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One-Pot, Catalytic, Asymmetric Synthesis of Polypropionates

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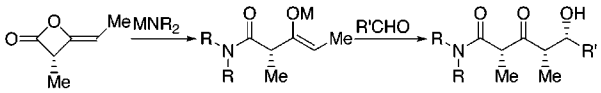
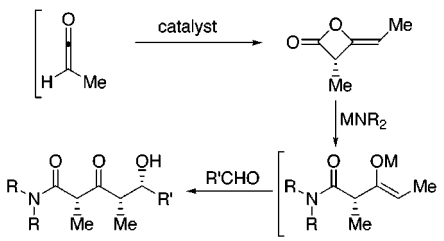
ABSTRACT



The opening of methylketene dimer, followed by aldol reactions of the resulting enolate, provides a convenient access to *syn*,*syn*-dipropionate aldol adducts of a variety of aldehydes. These aldol adducts are useful precursors in the synthesis of complex polypropionates.

The structural complexity and biological activities of the polyketides have made these molecules very attractive targets for synthetic organic chemists.[1] Polyketides biosynthesized from propionate precursors belong to an important subclass called the polypropionates. As potentially every carbon in the backbone of a polypropionate is a chiral center, the key to the synthesis of polypropionates is control of absolute and relative stereochemistry. Several groups have developed very selective, auxiliary-controlled Claisen condensations[2] and aldol additions[3] 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,[4] these reactions lack the stereochemical or substrate generality necessary for polypropionate synthesis. To rectify this deficiency, we have developed a catalytic, asymmetric reaction sequence that can add a dipropionate synthon to a growing polypropionate chain in a single experimental step (Scheme 1).[5]

Scheme 1



The reaction sequence is based on our tertiary amine-catalyzed dimerization of methylketene.[6] We postulated that addition of a metal amide to the dimer would afford a β-ketoamide enolate, which in turn could react with aldehydes to form polypropionates. Furthermore, it appeared that we would be able to carry out all these reactions without the isolation of any intermediates.

Although the method for methylketene generation from bromopropionyl bromide had been adequate for our previous work,[7] the limitation of this method to tetrahydrofuran (THF) as a solvent and the potential need for the use of highly Lewis acidic metals in the aldol reaction required us to turn to alternative methods for methylketene generation. Using a simple thermolysis device,[8] we were able to thermolyze propionic anhydride to produce methylketene as a reactant stream in nitrogen. Passage of this reactant stream through a solution of the tertiary amine catalyst in a number of

(1) O'Hagan, D. *The Polyketide Metabolites*; Horwood: New York, 1991.
(2) Drewes, S. E.; Malissar, D. G. S.; Roos, G. H. P. *Chem. Ber.* **1993**, *126*, 2663−2673, and references therein.
(3) Arya, P.; Qin, H. P. *Tetrahedron* **2000**, *56*, 917−947.
(4) Machajewski, T. D.; Wong, C. H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1353−1374. For another ketene-based method for polypropionate synthesis, see: Nelson, S. G.; Wan, Z. H. *Org. Lett.* **2000**, *2*, 1883−1886.
(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.
(6) (a) Calter, M. A. *J. Org. Chem.* **1996**, *61*, 8006−8007. (b) Calter, M. A.; Guo, X. *J. Org. Chem.* **1998**, *63*, 5308−5309.
(7) McCarney, C. C.; Ward, R. S. *J. Chem. Soc., Perkin Trans. I* **1975**, 1600−1603.
(8) Blau, K. *Chem. Ind.* **1963**, 33−34.

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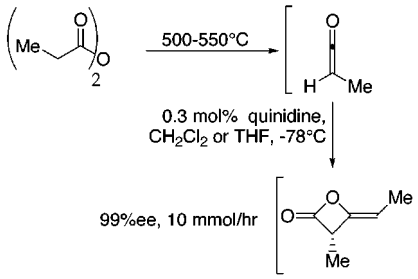
solvents afforded an essentially pure solution of methylketene dimer at a rate of 10 mmol/h (Scheme 2).[9] All subsequent

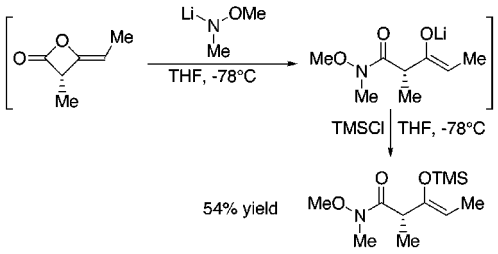
Scheme 2



yields were based on this reproducible yield of methylketene dimer. As reported earlier, the use of quinidine as a catalyst yielded the *S*-enantiomer in 99% ee, while the use of TMS-quinine yielded the *R*-enantiomer in 97% ee. All subsequent transformations were carried out on the *S*-enantiomer; however, use of the *R*-enantiomer obviously could afford the opposite enantiomeric series of aldol adducts.

Lappert showed that aluminum and boron amides will add to diketene and also that the resulting unconjugated enolate quickly tautomerizes to the conjugated form.[10] We were hopeful that the additional methyl group between the carbonyls in the present case would drastically slow this tautomerization. In fact, we recently showed that the lithium amide of *N*,*O*-dimethylhydroxylamine reacted with the dimer in the presence of trimethylsilyl chloride (TMSCl) to form the unconjugated silyl enol ether (Scheme 3).[11] This reaction

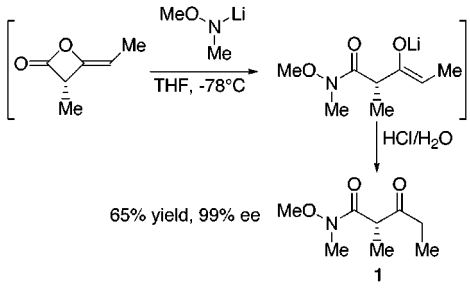
Scheme 3



presumably proceeded via the desired lithium enolate, indicating that this intermediate was at least temporarily stable.

Opening of the dimer with the lithium amide of *N*,*O*-dimethylhydroxylamine, followed by protonation, yielded *β*-ketoamide **1**, whose optical activity is at the level of that of the starting dimer (Scheme 4). The lack of epimerization

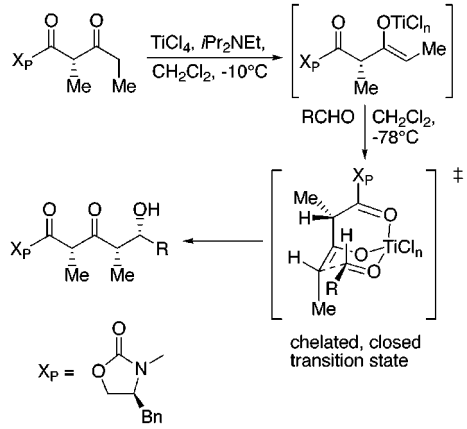
Scheme 4



indicated that the enolate did not isomerize appreciably to the conjugated form. However, the yields of **1** were only moderate, even though the mass recovery of the unpurified reaction mixture was greater than 90%, and all methods used to test the purity of this mixture indicated that it was >95% **1**. One can also perform the opening reactions in CH_2Cl_2, and the yield in this solvent was higher (74%).

Evans et al. have shown that various metal enolates of *β*-keto*imides* undergo highly diastereoselective aldol reactions (Scheme 5).[5a] The stereochemical outcome of the

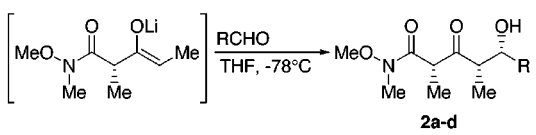
Scheme 5. From Reference 5a



reactions of *β*-ketoimide titanium enolates was consistent with a chelated, closed transition state. It was unclear how *β*-keto*amide* enolates would react.

In the event, the lithium enolate yielded *syn*,*syn* aldol adducts **2a**−**d** with a variety of aldehydes (Scheme 6, Table 1). The enantiomeric excess of **2a** was greater than 99%, indicating that no epimerization had occurred during the

Scheme 6



(9) The amount of methylketene dimer produced was quantified by conversion of the dimer to the amide by reaction with pyrrolidine, as described in ref 6b, followed by isolation.

(10) Horder, J. R.; Lappert, M. F. *J. Chem. Soc. A* **1969**, 173−177.

(11) Calter, M. A.; Bi, F. C. *Org. Lett.* **2000**, *2*, 1529−1532. As the silyl enol ether was used without isolation, we did not report an isolated yield for this compound in this reference.

Table 1. Selectivities and Yields for Aldol Reactions

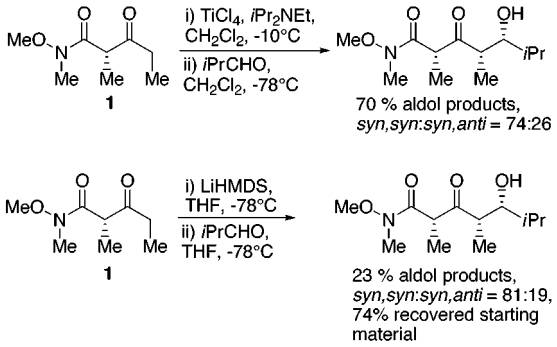
Product	R	*syn,syn*:*anti,syn* ratio[a]	% yield of *syn,syn* diastereomer
2 a	*i*Pr	95:5	52
2 b	*n*Pent	89:11	48
2 c	Ph	84:16	50
2 d		84:16	48

[a] Determined by GC analysis of the unpurified reaction mixture.

addition step. In CH_2Cl_2, the aldol reaction with isobutyraldehyde afforded the aldol adducts in 70% overall yield with a diastereoselectivity of 89:11.

Other metal enolates, generated in a similar fashion, gave lower conversion than the lithium enolate in the aldol reaction with isobutyraldehyde. For example, the dimethylaluminum enolate gave a 97:3 mixture of diastereomers, but only 75% conversion. The diethylboron enolate gave no aldol product. Also, the dimer opening protocol was much more successful than direct enolization of β-ketoamide **1** for generating enolates for the diastereoselective aldol reaction. For example, the chlorotitanium enolate, generated by direct enolization of **1**, afforded a 74:26 ratio of diastereomers (Scheme 7). Attempted enolization of **1** with lithium hexamethyldisilazide (LiHMDS) yielded mainly conjugated enolate, as evidenced by the low conversion and diastereoselectivity in the subsequent aldol reaction.

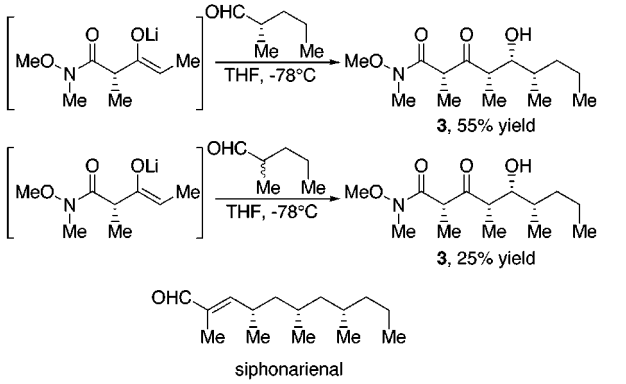
Scheme 7



Encouraged by the high selectivities realized using the lithium enolate formed by dimer opening in THF, we next applied this reaction to the synthesis of the siphonariene class of marine polypropionates (Scheme 8).[12] Reaction of the

(12) Norté, M.; Cataldo, F.; Gonzaléz, A. G.; Rodríguez, M. L.; Ruiz-Perez, C. *Tetrahedron* **1990**, *46*, 1669−1678.

Scheme 8



lithium enolate with (*S*)-2-methylpentanal[13] afforded aldol adduct **3** in 55% yield. A similar aldol adduct served as an advanced intermediate in Norté's synthesis of siphonarienal.[14] The synthesis was further streamlined by employing commercially available, racemic 2-methylpentanal. Reactions employing 1.1 equiv of this aldehyde afforded a 1.2:1 mixture of diastereomers, favoring the undesired diastereomer. This mixture easily separated on SiO_2 to afford a 25% percent yield of **3**. This preference for the anti-Cram diastereomer was in accord with the typical anti-Cram preference for *Z*-enolates.[15] Although the yield of **3** was low, this reaction was notable for its ability to produce an intermediate containing all the carbons and stereocenters of the 2,4,6-trimethylnonane moiety present in all the siphonarienes in one synthetic step from commercially available starting materials using a catalytic amount of a chirality source.

In summary, the ketene dimerization/opening/aldol reaction sequence provides a convenient and diastereoselective method for the one-step construction of polypropionate segments. Further research into the stereoselective generation of the other aldol diastereomers and the completion of the siphonariene synthesis continues.

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Supporting Information Available: Synthetic procedures and analytical data for **2a**−**d** and **3** and details for the stereochemical proof of **2a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) (*S*)-2-Methylpentanal was prepared from β-hydroxyamide (2*S*,3*S*)-**2** of ref 6b by xanthate formation, free radical deoxygenation, and amide reduction. (2*S*,3*S*)-**2** was prepared, as described in ref 6b, from the methylketene dimer.

(14) Norté, M.; Fernández, J. J.; Padilla, A. *Tetrahedron Lett.* **1994**, *35*, 3413−3416.

(15) (a) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1−115. (b) Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151−4157.