A General Diastereoselective Synthesis of Spiroacetals Related to Those in Ionophores via the Reaction of Lactones with Cerium(III) γ-Cerioalkoxide. MAD Reverses the Diastereoselectivity of the Addition of Methylmetallics to a β-Keto Ether[1,2]

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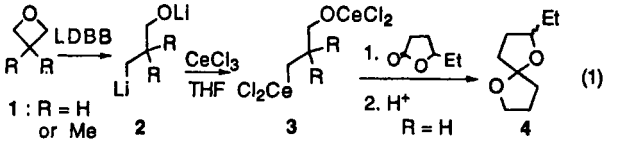
The following steps constitute a fairly general and stereoselective synthesis of spiroacetals. 1. Thiophenol is added to acrylic acid. 2. The latter is treated consecutively with butyllithium, $CeCl_3$, and an organolithium compound. 3. The resulting 3-(phenylthio) ketone is either reduced in the presence of zinc ion to yield mainly one diastereomer or treated with methyllithium or methylmagnesium chloride in the presence or absence of methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD, **25**) to yield selectively either of two diastereomeric 3-(phenylthio) alcohols. 4. The alcohol is treated with butyllithium, lithium 4,4′-di-*tert*-butylbiphenylide (LDBB), and $CeCl_3$, to yield a cerium(III) γ-cerioalkoxide, which is added to a lactone, the reaction being quenched with acid. In the addition to the keto ether in the absence of MAD, methyllithium or methylmagnesium chloride give very predominantly the erythro alcohol, presumably via Cram's chelate model, while in the presence of excess MAD, the threo product is very predominant, possibly because each oxygen atom is complexed with the bulky aluminum reagent. The methodology is demonstrated by the preparation of diastereomeric spiroacetals related to those found in a number of natural ionophores by using as the reaction partner of the carboxylate salt, α-lithio tetrahydrofuran or tetrahydropyran, readily generated by reductive lithiation of the corresponding α-(phenylthio) heterocycle with LDBB, and by employing methylmetallics rather than reducing agents for the reaction with the ketone.

Introduction

The spiroacetal grouping is found in a wide array of natural products having diverse biological activities. Consequently, a great deal of attention has been paid to the development of synthetic methods for spiroacetals. By far the most general method is the acid-induced cyclization of appropriate dihydroxy ketones or their equivalents.[3] Recent reports from this laboratory have described a highly efficient and potentially general method involving the addition of carbanion-oxyanions to lactones followed by acid-induced cyclization.[4,5] In this previous work, the dianions were generally produced by reductive cleavage of oxetanes[6,7] and tetrahydrofurans by lithium 4,4′-di-*tert*-butylbiphenylide[8] (LDBB). A key finding was that when lithium ions were the only Lewis acids present, the addition of cerium(III) chloride[9] led to greatly increased yields of spiroacetals from the dianions. The presence of boron trifluoride, required in order to achieve the reductive cleavage of tetrahydrofurans, appeared to negate the necessity to add the cerium salt. In the example shown in eq 1, **3** (R = H or methyl) was generated from oxetane or 3,3-dimethyloxetane and **3** (R = H) was converted to **4**, the major component of the pheromone of the Norway spruce pest.[4]



Although regiochemical control could be attained in the case of unsymmetrical oxetanes by the presence or absence of Lewis acids,[7] we considered that the preparation of lithium lithioalkoxides by reductive lithiation of oxygen heterocycles lacked broad generality in the substitution patterns that it could generate. We envisioned a more general method based on the reductive lithiation of phenyl

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(1) Dedicated to Professor Antonino Fava on the occasion of his 70th birthday.

(2) Taken from the Ph.D. thesis of Y. Ahn, Chemistry Department, University of Pittsburgh, 1993.

(3) (a) For a review on the chemistry and the synthesis of spiroacetal-containing natural products, see: Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617–1661. For reviews on spiroacetal synthesis, see: (b) Wierenga, W. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley Interscience: New York, 1981; Vol. 4, p 263. Kluge, A. F. *Heterocycles* **1986**, *24*, 1699. Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309. (c) Vaillancourt, V.; Pratt, N. E.; Perron, F.; Albizati, K. F. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley Interscience: New York, 1992; Vol. 8, p 533–691.

(4) Mudryk, B.; Shook, C. A.; Cohen, T. *J. Am. Chem. Soc.* **1990**, *112*, 6389–91. See also: Mudryk, B.; Cohen, T. *J. Am. Chem. Soc.* **1991**, *113*, 1866–67.

(5) A number of the methods cited in the reviews in ref 3 involve addition of a carbanion bearing a protected alcohol to a lactone followed eventually by deprotection and acid-induced ring closure. However in only two cases were carbanions bearing oxyanionic substituents used in the addition. In unpublished work cited in ref 3c, Martin and Albizati used a lithium enolate bearing a lithium alkoxide while McGuirk and Collum (McGuirk, P. R.; Collum, D. B. *J. Am. Chem. Soc.* **1982**, *104*, 4496–4497) used an allylic Grignard reagent generated by treatment of an olefin bearing an alcohol group with a super base. The only unstabilized anions used for such a purpose were generated by reductive lithiation as in ref 4 and the current work.

(6) Mudryk, B.; Cohen, T. *J. Org. Chem.* **1989**, *54*, 5657–5659.

(7) Mudryk, B.; Cohen, T. *J. Org. Chem.* **1991**, *56*, 5760–5761.

(8) Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924–1930.

(9) Imamoto, T.; Kusumoto, T.; Tawarayama, Y.; Sugiura, Y.; Mita, T.; Hatanaka, Y.; Yokoyama, M. *J. Org. Chem.* **1984**, *49*, 3904–3912. Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233–4236. Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392–4396. See also: Luche, J.-L.; Gemal, A. L. *J. Chem. Soc., Chem. Commun.* **1978**, 976–977.

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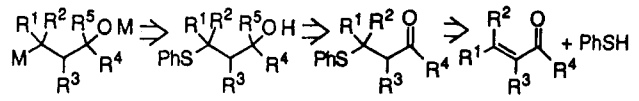
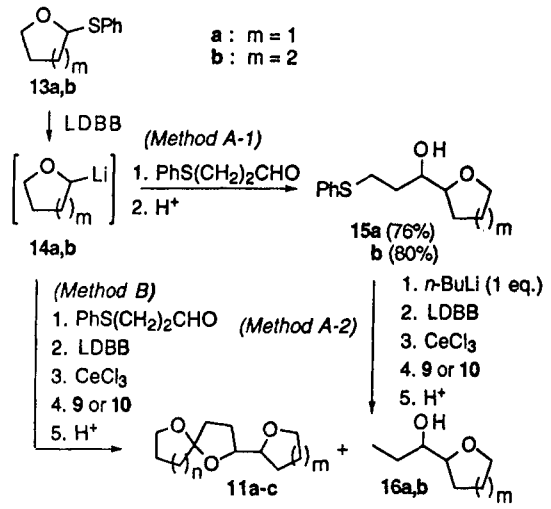
Scheme 1

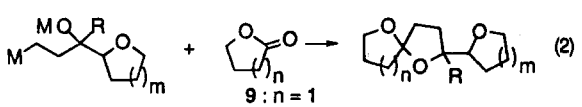


Scheme 2



thioethers by radical anions.[10] The retrosynthetic analysis is shown in Scheme 1 in which M is a metallic group. In principle, it appeared to be a simple matter to acquire a large variety of lithium γ-lithioalkoxides by such reductive lithiation. The key step would be the very high yield conjugate addition of thiophenol to α,β-unsaturated carbonyl compounds.[11]

In this paper we present the reduction to practice of this more general method for preparing spiroacetals via complex lithium γ-lithioalkoxides such as **5** and **6**. We also demonstrate a new and potentially powerful method for the control of diastereoselectivity in the addition of an organometallic to a β-keto ether. We chose spiroacetals **11a–c** and **12**, which resemble segments of many naturally occurring and frequently biologically active natural products, as our target molecules (eq 2). In particular, the spiroacetal **12** has the common structural feature of many naturally occurring ionophoric spiroacetals[3] with a methyl group and a cyclic ether moiety attached to the spiro[4.5] ring substructure such as in carriomycin, lonomycin, monensin, nigericin, septamycin, etc.



(2)

5a : M = Li, R = H, m = 1
b : M = Li, R = H, m = 2
6 : M = Li, R = Me, m = 1
7a : M = $CeCl_2$, R = H, m = 1
b : M = $CeCl_2$, R = H, m = 2
8 : M = $CeCl_2$, R = Me, m = 1

9 : n = 1
10 : n = 2

11a : R = H, m = 1, n = 2
b : R = H, m = 2, n = 2
c : R = H, m = 2, n = 1
12 : R = Me, m = 1, n = 2

Results and Discussion

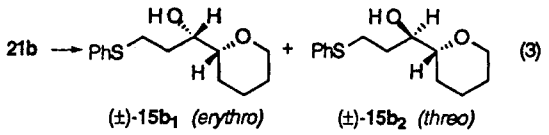
Our first approach was the syntheses of spiroacetals **11a–c** by using γ-lithioalkoxides which were generated by reductive lithiation of the adducts **15a,b** of organolithiums **14a,b** and readily available 3-(phenylthio)propanal (Scheme 2 and Table 1 entries 1–3).

Organolithiums **14a** and **14b** were generated[12] from **13a** and **13b**, respectively, by reductive lithiation using LDBB. Either the two-step (method A) or one-pot (method B) procedure furnished the spiroacetals **11a–c**, along with some unwanted byproducts **16a** and **16b**, presumably generated via proton abstraction from the reactant lactones **9** and **10**. Although methods A and B were successful in producing the spiroacetals **11a–c**, all four possible diastereomers were produced in comparable amounts (Table 1, entries 1–3). While acid-induced acetal formation is expected to give two epimers at the acetal (spiro) carbon atom, it was clear that attack of **14a** and **14b** on 3-(phenylthio)propanal lacked stereoselectivity. This conclusion is confirmed by the diastereomeric ratio of **15b** (1.05:1)[13] prepared by method A-1.

This lack of stereoselectivity prompted us to try another approach for the stereoselective synthesis of spiroacetals **11** and **12** by utilizing stereoselectively generated alcohols **15** and **23a** (the analog of **15a** in which the carbinol hydrogen atom is replaced with a methyl group). We now report the success of this new approach.

The preparation of the ketones **21**, which were to be converted stereoselectively to alcohols **15** and **23a**, from the adduct **19** of thiophenol and acrylic acid was investigated (Schemes 3 and 4, Table 2). The reaction of acyl chloride **20**, derived from carboxylic acid **19**, with heterocuprate[11] **18b** gave a fair yield (48%) of ketone **21b**. In order to shorten the sequence, however, a direct synthesis of **21b** from **19** using organolithium **14b** was attempted but it gave unsatisfactory yields of **21b** (entry 4, Table 2). Addition of 2 equiv of $CeCl_3$ to the lithium salt of **19** prior to the addition of **14b** increased the yield of **21b** to 72% (entry 1). The yield of **21b** was substantially lower when only 1 equiv of $CeCl_3$ was employed (entries 2 and 3). Similarly, ketone **21a** was prepared by the reaction of **19** with **14a** using 2 equiv of $CeCl_3$ (entry 5). We have reported elsewhere[14] our investigation of the scope of this considerably improved version of the venerable synthesis of ketones directly from carboxylic acids and the reasons for the effect of cerium chloride.

The chelation-controlled[15,16] stereoselective reduction of ketone **21b** to alcohol **15b** (eq 3) was investigated either



(3)

(±)-**15b**$_1$ (*erythro*) (±)-**15b**$_2$ (*threo*)

by using zinc borohydride[17] as a chelating and reducing

(10) Cohen, T.; Bhupathy, M. *Acc. Chem. Res.* **1989**, *22*, 152–161. Cohen, T. In *Heteroatom Chemistry*; Block, E., Ed.; VCH Publishers: New York, 1990; Chapter 7.

(11) Cherkauskas, J. P.; Cohen, T. *J. Org. Chem.* **1992**, *57*, 6–8.

(12) Cohen, T.; Matz, J. R. *J. Am. Chem. Soc.* **1980**, *102*, 6900. Cohen, T.; Lin, M.-T. *J. Am. Chem. Soc.* **1984**, *106*, 1130.

(13) The diastereomeric ratio was determined by ^{1}H NMR analysis.

(14) Ahn, Y.; Cohen, T. *Tetrahedron Lett.* **1994**, *35*, 203–206.

(15) Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 2748.

(16) (a) Fouquey, C.; Jacques, J.; Angiolini, L.; Tramontini, M. *Tetrahedron* **1974**, *30*, 2801. Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201. Still, W. C.; McDonald, J. H., III. *Tetrahedron Lett.* **1980**, *21*, 1031. Still, W. C.; Schneider, J. A. *Ibid.* **1980**, *21*, 1035. Bhupathy, M.; Cohen, T. *Tetrahedron Lett.* **1985**, *26*, 2619. Reetz, M. T. *Pure Appl. Chem.* **1985**, *57*, 1781 and references cited therein. Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Springer: Berlin, 1986, and references cited therein. Jefford, C. W.; Jaggi, D.; Boukouvalas, J. *Tetrahedron Lett.* **1986**, *27*, 4011. Singh, S. M.; Oehlschlager, A. C. *Can. J. Chem.* **1988**, *66*, 209. Henry, K. J., Jr.; Grieco, P. A.; Jagoe, C. T. *Tetrahedron Lett.* **1992**, *33*, 1817. (b) Review: Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556–569. See also (c) Reetz, M. T.; Kesseler, K.; Schmidtberger, S.; Wenderoth, B.; Steinbach, R. *Angew. Chem. Suppl.* **1983**, 1511–1526; *Angew, Chem., Int. Ed. Engl.* **1983**, *22*, 989. (d) Reetz, M. T.; Kesseler, K.; Jung, A. *Tetrahedron Lett.* **1984**, *25*, 729.

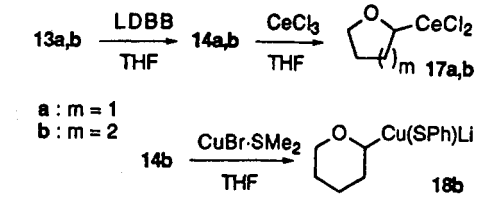
(17) Gensler, W. J.; Johnson, F.; Sloan, D. B. *J. Am. Chem. Soc.* **1960**, *82*, 6074.

Table 1. Formation of Spiroacetals 11 from 3-(Phenylthio)propanal

entry	method	ring size m	ring size n	reactants		products: 11 (yield,[a] diastereomeric ratio[b])	products: 16
1	A-2	1	2	**15a**[c]	10	**11a** (63%, 34:28:20:18)	**16a** (23%)[d]
2	B	1	2	**13a**	10	**11a** (50%, 34:28:20:18)	**16a** (26%)
3	B	2	1	**13b**	9	**11c** (37%, 23:29:32:16)	**16b** (27%)
4	A-2	2	2	**15b**[e]	10	**11b** (42%, 53:36:7:4)	**16b** (52%)

[a] Isolated yield of diastereomeric mixture. [b] The diastereomeric ratio was determined by GC. [c] This reactant alcohol **15a** was prepared from the reaction of **14a** with 3-(phenylthio)propanal (method A-1 in Scheme 2). [d] The diastereomeric ratio (52:48) was determined by ^{1}H NMR. [e] This reactant alcohol diastereomeric mixture **15b** was prepared by stereoselective reduction of ketone **21b** (entry 6 in Table 3). The diastereomeric ratio (7.50:1) of this reactant **15b** was determined by ^{1}H NMR.

Scheme 3



Scheme 4

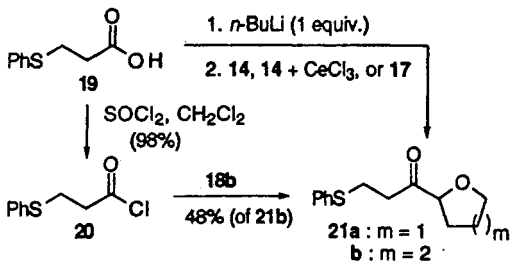


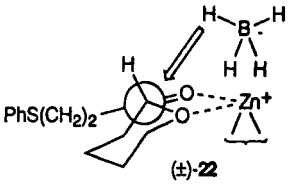
Table 2. Formation of Ketone 21 from Carboxylic Acid 19

entry	ring size (m)	condition (equiv)	ketone yield[a] (%)
1	2	(i) $CeCl_3$ (2); (ii) **14b** (1)	**21b** (72)
2	2	(i) $CeCl_3$ (1); (ii) **14b** (1)	**21b** (51)
3	2	**17b** (1)	**21b** (57)
4	2	**14b** (1)	**21b** (20–30)
5	1	(i) $CeCl_3$ (2); (ii) **14a** (1)	**21a** (54)

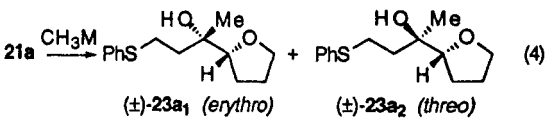
[a] Isolated yield.

agent[18] or by using zinc chloride[19] as a chelating agent followed by addition of a reducing agent[20] as shown in Table 3. The best result, essentially quantitative yield and an almost 10/1 ratio of stereoisomers, was obtained by using $Zn(BH_4)_2$ in 1:1 solvent mixture of THF/Et_2O at −78 °C (entry 1). Maintaining the low temperature (−78 °C) until the reaction was quenched gave better stereoselectivity than quenching at a higher temperature (for example, compare entries 1 and 6). The product alcohol isomer mixture from the reaction in entry 6, without further separation of each diastereomer, was directly used to demonstrate the synthesis of spiroacetal **11b** (Table 1, entry 4). It should be noted, that the reduction of α-hydroxy and -alkoxy ketones in the absence of chelating metal ions often gives nonstereoselective results.[21]

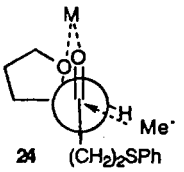
The structural assignments of **15b$_1$** and **15b$_2$** are based on Cram's rule[15] for the case of the diastereo-zeroplane consisting of a chelate ring. The Zn ion of $Zn(BH_4)_2$ coordinates with the oxygen atoms of the carbonyl group and the cyclic ether, forming complex **22** which favors attack of the hydride from the less-hindered side to yield erythro alcohol as the major product.



As mentioned above, many natural spiroacetals[3] contain a moiety such as **12** in which a methyl group replaces a hydrogen atom adjacent to one of the acetal oxygen atoms. In order to demonstrate the ability to incorporate this structural feature into the spiroacetals, approaches involving chelation-controlled[16b] and non-chelation-controlled stereoselective nucleophilic addition of a methyl group to the ketone **21a** were attempted (eq 4). The results of these approaches are summarized in Table 4.



As in the case of **15b**, the structural assignments of the products **23a$_1$** and **23a$_2$** were based on the Cram's rule[16] for a chelate ring. The erythro alcohol (±)-**23a$_1$** was obtained as the major product via the nucleophilic attack of the methyl group from the less-hindered side in the complex **24** from the reactions in entries 1–4 in Table 4. Although the highest stereoselectivity (11/1) was obtained by the use of methyl Grignard reagent, the best combination of yield (87%) and stereoselectivity (10/1) was attained using methyllithium in tetrahydrofuran.



In the hope of obtaining the threo alcohol (±)-**23a$_2$** as the major product, ketone **21a** was treated with a bulky

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Table 3. Preparation of Alcohol 15b by Stereoselective Reduction of Ketone 21b

entry	reagent(s) (equiv)	solvent (volume ratio)	temp[a] (°C)	time (h)	diastereomer ratio (erythro/threo)[b]	yield,[c] %
1	$Zn(BH_4)_2$ (1.4)	THF/Et_2O (1:1)	−78 (−78)	48	9.5/1	>99
2	$Zn(BH_4)_2$ (1.4)	THF	−78 (−78)	48	5.2/1	88 (9)
3	$Zn(BH_4)_2$ (1.4)	THF	−78 (−78)	24	4.9/1	73 (25)
4	$Zn(BH_4)_2$ (1.4)	THF	−78 (−78)	6	3.8/1	43 (54)
5	$Zn(BH_4)_2$ (1.4)	THF	−40 (−40)	2	3.1/1	94
6	$Zn(BH_4)_2$ (1.4)	THF/Et_2O (1:1)	−78 (0)	4	7.5/1	95
7	$Zn(BH_4)_2$ (1.4)	THF/Et_2O (3:1)	−78 (0)	4	4.9/1	95
8	$Zn(BH_4)_2$ (1.4)	THF/Et_2O (1:3)	−78 (0)	4	4.8/1	>99
9	$Zn(BH_4)_2$ (1.4)	Et_2O	−78 (0)	4	1.5/1	93
10	$Zn(BH_4)_2$ (1.4)	Et_2O	0 (0)	4	2.1/1	97
11	(i) $ZnCl_2$ (1.4) (ii) $Zn(BH_4)_2$ (1.4)	THF/Et_2O (1:1)	−78 (0)	4	6.1/1	91
12	(i) $ZnCl_2$ (3) (ii) DIBAL (6)	THF/Et_2O/hex (3.2:3.2:1)	−78 (0)	4	6.3/1	76 (24)
13	(i) $ZnCl_2$ (3) (ii) DIBAL (6)	THF/Et_2O (1:1)	−78 (−78)	20	5.4/1	87
14	(i) $ZnCl_2$ (3) (ii) DIBAL (6)	THF	−78 (−78)	19	5.1/1	90
15	(i) $ZnCl_2$ (3) (ii) DIBAL (6)	THF/hex (6:1)	−78 (−78)	7	6.4/1	79 (20)
16	(i) $ZnCl_2$ (3) (ii) K-Selectride (3)	THF	−88 (−88)	4	3.4/1	46

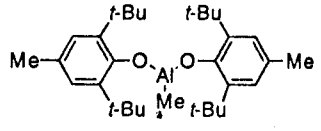
[a] The reaction mixture was stirred for an additional 15 min at the quenching temperature in parentheses before being quenched unless temperatures for reaction and quenching were the same. [b] The assignment was based on Cram's cyclic model. The diastereomeric ratios were determined by ^1H NMR analyses. [c] Combined isolated yields. The figures in parentheses are amounts (%) of recovered ketone.

Table 4. Preparation of Alcohol 23a by Stereoselective Addition of a Methylmetallic Reagent to Ketone 21a

entry	reagent(s)[a] (equiv)	solvent[b]	time (h)	alcohol **23a**[c] erythro/threo (% yield[d])	recovered **21a** (%)
1	MeLi (1)	THF/Et_2O (38:1)	4	9.7/1 (87)	11
2	MeLi (1)	toluene/Et_2O (40:1)	4	6.9/1 (78)	12
3	MeMgBr (1)	THF	4	11.1/1 (41)	47
4	MeMgCl (1.4)	THF	48	9.1/1 (81)	12
5	$MeCeCl_2$ (1)	THF	24	1.1/1 (22)	71
6	(i) MAD (3) (ii) MeLi (1.7)	toluene/Et_2O (24:1)	24	1/10.2 (80)	20
7	(i) MAD (1) (ii) MeLi (1.5)	toluene/Et_2O (27:1)	20	1/3.9 (83)	17
8	(i) MAD (1) (ii) MeMgCl (3)	toluene/THF (30:1)	41	1/2.2 (77)	23

[a] The reaction temperature was −78 °C in all cases. [b] The small amount of Et_2O or THF in toluene was from the solvent of commercial MeLi or MeMgCl. [c] The assignment was based on Cram's cyclic model. The diastereomeric ratios were determined by GC and ^1H NMR. [d] Combined isolated yield.

Lewis acid, Yamamoto's methylaluminumbis(2,6-di-*tert*-butyl-4-methylphenoxide)[22] (MAD) (**25**), in toluene prior to the MeLi addition. Gratifyingly, the direction of



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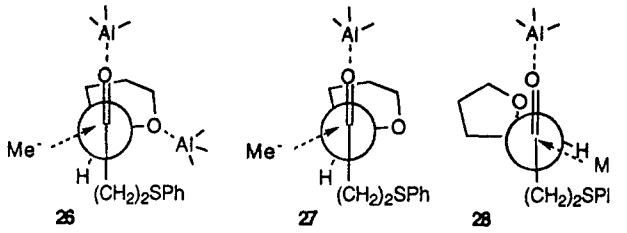
stereoselection was indeed reversed. Using 1 equiv of MAD led to an erythro/threo ratio of 1:3.9, an almost 40-fold change from the results in the absence of MAD. It is striking that when an excess (3 equiv) of MAD is used, this ratio increases to 1:10.2 which constitutes a 100-fold reversal. It is reasonable to assume a transition state such as **26** for the case in which excess MAD is present. Since the only Lewis base competition for the keto and tetrahydrofuran oxygen atoms is the trace of the poorly complexing diethyl ether in the solvent, it is presumed that the keto ether **21a** is capable of complexing one molecule of MAD at each of the two oxygen atoms leading to a 1:2 complex. Conformation **26** is favored to relieve the steric congestion between the bulky MAD molecules and to allow the nucleophile to attack in the favored arrangement with respect to the oxygen substituent.[23] The conformer **26** yields the threo alcohol (±)-**23a**$_2$ as the major product. When only 1 equiv of MAD is present, it would be expected to complex the molecule at the carbonyl oxygen atom and the Felkin–Anh transition state[23] **27** would prevail; this would yield the same diastereomer. The reason that excess MAD causes greater stereoselectivity than 1 equiv is probably that the complexation of the cyclic ether oxygen atom increases the electron deficiency of the C–O bond thus favoring transition state **26** even more over other conformations such as the less stable Felkin–Anh type transition state **28**.

Reetz[16c] observed a reversal from apparent chelation to nonchelation control in going from CH_3TiCl_3 to $CH_3Ti(O\text{-}i\text{-}Pr)_3$ in the attack of an α-alkoxy aldehyde but this

(22) (a) Maruoka, K.; Itoh, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 4573. Starowieyski, K. B.; Pasynkiewicz, S.; Skowronska-Ptasinska, M. *J. Organomet. Chem.* **1975**, *90*, C43–C44. See also: Nonoshita, K.; Banno, H.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1990**, *112*, 316 and references cited therein. (b) Maruoka, K.; Itoh, T.; Sakurai, M.; Nonoshita, K.; Yamamoto, H. *Ibid.* **1988**, *110*, 3588.

(23) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199–2202. Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145. Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61–70. Juaristi, E. *Introduction to Stereochemistry & Conformational Analysis*; John Wiley & Sons, Inc.: Toronto, 1991; pp 182–184. See also Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 3353–3361.



reversal was not observed[24] in the case of the corresponding ketone. At the time that the present results were obtained, there was apparently no precedent for reversal of diastereofacial selectivity of a ketone by using an excess of a sterically congested Lewis acid. Just before the original submission of this manuscript, Professor Hisashi Yamamoto informed us of extremely interesting results, now published,[25] somewhat related to those reported here. In the addition of alkylmetallics to cycloalkanones bearing an alkoxy group at the α-position, the use of 2 equiv of MAD in a methylene chloride/ether solvent caused a reversal of stereoselectivity from the product of chelation control to the other stereoisomer. However, in these ring ketones, rotation about the bond between the two oxygen-bearing carbon atoms is far more restricted than in the present system and the explanation given above can not be operative. In particular, no true Felkin–Anh transition state is possible and any transition state in which the ether oxygen atom is on the opposite face of the carbonyl group from the attacking alkyl anion yields the same product as that obtained from chelation control. Thus, it is possible that entirely different explanations hold for the present case and the case of 2-(benzyloxy)cycloalkanones and the reversal in the latter case might simply be a result of the known[22b] tendency of MAD to promote the production of equatorial alcohol.[26] Perhaps more relevant is the report in the same paper that when 2 equiv of MAD are used instead of $TiCl_4$ the diastereoselectivity in the Diels–Alder addition of an acrylate attached to an ester function reverses from the chelation to the nonchelation mode; however, in that case, unlike the present, 1 equiv of MAD does not cause such a reversal but merely decreases the chelation selectivity.

Each major diastereomeric component (erythro or threo) was purified from its minor component by column chromatography. The resulting pure erythro (**23a**$_1$) and threo (**23a**$_2$) alcohols were used in the spiroacetal syntheses (eqs 6 and 7).

From the reaction using erythro alcohol **23a**$_1$, the spiroacetal **12a** was obtained in 61% yield as the expected mixture of diastereomers about the spiroacetal carbon atom (eq 6). Similarly, the spiroacetal **12b** was obtained in 56% yield again as two diastereomers (eq 7). The alcohols **27** (24%) and **28** (23%) were also formed, presumably by proton abstraction by the intermediate carbanion from the reactant lactone **10**. Each pure diastereomer **12a**$_1$ or **12a**$_2$ equilibrated[27] to form a mixture of both diastereomers (**12a**$_1$:**12a**$_2$ = 60:40) by epimerization in a weakly acidic medium such as deuteriochloroform. Similarly, **12b**$_1$ or **12b**$_2$ equilibrated to form a diastereomeric mixture (**12b**$_1$:**12b**$_2$ = 62:38) in deuteriochloroform. Such epimerization may be useful in increasing the yield of a desired diastereomer by several cycles of partially converting an unwanted diastereomer into a desired one.

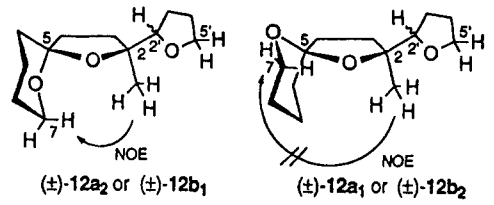
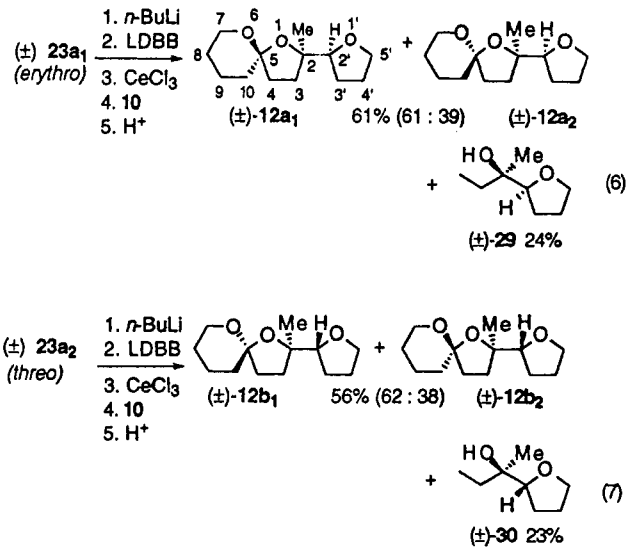


Figure 1.



The relative stereochemistry of the spiroacetals **12a** and **12b** was deduced by a combination of NOESY and COSY experiments. It is certain that the two diastereomeric spiroacetals produced from the same alcohol isomer differ from each other only in the relative stereochemistry at the C-5 spirocenter. Assuming that the anomeric effect[28] determines the conformation of the spiroacetal ring system, one would expect that upon irradiation of the methyl signal an enhanced nuclear Overhauser effect (NOE) on the C-7 protons would be exhibited in only one of the pair of diastereomers formed from each of the alcohol isomers (Figure 1).

The COSY and direct ^1H–^{13}C correlation (HETCOSY) NMR experiments for each spiroacetal isomer allowed the assignment of the signals of the C-7 protons. The C-7 carbon signal in each of the ^{13}C NMR spectra was differentiated from the C-5′ carbon signal by comparing them with the reported ^{13}C NMR chemical shift values[29] of 1,6-dioxaspiro[4.5]decane and its analogs, and of tetrahydrofuran[30] in C_6D_6. As expected, NOEs were observed between the C-7 protons and methyl protons in one isomer each from each pair of the spiroacetal products (eqs 6 and 7), and these isomers were assigned as **12a**$_2$ and

(24) Reetz, M. T.; Hüllmann, M. *J. Chem. Soc., Chem. Commun.* **1986**, 1600–1602.
(25) Maruoka, K.; Oishi, M.; Yamamoto, H. *Synlett* **1993**, 683–685.
(26) Another interesting possibility is that the ether oxygen atom is not complexed with MAD in the transition state (the solvent was stated to be ether/CH_2Cl_2 and the result with 1 equiv of MAD was not reported) and that the alkylmetallic was guided in to the carbonyl carbon atom by the ether oxygen atom.
(27) For examples, see ref 3a, pp 1627–1629.
(28) Deslongchamps, P.; Rowan, D. D.; Pothier, N.; Sauvé, T.; Saunders, J. K. *Can. J. Chem.* **1981**, *59*, 1105. See also ref 3a and references cited therein.
(29) Francke, W.; Reith, W.; Sinnwell, V. *Chem. Ber.* **1980**, *113*, 2686. Mori, K.; Watanabe, H.; Yanagi, K.; Minobe, M. *Tetrahedron* **1985**, *41*, 3663. See also: Kozluk, T.; Cottier, L.; Descotes, G. *Ibid.* **1981**, *37*, 1875.
(30) Our own ^{13}C NMR experiment of a similar compound, 2-methyltetrahydrofuran, also gave a consistent chemical shift value (δ 67.57 for C-5 in C_6D_6) which is comparable to the C-5′ chemical shift values of the diastereomeric spiroacetals **12a**.

12b$_1$, respectively. The other isomers which did not show NOEs were assigned as **12a$_1$** and **12b$_2$**, respectively (Figure 1).

Conclusions

A method has been demonstrated whereby spiroacetals can be prepared in a rather flexible manner in one pot by the addition of an organolithium containing an oxyanionic function to a lactone in the presence of $CeCl_3$ and acidic workup of the reaction mixture. The dianion is produced by reductive lithiation of a readily prepared phenyl thioether, a key step in its production being conjugate addition of thiophenol to an unsaturated carboxylic acid. In this work five-membered cyclic ethers are spiroannulated on to lactones. In a subsequent paper, it will be shown that a related procedure allows the production of dianions suitable for spiroannulation of six-membered rings on to lactones and that spiroacetals of high enantiomeric purity can result.[31] The requisite γ-phenylthio ketones can be prepared by the conjugate addition of the cuprate of a sulfur-stabilized carbanion to an enone. These two concepts illustrate one of the great advantages of the reductive lithiation procedure, the great versatility of divalent sulfur.

It has also been shown that the chelation-controlled addition of methyllithium to a β-keto cyclic ether can be reversed by the use of the exceptionally bulky Lewis acid MAD.

Experimental Section

NMR spectra were recorded on a Bruker WH-300 or AF-300 spectrometer operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C. ^{1}H and ^{13}C NMR chemical shifts are referenced to solvent peaks: δ_H 7.26 (residual $CHCl_3$) and δ_C 77.09 for $CDCl_3$, δ_H 7.15 (residual benzene-d_5) and δ_C 128.0 for benzene-d_6. Coupling constants, J, are reported in hertz and refer to apparent peak multiplicities and not true coupling constants. NOESY and COSY spectra were recorded on a Bruker AM-500 or AF-300 spectrometer. Infrared spectra were recorded on the IR/32 FTIR spectrometer. Low resolution and high resolution mass spectra were obtained in the electron impact mode at 70 eV. Gas-liquid chromatography was performed on a Hewlett-Packard 5890A gas chromatograph equipped with a fused silica capillary column (0.25 mm × 30 m) and a flame ionization detector, helium being used as a carrier gas. Melting points are uncorrected. Radial chromatography was performed on a Harrison chromatotron using Merck silica gel 60 PF_{254}. Thin-layer chromatography was performed on glass-supported 250-μm silica gel GF plates (Analtech). All commercially available chemicals, including alkyllithiums and Grignard reagents, were purchased from Aldrich.

For the preparation of **3-(phenylthio)propanal**, see the supplementary material of ref 32. The preparation of **lithium 4,4′-di-*tert*-butylbiphenylide (LDBB)** is described in footnote 17 of ref 33.

2-(Phenylthio)tetrahydrofuran (13a). A solution of dihydrofuran (7.01 g, 100.0 mmol) and thiophenol (11.02 g, 100.0 mmol) in 150 mL of chloroform was stirred at room temperature while gaseous HCl was passed through for 5 min. The reaction mixture was then stirred at room temperature for 5 h, quenched with 40 mL of water, and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layer was washed with 5% NaOH (2 × 40 mL) and with saturated NaCl solution (40 mL), dried ($MgSO_4$), and concentrated. Vacuum distillation, through a 10-cm Vigreux column, afforded 13.51 g (75%) of **13a** as a colorless liquid: bp 104–105 °C (0.65 Torr); IR (neat) 2977, 2872, 1584, 1482, 1439, 1048, 1026, 909, 743, 693 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.22–7.55 (m, 5 H, Ph), 5.67 (dd, X of ABX, J = 7.1, 3.6 Hz, 1 H, OC*H*SPh), 3.94–4.09 (m, 2 H, OCH_2), 1.85–2.46 (m, 4 H, alicyclic); ^{13}C NMR ($CDCl_3$) δ 135.74, 131.05, 128.82, 126.78, 87.13, 67.29, 32.66, 24.88; MS (EI) m/z (relative intensity) 180 (M$^+$, 14), 110 (15), 71 (100); HRMS (EI) calcd for $C_{10}H_{12}OS$ 180.0609, found 180.0603.

2-(Phenylthio)tetrahydropyran (13b). Using a procedure identical to that outlined for the synthesis of **13a**, the reaction of dihydropyran (8.41 g, 100.0 mmol) with thiophenol (11.02 g, 100.0 mmol) in 150 mL of chloroform with 5 min saturation of gaseous HCl gave 15.1 g (78%) of product **13b** as a colorless liquid: bp 83 °C (0.05 Torr); IR (neat) 3060, 2940, 2860, 1584, 1480, 1464, 1439, 1260, 1188, 1103, 1078, 1036, 1007, 868, 810, 743, 691 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.19–7.49 (m, 5 H, Ph), 5.21 (dd, X of ABX, J = 5.6, 3.9 Hz, 1 H, OC*H*SPh), 4.14–4.21 (m, 1 H, OC*H*H), 3.55–3.63 (m, 1 H, OCH*H*), 1.51–2.06 (m, 6 H, alicyclic); ^{13}C NMR ($CDCl_3$) δ 135.39 (s), 130.73 (d), 128.72 (d), 126.62 (d), 85.18 (d), 64.44 (t), 31.51 (t), 25.46 (t), 21.59 (t); MS (EI) m/z (relative intensity) 194 (M$^+$, 4), 110 (12), 85 (100); HRMS (EI) calcd for $C_{11}H_{14}OS$ 194.0765, found 194.0754.

General Procedure for the Preparation of Alcohols (15a and 15b) by Reactions of the α-Lithio Cyclic Ethers (14a and 14b) with 3-(Phenylthio)propanal. (Scheme 2, Method A-1). 2-(Phenylthio)tetrahydrofuran (**13a**) (361 mg, 2.00 mmol) or 2-(phenylthio)tetrahydropyran (**13b**) (389 mg, 2.00 mmol) was added dropwise to a preformed solution of lithium 4,4′-di-*tert*-butylbiphenylide (LDBB, 4.10 mmol) in THF (10 mL) at −78 °C, and the resulting deep red mixture was stirred for 1 h. A solution of 3-(phenylthio)propanal (333 mg, 2.00 mmol) in THF (3 mL) was then added dropwise to the mixture. The dark red color turned to a light yellow after 5–30 min of stirring at −78 °C. After the mixture had been warmed to room temperature, water (10 mL) was added, and the organic material was extracted with ether (3 × 30 mL). The combined ether layer was washed with 5% NaOH (2 × 30 mL) and with brine (30 mL) and dried ($MgSO_4$). The solvent was removed by rotary evaporation. The product **15a** or **15b** was isolated by radial chromatography (hexane/EtOAc, 4:1) as an oil. **1-(2′-Tetrahydrofuranyl)-3-(phenylthio)-1-propanol (15a)** (362 mg, 76%, two diastereomers): IR (neat) 3428, 2944, 2870, 1584, 1482, 1439, 1067, 1026, 922, 739, 693 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.12–7.35 (m, 5 H, Ph), 3.54–3.95 (m, 4 H, *H*CO), 3.13–3.22 (m, 1 H, C*H*HS), 2.95–3.07 (m, 1 H, CH*H*S), 2.67 (br s, 1 H, O*H*), 1.53–1.93 (m, 6 H, CCH_2C); ^{13}C NMR ($CDCl_3$) δ 136.36 (s), 128.88 (d), 128.82 (d), 125.74 (d), 82.17 (d), 82.02 (d), 72.43 (d), 70.78 (d), 68.48 (t), 68.13 (t), 33.07 (t), 32.19 (t), 30.12 (t), 29.76 (t), 27.82 (t), 26.14 (t), 26.01 (t), 24.88 (t); MS (EI) m/z (relative intensity) 238 (M$^+$, 31), 220 (9), 168 (16), 136 (11), 123 (61), 110 (63), 97 (68), 71 (100); HRMS (EI) calcd for $C_{13}H_{18}O_2S$ 238.1028, found 238.1035. **1-(2′-Tetrahydropyranyl)-3-(phenylthio)-1-propanol (15b)** (405 mg, 80%, two diastereomers): The spectral data of the mixture of diastereomers were consistent with those of individual diastereomers **15b$_1$** and **15b$_2$**. For the spectral data of each of the diastereomers (**15b$_1$** and **15b$_2$**), see below for the preparation of **15b** by stereoselective reduction of **21b**.

A Typical Procedure for the Preparation of Cerium(III) Chloride Suspension in THF. Cerium(III) chloride heptahydrate ($CeCl_3 \cdot 7H_2O$) (1.34 g, 3.6 mmol) was placed in a 50-mL two-necked flask equipped with a gas inlet valve and a stirring bar. The cerium chloride was stirred under vacuum (0.02 Torr) while being heated at 140 °C for 3 h and then was cooled to room temperature. The vacuum was replaced with an argon atmosphere, and THF (9 mL) was added. The resulting white slurry was stirred vigorously for 2 h at room temperature before being cooled to −78 °C.

General Procedures for the Reaction of Lactones with Cerium γ-Cerioalkoxides. (Scheme 2, Method A-2). *n*-Butyllithium (0.94 mL of a 1.60 M solution in hexane, 1.50 mmol) was added dropwise to a solution of **15a** (358 mg, 1.50 mmol, generated from the reaction of **14a** and 3-(phenylthio)propanal) or **15b** (379 mg, 1.50 mmol, diastereomeric ratio 7.50:1, generated from the reduction of ketone **21b**) in THF (15 mL) at −78 °C. After 30 min of stirring, the alkoxide solution was cannulated to a preformed solution of LDBB (3.15 mmol) in THF (8 mL) at −78 °C. The mixture was stirred for 30 min, and the resulting deep red solution was cannulated to a preformed $CeCl_3$ (3.6 mmol) suspension in THF (9 mL) at −78 °C. After the resulting light

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(32) Shook, C. A.; Romberger, M. L.; Jung, S.-H.; Xiao, M.; Sherbine, J. P.; Zhang, B.; Lin, F.-T.; Cohen, T. *J. Am. Chem. Soc.* *114*, 10754–10773.
(33) Cohen, T.; Doubleday, M. D. *J. Org. Chem.* **1990**, *55*, 4784–6.

brown solution had been stirred for 30 min, δ-valerolactone (**10**) (150 mg, 1.50 mmol) was added. The mixture was stirred for 4 h at −78 °C and then warmed to 0 °C. After 2 h of stirring, the reaction was quenched with 5% HCl (20 mL) at 0 °C, and the mixture was extracted with ether (3 × 30 mL). The combined ether layer was washed with brine (30 mL), dried ($MgSO_4$), and concentrated by rotary evaporation. The products were isolated as oils by radial chromatography to afford 200 mg (63%) of the spiroacetal **11a** and 45 mg (23%) of the protonation product **16a** (hexane/EtOAc, 4:1), or 142 mg (42%) of **11b** and 122 mg (52%) of **16b** (hexane/EtOAc, 9:1). The diastereomeric ratios of **11a** (34:28:20:18) and of **11b** (53:36:7:4) were determined by GC. The diastereomeric ratio of **16a** (52:48) was determined by ^1H NMR. **2-(2′-Tetrahydrofuranyl)-1,6-dioxaspiro[4.5]decane (11a)** (four diastereomers): IR (neat) 2944, 2870, 1458, 1439, 1366, 1221, 1080, 1049, 1034, 990, 941, 882 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.51–4.02 (m, 6 H, *H*CO), 1.38–2.07 (m, 14 H, CCH_2C); ^{13}C NMR ($CDCl_3$) δ 106.08, 105.83, 105.65, 83.18, 83.08, 82.43, 82.13, 81.36, 80.68, 80.50, 79.84, 68.66, 68.46, 68.35, 68.26, 61.47, 61.28, 38.31, 37.28, 37.01, 33.84, 33.55, 33.49, 31.25, 28.27, 28.21, 28.03, 27.86, 27.72, 26.26, 25.78, 25.76, 25.72, 25.65, 25.17, 20.13, 20.02; MS *m/z* (EI) (relative intensity) 212 (M^+, 0.5), 154 (3), 141 (M^+ − C_4H_7O, 100), 97 (22), 85 (27), 71 (23); HRMS (EI) calcd for $C_8H_{13}O_2$ (M^+ − C_4H_7O) 141.0916, found 141.0910. Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.99; H, 9.41. **1-(2′-Tetrahydrofuranyl)-1-propanol (16a)** (two diastereomers): IR (neat) 3440, 2965, 2874, 1462, 1455, 1069, 972 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.65–3.90 (m, 3 H from one diastereomer, 4 H from the other diastereomer, *H*CO), 3.28–3.34 (m, 1 H from one diastereomer, *H*CO), 2.61 (br s, 1 H, O*H*), 1.3–1.9 (m, 6 H, CCH_2C), 0.99 (t, J = 7.4 Hz, 3 H, CH_3 from one diastereomer), 0.98 (t, J = 7.4 Hz, 3 H, CH_3 from the other diastereomer); ^{13}C NMR ($CDCl_3$) δ 82.17 (d), 82.01 (d), 75.21 (d), 73.34 (d), 68.39 (t), 68.01 (t), 27.92 (t), 26.53 (t), 26.22 (t), 26.05 (t), 25.82 (t), 24.52 (t), 10.35 (q), 10.07 (q); MS (EI) *m/z* (relative intensity) 130 (M^+, 0.5), 101 (M^+ − Et, 7), 71 (100); HRMS (EI) calcd for $C_5H_9O_2$ (M^+ − Et) 101.0603, found 101.0587. **(2*R**,2′*S**,5*R**)- and (2*R**,2′*S**,5*S**)-2-(2′-Tetrahydropyranyl)-1,6-dioxaspiro[4.5]decane (11b)** (two major diastereomers separated from a product mixture of four diastereomers): IR (neat) 2940, 2849, 1439, 1368, 1223, 1094, 1046, 1036, 1001, 884 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.7–4.1 and 3.1–3.6 (m, 6 H, *H*CO), 1.2–2.1 (m, 16 H, CCH_2C); ^{13}C NMR ($CDCl_3$) δ 105.82, 105.70, 82.69, 81.42, 80.46, 79.65, 68.56, 61.66, 61.50, 42.47, 38.24, 36.95, 33.76, 33.45, 29.44, 28.02, 27.44, 26.26, 26.14, 25.49, 25.25, 23.16, 23.06, 20.25, 20.19; MS (EI) *m/z* (relative intensity) 226 (M^+, 3), 141 (100), 111 (10), 98 (12), 85 (23); HRMS (EI) calcd for $C_{13}H_{22}O_3$ 226.1569, found 226.1590. Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.97; H, 9.78. **(1*R**,2′*S**)-1-(2′-Tetrahydropyranyl)-1-propanol (16b)** (major diastereomer separated from a product mixture of two diastereomers): IR (neat) 3445, 2936, 2853, 1464, 1441, 1377, 1206, 1092, 1048, 978 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.96–4.00 (m, 1 H, *H*CO), 3.52 (m, 1 H, *H*CO), 3.45 (td, J = 11.2, 2.9 Hz, 1 H, *H*CO), 3.25 (dt, J = 9.8, 3.0 Hz, 1 H, *H*CO), 2.20 (s, 1 H, O*H*), 1.86 (m, 1 H, CC*H*HC), 1.39–1.57 (m, 7 H, CCH_2C), 0.95 (t, J = 7.4 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 80.10 (d), 75.18 (d), 68.74 (t), 26.23 (t), 24.84 (t), 24.76 (t), 23.10 (t), 10.42 (q); MS (EI) *m/z* (relative intensity) 144 (M^+, 1), 141 (85), 85 (100).

Method B: Compound **13a** (361 mg, 2.00 mmol) or **13b** (389 mg, 2.00 mmol) was added dropwise to a preformed solution of LDBB (4.10 mmol) in THF (8 mL) at −78 °C. After 1 h of stirring, a solution of 3-(phenylthio)propanal (333 mg, 2.00 mmol) in THF (3 mL) was added to the resulting deep red solution at −78 °C and the mixture was stirred for 30 min. The light yellow solution was cannulated to an additional preformed solution of LDBB (4.10 mmol) in THF (8 mL) at −78 °C. The mixture was stirred for 30 min, and the resulting dark brown solution was cannulated to a preformed $CeCl_3$ (4.8 mmol) suspension in THF (15 mL) at −78 °C. After the mixture had been stirred for 1 h, δ-valerolactone (**10**) (200 mg, 2.00 mmol) or γ-butyrolactone (**9**) (172 mg, 2.00 mmol) was added, and the mixture was stirred for 4 h at −78 °C. After being warmed to 0 °C, the mixture was stirred for 2 h, quenched with 5% HCl (20 mL), and extracted with ether (3 × 30 mL). The combined ether layer was washed with brine (30 mL), dried ($MgSO_4$), and concentrated. The products were isolated as oils by radial chromatography to afford 211 mg (50%) of **11a** and 67 mg (26%) of **16a** (hexane/EtOAc, 4:1), or 158 mg (37%) of **11c** and 79 mg (27%) of **16b** (hexane/EtOAc, 9:1). The diastereomeric ratios of **11a** (34:28:20:18) and of **11c** (23:29:32:16) were determined by GC. **2-(2′-Tetrahydropyranyl)-1,6-dioxaspiro[4.4]nonane (11c)**: two most polar diastereomers R_f 0.4 (hexane/EtOAc, 3:1); IR (neat) 2936, 2853, 1456, 1441, 1345, 1208, 1094, 1024, 895, 845, 669 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.8–4.0 (m, 4 H, *H*CO), 3.41 (m, 1 H, *H*CO), 3.20 (m, 1 H, *H*CO), 1.1–2.1 (m, 14 H, CCH_2C); ^{13}C NMR ($CDCl_3$) δ 115.17, 114.81, 82.07, 81.01, 80.58, 79.35, 68.71, 68.48, 67.13, 66.87, 35.19, 34.64, 34.32, 29.76, 28.40, 28.11, 27.75, 26.30, 26.17, 25.94, 24.68, 24.39, 23.26, 23.07; MS *m/z* (relative intensity) (EI) 212 (M^+, 0.3), 153 (0.5), 141 (1), 127 (100), 111 (6), 98 (13), 85 (18); (CI) 213 (MH^+, 100), 195 (32), 127 (87); HRMS (EI) calcd for $C_7H_{11}O_2$ (M^+ − C_5H_9O) 127.0759, found 127.0754; two least polar diastereomers R_f 0.3 and 0.2 (hexane/EtOAc, 3:1); IR (neat) 2934, 1455, 1345, 1206, 1092, 1022, 903, 731 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.78–4.04 (m, 4 H, *H*CO), 3.38–3.48 (m, 1 H, *H*CO) 3.23–3.31 (m, 1 H, *H*CO), 1.1–2.2 (m, 14 H, CCH_2C); ^{13}C NMR ($CDCl_3$) δ 114.78, 82.52, 81.88, 80.29, 79.94, 68.62, 68.25, 67.09, 66.93, 35.84, 34.71, 34.58, 34.49, 29.76, 27.34, 27.07, 26.36, 26.04, 24.69, 24.52, 23.26, 23.13; MS (EI) *m/z* (relative intensity) 212 (M^+, 0.3), 153 (0.8), 141 (0.7), 127 (100), 111 (8), 98 (16), 85 (19); HRMS (EI) calcd for $C_7H_{11}O_2$ (M^+ − C_5H_9O) 127.0759, found 127.0740.

3-(Phenylthio)propanoic Acid (19). Acrylic acid (14.4 g, 200 mmol) was added dropwise to a solution of thiophenol (22.5 g, 204 mmol) and triethylamine (22.3 g, 220 mmol) in THF (30 mL) at 0 °C. After being stirred for 1 h at 0 °C, the reaction mixture was warmed to room temperature, stirred overnight, quenched with 5% HCl (150 mL), and extracted with ether. The combined ether layer was washed with brine, dried over $MgSO_4$, and concentrated by rotary evaporation. Repeated recrystallization from hexane gave **19** (35.7 g, 98%) as a white solid: mp 58.5–59.5 °C; IR (KBr) 2946, 2654, 1692, 1426, 1402, 1242, 943 cm^{-1}; ^1H NMR ($CDCl_3$) δ 12.19 (s, 1 H, O*H*), 7.2–7.4 (m, 5 H, Ph), 3.18 (t, J = 7.2 Hz, 2 H, SCH_2), 2.70 (t, J = 7.2 Hz, 2 H, CH_2CO); ^{13}C NMR ($CDCl_3$) δ 178.47 (s), 134.83 (s), 130.18 (d), 129.04 (d), 126.67 (d), 34.16 (t), 28.60 (t); MS (EI) *m/z* (relative intensity) 182 (M^+, 100), 136 (12), 123 (88), 110 (31); HRMS (EI) calcd for $C_9H_{10}O_2S$ 182.0401, found 182.0405.

3-(Phenylthio)propanoyl Chloride (20). Thionyl chloride (71.4 g, 600 mmol) was added to a solution of carboxylic acid **19** (72.9 g, 400 mmol) in dichloromethane (125 mL) at 0 °C. After being stirred for 1 h at 0 °C, the reaction mixture was warmed to room temperature, stirred overnight, and concentrated. Vacuum distillation afforded 78.3 g (98%) of **20** as a colorless liquid: bp 126 °C (1.8 Torr); IR (neat) 3061, 1794, 1584, 1482, 1439, 1401, 1026, 955, 741, 693 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25–7.41 (m, 5 H, Ph), 3.18 (t, J = 2.6 Hz, 4 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 172.20 (s), 133.93 (s), 130.69 (d), 129.24 (d), 127.21 (d), 46.68 (t), 28.96 (t); MS (EI) *m/z* (relative intensity) 200 (M^+, 66), 137 (30), 123 (66), 109 (43), 55 (100); HRMS (EI) calcd for C_9H_9ClOS 200.0063, found 200.0064.

Reaction of Acyl Chloride 20 with Organocopper Reagent 18b. Compound **13b** (9.7 g, 50 mmol) was added dropwise to a preformed solution of LDBB (101 mmol) in THF (150 mL) at −78 °C and the resulting deep red mixture was stirred for 1 h. $(CH_3)_2S$·CuBr (12.3 g, 60 mmol) was added to the mixture and the latter was stirred for 3 h at −78 °C. A solution of **20** (10.0 g, 50 mmol) in THF (10 mL) was then added dropwise and the resulting mixture was stirred for 8 h at −78 °C. After the mixture had been warmed to room temperature, saturated aqueous NH_4Cl (100 mL) was added. The mixture was filtered on Celite and extracted with ether (3 × 40 mL). The combined ether layer was washed with 5% HCl (2 × 50 mL), with 5% NaOH (2 × 50 mL), and then with brine (50 mL). It was dried ($MgSO_4$) and concentrated. Column chromatography on silica gel (hexane/EtOAc, 9:1) afforded **21b** (6.0 g, 48%) as an oil and *S*-phenyl 3-(phenylthio)propanethiate (3.6 g, 26%) as an oil. **1-(2′-Tetrahydropyranyl)-3-(phenylthio)propanone (21b)**: IR (neat) 2940, 2851, 1719, 1584, 1482, 1439, 1090, 1048, 739, 691 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.15–7.40 (m, 5 H, Ph), 4.02 (dd, J = 11.4, 3.0 Hz, 1 H, C*H*HO), 3.77 (dd, J = 11.1, 2.3 Hz, 1 H, OC*H*CO), 3.43 (td, J = 10.7, 3.0 Hz, 1 H, CH*H*O), 3.14 (t, J = 7.2 Hz, 2 H, CH_2), 2.91 (t, J = 7.2 Hz, 2 H, CH_2), 1.83–1.87 (m, 2 H, alicyclic), 1.28–1.60 (m, 4 H, alicyclic); ^{13}C NMR ($CDCl_3$) δ 209.19 (s), 135.90 (s), 129.01 (d), 128.89 (d), 125.97 (d), 82.59 (d), 68.15 (t), 37.75 (t), 28.02 (t), 26.83 (t), 25.37 (t), 22.93 (t); MS (EI) *m/z* (relative

intensity) 250 (M^+, 24), 165 (2), 109 (21), 85 (100); HRMS (EI) calcd for $C_{14}H_{18}O_2S$ 250.1028, found 250.1036. ***S*-Phenyl 3-(phenylthio)propanethioate**: ^1H NMR ($CDCl_3$) δ 7.25–7.46 (m, 10 H, Ph), 3.28 (t, J = 7.4 Hz, 2 H, CH_2), 3.00 (t, J = 7.4 Hz, 2 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 195.52, 134.91, 134.38, 130.04, 129.46, 129.17, 129.05, 127.21, 126.62, 43.09, 29.05; MS (EI) m/z (relative intensity) 274 (M^+, 19), 218 (2), 165 (68), 137 (53), 123 (100), 109 (55); HRMS (EI) calcd for $C_{15}H_{14}OS_2$ 274.0486, found 274.0481.

Reaction of Carboxylic Acid 19 with Organolithium Reagent 14b. *n*-Butyllithium (3.13 mL of a 1.60 M solution in hexane, 5.00 mmol) was added dropwise to a solution of **19** (911 mg, 5.00 mmol) in THF (20 mL) at −78 °C and the mixture was stirred for 30 min to generate the lithium carboxylate. A solution of **14b** had been prepared by the addition of **13b** (972 mg, 5.00 mmol) to a preformed solution of LDBB (10.10 mmol) in THF (20 mL) followed by 1 h of stirring at −78 °C. After being warmed to −40 °C, the mixture was stirred for 1 h, quenched with 5% HCl (20 mL), and then extracted with ether (3 × 30 mL). The combined ether layer was washed with brine (30 mL), dried ($MgSO_4$), and concentrated by rotary evaporation. Column chromatography on silica gel (hexane/EtOAc, 9:1) gave **21b** in 20–30% yields (247–380 mg).

General Procedure for the Reaction of Carboxylic Acid 19 with Organolithium Reagent 14a and 14b Using Cerium(III) Chloride. *n*-Butyllithium (3.13 mL of 1.60 M solution in hexane, 5.00 mmol) was added dropwise to a solution of **19** (911 mg, 5.00 mmol) in THF (20 mL) at −78 °C. The mixture was stirred for 30 min and then cannulated to a preformed $CeCl_3$ (10.0 mmol) suspension in THF (20 mL) at −78 °C to generate the cerium carboxylate solution. A solution of **14a** or **14b** had been prepared by the addition of **13a** (901 mg, 5.00 mmol) or **13b** (972 mg, 5.00 mmol) to a preformed solution of LDBB (10.10 mmol) in THF (20 mL) followed by 1 h of stirring at −78 °C. The solution of **14a** or **14b** was then cannulated to the cerium carboxylate solution, and the resulting mixture was stirred for 16 h at −78 °C. After being warmed to −40 °C, the mixture was stirred for 1 h, quenched with 5% HCl (20 mL), and extracted with ether (3 × 30 mL). The combined ether layer was washed with brine (30 mL), dried ($MgSO_4$), and concentrated. Column chromatography on silica gel (hexane/EtOAc, 9:1) afforded **21a** (640 mg, 54%) as an oil or **21b** (899 mg, 72%). **1-(2′-Tetrahydrofuranyl)-3-(phenylthio)propanone (21a)**: IR (neat) 2952, 2872, 1717, 1584, 1482, 1439, 1350, 1069, 1026, 741, 693 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.13–7.32 (m, 5 H, Ph), 4.23–4.28 (m, 1 H, HCO), 3.84 (t, J = 6.5 Hz, 2 H, OCH_2), 3.12 (t, J = 6.9 Hz, 2 H, CH_2), 2.77–2.95 (m, 2 H, CH_2), 2.06–2.17 (m, 1 H, alicyclic), 1.74–1.91 (m, 3 H, alicyclic); ^{13}C NMR ($CDCl_3$) δ 210.40 (s), 135.71 (s), 129.11 (d), 128.85 (d), 126.04 (d), 83.24 (d), 69.23 (t), 37.85 (t), 28.86 (t), 26.92 (t), 25.46 (t); MS (EI) m/z (relative intensity) 236 (M^+, 31), 71 (100); HRMS (EI) calcd for $C_{13}H_{16}O_2S$ 236.0871, found 236.0856.

Reaction of Carboxylic Acid 19 with Preformed Organocerium Reagent 17b. *n*-Butyllithium (3.13 mL of 1.60 M solution in hexane, 5.00 mmol) was added dropwise to a solution of **19** (911 mg, 5.00 mmol) in THF (20 mL) at −78 °C, and the mixture was stirred for 30 min to generate the lithium carboxylate solution. A solution of **14b** that had been prepared by the addition of **13b** (972 mg, 5.00 mmol) to a preformed solution of LDBB (10.10 mmol) in THF (20 mL) followed by 1 h of stirring at −78 °C was then cannulated to a preformed $CeCl_3$ (5.0 mmol) suspension in THF (10 mL) at −78 °C to generate **17b**. After being stirred for 1 h, the **17b** solution was cannulated to the lithium carboxylate solution and the resulting mixture was stirred for 16 h at −78 °C. Then it was warmed to −40 °C, stirred for 1 h, and quenched with 5% HCl (20 mL). The same workup procedure as above followed by column chromatography on silica gel (hexane/EtOAc, 9:1) yielded 717 mg (57%) of **21b**.

Preparation of $Zn(BH_4)_2$ solution.[18b] $ZnCl_2$ (5.10 g, 37.4 mmol) in a 250-mL flask was successively fused (two or three times) under reduced pressure (0.1 Torr), and then 100 mL of anhydrous THF was added. After being refluxed 1–2 h under argon, the mixture was allowed to stand at 23 °C. This procedure produced the saturated supernatant solution of $ZnCl_2$ in THF (0.35 M).[17] The supernatant THF solution of $ZnCl_2$ (80 mL, 28.0 mmol) was then added to a stirred suspension of $NaBH_4$ (2.04 g, 54.0 mmol) in THF (300 mL). The mixture was stirred at room temperature for 48 h and stored under argon at room temperature. This procedure produced the supernatant THF solution of $Zn(BH_4)_2$ (71 mM).

In the same manner, a saturated supernatant solution of $ZnCl_2$ in ether (0.69 M)[19] was prepared by using 10.00 g of $ZnCl_2$ (73.4 mmol) and 100 mL of anhydrous ether. The supernatant ether solution of $Zn(BH_4)_2$ (142 mM) was also prepared by using the supernatant solution of $ZnCl_2$ (80 mL of 0.69 M solution in ether, 55.2 mmol) and a suspension of $NaBH_4$ (4.09 g, 108.0 mmol) in ether (300 mL).

Preparation of Alcohol 15b by Stereoselective Reduction of Ketone 21b. A Typical Procedure Using $Zn(BH_4)_2$ as a Chelating and Reducing Agent. The supernatant solution of $Zn(BH_4)_2$ (15.0 mL of 142 mM solution in ether, 2.13 mmol) was added via a syringe pump for 20 min into a solution of **21b** (376 mg, 1.50 mmol) in THF (15 mL) at −78 °C. After 48 h of stirring, the mixture was quenched with 5% HCl (10 mL) at −78 °C and then warmed to room temperature. Water (10 mL) was added, and the resulting mixture was extracted with ether (3 × 30 mL). The combined ether layer was washed with brine (30 mL), dried ($MgSO_4$), and concentrated. Column chromatography on silica gel (10%, then 20% EtOAc/hexane) afforded 377 mg (>99%) of **15b** as a mixture of two diastereomers (**15b**$_1$:**15b**$_2$ = 9.5:1). The diastereomeric ratio was determined by ^1H NMR analysis of the mixture. **A Typical Procedure Using $ZnCl_2$ as a Chelating Agent.** The supernatant solution of $ZnCl_2$ in THF (12.9 mL of 0.35 M solution, 4.52 mmol) was added to a solution of **21b** (376 mg, 1.50 mmol) in THF (17.1 mL) at 0 °C. The resulting cloudy mixture was stirred for 2 h at 0 °C and then cooled to −78 °C. A solution of DIBAL (9.0 mL of 1.00 M solution in hexane, 9.0 mmol) in THF (16.0 mL) was added via a syringe pump for 1 h into the mixture at −78 °C. After 7 h of stirring, the cloudy mixture was quenched with MeOH (1.5 mL) and stirred for 10 min at −78 °C. 5% HCl (20 mL) was added to the clear mixture and the mixture was warmed to room temperature. The same workup as described above followed by column chromatography on silica gel (10%, then 20% EtOAc/hexane) gave 75 mg (20%) of recovered **21b** and 298 mg (79%) of **15b** as a mixture of two diastereomers (**15b**$_1$:**15b**$_2$ = 6.4:1) (^1H NMR). Pure samples of each diastereomer were obtained as oils by repeated column chromatography on silica gel (10%, then 20% EtOAc/hexane). **(1*R**,2′*S**)-3-(Phenylthio)-1-(2′-tetrahydropyranyl)-1-propanol (15b$_1$)**: IR (neat) 3443, 2936, 2853, 1584, 1482, 1439, 1092, 1046, 895, 739, 691 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.13–7.35 (m, 5 H, Ph), 3.95–4.00 (m, 1 H, HCO), 3.77 (dt, J = 8.7, 3.9 Hz, 1 H, HCO), 3.43 (td, J = 7.7, 3.2 Hz, 1 H), 3.14–3.27 (m, 2 H), 2.95–3.04 (m, 1 H), 2.62 (br s, 1 H, OH), 1.27–1.85 (m, 8 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 136.52 (s), 128.84 (2C, d), 125.71 (d), 80.33 (d), 72.48 (d), 68.68 (t), 31.41 (t), 30.15 (t), 26.10 (t), 25.36 (t), 23.00 (t); MS (EI) m/z (relative intensity) 252 (M^+, 23), 234 ($M^+ - H_2O$, 4), 123 (26), 111 (38), 85 (100); HRMS (EI) calcd for $C_{14}H_{20}O_2S$ 252.1184, found 252.1181. **(1*R**,2′*R**)-3-(Phenylthio)-1-(2′-tetrahydropyranyl)-1-propanol (15b$_2$)**: IR (neat) 3459, 2938, 2851, 1584, 1482, 1439, 1090, 1046, 739, 691 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.13–7.36 (m, 5 H, Ph), 3.98–4.02 (m, 1 H, HCO), 3.57 (dt, J = 6.3, 6.3 Hz, 1 H, HCO), 3.41 (td, J = 11.0, 3.2 Hz, 1 H), 2.97–3.22 (m, 3 H), 2.84 (br s, 1 H, OH), 1.73–1.85 (m, 3 H, CH_2), 1.22–1.58 (m, 5 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 136.48 (s), 128.73 (2C, d), 125.62 (d), 80.42 (d), 72.88 (d), 68.36 (t), 32.19 (t), 29.57 (t), 27.50 (t), 25.82 (t), 22.87 (t); MS (EI) m/z (relative intensity) 252 (M^+, 21), 234 ($M^+ - H_2O$, 3), 168 (5), 123 (23), 111 (31), 85 (100); HRMS (EI) calcd for $C_{14}H_{20}O_2S$ 252.1184, found 252.1178.

Preparation of Alcohols 23a by Stereoselective Addition of Organometallic Reagents to Ketone 21a. A Typical Procedure Which Gives Erythro Alcohol 23a$_1$ as the Major Product. Methyllithium (0.79 mL of 1.33 M solution in Et_2O, 1.05 mmol) was added dropwise to a solution of **21a** (236 mg, 1.00 mmol) in THF (30 mL) at −78 °C. The mixture was stirred for 4 h before being quenched with 5% HCl (20 mL) at −78 °C. After ether extraction (3 × 30 mL), the combined ether layer was washed with brine (30 mL), dried ($MgSO_4$), and concentrated. Column chromatography on silica gel (3%, then 10% EtOAc/CH_2Cl_2) afforded 200.1 mg (79.3%) of **23a**$_1$ and 20.7 mg, (8.2%) of **23a**$_2$ as oils. **A Typical Procedure Which Gives Threo Alcohol 23a$_2$ as the Major Product.** Trimethylaluminum (1.50 mL of a 2.00 M solution in toluene, 3.00 mmol) was added to a solution of 2,6-di-*tert*-butyl-4-methylphenol (1.322 g, 6.00 mmol) in toluene

(30 mL) to generate MAD. The mixture was stirred for 2 h at room temperature and cooled to −78 °C. **21a** (236 mg, 1.00 mmol) was then added and the resulting mixture was stirred for 2 h at −78 °C. Methyllithium (1.3 mL of 1.33 M solution in Et_2O, 1.7 mmol) was added dropwise and the mixture was stirred for 24 h at −78 °C before being quenched with 5% HCl (20 mL) at −78 °C. The same workup procedure was described above, followed by column chromatography on silica gel (3% and then 10% EtOAc/CH_2Cl_2) gave 18.0 mg (7.1%) of **23a**$_1$ and 183.9 mg, (72.9%) of **23a**$_2$. **(2*R**,2′*S**)-4-(Phenylthio)-2-(2′-tetrahydrofuranyl)-2-butanol (23a$_1$)**: IR (neat) 3457, 2973, 2867, 1584, 1482, 1458, 1439, 1374, 1069, 934, 737, 691 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.15–7.35 (m, 5 H, Ph), 3.83 (t, *J* = 14.4 Hz, 1 H, *H*HCO), 3.80 (t, *J* = 14.4 Hz, 1 H, H*H*CO), 3.69 (dd, *J* = 8.4, 6.5 Hz, 1 H, *H*CO), 3.13 (td, *J* = 12.0, 5.0 Hz, 1 H, SC*H*H), 2.99 (td, *J* = 12.0, 5.0 Hz, 1 H, SCH*H*), 2.14 (br s, 1 H, O*H*), 1.63–1.93 (m, 6 H, CH_2), 1.24 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 136.62 (s), 128.91 (d), 128.75 (d), 125.78 (d), 85.41 (d), 73.18 (s), 68.65 (t), 36.78 (t), 27.88 (t), 26.36 (t), 25.90 (t), 23.81 (q); MS (EI) *m*/*z* (relative intensity) 252 (M$^+$, 8), 234 (7), 180 (36), 123 (100); HRMS (EI) calcd for $C_{14}H_{20}O_2S$ 252.1184, found 252.1166. **(2*R**,2′*R**)-4-(Phenylthio)-2-(2′-tetrahydrofuranyl)-2-butanol (23a$_2$)**: IR (neat) 3451, 2975, 2869, 1584, 1482, 1458, 1439, 1067, 930, 739, 691 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.11–7.34 (m, 5 H, Ph), 3.81 (t, *J* = 14.4 Hz, 1 H, *H*HCO), 3.79 (t, *J* = 14.4 Hz, 1 H, H*H*CO), 3.67 (dd, *J* = 7.9, 6.9 Hz, 1 H, *H*CO), 3.07 (td, *J* = 12.7, 5.8 Hz, 1 H, SC*H*H), 3.01 (td, *J* = 12.7, 5.8 Hz, 1 H, SCH*H*), 2.41 (br s, 1 H, O*H*), 1.69–2.00 (m, 6 H, CH_2), 1.10 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 136.74 (s), 128.75 (d), 128.46 (d), 125.49 (d), 84.60 (d), 72.85 (s), 68.61 (t), 39.50 (t), 27.82 (t), 26.07 (t), 26.01 (t), 21.38 (q); MS (EI) *m*/*z* (relative intensity) 252 (M$^+$, 11), 234 (5), 180 (37), 123 (100); HRMS (EI) calcd for $C_{14}H_{20}O_2S$ 252.1184, found 252.1191.

Reaction of Lactone 10 with γ-Cerioalkoxide Generated From Alcohol 23a. A Reaction Using Erythro Alcohol 23a$_1$. *n*-Butyllithium (1.49 mL of 1.34 M solution in hexane, 2.00 mmol) was added dropwise to a solution of **23a**$_1$ (505 mg, 2.00 mmol) in THF (15 mL) at −78 °C, and the mixture was stirred for 30 min at −78 °C to generate the lithium alkoxide. A preformed solution of LDBB (4.20 mmol) in THF (15 mL) was cooled to −78 °C and then cannulated to the lithium alkoxide solution. The resulting deep red solution was stirred for 30 min at −78 °C. A preformed $CeCl_3$ (4.2 mmol) suspension in THF (30 mL) was cooled to −78 °C and then cannulated to the deep red solution. After the resulting solution had been stirred for 30 min, δ-valerolactone (**10**) (200 mg, 2.00 mmol) was added. The mixture was stirred for 16 h at −78 °C and then warmed to 0 °C. After 3 h of stirring, the reaction mixture was quenched with 5% HCl (25 mL) at 0 °C and then extracted with ether (3 × 30 mL). The combined ether layer was washed with brine (30 mL), dried ($MgSO_4$), and concentrated by rotary evaporation. The products were isolated as oils by column chromatography on silica gel (10% and then 20% EtOAc/hexane with ca. 0.5% of triethylamine) to give **12a**$_1$ (166 mg, 37%), **12a**$_2$ (110 mg, 24%), and **27** (70 mg, 24%). Each of the pure samples of **12a**$_1$ and **12a**$_2$ equilibrated to form the mixture of both of them by epimerization in an acidic medium including $CDCl_3$. The diastereomic ratio of the equilibrated mixture (**12a**$_1$:**12a**$_2$ = 60:40) in $CDCl_3$ was determined by ^{1}H NMR analysis. **(2*R**,2′*S**,5*S**)-2-(2′-Tetrahydrofuranyl)-1,6-dioxaspiro[4.5]decane (12a$_1$)**: IR (neat) 2944, 2870, 1453, 1366, 1271, 1227, 1161, 1121, 1082, 1044, 1007, 976, 947, 882, 814 cm^{-1}; ^{1}H NMR (C_6D_6) δ 4.02 (td, *J* = 11.6, 2.4 Hz, 1 H, C7H), 3.71 (t, *J* = 7.6 Hz, 1 H, C2′H), 3.54–3.7 (m, 3 H, C5′H and one C7H), 1.2–2.1 (m, 14 H, alicyclic), 1.39 (s, 3 H, methyl); ^{13}C NMR (C_6D_6) δ 106.26 (s, C5), 86.33 (s, C2), 84.75 (d, C2′), 68.35 (t, C5′), 61.13 (t, C7), 39.13 (t), 34.41 (t), 32.96 (t), 27.31 (t), 26.32 (t), 25.91 (t), 24.90 (q, methyl), 20.73 (t); MS (EI) *m*/*z* (relative intensity) 208 (1), 168 (2), 155 (100), 111 (24), 99 (32); HRMS (EI) calcd for $C_9H_{15}O_2$ (M$^+$ − C_4H_7O) 155.1072, found 155.1059. Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 69.11; H, 9.86. **(2*R**,2′*S**,5*R**)-2-(2′-Tetrahydrofuranyl)-1,6-dioxaspiro[4.5]decane (12a$_2$)**: IR (neat) 2942, 2870, 1458, 1364, 1271, 1225, 1163, 1127, 1073, 1048, 1007, 947, 926, 874, 816 cm^{-1}; ^{1}H NMR (C_6D_6) δ 4.00 (t, *J* = 7.4 Hz, 1 H, C2′H), 3.89 (td, *J* = 11.6, 2.4 Hz, 1 H, C7H), 3.76 (dd, *J* = 14.4, 6.6 Hz, 1 H, C5′H), 3.54–3.61 (m, 2 H, one C5′H and one C7H), 2.2–2.4 (m, 1 H, alicyclic), 1.2–2.01 (m, 13 H, alicyclic), 1.20 (s, 3 H, methyl); ^{13}C NMR (C_6D_6) δ 106.00 (s, C5), 86.17 (s, C2), 85.17 (d, C2′), 68.50 (t, C5′), 61.45 (t, C7), 38.10 (t), 35.48 (t), 35.16 (t), 27.06 (t), 26.68 (t), 25.84 (t), 21.76 (q, methyl), 20.69 (t); MS (EI) *m*/*z* (relative intensity) 226 (M$^+$, 1), 208 (2), 168 (2), 155 (100), 111 (24), 99 (35); HRMS (EI) calcd for $C_9H_{15}O_2$ (M$^+$ − C_4H_7O) 155.1072, found 155.1059. **(2*R**,2′*S**)-2-(2′-Tetrahydrofuranyl)-2-butanol (27)**: IR (neat) 3457, 2973, 2876, 1462, 1455, 1372, 1134, 1073, 920 cm^{-1}; ^{1}H NMR (C_6D_6) δ 3.47–3.63 (m, 3 H, *H*CO), 2.00 (br s, 1 H, O*H*), 1.2–1.7 (m, 6 H, CH_2), 1.20 (s, 3 H, OCCH_3), 0.91 (t, *J* = 7.5 Hz, 3 H, CH_3); ^{13}C NMR (C_6D_6) δ 85.42 (d), 72.90 (s), 68.32 (t), 30.79 (t), 26.43 (t), 25.71 (t), 23.67 (q), 7.98 (q); MS (EI) *m*/*z* (relative intensity) 144 (M$^+$, 0.5), 129 (7), 115 (13), 111 (15), 73 (100). **A Reaction Using Threo Alcohol 23a$_2$.** The same procedure was used to convert **23a**$_2$ (505 mg, 2.00 mmol) into the spiroacetals **12b**$_1$ and **12b**$_2$. The products were isolated as oils by column chromatography on silica gel (10% and then 20% EtOAc/hexane with ca. 0.5% of triethylamine) to afford **12b**$_1$ (157 mg, 35%), **12b**$_2$ (96 mg, 21%), and **28** (67 mg, 23%). Each of the pure samples of **12b**$_1$ and **12b**$_2$ equilibrated to form the mixture of both of them by epimerization in $CDCl_3$. The diasteromeric ratio of the equilibrated mixture (**12b**$_1$:**12b**$_2$ = 62:38) in $CDCl_3$ was determined by ^{1}H NMR analysis. **(2*R**,2′*R**,5*R**)-2-(2′-Tetrahydrofuranyl)-1,6-dioxaspiro[4.5]decane (12b$_1$)**: IR (neat) 2944, 2870, 1453, 1366, 1229, 1169, 1157, 1119, 1080, 1046, 1005, 974, 949, 905, 882 cm^{-1}; ^{1}H NMR (C_6D_6) δ 3.95 (td, *J* = 11.6, 2.4 Hz, 1 H, C7H), 3.67 (dd, *J* = 14.4, 7.6 Hz, 1 H, C5′H), 3.54–3.63 (m, 3 H, C2′H, one C5′H and one C7H), 1.2–2.2 (m, 14 H, alicyclic), 1.27 (s, 3 H, methyl); ^{13}C NMR (C_6D_6) δ 106.46 (s, C5), 85.62 (s, C2), 85.49 (d, C2′), 68.67 (t, C5′), 61.07 (t, C7), 39.62 (t), 34.54 (t), 34.31 (t), 26.78 (t, 2 peaks), 26.66 (q, methyl), 25.97 (t), 20.82 (t); MS (EI) *m*/*z* (relative intensity) 226 (M$^+$, 1), 168 (1), 155 (100), 111 (22), 99 (25); HRMS (EI) calcd for $C_9H_{15}O_2$ (M$^+$ − C_4H_7O) 155.1072, found 155.1065. Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.88; H, 9.77. **(2*R**,2′*R**,5*S**)-2-(2′-Tetrahydrofuranyl)-1,6-dioxaspiro[4.5]decane (12b$_2$)**: IR (neat) 2942, 2870, 1451, 1366, 1223, 1183, 1163, 1125, 1080, 1003, 947, 926, 889, 874, 816 cm^{-1}; ^{1}H NMR (C_6D_6) δ 4.01 (td, *J* = 11.5, 2.6 Hz, 1 H, C7H), 3.97 (t, *J* = 7.5 Hz, 1 H, C2′H), 3.76 (dt, *J* = 8.0, 6.6 Hz, 1 H, C5′H), 3.54–3.64 (m, 2 H, one C5′H and one C7H), 2.14 (td, *J* = 11.9, 7.7 Hz, 1 H, alicyclic), 1.88–2.05 (m, 2 H, alicyclic), 1.26–1.71 (m, 11 H, alicyclic), 1.23 (s, 3 H, methyl); ^{13}C NMR (C_6D_6) δ 105.84 (s, C5), 86.53 (s, C2), 85.40 (d, C2′), 68.73 (t, C5′), 61.30 (t, C7), 38.00 (t), 35.68 (t), 31.70 (t), 27.17 (t), 26.45 (t), 25.87 (t) 23.77 (q, methyl), 20.70 (t); MS (EI) *m*/*z* (relative intensity) 226 (M$^+$, 1), 208 (1), 168 (1), 155 (100), 111 (25), 99 (29); HRMS (EI) calcd for $C_9H_{15}O_2$ (M$^+$ − C_4H_7O) 155.1072, found 155.1078. Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 69.16; H, 9.87. **(2*R**,2′*R**)-2-(2′-Tetrahydrofuranyl)-2-butanol (28)**: IR (neat) 3418, 2924, 2855, 1456, 1372, 1262, 1071, 700 cm^{-1}; ^{1}H NMR (C_6D_6) δ 3.49–3.63 (m, 3 H, *H*CO), 2.11 (br s, 1 H, O*H*), 1.4–1.7 (m, 6 H, CH_2), 0.98 (s, 3 H, OCCH_3), 0.95 (t, *J* = 7.6 Hz, 3 H, CH_3); ^{13}C NMR (C_6D_6) δ 84.52 (d), 72.91 (s), 68.41 (t), 33.05 (t), 26.39 (t), 26.06 (t), 21.19 (q), 8.37 (q); MS (EI) *m*/*z* (relative intensity) 144 (M$^+$, 0.5), 129 (5), 115 (8), 111 (2), 73 (100); HRMS (EI) calcd for $C_7H_{13}O_2$ (M$^+$ − CH_3) 129.0916, found 129.0905.

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Supplementary Material Available: ^{1}H and ^{13}C NMR spectra for all compounds prepared and 2D NMR spectra for the four isomers of **12a** (61 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.