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Asymmetric Synthesis of Hexapropionate Synthons by Sequential Enantiotopic Group Selective Enolization of Meso Diketones

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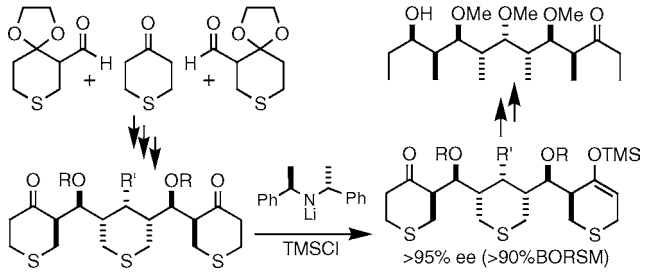
ABSTRACT



Meso 1,9-diketones (six to seven stereocenters) are readily obtained by stepwise or simultaneous two-directional aldol reactions of tetrahydro-4*H*-thiopyran-4-one with a thiopyran-derived aldehyde or dialdehyde. Enantioselective enolizations of these diketones with the lithium amide from (*R*,*R*)-bis(1-phenylethyl)amine occur with simultaneous kinetic resolution to give the mono-TMS enol ethers in >90% yields (BORSM) and >95% ee. The products are applicable to polypropionate synthesis.

Polyketide natural products continue to represent attractive targets for total synthesis in part because of their diverse biological activities and stereochemical complexity.[1] Among the various strategies developed for polypropionate synthesis, the most general require several stereoselective C−C bond-forming reactions to introduce new stereocenters, usually two at a time.[2] Herein, we report a conceptually different approach involving remarkably effective enantiotopic group selective enolizations of readily available meso 1,9-diketones that, in one step, establish up to seven stereocenters in a hexapropionate motif.[3]

We have been developing a strategy for rapid assembly of stereochemically diverse hexapropionate synthons (**3**) based on stepwise or simultaneous two-directional aldol reactions of thiopyranone **2** with thiopyran-derived aldehydes (e.g., **1**, **4**) (Scheme 1).[4] In principle, enantiopure diastereomers of bisaldol adduct **3** can be obtained using nonracemic aldehydes[4d] or via enantioselective aldol reactions;[4e] however, the meso diastereomers require enantioselective desymmetrization[5] to produce nonracemic hexapropionates **5**.

(1) O'Hagan, D. *The Polyketide Metabolites*; Ellis Horwood: New York, 1991.

(2) Reviews: (a) Koskinen, A. M. P.; Karisalmi, K. *Chem. Soc. Rev.* **2005**, *34*, 677−690. (b) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 489−503. For recent examples, see the following articles and references therein: (c) Chau, A.; Paquin, J.-F.; Lautens, M. *J. Org. Chem.* **2006**, *71*, 1924−1933. (d) Paterson, I.; Lyothier, I. *J. Org. Chem.* **2005**, *70*, 5494−5507. (e) Lohse-Fraefel, N.; Carreira, E. M. *Org. Lett.* **2005**, *7*, 2011−2014. (f) Bahadoor, A. B.; Flyer, A.; Micalizio, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 3694−3695. (g) Turks, M.; Huang, X.; Vogel, P. *Chem. Eur. J.* **2005**, *11*, 465−476. (h) Guindon, Y.; Brazeau, J.-F. *Org. Lett.* **2004**, *6*, 2599−2602. (i) Calter, M. A.; Song, W.; Zhou, J. *J. Org. Chem.* **2004**, *69*, 1270−1275.

(3) For recent desymmetrization-based strategies for polyketide synthesis, see: (a) Gerber-Lemaire, S.; Carmona, A. T.; Meilert, K. T.; Vogel, P. *Eur. J. Org. Chem.* **2006**, 891−900. (b) Marchionni, C.; Vogel, P. *Helv. Chim. Acta* **2001**, *84*, 431−472.

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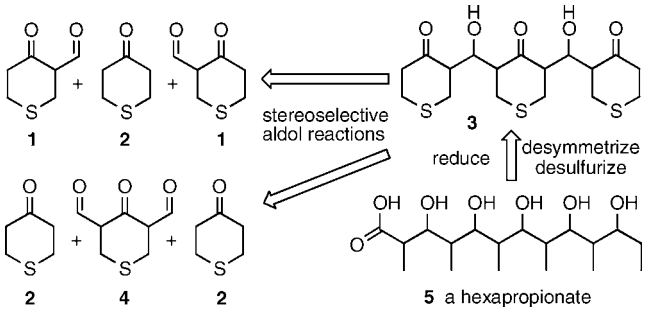
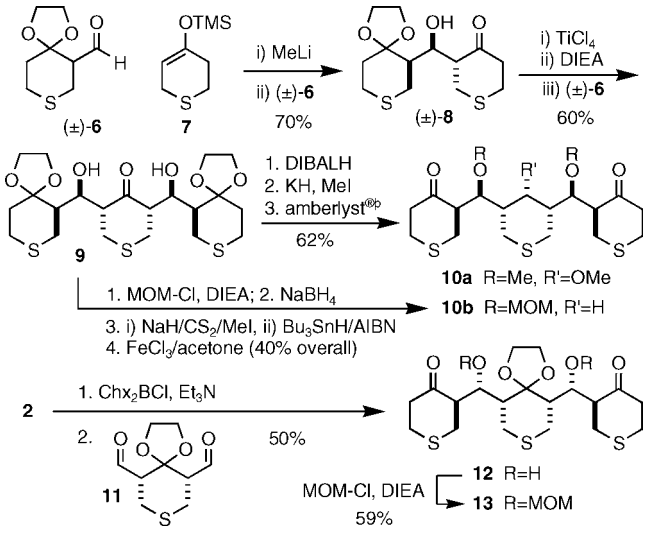
Scheme 1



The desymmetrization of meso bifunctional compounds is an especially powerful strategy for asymmetric synthesis when the enantiotopic functional groups can react sequentially, thereby coupling the initial asymmetric synthesis with a kinetic resolution and producing products with high stereoisomeric purity,[6] even from reactions with moderate group selectivity.[7] Synthetic applications of this strategy have been limited by the inherent challenges involved in the stereoselective synthesis of the requisite meso bifunctional substrates.[8] We previously reported a highly stereoselective synthesis of the meso bisaldol adduct **9** in two steps from the readily available[4c] building blocks **6** and **7** (Scheme 2).[4b]

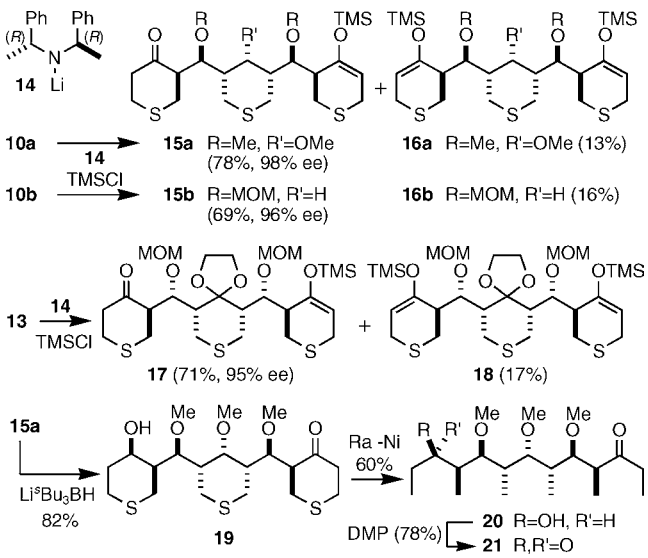
Scheme 2



This is a rare example of a stereoselective synthesis of a meso compound from two racemic reactants (i.e., **6** and **8**).[8a] Alternatively, two-directional aldol reaction of **11**[4e] with **2** via the boron enolate gave the meso bisaldol adduct **12**.[9] An advantage of the thiopyranone template is the possibility of desymmetrization of meso (and chiral) diastereomers of **3** by extension of the well-established enantioselective enolization of six-membered cyclic ketones.[10,11] Ketone enolization is an ideal reaction for sequential enantiotopic group-selective processes because it is both synthetically useful and easily "reversible" (e.g., by protonation).[12] Although enantiotopic group-selective enolization of a meso diketone has not been reported previously,[13] examples of kinetic resolution[14] of chiral ketones by enolborination[11] or by enolization with chiral lithium amides[15] are known.

The aldol adducts **9** and **12** were easily converted into the meso 1,9-diketones **10a**, **10b**, and **13** (Scheme 2). The desymmetrization of **10a** was investigated in detail. We were unable to effect enantioselective enolborination of **10a** under the conditions established[10] for kinetic resolution of 2-methylcyclohexanone.[16] Enantioselective enolization of **10a** was successfully achieved by deprotonation with **14** (Scheme 3).

Scheme 3



Under optimized conditions,[17] the reaction of **10a** with **14** was evaluated at various conversions (Table 1).[18] Using

(4) (a) Ward, D. E.; Man, C. C.; Guo, C. *Tetrahedron Lett.* **1997**, *38*, 2201−2202. (b) Ward, D. E.; Guo, C.; Sasmal, P. K.; Man, C. C.; Sales, M. *Org. Lett.* **2000**, *2*, 1325−1328. (c) Ward, D. E.; Sales, M.; Man, C. C.; Shen, J.; Sasmal, P. K.; Guo, C. *J. Org. Chem.* **2002**, *67*, 1618−1629. (d) Ward, D. E.; Akinnusi, O. T.; Alarcon, I. Q.; Jheengut, V.; Shen, J.; Quail, J. W. *Tetrahedron: Asymmetry* **2004**, *15*, 2425−2430. (e) Ward, D. E.; Jheengut, V.; Akinnusi, O. T. *Org. Lett.* **2005**, *7*, 1181−1184.

(5) Review: Willis, M. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1765−1784.

(6) (a) Sugimoto, T.; Kokubo, T.; Miyazaki, J.; Tanimoto, S.; Okano, M. *Bioorg. Chem.* **1981**, *10*, 311−323. (b) Wang, Y. F.; Chen, C. S.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1984**, *106*, 3695−3696. (c) Dokuzovic, Z.; Roberts, N. K.; Sawyer, J. F.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1986**, *108*, 2034−2039. (d) Schreiber, S. L.; Schreiber, T. S.; Smith, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 1525−1529.

(7) Ward, D. E.; Liu, Y.; Rhee, C. K. *Can. J. Chem.* **1994**, *72*, 1429−1446.

(8) (a) Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 1096−1109. (b) Ward, D. E.; How, D.; Liu, Y. *J. Am. Chem. Soc.* **1997**, *119*, 1884−1894.

(9) In additon to *meso*-**12** (50%), this reaction gave a chiral bisaldol diastereomer (8%) and the known (ref 4e) monaldol adduct (10%). Similar aldol reactions of **11** with the Li enolate of **2** or with **7** (in the presence of Lewis acids) gave only the monoaldol adduct. The monoaldol adduct exists as stable cyclic hemiacetal (from cyclization of the δ-hydroxyaldehyde) and is resistant to a second aldol reaction (for related examples, see: De Brabander, J.; Oppolzer, W. *Tetrahedron* **1997**, *53*, 9169−9202). The formation of bisaldol adducts from **11** using the boron enolate of **2** presumably results because the initially formed aldol borinate adduct is sufficiently stable to undergo a second aldol in preference to cyclization.

Table 1. Enantioselective Enolization of **10a** with **14**[a]

			isolated yields (%)		
entry	**14** (equiv)	^{1}H NMR ratio[b] **10a**:**15a**:**16a**	**10a**	**15a** (% ee)[c]	**16a**
1	0.5[d]	71:26:3	70	22 (86)	3
2	1.0[d]	19:69:12	20	61 (90)	12
3	1.4[d]	2:74:24		73 (92)	22
4	0.5	86:14:0.5	78	15 (81)	
5	1.2	52:46:10			
6	1.3	26:67:8	25	61 (94)	8
7	1.4	14:76:9			
8	1.5	4:80:15		78 (98)	13
9	1.7	0:62:38		58 (>98)	34

[a] A THF solution of **14** or **14**·LiCl at −78 °C was rapidly cannulated to a THF solution of **10** (0.2−0.3 mmol) and TMSCl (10 equiv) at −100 °C. [b] Crude products after workup. [c] Determined by ^{1}H NMR in the presence of (+)-Eu(hfc)$_3$/CF_3CO_2Ag. [d] Using **14**·LiCl (ref 19).

similar conditions, reactions using **14** were more selective than those using **14**·LiCl[19] (cf. entries 2 and 6). As expected,[6,7] the ee of **15a** increases with increasing conversion due to kinetic resolution in the formation of **16a** from **15a** (cf. entries 1−3; 4, 6, 8). At low conversions, the er of **15a** should approximate the enantiotopic group selectivity of the reaction. Curiously, reactions using small amounts of **14** or **14**·LiCl (e.g., entries 1 and 4) performed poorly, giving **15a** in low ee accompanied by an amount of **16a** that far exceeded expectations.[20] To assess the reaction selelctivity, the experimental data was compared to those calculated[7] for an idealized group selective process at various selectivities. The observed product distribution (**15a** and **16a**) and ee of **15a** formed in the reaction of **10a** with **14** correspond closely with those predicted[7] from the model reaction with an enantioselectivity of ca. 17:1 (Figure 1).[21,22]

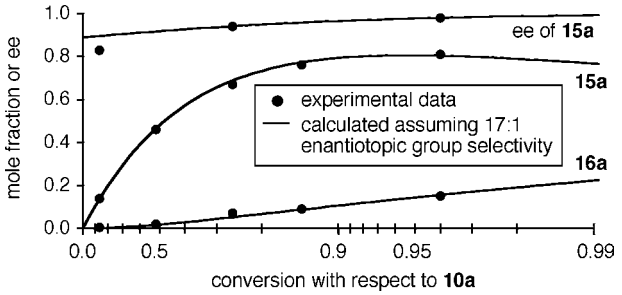


Figure 1. Observed and calculated mole fractions of **15a** and **16a** and ee of **15a** produced in the reaction of **10a** with **14**/TMSCl as a function of conversion of **10a**.

Although an enantioselectivity of 17:1 is somewhat lower than that observed for deprotonation of C_s-symmetrical cyclohexanones under similar conditions,[10,23] **15a** is easily obtained with greater enantiopurity because of the ee enhancement feature[6,7] of sequential enantiotopic group selective reactions. Using 1.5 equiv of **14**, the mono enol ether **15a** was obtained in 78% yield and 98% ee; however, synthetically useful results (>60% yield, >95% ee) were obtained over a broad range of conversions. Reactions of **14** with **10b** and **13** under the optimized conditions gave the corresponding mono enol ethers **15b** and **17** in good yields and with excellent enantiopurities. These processes are extremely efficient (>90% yield based on recovered diketone) because the bis enol ether byproducts **16a**, **16b**, and **18** are easily recycled to diketones **10a**, **10b**, and **13**, respectively, on treatment with $HF_{(aq)}$ (95% yields).

To demonstrate the feasibility of this approach to polypropionates, **10a** was converted into the acyclic ketol **20** by treatment with Li^{s}Bu$_3$BH followed by Raney Ni desulfurization (Scheme 3). Oxidation of **20** gave *meso*-**21**, indicating that desulfurization occurs without loss of stereochemical integrity.

(10) Review: O'Brien, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1439−1457.

(11) Ward, D. E.; Lu, W.-L. *J. Am. Chem. Soc.* **1998**, *120*, 1098−1099.

(12) Reversibility facilitates recycling which improves both the efficiency and efficacy of these processes and is especially important when enantioselectivity is modest. For a discussion, see ref 7.

(13) Examples of enantioselective deprotonation where enantiotopic hydrogens are activated by different (but not independent) carbonyl groups are known. Imides: (a) Adams, D. J.; Simpkins, N. S. *Chem. Commun.* **1998**, 1605−1606. (b) Adams, D. J.; Blake, A. J.; Cooke, P. A.; Gill, C. D.; Simpkins, N. S. *Tetrahedron* **2002**, *58*, 4603−4615. (c) Gill, C. D.; Greenhalgh, D. A.; Simpkins, N. S. *Tetrahedron* **2003**, *59*, 9213−9230. (d) Bennett, D. J.; Pickering, P. L.; Simpkins, N. S. *Chem. Commun.* **2004**, 1392−1393. *cis*-Piperidine-2,6-dicarboxylic acid diesters: (e) Goldspink, N. J.; Simpkins, N. S.; Beckmann, M. *Synlett* **1999**, 1292−1294. (f) Clive, D. L. J.; Wang, J.; Yu, M. *Tetrahedron Lett.* **2005**, *46*, 2853−2855. See ref 13b for an example of a *meso*-bicyclo[3.1.0]hexane-2,4-dione and a *meso*-1,2-cyclopropane-1,2-dicarboxylic acid diester.

(14) Kinetic resolution is equivalent to an enantiotopic group selective reaction; i.e., groups on enantiomeric substrates are enantiotopic by external comparison. See: Mislow, K.; Raban, M. *Top. Stereochem.* **1969**, *1*, 1−38.

(15) (a) Kim, H. D.; Kawasaki, H.; Nakajima, M.; Koga, K. *Tetrahedron Lett.* **1989**, *30*, 6537−6540. (b) Bambridge, K.; Simpkins, N. S.; Clark, B. P. *Tetrahedron Lett.* **1992**, *33*, 8141−8144. (c) Bambridge, K.; Clark, B. P.; Simpkins, N. S. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2535−2541.

(16) Unreacted **10a** was recovered after treatment with (−)-chlorobis(isopinocampheyl)borane and sparteine (CH_2Cl_2, −78 °C). Enolborination of **10a** was possible with chlorodicyclohexylborane and sparteine but the enantioselectivity was very low (<3:1).

(17) A THF solution of **14** (0.5−2 equiv) at −78 °C was rapidly cannulated to a THF solution of **10a** (0.2−0.3 mmol) and TMSCl (10 equiv) at −100 °C. Reactions conducted at −78 °C were very capricious and much less enantioselective. Slow addition of **14** was less enantioselective. External quench (i.e., addition of TMSCl after addition of **14**) gave considerably lower conversions.

(18) The yield and ee of **15a** are dependent on the reaction enantioselectivity and the conversion (see ref 7). Conversion of **10a** was modulated by varying the amount of **14** added. The conversion with respect to amount of **14** added varied from 0.5 to 0.9 and was scale dependent.

(19) Generated in situ from reaction of the corresponding amine hydrochloride with 2 equiv of BuLi. (a) Hall, P. L.; Gilchrist, J. H.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 9571−9574. (b) Mair, F. S.; Clegg, W.; O'Neil, P. A. *J. Am. Chem. Soc.* **1993**, *115*, 3388−3389. (c) Majewski, M.; Lazny, R.; Nowak, P. *Tetrahedron Lett.* **1995**, *36*, 5465−5468.

(20) The product distributions in entries 1 and 4 are similar to expecations for a nonselective reaction (e.g., using LDA as base). By contrast, a reaction with 9:1 group selectvity would not be expected to give 3% of the bis-product until ca. 50% conversion (ref 7).

(21) The expermental data in Figure 1 is taken from entries 4−8 in Table 1 with the mole fractions of **10a**, **15a**, and **16a** as determined by ^{1}H NMR of the crude reaction mixture after workup. Conversion is 1 minus the mole fraction of **10a**.

(22) See the Supporting Information for details.

(23) Lower selectivity may result because the initial coordination of lithium amide to ketone is an enantioselective step for C_s symmetrical diketones but not for C_s symmetrical ketones. If the enantioselectivity in the coordination step is lower than that in the deprotonation step (as expected) then dissociation of the complex must be much faster than deprotonation to prevent attenuation of the selectivity.

In summary, we have demonstrated enantiotopic group selective enolizations of meso 1,9-diketones that occur with simultaneous kinetic resolution to give the corresponding mono-TMS enol ethers with enhanced enantiopurity and in excellent overall yields. Applications of these products in polypropionate synthesis will be reported in due course.

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds synthesized. This material is available free of charge via the Internet at http://pubs.acs.org.

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