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Thiopyran Route to Polypropionates: Exploiting and Overcoming Double Stereodifferentiation and Mutual Kinetic Enantioselection in Aldol Couplings of Chiral Fragments

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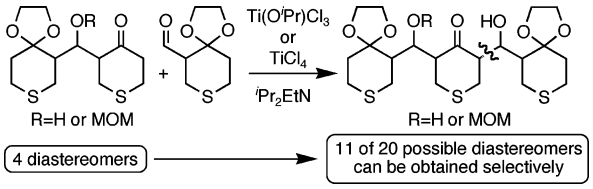

The aldol reaction of tetrahydro-4*H*-thiopyranone with 1,4-dioxa-8-thiaspiro[4.5]decane-6-carboxaldehyde (**I**) gives four possible diastereomeric adducts (**II**). Aldol reactions of **I** with each of the diastereomers of **II** and their corresponding methoxymethyl ethers **III** via the Ti enolates were investigated. Using racemic reactants, reactions with **II** proceeded with high levels of mutual kinetic enantioselection (MKE) and double stereodifferentiation (DS) to give one of the eight possible bisaldol adducts. Similar reactions of **III** proceeded with low levels of MKE and DS and gave two bisaldol adducts, one from each of the possible combinations of enantiomeric reactants. By extension, 11 of the 20 possible diastereomers of the bisaldol adduct could be obtained selectively. These adducts are useful for polypropionate synthesis.

Introduction

The diverse biological activities and stereochemical complexity of polypropionate natural products have attracted the attention of synthetic chemists for more than 30 years.[1,2] Numerous successful synthetic strategies have evolved during this time, and these have contributed substantially to the theory and practice of modern organic chemistry (e.g., acyclic stereocontrol).[3,4] In Nature, polypropionate motifs are synthesized by polyketide synthase (PKS) enzymes that effect iterative addition of methylmalonyl CoA to the growing polyketide chain and introduce (up to) two new stereocenters per cycle.[5] Similarly, synthetic chemists have devised a number of iterative methods that, in principle (i.e., with versatile and reliable stereoselectivity), could produce any of the possible stereoisomers from common precursors.[6,7] However, most of the reported syntheses of polypropionates follow a convergent path involving the stereoselective synthesis and then coupling of chiral (nonracemic) fragments.[8] Because the union of chiral fragments is complicated by double stereodifferentiation,[9] retrosynthetic planning requires judicious selection of a strategic bond for disconnection. Consequently, such convergent pathways tend to be specific to a very small number of stereoisomers; that is,

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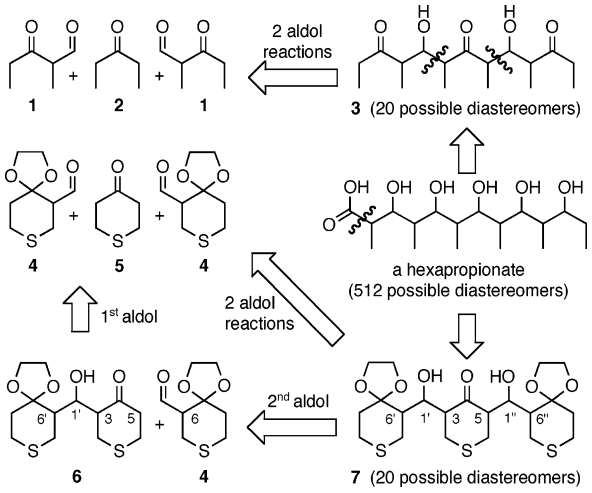
SCHEME 1



different stereoisomers generally require different synthetic routes and/or precursors.

Our synthetic approach to hexapropionates begins with an initial retrosynthetic disconnection of the carboxyl group to give the dihydroxytrione **3** after appropriate oxidation state adjustments (Scheme 1). This disconnection dramatically reduces the stereochemical complexity that, in the synthetic direction, would be restored by desymmetrization[10] and stereoselective reductions.[11] The identification of a symmetrical (in two dimensions) synthon such as **3** is advantageous because it can be derived from **1** and **2** by three routes differing only in the sequence of the aldol couplings (i.e., simultaneous or stepwise). Thus, depending on the flexibility of the stereocontrol in each of the two coupling steps, any of a large number of stereoisomers of **3** might be rapidly assembled from common precursors. We have been developing this strategy in the context of aldol reactions of tetrahydro-4*H*-thiopyran-4-one (**5**) with the thiopyran aldehyde **4** to generate synthetically useful tetrapropionate and hexapropionate synthons **6** and **7**, respectively (i.e., the thiopyran route to polypropionates).[12,13] Various transformations of **6** and **7** into polypropionate motifs (e.g., by reduction, desymmetrization, and desulfurization) have established their synthetic utility.[12]

In a preliminary study,[12b] attempts to effect one-pot simultaneous two-directional aldol couplings of **4** and **5** gave **7** in low yields with moderate stereoselectivity. However, a variety of diastereomers of **7** were obtained stereoselectively in a stepwise approach involving aldol coupling of the chiral reactants **4** and **6**. The diastereoselectivities observed in these reactions were substantially different from those reported for related acyclic reactants and suggested that double stereodifferentiation[9] was strongly modulated by the status of the hydroxyl group in **6** (i.e., free or protected). In this paper, we report a systematic investigation of the aldol reaction of **4** with each of the diastereomers of **6** that fully confirms our earlier conclusions and establishes a stereochemically versatile route to **7** (11 diastereomers) in 2−3 steps from **4** and **5**.

Results and Discussion

The common precursors (±)-**4**,[12c] **5**,[14] and **8**[14] are readily prepared from methyl acrylate on multigram scale. The initial aldol reaction of (±)-**4** with **5** can produce up to four diastereomers of the adduct **6** (Scheme 2), a useful tetrapropionate synthon.[12f] Using **8** as the enolate equivalent, the diastereoselectivity of the reaction with (±)-**4** is easily modulated simply by varying the mediator. Three of the four possible diastereomers can be produced with good to excellent stereoselectivity (**6as** with MeLi, **6ss** with $TiCl_4$, **6sa** with $MgBr_2 \cdot OEt_2$),[12c] and the fourth diastereomer can be obtained efficiently by isomerization (**6sa** → **6aa**).[15] Enantiomerically enriched aldol adducts **6** are obtained from analogous reactions using enantiomerically enriched aldehyde **4**.[16] Alternatively, the aldol reactions of (±)-**4** with **5** catalyzed by (*S*)-proline[12d] or 5-[(2*S*)-

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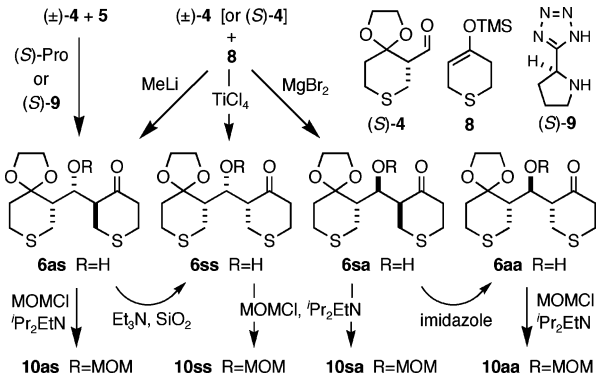
SCHEME 2



pyrrolidine-2-yl]-1*H*-tetrazole (**9**)[12f] proceed with dynamic kinetic resolution to give (−)-**6as** (>98% ee) in good yield; (+)-**6ss** (>98% ee, 78% yield) can be obtained by isomerization[12f] of (−)-**6as**.[17] Each of the diastereomers of **6** was converted to its corresponding MOM ether derivative **10** (ca. 95% yield).

Initially we chose to explore the aldol reactions of **4** with **6** and **10** using racemic compounds. For each racemic diastereomer of **6** (or **10**), the reaction with (±)-**4** can produce up to eight diastereomeric adducts, four each from the *like* and *unlike* combinations[18] of the reactant enantiomers. It is well-established that analysis of the product distribution from such reactions can determine both the diastereoselectivities (i.e., double stereodifferentiation, DS)[9] *and* the relative rates (i.e., mutual kinetic enantioselection, MKE)[19] of the *like* and *unlike* reactions (e.g., matched and mismatched).[20] Although this approach to studying the stereoselectivity of aldol reactions is somewhat complicated and relatively uncommon, a distinct advantage is that the complete stereoselectivity profile is revealed simultaneously. Thus, opportunities to exploit kinetic resolution or MKE are immediately apparent that would otherwise be difficult to identify. Because we were interested in preparing enantiomerically pure (or meso) stereoisomers of **7** using (±)-**4** wherever possible, the above strategy was particularly useful.

Aldol reactions of the racemic diastereomers of **6** with (±)-**4** were first examined. When we initiated this work,[21] there had been very few studies of aldol reactions of β-hydroxyketones and none involved reactions of chiral components.[22,23] We were able to obtain small amounts of bisaldols **7** (ca. 30% yield) from reaction of the Li enolate of (±)-**6as** (or (±)-**6ss**) with (±)-**4**; however, reactions were much cleaner and higher yielding via the putative Ti(IV) enolate generated by treatment of (±)-**6as** with $TiCl_4$ (1.1 equiv) followed by $^iPr_2EtN$ (2.4 equiv) and then (±)-**4** according to the procedure[22g] of Luke and Morris.[12b] Reaction under these conditions led to the isolation of three aldol adducts: **7a** (60%), **7b** (4%), and **7c** (6%) (Table 1 and Scheme 3).[24] Examination of the structures of the adducts reveals that both **7a** and (±)-**7c** result from a combination of reactants where the absolute configurations at C-6′ of **6as** and C-6 of **4** are *unlike*,[25] whereas (±)-**7b** results from a combination of reactants with *like*[25] configurations at C-6′ of **6as** and C-6 of **4**. The *unlike* reaction **6as** with **4** is highly diastereoselective in favor of **7a** (90% ds); of the four possible diastereomers, **7a** and **7c** are produced in a 10:1 ratio. Alternatively, (±)-**7b** results from a *like* reaction **6as** with **4**, and although possibly very diastereoselective also (only one bisaldol was detected), this reaction is less facile by a factor of ca. 16 compared to the *unlike* reaction. Thus, not only does the aldol reaction (±)-**6as** with (±)-**4** proceed with remarkable diastereoselectivity (**7a** is 85% of the total aldol products) but it also proceeds with significant mutual kinetic enantioselection (MKE). This is a very rare (perhaps unique) example of the formation of a meso compound by stereoselective coupling of racemic fragments.[26]

To determine the diastereoselectivity of the *like* reaction of **6as** with **4** and to verify the conclusions established with racemic reactants, we examined the reactions of enantioenriched (*S*)-(−)-**4** (ca. 90% ee) with the individual enantiomers of **6as** (ca. 90% ee) (Table 1). As expected, reaction of *ent*-**6as** with (*S*)-(−)-**4** under the conditions previously established for racemic reactants gave a 12:1 mixture of **7a** and **7c** (by ^1H NMR), respectively (67% combined yield); the presence of other diastereomers of **7** was not detected. In sharp contrast, a similar reaction of (−)-**6as** with (*S*)-(−)-**4** gave a mixture of six bisaldol adducts in ca. 50% overall yield. The major adduct (ca. 50% of the total) was **7a**, a result that implies racemization of **4** must occur under the reaction conditions because **7a** (and **7c**) cannot be an aldol product of (−)-**6as** and (*S*)-(−)-**4**.[25] Racemization was confirmed by isolation of (±)-**4** from the reaction mixture. Using standards and a combination of ^1H NMR and HPLC, the remaining adducts were tentatively identified as a 2:1.5:1:1:1 mixture of **7b**, **7j**, **7h**, **7d**, and **7c**, respectively (ca. 25% combined yield). This experiment clearly indicated that the *like* reaction of **6as** and **4** is not only much less facile than the *unlike* reaction but gives all four possible adducts with low diastereoselectivity. Thus, the *unlike* reaction of **6as** and **4** is "matched" and fast, whereas the *like* reaction is "mismatched" and much slower.

In our preliminary report,[12b] we showed that, in contrast to reactions of the β-hydroxy ketones (e.g., **6as**), reactions of **4** with related β-methoxy ketones via the Ti(IV) enolate gave very

(17) Structure labels with a (+)- or (−)- prefix refer to enantioenriched compounds with absolute configuration as illustrated; labels with an *ent*- prefix refer to enantioenriched compounds with absolute configuration opposite to that illustrated for the structure with the same number without a prefix.

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(24) See the Supporting Information for determination of the relative configurations of the bisaldol adducts.

(25) The combination of reactant enantiomers that leads to a given product **7** (or **11**) is conveniently characterized and determined by comparing the configurations at C-6′ and C-6″.

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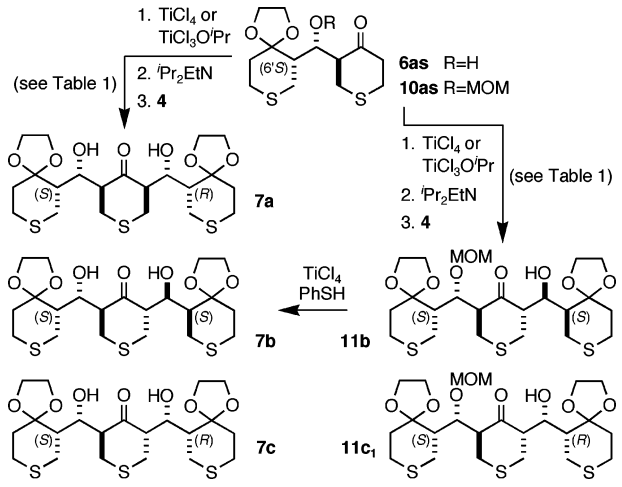
TABLE 1. Aldol Reactions of 4 with Ti Enolates of 6 and 10[a]

entry	ketone	aldehyde[b]	Ti source (equiv)	$^{i}Pr_2EtN$ (equiv)	aldol adducts[c]	yield[d] (%)
1	(±)-**6as**	(±)-**4**	$TiCl_4$ (1.1)	2.4	**7a** (60%), (±)-**7b** (4%), (±)-**7c** (6%)	70
2	(±)-**6as**	(±)-**4**	$Ti(O^iPr)Cl_3$ (1.1)	2.4	**7a** (82%)	82
3	*ent*-**6as**[e]	(*S*)-**4**[e]	$TiCl_4$ (1.1)	2.4	**7a**, **7c** (12:1)	67
4	(-)-**6as**[e]	(*S*)-**4**[e]	$TiCl_4$ (1.1)	2.4	**7a**, **7b**, **7c**, **7d**, **7h**, **7j** (25:7:3:4:3:4:4)	50
5	(±)-**6ss**	(±)-**4**	$TiCl_4$ (4)	2.4	(±)-**7c**, (±)-**7e**, (±)-**7f** (32:11:11)	54
6	(±)-**6ss**	(±)-**4**	$Ti(O^iPr)Cl_3$ (1.1) $TiCl_4$ (3)	2.4	(±)-**7c**, (±)-**7e**, (±)-**7f** (56:17:6)	79
7	(±)-**6ss**	(±)-**4**	$Ti(O^iPr)Cl_3$ (1.1)	3.0	(±)-**7d** (53%)	53
8	(+)-**6ss**[f]	(±)-**4**	$Ti(O^iPr)Cl_3$ (1.1)	3.0	(+)-**7d** (51%), **7f** (<2%)[g]	51
9	(±)-**6sa**	(±)-**4**	$TiCl_4$ (1.1)	2.4	(±)-**7g** (8%)	8
10	(±)-**6sa**	(±)-**4**	$Ti(O^iPr)Cl_3$ (1.1)	2.2	(±)-**7g**, (±)-**7h**, (±)-**7i** (13:1:1)	43
11	(±)-**6aa**	(±)-**4**	$TiCl_4$ (1.1)	2.3	(±)-**7j** (56%), (±)-**7k**(<3%)[g], (±)-**7m** (<3%)[g]	56
12	(±)-**6aa**	(±)-**4**	$Ti(O^iPr)Cl_3$ (1.1)	2.3	(±)-**7j**, (±)-**7k**, (±)-**7m** (15:1:1.5)	60[g]
13	(±)-**10as**	(±)-**4**	$TiCl_4$ (1.1)	1.4	(±)-**11b** (34%), (±)-**11c$_1$** (32%)	66
14	(±)-**10as**	(±)-**4**	$Ti(O^iPr)Cl_3$ (1.1)	1.4	(±)-**11b**, (±)-**11c$_1$** (1:1)	44
15	(-)-**10as**[f]	(*S*)-**4**[e]	$TiCl_4$ (1.1)	1.4	(-)-**11b** (70%), **11c$_1$** (5%)	75
16	(-)-**10as**[f]	(*R*)-**4**[e]	$TiCl_4$ (1.1)	1.4	**11b** (4%), (-)-**11c$_1$** (55%)	59
17	(±)-**10ss**	(±)-**4**	$TiCl_4$ (1.5)	2.1	(±)-**11c$_2$** (27%), (±)-**11e** (25%)	52
18	(±)-**10ss**	(±)-**4**	$Ti(O^iPr)Cl_3$ (1.1)	2.0	(±)-**11c$_2$**, (±)-**11d**, (±)-**11e** (38:9:31)	78
19	(±)-**10sa**	(±)-**4**	$TiCl_4$ (1.1)	1.5	(±)-**11h** (13%), (±)-**11i** (41%)	54
20	(±)-**10aa**	(±)-**4**	$TiCl_4$ (1.1)	1.5	(±)-**11k** (19%), (±)-**11m** (9%)	28
21	(±)-**10aa**	(±)-**4**	$Ti(O^iPr)Cl_3$ (1.1)	3.0	(±)-**11k** (24%), (±)-**11m** (17%)	41

[a] Reactions at −78 °C in CH_2Cl_2; see Experimental Section for detailed procedures. [b] Two equivalents. [c] Percentages in parentheses are isolated yields; ratios in parentheses are product mixtures as determined by ^1H NMR. [d] Combined isolated yield of adducts; reactions are "clean", and most of the remainder is recovered ketone. [e] Approximately 90% ee. [f] Greater than 98% ee. [g] Conversion (determined by ^1H NMR).

SCHEME 3



different diastereoselectivities and occurred with minimal MKE and DS. To test the generality of that conclusion, the β-alkoxy ketone (±)-**10as** was treated with $TiCl_4$ (1.1 equiv) followed by $^{i}Pr_2EtN$ (1.4 equiv) and then (±)-**4** at −78 °C according to the standard procedure.[27] The aldol adducts (±)-**11b** and (±)-**11c$_1$** were produced in a nearly 1:1 ratio and isolated in 34 and 32% yields, respectively (Table 1 and Scheme 3). Examination of the structures for (±)-**11b** and (±)-**11c$_1$** clearly indicates that these adducts are derived from different enantiomeric combinations of the reactants: (±)-**11b** from reactants with *like*[25] configurations at C-6′ of **10as** and C-6 of **4**; (±)-**11c$_1$** from reactants with *unlike*[25] configurations at C-6′ of **10as** and C-6 of **4**. Because (±)-**11b** and (±)-**11c$_1$** are formed in essentially equal amounts, the *like* and *unlike* reactions must occur with equal facility (i.e., with little or no MKE). Similarly, a low level of double stereodifferentiation for this coupling is implied because both the *like* and *unlike* reactions are apparently highly diastereoselective (only one of four possible aldol adducts is detected from each reaction).

The above conclusions were fully corroborated by examining similar reactions of (−)-**10as** with the individual enantiomers of **4** (Table 1). As expected, the reaction of (−)-**10as** (>98% ee) with (*S*)-**4** (90% ee) under the conditions used for the racemic reactants gave (−)-**11b** (70%) and **11c$_1$** (5%). The small amount of **11c$_1$** obtained is expected from statistical considerations.[28] A similar reaction of (−)-**10as** (>98% ee) with (*R*)-**4** (90% ee) gave (−)-**11c$_1$** (55%) and **11b** (4%).[28] In summary, aldol products with three different relative configurations (i.e., **7a**, **11b**, and **11c$_1$**) are selectively available from the aldol reaction of **4** with **6as** depending on the status of the hydroxy group (free vs MOM protected). We were anxious to test the generality of that outcome by examining similar reactions of **4** with the other three diastereomers of **6** (and **10**).

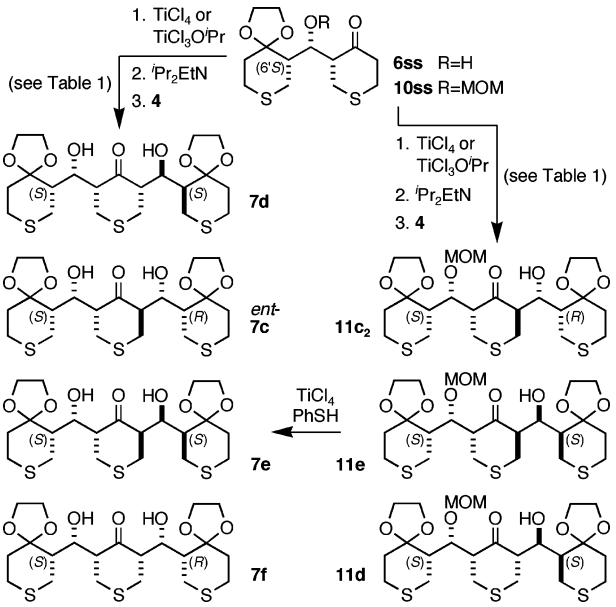
Using the conditions established with (±)-**6as**, we previously reported that the reaction of (±)-**6ss** with (±)-**4** gave a mixture of (±)-**7c** (60%), (±)-**7e** (8%), and **7f** (1−2%) (Scheme 4).[12b] This reaction was conducted several times, and although the yields and product ratios varied somewhat, the general trend was consistent. The reported result was obtained under optimized conditions on two occasions. We returned to this process expecting to prepare **7c** for application in a synthetic route to membrenone polypropionates.[29] Despite extensive experimentation, we have been unable to reproduce the previously reported result. Indeed, no aldol adducts are obtained from **6ss** under the conditions that work well for **6as**. The most obvious

(27) (a) Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215−8216. (b) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047−1049.

(28) Unbiased statistical coupling of two chiral reactants that are 100:1 and 20:1 mixtures of enantiomers, respectively, is expected to give a 16.7:1 mixture of diastereomers. The major diastereomer would have 99.9% ee, and the minor diastereomer would have 67% ee. For a discussion of this phenomenon, see ref 19a.

(29) Isolation: (a) Ciavatta, M. L.; Trivellone, E.; Villani, G.; Cimino, G. *Tetrahedron Lett.* **1993**, *34*, 6791−6794. Synthesis: (b) Sampson, R. A.; Perkins, M. V. *Org. Lett.* **2002**, *4*, 1655−1658. (c) Marshall, J. A.; Ellis, K. C. *Org. Lett.* **2003**, *5*, 1729−1732. (d) Yadav, J. S.; Srinivas, R.; Sathaiah, K. *Tetrahedron Lett.* **2006**, *47*, 1603−1606.

SCHEME 4



difference is that the former experiments with **6ss** (and **6as**) were conducted using $TiCl_4$ directly from a reagent bottle without any purification. With reagents currently at hand, control experiments using $TiCl_4$ directly from a reagent bottle or distilled from CaH_2 behaved essentially identically in aldol reactions of **4** with **6as** (to give **7a** in 50−60% yield) or **6ss** (no adducts formed). Deliberate adulteration of distilled $TiCl_4$ with O_2 or small amounts of water, MeOH, or *i*-PrOH did not lead to any improvement. We have no explanation for this discrepancy. In the course of our study, we were able to reproducibly obtain a 3:1:1 mixture of (±)-**7c**, (±)-**7e**, and **7f**, respectively (ca 40−50%), by treating (±)-**6ss** with a large excess of $TiCl_4$ (4 equiv) at −78 °C followed by ^{i}Pr$_2$EtN (2.4 equiv) and then (±)-**4** (Table 1). The reaction performed much better using Ti(O^{i}Pr)Cl_3 (1 equiv) and $TiCl_4$ (3 equiv) instead of $TiCl_4$ alone to give a 10:3:1 mixture of (±)-**7c**, (±)-**7e**, and **7f**, respectively, in near 80% combined yield. This reaction stereoselectivity is quite different from that observed with **6as**. Adducts **7c** and **7f** are derived from an *unlike* reaction[25] of **6ss** with **4**, whereas **7e** results from a *like* reaction.[25] Both reactions show good diastereoselectivity (*unlike*, two of four possible adducts in 10:1 ratio; *like*, only one adduct detected) and proceed with modest MKE [(10 + 1)/3 = 3.6]. The role of the relatively small amount of Ti(O^{i}Pr)Cl_3 used in this reaction is unclear at present.[30]

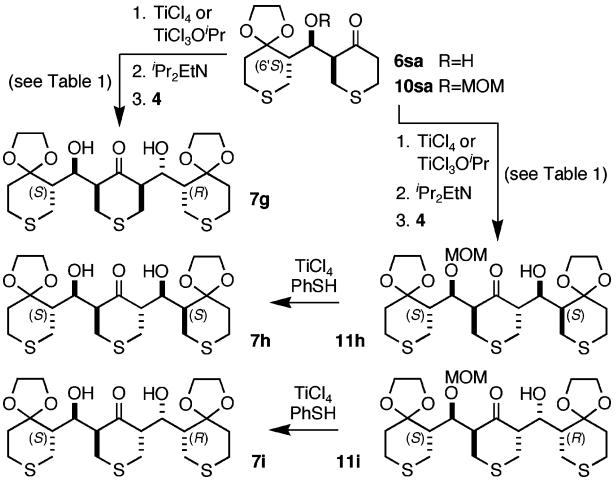
Interestingly, the reaction of (±)-**6ss** with (±)-**4** takes a completely different course when applying the standard conditions established with (±)-**6as** but using Ti(O^{i}Pr)Cl_3 in place of $TiCl_4$. Instead of no adducts being produced, a new adduct (±)-**7d** is obtained exclusively in moderate yield (Table 1). The bisaldol **7d** is derived from a highly diastereoselective *like* combination[25] of enantiomers of **6ss** with **4**, and because only one adduct is detected, a substantial MKE in favor of the *like* reaction is implied. This suggests that similar reactions of an enantioenriched reactant with a racemic reactant will occur with useful levels of kinetic resolution. To test that hypothesis, the aldol reaction of (+)-**6ss** (>98% ee) with (±)-**4** was conducted under the same conditions. As expected, (+)-**7d** was obtained as the only bisaldol adduct in a yield comparable to that from the reaction of racemic components. Recovered **4** was enriched in the *R*-enantiomer (ca. 25% o.p.), suggesting little racemization under these conditions. The profound effect of using Ti(O^{i}Pr)Cl_3 in this reaction prompted us to reexamine the reaction of (±)-**6as** with (±)-**4** with this reagent.[30] Indeed, under optimized conditions, **7a** was obtained in >80% yield as the only isolable adduct (<1% of **7b** or **7c** present in crude reaction mixture by ^{1}H NMR). This remarkably stereoselective reaction gives only one of eight possible adducts and allows the preparation of the synthetically useful[12e] meso **7a** (six stereocenters) in only two steps from (±)-**4** and **5** (>60% overall yield) on multigram scale.

Reaction of the $TiCl_4$-derived enolate of the β-alkoxy ketone (±)-**10ss** with (±)-**4** under the usual conditions[27] produced a nearly 1:1 mixture of (±)-**11c$_2$** (27%) and (±)-**11e** (24%) (Table 1). Analogous to the related reaction of (±)-**10as** (Scheme 3), the adducts (±)-**11c$_2$** and (±)-**11e** result from different combinations of reactant enantiomers: (±)-**11c$_2$** from an *unlike* reaction and (±)-**11e** from a *like* reaction.[25] Similarly, it follows that the *like* and *unlike* reactions must occur with near equal facility (i.e., with little or no MKE), and a low level of double stereodifferentiation is implied for this coupling because both reactions are apparently highly diastereoselective (only one of four possible aldol adducts is detected from each reaction). With careful optimization, the same reaction using the Ti(O^{i}Pr)Cl_3-derived enolate of (±)-**10ss** gave a much greater yield of adducts but with lower diastereoselectivity in the *like* reaction (i.e., **11e**:**11d** = 3.5:1) compared to the reaction using $TiCl_4$. Reaction of the Ti(O^{i}Pr)Cl_3-derived enolate of **10as** with **4**, using the conditions optimized for **10ss**, gave inferior results compared to those of the same reaction using $TiCl_4$. Thus, the highly beneficial effects of using Ti(O^{i}Pr)Cl_3 observed previously in the reactions of **4** with **6as** and **6ss** were not realized in similar reactions of **10as** or **10ss** (Table 1). Nonetheless, these results suggest that either enantiomer of **11c$_2$** or **11e** can be obtained selectively by reaction of the appropriate enantiomer of **10ss** with the appropriate enantiomer of **4**. As with **6as**, aldol products with three different relative configurations (i.e., **7d**, **11c$_2$**, and **11e**) are selectively available from the aldol reaction of **4** with **6ss** depending on the status of the hydroxy group (free vs MOM protected).

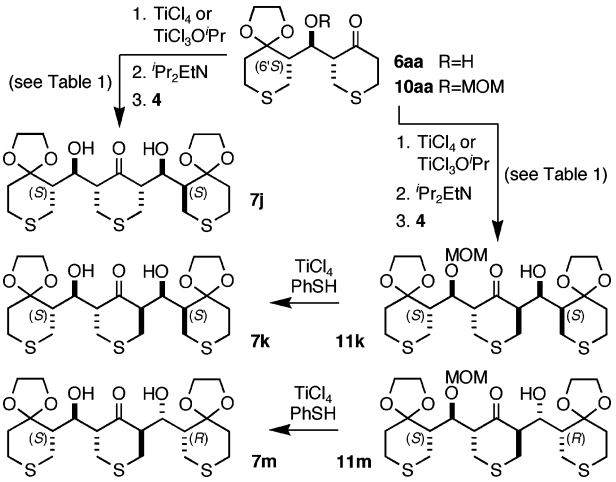
Aldol reactions of (±)-**4** with (±)-**6sa** and with (±)-**10sa** were similarly conducted (Table 1 and Scheme 5). The reaction of the $TiCl_4$-generated enolate of (±)-**6sa** with (±)-**4** performed poorly giving (±)-**7g** in very low yield (8%). As with **6as** and **6ss**, this reaction was substantially improved using Ti(O^{i}Pr)Cl_3 to generate the enolate of **6sa** and gave a 13:1:1 mixture (by ^{1}H NMR) of (±)-**7g**, (±)-**7h**, and (±)-**7i**, respectively, in 43% combined yield. The bisaldol **7g** is derived from a highly diastereoselective *unlike* combination[25] of enantiomers of **6sa** with **4** (**7g**:**7i** = 13:1), whereas **7h** results from a *like* combination.[25] The small amount of **7h** produced does not allow an assessment of the diastereoselectivity of the *like* reaction; however, the selective formation of **7g** suggests a substantial MKE in favor of the *unlike* reaction. This implies that, in analogy to the preparation of (+)-**7d**, reaction of enantiopure **6sa** with racemic **4** should occur with a high level of kinetic resolution to selectively give enantiopure **7g**.

(30) For an excellent discussion on the use of Ti(O^{i}Pr)Cl_3 for preparation of Ti enolates and its influence on stereoselectivity, see: (a) Solsona, J. G.; Romea, P.; Urpi, F.; Vilarrasa, J. *Org. Lett.* **2003**, *5*, 519−522. (b) Solsona, J. G.; Nebot, J.; Romea, P.; Urpí, F. *J. Org. Chem.* **2005**, *70*, 6533−6536. (c) Nebot, J.; Figueras, S.; Romea, P.; Urpi, F.; Ji, Y. *Tetrahedron* **2006**, *62*, 11090−11099.

SCHEME 5



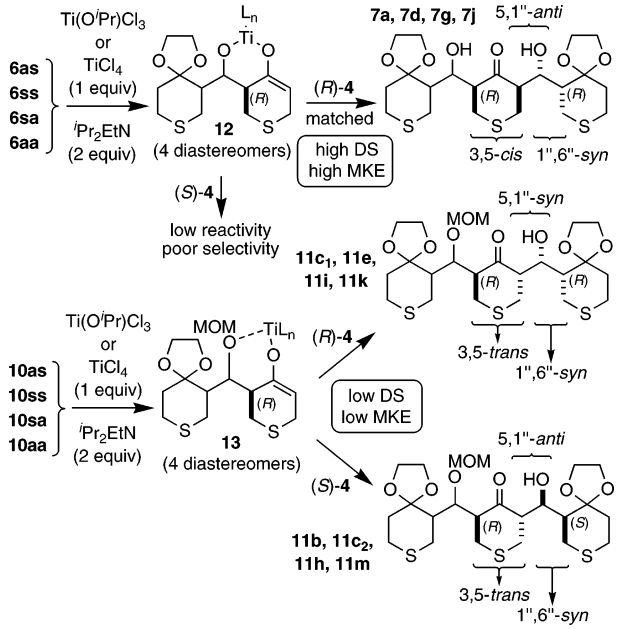
SCHEME 6



Reaction of (±)-**4** with the $TiCl_4$-generated enolate of the corresponding *β*-alkoxy ketone (±)-**10sa** under the usual conditions gave (±)-**11h** (41%) and (±)-**11i** (13%). Similar reactions using $Ti(O^iPr)Cl_3$ gave only negligible amounts of bisaldol adducts. As with the previous examples, these adducts are derived from different combinations of reactant enantiomers: (±)-**11h** from a *like* combination[25] and (±)-**11i** from an *unlike* combination.[25] In contrast to the reactions of (±)-**10as** and (±)-**10ss** that proceeded with negligible MKE, the relative proportions of **11h** and **11i** obtained suggest a modest kinetic preference (ca. 3:1) for the *like* combination of enantiomers of **4** and **10sa**. Nonetheless, these results imply that either enantiomer of **11h** or **11i** could be obtained selectively by reaction of the appropriate enantiomer of **10sa** with the appropriate enantiomer of **4** and that aldol products with three different relative configurations (i.e., **7g**, **11h**, and **11i**) are selectively available from the aldol reaction of **4** with **6sa** depending on the status of the hydroxy group (free vs MOM protected).

Finally, we examined the aldol reactions of (±)-**4** with (±)-**6aa** and with (±)-**10aa** under conditions similar to those described above (Table 1 and Scheme 6). Reactions of (±)-**4** with (±)-**6aa** using either $TiCl_4$ or $Ti(O^iPr)Cl_3$ to generate the enolate gave very similar results, producing a 15−20:1:1.5 mixture of (+)-**7j**, (±)-**7k**, and (±)-**7m**, respectively, in ca. 50−75% yield. Adducts **7j** and **7k** are derived from a *like* combination[25] of enantiomers of **4** and **6aa**, whereas **7m** results from an *unlike* combination.[25] Judging from the ratio of aldol products, the like reaction is much more facile (i.e., the MKE is >10:1) and is highly diastereoselective (≥15:1). Thus, either enantiomer of **7j** should be available from reaction of the appropriate enantiomer of **6aa** with racemic **4** (i.e., via kinetic resolution). Reaction of (±)-**4** with (±)-**10aa** using the $TiCl_4$-generated enolate gave (±)-**11k** (19%) and (±)-**11m** (9%). With some optimization, a similar reaction using $Ti(O^iPr)Cl_3$ to generate the enolate gave (±)-**11k** (24%) and (±)-**11m** (17%). In keeping with the results obtained with the other diastereomers of **10**, the two adducts from this aldol reaction arise from different combinations of enantiomers of **10aa** and **4**: **11k** from a *like* reaction[25] and **11m** from an *unlike* reaction.[25] In each case, a slight kinetic preference for the *like* reaction is apparent (i.e., MKE = 1.5−2:1). Considering the yield of adducts produced and our ability to detect other isomers (ca. 1−2% yield), both the *like* and *unlike* reactions appear to be very diastereoselective (i.e., only one adduct detected from each) and suggest a low level of DS in this coupling. As with the previous examples, these results imply that either enantiomer of **11k** or **11m** could be obtained selectively by reaction of the appropriate enantiomer of **10aa** with the appropriate enantiomer of **4** and that aldol products with three different relative configurations (i.e., **7j**, **11k**, and **11m**) are selectively available from the aldol reaction of **4** with **6aa** depending on the status of the hydroxy group (free vs MOM protected).

SCHEME 7



The aldol reactions of **4** with each of the diastereomers of **6** via a Ti enolate work best with a nominal 1:1:2 stoichiometry of ketone to Ti ($TiCl_4$ or $Ti(O^iPr)Cl_3$) to base. Under these conditions, we presume that a cyclic Ti enolate (e.g., **12**) is formed as proposed by Luke and Morris (Scheme 7).[22g] All of these reactions exhibit closely related stereoselectivities that can be understood by considering the three stereocontrol elements involved, that is, the enolate and aldehyde diastereoface selectivities and the aldol relative topicity. Each reaction occurs with substantial MKE to give a major (or sole) product that arises from (i) addition to **4** from the Felkin face to give a 1″,6″-*syn* relative configuration; (ii) addition to the enolate (e.g., **12**)

from the same face as the C-3 substituent to give a 3,5-*cis* relative configuration; and (iii) an *anti*-selective relative topicity to give a 5,1″-*anti* relative configuration. High MKE requires each of the stereocontrol elements to have high selectivity. In that case, all three individual diastereoselectivities (e.g., in this case, a preference for 3,5-*cis*, 5,1″-*anti*, 1″,6″-*syn* relative configurations) can be satisfied in only one of the four possible products from one of the two possible enantiomeric combinations of the chiral reactants **6** and **4**. That is, one combination of enantiomers will have the three diastereoselectivities mutually reinforcing (high DS) and be kinetically preferred (high MKE) over the other combination (mismatched), where only two of the three diastereoselectivities can be accommodated. We have previously shown that **4** has a very high propensity for Felkin addition.[12c] The required high selectivity for *cis* addition to the enolate and *anti* aldol relative topicity can be rationalized by reaction of a cyclic Ti enolate such as **12** via a "closed" transition state. Interestingly, the different diastereomers of **6** require different conditions to induce this highly selective aldol reaction with **4**. In particular, the 1′,3-*anti* diastereomers of **6** (i.e., **6as** and **6aa**) seem more cooperative than the 1′,3-*syn* diastereomers (i.e., **6ss** and **6sa**). This is likely a result of a varying propensity of the different diastereomers of **6** to form the cyclic enolate **12**, and the yields of aldol adducts obtained probably reflect the success of this process. Cyclization should be more facile for enolates from *anti* versus *syn* diastereomers as has been noted previously.[22g,i,31]

The aldol reactions of **4** with Ti enolates derived from the β-alkoxy ketones **10** also show very closely related stereoselectivities that are very different from the reactions of the related hydroxy ketones **6**. In each case, two products are formed predominantly, one from each of the possible combinations of reactant enantiomers (Scheme 7). The reactions occurred with little or no MKE, but both are very diastereoselective (i.e., no apparent mismatched reaction). Interestingly, both products result from reactions that have the same sense of diastereoface selectivity with respect to both the enolate (3,5-*trans*) *and* the aldehyde (Felkin; 1″,6″-*syn*) but differ in their aldol relative topicity (5,1″-*anti* vs 5,1″-*syn*). Because the two aldol adducts are formed in comparable amounts, the reaction must have little or no bias regarding relative topicity. This low diastereoselectivity in one of the three stereocontrol elements has two consequences. First, the level of MKE is limited by the least selective of the stereocontrol elements.[19,20] If the aldol relative topicity is unselective, then the MKE must be low regardless of the magnitude of the other diastereoselectivities. Second, DS is also limited by the least selective of the three stereocontrol elements.[19,20] However, for the two possible combinations of reactant enantiomers (i.e., the *like* and *unlike* reactions), the reaction diastereoselectivities will be governed by the remaining two stereocontrol elements. Thus, high diastereoselectivity for both reactions (i.e., no mismatched reaction) is possible if both stereocontrol elements are strongly biased.[32] Consequently, the results from these reactions can be rationalized by consideration of the known[12c] high propensity for Felkin addition to **4** and an assumed high diastereoface selectivity for addition to the Ti enolate of **10**. The structure of that enolate is uncertain.[30] A chelated structure (e.g., **13**) has been proposed for related acyclic Ti enolates of β-alkoxy ketones.[30b] Clearly, the diastereoface selectivities and the aldol relative topicities for Ti enolates derived from **6** are different from those for the Ti enolates from **10**. Perhaps the lower acidity but greater nucleophilicity of a chelated Ti enolate derived from **10** (e.g., **13**) leads to reaction via an open transition state from the more sterically accessible side opposite the substituent at C-3.

In conclusion, we have systematically examined the aldol reactions of (±)-**4** with each of the diastereomers of (±)-**6** and the corresponding MOM ether derivatives (±)-**10**. The stereoselectivities of these reactions have some unusual and useful features. In each case, the level of mutual kinetic enantioselection (MKE) and double stereodifferentiation (DS) observed in these reactions is strongly attenuated by the presence of the β-alkoxy group in **10** versus a β-hydroxy group in **6**. MKE and DS are exploited using the diastereomers of **6** to obtain, in each case, one of the eight possible aldol adducts. Using **10**, the effects of MKE and DS are overcome, allowing access to two different aldol stereoisomers. By extension, we have demonstrated that 11 of the 20 possible bisaldol diastereomers of **7** can be produced selectively in 2−3 steps from simple starting materials.[33] This rapid assembly of stereochemically diverse hexapropionate synthons should be applicable to a number of synthetic endeavors.

Experimental Section[34]

(3*S*,5*R*)-*rel*-3-[(*R*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]-5-[(*S*)-(6*R*)-1,4-dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4*H*-thiopyran-4-one (7a).[12b] Ti(O^iPr)Cl_3 (10.5 mmol; ca. 0.5 M in CH_2Cl_2) was added dropwise via syringe to a stirred solution of (±)-**6as** (2.97 g, 9.76 mmol) in CH_2Cl_2 (100 mL) at −78 °C under argon. After 5 min (a fine yellow slurry formed), $^iPr_2EtN$ (1.75 mL, 1.30 g, 10.0 mmol) was added dropwise via syringe to the reaction mixture at −78 °C. After 1 h (the reaction mixture was a deep red solution), (±)-**4** (3.67 g, 19.5 mmol) was added via syringe, and after 1 h, $^iPr_2EtN$ (2.50 mL, 1.85 g, 14.4 mmol) was added. The reaction mixture was stirred at −78 °C for 2 h and then was quenched by addition of saturated aqueous NH_4Cl and quickly worked up by dilution with water and extraction with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, concentrated, and fractionated by FCC (10−50% ethyl acetate in CH_2Cl_2) to give recovered (±)-**4** (2.03 g, 55%) and **7a** (3.96 g, 82%) as an off-white solid: mp 166−167 °C (ethyl acetate/hexane); IR ν_{max} 3518, 1698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.32 (2H, ddd, J = 5, 6, 6.5 Hz, HC-1′, HC-1″ [$J_{HC-1'-HC-3}$ = 6 Hz]), 4.10−3.88 (8H, m, H_2CO × 4), 3.25 (2H, ddd, J = 5, 6, 12 Hz, HC-3, HC-5 [$J_{HC-2-HC-3}$ = 5, 12 Hz]), 3.12 (2H, d, J = 6.5 Hz, HO × 2), 3.04 (2H, dd, J = 12, 13 Hz, HC-2, HC-6), 3.02 (2H, dd, J = 8.5, 14 Hz, HC-7′, HC-7″), 2.91−2.83 (4H, m, HC-2, HC-6, HC-7′, HC-7″), 2.73−2.67 (4H, m, H_2C-9′, H_2C-9″), 2.07 (2H, ddd, J = 3.5, 5, 8.5 Hz, HC-6′, HC-6″), 1.97 (2H, ddd, J = 5, 5.5, 14 Hz, HC-10′, HC-10″), 1.73 (2H, ddd, J = 5.5, 6.5, 14 Hz, HC-10′, HC-10″); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.0 (C-4), 109.2 (C-5′ and C-5″), 69.3 (C-1′ and C-1″), 64.9 (CH_2O), 64.6 (CH_2O), 57.6 (C-3 and C-5), 47.3 (C-6′ and C-6″), 36.3 (C-2 and C-6), 35.8 (C-10′ and C-10″), 27.9 (t × 2, C-7′ and C-7″), 26.8 (C-9′ and C-9″); HRMS m/z calcd for $C_{21}H_{32}O_7S_3$ + H 493.1388, found 493.1394

(31) Chemler, S. R.; Roush, W. R. *J. Org. Chem.* **2003**, *68*, 1319−1333.

(32) That is, a reaction that can produce four possible stereoisomers requires only two stereocontrol elements acting in concert to produce one product selectively.

(33) From the perspective of the diversity of relative configurations, the diastereomers of **11** (32 possible) are considered to be synthetically equivalent to the related diastereomers of **7** (20 possible). Thus, in this work, we have shown that 11 unique relative configurations (e.g., of the 20 possible diastereomers of **7**) can be obtained selectively by appropriate coupling **4** with **6** or **10**; i.e., **7a**, **11b** (=**7b**), **11c$_1$** or **11c$_2$** (=**7c**), **7d**, **11e** (=**7e**), **7g**, **11h** (=**7h**), **11i** (**7i**), **7j**, **11k** (=**7k**), **11m** (=**7m**). See the Supporting Information for examples of conversion of **11** into **7**.

(34) See the Supporting Information for general methods and procedures.

(FAB). Anal. Calcd for $C_{21}H_{32}O_7S_3$: C, 51.20; H, 6.55. Found: C, 51.29; H, 6.70.

(3*S*,5*S*)-*rel*-3-[(*R*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]-5-[(*R*)-(6*S*)-1,4-dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4*H*-thiopyran-4-one ((±)-11b) and (3*S*,5*S*)-*rel*-3-[(*R*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]-5-[(*S*)-(6*R*)-1,4-dioxa-8-thiaspiro[4.5]-dec-6-ylhydroxymethyl]tetrahydro-4*H*-thiopyran-4-one ((±)-11c$_1$). $TiCl_4$, (14 μL, 24 mg, 0.13 mmol) was added to a stirred solution of (±)-**10as** (40 mg, 0.12 mmol) in CH_2Cl_2 (2 mL) at −78 °C under argon (a globular yellow precipitate formed). After 2 min (a fine yellow suspension formed), $^iPr_2EtN$ (30 μL, 22 g, 0.17 mmol) was added dropwise over 1 min. After 1 h (the mixture became a dark red solution), (±)-**4** (43 mg, 0.23 mmol) was added. After 3 h (the solution gradually became light red), the reaction was quenched by sequential addition of MeOH (1 mL) and phosphate buffer (pH 7). The mixture was extracted with CH_2Cl_2, and the combined organic layers were dried over Na_2SO_4 and concentrated. Fractionation of the residue by flash column chromatography (20−80% ethyl acetate in hexane) gave (±)-**11b** (21 mg, 34%) and (±)-**11c$_1$** (20 mg, 32%). Spectral data for **11b**: IR ν_{max} 3516, 1713 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.75 (1H, d, J = 6 Hz, H_2CO), 4.58 (1H, d, J = 6 Hz, H_2CO), 4.55 (1H, ddd, J = 4, 5.5, 8 Hz, HC-1″), 4.28 (1H, dd, J = 4.5, 4.5 Hz, HC-1′), 4.13−3.94 (8H, m, H_2C-2′, H_2C-2″, H_2C-3′, H_2C-3′), 3.37 (3H, s, H_3CO), 3.11 (1H, d, J = 4 Hz, HO), 3.08−2.67 (12H, m, HC-3, HC-7″, HC-2, HC-5, HC-6, HC-7′, HC-6, HC-9″, HC-7′, HC-9′, HC-7′, HC-2), 2.54−2.51 (2H, m, HC-9′, HC-9″), 2.20−2.11 (3H, m, HC-6′, HC-10′, HC-10′), 2.04 (1H, ddd, J = 2, 2, 11 Hz, HC-6″), 1.73 (1H, ddd, J = 3.5, 13, 13 Hz, HC-10″), 1.68 (1H, ddd, J = 3, 13.5, 13.5 Hz, HC-10′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.2 (C-4), 110.1 (C-5′), 109.1 (C-5″), 97.8 (OCH_2O), 74.6 (C-1′), 68.7 (C-1″), 65.2 (H_2CO), 65.0 (H_2CO), 64.8 (2 × H_2CO), 58.4 (C-3), 57.0 (H_3CO), 54.5 (C-5), 50.4 (C-6′), 47.9 (C-6″), 37.1 (C-10″), 36.3 (C-10′), 32.4 (C-2), 32.4 (C-6), 28.7 (C-7′), 27.0 (C-9″), 27.0 (C-7″), 26.8 (C-9′); HRMS m/z calcd for $C_{23}H_{36}O_8S_3$: 536.1572, found 536.1572. Spectral data for **11c$_1$**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.72 (1H, ddd, J = 2.5, 3, 8 Hz, HC-1″), 4.70 (1H, d, J = 5.5 Hz, HCO_2), 4.58 (1H, d, J = 5.5 Hz, HCO_2), 4.39 (1H, dd, J = 4, 6 Hz, HC-1′), 4.12−3.94 (8H, m, H_2CO × 4), 3.35 (3H, s, H_3CO), 3.20 (1H, ddd, J = 1, 5, 13 Hz, HC-6), 3.15 (1H, d, J = 2.5 Hz, HOC-1″), 3.13 (1H, ddd, J = 5, 8, 8.5 Hz, HC-5), 3.03 (1H, m, HC-2), 2.97 (1H, dd, J = 10, 14 Hz, HC-7″), 2.92 (1H, ddd, J = 5, 5.5, 6.0 Hz, HC-3), 2.92 (1H, dd, J = 8.5, 13 Hz, HC-6), 2.92−2.87 (1H, m, HC-2), 2.84 (1H, ddd, J = 2, 3, 14 Hz, HC-7″), 2.82−2.73 (4H, m, H_2C-7′, HC-9′, HC-9″), 2.61−2.52 (2H, m, HC-9′, HC-9″), 2.18 (1H, ddd, J = 4, 5.5, 9 Hz, HC-6′), 2.18−2.11 (2H, m, HC-10′, HC-10″), 2.06 (1H, ddd, J = 3, 3, 10 Hz, HC-6″), 1.73 (1H, ddd, J = 3.5, 10.5, 13 Hz, HC-10″), 1.70 (1H, ddd, J = 3.5, 10.5, 13 Hz, HC-10′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.7 (C-4), 110.2 (C-5″), 108.7 (C-5′), 97.5 (OCH_2O), 73.9 (C-1′), 67.1 (C-1″), 64.9 (CH_2O), 64.8 (CH_2O), 64.7 (CH_2O), 64.4 (CH_2O), 58.5 (C-3), 56.2 (CH_3O), 53.8 (C-5), 50.0 (C-6′), 46.4 (C-6″), 36.2 (C-10′), 35.8 (C-10″), 32.0 (C-2), 31.4 (C-6), 28.4 (C-7′), 26.9 (C-9′ or C-9″), 26.8 (C-9′ or C-9″), 26.7 (C-7″); HRMS m/z calcd for $C_{23}H_{36}O_8S_3$ 536.1572, found 536.1561 (EI).

(3*S*,5*S*)-3-[(*R*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]-5-[(*R*)-(6*S*)-1,4-dioxa-8-thiaspiro[4.5]-dec-6-ylhydroxymethyl]tetrahydro-4*H*-thiopyran-4-one ((−)-11b). Using the same procedure as described for the racemic reactants, the reaction of (−)-**10as** (38 mg, 0.11 mmol; >98% ee) and (*S*)-**4** (44 mg, 0.23 mmol; 91% ee) gave **11c$_1$** (3 mg, 5% yield; ee not determined) and (−)-**11b** (41 mg, 70% yield; $[\alpha]^{24}_D$ −12 (*c* 1.0, $CHCl_3$) after fractionation by PTLC (80% ethyl acetate in hexane). NMR data for (−)-**11b** were essentially identical with those for (±)-**11b**.

(3*S*,5*S*)-3-[(*R*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]-5-[(*S*)-(6*R*)-1,4-dioxa-8-thiaspiro[4.5]-dec-6-ylhydroxymethyl]tetrahydro-4*H*-thiopyran-4-one ((−)-11c$_1$). Using the same procedure as described for the reaction of the racemic reactants, the reaction of (−)-**10as** (38 mg, 0.11 mmol; >98% ee) and (*R*)-**4** (44 mg, 0.23 mmol; 91% ee) gave **11b** (2.5 mg, 4%; ee not determined) and (−)-**11c$_1$** (32 mg, 55% yield; $[\alpha]^{24}_D$ −38 (*c* 1.0, $CHCl_3$) after fractionation by PTLC (80% ethyl acetate in hexane). NMR data for (−)-**11c$_1$** were essentially identical with those for (±)-**11c$_1$**.

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Supporting Information Available: Experimental procedures and spectroscopic data for the aldol adducts in Table 1 (and the isomers **7n** and **7o** not shown here) and **10ss**; determination of the relative configurations for the diastereomers of **7**and **11**; ^{1}H and ^{13}C NMR spectra for all reported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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