

New Chiral Synthons for Efficient Introduction of Bispropionates via Stereospecific Oxonia–Cope Rearrangements

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The synthesis of polypropionates, a common structural motif in many biologically active natural products, provides inspiration and impetus for exploring new carbon–carbon bond-forming reactions. Iterative aldol¹ or crotylation transformations² build polypropionate structures by forming every other carbon–carbon bond of a carbon chain, but more efficient processes use larger building blocks.³ In this communication, we report a novel approach to the stereospecific introduction of bispropionate synthons in a non-aldol fashion, which utilizes Lewis acid catalysis rather than base-promoted conditions.

The design for this synthon is based on allylic rearrangements pioneered by the Nokami laboratory,⁴ in which a chiral nonracemic homoallylic alcohol is condensed with aldehydes to accomplish transfer of crotyl and other allylic units, with chirality transfer and regioselectivity consistent with a 2-oxonia-[3,3]-sigmatropic rearrangement mechanism. We envisioned extension to a more highly functionalized bispropionate synthon **I** (Figure 1), so that rear-

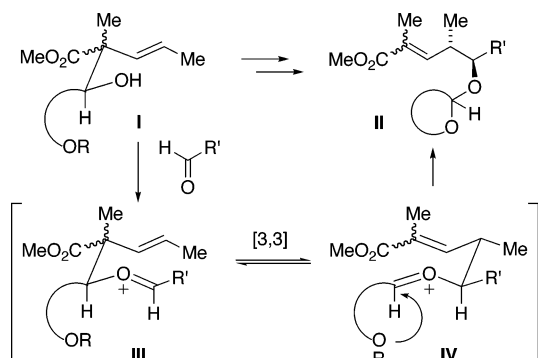
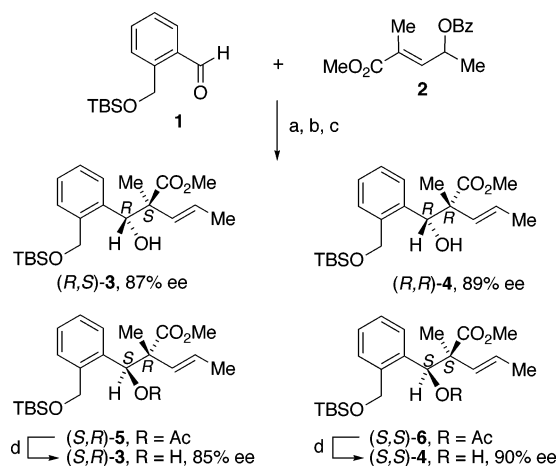


Figure 1. Design of bispropionate transfer synthon.

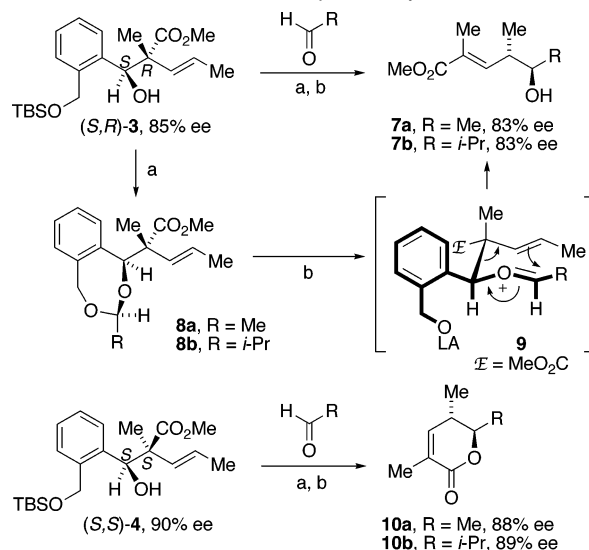
rangement of **III** to **IV** might be favored by concomitant reaction of tethered alcohol.⁵

Several compounds corresponding to synthon **I** were evaluated for this transformation, including isomeric compounds **3** and **4** (Scheme 1). Reductive coupling of allylic benzoate **2**⁶ with *ortho*-silyloxymethylbenzaldehyde **1**,⁷ using Tamaru's conditions⁸ of palladium/phosphine catalyst and diethylzinc, provided racemic diastereomers **3** and **4** as a 1:2.7 separable mixture, which in turn underwent kinetic resolution⁹ catalyzed by Fu's planar-chiral modified DMAP catalyst¹⁰ to provide the alcohols (*R,S*)-**3** and (*R,R*)-**4** and acetates (*S,R*)-**5** and (*S,S*)-**6** in excellent enantiomeric purity from each racemate. The acetate esters **5** and **6** were converted into (*S,R*)-**3** and (*S,S*)-**4**, respectively.^{11,12}

Reactions of (*S,R*)-**3** with acetaldehyde or isobutyraldehyde were promoted by Sn(OTf)₂¹³ to give initial formation of cyclic acetals **8a–b** rather than direct bispropionate transfer, but treatment of **8a–b** with SnCl₄ and Ag₂CO₃ provided products **7a–b** (Scheme 2). The *E*-alkene and *anti*-relationship of the two chiral centers correspond to a chair-like transition state **9**. The diastereomer (*S,S*)-**4** produced the lactones **10a–b** under identical conditions, with in situ intramolecular cyclization enforced by the *Z*-alkene. Rearrange-

Scheme 1. Preparation and Resolution of Bispropionate Synthons^a

^a Conditions: (a) Pd(OAc)₂ (6 mol %), PPh₃ (6 mol %), Et₂Zn (5 equiv), THF, 0 to 20 °C, 20 h; (b) silica gel chromatography to separate diastereomers ((±)-**3**, 21% yield; (±)-**4**, 59% yield); (c) Ac₂O (0.75 equiv), Et₃N (0.75 equiv), (*S*)-(–)-4-dimethylaminopyridinyl(pentaphenylcyclopentadienyl)iron (Fu's catalyst, 0.8 mol %), *t*-AmOH, 0 °C, 114 h (from (±)-**3**, (*R,S*)-**3**, 45% yield; (*S,R*)-**5**, 47% yield; from (±)-**4**, (*R,R*)-**4**, 46% yield; (*S,S*)-**6**, 44% yield); (d) H₂NNH₂, MeOH (73–75% yield).

Scheme 2. Initial Results with Simple Aldehydes^a

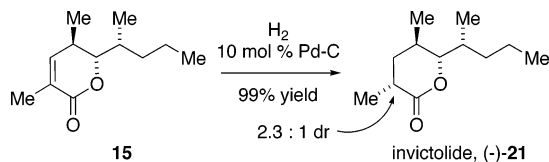
^a Conditions: (a) Sn(OTf)₂ (10 mol %), CH₂Cl₂, 20 °C, 1 h; (b) SnCl₄ (0.6 equiv), Ag₂CO₃ (2 equiv), MeNO₂/CH₂Cl₂, 20 °C, 75 min, **7a**, 67% yield from (*S,R*)-**3**; **7b**, 73% yield from (*S,R*)-**3**; **10a**, 94% yield from (*S,S*)-**4**; **10b**, 92% yield from (*S,S*)-**4**.

ment of acetals **8** arising from diastereomer **3** occurs observably faster than the corresponding process from diastereomer **4**, but isolated yields of the acyclic alcohols **7** are consistently lower than those for the production of lactones **10**, as the product alcohols **7**

Table 1. Synthesis of Bispropionates from Synthons **3** and **4**

synthon	aldehyde	procedure ^a	product (isolated yield, dr)
(<i>R,S</i>)- 3 (87% ee)		A	
	11 (96% ee)		13 (75% yield, 12 : 1 dr)
(<i>S,R</i>)- 3 (85% ee)		A	
	11		14 (78% yield, 10 : 1 dr)
(<i>R,R</i>)- 4 (89% ee)		A	
	11		15 (89% yield, 14 : 1 dr)
(<i>S,S</i>)- 4 (90% ee)		A	
	11		16 (85% yield, 14 : 1 dr)
(<i>R,S</i>)- 3 (87% ee)		B	
	12 (85% ee)		17 (69% yield, >20 : 1 dr)
(<i>S,R</i>)- 3 (85% ee)		B	
	12		18 (62% yield, 9 : 1 dr)
(<i>R,R</i>)- 4 (89% ee)		A	
	12		19 (80% yield, >20 : 1 dr)
(<i>S,S</i>)- 4 (90% ee)		A	
	12		20 (47% yield, 6 : 1 dr)

^a Procedure A: TMSOTf (10 mol %), CH₂Cl₂, -78 °C, 4 h, pyridine quench; then SnCl₄ (0.6 equiv), Ag₂CO₃ (2 equiv), MeNO₂/CH₂Cl₂, 20 °C. Procedure B: same as procedure A, except followed by Ac₂O, pyridine.

Scheme 3. A Short Synthesis of Invictolide

decompose upon prolonged contact with the Lewis acids that promote this transformation.

This methodology was then evaluated with (*R*)-2-methylpentanal (**11**)¹⁴ and (2*R*,3*S*)-3-acetoxy-2,4-dimethylpentanal (**12**)¹⁵ (Table 1). In these cases, catalytic TMSOTf was used in the first step (procedure A) to minimize epimerization of the chiral aldehydes. From aldehyde **12**, the initial products from **3** were observed to undergo partial migration of the acetate protective group,¹⁶ thus acetylation of the product mixture was employed to produce **17** and **18** (procedure B). The bispropionate transfer reaction occurs without observable double diastereoselection from α -chiral aldehyde **11**, but some diminution in yield and stereoselectivity is observed

for Felkin model “mismatched” cases with aldehyde **12** (i.e., from (*S,R*)-**3** and (*S,S*)-**4**). To validate the structural assignment for product **15**, we prepared (–)-invictolide **21**¹⁷ by Pd–C-catalyzed hydrogenation of **15** (Scheme 3).^{17b}

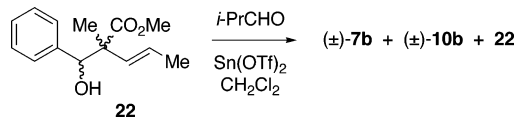
In summary, the new bispropionate synthons **3** and **4** are easily prepared in stereochemically pure form and undergo stereospecific transfer to a variety of aldehydes to provide rapid access to highly functionalized polypropionate products. Current research activities include the application of this synthetic methodology to more complex natural product structures.

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Supporting Information Available: Procedures and characterization data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (5) The tethered benzylic silyl ether of synthons **3** and **4** is required not only to drive the oxonia–Cope equilibrium to products but also to provide another polar substituent for chromatographic separation of diastereomers **3** and **4**. Sn(OTf)₂-promoted reaction of isobutyraldehyde with the corresponding benzaldehyde-derived **22** (inseparable mixture of stereoisomers) gave a poor yield of racemic products **7b** and **10b** mixed with recovered **22**.



- (6) Racemic compound **2** was formed from commercial (*E*)-2-methylpent-2-enoate methyl ester in two steps: (i) *N*-bromosuccinimide, *hν*, CCl₄, reflux (Sydnes, L. K.; Skattebøl, L.; Chapleo, C. B.; Leppard, D. G.; Svanholt, K. L.; Dreiding, A. S. *Helv. Chim. Acta* **1975**, 58, 2061); (ii) sodium benzoate, DMF, 100 °C (66% yield, two steps).
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- (14) **11** was prepared by Swern oxidation of (*R*)-2-methyl-1-pentanol. (a) Myers, A. G.; Yang, B. H.; Chen, H.; McKinsty, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, 119, 6496. (b) Myers, A. G.; Yang, B. H.; Chen, H.; Gleason, J. L. *J. Am. Chem. Soc.* **1994**, 116, 9361.
- (15) Preparation of **12**: (a) (*Z*)-(+)-crotyldiisopinocampheylborane, isobutyraldehyde; (b) Ac₂O, pyridine; (c) O₃; Me₂S (52% yield, three steps).
- (16) The corresponding silyl ether-protected analogues of **12** underwent desilylation in the course of attempted allylic rearrangement, thus the acetate protective group was preferred with this substrate.
- (17) Invictolide (**21**) is a component of the queen recognition pheromone of *Solenopsis invicta*. Structure determination and synthesis: (a) Rocca, J. R.; Tumlinson, J. H.; Glancey, B. M.; Lofgren, C. S. *Tetrahedron Lett.* **1983**, 24, 1893. (b) Honda, T.; Yamane, S.-i.; Ishikawa, F.; Katoh, M. *Tetrahedron* **1996**, 52, 12177 and cited ref 4 within.

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