A Highly Chemo- and Stereoselective Synthesis of β-Keto Esters via a Polymer-Supported Lipase Catalyzed Transesterfication

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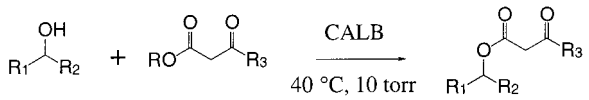
Introduction

A new research effort from our laboratory concerned the [3,3] sigmatropic rearrangement of allylic β-keto esters.[1] As such, we required a general method of synthesizing these compounds both as racemates and single enantiomers. β-Keto esters are noteworthy in that they represent an important class of organic building blocks used in the synthesis of complex natural products.[2] A seemingly straightforward method to prepare these molecules is through an alcohol-based transesterification.[3] Yet the synthesis of allylic and propargylic β-keto esters is not trivial by this route due to their acid/base lability and sigmatropic rearrangement of the β-keto ester.[4,5] To circumvent these problems, a report has appeared describing the heating of alcohols with β-keto esters in toluene.[4] However, the reaction times were lengthy and yields variable for many of the substrates. Another mild method uses crystalline microporous nanosilicates (zeolites) as the catalyst for the transesterification in refluxing toluene to avoid potential side reactions, but here the yields were even lower compared to the former case.[5] Furthermore, none of these or any of the conventional methods display stereoselectivity or chemoselectivity between aliphatic alcohols or phenols.

Results and Discussion

Lipases are a class of serine hydrolases that can exhibit excellent stereoselectivity and good catalytic activity for transesterification reactions in organic solvents.[6] Hence, lipases could be viewed as candidates for the preparation of chiral β-keto esters. Indeed, using diketene as the acyl donor, the synthesis of chiral acetoacetate esters by lipase catalysis was recently reported.[7] While this study was informative it was narrow in scope. Expansion on this theme using methyl or ethyl β-keto esters as the acyl donors would give a broader range of compounds. Furthermore, these structures could be synthesized in combination with the kinetic resolution of secondary alcohols so as to achieve a direct route to chiral β-keto esters. We now report a general method that avoids the use of bulk solvent wherein a range of alcohols were reacted with methyl or ethyl β-keto esters to obtain the desired transesterified products in excellent yield and with high chemo- and stereoselectivity.

Scheme 1



The catalyst used in our study was *Candida antarctica* lipase B (CALB) immobilized on a macroporous resin. We used an immobilized lipase as it enables ease of handling and recovery of the catalyst (Scheme 1). The simplicity of our method is demonstrated in the following typical experiment. A homogeneous mixture of alcohol (5 mmol) and β-keto ester (40 mmol) was treated with 10% (w/w of alcohol) of the catalyst and swirled in a flask connected to a Büchi rotavapor at 40 °C and 10 Torr.[8] After 8 h, the reaction mixture was filtered, rinsed (CH_2Cl_2), concentrated, and purified by chromatography to yield the desired product (Table 1). The immobilized lipase could be reused without loss of activity by first washing the beads with CH_2Cl_2 and then drying them in a desiccator. Because a one-pot operation was used, we were able to further generalize our studies such that reactions were also performed in parallel by the use of a vaccum oven. Furthermore, this strategy could be used to create a lipase-catalyzed β-keto ester library. In virtually all cases we investigated, excellent results were obtained, generally superior to those found in the literature.[3−5]

Both primary and secondary alcohols were appropiate substrates for the lipase as were allylic and propargylic alcohols. Interestingly, the lipase also efficiently acylated the polymer poly(ethylene glycol) monomethyl ether (MeO-PEG_{5000}) (entry 6). The ability of CALB to use MeO-PEG_{5000} as a substrate is noteworthy in that it can provide a variety of β-keto ester terminated PEGs that could be used as starting points in a polymer supported synthesis of heterocycles.[9] Using **8**, chemoselectivity between a phenol and alcohol was examined. The exclusive formation of **24** elucidates CALB's chemoselectivity for alkyl alcohols compared to phenols. CALB was also able to utilize the well-known annelating reagent ethyl 3-oxo-4-pentenoate (**15**, Nazarov's reagent) as an acyl donor to form **27** in excellent yield (entry 11).[10] This procedure could be applied for the one-step preparation of various annelating agents (3-oxo-4-pentenoate esters), since they do not have to be individually prepared from

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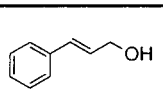
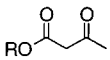
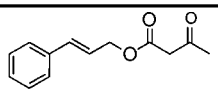
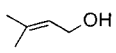
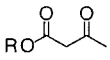
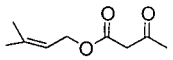
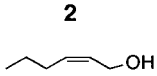
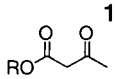
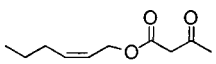
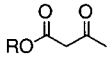
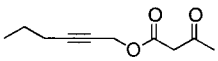
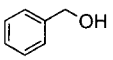
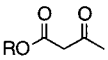
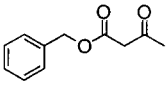
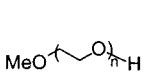
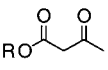
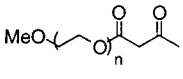
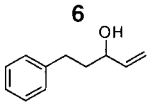
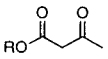
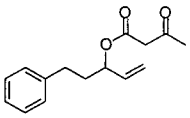
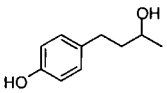
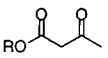
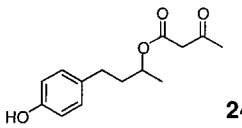
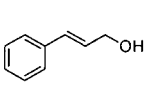
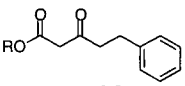
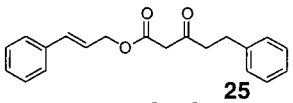
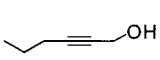
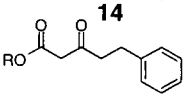
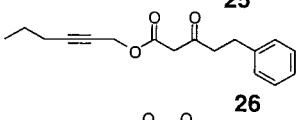
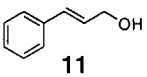
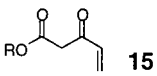
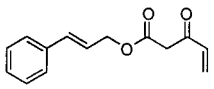
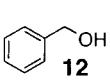
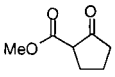
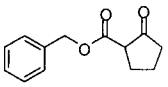
Table 1. Transesterifications of Alcohols and Methyl or Ethyl Acetoacetates Catalyzed by CALB[a]

Entry	Alcohol	β-keto ester[b]	Product[c]	% yield[d]
1	 **1**	 **13**	 **17**	95
2	 **2**	 **13**	 **18**	95
3	 **3**	 **13**	 **19**	98
4	 **4**	 **13**	 **20**	92
5	 **5**	 **13**	 **21**	94
6	 **6**	 **13**	 **22**	97
7	 **7**	 **13**	 **23**	95
8	 **8**	 **13**	 **24**	95
9	 **9**	 **14**	 **25**	92
10	 **10**	 **14**	 **26**	93
11	 **11**	 **15**	 **27**	94
12	 **12**	 **16**	 **28**	92

[a] No reaction occurred in the absence of catalyst, and the catalyst could be reused without loss of activity. [b] R = CH_3 or CH_2CH_3. [c] All new compounds gave satisfactory spectral data (^{1}H NMR, ^{13}C NMR, and HRMS). [d] Isolated yield.

the corresponding acetate ester (two steps).[11] Furthermore, it should be noted that attempts to prepare **27** by conventional methods using the 5-acyl derivative of Meldrum's acid were unsuccessful.[12]

To investigate CALB's ability to resolve racemic secondary alcohols, reactions were run with mixtures of the alcohol (5 mmol) and *β*-keto ester (7.5 mmol) to which 10% (w/w of alcohol) of the catalyst was added. After 1.5 h (~50% conversion of the alcohol), the reaction was stopped by filtration of the immobilized lipase and worked up in a similar manner as detailed (vide supra). CALB displayed good *E* values[13] for all of the tested alcohols, and the ee values were above 90% (Table 2). The successful formation of (*R*)-**33** demonstrates that the method could be a direct starting point for transfer of chirality in nonracemic cyclic and acyclic systems.[1,14]

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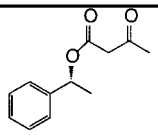
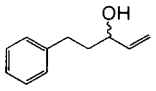
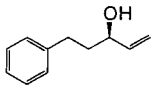
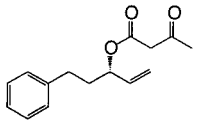
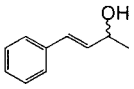
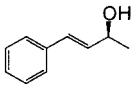
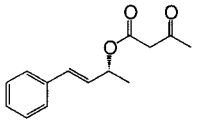
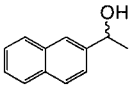
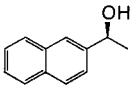
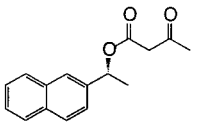
(12) Oikawa, Y.; Sugano, K.; Yonemitsu, O. *J. Org. Chem.* **1978**, *43*, 2087.
(13) E = enantiomeric ratio. Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294.
(14) (a) Hill, R. K. *Asymmetric Synthesis*; Academic Press: Orlando, 1984; Vol. 3, p 503. (b) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423. (c) Tanabe, M.; Hayashi, K. *J. Am. Chem. Soc.* **1980**, *102*, 862. (d) Koreeda, M.; Brown, L. *J. Org. Chem.* **1983**, *48*, 2122.

Table 2. Kinetic Resolution of *sec*-Alcohol Racemates with Methyl Acetoacetate Catalyzed by CALB

Entry	Substrate	Products[a]			% Conv.	$\%ee_s$[b] (yield)[e]	$\%\ ee_p$[c] (yield)[e]	E[d]
1	 **29**	 **(*S*) - 29**	 **(*R*) - 32**		51	98 (45)	96 (41)	226
2	 **7**	 **(*R*) - 7**	 **(*S*) - 23**		51	96 (44)	92 (42)	70
3	 **30**	 **(*S*) - 30**	 **(*R*) - 33**		48	90 (38)	97 (41)	203
4	 **31**	 **(*S*) - 31**	 **(*R*) - 34**		51	96 (46)	93 (40)	103

[a] The absolute configuration was based on the optical rotation, which was in accordance with those in the literature. [b] Determined by using chiral HPLC on a Chiralcel OD-H column (hexane/ 2-propanol mixtures, $\lambda = 254$ nm). [c] Determined on the alcohol corresponding to the acetoacetate formed,[7] by using chiral HPLC on a Chiralcel OD-H column. [d] $E = \ln[1 - c(1 + ee_p)]/\ln[1 - c(1 - ee_p)]$, $c = ee_s/ee_s + ee_p$.[16] [e] Isolated yield.

Furthermore, this protocol presents an additional advantage to previous methods utilizing diketene as the acyl donor for the lipase,[7,15] since it can accommodate a greater variety of acyl donors (i.e., β-keto esters).

In summary, we have described the first general route to prepare β-keto esters by a lipase-catalyzed transesterification. We believe our methodology will be of ample use due to its mild, solvent-free conditions. Moreover, it also provides a simple scheme to optically active β-keto esters that are useful building blocks and starting materials for natural product synthesis.[2,14c,d,16]

Experimental Section

General Methods. Methyl and ethyl acetoacetate were obtained from Aldrich Chemical Co. and distilled prior to use. β-Ketoester **14** and Nazarov's reagent **15** were synthesized according to literature procedures.[10,17] Chiral HPLC analyses were carried out using a Daicel Chiralcel OD Column (250 mm, 4.6 mm, eluent: hexane/2-Propanol). Column chromatography purification was done using Merck 60 silica gel (particle size 0.04−0.063 mm). The lipase (component B) Novozym 435 derived from *C. antarctica* is a product of Novo Nordisk A/S Denmark. The enzyme used was an immobilized preparation on a macroporous poly(propylene) resin, containing 1% (w/w) enzyme, with a catalytic activity of approximately 25 000 LU/g preparation. CALB was dried in a desiccator over P_2O_5 prior to use. All glassware was oven dried prior to use. High-resolution mass spectra (HRMS) were recorded on an Ion Spec Fourier transform mass spectrometer using dihydroxybenzoic acid (DHB) as the matrix.

Lipase-Catalyzed Transesterifications. A homogeneous mixture of alcohol (5 mmol) and β-ketoester (20 mmol) was treated with 10% (w/w of alcohol) of the catalyst and swirled in a 50-mL flask connected to a Büchi rotavapor at 40 °C and 10 Torr. For entries 9−12 (Table 1), the ratio was 1.2:1 between alcohol and β-ketoester, respectively. After 8 h, 20 mL of CH_2Cl_2 was added and the polymer-supported lipase removed by filtration. The solvent was removed under reduced pressure and the crude product purified by silica gel column chromatography with increasing amounts of EtOAc in hexane. The spectral data for **17**−**19** and **21** were in accordance with those reported in the literature.[3−5,18]

Lipase-Catalyzed Parallel Reactions. Vials containing different mixtures of alcohols (1 mmol) and β-ketoesters (8 mmol) together with 10 mg of CALB were placed in a vaccum oven at 40 °C and 10 Torr. After 24 h, 3 mL of CH_2Cl_2 was added to each vial and the lipase filtered. The workup was performed as described (vide supra).

Lipase-Catalyzed Kinetic Resolutions. The reactions were performed as described for the lipase-catalyzed transesterifications (vide supra), except with a ratio of 3:2 between β-ketoester and alcohol and reacted for 1.5 h (~50% conversion). Due to solubility problems, the ratio was 4:1 for alcohol **31**. The spectral data for (*R*)-**32** and (*R*)-**34** were in accordance with those reported in the literature.[7]

Hex-2-ynyl 3-oxobutanoate (20): chromatography, EtOAc/hexane 10:40 → 10:30; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.95 (t, $J = 7.3$ Hz, 3H), 1.51 (m, 2H, 2.26 (s, 3H), 3.47 (s, 2H), 4.71 (bs, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.3, 166.7, 88.4, 73.7, 53.9,

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(17) Weiler, L. *J. Am. Chem. Soc.* **1970**, *92*, 6707.
(18) Doyle, M. P.; Austin, R. E.; Bailey, A. S.; Dwyer, M. P.; Dyatkin, A. B.; Kalinin, A. V.; Kwan, M. M.; Liras, S.; Oalman, C. J.; Pieters, R. J.; Protopopova, Raab, C. E.; Roos, G. H. P.; Zhou, Q.-L.; Martin, S. F. *J. Am. Chem. Soc.* **1995**, *117*, 5763.

50.1, 30.3, 22.0, 20.9, 13.6; HRMS calcd for $C_{10}H_{14}O_3$ (M + Na^+) 205.0835, found 205.0843.

MeO-PEG-3-oxobutanoate (22). Poly(ethyleneglycol) monomethyl ether (M_w 5000) (5.0 g, 1 mmol) was dissolved in methyl acetoacetate (10 mL, 80 mmol) and reacted with CALB (500 mg) according to the general transesterification procedure. After 8 h, the reaction mixture was dissolved in THF (50 mL), filtered, and precipitated into diethyl ether (800 mL) at 0 °C. The white precipitate was collected to afford the product as a white solid (4.98 g, 97%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.24 (s, 3H), 3.34 (s, 3H), 3.45 (s, 2H), 3.50−3.70 (bs, 450H), 4.27 (t, J = 7.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.6, 167.3, 72.1, 70.8, 69.1, 64.5, 59.2, 50.2, 30.3.

Ethenyl 3-phenylpropyl-3-oxobutanoate (*S*)-(23): $[\alpha]^{25}_D$ = −3.7° (c = 2.1, CH_2Cl_2), 90% ee; chromatography, EtOAc/hexane 10:90 → 20:80; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.91−2.09 (m, 2H), 2.28 (s, 3H), 2.62−2.77 (m, 2H), 3.47 (s, 2H), 5.26 (d, J = 10.6 Hz, 1H), 5.33 (d, J = 12.5 Hz, 1H), 5.36 (m, 1H), 7.17−7.25 (m, 3H), 7.27−7.34 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.6, 166.5, 141.3, 135.9, 128.6, 128.5, 126.2, 117.7, 75.6, 50.4, 35.8, 31.5, 30.3; HRMS calcd for $C_{15}H_{18}O_3$ (M + Na^+) 269.1148, found 269.1155.

Methyl 3-(4-hydroxyphenyl)propyl-3-oxobutanoate (24): chromatography, EtOAc/hexane 10:90 → 50:50; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.72 (d, J = 6.6 Hz, 3H), 1.77−1.90 (m, 1H), 1.91−1.97 (m, 1H), 2.28 (s, 3H), 2.52−2.69 (m, 2H), 3.33 (s, 2H), 4.99 (m, 1H), 6.75 (d, J = 7.8 Hz, 2H), 7.02 (d, J = 7.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.3, 167.2, 154.2, 133.6, 129.7, 115.6, 77.2, 50.7, 37.9, 31.02, 30.5, 20.2; HRMS calcd for $C_{14}H_{18}O_4$ (M + Na^+) 273.1097, found 273.1094.

Cinnamyl 3-oxo-5-phenylpentanoate (25): chromatography, EtOAc/hexane 20:80 → 10:30; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.82−3.05 (m, 4H), 4.79 (d, J = 6.2 Hz, 2H), 6.23 (m, 1H), 6.64 (d, J = 15.8 Hz, 1H), 7.20−7.42 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.8, 167.0, 140.7, 136.2, 135.1, 128.8, 128.7, 128.5, 126.9, 126.4, 122.7, 66.1, 49.6, 44.7, 29.6; HRMS calcd for $C_{20}H_{20}O_3$ (M + Na^+) 331.1305, found 331.1305.

Hex-2-ynyl 5-phenyl-3-oxopentanoate (26): chromatography, EtOAc/hexane 10:40 → 10:30; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.95 (t, 3H, J = 7.3 Hz), 1.50 (m, 2H), 2.96 (m, 4H), 3.47 (s, 2H), 4.72 (bs, 2H), 7−15−7.30 (m, 5H); 201.6, 166.7, 141.3, 140.8, 128.8, 128.6, 126.4, 88.4, 73.8, 54.0, 49.5, 45.5, 29.7, 22.08, 20.9, 13.6; HRMS calcd for $C_{17}H_{20}O_3$ (M + Na^+) 295.1306, found 295.1312.

Cinnamyl 3-oxo-4-pentenoate (27): chromatography, EtOAc/hexane 20:80 → 10:30; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.60 (s, ketonic *H* at C(2)), 4.78 (d, J = 5.9 Hz, 2H), 5.10 (s, enolic *H* at C(2)), 5.50 (t, 1H), 5.94−6.36 (m 3H), 6.64 (d, J = 15.7 Hz, 2H), 7.25−7.40 (m, 5H), 11.8 (s, enol *OH*); HRMS calcd for $C_{14}H_{14}O_3$ (M + Na^+) 253.0835, found 253.0846.

Benzyl 2-oxocyclopentanecarboxylate (28): chromatography, EtOAc/hexane 10:90 → 20:80; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.81−1.90 (m, 1H), 2.10−2.14 (m, 1H), 2.2−2.4 (m, 4H), 3.21 (t, J = 9.2 Hz, 1H), 5.18 (s, 2H), 7.36 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.3, 169.5, 135.8, 128.8, 128.5, 128.3, 67.2, 55.0, 38.3, 27.6, 21.3; HRMS calcd for $C_{13}H_{14}O_3$ (M + Na^+) 241.0835, found 241.0837.

Methyl 3-phenylprop-2-enyl-3-oxobutanoate ((*R*)-33): $[\alpha]^{25}_D$ = +81.1° (c = 1.1, CH_2Cl_2), 93% ee; chromatography, EtOAc/hexane 10:90 → 40:60; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.40 (d, J = 6.6 Hz, 2H), 2.23 (s, 3H), 3.42 (s, 2H), 5.55 (m, 1H), 6.21-(dd, J = 15.9, 6.6 Hz, 1H), 6.58 (d, J = 16.1 Hz, 1H), 7.21−7.39 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.7, 166.6, 136.4, 132.4, 128.8, 128.4, 128.3, 126.8, 72.6, 50.6, 30.3, 20.5; HRMS calcd for $C_{14}H_{16}O_3$ (M + Na^+) 255.0992, found 255.1004.

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra of **22**−**24**, **28**, and **33**. This material is available free of charge via the Internet at http://pubs.acs.org.

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