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Thiopyran Route to Polypropionates: Aldol Diastereoselectivity of Linear and Two-Directional Iterative Homologations

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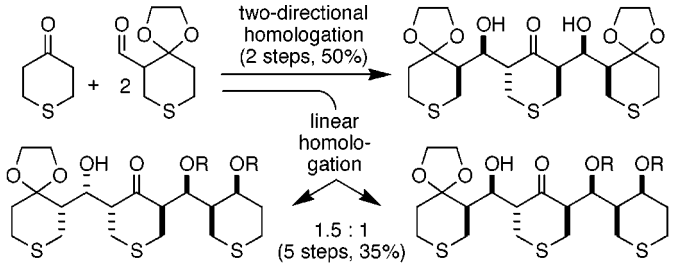
ABSTRACT



Aldol reaction of tetrahydro-4*H*-thiopyran-4-one with racemic 1,4-dioxa-8-thiaspiro[4.5]decane-6-carboxaldehyde is easily controlled to give the 2,3-*anti*-3,4-*syn* or the 2,3-*syn*-3,4-*syn* adduct. Aldol homologations of these *β*-hydroxy ketones with the same aldehyde occur with considerable mutual kinetic enantioselection (MKE) and, in each case, selectively give one of the eight possible diastereomers. Similar reactions of related *β*-methoxy ketones are also very diastereoselective but proceed without significant MKE, resulting in two diastereomers. The adducts can be used for polypropionate synthesis.

Cyclic sulfides are useful templates to facilitate and control various chemical transformations.[1] In particular, thiopyran-derived scaffolds have been used to construct a variety of synthetic targets.[2] In this regard, an attractive strategy for polypropionate synthesis involves aldol reaction of tetrahydro-4*H*-thiopyran-4-one derivatives followed by desulfurization.[3,4] We have previously established highly stereoselective methods for the preparation of either **3** or **4** from the reaction of **1** with **2** (Scheme 1).[4] Herein we report the aldol diastereoselectivities for linear and two-directional homologations of **3** and **4** with **2**.

Initial efforts focused on the two-directional aldol homologation of unprotected **3** with **2**.[5,6] Reaction of **3** with

(1) (a) Belen'kii, L. I. In *Chemistry of Organosulfur Compounds*; Belen'kii, L. I., Ed.; Ellis Horwood: Chichester, 1990; p 193. (b) Ingall, A. H. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 3, p 885. (c) Kuthan, J.; Sebek, P.; Böhm, S. In *Advances in Hetereocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: San Diego, 1994; Vol. 59, p 179. (d) *Chemistry of Heterocyclic Compounds*, Vol. 44, Part 4: Thiophene and its Derivatives; Gronowitz, S., Ed.; Wiley: New York, 1991.

(2) Review: (a) Vedejs, E.; Krafft, G. A. *Tetrahedron* **1982**, *38*, 2857. (b) Vedejs, E. *Stud. Nat. Prod. Chem.* **1991**, *8 (*Stereoselective Synthesis, Part E*)*, 205. (c) Ward, D. E.; Gai, Y. *Can. J. Chem.* **1997**, *75*, 681. (d) Ward, D. E.; Gai, Y.; Lai, Y. *Synlett* **1995**, 261 and references therein.

(3) (a) Woodward, R. B.; Logusch, E.; Nambiar, K. P.; Sakan, K.; Ward, D. E.; Au−Yeung, B.-W.; Balaram, P.; Browne, L. J.; Card, P. J.; Chen, C. H.; Chênevert, R. B.; Fliri, A.; Frobel, K.; Gais, H.-J.; Garratt, D. G.; Hayakawa, K.; Heggie, W.; Hesson, D. P.; Hoppe, D.; Hoppe, I.; Hyatt, J. A.; Ikeda, D.; Jacobi, P. A.; Kim, K. S.; Kobuke, Y.; Kojima, K.; Krowicki, K.; Lee, V. J.; Leutert, T.; Malchenko, S.; Martens, J.; Matthews, S. R.; Ong, B. S.; Press: J. B.; RajanBabu, T. V.; Rousseau, G.; Sauter, H. M.; Suzuki, M.; Tatsuta, K.; Tolbert, L. M.; Truesdale, E. A.; Uchida, I.; Ueda, Y.; Uyehara, T.; Vasella, A. T.; Vladuchick, W. C.; Wade, P. A.; Williams, R. M.; Wong, H. N.-C. *J. Am. Chem. Soc.* **1981**, *103*, 3210−3213. (b) Hayashi, T. *Tetrahedron Lett.* **1991**, *32*, 5369.

(4) Ward, D. E.; Man, C. C.; Guo, C. *Tetrahedron Lett.* **1997**, *38*, 2201.

(5) We were unable to convert the hydroxyl group in **3** or **4** to an ether without extensive decomposition.

(6) For studies on aldol reactions of *β*-hydroxy ketones, see: (a) McCarthy, P. A.; Kageyama, M. *J. Org. Chem.* **1987**, *52*, 4681. (b) Martin, V. A.; Murray, D. H.; Pratt, N. E.; Zhao, Y.; Albizati, K. F. *J. Am. Chem. Soc.* **1990**, *112*, 6965. (c) Pratt, N. E.; Zhao, Y.; Hitchcock, S.; Albizati, K. F. *Synlett* **1991**, 361. (d) Luke, G. P.; Morris, J. *J. Org. Chem.* **1995**, *60*, 3013.

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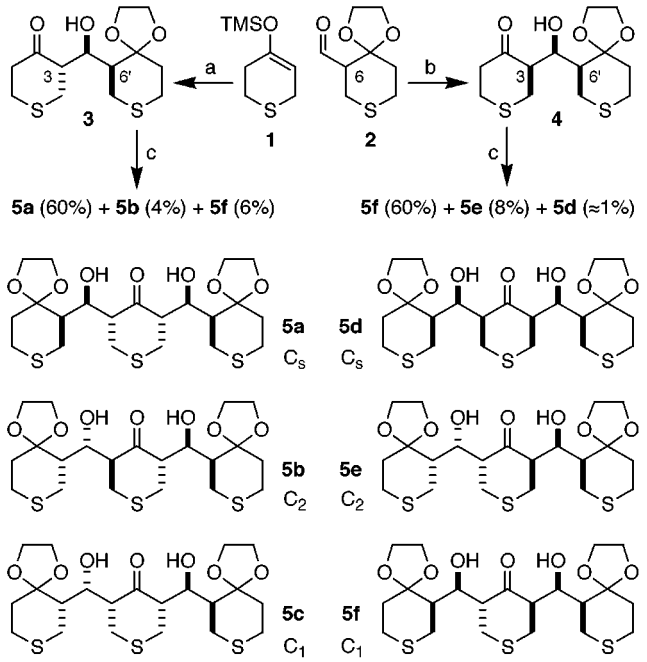
Scheme 1[a]



[a] Reagents: (a) i. MeLi/ether (1 equiv, 0−22 °C, 1 h), ii. **2**/THF (0.7 equiv, −78 °C, 30 s); (b) i. $TiCl_4/CH_2Cl_2$ (1 equiv, −78 °C, 10 min), ii. **1** (1.5 equiv, −78 °C, 1 h); (c) i. $TiCl_4/CH_2Cl_2$ (1.1 equiv, −78 °C, 2 min), ii. DIEA (2.4 equiv, −78 °C, 2 h), iii. **2** (1.2 equiv, −78 °C, 2.5 h).

LDA (2.2 equiv) followed by addition of **2** or benzaldehyde did not produce the expected aldol products.[6c] Successful aldol reaction of **2** with tetrahydrothiopyran-4-one required use of the "amine-free" Li enolate prepared from **1** and MeLi;[4] however, reactions of a trimethylsilyl enol ether derivative of **3**[7] with **2** under those conditions (or in the presence of $TiCl_4$) also failed to give aldol adducts in our hands. Finally, under optimized conditions, addition of *t*-BuLi (1.0 equiv)[8] to a THF solution of **3** at −78 °C followed by addition of **2** gave a 3:1 mixture of **5a** and **5b** in 30% combined yield after workup and chromatography.[9] Under the same conditions, a 3:1.5:1 mixture of **5f**, **5d**, and **5e**, respectively, was obtained in 30% yield from the reaction of **4** with **2**.[9] Bisaldol products **5** were obtained with much higher diastereoselectivity and with improved yields using Ti(IV) enolates (Scheme 1).[6d] Reaction of **2** (1.2 equiv) with the putative Ti enolate generated by treatment of **3** with $TiCl_4$ (1.1 equiv) and then diisopropylethylamine (DIEA, 2.4 equiv) was extremely clean, giving **5** (65−75%)[10] along with recovered **3** (25%) and **2** (35%). The bisaldol product was largely **5a**, but careful fractionation yielded the minor diastereomers **5b** (ca. 4% from **3**) and **5f** (ca. 6% from **3**). A similar reaction of **2** with the Ti enolate of **4** gave **5f** (60%) and **5e** (8%) along with recovered starting materials.[11]

Sequential Ti(IV)-mediated aldol reactions of tetrahydrothiopyran-4-one with **2** produced bisaldols in "one pot" and in good yield but with much lower diastereoselectivity.[12]

There have been few studies[6] of aldol reactions of β-hydroxy ketones and, to the best of our knowledge, none involving the reaction of a racemic aldehyde with a racemic β-hydroxy ketone. In principle, the reaction of (±)-**2** with (±)-**3** (or (±)-**4**) can produce up to eight diastereoisomeric aldol adducts.[13] Examination of the product distribution[14] reveals that not only does the reaction proceed with remarkable diastereoselectivity (**5a** is 85% of the total aldol products) but also with significant mutual kinetic enantioselection (MKE)[15a] (i.e., [**5a** + **5f**]:**5b**, 16:1).[14,15] Thus, both *meso* adduct **5a** and racemic adduct **5f** result from the two possible combinations of an enantiomer of **2** with an enantiomer of **3** where the absolute configurations at C-6 of **2** and C-3 of **3** are *unlike*.[16] These enantiotopic reactions are highly diastereoselective in favor of **5a** (90% ds); of the four possible diastereomers, **5a** and **5f** are produced in a 10:1 ratio. Alternatively, **5b** results from a *like* combination of enantiomers of **2** and **3**, and although possibly very diastereoselective also,[17] these reactions are less facile by a

(7) The TMS enol ether TMS ether of **3** was prepared in 75% yield by reaction with excess LDA in the presence of TMSCl in THF at −78 °C.

(8) The exact amount of *t*-BuLi added was controlled by the red end point reached in the presence of 1,10-phenanthroline (Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165).

(9) The relative stereochemical configurations for bisaldols **5** were assigned by DIBAL-H reduction and conversion of the resulting triol into an acetonide and/or carbonate derivative (Scheme 2). Symmetrical adducts (e.g., **5a**,**b**,**d**,**e**) were easily distinguished from unsymmetrical ones (e.g., **5c**,**f**) by ^{1}H and ^{13}C NMR spectroscopy. The C_s symmetrical adducts (e.g., **5a**,**d**) were distinguished from the C_2 symmetrical ones (e.g., **5b**,**e**) by NMR of the corresponding triols resulting from DIBAL-H reduction; C_s symmetric bisaldols give C_s symmetric triols but C_2 symmetric aldols give unsymmetrical triols. Analysis of the ^{1}H and ^{13}C NMR spectra of the acetonides and/or cyclic carbonates (i.e., **6**−**10**) derived from the triols established the relative configuration of the four stereogenic centers on the tetrahydrothiopyrano[4,3-*d*]-1,3-dioxin ring system (**6a** from the symmetrical triol from **5a**; **8a** and **10a** from the unsymmetrical triol from **5b**; **7a** from the symmetrical triol from **5d** (see note 11); **13a** from the unsymmetrical triol from **5e**; **9a**, **10a**, and **10b** from the unsymmetrical triol from **5f**). Particularly useful in this analysis were the three $^3J_{HH}$ among HC-4, 4a, 8a, and 8. Acetonides from 1,3-*syn* vs 1,3-*anti* diols are readily distinguished by the δ_C's for the methyl groups (Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511). Because the stereochemical integrity of the 1,4-dioxa-8-thiaspiro[4.5]decyl fragments in **3** or **4** is maintained during reaction with **2** (isomerization at C-6′ by retro-aldol is ruled out because **3** and **4** give different products and are recovered intact), the relative configuration of the cyclic derivative of the triol together with the symmetry (i.e., C_s or C_2) of the starting bisaldol readily established the structures for **5a**,**b**,**d**,**e**. The triol derived from unsymmetrical aldol adduct **5f** gave a single acetonide and two carbonates firmly establishing the "middle" four of the six stereocenters. The relative configurations of the 1,4-dioxa-8-thiaspiro-[4.5]decyl fragments are assigned with confidence as shown because **5f** is produced both from **3** and from **4** and this configuration is consistent with the exclusive 3,4-*syn* diastereoselectivity firmly established for all other aldol products of **2** (note: with 3,4-*syn* aldol diastereoselectivity, only six bisaldol products (i.e., **5a**,**b**,**c**,**d**,**e**,**f**) are possible from **1** and **2**).

(10) Bisaldols **5** were somewhat prone to retro-aldol during workup, but the isolated products were stable.

(11) A small amount (ca. 1%) of a third bisaldol was detected but not isolated. This product was tentatively identified as **5d** because DIBAL-H reduction of a sample of **5f** containing ca. 10% of **5d** led to the isolation of a symmetric triol (8%) which gave an acetonide identified as **7a**.

(12) Sequential addition of $TiCl_4$, DIEA, **2**, DIEA, and **2** to a solution of tetrahydrothiopyran-4-one in CH_2Cl_2 at −78 °C gave **5f** (30%), **5a** (20%), **5e** (4%), **3** (20%), and **4** (15%).

(13) Assuming no isomerization of the ketone.

(14) (a) Horeau, A. *Tetrahedron* **1975**, *31*, 1307. (b) Heathcock, C. H.; Pirrung, M. C.; Lampe, L.; Buse, C. T.; Young, S. D. *J. Org. Chem.* **1981**, *46*, 2290.

(15) Reviews: (a) Oare, D. A.; Heathcock, C. H. *Top. Stereochem.* **1989**, *19*, 227. (b): Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249

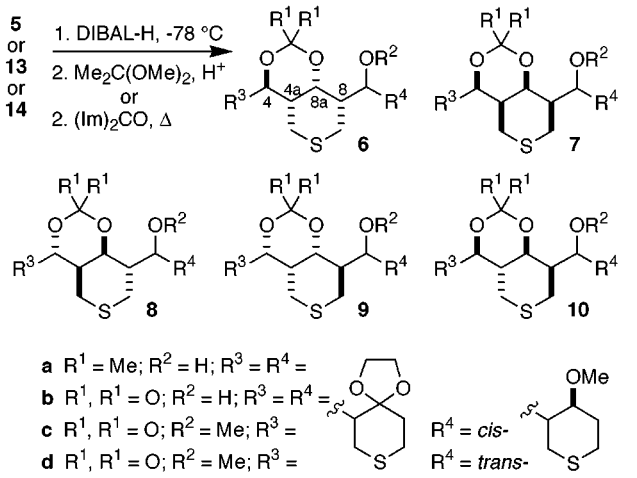
(16) (a) That is, (6*R*)-**2** + (3*S*,1′*R*,6′*S*)-**3** or (6*S*)-**2** + (3*R*,1′*S*,6′*R*)-**3**. (b) Seebach, D.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 654.

(17) Alternative products of this reaction (e.g., **5c**) were not detected.

factorof ca. 16 compared to the *unlike* combination.[14] By contrast, the reaction of **2** with **4** showed *like* selectivity (i.e., [**5f** + **5d**]:**5e**, 7.5:1).

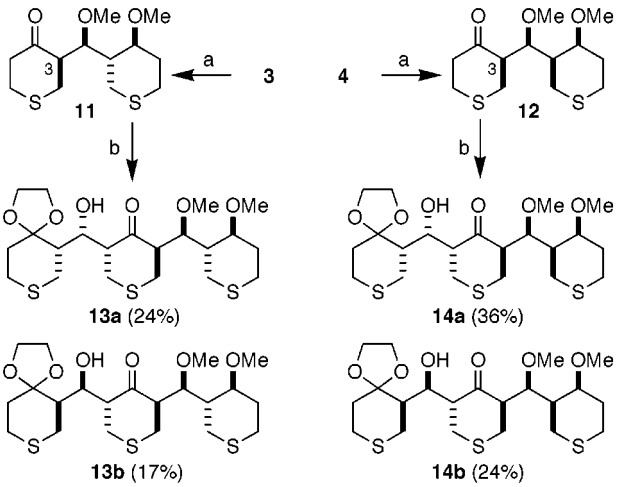
To investigate linear aldol homologation of **1** with **2**, the initial aldol adducts **3** and **4** were converted into **11** and **12**, respectively, by standard methods (Scheme 3). Treatment of **12** with $TiCl_4$ (1.1 equiv) and DIEA (1.2 equiv) at −78 °C followed by addition of **2** (1.2 equiv) under conditions analogous to those described above gave adducts **14a** (36%) and **14b** (24%) along with recovered **2** and **12**.[18] Addition of **2** to the "amine-free" lithium enolate of **12** also gave **14a** (29%) and **14b** (23%),[18] but attempted reaction of the trimethylsilyl enol ether of **12** with **2** in the presence of $TiCl_4$ failed to give adducts.[19] Under similar conditions, reaction of **11** with **2** gave **13a** (24%) and **13b** (17%) using the Ti(IV) enolate and the same products in 21% and 22% yields, respectively, using the "amine-free" Li enolate.[18] The structures for aldol adducts **13** and **14** were determined by conversion to the corresponding carbonates (Scheme 2).[20]

Scheme 2



Aldol reaction of (±)-**11** or (±)-**12** with (±)-**2** can also produce up to eight diastereomers.[13] The structures of the adducts reveal that **13a** results from the *unlike* combination of **2** and **11** whereas **13b** results from the *like* combination.[16b,21] Both *like* and *unlike* combinations are highly diastereoselective; however, in contrast to **3** and **4**, the level of mutual kinetic enantioselection in the reaction of **11** with **2** is modest and results in only a slight preference (1.5:1) for the *unlike* combination (i.e., **13a**). Similarly, the *like* and *unlike* aldol couplings of **2** with **12** are highly diastereoselective and occur with only a slight kinetic preference for the *unlike* combination (i.e., **14a**) (Scheme 3).[21]

Scheme 3[a]



[a] Reagents: (a) i. DIBAL-H (2 equiv, THF, −78 °C, 3 h; 80−90%), ii. KH, MeI (95%), iii. Amberlyst-15, acetone (80−85%); (b) i. $TiCl_4$ (1.1 equiv, CH_2Cl_2, −78 °C, 2 min), ii. DIEA (1.2 equiv, −78 °C, 2 h), iii. **2** (1.2 equiv, −78 °C, 2.5−4 h).

The aldol diastereoselectivities for the reactions of **2** with the Li and Ti enolates of **3**, **4**, **11**, and **12** are summarized in Table 1. Mutual kinetic enantioselection results from high diastereoface selectivities for both the aldehyde and the

Table 1. Diastereoselectivities for Aldol Reactions of Racemic **2** with Racemic **3**, **4**, **11**, and **12**

			major	diastereoselectivity		
no.	reactants[a] (MKE)	reactn mode[b]	product (% ds)[c]	aldehyde face[d]	enolate face[e]	rel. topicity
1	**2** + **3** (Li)	*like*	**5b**	*ul*-1,2	*lk*-1,3	*anti*
	(*unlike*, 3:1)	*unlike*	**5a**	*ul*-1,2	*ul*-1,3	*anti*
2	**2** + **3** (Ti)	*like*	**5b**	*ul*-1,2	*lk*-1,3	*anti*
	(*unlike*, 16:1)	*unlike*	**5a**(90)	*ul*-1,2	*ul*-1,3	*anti*
3	**2** + **4** (Li)	*like*	**5f**(65)	*ul*-1,2	*lk*-1,3	*anti*
	(*like*, 4.5:1)	*unlike*	**5e**	*ul*-1,2	*lk*-1,3	*syn*
4	**2** + **4** (Ti)	*like*	**5f**(95)	*ul*-1,2	*lk*-1,3	*anti*
	(*like*, 7.5:1)	*unlike*	**5e**	*ul*-1,2	*lk*-1,3	*syn*
5	**2** + **11** (Li)	*like*	**13b**	*ul*-1,2	*lk*-1,3	*anti*
	(1:1)	*unlike*	**13a**	*ul*-1,2	*lk*-1,3	*syn*
6	**2** + **11** (Ti)	*like*	**13b**	*ul*-1,2	*lk*-1,3	*anti*
	(*unlike*, 1.5:1)	*unlike*	**13a**	*ul*-1,2	*lk*-1,3	*syn*
7	**2** + **12** (Li)	*like*	**14b**	*ul*-1,2	*lk*-1,3	*anti*
	(*unlike*, 1.2:1)	*unlike*	**14a**	*ul*-1,2	*lk*-1,3	*syn*
8	**2** + **12** (Ti)	*like*	**14b**	*ul*-1,2	*lk*-1,3	*anti*
	(*unlike*, 1.5:1)	*unlike*	**14a**	*ul*-1,2	*lk*-1,3	*syn*

[a] Enolate type is indicated in parentheses. [b] See note 21. [c] Only one diastereomer isolated unless otherwise noted. [d] See note 22. [e] Cf. note 23.

(18) The isolated yields of adducts were >90% on the basis of recovered starting materials.

(19) TMS enol ethers were obtained in >80% yield by reactions of **11** or **12** with LDA in the presence of TMSCl. The corresponding Li enolates were generated by subsequent reactions with MeLi.

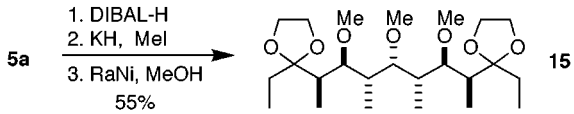
(20) **9d** from **13a**; **10d** from **13b**; **9c** from **14a**; **10c** from **14b**. Analysis of the ^{1}H NMR spectra of the carbonates **9c**,**d** and **10c**,**d** established the relative stereochemical configurations at C-4, 4a, 8, 8a and thereby the corresponding stereocenters in the precursor aldols. The remaining stereocenters are assigned by assuming no isomerization of the starting ketones (**11** and **12** are recovered in high yield from the aldol reactions) and the usual 3,4-*syn* diastereoselectivity for aldol reactions with **2**.

(21) *like* and *unlike* are with respect to stereochemical configurations at C-6 of **2** and C-3 of **3**, **4**, **11**, or **12**. See ref 16b.

ketone coupled with high relative topicity (i.e., simple diastereoselectivity) for the aldol reaction. Thus, all three diastereoselectivities are mutually reinforcing (matched) in one combination (e.g., *unlike* for **2** + **3** and *like* for **2** + **4**); in the other combination (mismatched), only two of the three diastereoselectivities can be accommodated. Accordingly, the level of mutual kinetic enantioselection is limited by the lowest of the three types of diastereoselectivity in this reaction.[14,15] Aldehyde **2** shows very high *ul*-1,2[16b,22] diastereoface selectivity in all reactions. Comparing the major products from the *like* and *unlike* reaction modes indicates that both the Li and Ti enolates of **3** are *anti* selective but the Ti enolate shows much higher *ul*-1,3[16b,23] diastereoface selectivity. By contrast, both Li and Ti enolates of **4** are highly *lk*-1,3 diastereoface selective but the Ti enolate is more *anti* selective. The much greater mutual kinetic enantioselection displayed by the Ti enolates of **3** and **4** compared to those of the Li analogues is attributed to greater diastereoface and *syn*/*anti* selectivities in the former.[24] Interestingly, the diastereotopic face selectivity for the enolate corresponding to **3** is opposite to that for **4**. Both products from **11** and **2** (**13a** and **13b**) result from aldol reactions with the same diastereoface selectivities with respect to both the aldehyde (*ul*-1,2 for **2**)[16b] and the enolate (*lk*-1,3 for both Li and Ti enolates of **11**)[16b] but with different relative topicities (i.e., *syn* for **13a**, *anti* for **13b**). Similar conclusions apply to adducts **14a** and **14b** from the reaction of **12** with **2**. This suggests that the modest mutual kinetic enantioselection observed in these reactions results from poor *syn*/*anti* aldol diastereoselectivity for the both the Li and Ti enolates of **11** and **12**.

It is instructive to compare β-hydroxy ketone **4** to the structurally related β-methoxy ketone **12**. Reactions of the Ti enolates of these racemic ketones with (±)-**2** show the same aldol diastereoselectivity in both the *like* (cf. **5f** and **14b**) and *unlike* (cf. **5e** and **14a**) enantiomer combinations.[21] However, the high *anti* selectivity of **4** results in a substantial (7.5:1) kinetic preference for the *like* combination whereas **12** is slightly *syn* selective and shows modest mutual kinetic enantioselection (1.5:1) in favor of the *unlike* combination. By contrast, a study of aldol reactions of 2-methylpropanal with the Li (*Z*)-enolates of various *O*-protected derivatives of 5-hydroxy-4,6-dimethyl-3-heptanone indicated that β-alkoxy ketones gave much greater simple diastereoselectivity (*syn* selective) than the related β-hydroxy ketone.[6a] Similarly, aldol reactions of boron and Li (*E*)-enolates of the same ketone with chiral aldehydes showed high *anti* selectivity in both the *like* and *unlike* enantiomer combinations.[25]

In conclusion, polypropionate assembly using thiopyran templates results in aldol diastereoselectivities substantially different from those observed in related reactions of *acyclic* chiral aldehydes with *acyclic* chiral ketones. Further work is necessary to clearly establish the scope of this approach, but our preliminary results already indicate that a variety of stereochemical arrays can be produced with high diastereoselectivity in only two C−C bond-forming steps.[26] For application to polypropionate synthesis, desulfurization without loss of stereochemical integrity is necessary; to further demonstrate the feasibility of this process,[3a,4] *meso* **5a** was converted into *meso* **15**.



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Supporting Information Available: General procedures and spectroscopic data for **5**−**10** and **13**−**15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) That is, addition to the *Si* face of (6*R*)-**2** and the *Re* face of (6*S*)-**2**.

(23) That is, *ul*-1,3 is addition to the *Si* face of the enolate of the 3*R* enantiomer of **3** (and **4**, **11**, **12**) or to the *Re* face of 3*S* enantiomer(s).

(24) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpí, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047.

(25) Evans, D. A.; Yang, M. G.; Dart, M. J.; Duffy, J. L. *Tetrahedron Lett.* **1996**, *37*, 1957. The *O*-TBDMS derivative of the ketone and the *O*-PMB derivative of 3-hydroxy-2,4-dimethylpentanal were used. MKE was not determined as enantiopure substrates were employed.

(26) In addition to the *meso* **5a**, either enantiomer of **5b**, **5e**, **5f**, **13a**, **13b**, **14a**, or **14b** is (in principle) available using enantiopure **2**.