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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 aldol[1] or crotylation transformations[2] 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 rearrangement of **III** to **IV** might be favored by concomitant reaction of tethered alcohol.[5]

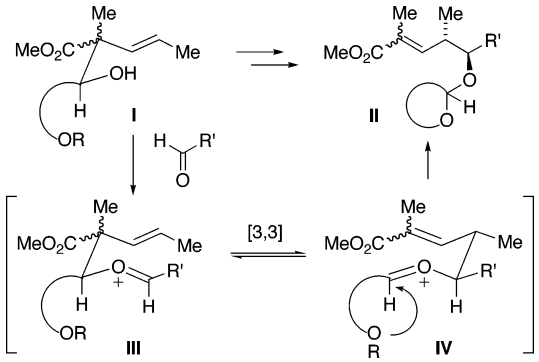
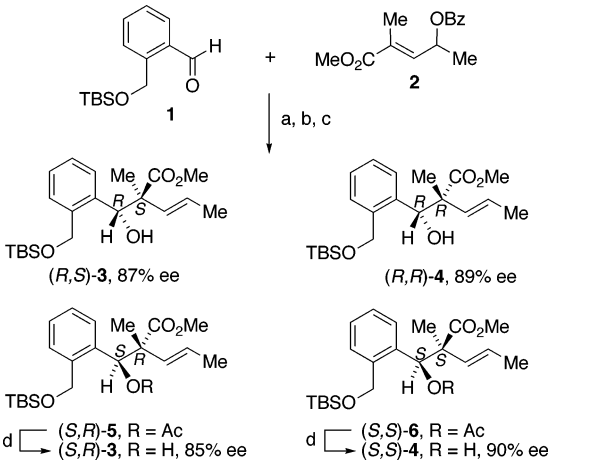


Figure 1. Design of bispropionate transfer synthon.

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 conditions[8] of palladium/phosphine catalyst and diethylzinc, provided racemic diastereomers **3** and **4** as a 1:2.7 separable mixture, which in turn underwent kinetic resolution[9] catalyzed by Fu's planar-chiral modified DMAP catalyst[10] 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]

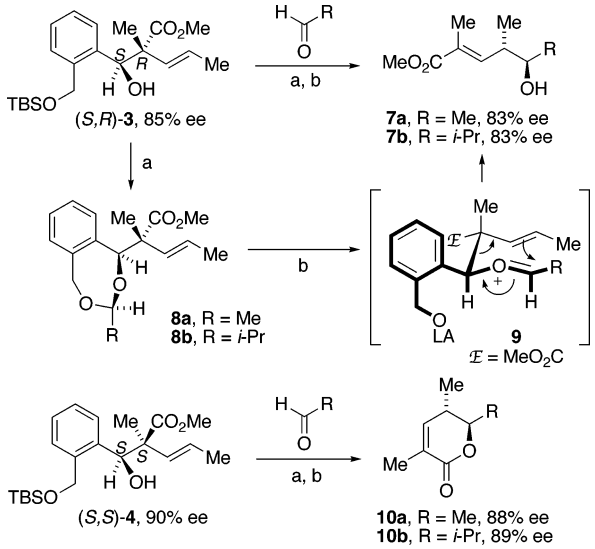
Reactions of (*S*,*R*)-**3** with acetaldehyde or isobutyraldehyde were promoted by $Sn(OTf)_2$[13] to give initial formation of cyclic acetals **8a**−**b** rather than direct bispropionate transfer, but treatment of **8a**−**b** with $SnCl_4$ and Ag_2CO_3 provided products **7a**−**b** (Scheme 2). The *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. Rearrangement 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**

Scheme 1. Preparation and Resolution of Bispropionate Synthons[a]



[a] Conditions: (a) $Pd(OAc)_2$ (6 mol %), PPh_3 (6 mol %), Et_2Zn (5 equiv), THF, 0 to 20 °C, 20 h; (b) silica gel chromatography to separate diastereomers ((±)-**3**, 21% yield; (±)-**4**, 59% yield); (c) Ac_2O (0.75 equiv), Et_3N (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) H_2NNH_2, MeOH (73−75% yield).

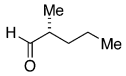
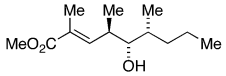
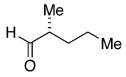
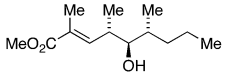
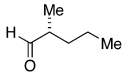
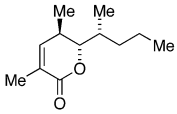
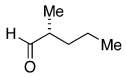
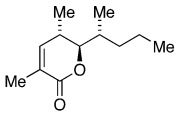
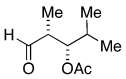
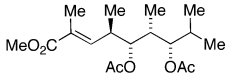
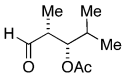
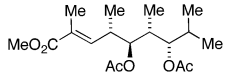
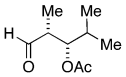
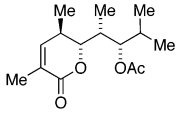
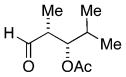
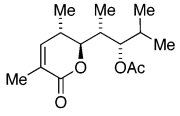
Scheme 2. Initial Results with Simple Aldehydes[a]



[a] Conditions: (a) $Sn(OTf)_2$ (10 mol %), CH_2Cl_2, 20 °C, 1 h; (b) $SnCl_4$ (0.6 equiv), Ag_2CO_3 (2 equiv), $MeNO_2/CH_2Cl_2$, 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**.

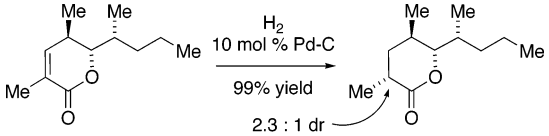
10.1021/ja061082f CCC: $33.50

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

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

[a] Procedure A: TMSOTf (10 mol %), CH_2Cl_2, −78 °C, 4 h, pyridine quench; then $SnCl_4$ (0.6 equiv), Ag_2CO_3 (2 equiv), $MeNO_2/CH_2Cl_2$, 20 °C. Procedure B: same as procedure A, except followed by Ac_2O, 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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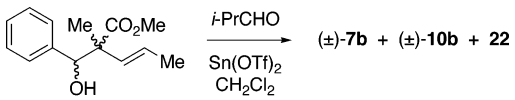
(5) The tethered benzylic silyl ether of synthons **3** and **4** is required not only to drive the oxonia−Cope equilibrium to products but also to provide another polar substituent for chromatographic separation of diastereomers **3** and **4**. $Sn(OTf)_2$-promoted reaction of isobutyraldehyde with the corresponding benzaldehyde-derived **22** (inseparable mixture of stereoisomers) gave a poor yield of racemic products **7b** and **10b** mixed with recovered **22**.



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(6) Racemic compound **2** was formed from commercial (*E*)-2-methylpent-2-enoate methyl ester in two steps: (i) *N*-bromosuccinimide, *hν*, CCl_4, 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.; McKinstry, 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) Ac_2O, pyridine; (c) O_3; Me_2S (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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