The ee of the product was measured by ^1H NMR using Eu(hfc)$_3$ in $CDCl_3$. $[\alpha]^{22}_D$ +9.9° (c = 0.02 M; $CHCl_3$) for a sample having ee of 48% by NMR.

***cis*-[(3,5-Dimethyl-1-cyclohexen-1-yl)oxy]trimethylsilane (14).** *n*-Butyllithium (0.55 mmol, 0.30 mL of a 1.88 M solution in hexanes) was added dropwise to a solution of **12c** (89.9 mg, 0.55 mmol) in THF (3 mL) at 0 °C. The mixture was stirred for 1 h at 0 °C and then was cooled to −78 °C and TMSCl (0.32 mL; 2.5 mmol) was added followed by dropwise addition of **6** (63 mg; 0.50 mmol) in THF (1 mL). After 1 min Et_3N (1 mL) was added, and the solution was allowed to warm to room temperature. Solvents and excess of the reagents were removed under vacuum and the residue was poured into saturated $NaHCO_3$ solution (10 mL). The product was extracted with Et_2O (2 × 10 mL), and the ether extracts were washed with 0.1 M citric acid (2 × 15 mL) and water. Drying ($MgSO_4$) followed by solvent removal gave the crude product which was purified by flash chromatography (SiO_2, pentane) which yielded **14** (58.5 mg; 59%) as colorless oil: bp 190 °C; ^1H NMR δ 0.18 (s, 9 H), 0.69 (m, 1 H), 0.95 (m, 6 H), 1.66 (m, 3 H), 1.96 (m, 1 H), 2.26 (m, 1 H), 4.70 (s, 1 H); ^{13}C NMR δ 0.3, 22.0, 22.7, 29.7, 30.3, 38.5, 40.8, 110.9, 149.7; IR (neat) 1665 cm^{-1}; MS (CI-NH_3) m/e 199 (100, M + 1), 183 (30), 144 (19), 90 (32). Anal. Calcd for $C_{11}H_{22}OSi$: C, 66.60; H, 11.18. Found: C, 66.40; H, 11.00.

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Registry No. **6**, 7214-52-0; **8**, 141396-51-2; **9**, 141396-52-3; **10**, 141396-53-4; **11a**, 122348-66-7; **11b**, 133469-22-4; **11c**, 23294-41-9; **11d**, 87861-38-9; **12a**, 141396-54-5; **12b**, 66399-53-9; **12c**, 19302-32-0; **12d**, 17480-69-2; **13a**, 128350-75-4; **13b**, 141435-15-6; **14a**, 128441-45-2; **14b**, 141435-16-7; PhCHO, 100-52-7; (*R*)-1-phenylethylamine, 3886-69-9; (*S*)-1-cyclohexylethylamine, 17430-98-7; 2,2-dimethylpropanal, 630-19-3; diethyl ketone, 96-22-0; (*S*)-1-phenylethylamine, 2627-86-3; cyclohexanone, 108-94-1.

Diastereoselective Cyclocondensation of Electron-Rich Dienes with Chiral Thio-Substituted Aldehydes

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The Lewis acid-promoted cyclocondensation between two electron-rich dienes with a series of racemic α- and β-thio-substituted aldehydes has been studied. Boron trifluoride etherate proved to be the catalyst of choice, affording satisfactory chemical yields and generally good diastereoselectivities. Other Lewis acidic catalysts gave lower yields and in some cases reversed the sense of the diastereoselection. A rationalization of the stereochemical results is presented.

The Lewis acid (LA)-promoted cyclocondensation of electron-rich dienes with aldehydes recently emerged as a powerful synthetic tool for the stereoselective assembly of a wide range of biologically relevant compounds.[1] Control of the stereochemistry of the reaction[1] has been achieved in three ways: by employing chiral catalysts,[2,3] chiral dienes,[2] and chiral dienophiles.[4-7] Among the latter, alkoxy-[4] and aminoaldehydes[5] were mainly investigated. Chiral thio-substituted aldehydes, however, have not been exploited for this reaction, despite the well-recognized efficiency of sulfur-containing groups as elements of stereocontrol[8] and the impressive number of synthetic

Table I. Diastereoselective Synthesis of Pyranones 9–12, 16, and 17 by Cyclocondensation of Diene 7 with Aldehydes 1–6 in the Presence of LA[a]

aldehyde	LA	product	yield[b] (%)	diastereoisomeric ratio a:b[c]
1	BF_3·OEt_2	**9ab**	54	≥98:2
1	$TiCl_4$	**9ab**	36	≥98:2
1	$TiCl_2$(O-*i*-Pr)$_2$	**9ab**	32	≥98:2
1	VCl_3·THF_3	**9ab**	42	≥98:2
1	$MgBr_2$	**9ab**	37	88:12
1	Eu(fod)$_3$[d]	**9ab**	46	55:45
2	BF_3·OEt_2	**10ab**	56	≥98:2
2	$TiCl_4$	**10ab**	36	51:49
3	BF_3·OEt_2	**11ab**	51	95:5
3	$MgBr_2$	**11ab**	31	59:41
4	BF_3·OEt_2	**12ab**	54	46:54
4	$TiCl_4$	**12ab**	32	≤2:98
5	BF_3·OEt_2	**16ab**	60	40:60
5	$TiCl_4$	**16ab**	33	79:21
6	BF_3·OEt_2	**17ab**	74	54:46
6	$TiCl_4$	**17ab**	30	84:16

[a] Aldehyde:diene:catalyst = 1:1.2:1 mol ratio, at −78 °C unless otherwise stated. [b] Isolated yields. [c] As determined by 300-MHz ^1H NMR spectroscopy. [d] At room temperature.

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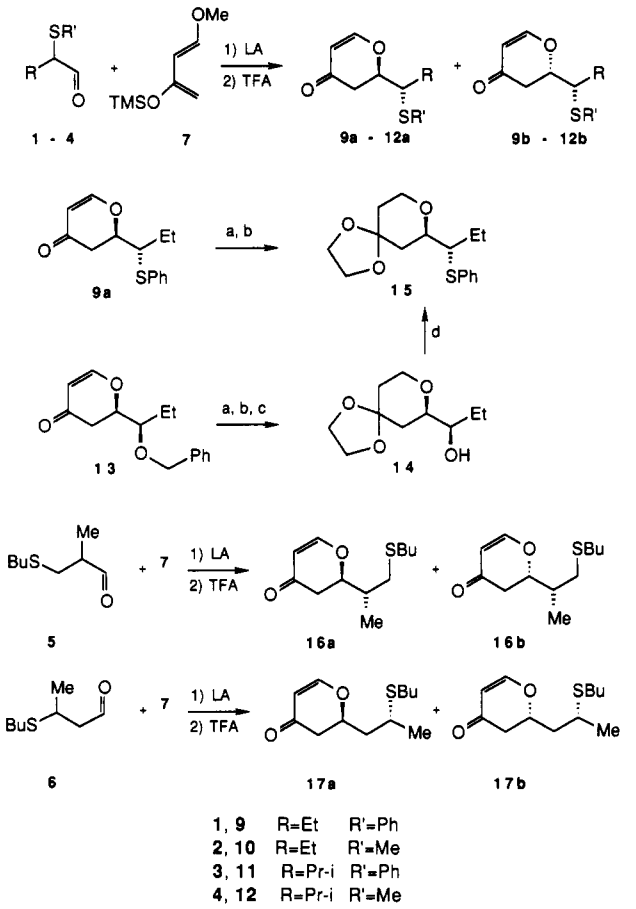
Scheme I[a]



1, 9 R=Et R'=Ph
2, 10 R=Et R'=Me
3, 11 R=Pr-i R'=Ph
4, 12 R=Pr-i R'=Me

[a] Reagents: (a) L-Sel, THF, −78 °C; (b) $HOCH_2CH_2OH$, pTsOH, benzene, reflux; (c) Pd/C, H_2, THF, rt; (d) PhSSPh, Bu_3P, THF, reflux.

Table II. Diastereoselective Synthesis of Pyranones 18–21 by Cyclocondensation of Diene 8 with Aldehydes 1–4 in the Presence of $BF_3 \cdot OEt_2$

aldehyde	solvent	product	yield (%)	diastereoisomeric ratio a:b:(c)
1	CH_2Cl_2	18	60	75:25
1	toluene	18	76	34:66
2	CH_2Cl_2	19	52	73:27
2	toluene	19	50	25:75
3	CH_2Cl_2	20	55	51:49
3	toluene	20	66	19:81
4	CH_2Cl_2	21	36	38:62
4	toluene	21	30	10:70:(20)

transformations provided by these functionalities.[9]

As a part of our studies on the LA-promoted addition of carbon nucleophiles to chiral thio-substituted aldehydes,[10] we report here the cyclocondensation of racemic aldehydes **1–6**[10b] with electron-rich dienes **7** and **8**[11] and a study on the factors influencing the diastereoselectivity of this process.

Proper reaction conditions were established for the cycloaddition of **1** with Danishefsky's diene **7** (1.2 mol equiv) in the presence of different LA (1.0 mol equiv) to give, after acidic workup, 2-[1′-(phenylthio)propyl]-2,3-dihydro-4*H*-pyran-2-one (**9a,b**) (Table I). The diastereoselectivity of the reaction was determined by 300-MHz ^1H NMR spectroscopy on the crude products and the results confirmed on the cycloadducts purified by flash chromatography. Assignment of stereochemistry was based on the correlation of **9a** with compound **13**, of known stereochemistry,[12] via tetrahydropyran **15**. As described by Danishefsky et al.,[12] dihydropyranone **13** was obtained as a single syn isomer by reaction of diene **7** with 2-(benzyloxy)butanal under $MgBr_2$ catalysis. Reduction of the C–C double bond, followed by ketone protection as ketal and debenzylation, afforded in 53% overall yield alcohol **14**. This was transformed into the *anti*-phenylthio derivative **15** (60% yield) by exposure to diphenyl disulfide in the presence of tributylphosphine in refluxing THF,[13] a reaction that has been shown to proceed with inversion. Compound **15** was also obtained from **9a** by double-bond reduction and ketalization (63% overall yield), thus establishing the anti configuration of **9a**.

As can be seen from the data reported in Table I, the use of $BF_3 \cdot OEt_2$ at −78 °C gave the best results, providing satisfactory yields[14] and complete stereocontrol. Other LAs were less efficient, leading either to low yields because of diene decomposition (as in the case of the Ti-containing LAs), or to less stereoselective cyclocondensations. The reaction of diene **7** with aldehydes **2–4**, featuring different alkyl- and thio-substituted groups at the stereocenter, to give cycloadducts **10a,b–12a,b** was then investigated (Table I). In the presence of $BF_3 \cdot OEt_2$, anti products **10a** and **11a** were obtained as largely predominant isomers from aldehydes **2** and **3**, respectively, while a slight excess of *syn*-**12b** was obtained from **4**.[15]

Stereochemical assignment of these products resided on a common chromatographic behavior (anti isomers always eluted faster than syn) and on ^1H-NMR chemical shift value and coupling constant trend considerations for diagnostic protons (Table III). For instance, the chemical shift of H-2 always increases and that of H-2′ always de-

Table III. Selected ^1H-NMR Data (δ) for Pyranones 9–12 (J in Hz)

compd	H-2	H-3_{eq}[a,b]	H-3_{ax}[b]	H-2′	$J_{2,3eq}$	$J_{2,3ax}$	$J_{2,2'}$
9a	4.48	2.61	2.74	3.22	4.0	14.0	6.4
9b	4.53	2.55	2.88	3.19	3.3	14.4	3.3
10a	4.48	2.58	2.83	2.94	3.5	14.0	5.8
10b	4.56	2.46	2.93	2.56	3.6	14.5	3.6
11a	4.56	2.56	2.82	3.23	3.5	13.8	8.2
11b	4.73	2.38	3.12	2.97	3.2	11.6	3.2
12a	4.48	2.79	2.80	2.59	8.5	8.5	8.5
12b	4.69	2.36	3.12	2.27	3.5	15.0	3.5

[a] H_{eq-3} shows a $J_{3eq,S}$ of ca. 1.0 Hz. [b] $J_{3eq,3ax} \geq 16.0$ Hz.

(8) For other stereoselective additions to chiral thio-substituted aldehydes see: (a) Shimagachi, M.; Maeda, T.; Matsuzaki, Y.; Hori, I.; Nakata, T.; Oishi, T. *Tetrahedron Lett.* **1984**, *25*, 4775. (b) Shimagaki, M.; Takubo, H.; Oishi, T. *Tetrahedron Lett.* **1985**, *26*, 6235. (c) Aggarwal, V. K.; Warren, S. *Tetrahedron Lett.* **1987**, *28*, 1925. (d) Paterson, I.; Laffan, D. D. P.; Rawson, D. J. *Tetrahedron Lett.* **1988**, *29*, 1461. Aggarwal, V. K.; Coldham, I.; McIntyre, S.; Sansbury, F. H.; Villa, M.-J.; Warren, S. *Tetrahedron Lett.* **1988**, *29*, 4885. (f) Coldham, I.; Collington, E. W.; Hallett, P.; Warren, S. *Tetrahedron Lett.* **1988**, *29*, 5321. (g) McIntyre, S.; Warren, S. *Tetrahedron Lett.* **1990**, *31*, 3457. (h) Sato, T.; Otera, J.; Nozaki, H. *J. Org. Chem.* **1990**, *55*, 6116.

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(14) A larger amount of diene (3.0–4.0 mol equiv) improved the yields only in the case of the $MgBr_2$-catalyzed reaction (up to 50%), leaving the diastereoselectivity virtually unchanged (**9a:9b** ratio 86:14). An increase in the reaction temperature was not beneficial.

(15) Other trends can be observed for both protons at C-3 and for the sulfur-bound carbon atom (see Tables III and V).

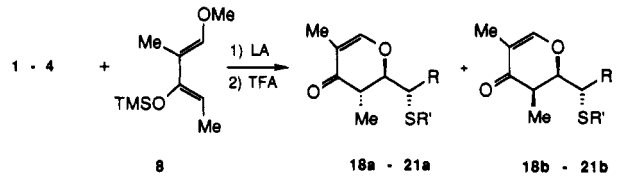
creases on passing from anti to syn isomers. Moreover, the H-2/H-2′ coupling constants is always larger for anti-configurated compounds and smaller for syn compounds.[15] When aldehydes 2–4 were reacted with diene 7 in the presence of $MgBr_2$ or $TiCl_4$, lower yields were obtained (Table I). In all cases, however, the diastereofacial control changed markedly, stereorandom reactions being obtained for **10a,b** and **11a,b** and a completely syn selective process occurred for **12a,b**.

These results parallel those observed in the Mukaiyama addition of silylated carbon nucleophiles to 1–4 and related aldehydes,[10,16] for which the stereochemical outcome of the reactions depended on the nature of the LA, of the sulfur protecting group, and on the steric demand of the residue at the stereocenter. The diastereoselectivity observed in these cyclocondensations can be tentatively rationalized in terms of the widely accepted Felkin–Anh[17] and Cram chelated[18] models. In the reactions promoted by nonchelating $BF_3{\cdot}OEt_2$, high anti diastereoselectivity is generally achieved since the thio group is an excellent "large" ligand in the Felkin–Anh rationale.[19] However, when the alkyl residue is bulky enough to compete for the "large" role with the sulfur-containing group (as in 4 where R = *i*-Pr and R′ = Me), the reaction is stereorandom. On the contrary, in the presence of coordinating catalysts such as $TiCl_4$ or $MgBr_2$ a chelation-controlled model rationalizes the formation of syn products, which is observed when the sulfur protecting group allows chelation and the alkyl residue is relatively large as in 4.

For the sake of completeness the reaction of the two racemic β-thio-substituted aldehydes 5 and 6 with diene 7 and $BF_3{\cdot}OEt_2$ or $TiCl_4$ was also studied. As reported in Table I, only the $TiCl_4$-promoted reactions led to an appreciable level of stereocontrol (although in the usual low yield), favoring the anti products **16a** and **17a** starting from α-methyl-β-thio aldehyde 5 and β-methyl-β-thio aldehyde 6, respectively. Both results can be interpreted in terms of a diene addition to a chelated conformation of the aldehydes. As expected, the $BF_3{\cdot}OEt_2$-catalyzed reactions were less selective, likely because in the case of 5 the two ligands at the stereocenter are of comparable size and in the case of 6 the stereocenter is in a relatively remote β-position. Also, these results are in full agreement with those observed in the case of the Mukaiyama aldol reactions of 5 and 6.[10]

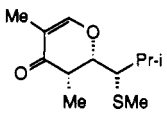
In comparing the stereochemical outcome of the cyclocondensations of 1–6 with 7 with those of related α- and β-alkoxy aldehydes,[12,20] it is evident that a sulfur atom at the stereocenter promotes more efficient Felkin–Anh type and less efficient chelation stereocontrol with respect to an oxygen atom in the same position. This is once again in line with our previous observations on the stereochemical behavior of chiral thio-substituted aldehydes.[10]

Scheme II



8 18a - 21a 18b - 21b

18 R=Et R'=Ph
19 R=Et R'=Me
20 R=Pr-i R'=Ph
21 R=Pr-i R'=Me



21c

Table IV. Selected ^{1}H-NMR Data (δ) for Pyranones 18–21 (*J* in Hz)

compd	H-2	H-3	Me-3	H-2′	$J_{2,3}$	$J_{2,2'}$
18a	4.10	2.70	1.07	3.22	12.0	3.5
18b	4.10	2.99	0.84	3.13	3.0	10.5
19a	4.16	2.74	1.13	2.62	10.5	4.5
19b	4.07	2.90	1.04	2.65	3.0	11.0
20a	4.18	2.88	1.14	3.23	6.7	8.0
20b	4.26	2.89	0.56	3.23	2.8	11.0
21a	4.13	2.99	1.23	2.58	5.0	8.5
21b	4.12	2.98	1.11	2.66	2.5	11.4
21c	4.29	2.47	1.05	2.64	3.0	10.0

The cyclocondensation was then extended to (*E*,*Z*)-3-[(*tert*-butyldimethylsilyl)oxy]-1-methoxy-2-methyl-1,3-pentadiene (8),[11] which was reacted with 1–4 under $BF_3{\cdot}OEt_2$ catalysis in both dichloromethane and toluene to give, after acidic workup, 2,3-dihydro-3,5-dimethyl-4*H*-pyran-4-ones **18–21** as mixtures of diastereoisomers (Table II). The reactions proceeded in chemical yields comparable to or higher than those observed with diene 7, with the exception of aldehyde 4. Only two products were observed in the case of cycloadducts **18a,b–20a,b**. 300-MHz ^{1}H NMR spectroscopy (Table IV) showed that these were epimers at C-3, on the basis of the H-2/H-3 coupling constant values[6a,11,12] (larger for trans isomers and smaller for cis isomers), and of NOE experiments (see below). As expected[6a,11,12] the trans products **18a–20a** moderately predominated in CH_2Cl_2 and the cis products in toluene.[11] Therefore, in the synthesis of **18–20** the high diastereofacial preference observed for 1–3 with 7 was maintained, with only C-2/C-2′ anti compound being obtained. Aldehyde 4 behaved differently: it gave two products **21a** and **21b** in CH_2Cl_2 and three cycloadducts in toluene, of which **21b** and **21a** were the major and minor isomers, respectively.

However attribution of configuration to dihydropyranones **21** was not straightforward on the basis of NMR data, since the coupling constant values largely deviated from those generally observed for these (Table IV) and similar cycloadducts.[6a,11,12] A combined molecular mechanics/^{1}H NMR study was therefore undertaken in order to elucidate this point and to support the structural assignment to **18–20**.

The calculations were performed using Still's program MACROMODEL,[22] which includes automatic routines for conformational searches and a special routine for computation of ^{1}H NMR coupling constants, based on Altona's version of the Karplus equation.[23]

(16) The possibility that the cyclocondensation proceeds stepwise via a Mukaiyama aldol addition followed by cyclization must be taken into account (see ref 1).

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(20) For instance, the reaction of 2-(benzyloxy)butanal (an oxygen-bearing analogue of 2) with 7 under $BF_3{\cdot}OEt_2$ and $MgBr_2$ catalysis gave a 58:42 and a >98:2 mixture of anti:syn products, respectively; the reaction of 3-(benzyloxy)-2-methylpropanal (an oxygen-bearing analogue of 5) with 7 and $MgBr_2$ gave a 86:14 mixture of anti:syn products (see ref 12).

(21) This stereochemical dependence upon a similar change of the solvent has been rationalized in terms of a possible mechanistic variation from a pericyclic to a Mukaiyama aldol process (see ref 6a).

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Using the MM2 force field[24] as implemented in MACROMODEL 3.0 we first studied pyranones **9a,b–12a,b**. This was necessary in order to establish the quality of the computational results. Only those conformers with steric energy within 2.5 kcal/mol from the minimum energy conformer were considered for the evaluation of the averaged coupling constants, weighted with a Boltzmann distribution at 25 °C (the temperature at which the NMR spectra were recorded).[25] On the basis of NMR studies on related compounds,[26] only the 2-equatorially substituted pyranones were considered. The calculated data were compared with the experimental values. The agreement was generally good and strongly supported the attribution of configuration. Calculated $J_{2,3eq}$ (2.3–2.5 Hz) are slightly underestimated (ca. 1 Hz), while $J_{2,3ax}$ (11.5–11.6 Hz) deviated from the experimental values to a larger extent.

In the case of adducts **18–21** the data for all four possible isomers were computed. As already suggested by examining the experimental values of $J_{2,3}$ and $J_{2,2'}$ (Table IV), two different situations were met with, depending on the nature of the R residue. When R = Et, as in cycloadducts **18** and **19**, the agreement between observed and calculated coupling constants was still good and supported the stereochemical assignment. The calculated $J_{2,3}$ values are in the range 10.3–10.7 Hz for trans and 2.1–2.2 Hz for cis isomers and the $J_{2,2'}$ values in the range 1.5–2.3 Hz for trans and 8.8–9.8 Hz for cis isomers. In the case of **19a,b**, the calculated $J_{2,2'}$ for trans/anti (2.1 Hz) and trans/syn (2.0 Hz) isomers equally deviate from the experimental value of 4.5 Hz. When R = *i*Pr as in **20** and **21**, a satisfactory agreement between experimental and computed data was obtained only when 2-axially substituted pyranones were included in the calculations: the increased bulkiness of the R substituent and its steric interactions with the methyl group at the C-3 position can rationalize this effect.[27] The steric interaction seemed particularly relevant for the "diequatorial" trans/anti isomers **20a** and **21a**, whose calculated *J* values were improved when the 2-axially substituted conformers were taken into account.[28]

2D-NOESY experiments were performed on compounds **18–21**. The H-2/H-2′, H-2/H-3, H-2/Me-3, and H-2′/Me-3 distances, evaluated according to literature procedures[29,30] with a correlation time of 1.7×10^{-11} s, were in good agreement (<0.2 Å) with those obtained by MACROMODEL (see above).

On the basis of these calculations the indicated configuration was tentatively assigned to **20a,b** and **21a,b,c**. If this attribution is correct, it seems that the increased bulkiness of the diene **8** improves the *anti* diastereofacial selectivity in the cyclocondensation of aldehydes **3** and **4** with respect to that observed with **7**, a fact for which we do not have at present any reasonable explanation.

Conclusion

In conclusion, we have shown that a thio-substituted stereocenter in the α- or β-position on a chiral aldehyde can be exploited to promote good levels of diastereofacial control in the cyclocondensation with electron-rich dienes. A comparison between our results and those obtained in related reactions with chiral alkoxy aldehydes indicates that a thio-substituted group at the stereocenter gives rise to more selective Felkin–Anh-type and less-selective chelation-controlled processes with respect to an alkoxy substituent.

Table V. Selected ^{13}C-NMR Data (δ) for Pyranones 9–12 and 18–21

compd	C-2	C-3	Me-3	C-5
9a	81.2	39.2		54.9
9b	80.6	38.3		54.0
10a	82.0	38.8		52.0
10b	81.5	39.0		51.8
11a	80.5	40.0		61.0
11b	80.5	40.5		60.7
12a	80.8	39.5		59.2
12b	81.0	40.7		58.8
18a	85.0	41.3	12.2	52.6
18b	82.7	41.7	9.6	50.7
19a	86.2	41.5	12.0	49.9
19b	82.4	41.7	9.5	46.5
20a	85.0	41.6	13.1	57.7
20b	82.3	41.5	9.6	57.2
21a	84.9	41.7	14.7	56.1
21b	81.8	41.4	10.0	54.5
21c	85.3	42.1	9.5	56.6

Experimental Section

^{1}H- and ^{13}C-NMR spectra were obtained on an 80- or a 300-MHz instrument in $CDCl_3$ as solvent. Silica gel was used for analytical and flash chromatography. Organic extracts were dried over Na_2SO_4 and filtered before removal of the solvent. All reactions employing dry solvents were run under argon. THF and Et_2O were distilled from $LiAlH_4$, CH_2Cl_2 from CaH_2, and benzene and toluene from Na. Dry solvents were stored over molecular sieves under argon.

BF_3·OEt_2 was distilled before use and used neat; $TiCl_4$ was used as commercially available 1 M solution in CH_2Cl_2; $MgBr_2$·OEt_2 and Eu(fod)$_3$ are commercially avaliable; VCl_3·THF_3[31] and $TiCl_2$(O-*i*-Pr)$_2$[32] were prepared as described. Aldehydes **1**,[33] **2**,[34] **3**,[35] **4**,[35] **5**,[36] and **6**[37] are known compounds. α-Thio aldehydes **1–4**[35] and β-thio aldehydes **5–6**[38] were prepared according to literature procedures. Diene **7** is commercially avaliable; diene **8** was prepared as described.[11]

(2*R,2′*S**)- and (2*S**,2′*S**)-2-[1-(Phenylthio)propyl]-2,3-dihydro-4*H*-pyran-4-one (9a and 9b).** To a stirred 0.1 M solution of aldehyde **1** (180 mg, 1 mmol) in CH_2Cl_2 (10 mL) cooled at −78 °C was added neat BF_3·OEt_2 (0.123 mL, 1 mmol) over 2 min. After 5 min of stirring at −78 °C, diene **7** (0.233 mL, 1.2 mmol) was added in 5 min and the mixture stirred for 4 h at −78 °C. The reaction was quenched by addition of saturated $NaHCO_3$ solution at −78 °C, and the mixture was warmed to rt and filtered (if necessary) through a Celite cake. The organic phase was separated, the aqueous phase was extracted twice with CH_2Cl_2, and the combined organic extracts were dried and concentrated. The residue was dissolved in wet CH_2Cl_2, and a few drops of CF_3COOH were added. The dark solution was allowed to stir at rt overnight. Solid Na_2CO_3 was then added, the mixture was filtered, the filtrate was concentrated, and the crude product was

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analyzed by NMR. The product was then purified by flash chromatography with a 60:40 diethyl ether–hexanes mixture as eluant to give a pale yellow oil: IR 3050, 2960, 1675, 1590, 1260 cm^{-1}. Anal. Calcd for $C_{14}H_{16}O_2S$: C, 67.72; H, 6.49. Found: C, 67.58; H, 6.39.

By the same procedure compounds **10–12** and **16–21** were obtained after flash chromatography with the same eluant as pale yellow oils unless otherwise stated. The reaction in toluene was carried out similarly. Solid LAs were added as 1 M solutions. Yields and diastereoisomeric ratios are reported in Tables I and II; selected NMR data in Tables III–V. Elemental analyses were obtained on the diastereoisomeric mixtures.

(2*R,2′*S**)- and (2*S**,2′*S**)-2-[1-(methylthio)propyl]-2,3-dihydro-4*H*-pyran-4-one (10a and 10b)**: IR 2960, 1680, 1595, 1260 cm^{-1}. Anal. Calcd for $C_9H_{14}O_2S$: C, 58.03; H, 7.58. Found: C, 57.81; H, 7.51.

(2*R,2′*S**)- and (2*S**,2′*S**)-2-[2-methyl-1-(phenylthio)-propyl]-2,3-dihydro-4*H*-pyran-4-one (11a and 11b)**: IR 3050, 2960, 1675, 1595, 1260 cm^{-1}. Anal. Calcd for $C_{15}H_{18}O_2S$: C, 68.67; H, 6.91. Found: C, 68.81; H, 6.83.

(2*R,2′*S**)- and (2*S**,2′*S**)-2-[2-methyl-1-(methylthio)-propyl]-2,3-dihydro-4*H*-pyran-4-one (12a and 12b)**: IR 2960, 1670, 1600, 1260 cm^{-1}. Anal. Calcd for $C_{10}H_{16}O_2S$: C, 59.97; H, 8.05. Found: C, 60.09; H, 8.00.

(2*R,2′*R**)- and (2*S**,2′*R**)-2-[2-(Butylthio)-1-methylethyl]-2,3-dihydro-4*H*-pyran-4-one (16a and 16b).** Selected ^{1}H-NMR data of **16a**: δ 4.38 (ddd, 1 H, J = 14.8, 6.6, 3.8 Hz, H-2), 2.40–2.75 (m, 6 H), 2.13 (dq, 1 H, J = 7.0, 3.8 Hz, H-2′), 1.06 (d, 3 H, J = 7.0 Hz, Me-2′). Of **16b**: δ 4.57 (dt, 1 H, J = 14.8, 3.6 Hz, H-2), 2.40–2.75 (m, 6 H), 1.92 (dq, 1 H, J = 7.0, 3.6 Hz, H-2′), 1.09 (d, 3 H, J = 7.0 Hz, Me-2′). Selected ^{13}C-NMR data of **16a**: δ 80.7 (C-2), 39.3 (C-3), 37.0 (C-2′), 35.2 (C-S). Of **16b**: δ 81.8 (C-2), 38.5 (C-3), 37.2 (C-2′), 34.9 (C-S); IR 2960, 1680, 1595, 1260 cm^{-1}. Anal. Calcd for $C_{12}H_{20}O_2S$: C, 63.12; H, 8.83. Found: C, 62.97; H, 8.73.

(2*R,2″*R**)- and (2*S**,2″*R**)-2-[2-(Butylthio)propyl]-2,3-dihydro-4*H*-pyran-4-one (17a and 17b).** Selected ^{1}H-NMR data of **17a**: δ 4.76 (ddt, 1 H, J = 10.0, 5.0, 3.3 Hz, H-2), 2.97 (ddq, 1 H, J = 9.7, 4.3, 7.0 Hz, *H*C-Me), 1.55–2.60 (m, 6 H), 1.35 (d, 3 H, J = 7.0 Hz, Me). Of **17b**: δ 4.59 (ddt, 1 H, J = 8.5, 7.7, 5.5 Hz, H-2), 2.94 (ddq, 1 H, J = 8.5, 5.8, 7.0 Hz, *H*C-Me), 1.55–2.60 (m, 6 H), 1.32 (d, 3 H, J = 7.0 Hz, Me). Selected ^{13}C-NMR data of **17a**: δ 77.0 (C-2), 41.8 (C-3), 36.2 (CS), 29.7 (C-2′). Of **17b**: δ 77.3 (C-2), 41.6 (C-3), 35.3 (C-S), 29.9 (C-2′); IR 2960, 1680, 1600, 1260 cm^{-1}. Anal. Calcd for $C_{12}H_{20}O_2S$: C, 63.12; H, 8.83. Found: C, 63.08; H, 8.80.

(2*R,2′*S**,3*S**)- and (2*R**,2′*S**,3*R**)-3,5-dimethyl-2-[1-(phenylthio)propyl]-2,3-dihydro-4*H*-pyran-4-one (18a and 18b)**: IR 3050, 2960, 1675, 1625, 1390, 1170 cm^{-1}. Anal. Calcd for $C_{16}H_{20}O_2S$: C, 69.53; H, 7.29. Found: C, 69.58; H, 7.37. The reaction in CH_2Cl_2 gave a low-melting mixture of isomers; the reaction in toluene gave the mixture of isomers indicated in Table II as a white solid melting at 105–110 °C.

(2*R,2′*S**,3*S**)- and (2*R**,2′*S**,3*R**)-3,5-dimethyl-2-[1-(methylthio)propyl]-2,3-dihydro-4*H*-pyran-4-one (19a and 19b)**: IR 2960, 1670, 1625, 1400, 1180 cm^{-1}. Anal. Calcd for $C_{11}H_{18}O_2S$: C, 61.64; H, 8.47. Found: C, 61.49; H, 8.58. The mixture of isomers obtained in toluene (Table II) melted at 65–68 °C. The isomeric mixture obtained in CH_2Cl_2 was a waxy material.

(2*R,2′*S**,3*S**)- and (2*R**,2′*S**,3*R**)-3,5-dimethyl-2-[2-methyl-1-(phenylthio)propyl]-2,3-dihydro-4*H*-pyran-4-one (20a and 20b)**: IR 3060, 2960, 1680, 1625, 1400, 1180 cm^{-1}. Anal. Calcd for $C_{17}H_{22}O_2S$: C, 70.31; H, 7.64. Found: C, 70.37; H, 7.65. The reaction in CH_2Cl_2 gave a thick oil that solidified in the freezer. The reaction in toluene gave the mixture of isomers indicated in Table II as a white solid melting at 99-105 °C.

(2*R,2′*S**,3*S**)-, (2*R**,2′*S**,3*R**)-, and (2*S**,2′*S**,3*S**)-3,5-dimethyl-2-[2-methyl-1-(methylthio)propyl]-2,3-dihydro-4*H*-pyran-4-one (21a, 21b, and 21c)**: IR 2960, 1680, 1625, 1400, 1180 cm^{-1}. Anal. Calcd for $C_{12}H_{20}O_2S$: C, 63.12; H, 8.83. Found: C, 63.21; H, 8.90.

NMR Experiments on 18–21. ^{1}H 300-MHz phase-sensitive NOESY spectra of a 20 mM solution of **18–21** were recorded in $CDCl_3$ at 300 K, without sample spinning, with a mixing time of 1.4 s and a relaxation delay of 8 s. The original data matrix was 256 × 1K, and 256 transients were collected for each t_1 increment. The spectra were processed employing a Lorentzian–Gaussian filter. ^{13}C spin-lattice relaxation times were measured by the inversion-recovery method.

(2*R,2′*S**)-7-[1-(Phenylthio)propyl]-1,4,8-trioxaspiro-[4.5]decane (15). Synthesis from 9a.** To a stirred solution of **9a** (250 mg, 1 mmol) in dry THF (10 mL) cooled at −78 °C was added a 1 M solution of L-Selectride in THF (1.2 mL, 1.2 mmol) dropwise. The reaction was allowed to warm to −40 °C, and after 10 min of stirring at −40 °C, quenched by addition of saturated NH_4Cl. The mixture was then extracted twice with diethyl ether, dried, and concentrated to give the crude product that did not contain any starting material by TLC and ^{1}H-NMR analysis. The pyranone (ν C=O at 1715 cm^{-1}) was dissolved in dry benzene (15 mL) and refluxed for 0.5 h in the presence of cat. pTsOH and ethylene glycol (0.5 mL) under a Dean-Stark apparatus. When TLC analysis showed the complete disappearance of the starting material, solid $NaHCO_3$ was added to the cooled reaction mixture; this was filtered, washed with water, dried, and evaporated to give the crude product that was purified by flash chromatography with a 60:40 hexanes–diethyl ether mixture as eluant, to give a pale yellow oil (0.185 mg, 63% yield): selected ^{1}H-NMR data δ 3.63 (ddd, 1 H, J = 2.4, 6.5, 11.6 Hz, H-2), 3.02 (dt, 1 H, J = 6.5, 7.2 Hz, H-2′), 2.00 (dd, 1 H, J = 11.6, 16.0 Hz, H-3), 1.61 (dd, 1 H, J = 2.4, 16.0 Hz, H-3); ^{13}C-NMR δ 107.0, 77.5, 65.6, 64.4, 64.2, 55.7, 38.6, 35.5, 24.1, 11.5; IR 2940, 1600, 1450, 1130, 1100, 1070, 740, 700 cm^{-1}. Anal. Calcd for $C_{16}H_{22}O_3S$: C, 65.27; H, 7.53. Found: C, 65.37; H, 7.59.

Synthesis from 13. Compound **13** (500 mg, 2 mmol), prepared according to Danishefsky et al.,[12] was transformed (53% overall yield) into **(7*R**,7′*R**)-7-(1-hydroxypropyl)-1,4,8-trioxaspiro[4.5]decane (14)** by L-Selectride reduction and ketalization as described above, followed by hydrogenolysis (10% Pd/C, H_2, THF, rt, 30 min). This compound was obtained as an oil after chromatography with an 80:20 diethyl ether–hexanes mixture as eluant. ^{1}H-NMR δ 4.01 (ddd, 1 H, H-C9, J = 13.0, 5.5, 1.6 Hz), 3.95 (s, 4 H, H-C2 and H-C3), 3.62 (ddd, 1 H, H-C9, J = 13.0, 11.5, 2.3 Hz), 3.30–3.40 (m, 2 H, H-C7 and H-C7′), 2.38 (bs, 1 H, OH), 1.40–1.85 (m, 6 H, H-C10, H-C7, and H-C6), 0.98 (t, 3 H, Me, J = 7.0 Hz); IR 3450, 2940, 1210, 1130, 1070 cm^{-1}. Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.96. Found: C, 59.30; H, 9.04.

A stirred solution of **14** (246 mg, 1 mmol), diphenyl disulfide (436 mg, 2 mmol), and tributylphosphine (0.5 mL, 2.5 mmol) in dry THF (10 mL) was refluxed for 15 h. Evaporation of the solvent followed by flash chromatography gave compound **15** as a single isomer, identical by ^{1}H- and ^{13}C-NMR to the sample obtained from **9a**.

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Registry No. **1**, 132331-35-2; **2**, 132331-36-3; **3**, 132331-33-0; **4**, 132331-34-1; **5**, 138092-15-6; **6**, 138092-02-1; **7**, 54125-02-9; **8**, 72486-93-2; **9a**, 140928-69-4; **9b**, 140928-70-7; **10a**, 140928-71-8; **10b**, 140928-72-9; **11a**, 140928-73-0; **11b**, 140928-74-1; **12a**, 140928-75-2; **12b**, 141017-02-9; **13**, 140928-77-4; **14**, 140928-78-5; **15**, 140928-76-3; **16a**, 140928-79-6; **16b**, 140928-80-9; **17a**, 140928-81-0; **17b**, 140928-82-1; **18a**, 140928-83-2; **18b**, 140928-84-3; **19a**, 140928-85-4; **19b**, 140928-86-5; **20a**, 140928-87-6; **20b**, 140928-88-7; **21a**, 140928-89-8; **21b**, 140928-90-1; **21c**, 140928-91-2; PhSSPh, 882-33-7.