Influence of the β-Alkoxy Group on the Diastereoselectivity of Aldol Reactions of Tetrahydro-4*H*-thiopyran-4-one with 4-Alkoxytetrahydro-2*H*-thiopyran-3-carboxaldehydes

Dale E. Ward,* Marcelo Sales, Chuk C. Man, Jianheng Shen, Pradip K. Sasmal, and Cheng Guo

Department of Chemistry, University of Saskatchewan, 110 Science Place, Saskatoon SK S7N 5C9, Canada

dale.ward@usask.ca

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The diastereoselectivity of the aldol reaction of tetrahydro-4*H*-thiopyran-4-one (**3**) with 1,4-dioxa-8-thiaspiro[4.5]decane-6-carboxaldehyde (**9a**) under a variety of conditions is examined. Under optimized conditions, three of the four possible diastereomers from this aldol reaction can be obtained selectively (3−16:1). Reactions of **9a** with the Li, B, Mg(II), and Ti(IV) enolates of **3** and with the corresponding trimethylsilyl enol ether **4b** in the presence of $BF_3{\cdot}OEt_2$, $SnCl_4$, or $TiCl_4$ as promoters gave the Felkin adducts exclusively (>95%) as mixtures of syn (**11a**) and anti (**12a**) diastereomers. Use of the "amine-free" Li enolate of **3** gave **12a** with a much higher diastereoselectivity (9:1) and yield (70%) than that obtained using the lithium diisopropylamide-generated Li enolate of **3** (2−3:1; 15−40%). The $TiCl_4$-promoted reaction of **4b** with **9a** gave **11a** with excellent selectivity (16:1). In contrast, the $MgBr_2{\cdot}OEt_2$-promoted reaction of **4b** with **9a** gave the anti-Felkin adducts exclusively as a 3:1 mixture of syn (**13a**)/anti (**14a**) diastereomers. Similar aldol reactions of **3** with the cis and trans isomers of 4-(methoxy)methoxytetrahydro-2*H*-thiopyran-3-carboxaldehyde (**9b** and **9c**) were examined to probe the influence of the ketal protecting group in **9a** on the observed aldol diastereoselectivity. The results are rationalized by applying Evans' stereochemical model for merged 1,2- and 1,3-asymmetric induction (nonchelation), with the exception of the $MgBr_2{\cdot}OEt_2$-promoted reactions of **4b** with **9a**, **9b**, and **9c**, which are accommodated by assuming chelation control. Comparison of the reactions of **9a**, **9b**, and **9c** suggests that the ketal group in **9a** uniquely allows high levels of either Felkin or anti-Felkin selectivity to be achieved.

Introduction

The use of cyclic templates to facilitate and control various chemical transformations is a well-established synthetic strategy. Cyclic sulfides have been widely used for this purpose and offer several advantages, including ready preparation, versatile chemistry, and relative ease of removal of the sulfur from the final product.[1] In particular, thiopyran-derived scaffolds have been exploited in the construction of a variety of synthetic targets.[2,3] For example, Woodward et al. took advantage of the concave topology of a cis-fused dithiadecalin template to install 8 of the 10 stereogenic centers present in the macrocyclic lactone of erythromycin A.[4] An alternative and potentially more general strategy for polypropionate synthesis involves aldol reactions of tetrahydro-4*H*-thiopyran-4-one derivatives, followed by desulfurization.[5,6] We have previously reported on the linear and two-directional iterative aldol homologations of tetrahydro-4*H*-thiopyran-4-one (**3**) with 1,4-dioxa-8-thiaspiro[4.5]-decane-6-carboxaldehyde (**9a**) as a means to prepare stereochemically complex polypropionate synthons (six to eight stereogenic centers) in only a few steps.[6b] The ability to control the stereoselectivity of the aldol couplings is crucial to the success of this approach. Although the development of methods for stereoselective aldol reactions has been intensively investigated for more that 20 years,[7] studies on reactions of cyclic ketones or cyclic aldehydes are rare. In this contribution, we report optimized conditions that allow three of the four possible diastereomers from the aldol reaction of **3** with **9a** to be

* Corresponding author.

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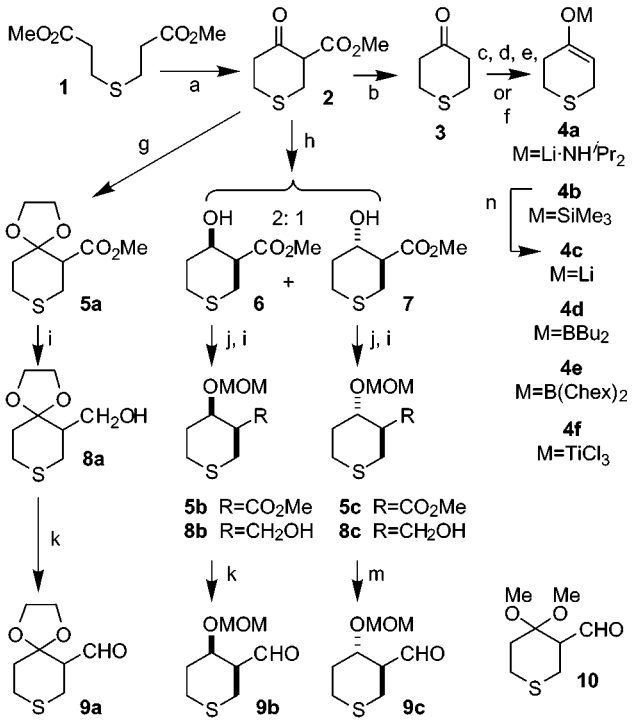
Scheme 1. Preparation of Starting Materials[a]



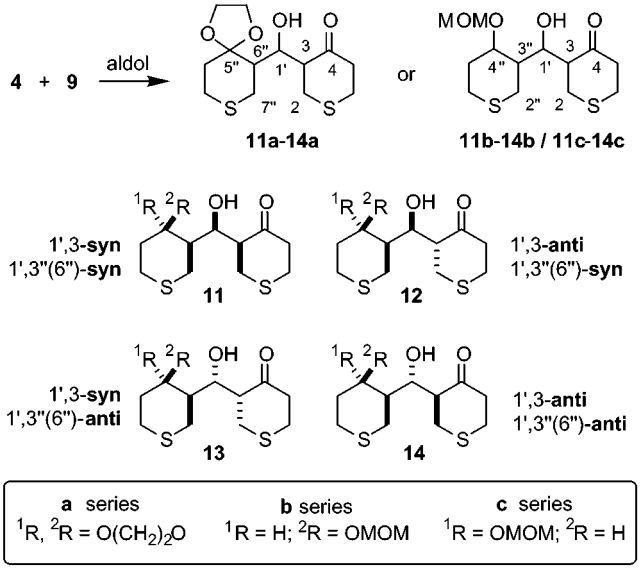
[a] Reagents: (a) NaOMe (90%). (b) 10% H_2SO_4 (80%). (c) LDA, THF, −78 °C (**4a**; >95% assumed). (d) TMSCl, Et_3N, rt (**4b**; >95%). (e) R_2B−X, *i*-Pr_2EtN, −78 °C, 3 h (>95% assumed). (f) (i) $TiCl_4$; (ii) *i*-Pr_2EtN, −78 °C, 2 h (**4f**). (g) $(HOCH_2)_2$, *p*-TsOH, C_6H_6, reflux (90%). (h) $NaBH_3CN$, citric acid, EtOH (73%). (i) $LiAlH_4$ (86−94%). (j) MOM-Cl, *i*-$PrEt_2N$ (>95%). (k) From **8**: (i) DMSO, $(COCl)_2$; (ii) *i*-Pr_2EtN (55−89%). (m) From **5c**: DIBAl−H (69%). (n) MeLi, THF/ether, rt (>95%).

obtained selectively. We also report on the unique influence of the ketal protecting group in **9a** on the stereoselectivity of the aldol reactions.

Results

Our ongoing interest in desymmetrization[8,9] and the ready availability of **2** and **3** (Scheme 1) prompted consideration of various coupling reactions as a means to prepare symmetric bifunctional substrates that could be used as tri- or tetrapropionate synthons. Initially, we attempted aldol reactions of the lithium diisopropylamide-generated (lithium diisopropylamide = LDA) enolate **4a** with **10** but were unable to obtain adducts. Subsequently, Hayashi reported that aldol reactions of **4a** with a variety of aldehydes gave adducts with high anti diastereoselectivity.[5] Of particular interest to us, the reaction of **4a** with aldehyde **9a** was reported to give **12a** (Scheme 2) in 85% yield with excellent diastereoselectivity (50:1).[5] In light of this information, we decided to

Scheme 2. Aldol Reactions of 4 with 9



a series	**b** series	**c** series
^1R, ^2R = $O(CH_2)_2O$	^1R = H; ^2R = OMOM	^1R = OMOM; ^2R = H

examine aldol reactions of **4** with **9a**. **9a** was readily prepared from **2**, as outlined in Scheme 1. Despite considerable experimentation,[10] we were unable to reproduce the reported[5] aldol reaction of **4a** with **9a**; in our hands, aldol products were obtained as separable 2−3:1 mixtures of **12a**/**11a** in 15−40% combined yield. Initially, we suspected that the "profound tendency toward retroaldolization" reported[5] for aldol adducts of **3** was responsible for our difficulties; however, both **11a** and **12a** were recovered unchanged (>85% yield) after treatment with LDA under the above conditions.[11]

We decided to examine the reaction of **4c** with **9a** on the basis of a note[12] in Woodward's erythromycin A synthesis indicating that a key aldol-coupling of a dithiadecalone proceeded in substantially higher yield when using the "amine-free" Li enolate than when using the LDA-generated Li enolate. It is well established that the *i*-Pr_2NH product formed from the reaction of LDA with ketones is associated with the enolate (e.g., **4a**) and that the presence of an amine can influence the ensuing enolate reactions;[13] however, any such effects on aldol diastereoselectivity have not been well-documented. We were delighted to find that the reaction of **4c** (prepared from **4b** and MeLi)[14] with **9a** produced a separable 9:1 mixture of **12a**/**11a** in 70% isolated yield (Table 1, entry 2). This increase in aldol diastereoselectivity using an

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(10) The reported[5] procedure is typical: addition of **3** to LDA (1 equiv) in THF at −78 °C; after 30 min, addition of **9a** (1.2 equiv); after 0.5 min, quenching by addition of NH_4Cl. We calibrated these conditions using cyclohexanone and benzaldehyde and obtained the aldol product (75% yield; 4:1 anti/syn) as reported: Hirama, M.; Noda, T.; Takeshi, S.; Ito, S. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2645−2646; Majewski, M.; Gleave, D. M. *Tetrahedron Lett.* **1989**, *30*, 5681−5684. Addition of TMSCl instead of **9a** gave **4b** (88% yield). Addition of benzaldehyde instead of **9a** gave a mixture of aldol diastereomers (30−50%; 4−6:1 anti/syn), a result inferior to that reported[5] (98%; 9:1 anti/syn). We attempted numerous modifications of the procedure (i.e., reaction time with **9a** (0.5−60 min), concentration (0.05−0.5 M), stoichiometry (**9a**/**3** = 0.5−3:1), quench (HOAc, TESOTf, DIBAl−H), and work-up procedure).

(11) We have found various aldol adducts of **3** to be stable to retroaldol reaction; see reference 6c.

(12) See footnote 16 in reference 4.

(13) Review: Seebach, D. *Angew. Chem., Int. Ed.* **1988**, *27*, 1624−1654.

(14) Stork, G.; Hudrlik, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4462−4464; *J. Am. Chem. Soc.* **1968**, *90*, 4464−4465.

Table 1. Diastereoselectivity of Aldol Reactions of 4 with 9

entry	enolate derivative (equiv)	aldehyde (equiv)	promoter (equiv)	aldol adducts (series)[a]	yield (%) [b]	ratio of aldols [c] 11	12	13	14
1	**4a** (1)	**9a** (1.2)	[d]	**a**	15−40	1	2.5		
2	**4c** (1.5)	**9a** (1)	[d]	**a**	70	1	9		
3	**4c** (2)	**9a** (1)	$MgBr_2{\cdot}OEt_2$ (2)[e]	**a**	75	1	2.5		
4	**4d** (1)	**9a** (4)	[f]	**a**	82	1	10		
5	**4e** (1)	**9a** (4)	[f]	**a**	84	1	15		
6	**4f** (1)	**9a** (1.2)	[g]	**a**	46[h]	3.6[h]	1		
7	**4b** (2)	**9a** (1)	$BF_3{\cdot}OEt_2$ (1)[i]	**a**	70	2	1		
8	**4b** (2)	**9a** (1)	$SnCl_4$ (2)[j]	**a**	72	1	3		
9	**4b** (1.5)	**9a** (1)	$TiCl_4$ (1)[i]	**a**	87	16	1		
10	**4b** (2)	**9a** (1)	$MgBr_2{\cdot}OEt_2$ (1)[j]	**a**	23			1.7	1
11	**4b** (2)	**9a** (1)	$MgBr_2{\cdot}OEt_2$ (3)[k]	**a**	89			3	1
12	**4c** (2)	**9b** (1)	[d]	**b**	61	1	4		1.5
13	**4c** (2)	**9c** (1)	[d]	**c**	64		1		
14	**4b** (1.5)	**9b** (1)	$TiCl_4$ (1)[i]	**b**	27		1		1.3
15	**4b** (2)	**9c** (1)	$TiCl_4$ (1)[i]	**c**	81	20		1	2
16	**4b** (2)	**9b** (1)	$MgBr_2{\cdot}OEt_2$ (3)[k]	**b**	84			3.5	1
17	**4b** (2)	**9c** (1)	$MgBr_2{\cdot}OEt_2$ (3)[k]	**c**	74	4		7	1

[a] The series of adducts **11**−**14** as shown in Scheme 2. [b] The total isolated yield of all aldol adducts. [c] Determined by isolation or by ^{1}H NMR of purified products (relative error estimated at ±10%); see Experimental Section. These ratios were consistent with those suggested from ^{1}H NMR of the crude reaction mixtures. The detection limit for minor diastereomers is estimated to be 3%. [d] Reaction at −78 °C for 1−5 min. [e] Reaction of **4c** with $MgBr_2$ for 5 min at −78 °C and then with **9a** for 5 min at −78 °C. [f] Reaction at −78 °C for 3 h. [g] Reaction at −78 °C for 5 h. [h] See text. [i] Reaction at −78 °C for 1 h. [j] Reaction at 0 °C for 4 h. [k] Reaction at 0 °C for 1 h.

amine-free Li enolate may have some generality and should be studied further.[15]

Reactions of Ti, Mg, and B enolates of **3** with **9a** were also investigated (Table 1). Compared to the Li enolate **4c**, inferior diastereoselectivity in favor of **12a** was obtained with the putative Mg(II) enolate (Table 1, entry 3). Although the boron enolates **4d** and **4e** performed slightly better than did **4c** in terms of yield and stereoselectivity of the aldol reaction (compare entry 2 with entries 4 and 5), the simplicity of the experimental procedure using **4c** was an advantage in reactions carried out on a preparative scale. The reaction of **9a** with the Ti(IV) enolate **4f** (prepared by addition of *i*-Pr_2EtN to a mixture of **3** and $TiCl_4$) gave **11a** (26%) in addition to a 1:1 mixture of two bisaldol adducts (20%).[6b] On the basis of the structures of the bisaldols adducts, we estimate that the initial aldol reaction between **4f** and **9a** produced a 3.6:1 mixture of **11a**/**12a**.[16]

Several Lewis acid-mediated reactions of **4b** with **9a** were examined (i.e., Mukaiyama reactions).[17] Whereas the reactions mediated by $BF_3{\cdot}OEt_2$ and $SnCl_4$ gave mixtures of **11a** and **12a** with modest stereoselectivity (Table 1, entries 7 and 8), the $TiCl_4$-promoted reaction gave **11a** in good yield and with excellent diastereoselectivity (Table 1, entry 9). All of the above aldol reactions of **9a** with **4a**, **4b**, or **4c** gave only the 1′,6″-syn diastereomers **11a** and **12a**. By contrast, reaction of **9a** with **4b** in the presence of $MgBr_2{\cdot}OEt_2$ exclusively gave the 1′,6″-anti diastereomers **13a** and **14a**. The diastereoselectivity in favor of **13a** was improved with excess $MgBr_2{\cdot}OEt_2$ (cf. entries 10 and 11); this effect has been noted in other processes.[18]

To the best of our knowledge, stereoselective aldol reactions of ketals of *β*-ketoaldehydes have not been previously reported. Because of the unusual and useful diastereoselectivity observed in the reactions of **9a** with **4**, we sought to ascertain the role of the ketal group in this selectivity. Toward this end, we prepared the cis and trans (methoxy)methyl (MOM) ether-protected *β*-hydroxyaldehydes **9b** and **9c** (Scheme 1) and examined their aldol reactions with **4b** and **4c** under the conditions that gave the most diastereoselective reactions with **9a** (Table 1, entries 12−17). Interestingly, **9a** and **9c** had very similar stereoselectivities in their reactions both with **4c** (i.e., high selectivity for the 1′,3-anti-1′,3″(6″)-syn products **12a** and **12c**) and with **4b** in the presence of $TiCl_4$ (i.e., high selectivity for the 1′,3-syn-1′,3″(6″)-syn products **11a** and **11c**) but very dissimilar stereoselectivities in their reactions with **4b** in the presence of $MgBr_2{\cdot}OEt_2$. By contrast, **9a** and **9b** had very similar stereoselectivities in their reactions with **4b** in the presence of $MgBr_2{\cdot}OEt_2$ (i.e., high selectivity for 1′,3″-(6″)-anti products **13a**/**14a** and **13b**/**14b**) but very dissimilar selectivities in the other reactions.[19] In no case was a 1′,3-anti-1′,3″(6″)-anti aldol (i.e., **14**) the major product.

Determination of Stereochemical Configurations. In previous work, Hayashi[5] proposed the 1′,3-anti-

(15) Improved diastereoselectivity was noted in other reactions. Reaction of the "amine-free" Li enolate of cyclohexanone (prepared from the trimethylsilyl enol ether and MeLi as described for **4c**) with benzaldehyde under the same conditions (−78 °C, 5 min) gave a 12:1 mixture of anti and syn aldol adducts, respectively (75%), and a similar reaction of **4c** with benzaldehyde gave a >10:1 mixture of anti and syn aldol adducts, respectively (60%). See reference 10 for the results of the same reactions using LDA-generated enolates.

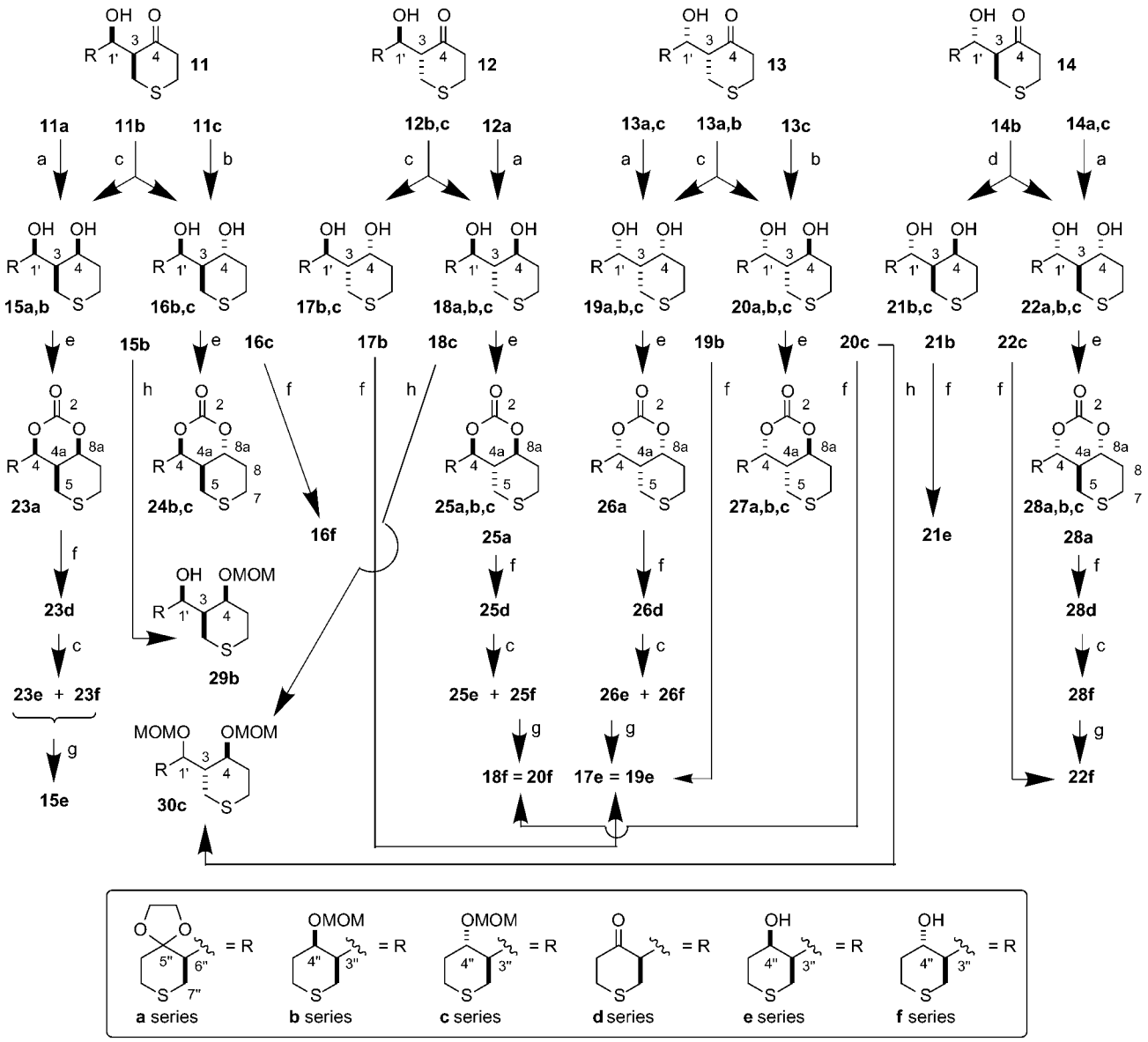
(16) We have previously established (ref 6b) that the same bisaldol adducts are produced from reactions of **9a** with the Ti(IV) enolates of **11a** and **12a**. One of the bisaldols was identical to the major product from **11a**, and the other was the major product from **12a**. Thus, it is plausible that the 1:1 mixture of bisaldols (20%) comes from an equal mixture of **11a** and **12a** and, consequently, an estimated 3.6:1 ratio of **11a** to **12a** in the initial aldol reaction. Presumably, the bisaldols result from incomplete enolate formation from **3**, thereby leaving excess base to generate the Ti(IV) enolate from the initially formed Ti(IV) aldolates corresponding to **11a** and **12a**.

(17) (a) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503−7509. (b) Genari, C. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1993; Vol. 2, Chapter 2.4, p 629.

(18) Ward, D. E.; Hrapchak, M. J.; Sales, M. *Org. Lett*. **2000**, *2*, 57−60.

(19) Aldehyde **9b** was not stable to $TiCl_4$ (mainly elimination); the low yields of **14b** and **11b** obtained from the $TiCl_4$-promoted reaction of **4b** with **9b** prevent us from drawing firm conclusions about the diastereoselectivity in this reaction.

Scheme 3. Determination of Aldol Stereochemistry[a]



[a] Reagents: (a) DIBAL-H. (b) $NaBH(OAc)_3$. (c) $NaBH_4$. (d) $NaBH_3CN$. (e) Im_2CO. (f) H^+. (g) NaOH, MeOH. (h) MOM-Cl, *i*-$PrEt_2N$.

1′,6″-syn relative configurations[20] (i.e., **12a**) for the aldol adduct obtained from the reaction of **4a** with **9a** on the basis of a "large" (the value was not reported) $^3J_{HC-1'/HC-3}$ coupling constant (indicating a 1′,3-anti relative configuration)[21] and assuming Cram diastereoface selectivity for the addition to the aldehyde group in **9a** (leading to a 1′,6″-syn relative configuration). In our hands (vide supra), the same reaction gave a 2−3:1 mixture of two aldol adducts (i.e., **12a**/**11a**); assignment of the C-1′/C-3 relative stereochemical configurations in our products was tenuous because the apparent $^3J_{HC-1'/HC-3}$ coupling constants for the major (**12a**) and minor (**11a**) isomers were 6.5 and 8.5 Hz, respectively, and the validity of those apparent *J* values was questionable because of possible second-order effects due to the similar chemical shifts for HC-3 and H_2C-2.[21] The assumption of Cram diastereoface selectivity also seemed uncertain in light of numerous examples of "anti-Cram" diastereoselectivity in aldol reactions of aldehydes with *β*-alkoxy substituents.[22] Thus, to unambiguously establish the relative stereochemical configurations for **11a** and **12a**, we prepared a series of chemical derivatives, as summarized in Scheme 3.[6a] A similar approach allowed determination of the relative stereochemical configurations for all of the aldol adducts **11**−**14**.

The C-1′/C-3 relative configuration for each aldol adduct was determined by preparing a cyclic carbonate derivative (**23**−**28**). Reduction of the aldols **11**−**14** to give

(20) For simplicity and to allow easy comparison to similar aldol reactions, the syn (same side) and anti (opposite sides) stereochemical descriptors for aldols **11**−**14** refer to the relative disposition of the designated pairs of non-hydrogen substituents with respect to the plane defined by the carbon chain C-4−C-3−C-1′−C-3″(or C-6″)−C-4″(or C-5″) in an extended (zigzag) conformation.

(21) According to the Stiles−House rule for intramolecularly H-bonded aldols, the $^3J_{H-C(OH)-C(CO)-H}$ coupling constant for the threo (anti) isomer (6−9 Hz) is larger than that for the erythro (syn) isomer (2−4 Hz): (a) Stiles, M.; Winkler, R. R.; Chang, Y.-L.; Traynor, L. *J. Am. Chem. Soc.* **1964**, *86*, 3337−3342. (b) House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310−3324.

(22) Reviews: (a) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095−1120. (b) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191−1223.

Table 2. Derivatives Used to Establish the Relative Stereochemical Configurations of 11−14

entry	aldol	relative configurations[a] (C-1′/C-3, C-1′/C-3″(6″))	carbonate derivative	$^3J_{HC-4/HC-4a}$ (Hz)[b]	HC-4/HC-4a relative orientation[c]	triol derivative	symmetry (no. of δ_C's)[d]
1	**11a**	syn, syn	**23a**	2	cis	**16e**	symmetric (6)
2	**12a**	anti, syn	**25a**	10	trans	**18f**	unsymmetric (11)
3	**13a**	syn, anti	**27a**	4.5	cis	**19e**	unsymmetric (11)
4	**14a**	anti, anti	**28a**	10	trans	**22f**	symmetric (6)
5	**11b**	syn, syn	**24b**	4.5	cis	**29b**	symmetric (8)
6	**12b**	anti, syn	**25b**	10	trans	**17e**	unsymmetric (11)
7	**13b**	syn, anti	**27b**	3.5	cis	**19e**	unsymmetric (11)
8	**14b**	anti, anti	**28b**	8.5	trans	**21e**	symmetric (6)
9	**11c**	syn, syn	**24c**	7[e]	cis	**18f**	symmetric (6)
10	**12c**	anti, syn	**25c**	11[e]	trans	**30c**	unsymmetric (17)
11	**13c**	syn, anti	**27c**	6[e]	cis	**20f**	unsymmetric (11)
12	**14c**	anti, anti	**28c**	10[e]	trans	**22f**	unsymmetric (11)

[a] See ref 20. [b] The coupling constant was determined assuming first-order behavior. [c] With respect to the carbonate derivative; see ref 25. [d] Symmetry of the triol derivative; see ref 26. [e] The spin systems for the two thiopyran fragments in the **c** series of aldols (**11**−**14**) are very similar; the assignment was confirmed by NOE (correlation between HC-4′ and the MOM-CH_2).

1,3-diols **15**−**22** was accomplished with a variety of reagents: DIBAL-H (1,3-syn selective),[23] $NaBH(OAc)_3$ (1,3-anti selective),[24] $NaBH_4$, and $NaBH_3CN$ (unselective). The C-3/C-4 relative configuration (i.e., cis or trans) for each of the products (**15**−**22**) was readily determined by analysis of the $^3J_{H-H}$ coupling constants observed for HC-4, assuming a chair conformation for the 3-substituted tetrahydro-2*H*-thiopyran-4-ol fragment. For each aldol (except **11a**), a trans alcohol derivative (i.e., **16**, **18**, **20**, or **22**) was obtained selectively or was isolated from a mixture of cis and trans products. Reactions of the 11 trans alcohols **16b,c**, **18a**−**c**, **20a**−**c**, and **22a**−**c** with 1,1′-carbonyldiimidazole (Im_2CO) gave the corresponding trans fused cyclic carbonates **24b,c**, **25a**−**c**, **27a**−**c**, and **28a**−**c**, respectively. The relative orientations of HC-4/HC-4a (i.e., cis or trans) in these carbonates were established from their respective $^3J_{HC-4/HC-4a}$ coupling constants,[25] thereby establishing the C-1′/C-3 relative configurations in the precursor aldols (Table 2). For **11a**, the carbonate **23a** (prepared from the cis alcohol **15a**) had a $^3J_{HC-4/HC4a}$ coupling constant of 2 Hz, indicating a cis relationship between HC-4 and HC-4a (Table 2, entry 1); this assignment was confirmed by the observation of a positive NOE for HC-4 upon irradiation of HC-8a.

The relative configurations at C-3/C-6″ in aldols **11a**−**14a** and at the equivalent C-3/C-3″ positions in aldols **11b**−**14b** and **11c**−**14c** (i.e., syn or anti)[20] were established from the symmetry of triol derivatives prepared with identical relative configurations at C-3/C-4 and at C-3″/C-4″ (i.e., both cis or both trans).[26] Thus, for aldols **12a** and **14a**, acid hydrolysis of the ketals in the derived trans carbonates (**25a** and **28a**) gave the corresponding ketones **25d** and **28d**, respectively.[27] Nonselective reductions of **25d** and **28d** ($NaBH_4$) gave cis/trans mixtures of alcohols **25e,f** and **28e,f**, respectively.[28] Hydrolyses of the trans hydroxycarbonates **25f** and **28f** gave the unsymmetric triol **18f** (identical to **20f**) and the symmetric triol **22f**, respectively, thereby fully defining the stereochemical configurations for **12a** and **14a**. The stereostructures of aldols **11a** and **13a** were established using the same procedure but starting from the derived cis carbonates **23a** and **26a**; after hydrolysis of the ketals and reduction of the resulting ketones, base hydrolysis of the corresponding cis hydroxycarbonates **23e** and **26e** gave triols **15e** (symmetric) and **19e** (unsymmetric), respectively. For aldols **11b**−**14b** derived from **9b**, the corresponding cis diols **17b**, **19b**, and **21b** were used to prepare triols **17e** (identical to **19e**; unsymmetric) and **21e** (symmetric) by hydrolyses of the MOM ethers; the bis-MOM ether derivative **29b** was prepared from cis diol **15b** by reaction with MOM-Cl. For the aldols **11c**−**14c** derived from **9c**, the corresponding trans diols **16c**, **20c**, and **22c** were used to prepare triols **16f** (symmetric), **20f** (identical to **18f**; unsymmetric), and **22f** (symmetric), respectively; the same unsymmetrical tris-MOM derivative **30c** was obtained from the trans diols **18c** and **20c**. Table 2 summarizes the carbonate and triol derivatives used to assign the relative stereochemical configurations in aldols **11a**−**14a**, **11b**−**14b**, and **11c**−**14c**.

Table 3 shows the apparent $^3J_{HC-1'/HC-3}$ and δ_H HC-1′ values for aldols **11**−**14**. Clearly, the use of the $^3J_{HC-1'/HC-3}$ coupling constant to assign simple aldol diastereoselectivity (i.e., syn or anti for C-1′/C-3)[21] is completely unreliable for these systems.[29] Half of the 1′,3-anti aldols (entries 4, 8, and 14) have "small" coupling constants (≤5 Hz), and two of the syn aldols (entries 1 and 9) have "large" coupling constants (>8 Hz). Comparing pairs of syn/anti diastereomers (i.e., entries 1/2, 3/4, 5/6, 7/8, 9/10, and 11/12), four of the six have similar $^3J_{HC-1'/HC-3}$ coupling constants (difference is ≤1 Hz). Only two examples (entries 1/2 and 11/12) have as much as a 2 Hz difference between their $^3J_{HC-1'/HC-3}$ coupling constants, and the syn isomer has the greater *J* value in one of these (cf. entries 1 and 2). On the other hand, the

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(24) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560−3578.

(25) The trans ring fusion in carbonates **24**, **25**, **27**, and **28** ensures that HC-4a has an axial orientation; thus, for HC-4/HC-4a, trans H's will have an axial−axial disposition (J = 8.5−11 Hz) and cis H's will have an axial−equatorial disposition (J = 3.5−7 Hz).

(26) Aldols with a syn relative configuration at C-3/C-6″ or C-3/C-3″ give symmetrical (C_s) triol derivatives. Aldols with an anti relative configuration at C-3/C-6″ or C-3/C-3″ give unsymmetrical (pseudo-C_2-symmetric) triol derivatives.

(27) Ketal hydrolyses were shown to occur without epimerization by isolating products without deuterium incorporation from reactions using $DClO_4/D_2O$.

(28) The C-3″/C-4″ relative configurations (i.e., cis or trans) of the product alcohols were readily determined by analysis of the $^3J_{H-H}$ coupling constants observed for HC-4″, assuming a chair conformation for the 3-substituted tetrahydro-2*H*-thiopyran-4-ol fragment.

(29) For a detailed discussion of the pitfalls of using ^{1}H NMR to assign stereochemical configurations of aldols of cyclic ketones, see: Kitamura, M.; Nakano, K.; Okada, M.; Noyori, R. *J. Am. Chem. Soc.* **2001**, *123*, 8939−8950.

Table 3. Apparent $^3J_{HC-1'/HC-3}$ and δ_H HC-1′ for 11−14

entry	aldol	C-1′/C-3 relative configuration[a]	δ_H HC-1′	$^3J_{HC-1'/HC-3}$ (Hz)[b]
1	**11a**	syn	4.79	8.5
2	**12a**	anti	4.50	6.5
3	**13a**	syn	4.57	3.5
4	**14a**	anti	4.24	3.5
5	**11b**	syn	4.23	5.5
6	**12b**	anti	3.96	6
7	**13b**	syn	4.20	3.5
8	**14b**	anti	3.77	3.5
9	**11c**	syn	4.84	8.5
10	**12c**	anti	4.47	9.5
11	**13c**	syn	4.52	3
12	**14c**	anti	4.07	5

[a] See reference 20. [b] The coupling constant was determined assuming first-order behavior.

δ_H HC-1′ values for the syn aldols are consistently greater (i.e., at lower field) than the values for the corresponding anti aldols and within each series; the order (low field to high field) of the δ_H HC-1′ values is 1′,3-syn-1′,3″(or 6″)-syn > 1′,3-syn-1′,3″(or 6″)-anti > 1′,3-anti-1′,3″(or 6″)-syn > 1′,3-anti-1′,3″(or 6″)-anti.[20]

Discussion

The directed aldol reaction of **3** (via **4**) with **9** can produce four diastereoisomeric products, **11**−**14**. The control elements influencing the stereochemical outcome of this reaction involve the diastereoface selectivity for addition to the aldehyde carbonyl group in **9** (i.e., to give 1′,3″(6″)-syn or 1′,3″(6″)-anti products) and the simple diastereoselectivity (i.e., relative topicity) for the aldol reaction (i.e., to give 1′,3-syn or 1′,3-anti products). The stereoselectivity of aldol reactions of enolate derivatives from cyclic ketones is often low and unpredictable.[30] Nonetheless, in the only previously described examples of aldol reactions of **3**,[5] a high propensity for anti relative topicity (10−99:1) was reported for reactions of the corresponding Li,[10] B, Sn(IV), and Ti(IV) enolates with simple aldehydes. Similarly, both the B[31] and Li (especially amine-free)[10,15] enolates of cyclohexanone react with aldehydes to give the anti adducts with high selectivity. On the other hand, Mukaiyama-type reactions[17] of cyclohexanone enol trimethylsilyl ether with aldehydes using a variety of Lewis acid promoters typically give adducts with modest stereoselectivity (syn/anti from 3:1 to 1:3).[32] These results can be rationalized by the preference for "closed" chairlike Zimmerman−Traxler transition states[33] in aldol reactions of Li and B enolates, whereby the minimization of nonbonded interactions favors the formation of anti aldol adducts from the necessarily (*E*)-enolates derived from cyclic ketones.[7a−c,34] By contrast, Mukaiyama aldol reactions are thought to proceed via open transition states having either antiperiplanar or synclinal geometries, and both the direction and degree of simple diastereoselectivity are dependent on a number of factors.[17,22a,35]

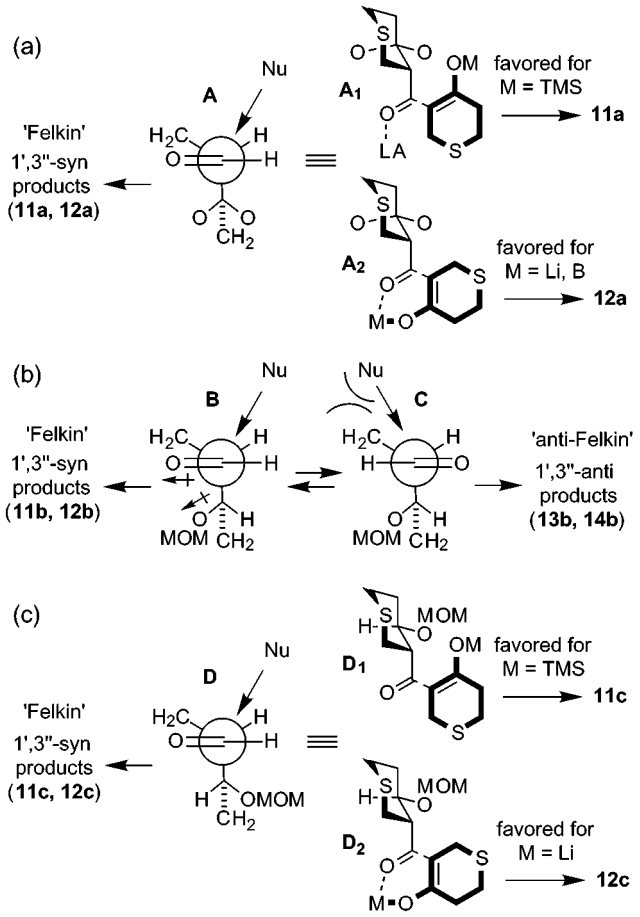

Figure 1. Proposed nonchelation transition-state models for reactions of **4** with (a) **9a**, (b) **9b**, and (c) **9c**.

Models to rationalize and predict the diastereoface selectivity in additions of enolates to chiral aldehydes have been discussed extensively in the literature.[22] The Felkin−Ahn model[36] is widely used to account for the effect of a stereogenic center α to the aldehyde carbonyl (1,2 induction), and the influence of a heteroatom substituent *β* to the carbonyl group (1,3 induction) has been reconciled using chelation[37,38] or nonchelation[39−41] models. The stereochemical model recently proposed by Evans[40] merges the effects of 1,2 and 1,3 asymmetric induction and thus is well suited for application to aldehydes such as **9**. Figure 1 shows the proposed nonchelation transition-state (TS) models for aldol reactions of **4** with **9**, according to the Evans model.[40] Thus, **9c** is analogous to an acyclic "anti" α-methyl-*β*-alkoxyaldehyde (cf. **32**),

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(31) (a) Evans, D. A.; Vogel, E.; Nelson, J. V. *J. Am. Chem. Soc.* **1979**, *101*, 6120−6123. (b) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099−3111.
(32) (a) Nakamura, H.; Matsuhashi, H.; Arata, K. *Synlett* **2000**, 668−670. (b) Raju, S. V. N.; Ponrathnam, S.; Rajan, C. R.; Srinivasan, K. V. *Synlett* **1996**, 239−240 and references therein.
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(35) Denmark, S. E.; Lee, W. *J. Org. Chem.* **1994**, *59*, 707−709.
(36) (a) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199−2204. (b) Ahn, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61−70. (c) Ahn, N. T. *Top. Curr. Chem.* **1980**, *88*, 145−162.
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(38) Evans, D. A.; Allison, B. D.; Yang, M. G. *Tetrahedron Lett.* **1999**, *40*, 4457−4460.
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(40) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322−4343.
(41) Bonini, C.; Esposito, V.; D'Auria, M.; Righi, G. *Tetrahedron* **1997**, *53*, 13419−13426.

where the α and *β* substituents reinforce addition to the same aldehyde diastereoface (Figure 1, TS **D**) and high 1′,3″-syn selectivity (i.e., Felkin-type) is predicted and observed (Table 1, entries 13 and 15). Reaction of **9c** with the Li enolate **4c** via the expected closed TS $\mathbf{D_2}$ gives the 1′,3-anti aldol **12c**, whereas the $TiCl_4$-promoted reaction of **9c** with **4b** via the open antiperiplanar TS $\mathbf{D_1}$ gives the 1′,3-syn aldol **11c**. In contrast, **9b** is analogous to an acyclic "syn" α-methyl-*β*-alkoxyaldehyde (cf. **31**), where the substituents direct addition to opposite faces of the aldehyde (Figure 1, Felkin TS **B** has an unfavorable dipole interaction and anti-Felkin TS **C** presents an unfavorable steric interaction with the nucleophile), thereby offering a rationale for the low 1′,3″-syn/anti selectivity observed (Table 1, entries 12 and 14). For aldehyde **9a**, TS **A** predicts 1′,3″-syn selectivity (i.e., Felkin-type), as is observed (Table 1, entries 1−9). Although TS **A** has an unfavorable interaction between the carbonyl and cis *β*-oxygen of the ketal group, all other possible conformations with staggered relationships between the forming bond and the α-substituents have additional unfavorable steric or dipole interactions.[42] Reactions of **9a** with the Li (**4c**), B (**4d** and **4e**), and Mg enolates via the expected closed TS $\mathbf{A_2}$ would preferentially give the 1′,3-anti aldol **12c**, as observed (Table 1, entries 1−5). The reactions of **4b** with **9a** promoted by $BF_3{\cdot}OEt_2$, $SnCl_4$, or $TiCl_4$ give only the Felkin adducts **11a** and **12a** (Table 1, entries 7−9), but the wide variation in the observed **11a**/**12a** ratio suggests that reactions can occur via both antiperiplanar (i.e., via $\mathbf{A_1}$ to give **11a**) and synclinal TSs (i.e., via $\mathbf{A_2}$ with M = TMS and without coordination to give **12a**). Perhaps the relative propensity for formation of **12a** in these reactions is dependent upon the nature of the interaction between the coordinated Lewis acid and the TMSO group in the synclinal TS. In any event, the use of $TiCl_4$ gave **11a** with high selectivity (Table 1, entry 9).

In contrast to the above reactions that give the Felkin aldol adducts **11** and **12** with high selectvity,[19] the $MgBr_2{\cdot}OEt_2$-promoted reactions of **4b** with **9a**, **9b**, and **9c** predominantly give the anti-Felkin adducts **13** and **14** (Table 1, entries 10, 11, 16, and 17). These results can be rationalized by assuming that the Mg(II)-mediated reactions proceed through a chelated intermediate (i.e., chelation-controlled selectivity).[38] Chelated intermediates have often been invoked to explain the formation of anti-Felkin products in aldol reactions of *β*-alkoxy aldehydes;[22,43] however, Evans et al. have established that the same products can also result from nonchelated intermediates.[40,44] The ability of $MgBr_2$, $TiCl_4$, and $SnCl_4$ to form chelates with *β*-alkoxyaldehydes has been firmly established by NMR;[45] however, the use of these Lewis acids does not necessarily result in a reaction via a chelated intermediate.[38] For example, chelate organization is unlikely in both the $TiCl_4$- and $SnCl_4$-mediated reactions of **4b** with **9a** because the exclusive Felkin diastereoselectivity in these cases is also obtained in the presence of $BF_3{\cdot}OEt_2$, where chelation is prevented (Table 1, entries 7−9). On the other hand, the dramatic reversal of the diastereoface selectivity for addition of **4b** to **9** in the presence of $MgBr_2{\cdot}OEt_2$ strongly supports the hypothesis of a chelated intermediate in these reactions.[46] Figure 2 shows proposed chelated transition-state (TS) models that can account for these results. The exclusive anti-Felkin selectivity observed in the reactions of **4b** with **9a** and **9b** (Table 1, entries 11 and 16) can be rationalized by examination of the chelated models **E**[47] and **F**, which suggest high selectivity because the least-hindered approach and the "axial" face of the carbonyl carbon are coincident. Similarly, the modest selectivity observed in the reaction of **9c** (Table 1, entry 17) is accounted for in the chelated model **G**, which indicates that the faces of the carbonyl are not differentiated decisively.

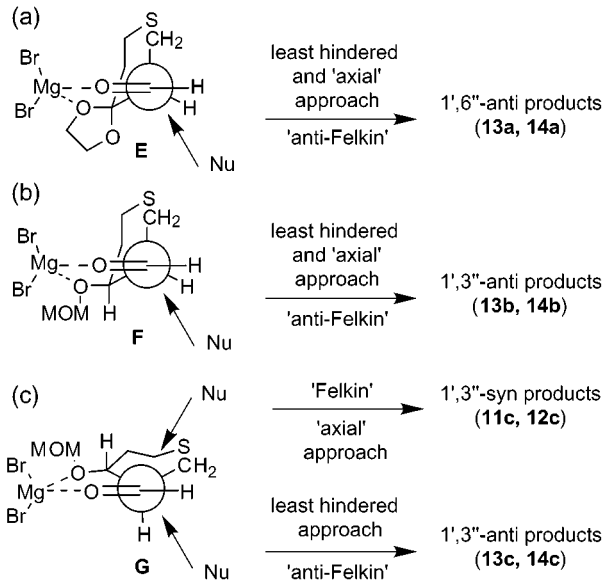

Figure 2. Proposed chelated transition-state models for reactions of **4b** with (a) **9a**, (b) **9b**, and (c) **9c**.

It is instructive to compare the diastereoselectivities observed in aldol reactions of **4** with **9b** and **9c** to those reported[48] for similar aldol reactions of the structurally related acyclic analogues **31**−**33** (Scheme 4). The trans

(42) The sulfur in **9** can also be considered a *β*-heteroatom substituent in this model. If the tetrahydrothiopyran ring adopts a chair conformation and the formyl group has an equatorial orientation as expected, then the C−S bond is necessarily anti to the C−CHO bond and neither steric nor dipole interactions are possible. If the formyl group has an axial orientation, then the staggered conformation of **9a** without unfavorable dipole interactions between the carbonyl and ketal oxygens has an unfavorable dipole interaction with the C−S bond; this conformation would also suggest Felkin selectivity for addition to the carbonyl. For examples of aldol reactions with acyclic *β*-thio-substituted aldehydes, see: Annunziata, R.; Cinquini, M.; Cozzi, F.; Cozzi, F. G.; Consolandi, E. *J. Org. Chem*. **1992**, *57*, 456−461.

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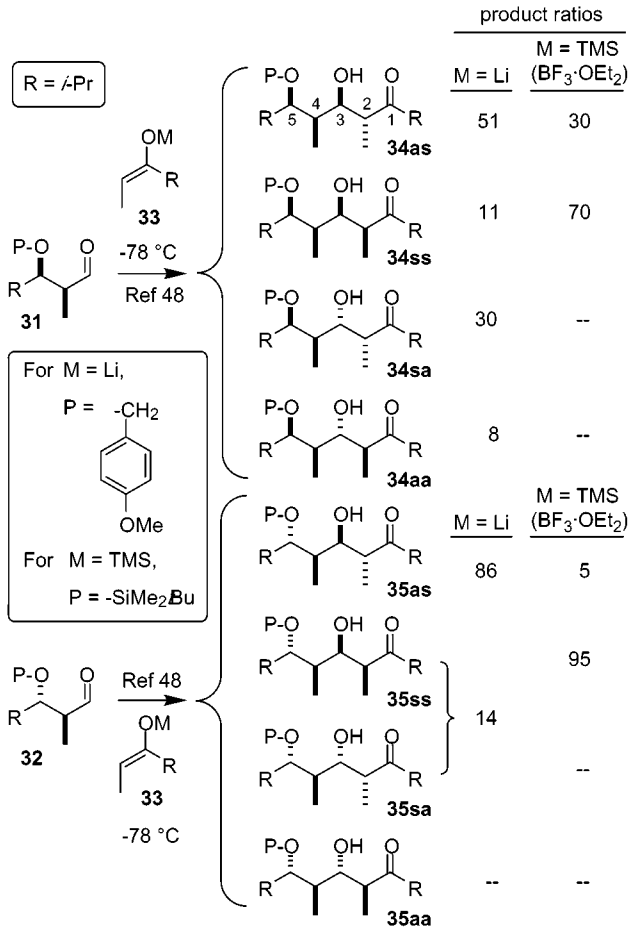
(45) (a) Keck, G. E.; Castellino, S. E. *J. Am. Chem. Soc.* **1986**, *108*, 3847−3849. (b) Keck, G. E.; Castellino, S. *Tetrahedron Lett.* **1987**, *28*, 281−284.

(46) The superior ability of $MgBr_2$ (compared to $SnCl_4$ and $TiCl_4$) to chelate *β*-alkoxy aldehydes has been noted previously; see reference 45.

(47) TS **E** (Figure 2) indicates chelation of the carbonyl oxygen and the cis oxygen of the ketal group. In principle, chelation involving the trans oxygen of the ketal is also possible. Such a structure (cf. **G** with the H geminal to the O-MOM group replaced with an OCH_2) would also suggest predominant formation of anti-Felkin products with increased selectivity compared to **G** because of the increased steric hindrance to Felkin approach caused by the ketal. The very close similarity in the diastereoselectivities of the reactions of **9a** and **9b** under these conditions favors cis chelation as indicated in TS **E**.

(48) (a) Evans, D. A.; Yang, M. G.; Dart, M. J.; Duffy, J. L.; Kim, A. S. *J. Am. Chem. Soc.* **1995**, *117*, 9598−9599. (b) Evans, D. A.; Yang, M. G.; Dart, M. J.; Duffy, J. L. *Tetrahedron Lett*. **1996**, *37*, 1957−1960.

Scheme 4. Aldol Diastereoselectivity for Acyclic Substrates[48]



aldehyde **9c** and the related anti aldehyde **32** give very similar diastereoselectivities under similar conditions. Thus, reactions of the Li (*E*)-enolates **4c** (with **9c**) and **33** (with **32**) are highly selective for Felkin addition and anti relative topicity to give the adducts **12c** (exclusive) and **35as** (86% ds),[49] respectively; the related Mukaiyama reactions (i.e., **4b** and **9c**, $TiCl_4$; **33** (M = TMS) and **32**, $BF_3{\cdot}OEt_2$) are also highly selective for Felkin addition, but with syn relative topicity to give adducts **11c** (87% ds)[49] and **35ss** (95% ds).[49] Interestingly, the minor adduct from the Mukaiyama reaction of **32** also results from a Felkin addition, whereas the minor adducts from the reaction of **9c** are anti-Felkin. The diastereoselectivities of the reactions of the cis aldehyde **9b** and the related syn aldehyde **31** are also similar to each other but are much lower than those discussed above.[19] For example, reactions of the Li (*E*)-enolates **4c** (with **9b**) and **33** (with **31**) gave only modest diastereoselectivity. In both cases, the major product arose from Felkin addition with anti relative topicity to give adducts **12b** (60% ds)[49] and **34as** (51% ds).[49] The anti/syn diastereoselectivities among the Felkin adducts are also similar in the two reactions (i.e., **12b**/**11b**, 4:1; **34as**/**34ss**, 4.5:1); however, the anti-Felkin syn adduct **34sa** is the second most-abundant product (30%) from **31**, but the analogous diastereomer (i.e., **13b**) is not detected in the reaction of **9b**. Thus, considering the presence of the sulfur atom and the associated ring that restricts the number of possible transition states, the diastereoselectivities for aldol reactions of **9b** and **9c** are strikingly similar to those obtained with the related acyclic analogues **31** and **32**, and the major products can be rationalized using established TS models.

In conclusion, comparison of the aldol reactions of **9a** with those of **9b** and **9c** suggests that the ketal group in **9a** is a useful stereocontrol element for aldehyde diastereoface selectivity. Under nonchelating conditions, **9a** exhibits very high Felkin selectivity (similar to **9c** but much higher than **9b**); under chelating conditions, very high anti-Felkin selectivity is obtained (similar to **9b** but much higher than **9c**). Under optimized conditions, three of the four possible diastereomers from the reaction of **4b** with **9a** can be produced selectively by varying the mediator: with MeLi (via **4c**), **12a** (9:1); with $TiCl_4$, **11a** (16:1); with $MgBr_2{\cdot}OEt_2$, **13a** (3:1). The fourth diastereomer **14a** can be obtained in good yield by isomerization of **13a**.[6c] In the context of polypropionate synthesis, additional aldol reactions of **11a**−**14a** with **9a** (two-directional or linear) can be envisaged.[6b] Such reactions raise several interesting stereoselectivity issues (e.g., double diastereoselection, mutual kinetic enantioselection, etc.). Our efforts in this area will be reported in due course.

Experimental Section[50]

Materials. Numerous methods for the preparation of **2** (and related esters), usually by Dieckmann cyclization of **1**, have been reported.[51,52] Most of these methods involve the use of NaOMe or NaH in various modifications of Fehnel and Carmack's improvement[51a] of the original procedure by Bennett and Scorah.[51b] Compared to the Fehnel and Carmack protocol (2 equiv of alcohol-free NaOMe in ether; 64% yield on a 1.4 mol scale), the modified procedures are typically reported on a much smaller scale (<0.1 mol), and the yields obtained vary widely (13−81%; most around 75%). Our experiments suggest that **2** decomposes readily under basic conditions in protic solution, perhaps explaining the variable yields noted above. The procedure detailed below is simple, reliable, and easily scalable. The important modifications over the previous method involve the in situ generation of NaOMe, the use of sufficient THF to have a (nearly) homogeneous reaction mixture, and careful quenching of the reaction. Ketone **3** was prepared from **2** by the known procedure.[51a,52e] All other reagents were commercially available and, unless otherwise noted, were used as received.

Methyl Tetrahydro-4-oxo-2*H*-thiopyran-3-carboxylate (2). Anhydrous methanol (freshly distilled from $Mg(OMe)_2$; 43.0 mL, 34.0 g, 1.06 mol) was added dropwise to a stirred suspension of finely cut sodium metal (23.0 g, 1.00 mol) in ether (100 mL) and THF (100 mL) at 0 °C under argon (caution: H_2 evolution). The mixture was stirred for 12 h at rt (some Na metal remained), and then a solution of the diester **1** (100 g, 0.485 mmol) in ether (200 mL) was added dropwise at 0 °C. The reaction mixture was stirred at rt until the Na

(49) Percent diastereoselectivity (ds) is defined here as the mole fraction of the major (or designated) diastereomer.

(50) See Supporting Information for general methods and procedures.

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metal was completely consumed and the diester was not detected by TLC (30% ethyl acetate in hexane) (ca. 24−60 h). The reaction mixture was transferred via cannula to a vigorously stirred solution of acetic acid (85 mL, 89 g, 1.5 mol) in water (200 mL) at 0 °C. The organic layer was separated, and the aqueous layer was extracted with ether (3×). The combined organic layers were washed sequentially with saturated aqueous $NaHCO_3$ (2×), water, and brine, dried over Na_2SO_4, and concentrated to give **2** as a pale-yellow viscous oil (74−83 g, 88−98%). Spectral data for the product was in accord with that previously reported.[52a]

3,6-Dihydro-4-trimethylsilyloxy-2*H*-thiopyan (4b).[53] A solution of **3** (5.34 g, 46.0 mmol), Et_3N (64 mL, 46 g, 0.46 mol), and TMSCl (29 mL, 25 g, 0.23 mol) in CH_2Cl_2 (50 mL) was stirred at rt under argon in a capped vessel for 10 days. The reaction mixture was concentrated, diluted with ether, and filtered through Celite. The combined filtrate and washings were concentrated, and the residue was placed under high vacuum (0.5 Torr) for several hours to give **4b** as a yellow oil (8.0−8.5 g, 92−98%), which was homogeneous by ^{1}H NMR and was used without further purification. The material slowly decomposed (mainly by hydrolysis) upon storage under argon at −15 °C. Thus, if the material was not used promptly, a convenient method of storage involved making a solution of known concentration in benzene (ca. 1 M) containing 2 equiv of Et_3N. This solution could be stored for months at −15 °C with negligible decomposition. The product was recovered as required by the concentration of aliquots. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.06−5.04 (1H, m), 3.15−3.14 (2H, m), 2.76−2.72 (2H, m), 2.27−2.23 (2H, m), 0.17 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.3 (s), 102.2 (d), 31.2 (t), 25.7 (t), 25.1 (t), 0.3 (q × 3); HRMS *m*/*z* calcd for $C_8H_{16}OSSi$ 188.0708, found 188.0705 (EI).

General Procedure for Preparation of the Amine-Free Lithium Enolate 4c.[53a] Methyllithium (1−1.5 M in diethyl ether, 1 equiv) was added dropwise via syringe to a stirred solution of the trimethylsilyl enol ether of the tetrahydro-4*H*-thiopyran-4-one in ether (2 mL/mmol of enol ether) at 0 °C under argon. The reaction mixture was warmed to rt (note: the Li enolate precipitated from the solution), and after 1 h, THF (2 mL/mmol of enol ether) was added via syringe. After stirring for 5 min (note: enolate dissolved), the reaction mixture was cooled to −78 °C.

Methyl 1,4-Dioxa-8-thiaspiro[4.5]decane-6-carboxylate (5a).[3b] A solution of β-ketoester **2** (30 g, 0.17 mol), ethylene glycol (43 g, 0.69 mol) and *p*-TsOH·H_2O (1.7 g, 8.9 mmol) in benzene (800 mL) was heated under reflux for 16 h with removal of water via a Dean−Stark trap. The cooled (rt) reaction mixture was concentrated under reduced pressure, diluted with ether, washed sequentially with saturated aqueous $NaHCO_3$ (2×), water, and brine, dried over Na_2SO_4, and concentrated to give **5a** as a colorless oil (32−37 g, 85−98%), which was homogeneous by TLC and NMR and was used without further purification. IR $\tilde{\nu}_{max}$ 1733 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.00−3.86 (4H, m), 3.71 (3H, s), 3.11 (1H, ap dd, J = 8.5, 13.5 Hz), 2.96−2.78 (3H, m), 2.67 (1H, dddd, J = 1.5, 3.5, 7, 13.5 Hz), 2.25 (1H, ddd, J = 3.5, 7, 13.5 Hz), 1.82 (1H, ddd, J = 3.5, 9.5, 13.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0 (s), 107.2 (s), 65.1 (t), 64.7 (t), 51.8 (d), 51.2 (q), 36.0 (t), 29.6 (t), 26.7 (t); HRMS *m*/*z* calcd for $C_9H_{14}O_4S$ 218.0613, found 218.0604 (EI). Anal. Calcd for $C_9H_{14}O_4S$: C, 49.53; H, 6.46. Found: C, 49.58; H, 6.39.

Methyl (3*S,4*R**)-tetrahydro-4-(methoxymethoxy)-2*H*-thiopyran-3-carboxylate (5b).** MOM-Cl (3.2 mL, 3.4 g, 42 mmol) was added dropwise over 2 min to a stirred solution of **6** (3.76 g, 21.3 mmol) and DIEA (7.4 mL, 5.5 g, 43 mmol) in CH_2Cl_2 (20 mL) at 0 °C. The reaction was allowed to stand at rt with periodic monitoring by TLC (50% ethyl acetate in hexane). After 3 days (reaction complete by TLC), the mixture was diluted with CH_2Cl_2 (200 mL), washed with 1 M HCl (2 ×) and H_2O, dried over Na_2SO_4, and concentrated to give **5b** (4.75 g, quantitative), which was homogeneous by ^{1}H NMR and TLC and was used in the next step without further purification. IR $\tilde{\nu}_{max}$ 1738 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.65 (1H, d, J = 7 Hz), 4.60 (1H, d, J = 7 Hz), 4.37−4.33 (1H, m), 3.71 (3H, s), 3.33 (3H, s), 3.17 (1H, dd, J = 12, 13.5 Hz), 3.03−2.92 (1H, m), 2.77 (1H, ddd, J = 3, 3.5, 12 Hz), 2.61 (1H, ddd, J = 2, 3, 13.5 Hz), 2.38−2.25 (2H, m), 1.87−1.75 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 95.9, 72.2, 55.8, 51.9, 48.1, 31.9, 23.7, 22.2; HRMS *m*/*z* calcd for $C_9H_{16}O_4S$ 220.0769, found 220.0768 (EI).

Methyl (3*R,4*R**)-tetrahydro-4-(methoxymethoxy)thiopyran-3-carboxylate (5c).** Using the above procedure, **7** (5.32 g, 30.2 mmol) was converted into **5c** (7.0 g, quantitative), which was homogeneous by ^{1}H NMR and TLC and was used in the next step without further purification. IR $\tilde{\nu}_{max}$ 1736 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.69 (1H, d, J = 7 Hz), 4.63 (1H, d, J = 7 Hz), 3.80 (1H, ddd, J = 4, 9, 10 Hz), 3.73 (3H, s), 3.34 (3H, s), 2.88−2.58 (5H, m), 2.42−2.32 (1H, m), 1.76 (1H, dddd, J = 4, 10, 10, 14 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 95.7, 75.7, 55.7, 52.0, 50.2, 32.8, 29.7, 26.9; HRMS *m*/*z* calcd for $C_9H_{16}O_4S$ 220.0769, found 220.0771 (EI).

Methyl (3*S,4*R**)-tetrahydro-4-hydroxy-2*H*-thiopyran-3-carboxylate (6) and Methyl (3*R**,4*R**)-tetrahydro-4-hydroxy-2*H*-thiopyran-3-carboxylate (7).**[52f,54] $NaCNBH_3$ (14.0 g, 0.223 mol) was added in four equal portions at 5 min intervals to a stirred solution of β-ketoester **2** (40.0 g, 0.225 mol) and citric acid (48 g, 0.228 mol) in ethanol (200 mL) at 0 °C. (Note: addition of $NaCNBH_3$ is exothermic.) The ice bath was removed, and the progress of the reaction was monitored by TLC (50% ethyl acetate in hexane); after ca. 40 min, **2** had been consumed. The reaction mixture was concentrated and then taken up in ethyl acetate and washed with H_2O and brine, dried over Na_2SO_4, and concentrated to give the crude hydroxyesters (a 2:1 mixture of **6**/**7** by ^{1}H NMR) as a light-yellow oil (32.6 g). (Note: If the reaction was left for longer than 1 h, a gel-like suspension that impeded the removal of ethanol by rotary evaporation formed. In these cases, the mixture was diluted with ethyl acetate and washed with brine (3×). The aqueous phases were extracted with ethyl acetate, and the combined organic layers were dried over Na_2SO_4 and concentrated to give the crude hydroxyesters **6** and **7**.) The crude product was fractionated by DFC (5−50% ethyl acetate in hexane) to give the cis hydroxyester **6** as a colorless oil (19.89 g, 49%) and the trans hydroxyester **7** as a colorless solid (9.85 g, 24%). **6**: IR $\tilde{\nu}_{max}$ 3503, 1719 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.17 (1H, ddd, J = 3, 3, 5.5 Hz), 3.72 (3H, s), 3.16 (1H, dd, J = 10.5, 13 Hz), 3.10−2.90 (1H, m), 2.99 (1H, ddd, J = 3, 11.5, 14 Hz), 2.85 (1H, ddd, J = 3, 3, 10.5 Hz), 2.57 (1H, dd, J = 3, 13.5 Hz), 2.32 (1H, dddd, J = 1.5, 4, 5, 13.5 Hz), 2.16 (1H, dddd, J = 3, 5.5, 5.5, 14 Hz), 1.89 (1H, dddd, J = 3, 3, 11, 14 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5 (s), 66.0 (d), 52.4 (q), 47.6 (d), 33.5 (t), 25.3 (t), 23.1 (t); HRMS *m*/*z* calcd for $C_7H_{12}O_3S$ 176.0507, found 176.0508 (EI). **7**: IR $\tilde{\nu}_{max}$ 3452, 1728 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.72 (1H, ddd, J = 4, 11, 11 Hz), 3.70 (3H, s), 3.00 (1H, br s), 2.83 (1H, ddd, J = 2, 3, 12 Hz), 2.71−2.61 (3H, m), 2.62 (1H, ddd, J = 3, 11.5, 11.5 Hz), 2.28 (1H, dddd, J = 3.5, 3.5, 3.5, 13.5 Hz), 1.68 (1H, dddd, J = 5, 11, 11, 13 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0 (s), 70.3 (d), 52.3 (q), 52.0 (d), 35.3 (t), 29.8 (t), 27.7 (t); HRMS *m*/*z* calcd for $C_7H_{12}O_3S$ 176.0507, found 176.0508 (EI).

1,4-Dioxa-8-thiaspiro[4.5]decane-6-methanol (8a).[3b] A solution of **5a** (22.5 g, 103 mmol) in anhydrous ether (100 mL) was added dropwise via syringe to a stirred suspension of $LiAlH_4$ (4.5 g, 113 mmol) in ether (200 mL) at 0 °C under argon. After 1 h, the reaction was quenched[55] by sequential dropwise addition of water (4.5 mL), 15% (w/v) sodium hydroxide (4.5 mL), and water (13.5 mL). The resultant gray suspension was stirred until granular white flakes formed (ca. 1−1.5 h) and then filtered through Celite using 1:1 ether/hexane. The combined filtrate and washings were washed with brine, dried over Na_2SO_4, and concentrated to give **8a** as

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a pale-yellow viscous oil (17.0−18.5 g, 86−94%), which was homogeneous by TLC and NMR and was used without further purification. IR $\tilde{\nu}_{max}$ 3442 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.03−3.97 (4H, m), 3.91 (1H, dd, J = 6.5, 11 Hz), 3.66 (1H, dd, J = 4.5, 11 Hz), 2.80−2.71 (3H, m), 2.65 (1H, ddd, J = 4, 7, 13.5 Hz), 2.25 (1H, br s), 2.19−2.13 (1H, m), 2.07 (1H, ddd, J = 3.5, 7, 13.5 Hz), 1.77 (1H, ddd, J = 4, 9.5, 13.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 109.5 (s), 64.7 (t), 64.4 (t), 62.3 (t), 47.0 (d), 35.1 (t), 29.3 (t), 26.6 (t); HRMS *m*/*z* calcd for $C_8H_{14}O_3S$ 190.0664, found 190.0672 (EI).

(3′*R,4′*R**)-[Tetrahydro-4-(methoxymethoxy)-2*H*-thiopyran-3-yl]methanol (8b).** Using the above procedure, reduction of the cis ester **5b** (2.423 g, 11.0 mmol) with $LiAlH_4$ (543 mg, 14.3 mmol) in ether (50 mL) and THF (7 mL; used to dissolve **5b**) gave **8b** as a clear oil (1.899 g, 90%), which was homogeneous by ^{1}H NMR and TLC and was used in the next step without further purification. IR $\tilde{\nu}_{max}$ 3426 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.67 (1H, d, J = 6.5 Hz), 4.60 (1H, d, J = 6.5 Hz), 3.95 (1H, br t, J = 2.5, 2.5 Hz), 3.63 (1H, dd, J = 7.5, 11 Hz), 3.61 (1H, dd, J = 7.5, 11 Hz), 3.38 (3H, s), 2.96−2.71 (2H, m), 2.40−2.25 (3H, m), 2.18 (1H, dddd, J = 2, 4, 4, 13 Hz), 2.03 (1H, m), 1.77 (1H, dddd, J = 2.5, 4, 11.5, 14 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 95.8, 73.2, 64.2, 56.1, 43.8, 31.3, 25.9, 23.6; HRMS *m*/*z* calcd for $C_8H_{16}O_3S$ 192.0820, found 192.0820 (EI).

(3′*R,4′*S**)-[Tetrahydro-4-(methoxymethoxy)-2*H*-thiopyran-3-yl]methanol (8c).** Using the above procedure, **5c** (1.016 g, 4.62 mmol) was converted to **8c** (832 mg, 94%), which was homogeneous by ^{1}H NMR and TLC and was used in the next step without further purification. IR $\tilde{\nu}_{max}$ 3451 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.73 (1H, d, J = 7 Hz), 4.60 (1H, d, J = 7 Hz), 3.82 (1H, dd, J = 4.5, 11 Hz), 3.66 (1H, dd, J = 4.5, 11 Hz), 3.44 (1H, ddd, J = 3.5, 10, 10 Hz), 3.40 (3H, s), 2.75−2.53 (4H, m), 2.45 (1H, br s), 2.31 (1H, dddd, J = 3.5, 4, 4, 13 Hz), 1.96−1.87 (1H, m), 1.79−1.66 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 95.5 (t), 77.8 (d), 64.7 (t), 56.0 (q), 46.3 (d), 33.4 (t), 30.1 (t), 27.4 (t); HRMS *m*/*z* calcd for $C_8H_{16}O_3S$ 192.0820, found 192.0820 (EI).

1,4-Dioxa-8-thiaspiro[4.5]decane-6-carboxaldehyde (9a). Swern Oxidation. A solution of DMSO (2.3 mL, 2.5 g, 32 mmol) in CH_2Cl_2 (5.0 mL) was added dropwise via syringe to a stirred solution of oxalyl chloride (1.4 mL, 16 mmol) in CH_2Cl_2 (30 mL) at −78 °C under argon. After 30 min at −78 °C, a solution of **8a** (2.00 g, 10.5 mmol) in CH_2Cl_2 (10 mL) was added dropwise via syringe to the reaction mixture. After another 30 min, *i*-Pr_2EtN (9.2 mL, 53 mmol) was added, and the reaction mixture was allowed to warm to rt. The mixture was diluted with CH_2Cl_2, washed sequentially with aqueous NH_4Cl and $NaHCO_3$, dried over Na_2SO_4, and concentrated. Fractionation by FCC (35% ethyl acetate in hexane) gave **9a** as a pale-yellow oil (1.30−1.70 g, 66−86%).

PCC Oxidation. PCC (4.90 g, 22.7 mmol) was added in three equal portions at 15 min intervals to a vigorously stirred suspension of **8a** (2.00 g, 10.5 mmol), NaOAc (2.58 g, 31.5 mmol), and Celite (5 g) in CH_2Cl_2 (50 mL) at 0 °C under argon. The reaction mixture was allowed to warm to rt, and after 3 h, it was filtered through a short plug of SiO_2 using ether. The combined filtrate and washings were concentrated and fractionated by FCC (25% ethyl acetate in hexane) to give **9a** as a colorless oil (1.1−1.4 g, 55−70%). IR $\tilde{\nu}_{max}$ 2840, 2737, 1721 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.85 (1H, s), 4.07−3.94 (4H, m), 2.96 (1H, dd, J = 9.5, 13.5 Hz), 2.86 (1H, br d, J = 13.5 Hz), 2.81−2.72 (2H, m), 2.64 (1H, m), 2.08 (1H, ddd, J = 3, 6, 13.5 Hz), 1.89 (1H, ddd, J = 3.5, 10, 13.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.3 (d), 107.8 (s), 64.9 (t), 64.7 (t), 56.6 (d), 36.2 (t), 26.7 (t), 26.4 (t); HRMS *m*/*z* calcd for $C_8H_{12}O_3S$ 188.0507, found 188.0512 (EI). Anal. Calcd for $C_8H_{12}O_3S$: C, 51.04; H, 6.43. Found: C, 51.20; H, 6.58.

(3*S,4*R**)-Tetrahydro-4-(methoxymethoxy)-2*H*-thiopyran-3-carboxaldehyde (9b).** Swern oxidation of **8b** (701 mg, 3.65 mmol), according to the above procedure, gave a light-yellow oil (672 mg) after workup, which was fractionated by FCC (30% ethyl acetate in hexane) to give the cis aldehyde **9b** (617 mg, 89%). IR $\tilde{\nu}_{max}$ 2823, 2722, 1726 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.63 (1H, s), 4.69 (1H, d, J = 7 Hz), 4.57 (1H, d, J = 7 Hz), 4.40 (1H, ddd, J = 2.5, 2.5, 5 Hz), 3.31 (3H, s), 3.04 (1H, ap dd, J = 12.5, 12.5 Hz), 2.93 (1H, ap dd, J = 12, 12.5 Hz), 2.70−2.60 (2H, m), 2.41−2.26 (2H, m), 1.90−1.78 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.1, 95.3, 70.6, 53.9, 46.9, 31.3, 23.2, 22.9; HRMS *m*/*z* calcd for $C_8H_{14}O_3S$ 190.0664, found 190.0666 (EI).

(3*S,4*S**)-Tetrahydro-4-(methoxymethoxy)-2*H*-thiopyran-3-carboxaldehyde (9c). Swern Oxidation of 8c.** Using the above procedure, **8c** (761 mg) was converted into the trans aldehyde **9c** (170 mg, 23%).

DIBAH Reduction of 5c.[56] Cold DIBAL-H (0.5 M in toluene; 26.2 mL, 13 mmol) was added dropwise via syringe pump over 3 h to a stirred solution of the ester **5c** (1.581 g, 7.18 mmol) in toluene (10 mL) at −78 °C under argon. This addition was achieved by having the output from the syringe pump run down the side of a coldfinger condenser (dry ice/acetone) mounted above the reaction mixture. After 3 h, the reaction was quenched by the addition of cold MeOH (9 mL) via syringe pump over 2 h as above. The reaction mixture was allowed to warm to rt over several hours and then ice-cold 1 M HCl (50 mL) was added. After 10 min of vigorous stirring, the mixture was diluted with brine and extracted with CH_2Cl_2 (3×). The combined organic layers were dried over Na_2SO_4, concentrated, and fractionated by MPC (30% ethyl acetate in hexane) to give **8c** (193 mg, 14%) and **9c** (939 mg, 69%). IR $\tilde{\nu}_{max}$ 2824, 2725, 1721 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.80 (1H, d, J = 1.5 Hz), 4.73 (1H, d, J = 7 Hz), 4.62 (1H, d, J = 7 Hz), 3.94 (1H, ddd, J = 3.5, 8, 8 Hz), 3.35 (3H, s), 2.97 (1H, br d, J = 12.5 Hz), 2.86−2.66 (3H, m), 2.52 (1H, ddd, J = 3, 9, 13.5 Hz), 2.23 (1H, dddd, J = 3, 3.5, 7.5, 13 Hz), 1.85 (1H, dddd, J = 3, 8, 9, 13.5 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 202.6 (d), 95.4 (t), 73.5 (d), 55.9 (q), 54.1 (d), 31.7 (t), 26.1 (t), 25.7 (t); HRMS *m*/*z* calcd for $C_8H_{14}O_3S$ 190.0664, found 190.0664 (EI).

Aldol Reaction of 4b and 9a ($TiCl_4$). Freshly distilled $TiCl_4$ (0.30 mL, 0.51 g, 2.7 mmol) was added dropwise over 1 min to a stirred solution of **9a** (500 mg, 2.66 mmol) in CH_2Cl_2 (35 mL) at −78 °C under argon. The resulting fine, yellow suspension was stirred for 10 min, and then a solution of **4b** (736 mg, 3.91 mmol) in CH_2Cl_2 (7.5 mL) was added dropwise via syringe over 2 min, whereupon the yellow suspension turned to a clear dark-orange and then to a red solution. After 1 h at −78 °C, the reaction was allowed to warm to rt over 30 min before being quenched by the sequential addition of a solution of Et_3N (80 mg, 0.79 mmol) and MeOH (100 mg, 3.1 mmol) in CH_2Cl_2 (1 mL) and then saturated NH_4Cl (5 mL). The mixture was diluted with water and extracted with CH_2Cl_2 (3×), and the combined organic layers were dried over Na_2SO_4, concentrated, and fractionated by FCC (20−50% ethyl acetate in hexane) to give **12a** (18 mg, 5%) and **11a** (663 mg, 82%) as white solids.

Aldol Reaction of 4b and 9a (BF_3·OEt_2). Using the same procedure as above but replacing $TiCl_4$ with BF_3·OEt_2, **9a** (73 mg, 0.039 mmol) gave a 2:1 mixture of **11a**/**12a** (70%).

Aldol Reaction of 4b and 9b ($TiCl_4$). The cis aldehyde **9b** was unstable in the presence of $TiCl_4$ (elimination). Using the above procedure, **9b** (73 mg, 0.38 mmol) gave **12b** (11 mg, 9%) and **14b** (15 mg, 12%) and recovered **9b** (16 mg, 22%) after fractionation by MPC (30% ethyl acetate in hexane).

Aldol Reaction of 4b and 9c ($TiCl_4$). Using the above procedure with $TiCl_4$ (0.018 mL, 31 mg, 0.16 mmol), **9c** (30 mg, 0.16 mmol) and **4b** (60 mg, 0.32 mmol) in CH_2Cl_2 (5 mL) gave, after workup, a light-orange oil (78 mg), which contained a 10:1 mixture of **11c**/**14c** and ca. 8% of the remaining **9c** (^{1}H NMR). The crude product was fractionated by MPC (35% ethyl acetate in hexane) to give a 20:2:1 mixture of **11c**/**14c**/**13c** (40 mg, 81%). A pure sample of **11c** was obtained by fractionation of a portion of the above mixture by PTLC (50% ethyl acetate in hexane).

Aldol Reaction of 4b and 9a ($MgBr_2$). $MgBr_2$·OEt_2 (4.45 g, 17.4 mmol) was added to a stirred solution of **9a** (1.08 g, 5.74 mmol) in CH_2Cl_2 (26 mL) at rt under argon. After 2 min,

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the resulting creamy, off-white suspension was placed in an ice bath, and after 15 min, a solution of **4b** (2.16 g, 11.5 mmol) in CH_2Cl_2 (1 mL) was added dropwise via syringe over 3 min. After stirring for 1 h at 0 °C, the reaction mixture was poured into ice-cold phosphate buffer (pH 7, 50 mL) with vigorous stirring. The mixture was diluted with water and extracted with CH_2Cl_2 (3×). The combined organic layers were dried over Na_2SO_4 and concentrated to give an orange oil that contained a 3:1 mixture of **13a**/**14a**, in addition to **3** and **9a** (ca. 3%). The relatively volatile **3** (621 mg, 47% based on **4b**) was easily recovered from the crude mixture by sublimation at high vacuum (rt). The remaining residue was crystallized from methanol to give **13a** (mp 152−153 °C; 1.07 g, 61%). The mother liquor (ca. 4:1 mixture of **14a**/**13a**) was concentrated and fractionated by MPC (25−50% ethyl acetate in hexane) to give **13a** (101 mg, 6%) and **14a** (381 mg, 22%).

Aldol Reaction of 4b and 9a ($SnCl_4$). Using the same procedure as above but using $SnCl_4$ (1 M in CH_2Cl_2, 2 equiv) in place of $MgBr_2{\cdot}OEt_2$ (3 equiv), **9a** (25 mg, 0.13 mmol) gave a 3:1 mixture of **12a**/**11a** (72%).

Aldol Reaction of 4b and 9b ($MgBr_2$). Using the above procedure, the cis aldehyde **9b** (573 mg, 3.01 mmol) gave an orange-yellow oil on workup that contained a 4:1 mixture of **13b**/**14b** in addition to **3** and **9b** (ca. 2%). The relatively volatile **3** (321 mg, 46% on the basis of **4b**) was easily recovered from the crude mixture at high vacuum (rt). The remaining residue was crystallized from methanol to give **13b** (525 mg, 57%), and the mother liquor was fractionated by MPC (30% ethyl acetate in hexane) to give a 2.5:1 mixture of **14b**/**13b** (257 mg, 27%). A pure sample of **14b** was obtained by fractional crystallization of the above mixture from methanol, resulting in a mother liquor enriched in **14b** (ca. 5:1) that was further fractionated by PTLC (2% methanol in CH_2Cl_2, multiple development).

Aldol Reaction of 4b and 9c ($MgBr_2$). Using the above procedure, the trans aldehyde **9c** (206 mg, 1.08 mmol) gave a 7:4:1 mixture of **13c**/**11c**/**14c**(245 mg, 74%) after fractionation by MPC (30% ethyl acetate in hexane). A pure sample of **13c** was obtained by further fractionation of a portion of the mixture by PTLC (2% methanol in CH_2Cl_2). A pure sample of **14c** could not be obtained. Extensive fractionation of the mixture by PTLC (2% methanol in CH_2Cl_2) gave a 1.5:1 mixture of **14c**/**13c**.

Aldol Reaction of 4c and 9a. A solution of **9a** (2.32 g, 12.3 mmol) in THF (5 mL) was added rapidly via syringe to a stirred solution of the amine-free **4c** (prepared as above from **4b**: 3.48 g, 18.5 mmol) at −78 °C. After 5 min, it was quenched by the rapid addition of a solution of glacial acetic acid (1.5 mL) in THF (5 mL). The reaction mixture was removed from the cooling bath, and CH_2Cl_2 (100 mL) and water (50 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (2×), and the combined organic layers were washed sequentially with aqueous $NaHCO_3$ and water, dried over Na_2SO_4, and concentrated to give a pale-yellow semisolid. Trituration of the crude product with ether gave a yellowish powder that was recrystallized from benzene to give the pure **12a** (2.06 g, 55%; mp 148−149 °C). The ether from trituration and the mother liquor from recrystallization were combined and concentrated, and **3** (910 mg, 42%) was recovered by sublimation (rt, 0.5 Torr). The residue was fractionated by FCC (10−50% EtOAc in hexane) to recover **9a** (541 mg, 23%) and to give **11a** (270 mg, 7%) and **12a** (300 mg, 8%).

Aldol Reaction of 4c and 9b. Using the same procedure as above, the reaction of **9b** (580 mg, 3.05 mmol) with the amine-free **4c** (prepared as above from **4b**: 1.15 g, 6.11 mmol) gave, after workup, a yellow oil (1.413 g) that contained a 4.1:1.7:1 mixture of **12b**/**14b**/**11b** (^{1}H NMR). Fractionation of the crude product by MPC (25% ethyl acetate in hexane) gave **11b** (88 mg, 9%), **12b** (220 mg, 24%), and a 1.1:1 mixture of **14b**/**12b** (258 mg, 28%).

Aldol Reaction of 4c and 9c. Using the same procedure as above, the reaction of the trans aldehyde **9c** (525 mg, 2.76 mmol) with the amine-free **4c** (prepared from **4b**: 1.08 g, 5.73 mmol) gave **12b** (542 mg, 64%) after fractionation by MPC (35% ethyl acetate in hexane). The presence of other aldol diastereomers was not detected by ^{1}H NMR analysis of the crude product.

Aldol Reaction of 4d (4e) with 9a. A solution of **3** (20 mg, 0.17 mmol) in CH_2Cl_2 (0.5 mL) was added to a stirred solution of Bu_2BOTf (1 M in CH_2Cl_2; 0.26 mL) and *i*-Pr_2EtN (0.090 mL, 67 mg, 0.52 mmol) in CH_2Cl_2 (5 mL) at −78 °C under argon. After 3 h, a solution of **9a** (130 mg, 0.69 mmol) in CH_2Cl_2 (0.5 mL) was added to the reaction mixture. After 3 h, the reaction was quenched by the sequential addition of phosphate buffer (pH 7, 0.5 mL), methanol (3.5 mL), and 30% H_2O_2 (0.2 mL). The mixture was stirred at 0 °C for 15 min, and then aqueous Na_2SO_3 was added to reduce the H_2O_2. The mixture was diluted with water and extracted with CH_2Cl_2 (3×), and the combined organic layers were dried over Na_2SO_4, concentrated, and fractionated by FCC (20−40% ethyl acetate in hexane) to give recovered **9a** (58 mg, 45%), **11a** (4 mg, 8%), and **12a** (39 mg, 74%). A similar experiment using (c-$C_6H_{11})_2BCl$ in place of Bu_2BOTf gave a 15:1 mixture of **11a**/**12a** (44 mg, 84%).

Aldol Reaction of 4f with 9a. $TiCl_4$ (0.030 mL, 52 mg, 0.28 mmol) was added to a stirred solution of **3** (29 mg, 0.25 mmol) in CH_2Cl_2 (4 mL) at −78 °C under argon. After 5 min, *i*-Pr_2EtN (0.052 mL, 39 mg, 0.30 mmol) was added, and after 2 h at −78 °C, a solution of **9a** (56 mg, 0.30 mmol) in CH_2Cl_2 (0.5 mL) was added. After 5 h, the reaction was quenched by the addition of aqueous NH_4Cl. The mixture was diluted with water and extracted with CH_2Cl_2 (3×), and the combined organic layers were dried over Na_2SO_4, concentrated, and fractionated by FCC (20−50% ethyl acetate in hexane) to give **11a** (20 mg, 26%) and a 1:1 mixture of C_s/C_1 bisaldols (26 mg, 20%).[6b]

(1′*S,3*S**,6″*R**)-3-[(1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl)-hydroxymethyl]tetrahydro-4*H*-thiopyran-4-one (11a).** IR $\tilde{\nu}_{max}$ 3507, 1703 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.79 (1H, dd, J = 3, 8.5 Hz, HC-1′ ($^3J_{HC-1'/HC-3}$ = 8.5 Hz)), 4.10−3.96 (4H, m), 3.19−2.88 (7H, m), 2.81−2.67 (4H, m), 2.58−2.54 (1H, m), 2.11 (1H, ddd, J = 3, 5.5, 14 Hz), 1.93 (1H, ddd, J = 3, 3, 10.5 Hz), 1.73 (1H, ddd, J = 3.5, 11.5, 14 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.1 (s), 109.8 (s), 66.1 (d), 64.6 (t), 64.2 (t), 56.0 (d), 46.2 (d), 44.2 (t), 35.6 (t), 32.6 (t), 31.2 (t), 26.4 (t), 26.3 (t); HRMS *m*/*z* calcd for $C_{13}H_{20}O_4S_2$ 304.0803, found 304.0799. Anal. Calcd for $C_{13}H_{20}O_4S_2$: C, 51.29; H, 6.62. Found: C, 51.43; H, 6.44.

(1′*S,3*R**,6″*R**)-3-[(1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl)-hydroxymethyl]tetrahydro-4*H*-thiopyran-4-one (12a).** IR $\tilde{\nu}_{max}$ 3488, 3409, 1711 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.50 (1H, dd, J = 4.5, 6.5 Hz, HC-1′ ($^3J_{HC-1'/HC-3}$ = 6.5 Hz)), 4.05−3.92 (4H, m), 3.08−2.58 (12H, m), 2.12 (1H, ddd, J = 4.5, 4.5, 9 Hz), 2.03 (1H, ddd, J = 3.5, 6.5, 13.5 Hz), 1.74 (1H, ddd, J = 4, 9.5, 13.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.5 (s), 109.3 (s), 69.3 (d), 64.4 (t), 64.3 (t), 55.5 (d), 47.0 (d), 44.4 (t), 35.5 (t), 34.3 (t), 31.4 (t), 27.4 (t), 26.5 (t); HRMS *m*/*z* calcd for $C_{13}H_{20}O_4S_2$ 304.0803, found 304.0801. Anal. Calcd for $C_{13}H_{20}O_4S_2$: C, 51.29; H, 6.62. Found: C, 51.59; H, 6.55.

(1′*R,3*R**,6″*R**)-3-[(1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl)-hydroxymethyl]tetrahydro-4*H*-thiopyran-4-one (13a).** IR $\tilde{\nu}_{max}$ 3497, 1706 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.57 (1H, ddd, J = 2.5, 3.5, 7.5 Hz, HC-1′ ($^3J_{HC-1'/HC-3}$ = 3.5 Hz)), 4.10−3.89 (4H, m), 3.85 (1H, d, J = 2.5 Hz, OH), 3.13 (1H, dd, J = 11, 13.5 Hz), 3.0 (1H, ddd, J = 4, 10.5, 13.5 Hz), 2.91−2.57 (9H, m), 2.22−2.13 (1H, m), 2.07 (1H, ddd, J = 3.5, 7.5, 8 Hz), 1.82−1.71 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.1 (s), 110.8 (s), 69.7 (d), 64.8 (t), 64.1 (t), 55.3 (d), 46.2 (d), 44.1 (t), 34.9 (t), 29.7 (t), 29.4 (t), 29.3 (t), 26.7 (t); HRMS *m*/*z* calcd for $C_{13}H_{20}O_4S_2$ 304.0803, found 304.0807. Anal. Calcd for $C_{13}H_{20}O_4S_2$: C, 51.29; H, 6.62. Found: C, 51.34; H, 6.66.

(1′*R,3*S**,6″*R**)-3-[(1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl)-hydroxymethyl]tetrahydro-4*H*-thiopyran-4-one (14a).** IR $\tilde{\nu}_{max}$ 3496, 1702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.24 (1H, ddd, J = 3.5, 3.5, 7.5 Hz, HC-1′ ($^3J_{HC-1'/HC-3}$ = 3.5 Hz)), 4.12−3.95 (4H, m), 3.93 (1H, d, J = 3.5 Hz, OH), 3.25 (1H, dd, J = 11.5, 14.5 Hz), 3.02 (1H, ddd, J = 4, 10, 13.5 Hz), 2.95−2.56 (9H, m), 2.41 (1H, ddd, J = 3, 7.5, 7.5 Hz), 2.15 (1H, ddd, J = 4, 9, 13.5 Hz), 1.79 (1H, ddd, J = 3.5, 7, 13.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.1 (s), 110.5 (s), 72.9 (d), 64.7 (t), 64.2

(t), 54.7 (d), 46.4 (d), 44.2 (t), 34.5 (t), 33.2 (t), 30.0 (t), 29.4 (t), 26.8 (t); HRMS *m/z* calcd for $C_{13}H_{20}O_4S_2$ 304.0803, found 304.0801.

(1′*R,3*S**,3″*R**,4″*R**)-3-[Hydroxy(4-(methoxymethoxy)-tetrahydro-2*H*-thiopyran-3-yl)methyl]tetrahydrothiopyran-4-one (11b).** IR $\tilde{\nu}_{max}$ 3496, 1701 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.74 (1H, d, J = 7 Hz), 4.60 (1H, d, J = 7 Hz), 4.23 (1H, br t, J = 5.5, 5.5 Hz, HC-1′ ($^3J_{HC-1'/HC-3}$ = 5.5 Hz)), 3.96 (1H, ddd, J = 2, 2.5, 5 Hz), 3.36 (3H, s), 3.07−2.85 (8H, m), 2.75−2.71 (2H, m), 2.57 (1H, br dd, J = 3, 13 Hz), 2.34−2.28 (2H, m), 1.90 (1H, dddd, J = 2.5, 3, 5.5, 11.5 Hz), 1.77 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.37, 94.86, 73.92, 71.17, 56.36, 54.77, 45.27, 43.74, 31.57, 31.29, 31.23, 23.86, 22.49; HRMS *m/z* calcd for $C_{13}H_{22}O_4S_2$ 306.0960, found 306.0956 (EI).

(1′*R,3*R**,3″*R**,4″*R**)-3-[Hydroxy(4-(methoxymethoxy)-tetrahydro-2*H*-thiopyran-3-yl)methyl]tetrahydrothiopyran-4-one (12b).** IR $\tilde{\nu}_{max}$ 3508, 1700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.71 (1H, d, J = 7 Hz), 4.59 (1H, d, J = 7 Hz), 3.96 (1H, ddd, J = 3, 6, 7.5 Hz, HC-1′ ($^3J_{HC-1'/HC-3}$ = 6 Hz)), 3.89 (1H, ddd, J = 2.5, 3, 5 Hz), 3.41 (3H, s), 3.15−2.94 (7H, m), 2.90 (1H, br dd, J = 12, 13 Hz), 2.81−2.71 (2H, m), 2.64 (1H, br d, J = 13.5 Hz), 2.34 (1H, br ddd, J = 3.5, 4, 13 Hz), 2.26 (1H, dddd, J = 2.5, 4, 5, 14.5 Hz), 2.14 (1H, dddd, J = 3, 3.5, 6, 11 Hz), 1.77 (1H, dddd, J = 2.5, 3.5, 12, 14.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.84 (s), 94.89 (t), 74.97 (d), 74.37 (d), 56.39 (q), 54.06 (d), 45.12 (d), 45.05 (t), 35.20 (t), 31.69 (t), 31.15 (t), 24.98 (t), 23.09 (t); HRMS *m/z* calcd for $C_{13}H_{22}O_4S_2$ 306.0960, found 306.0961 (EI).

(1′*S,3*R**,3″*R**,4″*R**)-3-[Hydroxy(4-(methoxymethoxy)-tetrahydro-2*H*-thiopyran-3-yl)methyl]tetrahydrothiopyran-4-one (13b).** IR $\tilde{\nu}_{max}$ 3464, 1697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.71 (1H, d, J = 6.5 Hz), 4.67 (1H, d, J = 6.5 Hz), 4.23 (1H, m), 4.20 (1H, ddd, J = 3.5, 5, 9 Hz, HC-1′ ($^3J_{HC-1'/HC-3}$ = 3.5 Hz)), 3.43 (3H, s), 3.21 (1H, d, J = 5 Hz, OH), 3.11 (1H, dd, J = 10.5, 14 Hz), 3.06−2.82 (5H, m), 2.80−2.66 (3H, m), 2.35−2.25 (2H, m), 2.10 (1H, dd, J = 2, 13.5 Hz), 1.83 (1H, dddd, J = 2, 3, 9, 11 Hz), 1.73 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.0, 96.3, 71.4, 69.2, 56.3, 54.9, 44.7, 43.6, 31.9, 30.4, 29.9, 24.7, 22.4; HRMS *m/z* calcd for $C_{13}H_{22}O_4S_2$ 306.0960, found 306.0962 (EI).

(1′*S,3*S**,3″*R**,4″*R**)-3-[Hydroxy(4-(methoxymethoxy)-tetrahydro-2*H*-thiopyran-3-yl)methyl]tetrahydrothiopyran-4-one (14b).** IR $\tilde{\nu}_{max}$ 3501, 1701 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.72−4.69 (2H, m), 4.24 (1H, br s), 3.77 (1H, ddd, J = 3.5, 8.0, 10 Hz, HC-1′ ($^3J_{HC-1'/HC-3}$ = 3.5 Hz)), 3.42 (3H, s), 3.29 (1H, d, J = 10 Hz), 3.16 (1H, dd, J = 9.5, 13 Hz), 3.04−2.88 (6H, m), 2.83−2.67 (2H, m), 2.39−2.28 (2H, m), 2.22−2.10 (2H, m), 1.82−1.73 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.41, 96.25, 74.14, 71.60, 56.28, 54.29, 45.12, 45.01, 35.10, 31.95, 31.14, 25.73, 22.66; HRMS *m/z* calcd for $C_{13}H_{22}O_4S_2$ 306.0960, found 306.0956 (EI).

(1′*R,3*S**,3″*R**,4″*S**)-3-[Hydroxy(4-(methoxymethoxy)-tetrahydro-2*H*-thiopyran-3-yl)methyl]tetrahydrothiopyran-4-one (11c).** IR $\tilde{\nu}_{max}$ 3472, 1702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.84 (1H, ddd, J = 4, 5, 8.5 Hz, HC-1′ ($^3J_{HC-1'/HC-3}$ = 8.5 Hz)), 4.73 (1H, d, J = 6.5 Hz), 4.63 (1H, d, J = 6.5 Hz), 3.47 (1H, ddd, J = 3.5, 9, 9, Hz), 3.47 (3H, s), 3.17 (1H, d, J = 5 Hz, OH), 3.12 (2H, ap d, J = 5 Hz), 2.99−2.94 (2H, m), 2.86 (1H, ap ddd, J = 5, 5, 8.5 Hz), 2.79 (1H, ddd, J = 2, 3, 13.5 Hz), 2.72−2.65 (3H, m), 2.64 (1H, dd, J = 9.5, 13.5 Hz), 2.57 (1H, ddd, J = 3, 11, 13.5 Hz), 2.20 (1H, dddd, J = 3, 3.5, 6, 13 Hz), 1.79 (1H, dddd, J = 3.5, 9, 11, 13 Hz), 1.72 (1H, dddd, J = 3, 4, 9, 9.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.29, 96.33, 76.79, 66.30, 56.55, 55.26, 45.61, 44.19, 33.32, 33.11, 31.50, 26.85, 26.24; HRMS *m/z* calcd for $C_{13}H_{22}O_4S_2$ 306.0960, found 306.0962 (EI).

(1′*R,3*R**,3″*R**,4″*S**)-3-[Hydroxy(4-(methoxymethoxy)-tetrahydro-2*H*-thiopyran-3-yl)methyl]tetrahydrothiopyran-4-one (12c).** IR $\tilde{\nu}_{max}$ 3516, 1701 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.72 (1H, d, J = 6.5 Hz), 4.70 (1H, d, J = 6.5 Hz), 4.47 (1H, ddd, J = 2.5, 4, 9.5 Hz, HC-1′ ($^3J_{HC-1'/HC-3}$ = 9.5 Hz)), 3.61 (1H, ddd, J = 4, 10, 10.5 Hz), 3.43 (3H, s), 3.22 (1H, d, J = 4 Hz, OH), 3.03−2.93 (2H, m), 2.92−2.83 (2H, m), 2.82−2.65 (5H, m), 2.58 (1H, m, J = 2.5, 3.5, 4, 13.5 Hz), 2.51 (1H, ddd, J = 2.5, 3, 13.5 Hz), 2.42 (1H, dddd, J = 3, 4, 4, 12.5 Hz), 1.77 (1H, dddd, J = 3, 3, 9.5, 10 Hz), 1.74 (1H, dddd, J = 3, 10.5, 12, 12.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.35 (s, CO), 96.52 (t), 76.18 (d), 67.72 (d), 56.03 (q), 55.45 (d), 45.73 (d), 44.99 (t), 34.90 (t), 32.42 (t), 31.07 (t), 27.75 (t), 26.31 (t); HRMS *m/z* calcd for $C_{13}H_{22}O_4S_2$ 306.0960, found 306.0954 (EI).

(1′*S,3*R**,3″*R**,4″*S**)-3-[Hydroxy(4-(methoxymethoxy)-tetrahydro-2*H*-thiopyran-3-yl)methyl]tetrahydrothiopyran-4-one (13c).** IR $\tilde{\nu}_{max}$ 3483, 1701 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.70 (1H, d, J = 6.5 Hz), 4.67 (1H, d, J = 6.5 Hz), 4.52 (1H, ddd, J = 3, 5, 8 Hz, HC-1′ ($^3J_{HC-1'/HC-3}$ = 3 Hz)), 3.95 (1H, ddd, J = 3, 6, 7 Hz), 3.40 (3H, s), 3.16 (1H, d, J = 5 Hz, OH), 3.09−2.87 (7H, m), 2.80−2.75 (2H, m), 2.43 (1H, dddd, J = 1, 3.5, 7, 12.5 Hz), 2.32 (1H, ddd, J = 1, 6.5, 13.5 Hz), 2.20 (1H, dddd, J = 3, 3.5, 10, 13.5 Hz), 1.94−1.85 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.45, 95.65, 74.40, 69.99, 55.95, 55.66, 45.10, 42.02, 30.86, 30.46, 29.86, 27.44, 24.85; HRMS *m/z* calcd for $C_{13}H_{22}O_4S_2$ 306.0960, found 306.0962 (EI).

(1′*S,3*S**,3″*R**,4″*S**)-3-[Hydroxy(4-(methoxymethoxy)-tetrahydro-2*H*-thiopyran-3-yl)methyl]tetrahydrothiopyran-4-one (14c).** A 1.5:1 mixture of **14c**/**13c** was obtained. Spectral data for **14c** was deduced from that of the mixture by comparison with the data for pure **13c**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.70 (2H, ap s), 4.07 (1H, ddd, J = 5, 5, 6.5 Hz, HC-1′ ($^3J_{HC-1'/HC-3}$ = 5 Hz)), 3.87 (1H, ddd, J = 3, 8, 8 Hz), 3.40 (3H, s), 3.33 (1H, d, J = 6.5 Hz, OH), 3.15−2.88 (5H, m), 2.85−2.68 (4H, m), 2.55 (1H, dd, J = 8, 13.5 Hz), 2.51 (1H, ddd, J = 2.5, 9, 12.5 Hz), 2.29 (1H, dddd, J = 3, 3.5, 8, 13.5 Hz), 2.06 (1H, dddd, J = 3, 5, 8, 8 Hz), 1.83 (1H, dddd, J = 3, 8, 9, 13.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.62, 95.86, 74.92, 74.41, 56.24, 56.06, 45.08, 43.80, 34.10, 31.78, 31.06, 29.98, 25.86.

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Supporting Information Available: Experimental procedures and spectroscopic data for **15**−**30** and ^{1}H 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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