One-Pot, Catalytic, Asymmetric Syntheses of All Four Stereoisomers of a Dipropionate Synthon

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The structural complexity and biological activities of the polypropionates have made these molecules attractive targets for synthetic organic chemists.[1] The key to constructing polypropionates is control of absolute and relative stereochemistry, as potentially every carbon in the backbone of these molecules is a chiral center. Several very selective, auxiliary-controlled Claisen condensations[2] and aldol additions[3] are available for polypropionate construction, but any scheme involving auxiliaries requires the synthesis, attachment, and removal of the auxiliary. Although several groups have developed more efficient strategies based on catalytic, asymmetric aldol reactions of propionate enolates,[4] these reactions lack the stereochemical or substrate generality necessary for polypropionate synthesis. To rectify this deficiency, we have developed a biomimetic, catalytic, asymmetric reaction sequence that can produce any stereoisomer of a general dipropionate synthon from commercially available materials without intermediate isolations (Scheme 1).[5]

The reaction sequence is based on our recently developed tertiary amine-catalyzed dimerization of methylketene, generated in situ from α-bromopropionyl bromide.[6] Trapping of the ketene dimer with a secondary amine, followed by reduction under the appropriate conditions, affords either diastereomer of the dipropionate synthon. As both enantiomers of the ketene dimer are readily available, one can access any stereoisomer of the final product.

We began with pyrrolidine as the secondary amine trapping agent and the illustrated conditions for either syn or anti reduction (Scheme 2).[7] In all cases, the diastereomeric purities of the *β*-hydroxy amide products were satisfactory; however, the enantiomeric purity of the products depended on the amount of pyrrolidine added (Table 1). As the 98% ee of the *R* ketene dimer had been established independently,[6] the loss of optical activity occurred during or after the trapping of the dimer with pyrrolidine. We postulated that loss of optical activity occurred via epimerization of the *β*-keto amide by pyrrolidine after trapping.[2a] To test this postulate, we treated the ketene dimer with less than 1 equiv of pyrrolidine, based on a reproducible 55% yield of ketene dimer. As illustrated in Table 1, the ee of the *β*-hydroxy amide increased to the levels observed for the ketene dimer.

Scheme 1

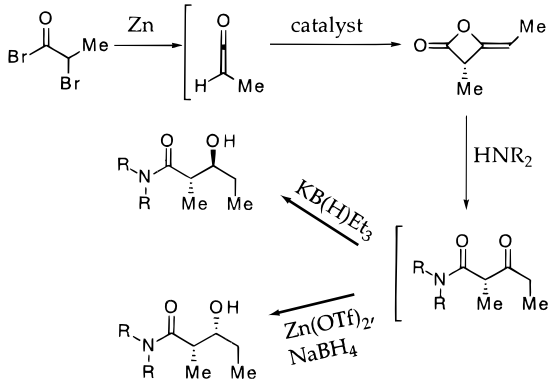

Table 1. Enantioselectivities and Yields for the Production of 1

catalyst	equiv of pyrrolidine	reduction condns[a]	% ee of **1** (config)	% yield of **1**[b]
quinidine	1.1	A	91 (2*S*,3*S*)	55
quinidine	0.9	A	98 (2*S*,3*S*)	48
quinidine	0.9	B	99 (2*S*,3*R*)	42
trimethylsilyl quinine	0.9	A	96 (2*R*,3*R*)	48
trimethylsilyl quinine	0.9	B	96 (2*R*,3*S*)	42

[a] A = $KB(H)Et_3$, THF, −78 °C, *anti*-**1**:*syn*-**1** > 95:5. B = $Zn(OTf)_2$, $NaBH_4$, THF, −78 °C, *syn*-**1**:*anti*-**1** = 95:5. [b] Overall yield from bromopropionyl bromide.

With ready access to all four stereoisomers of **1**, we next sought to synthesize the *N*,*O*-dimethylhydroxylamides (Scheme 3, Table 2). These "Weinreb" amides are amenable to subsequent refunctionalization, such as ketone and aldehyde formation.[8] However, the relatively low nucleophilicity of *N*,*O*-dimethylhydroxylamine necessitated long reaction times and elevated temperatures to achieve adequate conversion, resulting in much epimerization. Therefore, addition of the amine to the ketene dimer required catalysis.

Standard acyl-transfer catalysts, such as DABCO and DMAP,[9] did increase reaction rates; however, the ee of the product was still low (Table 2). As loss of optical activity could be occurring by a reversal of the ketene dimerization step, we next assayed HOBT as an acyl-transfer catalyst. HOBT contains an acidic proton, which could trap the putative ammonium enolate intermediate and prevent retrodimerization reaction.[10] However, catalysis with HOBT still resulted in a product with low optical activity, which probably results from epimerization of the *β*-keto *ester* intermediate formed by nucleophilic attack of the HOBT oxygen on the ketene dimer. Catalysis proceeding through a *β*-keto *amide* would probably not result in epimerization, as tertiary *β*-keto amides resist epimerization.[2a] Therefore, we next assayed pyridone because it both has an acidic proton and favors nucleophilic attack with nitrogen, so that acyl-transfer catalysis would proceed via a *β*-keto amide (Scheme 4). In the event, use of pyridone afforded all four stereoisomers of **2** in high diastereo- and enantioselectivities.

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(2) (a) Evans, D. A.; Ennis, M. D.; Le, T.; Mandel, N.; Mandel, G. *J. Am. Chem. Soc.* **1984**, *106*, 1154−1156. (b) Drewes, S. E.; Malissar, D. G. S.; Roos, G. H. P. *Chem. Ber.* **1993**, *126*, 2663−2673 and references therein.

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(4) (a) Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* **1994**, *116*, 4077−4078. (b) Evans, D. A.; Kozlowski, M. C.; Burgey, C. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1998**, *119*, 77893-7894. (c) Evans, D. A.; MacMillan, D. W. C.; Campos, K. R. *J. Am. Chem. Soc.* **1998**, *119*, 110859−10860.

(5) For the use of other dipropionate synthons available from auxiliary-controlled reactions or chiral pool methodology, see: (a) Evans, D. A.; Clark, J. S.; Metternich, R.; Novack, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990**, *112*, 866−868. (b) Evans, D. A.; Ng, H. P.; Clark, J. S.; Rieger, D. L. *Tetrahedron* **1992**, *48*, 2127−2142. (c) Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041−2114.

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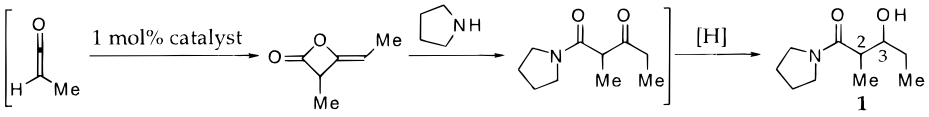
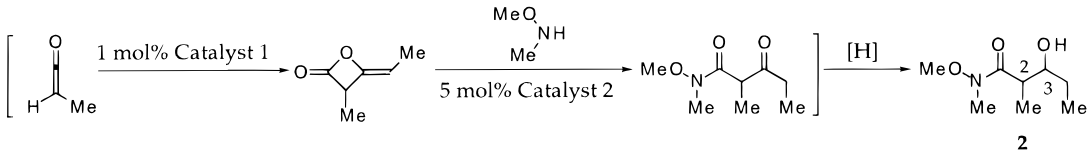
Scheme 2



Scheme 3



Scheme 4

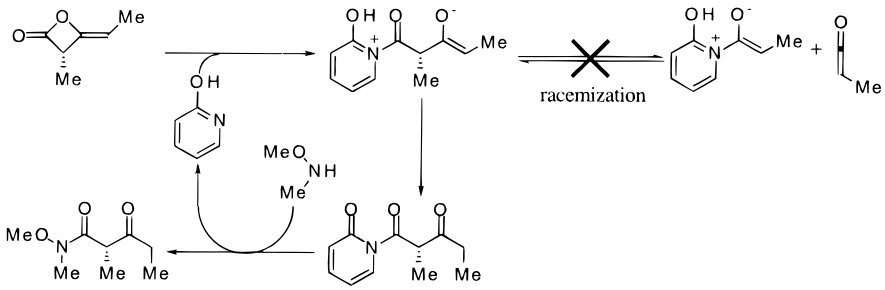


Table 2. Catalysts and Enantioselectivies for the Production of 2

catalyst 1	catalyst 2	reduction condns[a]	% ee of **2** (confign)	% yield of **2**[b]
quinidine		A	90 (2*S*,3*S*)	5
quinidine	DABCO	A	19 (2*S*,3*S*)	24.5
quinidine	DMAP	A	77 (2*S*,3*S*)	
quinidine	HOBT	A	66 (2*S*,3*S*)	
quinidine	pyridone	A	99 (2*S*,3*S*)	40
quinidine	pyridone	B	99 (2*S*,3*R*)	46
trimethylsilyl quinine	pyridone	A	95 (2*R*,3*R*)	40
trimethylsilyl quinine	pyridone	B	95 (2*R*,3*S*)	46

[a] A = KB(H)Et_3, THF, −78 °C, *anti*-**1**:*syn*-**1** = 99:1. B = $Zn(OTf)_2$, $NaBH_4$, THF, −78 °C, *syn*-**1**:*anti*-**1** = 98.5:1.5. [b] Overall yield from bromopropionyl bromide.

In summary, this reaction sequence can afford any of the four stereoisomers of a dipropionate synthon, using only a catalytic amount of a source of chirality. All the substrates, reagents, and catalysts are commercially available at low cost,[11] and one can run the entire sequence in the course of 1 day. The success of this sequence lies in the ability to use only substrates and catalysts for all but the final step, preventing the interferences usually experienced in sequential reagent-based transformations. We are currently exploring methods for stereoselectively combining the dipropionate synthons to form higher propionates.

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Supporting Information Available: Synthetic procedures and analytical data for **1** and **2** (4 pages).

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(11) TMS-quinine is not commercially available; however, it can be prepared easily from commercial quinine and trimethylsilyl chloride. See ref 6.