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New Chiral Synthons for Efficient Preparation 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 non-racemic 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** might be favored to **IV** 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 corresponds 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

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diastereomer **4**, but isolated yields of the acyclic alcohols **7** are consistently lower than for the production of lactones **10**, as the product alcohols **7** 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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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 provides 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, hv, CCl₄, reflux (Sydnes LK, Skattebøl L, Chapleo CB, Leppard DG, Svanholt KL, Dreiding AS. *Helv. Chim. Acta.* 1975; 58:2061.; (ii) sodium benzoate, DMF, 100 °C (66% yield, two steps).
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15. ^a Preparation of 12: (Z)-(+)-crotyldiisopinocampheylborane, isobutyraldehyde; ^b Ac₂O, pyr.; (c) O₃; Me₂S (52% yield, 3 steps).
16. The corresponding silyl ether-protected analogs 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: Rocca JR, Tumlinson JH, Glancey BM, Lofgren CS. *Tetrahedron Lett.* 1983; 24:1893. Honda T, Yamane S.-i. Ishikawa F, Katoh M. *Tetrahedron.* 1996; 52:12177., and cited reference 4 within.

Figure 1.
Design of bispropionate transfer synthon

^a Conditions: (a) $\text{Pd}(\text{OAc})_2$ (6 mol %), PPh_3 (6 mol %), Et_2Zn (5 equiv), THF, 0 °C to 20 °C, 20 h. (b) silica gel chromatography to separate diastereomers (($\pm$)-**3**, 21% yield; ($\pm$)-**4**, 59% yield). (c) Ac_2O (0.75 equiv), Et_3N (0.75 equiv), (*S*)-(-)-4-dimethylaminopyrindinyl(pentaphenylcyclopentadienyl)iron (Fu's catalyst, 0.8 mol %), *t*-AmOH, 0 °C, 114 h (from ($\pm$)-**3**: (*R,S*)-**3**, 45% yield; (*S,R*)-**5**, 47% yield; from ($\pm$)-**4**: (*R,R*)-**4**, 46% yield; (*S,S*)-**6**, 44% yield). (d) H_2NNH_2 , MeOH (73 – 75% yield).

Scheme 1.

Preparation and resolution of bispropionate synthons ^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**.

Scheme 2.

Initial results with simple aldehydes ^a

Scheme 3.
A short synthesis of invictolide

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

synthon	aldehyde	procedure ^a	product (isolated yield, dr)
(<i>S,S</i>)- 4 (90% ee)	12	A	20 (47% yield, 6 : 1 dr)

^aProcedure 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.