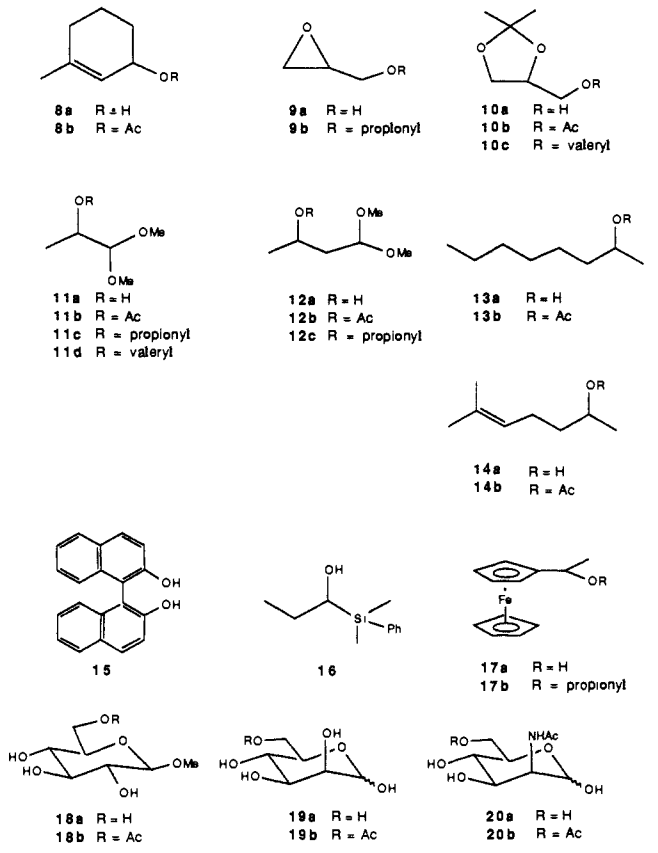
the optical purity of **6**, it was converted to (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetate (MTPA)[18] ester and analyzed by ^{1}H NMR spectroscopy in the presence of Eu(hfc)$_3$ to establish an ee of 97%. To determine the absolute configuration, compound **6** was converted to the 3-tetrahydropyran derivative by reaction with dihydropyran–pyridinium tosylate followed by reductive hydrolysis (LiBH$_4$/ether) to remove the acyl group. The rotation of this product ($[\alpha]^{25}_D$ −7.5° (*c* 1.5, CHCl$_3$)) was the same as but opposite to that prepared from *N*-Z-L-serine methyl ester.[19] This result confirmed that the *pro-R* hydroxy group of **5** was preferentially acylated by PPL. The kinetic constants for the transesterification of **3b** using PPL were determined to be α = 8.8, E_1 = 0.02, and E_2 = 0.35.

To prepare (*S*)-**6**, compound **7** (R = *n*-butyl) was hydrolyzed by PPL in a phosphate buffer at 28 °C and pH 7 to give (*S*)-**6** in 55% yield and >97% ee. Compound **5** was also incubated with PSL with various enol esters (**1a–e**) as acylating reagents. We have found the rate of transesterification of vinyl ester is about 2–4 times faster than that of isopropenyl esters, and the rate for enol pentanoate is about 3–5 times faster than for enol acetate. However, the enantioselectivity was not significantly different; in every case (*R*)-**6** was obtained in 59–65% ee.

Transesterification of Chiral Alcohols. At this stage, we were encouraged to test the same procedure for the resolution of other chiral alcohols (**8–17a**; Chart I) and sugars. The results are summarized in Table I. Esterification of **10a**, **13a**, and **14a** with PPL using vinyl acetate gave **10b**, **13b**, and **14b** with 42%, 98%, and 98% ee, respectively (entries 12, 20, 22). The unreacted alcohols **10a**, **13a**, and **14a** were obtained in 65%, >98%, and >98% ee when the extents of conversions were 80%, 58%, and 62%, respectively (entries 14, 21, and 23). Compound (*S*)-**14a** is a useful pheromone, which has been prepared via lipase-catalyzed transesterification of the racemic alcohol using trichloroethyl propionate[6] and trifluoroethyl laurate[20] and via alcohol dehydrogenase catalyzed reduction of the ketone precursor,[6] all giving (*S*)-**14a** with >98% ee. The procedure described here with readily available vinyl acetate is faster and the products are easier to isolate. The resolution of ferrocenylethanol **17a** represents an interesting example of enzyme-catalyzed kinetic resolution of chiral organometallic compounds. The ester **17b** in aqueous ethanol decomposes via solvolysis to ferrocenylethyl ethyl ether[21] and **17a**. The resolution therefore must be carried out in nonpolar aprotic solvents such as toluene. Indeed, compounds (*R*)-**17a** and (*S*)-**17b** were obtained in 84% ee in PPL-catalyzed acylation with vinyl propionate (entries 26 and 27). The other chiral alcohols **8a**, **10a**, and **11a** were acylated with PSL catalysis to give **8b**, **10b**, and **11b** with 67%, 18%, and 70% ee, respectively (entries 3, 10, and 17). To enhance the optical purity, the optically active **8b**, **10b**, and **11b** obtained above were subjected to hydrolysis catalyzed by the same enzyme. The alcohols (*R*)-**8a**, (*S*)-**10a**, and (*R*)-**11a** were obtained in 92%, 82%, and 94% ee at 50%, 30%, and 60%

(18) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
(19) For correlation, Z-L-serine methyl ester was converted to the THP derivative followed by LiBH$_4$ reduction of the ester group to the alcohol.
(20) Stokes, T. M.; Oehlschlager, A. C. *Tetrahedron Lett.* **1987**, *28*, 2091–2094.
(21) Gokel, G. W.; Marquarding, D.; Ugi, I. K. *J. Org. Chem.* **1972**, *37*, 3052–3058. The acetate was subjected to S$_N$1 and S$_N$2 displacement. When the enzymatic resolution was carried out in aqueous solution, racemic **17a** and **17b** were obtained.

Chart I



degree of conversion, respectively (entries 4, 13, and 18). Optically active **11a** and **12a** are useful as substrates in aldolase-catalyzed synthesis of novel sugars,[22] and compound **8a** was used in natural product synthesis via radical-mediated cyclization.[23] On the other hand, treatment of racemic glycidol **9a** and **10a** (glycerol acetonide) with PPL gave the corresponding esters with 39–54% and 30–42% ee (entries 8, 9, 11, 12, and 15). The transesterification of glycidyl butyrate with butanol gave an even lower ee (11%).[24] This is less selective than expected considering the reported results in the PPL-catalyzed hydrolysis of this ester.[25] Different enzymes and acylating reagents (the enol esters described here and other ethyl esters) have been examined in the transesterification of **8a–12a**; however, the stereoselectivity was not enhanced. All attempts to acylate compounds **15** and **16** with various lipases and cholesterol esterase using vinyl acetate, vinyl propionate, and ethyl acetate as acylating reagents failed, presumably due to steric hindrance.[26] The acetate esters, however, are substrates for several esterases. The enantioselectivities are under investigation.

To compare the structural effect of different enol esters on the rate and stereoselectivity of the enzymatic transesterification, we have carried out the resolution of **10a** using CCL as catalyst. The results are shown in Table II. The reaction rate of enol esters was 10–100 times faster than that of ethyl acetate. Among the enol esters, vinyl esters reacted faster than isopropenyl esters and vinyl propionate was faster than vinyl acetate, but enol valerates were slower than enol acetates. We also compared the reaction rate of transesterification using different acylating reagents with that of hydrolysis. As indicated in the resolution of **13** using PPL as catalyst, the relative rates for the hydrolysis of **13b** and transesterification of **13a** with vinyl acetate and ethyl acetate were found to be 600:55:1. The longer enol esters gave higher enantioselectivity. The lower selectivity in the ethyl acetate reaction may be due to the reversible nature of the reaction.

Table II. Reaction Rates and Enantioselectivity of CCL-Catalyzed Transesterification of **10a** with Various Acylating Reagents[a] and of PPL-Catalyzed Reactions with **13**[b]

ester	substrate	enzyme	rel rate	% conversion	E[c]
CH_3CO_2Et	**10a**	CCL	1[d]	16	1.2[e]
1a	**10a**	CCL	20	42	1.4
1b	**10a**	CCL	8	44	2.7
1c	**10a**	CCL	62	37	1.4
1d	**10a**	CCL	122	53	2.0
1e	**10a**	CCL	13	23	3.1
$CH_3CO_2CH_2CF_3$	**10a**	CCL	1.5	34	1.4
CH_3,cO_2Et	**10a**	CCL	0.4[f]		
1a	**10a**	CCL	1700[g]		
1c	**13a**	PPL	5.5	58	96
CH_3CO_2Et	**13a**	PPL	0.1	58	80
H_2O	**13b**	PPL	60	58	90

[a] Reaction condition: the alcohol substrate (2 mmol) was dissolved in benzene (4 mL) along with 120 μL of dodecane as an internal standard. The acylating agent (2 equiv) and CCL (265 mg) were added, and the suspension was stirred at 28 °C. At various intervals, the degree of conversion was determined by GC (20-m DB-5 megabore column; initial temperature, 80 °C; initial time, 1 min; gradient, 10 °C/min; flow rate 15 mL/min). After a certain degree of conversion, the reaction was terminated by filtration and the filtrate was evaporated. The residue was purified on a silica gel column (CH_2Cl_2–*n*-hexane = 1:3 → 1:0) to obtain the ester product. The optical purity of the product was determined by ^1H NMR in the presence of Eu(hfc)$_3$ (10 mg of acetate, propionate, or pentanoate was added 40 mg, 40 mg or 28 mg of the shift agent, respectively). [b] Conditions: for transesterification, PPL (520 mg), solvent (8 mL), substrate (4 mmol), acylating reagent (2 equiv), temperature (28 °C). For solvent, the same as above except that phosphate (0.1 M, pH 7) was used as solvent. [c] A measure of enantioselectivity determined by the method reported previously: Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7194. [d] The initial rate was 0.8 μmol of ester product formed min^{-1} (g of enzyme)$^{-1}$. [e] The E value was obtained without considering the reverse reaction. [f] The tributyltin ether of glycerol acetonide was used as substrate. [g] No transesterification was observed in 0.05 M phosphate buffer at pH 7. The rate of hydrolysis of **1a** was measured.

Table III. Effect of Organic Solvents on CCL-Catalyzed Transesterifications of Glycerol Acetonide and **1a**

reaction solvent[a]	rel rate	E
benzene	50	1.4
isopropenyl acetate	37	1.6
chloroform	9	1.5
tetrahydrofuran	1[b]	1.5

[a] Reaction conditions are the same as those described in Table II. [b] The initial rate was 0.32 μmol of ester formed min^{-1} (g of enzyme)$^{-1}$.

The effect of organic solvent on the CCL-catalyzed transesterification was also examined. As shown in Table III, the rate of transesterification was slower in more polar solvents than in less polar solvents.

Regioselective Acylation of Sugars. The same procedure was also applied to the regioselective acylation of sugars (**18–20a**). All of them were selectively acylated at the primary position with >90% regioselectivity.[27] These acyl sugars can only be prepared in organic solvents in enzymatic reactions. Due to the solubility problem of sugars in organic solvents, pyridine or dimethylformamide must be used. All lipases tested are catalytically active in pyridine but inactive in DMF. In a study of the solvent effect on the activity of lipases in organic solvents, we have found that the rate of CCL-catalyzed acylation was enhanced in the presence of benzene. A mixture of benzene and pyridine was thus used

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for the preparation of **18b**. Compounds **19b** and **20b** were used in aldolase-catalyzed syntheses of sialic acid derivatives.[28]

In conclusion, many valuable chiral synthons have been prepared in high optical purity via lipase-catalyzed transesterifications. The combination of two irreversible enzymatic processes, ester hydrolysis and ester synthesis, enable effective syntheses of a number of optically active monoesters and alcohols in both enantiomeric forms, even with a moderately enantioselective enzyme. The same procedures can also be applied to the resolution of chiral ferrocenylethanol to prepare both enantiomers, a process which is impossible to accomplish in aqueous solution.

In this irreversible transesterification study we have found that most lipases and cholesterol esterase catalyze enantioselective ester syntheses in various organic media. The leaving groups (acetone or acetaldehyde) of enol esters used in the processes are volatile and easy to remove, making the product separation very simple. With regard to the rate of transesterification, vinyl esters were about 20–100 times faster than ethyl esters and about 5 times faster than isopropenyl esters, and generally the long-chain esters were faster than short-chain esters. As compared to lipase-catalyzed hydrolysis, vinyl esters react 10 times slower. Because the transesterification reaction is carried out in neutral apolar organic solvents, this procedure is suitable for acid-, base- or water-sensitive substances.

In summary, the simplicity of the experimental operation makes this irreversible transesterification useful for the preparation of chiral alcohols or esters which may be difficult to prepare by other means.

Experimental Section

Nuclear magnetic resonance spectra were recorded on a Varian XL-200E spectrometer. All chemical shifts were reported in ppm with tetramethylsilane as internal standard unless otherwise indicated. Rotations were determined on a Perkin-Elmer 240 polarimeter. Gas chromatographic (GC) analyses were performed on a Hewlett-Packard 5890 instrument with a 20-m DB-5 megabore column. The lipases from *Pseudomonas* species (PSL, Type XIII), porcine pancreas (PPL, Type II), and *Candida cylindracea* (CCL, Type VII) were obtained from Sigma Chemical Co. Cholesterol esterase was obtained from Amano Pharmaceutical Co. Vinyl acetate (bp 72 °C) and isopropenyl acetate (bp 94 °C) were from Aldrich. Vinyl propionate (bp 93–4 °C) was from Pfaltz and Bauer, Inc. Some experimental protocols are described in the tables. The following are the procedures for specific reactions.

General Procedure of Lipase-Catalyzed Transesterifications of Alcohols with Enol Esters. The alcohol substrate and enol ester were dissolved in a solvent. After enzyme was added, the suspension was stirred at 28 °C, and the reaction was monitored by GC for the conversion. Once the required extent of conversion was reached, the enzyme was filtered off and the solvent was removed by evaporation in vacuum. The ester product and the unreacted alcohol were separated by chromatography on a silica gel column.

PSL-Catalyzed Transesterification of 2-*O*-Benzylglycerol (2) with Isopropenyl Acetate (1a). A solution of 2-*O*-benzylglycerol (**2**) (300 mg, 1.65 mmol) and isopropenyl acetate (**1a**) (0.73 mL, 6.6 mmol) in 4 mL of chloroform was mixed with 10 mg of PSL. After 27 h, the amounts of diacetate, monoacetate, and diol were quantitatively determined to be 43:57:0 by GC analysis. The reaction was terminated and worked up as in the general procedure. The products were separated by column chromatography (ethyl acetate–*n*-hexane = 1:3) on silica gel to give 196 mg (53%) of monoacetate (*S*)-**3**, $[\alpha]^{23}_D$ −20.1° (*c* 1, $CHCl_3$), and 175 mg of diacetate **4**. Monoacetate (*S*)-**3**: ^{1}H NMR δ 2.08 (3 H, s), 3.60–3.78 (3 H, m), 4.23 (2 H, d, *J* = 4.8 Hz), 4.61 (1 H, d, *J* = 11.8 Hz), 4.72 (1 H, d, *J* = 11.8 Hz), 7.35 (5 H, s). Diacetate **4**: ^{1}H NMR δ 2.06 (6 H, s), 3.81 (1 H, tt, *J* = 5.2 Hz), 4.15 (2 H, dd, *J* = 5.2, 11.8 Hz), 4.25 (2 H, dd, *J* = 5.2 Hz and 11.8 Hz), 4.66 (2 H, s), 7.34 (5 H, s). The optical purity of the monoacetate (15 mg) was determined to be 96% by ^{1}H NMR spectroscopy in the presence of Eu(hfc)$_3$ (30 mg). The relative intensities of the acetoxy group at 3.05 (major) and 2.90 (minor) were used for ee determination.

PPL-Catalyzed Transesterification of 2-*N*-Z-serinol (5) with Vinyl Valerate (1e). A solution of **5** (225 mg, 1 mmol) and vinyl valerate (512 mg, 4 mmol) in 22.5 mL of THF was incubated with 900 mg of PPL at 28 °C with stirring. After 11 h, the reaction was terminated. The products were separated by chromatography on a silica gel column (ethyl acetate–*n*-hexane = 1:4 → 1:1) to afford 238 mg (77%) of monovalerate (*R*)-**6**, $[\alpha]^{23}_D$ +3.2° (*c* 1.0, $CHCl_3$), and 75 mg of divalerate **7**. Monovalerate (*R*)-**6**: ^{1}H NMR 0.91 (3 H, t, *J* = 7.2 Hz), 1.34 (2 H, tq, *J* = 7.2, 7.2 Hz), 1.60 (2 H, tt, *J* = 7.2, 7.2 Hz), 2.33 (2 H, t, *J* = 7.2 Hz), 3.65 (2 H, m), 3.94 (1 H, m), 4.23 (2 H, d, *J* = 5.6 Hz), 5.11 (2 H, s), 5.2 (1 H, br), 7.36 (5 H, s). Divalerate **7**: ^{1}H NMR 0.91 (6 H, t, *J* = 7.2 Hz), 1.33 (4 H, tq, *J* = 7.2, 7.2 Hz), 1.59 (4 H, tt, *J* = 7.2, 7.2 Hz), 2.31 (4 H, t, *J* = 7.2, 7.2 Hz), δ 4.02–4.30 (5 H, m) 5.11 (7 H, s), 5.05–5.20 (1 H, br), 7.36 (5 H, s). To determine the optical purity of the monoester it was treated with (+)-2-methoxy-2-(trifluoromethyl)-phenylacetyl chloride [(+)-MTPA chloride], and the resulting (+)-MTPA ester (20 mg) was analyzed by ^{1}H NMR spectroscopy in the presence of Eu(hfc)$_3$ (80 mg) to establish an enantiomeric excess greater than 97%. The relative intensities of the benzylic methylene group at 4.8 (major) and 4.6 (minor) were measured for ee determination.

PSL-Catalyzed Transesterification of 8a with Isopropenyl Acetate (1a). A solution of **1a** (0.44 mL, 4 mmol) and **8a** (224 mg, 2 mmol) in 2 mL of *n*-hexane was mixed with 3 mg of PSL at 28 °C with stirring. After 20 h, the amounts of acetate **8b** and alcohol **8a** were quantitatively determined to be 32:68 by GC analysis. The reaction mixture was worked up as usual, and the products were separated by silica gel column chromatography (dichloromethane–*n*-hexane = 1:3 → 1:0) to afford 91 mg (29.5%) of acetate **8b**, $[\alpha]^{23}_D$ +138.3° (*c* 0.8, $CHCl_3$), and 138 mg (61.8%) of alcohol **8a**, $[\alpha]^{23}_D$ −26.7° (*c* 1.5, $CHCl_3$). Acetate **8b**: ^{1}H NMR δ 1.6–2.0 (6 H, m), 1.71 (3 H, s), 2.03 (3 H, s), 5.24 (1 H, m), 5.47 (1 H, m). The optical purity of monoacetate (+)-**8b** (9 mg) was determined to be 67% ee by ^{1}H NMR spectroscopy in the presence of Eu(hfc)$_3$ (57 mg). The relative intensities of the methyl group in double bond at 2.27 (major) and 2.31 (minor) were measured for ee determination. The alcohol (−)-**8a** was converted to the corresponding acetate by treatment with acetic anhydride in pyridine and then analyzed by the same procedure: ee = 29%. Compounds **8a** and **8b** were assigned *S* and *R*, respectively, on the basis of rotations compared to the reported values.[29]

PPL-Catalyzed Transesterification of Glycidol 9a with Vinyl Propionate (1d). To a 100-mL round-bottomed flask was added glycidol (2.3 g, 31 mmol) **9a**, vinyl propionate (7.0 g, 70 mmol), toluene (0.61 g) as an internal standard, and 80 mL of chloroform. The enzyme (PPL, 5 g) was suspended in the reaction mixture and the suspension was stirred. At 43% conversion (3.5 h), 5 g of Celite was added to the suspension and the mixture was filtered. The filtrate was extracted with three 15-mL portions of distilled water and then washed once with 15 mL of saturated brine. The solvent was removed under reduced pressure and a yellow oil was obtained, corresponding to pure glycidol propionate **9b** (0.95 g, 23.2% yield from racemic glycidol). The optical purity as determined by using Eu(hfc)$_3$ was 54%, while the optical rotation was found to be +15.2° (*c* 4, $CHCl_3$) corresponding to an optical purity of 53.5% (lit.[25] for *R* ester is −28.4°). **9b**: ^{1}H NMR δ 4.05 (dd, 1 H), 3.90 (dd, 1 H), 3.24 (m, 1 H), 2.85 (m, 1 H), 2.65 (m, 1 H), 2,35 (q, 3 H), 1.15 (t, 3 H); ^{13}C NMR 174.19, 64.83, 49.38, 44.65, 27.33, 9.01.

PPL-Catalyzed Transesterification of 10a with Vinyl Esters. In a representative procedure, 1 g of **10a** (7.5 mmol) and 2.3 g of vinyl acetate (**1c**) (26.7 mmol) in 50 mL of chloroform was incubated with PPL (2 g) along with 0.5 g of toluene as an internal standard. After the reaction had proceeded to 40% conversion, the mixture was worked up as usual to give the ester with an optical purity of 42% by analysis with Eu(hfc)$_3$. The relative intensities of the methyl group of the isopropyl group at 2.63 (major) and 2.57 (minor) were measured to determine ee. In a similar manner the esterification was allowed to proceed to 80% conversion and the unreacted alcohol was isolated as described above. Compound **10b** was found to have an optical purity of 65% ee. **10b**: ^{1}H NMR δ 4.40 (m, 1 H), 4.05 (m, 3 H), 3.72 (m, 1 H), 2.07 (s, 3 H), 1.35 (s, 3 H).

PSL-Catalyzed Transesterification of 11a and 12a. To a stirred solution of **11a** (480 mg, 4 mmol) and vinyl acetate **1c** (20 mmol) in petroleum ether (20 mL) was added 9.6 mg of PSL. After the reaction had proceeded to 30%, the reaction suspension was treated as in the general procedure. The products were separated on a silica gel column (petroleum ether–ethyl acetate = 9:1 → 3:1). **11b**: ^{1}H NMR ($CDCl_3$) δ 1.16 (3 H, d, *J* = 5.5 Hz), 2.00 (3 H, s), 3.33 (3 H, s), 3.36 (3 H, s), 4.20 (1 H, d, *J* = 5.5 Hz), 4.80–4.99 (1 H, m).

To determine the optical purity of **11b**, it was transformed to (+)-MTPA ester by hydrolysis with 1 N NaOH followed by reaction with (+)-MTPA-Cl. The resulting (+)-MTPA ester was analyzed by ^{1}H NMR spectroscopy. The relative intensities of methine group at 4.32 and

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4.22 ppm were used for ee determination. The same procedure was used for the resolution of **12a**, except that **1e** and CCL were used. The methine group shifts of the MTPA ester at 4.38 and 4.17 ppm were used for ee determination.

PPL-Catalyzed Transesterification of (±)-2-Octanol 13a with Vinyl Acetate (1c). 2-Octanol (520 mg, 4 mmol) was dissolved in 8 mL of benzene along with 240 μL of dodecane as an internal standard. Two equivalents of vinyl acetate was added along with 520 mg of PPL. The suspension was stirred at 28 °C. After the reaction had proceeded to 37%, the reaction suspension was worked as in the general procedure. The products were separated on a silica gel column. The optical purities of isolated ester **13b** and alcohol **13a** were determined by ^{1}H NMR spectroscopy in the presence of Eu(hfc)$_3$ (12 mg of acetate or alcohol was added to 84 or 72 mg of Eu(hfc)$_3$, respectively). The relative intensities of the methyl groups near the chiral center at 8.72 (major) and 8.64 (minor) (alcohol) and 4.34 (major) and 4.42 (minor) (ester) were used for ee determination. The ester was found to have an optical purity of 98% ee. In a similar manner, the esterification was allowed to proceed to 58% conversion and the unreacted alcohol was isolated. The alcohol was found to have an optical purity of >98% ee. The specific rotation of unreacted alcohol was +8.7° (*c* 1.0, $CHCl_3$) or +8.9° (neat). Authentic (*S*)-2-octanol from Aldrich: $[\alpha]^{17}$ +9° (neat). This result confirms that the unreacted alcohol has the *S* configuration. **13b**: ^{1}H NMR ($CDCl_3$) δ 0.88 (3 H, t, *J* = 6.8 Hz), 1.20 (3 H, d, *J* = 6.2 Hz), 1.27 (8 H, s), 1.41–1.66 (2 H, m), 2.02 (3 H, s), 4.88 (1 H, qt, *J* = 6.2, 12.6 Hz).

PPL-Catalyzed Transesterification of 14a with Vinyl Acetate (1c). **14a** (513 mg, 4 mmol) was dissolved in 8 mL of benzene along with 240 μL of dodecane as an internal standard. Two equivalents (8 mmol) of vinyl acetate was added along with 512 mg of PPL. The suspension was stirred at 28 °C. After the reaction had proceeded to 27%, the reaction was terminated and treated as in the general procedure. The products were separated by chromatography on a silica gel column (CH_2Cl_2–*n*-hexane = 0:1 → 1:4), giving acetate ester **14b** and unreacted alcohol **14a**. The optical purities of isolated ester and alcohol were determined by ^{1}H NMR spectroscopy in the presence of Eu(hfc)$_3$. The relative intensities of the methyl group near the chiral center at 9.75 (major) and 9.56 (minor) (alcohol) and at 4.92 (major) and 5.02 (minor) (ester) were used for ee determination. The ester was found to have 98% ee.

In a similar manner, the esterification was allowed to proceed to 62% conversion and the unreacted sulcatol was isolated. The ee of unreacted sulcatol was found to be >98%. The specific rotation of unreacted alcohol was +15.1° (*c* 2, *b*, EtOH) [lit.[6] (*S*)-sulcatol, $[\alpha]^{25}_D$ +15.6° (*c* 0.015, EtOH)]. This result confirms that the unreacted alcohol has the *S* configuration. The ^{1}H NMR spectrum of **14b** corresponded to that reported.[6]

PPL-Catalyzed Transesterification of Ferrocenylethanol (17a) and Vinyl Propionate (1d) in Toluene. A mixture of ferrocenylethanol (1 g, 4.4 mmol), vinyl propionate (6 mL, 52.8 mmol), and PPL (3 g) in toluene (25 mL) was shaken for 6 days. The reaction was stopped at ~40% conversion (determined by NMR and based on the ratio of the methyl doublet of the reactant alcohol to that of the product ester). The mixture was then filtered to remove the enzyme, and the filtrate was evaporated to give a mixture of products (0.72 g), which were separated by silica gel chromatography with hexane–ethyl acetate = 5:1 (v/v) as the solvent system to give the ester [**17b**, $[\alpha]_D$ −11.2° (*c* 1, EtOH)]. The alcohol [**17a**, 0.31 g, mp 70–71 °C, $[\alpha]^{25}_D$ +25.9 (*c* 1, benzene) (lit.[21] $[\alpha]^{25}_D$ +30.1°)] was also prepared from a similar reaction and proceeded to 60% conversion. The enantiomeric excesses of **17a** and **17b** were determined to be 84% and 84%, respectively, with ^{1}H NMR in the presence of Eu(hfc)$_3$ (the methyl doublet of **17a** at 3.35 ppm and the methyl triplet of the acyl portion of **17b** at 2.82 ppm were measured). The configurations were determined to be *S* for **17a** and *R* for **17b** on the basis of the rotation compared to the reported values.[21] **17b**: ^{1}H NMR δ 1.10 (t, 3 H), 1.55 (d, 3 H), 2.30 (q, 2 H), 4.20–4.44 (m, 9 H), 5.80 (q, 1 H); ^{13}C NMR ($CDCl_3$) 9.22, 20.12, 27.92, 65.95, 67.92, 68.24, 68.70, 88.15, 173.89. The NMR data of **17a** were the same as reported.[21]

CCL-Catalyzed Transesterification of Methyl β-D-Glucopyranoside 18a with Vinyl Acetate (1c). Methyl β-D-glucopyranoside (**18a**) (388 mg, 2 mmol) and vinyl acetate (4 mmol) were dissolved in 12 mL of benzene–pyridine (2:1). Then 388 mg of CCL was added, and the suspension was stirred at 28 °C. After 24 h, an additional 388 mg of CCL was added, and this was repeated after 48 h. The suspension was stirred at 28 °C for 5 days and then worked up as usual to afford **18b** as a solid, which was crystallized from ethyl acetate–*n*-hexane; mp 129–130 °C; $[\alpha]^{25}_D$ −27.1° (*c* 1.4, CH_3OH); ^{1}H NMR (CD_3COCD_3) δ 2.02 (3 H, s), 2.98 (1 H, s), 3.13–3.25 (1 H, m), 3.30–3.55 (3 H, m), 3.45 (3 H, s), 4.15–4.25 (2 H, m), 4.30–4.45 (3 H, m); ^{13}C NMR (CD_3COCD_3) 104.56 (C1), 74.29 (C2), 77.36 (C3), 70.85 (C4), 74.33 (C5), 64.01 (C6), 20.42 and 170.69 (acetyl), 56.39 (methoxy).

Preparation of Isopropenyl Valerate (1b). The procedure was similar to that reported for the preparation of other isopropenyl esters with some modifications.[31] To a 250-mL round-bottom flask were added 10 mL of valeric acid (91.9 mmol), which had been freshly distilled, and 20 mL of valeric anhydride. Then, 200 mL of freshly distilled isopropenyl acetate was added followed by 2 drops of concentrated sulfuric acid. The mixture was then heated to reflux under an atmosphere of argon for 10 h, after which time all the valeric acid had been consumed as evidenced by capillary GC. The reaction mixture was allowed to cool to room temperature, and 0.5 g of sodium bicarbonate was added to quench the acid catalyst. The isopropenyl acetate was then removed by evaporation under reduced pressure. The orange liquid remaining was poured into 300 mL of 0 °C saturated sodium bicarbonate which was overlayed with 100 mL of diethyl ether. The mixture was stirred vigorously, and the ether layer was analyzed by GC for the disappearance of the mixed valeric acetic anhydride. After all the anhydride was consumed (6 h), the ether layer was separated, and the aqueous layer was washed with 100 mL of ether. The combined ether layers were washed with 5 × 25 mL portions of saturated sodium bicarbonate to remove the valeric acid. The ether layer was then washed with saturated brine (30 mL) and the ether was then dried over sodium sulfate. The ether was removed under reduced pressure, and the isopropenyl ester was purified by vacuum distillation (bp 50–52 °C, 8 mmHg). A 7.85-g portion of a clear, colorless liquid **1b** was obtained (60.1% yield): ^{1}H NMR ($CDCl_3$) δ 4.65 (m, 2 H), 2.35 (t, 2 H), 1.90 (s, 3 H), 1.65 (m, 2 H), 1.35 (m, 2 H), 0.90 (s, 3 H); ^{13}C NMR δ 171.89, 153.00, 101.87, 34.02, 26.92, 22.16, 19.52, 13.16. In a similar manner isopropenyl butyrate was prepared from butyric acid in 54% yield. A 3.68-g portion of isopropenyl butyrate was prepared from 4.85 mL of butyric acid and 10 mL of butyric anhydride; ^{1}H NMR δ 4.60 (m, 2 H), 2.30 (t, 2 H), 1.85 (s, 3 H), 1.60 (m, 2 H), 0.90 (t, 3 H).

Preparation of Vinyl Valerate (1e). The method of Swern and Jordan[32] was used. Freshly distilled valeric acid (40 mL, 0.37 mol) and vinyl acetate (300 mL) were placed in a three-necked 500-mL round-bottomed flask fitted with a reflux condenser, a gas inlet tube, and a thermometer. The solution was stirred under argon and mercuric acetate (1.2 g, 0.37 mmol) was added. The reaction mixture was stirred under argon for 30 min, after which time 10 drops of 100% sulfuric acid was added. The solution was heated to reflux for 6 h and then was allowed to cool to room temperature. Sodium acetate (1.0 g) was added to quench the acid catalyst. The excess vinyl acetate was removed by distillation under argon. The product **1e** was isolated by distillation (bp 135–145 °C) as a clear, colorless liquid (29.4 g, 62% yield): ^{1}H NMR δ 7.24 (m, 1 H), 4.80 (m, 1 H), 4.48 (m, 1 H), 2.32 (t, 2 H), 1.60 (m, 2 H), 1.30 (m, 2 H), 0.85 (t, 3 H); ^{13}C δ NMR 170.69, 141.11, 97.22, 33.54, 26.57, 22.10, 13.57.

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