Asymmetric Synthesis Based on 1,3-Oxathianes. 4. Mechanism of Asymmetric Induction in the Reactions of Oxathianyl Ketones[1]

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Abstract: The stereoselectivity of the reaction between oxathianyl ketones **7–14**, which contain two possible sites of chelation, and methylmagnesium bromide, L-Selectride (Aldrich), and diisobutylaluminum hydride has been studied in order to illuminate the factors involved in the high levels of asymmetric induction obtained in the oxathiane system. Models A, B, and C (Figure 1) are proposed to rationalize the experimental results. A is the Cram chelate rule[2] model, while B and C correspond to the Cornforth dipolar model[3] or the Felkin model with L = oxygen of the oxathiane.[4] The stereoselectivities observed support the assumption that chelation of an organometallic reagent with the carbonyl and ether oxygens of the oxathiane is necessary for a high degree of asymmetric induction and show that competing chelation to an exocyclic ether oxygen may be prevented by protection with a triisopropylsilyl (TIPS) group.

The mechanism of asymmetric induction in the reactions of chiral α-alkoxy ketones has been a subject of continued speculation since the first systematic study by Cram and Kopecky.[2] Recently workers in the field of asymmetric synthesis have begun to explore the mechanistic basis for stereoselection in greater depth[5-9] and theoretical approaches[10] have been used in an attempt to reduce the plethora of models[2-4,11] available to a reasonable (consistently predictive) number. Synthetic work in our laboratory[12] has shown that the results of addition of chelating nucleophiles to chiral 1,3-oxathianyl ketones, which proceeds in very high diastereomeric excess (90–100% de), can be explained in terms of Cram's chelate rule[2] while addition of nonchelating nucleophiles such as diisobutylaluminum hydride[1,12d,13] gives the product of opposite configuration ("anti-Cram chelate" product) in moderate to good stereoselectivity. In order to explain these results and to obtain evidence for the role of chelation in additions to oxathianyl ketones beyond the simple observation that the product predicted by Cram's chelate rule predominates, we have synthesized the benzyl-, trityl-, and silyl-protected α- and β-hydroxy ketones **7–14** and examined their reactivity toward methylmagnesium bromide, L-Selectride (Aldrich), and diisobutylaluminum hydride.[9b] We expected that if endocyclic chelation between the carbonyl oxygen, the Lewis acidic reagent, and the oxathiane oxygen (Figure 1, structure A) is in fact the controlling factor in the high diastereofacial selectivity normally observed,[12] the presence of the exocyclic ether oxygen with its potential for competitive chelation[8] should change the stereochemical course of reactions with these substrates. We also felt that if the acyclic oxygen proved deleterious to the stereoselectivity, prevention of chelation by this oxygen would be a synthetically desirable goal. We now report the results of these studies; protection of the exocyclic oxygen by a triisopropylsilyl (TIPS) group inhibits competing chelation very effectively.

Results

Ketones **7–14** and **29**[12e] were prepared by condensation of aldehydes **1–6**[14] and acetaldehyde with the lithium salt of the parent oxathiane [12j] followed by Swern oxidation as shown in Scheme I. These ketones were then reduced or alkylated to give the corresponding secondary and tertiary carbinols, respectively, with the results reported in Table I. The product mixtures were analyzed for diastereomeric excess (de) by proton NMR with use of the ratio of the ^1H signals due to the C(2) protons of the oxathiane or by ^{13}C NMR with use of the ratio of signals due to several corresponding carbons. In the reaction of **8** and **10** with CH_3MgBr at −78 °C the very high selectivity rendered identification of signals due to the minor diastereomer difficult, and therefore **8** and **10** were also alkylated with CH_3Li at room temperature to provide a mixture of diastereomers in which each epimer could be readily identified. The relative configuration of **24** and **25** was established by deprotection to give the common diol **27**, and their absolute configuration was ascertained by conversion of **25** into (*S*)-(+)-mevalolactone[9b] by homologation (see Experimental Section). The relative configuration of **21** and **22** was similarly established by deprotection to give **23** while their absolute configuration was determined by conversion of **22** into **32** (Scheme II) which has been correlated to diethyl (*S*)-(−)-acetylcitramalate.[12g] The absolute configuration of the secondary oxathianyl carbinols **15–20** was proven by conversion to **33** and **34** (Scheme III) of known configuration.[13] The configuration of **28** was not determined directly; however, the isomer produced in

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(2) Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 2748. See also ref 12a.
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(5) (a) Reetz, M. T.; Kessler, K.; Schmidtberger, S.; Wenderoth, B.; Steinbach, R. *Angew. Chem.* **1983**, 1511. (b) Reetz, M. T.; Maus, S. *Tetrahedron* **1987**, *43*, 101. (c) Reetz, M. T.; Hüllmann, M.; Seitz, T. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 477. (d) Reetz, M. T.; Hüllmann, M. *J. Chem. Soc., Chem. Commun.* **1986**, 1600. (e) Reetz, M. T. *Angew. Chem. Int. Ed. Engl*, **1984**, *23*, 556. (f) Reetz, M. T., In *Organotitanium Reagents in Organic Synthesis*; Springer-Verlag: Berlin, 1986.
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(12) (a) Eliel, E. L. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1983; Vol. 2, p 125. (b) Eliel, E. L.; Morris-Natschke, S. *J. Am. Chem. Soc.* **1984**, *106*, 2937. (c) Lynch, J. E.; Eliel, E. L. *J. Am. Chem. Soc.* **1984**, *106*, 2943. (d) Ko, K.-Y.; Eliel, E. L. *J. Org. Chem.* **1986**, *51*, 5353. (e) Frye, S. V.; Eliel, E. L. *J. Org. Chem.* **1985**, *50*, 3402. (f) Kogure, T.; Eliel, E. L. *J. Org. Chem.* **1984**, *49*, 576. (g) Frye, S. V.; Eliel, E. L. *Tetrahedron Lett.* **1985**, 3907. (h) Ohwa, M.; Eliel, E. L. *Chem. Lett.* **1987**, 41. (i) Eliel, E. L. *Phosphorus and Sulfur* **1985**, *24*, 73. (j) Eliel, E. L.; Lynch, J. E.; Kume, F.; Frye S. V. *Org. Synth.* **1987**, *65*, 215.

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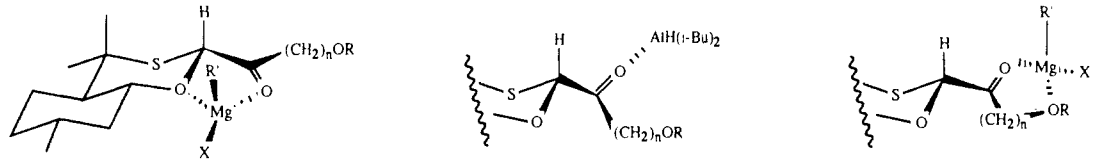
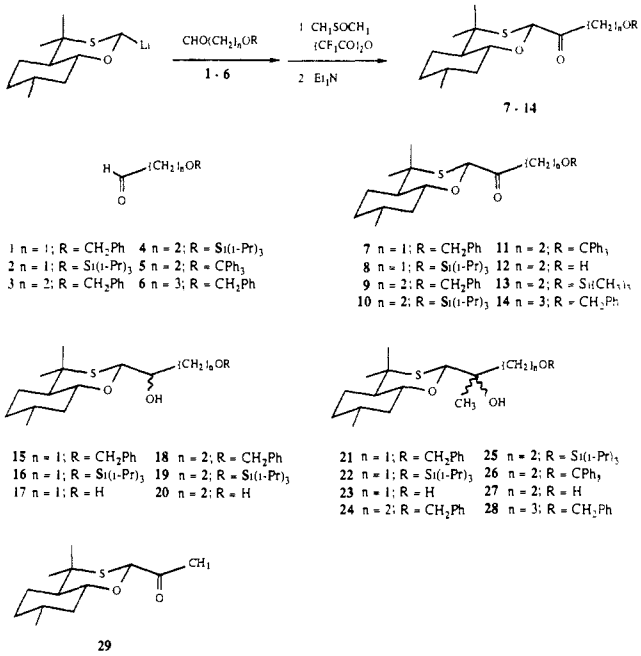


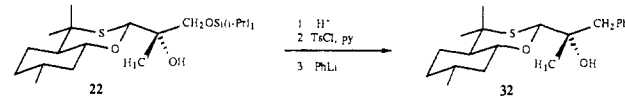
A B C

Figure 1. Models for nucleophilic addition to oxathianyl ketones.

Scheme I



Scheme II



Scheme III

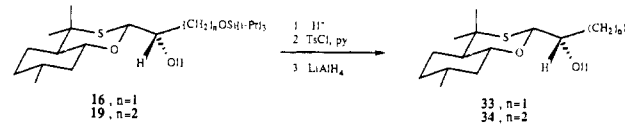
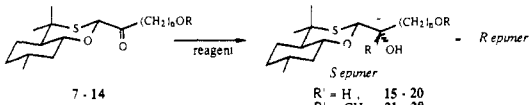


Table I. Stereoselectivity of Reduction and Alkylation of Oxathianyl Alkoxy Ketones



entry	compd, *n*	*R*	*R'*	reagent	de
1	**7** → **15**, 1	CH_2Ph	H	L-Selectride[a]	−72[b]
2	**8** → **16**, 1	$Si(i\text{-}Pr)_3$	H	L-Selectride[a]	+33
3	**9** → **18**, 2	CH_2Ph	H	L-Selectride[a]	+9
4	**10** → **19**, 2	$Si(i\text{-}Pr)_3$	H	L-Selectride[a]	+76
5	**13** → **20**, 2	$Si(CH_3)_3$	H	L-Selectride[a]	−33
6	**7** → **15**, 1	CH_2Ph	H	DIBAL[a]	−57
7	**8** → **16**, 1	$Si(i\text{-}Pr)_3$	H	DIBAL[a]	−60
8	**9** → **18**, 2	CH_2Ph	H	DIBAL[a]	−66
9	**10** → **19**, 2	$Si(i\text{-}Pr)_3$	H	DIBAL[a]	−77
10	**7** → **21**, 1	CH_2Ph	CH_3	CH_3MgBr[c]	−33
11	**8** → **22**, 1	$Si(i\text{-}Pr)_3$	CH_3	CH_3MgBr[c]	+95
12	**9** → **24**, 2	CH_2Ph	CH_3	CH_3MgBr[c]	−17
13	**10** → **25**, 2	$Si(i\text{-}Pr)_3$	CH_3	CH_3MgBr[c]	+95
14	**11** → **26**, 2	CPh_3	CH_3	CH_3MgBr[c]	+72
15	**14** → **28**, 3	CH_2Ph	CH_3	CH_3MgBr[c]	+62
16	**8** → **22**, 1	$Si(i\text{-}Pr)_3$	CH_3	CH_3Li[d]	−56
17	**10** → **25**, 2	$Si(i\text{-}Pr)_3$	CH_3	CH_3Li[d]	+38
18	**10** → **25**, 2	$Si(i\text{-}Pr)_3$	CH_3	$(CH_3)_2Mg$[c]	+96
19	**13** → **27**, 2	$Si(CH_3)_3$	CH_3	$(CH_3)_2Mg$[c]	+46

[a] Toluene, −78 °C. [b] Determined by ^1H or ^{13}C NMR; the negative sign indicates the *R* epimer is formed in excess and positive sign the *S* epimer (Cram-chelate product). [c] THF, −78 °C. [d] THF, 25 °C.

excess by addition of CH_3MgBr to **14** is epimeric to the isomer formed in excess by addition of $PhCH_2O(CH_2)_3MgBr$ to **29**. Our previous observation[12h] that Grignard reagents capable of internal complexation react to give the Cram chelate rule product, albeit in lower than normal de, and the relatively high de of **28** produced from 14 supports our assignment of configuration to **28**.

Discussion

The results presented in Table I can be rationalized by reference to Figure 1 wherein we assume that nucleophilic attack on oxathianyl ketones always occurs from the (less encumbered) side of the axial C(2) hydrogen. The bridged structure A[2] is expected to control the stereoselectivity when the reagent is capable of chelation with the oxathianyl ketone and the R group of the terminal alkoxy function inhibits competing exocyclic chelation.[9,15] Structures B and C, which resemble the Cornforth dipolar model[3] or the Felkin model[4] (with L = oxygen of the oxathiane), are assumed to be important in the absence of chelation to the oxathiane oxygen: B when the reagent is incapable of chelation (e.g., with DIBAL),[1,12d,13] C when the terminal alkoxy group competes with the oxathiane oxygen for chelation with the reagent.[8] The competition between A and C would be expected to depend upon the number (*n*) of methylene units separating the terminal alkoxy group from the carbonyl function and should lead to low selectivities in cases where neither chelate is appreciably favored over the other. Let us take the qualitative results for the α-alkoxy ketones **7** and **8** as an example: the reactivity of **7**, where the benzyl ether oxygen is available for chelation,[5e,6a,8,9,16] is predicted, via B and C, to give the *R* epimer (negative sign in Table I) for both chelating and nonchelating reagents and this was observed (entries 1, 6, 10). On the assumption (see below) that the triisopropylsilyloxy group (TIPSO) does not chelate, ketone **8** is predicted to react with chelating reagents (L-Selectride, Grignard reagents) via A but with nonchelating reagents (DIBAL) via B thus leading to a reversal in stereoselectivity as one changes from chelating to nonchelating reagents. This also turns out to be the case (entries 2, 7, 11). Quantitatively, however, the high anti-Cram chelate (*R* epimer) selectivity in entry 1 and the low Cram chelate selectivity in entry 2 indicate that the situation is more complex than this simple model suggests. The interaction of the three contiguous C–O dipoles in **7** and **8** may favor intermediates B and C and thus reduce the effect of Li chelation which favors A during reduction with L-Selectride (entries 1, 2). The return to high Cram chelate selectivity in entry 11 suggests that the stronger Mg chelation[12b,17]

(13) Ko, K.-Y. Ph.D. Thesis, University of North Carolina at Chapel Hill, 1985.

(14) Methods for preparation of aldehydes **1**,**3**, **5**, and **6** have been previously described.**1**: (a) Marshall, J. A.; Grote, J.; Shearer, B. *J. Org. Chem.* **1986**, *51*, 1633. **3**: (b) Kozikowski, A. P.; Stein, P. D. *J. Org. Chem.* **1984**, *49*, 2301. **5**: (c) Paul, P.; Tchelitcheff, F. *Bull. Soc. Chim. Fr.* **1948**, 197.**6**: (d) Sternbach, D.; Shibuya, M.; Jaisli, F.; Bonetti, M. Eschenmoser; A. *Angew. Chem.* **1979**, *91*, 670.

(15) For other evidence regarding prevention of chelation by protecting groups, cf. ref 5d and e and references therein and ref 6b-d.

(16) Still, W. C.; McDonald, J. H. *Tetrahedron Lett.* **1980**, 1031. Still, W. C.; Schneider, J. A. *Ibid.* **1980**, 1035.

is able to overcome the tendency for some reaction to proceed via B and C. Interestingly, the addition of CH_3Li to **8** at 25 °C gave the anti-Cram chelate product in excess (entry 16) again suggesting that chelation control by lithium may be overcome by other effects on the reactivity of **7** and **8**.[18]

Similar results were obtained for the β-alkoxy ketones **9–13** except that the ability of the β-benzyloxy ether in **9** to compete with the oxathiane oxygen for chelation, as in C, was seemingly diminished relative to the α-benzyloxy ether in **7** (compare entries 3 and 12 to 1 and 10). In this series TIPS was compared to trityl (entry 13 vs 14): the TIPS group seems to be more effective at preventing chelation.[15] In order to probe whether this result was due to an electronic or a steric effect of the silicon upon the chelating ability of the ether oxygen the reactivity of ketone **13** protected with the trimethylsilyl (TMS) group was examined. Ketone **13** was decomposed by CH_3MgBr and therefore its reactivity with L-Selectride and $(CH_3)_2Mg$ was examined (entries 5 and 19). Comparison of entries 4 and 5, and 18 and 19 shows that the TIPS group is substantially better than TMS[19] in producing the *S* epimer (endocyclic chelate product) in excess and supports our earlier suggestion[9] that the prevention of exocyclic chelation by TIPS is in large part due to a steric effect. However, it is possible that the increase in the C–Si–C bond angle in TIPS relative to TMS causes a change in bonding between silicon and oxygen and/or changes the Si–O–C bond angle, either of which may affect the ability of oxygen to chelate.[6b,d,20] (The only direct experimental study comparing the basicity of alkoxysilanes to that of ethers of which we are aware is that of West, Wilson, and Powell, who measured the equilibrium constant for hydrogen bonding to phenol for a series of ethers and alkoxysilanes and showed that the basicities of the two sets of compounds overlap.[21] Thus difference in Brønsted basicity is not responsible for the difference between the chelating abilities of BzO and TIPSO.)

The addition of another methylene link between the ketone carbonyl and the alkoxy group in **14** apparently diminishes the importance of C (a seven-membered chelate ring would be required[22]) since the addition of CH_3MgBr to **14** gave 62% de of the *S* epimer (Cram chelate product, entry 15).

Recent theoretical studies have attempted to define the most important factors affecting the activation energy of nucleophilic addition to ketones with chiral centers at C_α.[10] Anh's calculations[10a] indicate that the Felkin model is valid for α-heteroatom substituted ketones if L is defined as the group with the lowest lying σ* orbital. In the oxathiane system the C–S bond is expected to have the lowest lying σ* orbital,[23] and therefore the sulfur atom becomes L in the Felkin model. The reactive conformation is then predicted to be equivalent to conformation A (Figure 1) as far as the stereochemical outcome of nucleophilic addition is concerned. This prediction contradicts the results presented in Table I since reaction appears to occur via B and C whenever chelation does not force reaction through A. In the Cornforth model[3,24] as well as in the original Felkin model[4] the L group is considered to be the most electronegative atom with the Cornforth model requiring antiperiplanar alignment between the electronegative L and the carbonyl dipole in the transition state. These two models (L = oxygen) predict the same stereoisomer to be formed in excess in the oxathiane system when chelation is not the predominate factor and are consistent with the results in Table I. We do not present this as evidence against the Anh modification of the Felkin model since the reactivity of ketones containing two heteroatoms at the chiral C_α has not been studied theoretically; however, theoretical studies of this system might provide a test of the relative importance of various electronic factors (participation of σ* orbitals,[10a] electron donation,[10b] and bond polarity effects[4]) which differ for the α C–S and C–O bonds.[25]

Conclusion

This work suggests that the inclusion of alkoxy groups capable of chelation in the side chain of oxathianyl ketones competitively inhibits chelation to the ring oxygen (cf. Figure 1, structures A and C) and further supports the earlier assumption[12] that chelation to the ring oxygen causes the high stereoselectivity in the oxathiane system. Thus, to preserve the high diastereoselectivity in the 1,3-oxathiane based synthesis, it is necessary to prevent competitive chelation in both the substrate (this work) and the reagent (ref 12h); this can be achieved by protecting potentially competing oxygen substituents with a triisopropylsilyl group. The fact that the stereoselectivity of reductions with DIBAL is unaffected by replacement of benzyloxy by triisopropylsilyloxy groups in the side chain of oxathianyl ketones provides additional evidence for the assumption[12j,13] that DIBAL is a nonchelating reagent. When side chain chelation does occur, the diastereomer produced in excess by L-Selectride reduction is the same as the diastereomer produced by DIBAL reduction; this is consistent with transition states B and C (Figure 1) being of lowest energy in the absence of chelation to the ring oxygen. Apparently chelating and nonchelating reagents react through different conformations in the oxathiane system; a similar proposal has been put forth by Reetz in his studies of the reaction of β-alkoxyaldehydes with organotitanium reagents.[5e,f] The ability of the triisopropylsilyl group to prevent chelation may be useful in other diastereoselective syntheses when coordination at a site other than the OR (or OH) group is desired or when a change in the sense of diastereofacial selectivity is to be achieved. Similar results have been reported with other bulky silyl protecting groups.[15]

Experimental Section

General Methods. Proton and carbon-13 NMR spectra were recorded on an IBM/Bruker AC200 (200 or 50.2 MHz), a Bruker WM-250 (250 or 62.9 MHz), or a Varian XL-400 (400 or 100.2 MHz) spectrometer. Chemical shifts are expressed as parts per million downfield from internal tetramethylsilane (Me_4Si); coupling patterns are designated s (singlet), d (doublet), t (triplet), q (quartet), AB (AB pattern), or m (multiplet). NMR spectra were obtained on the mixtures of diastereomers with signals due to each epimer being assigned on the basis of their relative intensity. IR spectra were obtained as neat liquid films between sodium chloride plates on a Beckman 4250 spectrometer and were calibrated with the 1601-cm^{-1} band of polystyrene. Intensities are reported as s (strong), m (medium), w (weak), and br (broad). Optical rotations were measured on a Perkin-Elmer 141 polarimeter equipped with sodium and mercury light sources by using a 1-dm thermostated cell; reported temperatures are uncorrected. Melting points were observed on an Electrothermal melting point apparatus and are uncorrected. Solvents and reagents were used as received from Aldrich except as described here (solvent distilled from/drying agent): tetrahydrofuran (THF)/sodium benzophenone; toluene/$LiAlH_4$; diethyl ether/$LiAlH_4$; dimethyl sulfoxide/CaH; methylene chloride/P_2O_5; triethylamine/$LiAlH_4$.

Aldehydes 1–6. Aldehydes **1** and **3–6** were prepared by oxidation of the corresponding monoprotected diols with CrO_3·(pyridine)$_2$. Preparation of **1**, **3**, **5**, and **6** has been previously described[14] as has the preparation[14b] of the *tert*-butyldimethylsilyl counterpart of **4**; the triisopropylsilyl compound was prepared analogously (see below).

(17) Yamaguchi, S.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1972**, *37*, 3174.

(18) We have previously observed[12b,d,13] that the addition of L-Selectride and CH_3Li to simple alkyl oxathianyl ketones is less selective than the addition of Grignard reagents.

(19) Reetz has also observed a substantial difference between the abilities of *t*-Bu$(CH_3)_2$Si and TMS to prevent chelation during the addition of CH_3-Ti$[OCH(CH_3)_2]_2$ to chiral α-alkoxy ketones.[5d]

(20) Michl, J., personal communication.

(21) West, R.; Wilson, L. S.; Powell, D. L. *J. Organomet. Chem.* **1979**, *178*, 5. For a different interpretation of the effect of silicon protecting groups on the chelating ability of ether oxygens, cf. ref 6b–d.

(22) **Note Added in Proof**: However, seven-membered chelate rings even involving coordination of *t*-BuMe_2SiO to Li have been observed in the solid state: Willard, P. G.; Hintze, M. J. *J. Am. Chem. Soc.* **1987**, *109*, 5539. If some of the tendency to chelate in this fashion survives in THF solution, it may explain the somewhat diminished stereoselectivity in the reaction of **14**.

(23) Bernardi, F.; Bottoni, A.; Venturini, A.; Mangini, A. *J. Am. Chem. Soc.* **1986**, *108*, 8171. Lehn, J. M.; Wipff, G. *J. Am. Chem. Soc.* **1976**, *98*, 7498.

(24) For a recent example of the use of the Cornforth model cf.: Bloch, R.; Gilbert, L. *Tetrahedron Lett.* **1987**, 423.

(25) The detailed role of α sulfur substitution on the stereoselectivity in the oxathiane system is under investigation: Alvarez, M. T., unpublished observations. See also: Shimigaki, M.; Takubo, H.; Oishi, T. *Tetrahedron Lett.* **1985**, 6235. Reich, H. J.; Holtan, R. C.; Borkowsky, S. L. *J. Org. Chem.* **1987**, *52*, 312.

Aldehyde 2. To freshly distilled allyl alcohol (bp 96–99 °C, 1.16 g, 20 mmol) was added triisopropylsilyl chloride (3.86 g, 20 mmol), imidazole (3.4 g, 50 mmol), and dimethylformamide (7 mL).[26] The resulting solution was allowed to stir under N_2 for 72 h at room temperature (reaction followed by TLC, 5% EtOAc/hexane), ether (20 mL) and saturated NH_4Cl (20 mL) were added, the layers separated, and the organics washed with 2% aqueous HCl (2×10 mL), dried ($MgSO_4$), concentrated, and flash chromatographed (1% EtOAc/hexane) to give 3.56 g (85%) of triisopropylsilylated allyl alcohol. Next, 2.15 g (10 mmol) of this material was dissolved in dry CH_2Cl_2 (100 mL), the solution cooled to −78 °C, and dry ozone in oxygen bubbled through until the solution turned blue. Dry N_2 was then passed through the solution, it was allowed to warm to room temperature, dimethyl sulfide (10 mL) was added, and the reaction was stirred for 1 h. Concentration and flash chromatography (4% EtOAc/hexane) gave 0.984 g (45%) of aldehyde **2**: ^{1}H NMR (200 MHz, $CDCl_3$) ∂ 9.75 (t, J =1.0 Hz, 1 H), 4.26 (t, J = 1.0 Hz, 2 H), 1.09 (m, 21 H); IR (neat) 3000–2850 (s), 1750 (s), 1140 (s) cm^{-1}.

Oxathianyl Ketone 7 (n = 1; R = CH_2Ph). To the optically pure parent oxathiane[12] (1.0 g, 5.0 mmol) in absolute THF (15 mL) at −78 °C under N_2 was added, dropwise, 1.5 M *n*-BuLi (3.3 mL, 5.3 m mol) in hexane. After being stirred for 3 min the solution was allowed to warm to 0 °C and was immediately recooled to −78 °C. Aldehyde **1** (0.826 g, 5.5 mmol) in THF (7 mL) was then added dropwise over 1 h. After being stirred at −78 °C for an additional 3 h, the solution was allowed to stand overnight at −25 °C. Water (2 mL) and saturated NH_4Cl (2 mL) were then added, the layers separated, and the organic layers dried ($MgSO_4$), concentrated, and flash chromatographed (15% EtOAc/hexane) to give a clear oil (0.822 g, 43%). Next, to a cold (−78 °C) solution of dry Me_2SO (460 mg, 6 mmol) in dry CH_2Cl_2 (5 mL) under N_2 was added, dropwise, trifluoroacetic anhydride (1.25 g, 6 mmol) in dry CH_2Cl_2 (7 mL), and the resulting solution stirred for 0.5 h. The carbinol obtained above was dissolved in dry CH_2Cl_2 (10 mL) and added dropwise to the oxidant solution, the reaction was allowed to stir for 2 h, triethylamine (1.18 g, 12 mmol) was added, and the solution was warmed to 0 °C. It was then poured into 5% aqueous HCl (50 mL) and shaken thoroughly, and the organic layer was washed with saturated $NaHCO_3$ (20 mL), dried ($MgSO_4$), concentrated, and flash chromatographed (7% EtOAc/hexane) to give 0.520 g (30% overall) of **7** as a clear oil: ^{1}H NMR (200 MHz, $CDCl_3$) ∂ 7.34 (m, 5 H), 5.58 (s, 1 H), 4.59 (d, J = 2.1 Hz, 2 H), 4.50 (d, J = 2.1 Hz, 2 H), 3.42 (dt, J = 4.3, 10.5 Hz, 1 H), and others; ^{13}C NMR (50.3 MHz, $CDCl_3$) ∂ 202.0, 137.3, 1 28.3 , 127.8, 127.7, 81.3, 76.9, 73.2, 71.8, 50.2, 43.9, 41.3, 34.4, 31.2, 29.1 , 24.1, 22.3, 21.9.

Oxathianyl Ketone 8 (n = 1; R = TIPS). Use of aldehyde **2** in the above procedure gave 0.730 g (65% overall yield) of **8** as an oil: ^{1}H NMR (250 MHz, $CDCl_3$) ∂ 5.69 (s, 1 H), 4.67 (A of AB, J_{AB} = 18.7 Hz, 1 H), 4.59 (B of AB, J_{AB} = 18.7 Hz, 1 H), 3.43 (dt, J = 4.3, 10.5 Hz, 1 H), and others; ^{13}C NMR (62.9 MHz, $CDCl_3$) ∂ 202.5, 80.7, 77.0, 66.6, 50.4, 43.9, 41.4, 34.5, 31.3, 29.2, 24.2, 22.3, 22.0, 17.8, 11.9. Anal. Calcd for $C_{22}H_{42}O_3SiS$: C, 63.71; H, 10.21. Found: C, 63.81; H, 10.14.

Oxathianyl Ketone 9 (n = 2; R = CH_2Ph). Use of aldehyde **3** gave 2.68 g (42% overall yield) of **9** as an oil: ^{1}H NMR (250 MHz, $CDCl_3$) ∂ 7.31 (m, 5 H), 5.46 (s, 1 H), 4.50 (s, 2 H), 3.75 (t, J = 6.4 Hz, 2 H), 3.38 (dt, J = 4.3, 10.5 Hz, 1 H), 2.95 (t, J = 6.4 Hz, 2 H), and others; ^{13}C NMR (62.9 MHz, $CDCl_3$) ∂ 203.5, 138.1, 128.2, 127.6, 127.5, 82.6, 77.0, 73.0, 64.8, 50.3, 43.9, 41.5, 3 8.5, 34.5, 31.3, 29.3, 24.2, 22.4, 22.0. Anal. Calcd for $C_{21}H_{30}O_3S$: C, 69.57; H, 8.34. Found: C, 69.18; H, 8.21.

Oxathianyl Ketone 10 (n = 2; R = TIPS). The procedure above with aldehyde **4** gave 0.605 g (56% overall yield) of **10** as an oil: ^{1}H NMR (200 MHz, $CDCl_3$) ∂ 5.43 (s, 1 H), 3.91 (t, J = 6.5 Hz, 2 H), 3.36 (dt, J = 4.3, 10.5 Hz, 1 H), 2.80 (t, J = 6.5 Hz, 2 H), and others; ^{13}C NMR (50.3 MHz, $CDCl_3$) ∂ 203.8, 82.9, 77.1, 58.9, 50.3, 43.8, 41.5, 34.6, 31.3, 29.3, 24.2, 22.4, 22.0, 17.9, 11.9.

Oxathianyl Ketone 11 (n = 2; R = CPh_3). By a procedure similar to the above aldehyde **5** gave 0.767 g (47% overall yield) of **11** as fine white crystals: mp 145–146 °C; ^{1}H NMR (250 MHz, $CDCl_3$) ∂ 7.31 (m, 15 H), 5.46 (s, 1 H), 3.40 (t, J = 6.7 Hz, 2 H), 3.34 (dt, J = 4.4, 10.7 Hz, 1 H), 2.92 (dt, J = 1.5, 6.7 Hz, 2 H), and others; ^{13}C NMR (62.9 MHz, $CDCl_3$) ∂ 203.6, 143.9, 128.6, 127.8, 127.7, 127.6, 127.1, 126.9, 86.7, 82.7, 77.1, 58.8, 50.3, 43.8, 41.5, 39.0, 34.6, 31.4, 29.3, 24.3, 22.4, 22.0. Anal. Calcd for $C_{33}H_{38}O_3S$: C, 77.00; H, 7.44. Found: C, 77.02; H, 7.22.

Oxathianyl Ketone 12 (n = 2; R = H). Ketone **10** (0.440 g, 1.0 mmol) was dissolved in 2% HCl in 95% EtOH (15 mL) and allowed to stir for 1.5 h at which time saturated K_2CO_3 (10 mL) was added, the solution extracted with ether (3 × 10 mL),and the combined organics washed with saturated NaCl (20 mL), dried ($MgSO_4$), concentrated, and flash chromatographed (30% EtOAc/hexane) to give 278 mg (98%) of **12** as white needles. Recrystallization from hexanes provided an analytical sample: mp 77.0–78.0 °C; ^{1}H NMR (200 MHz, CDCl3) ∂ 5.49 (s, 1 H), 3.87 (t, J = 5.5 Hz, 2 H), 3.46 (dt, J = 4.3, 10.5 Hz, 1 H), 2.92 (t, J = 5.5 Hz, 2 H), 2.40 (br s, 1 H), and others; ^{13}C NMR (50.3 MHz, $CDCl_3$) ∂ 206.0, 82.4, 76.9, 57.5, 50.2, 44.0, 41.3, 40.4, 34.4, 31.2, 29.2, 24.1, 22.4, 21.9. Anal. Calcd for $C_{14}H_{24}O3S$: C, 61.73; H,8.88. Found: C, 61.77; H, 8.84.

Oxathianyl Ketone 13 (n = 2; R = TMS). Ketone 12 (55 mg, 0.2 mmol) was dissolved in THF (2 mL) under N_2, triethylamine (0.1 mL, 0.7 mmol) and trimethylsilyl chloride (0.1 mL, 0.8 mmol) were added, and the resulting suspension was stirred at room temperature for 5 h. The solution was then filtered, the filtrate rinsed with ether (10 mL), and the organics washed with saturated NH_4Cl, dried ($MgSO_4$), and concentrated to give **13** as an oil: ^{1}H NMR (200 MHz, $CDCl_3$) ∂ 5.40 (s, 1H), 3.79 (t, J = 6.6 Hz, 2H), 3.36 (dt, J = 4.4, 10.5 Hz, 1 H), 2.81 (t, J = 6.6 Hz, 2 H), and others; ^{13}C NMR (50.3 MHz, $CDCl_3$) ∂ 203.7, 82.7, 77.0, 57.5, 50.3, 43.8, 41.5, 34.5, 31.3, 29.2, 24.2, 22.4, 21.9, −0.7.

Oxathianyl Ketone 14 (n = 3; R = CH_2Ph). By similar procedures used for the preparation of **7** above, aldehyde **6** gave 1.73 g (77% overall) of **14** as an oil: ^{1}H NMR (250 MHz, $CDCl_3$) ∂ 7.31 (m, 5 H), 5.44 (s, 1 H), 4.46 (s, 2 H), 3.47 (t, J = 6.7, 2 H), 3.39 (dt, J = 4.3, 10.5 Hz, 1 H), 2.77 (t, J = 6.7, 2 H), and others; ^{13}C NMR (62.9 MHz, $CDCl_3$) ∂ 204.9, 138.3, 128.1, 127.3, 127.2, 82.4, 76.8, 72.6, 69.1, 50.2, 43.7, 41.4, 34.6, 34.2, 31.2, 29.2, 24.1, 23.3, 22.3, 21.9. Anal. Calcd for $C_{22}H_{32}O_3S$: C, 70.17; H, 8.57. Found: C, 69.93; H, 8.46.

Oxathianylcarbinol 15 (n = 1; R = CH_2Ph). (a) L-Selectride. To ketone **7** (60 mg, 0.17 mmol) in toluene (10 mL) at −78 °C under N_2 was added dropwise 1.0 M L-Selectride (0.4 mL, 0.4 mmol) in THF. After being stirred for 4 h, the reaction was quenched at −78 °C by addition of H_2O, NaOH (50 mg, 1.3 mmol) and 30% H_2O_2 (0.5 mL) were then added, and the reaction was stirred overnight. Next, H_2O (5 mL) and ether (10 mL) were added, the layers separated, and the organics washed with saturated NH_4Cl, dried ($MgSO_4$), and concentrated to give **15** (100% crude yield) as a mixture of epimers: 72% diastereomeric excess (de, determined by integration of the ^{1}H signals for the two epimers) of the *R* epimer (anti-Cram chelate product).

(b) DIBAL. To ketone **7** (16 mg, 0.05 mmol) in toluene (5 mL) at −78 °C under N_2 was added, dropwise, 1.0 M DIBAL (0.2 mL, 0.2 mmol) in hexanes. The reaction was stirred for 2 h and then quenched at −78 °C by addition of saturated NH_4Cl, ether was added (5 mL), the layers were separated, and the organics were washed with saturated NaCl, dried ($MgSO_4$), and concentrated to give **15** (100% crude yield) as a mixture of epimers: 57% de of the *R* epimer (anti-Cram chelate product).

***S* epimer**: more polar isomer on TLC (20% EtOAc/hexanes); ^{1}H NMR (200 MHz, $CDCl_3$) ∂ 7.34 (m, 5 H), 5.07 (d, J = 5.2 Hz, 1 H), 4.56 (s, 2 H), 3.94 (m, 1 H), 3.60 (m, 2 H), 3.37 (dt, J = 4.3, 10.5 Hz, 1 H), 2.63 (d, J = 4.9 Hz, 1 H), and others; ^{13}C NMR (50.3 MHz, $CDCl_3$) ∂ 138.0, 128.2, 127.6, 127.5, 79.9, 77.2, 73.2, 72.3, 70.4, 50.7, 42.7, 41.5, 34.5, 31.3, 29.6, 24.2, 22.6, 22.0.

***R* epimer**: ^{1}H NMR (200 MHz, $CDCl_3$) ∂ 7.34 (m, 5 H), 5.06 (d, J = 5.6 Hz, 1 H), 4.56 (s, 2 H), 3.86 (m, 1 H), 3.60 (m, 2 H), 3.39 (dt, J = 4.3, 10.5 Hz, 1 H), 2.79 (d, J = 4.1 Hz, 1 H), and others; ^{13}C NMR (50.3 MHz, $CDCl_3$) ∂ 138.0, 128.2, 127.6, 127.5, 78.8, 77.2, 73.2, 72.3, 70.4, 50.7, 43.0, 41.5, 34.5, 31.3, 29.5, 24.2, 22.7, 22.0.

Oxathianylcarbinol 16 (n = 1; R = TIPS). (a) L-Selectride. Following the same procedure as above with ketone **8** gave **16** as a mixture of epimers: 33% de of the *S* epimer (Cram chelate product).

(b) DIBAL. The same procedure as above with ketone **8** gave **16** as a mixture of epimers: 60% de of the *R* epimer.

***S* epimer**: more polar isomer on TLC (20% EtOAc/hexanes); ^{1}H NMR (200 MHz, $CDCl_3$) ∂ 5.09 (d, J = 5.7 Hz, 1 H), 3.82 (m, 3 H), 3.39 (dt, J = 4.2, 10.5 Hz, 1 H), 2.64 (d, J = 5.4 Hz, 1 H), and others; 13 °C NMR (50.3 MHz, $CDCl_3$) ∂ 79.7, 77.2, 73.6, 63.2, 50.7, 42.5, 41.6, 34.7, 31.4, 26.6, 24.4,22.7, 22.1, 17.9, 11.9.

***R* epimer**: ^{1}H NMR (200 MHz, $CDCl_3$) ∂ 5.13 (d, J = 3.0 Hz, 1 H), 3.74 (m, 3 H), 3.43 (dt, J = 4.3, 10.6 Hz, 1 H), 2.67 (d, J = 4.8 Hz, 1 H), and others; 13 °C NMR (50.3-MHz, $CDCl_3$) ∂ 78.6, 77.2, 73.6, 63.2, 50.7, 43.0, 41.6, 34.7, 31.4, 26.6, 24.4, 22.7, 22.1, 17.9, 11.9.

Anal. Calcd for $C_{22}H_{44}O_3SiS$: C, 63.41; H, 10.64. Found: C, 62.87; H, 10.79.

Oxathianylcarbinol 17 (n = 1; R = H). (a) From 16. Carbinol **16** (0.665 g, 1.6 mmol, 12% de of the *R* epimer obtained directly from condensation of **2** with the parent oxathiane; the isomer in excess was epimeric to the isomer produced in excess by L-Selectride reduction of ketone **8**, vide supra) was dissolved in 2% HCl in 95% EtOH (20 mL) and allowed to stir for 2 h at which time TLC analysis (50% EtOAc/hexanes) showed the reaction to be complete, saturated K_2CO_3 (10 mL)

(26) Cunico, R. F.; Bedell, L. *J. Org. Chem.* **1980**, *45*, 4797.

was added, the solution was extracted with ether (3x10 mL), and the combined organics were washed with saturated NaCl (20 mL), dried ($MgSO_4$), concentrated, and flash chromatographed (50% EtOAc/hexane) to give 0.399 g (96%) of **17** as mixture of epimers: 12% de of the *R* epimer.

(b) From 15. Carbinol **15** (20 mg, 0.06 mmol, 78% de of the *R* epimer; produced in excess by L-Selectride reduction of ketone **7**) was dissolved in absolute ethanol (5 mL), 10% Pd·C (5 mg) added, and the mixture hydrogenated (45 psi) overnight. Filtration and evaporation of the solvent gave a sample for NMR analysis: 78% de of the *R* epimer.

***S* epimer**: ^{1}H NMR (200 MHz, $CDCl_3$) ∂ 5.11 (d, J = 4.3 Hz, 1 H), 3.87 (m, 1 H), 3.71 (m, 2 H), 3.42 (dt, J = 4.4, 10.2 Hz, 1 H), 2.98 (d, J = 6.8 Hz, 1 H), 2.48 (dd, J = 4.3, 7.1 Hz, 1 H), and others; ^{13}C NMR (50.3 MHz, $CDCl_3$) ∂ 81.3, 77.5, 72.6, 63.4, 50.9, 43.3, 41.6, 34.6, 31.3, 29.6, 24.3, 22.7, 22.0.

***R* epimer**: ^{1}H NMR (200 MHz, $CDCl_3$) ∂ 4.99 (d, J = 5.8 Hz, 1 H), 3.87 (m, 1 H), 3.71 (m, 2 H), 3.44 (dt, J = 4.4, 10.2 Hz, 1 H), 3.00 (d, J = 4.2 Hz, 1 H), 2.38 (t, J = 5.7 Hz, 1 H), and others; ^{13}C NMR (50.3 MHz, $CDCl_3$) ∂ 79.5, 77.3, 73.2, 63.2, 50.8, 43.2, 41.6, 34.6, 31.3, 29.5, 24.3, 22.8, 22.0.

Oxathianylcarbinol 18 (n = 2; R = CH_2Ph). (a) L-Selectride. By the same procedure used in the reduction of **7** ketone **9** gave **18** as a mixture of epimers: 9% de of the *S* epimer.

(b) DIBAL. By the same procedure used in the reduction of **7** ketone **9** gave **18** as a mixture of epimers: 66% de of the *R* epimer.

***S* epimer**: ^{1}H NMR (200 MHz, $CDCl_3$) ∂ 7.34 (m, 5 H), 4.93 (d, J = 4.5 Hz, 1 H), 4.50 (s, 2 H), 3.95 (m, 1 H), 3.66 (m, 2 H), 3.39 (dt, J = 4.2, 10.4 Hz, 1 H), 2.95 (br s, 1 H), and others; ^{13}C NMR (50.3 MHz, $CDCl_3$) ∂ 138.0, 128.1, 127.4, 127.3, 82.3, 81.9, 77.0, 73.0, 67.2, 50.6, 42.5, 41.5, 37.0, 34.5, 31.2, 29.5, 24.1, 22.6, 21.9.

***R* epimer**: ^{1}H NMR (200 MHz, $CDCl_3$) ∂ 7.34 (m, 5 H), 4.85 (d, J = 5.9 Hz, 1 H), 3.86 (m, 1 H), 3.66 (m, 2 H), 3.39 (dt, J = 4.2, 10.4 Hz, 1 H), 2.95 (br s, 1 H), and others; ^{13}C NMR (50.3 MHz, $CDCl_3$) ∂ 138.0, 128.1, 127.4, 127.3, 82.3, 81.9, 76.9, 72.9, 67.9, 50.6, 42.5, 41.4, 36.3, 34.5, 31.2, 29.4, 24.1, 22.5, 21.9.

Oxathianylcarbinol 19 (n = 2; R = TIPS). (a) L-Selectride. By the same procedure used in the reduction of **7** ketone **10** gave **19** as a mixture of epimers: 76% de of the *S* epimer.

(b) DIBAL. By the same procedure used in the reduction of **7** ketone **10** gave **19** as a mixture of epimers: 77% de of the *R* epimer.

***S* epimer**: more polar isomer on TLC (20% EtOAc/hexanes); ^{1}H NMR (200 MHz, $CDCl_3$) ∂ 4.94 (d, J = 5.1 Hz, 1 H), 3.96 (m, 3 H), 3.56 (d, J = 2.9 Hz, 1 H), 3.42 (dt, J = 4.1, 10.6 Hz, 1 H), and others ; ^{13}C NMR (50.3 MHz, $CDCl_3$) ∂ 82.4, 77.2, 73.3, 62.5, 50.9, 42.5, 41.7, 34.7, 34.5, 31.4, 29.6, 24.3, 22.8, 22.0, 17.9, 11.7.

***R* epimer**: ^{1}H NMR (200 MHz, $CDCl_3$) ∂ 4.90 (d, J = 5.8 Hz, 1 H), 3.93 (m, 3 H), 3.42 (dt, J = 4.1, 10.6 Hz, 1 H), 3.39 (d, J = 2.7 Hz, 1 H), and others; ^{13}C NMR (50.3 MHz, $CDCl_3$) ∂ 82.1, 77.2, 72.3, 61.5, 50.8, 42.5, 41.7, 35.0, 34.5, 31.4, 29.6, 24.3, 22.8, 22.0, 17.9, 11.7.

Oxathianylcarbinol 20 (n = 2; R = H). L-Selectride. By the same procedure used in the reduction of **7** ketone **13** gave, after acidic workup (desilylation), **20** as a mixture of epimers: 33% de of the *R* epimer.

From 19. By the procedure given above for deprotection of **16**, carbinol **19** [67% de of the *S* epimer obtained by flash chromatographic separation (10% EtOAc/hexanes) of the crude diastereomer mixture produced by condensation of **4** with the parent oxathiane] gave 0.265 g (95%) of **20** as small white crystals: 67% de of the *S* epimer; mp 98.0–99.2 °C.

From 18. By the procedure given above for deprotection of **15** carbinol **18** (66% de of the *R* epimer) gave a sample of **20** for NMR analysis: 64% de of the *R* epimer.

***S* epimer**: ^{1}H NMR (200 MHz, $CDCl_3$) ∂ 4.97 (d, J = 4.2 Hz, 1 H), 4.00 (m, 1 H), 3.84 (m, 2 H), 3.45 (dt, J = 4.2, 10.5 Hz, 1 H), 2.71 (br s, 2 H), and others; ^{13}C NMR (50.3 MHz, $CDCl_3$) ∂ 82.3, 77.4, 73.1, 60.9, 50.9, 42.9, 41.6, 34.6, 34.3, 31.4, 29.7, 24.4, 22.8, 22.0.

***R* epimer**: ^{1}H NMR (200 MHz, $CDCl_3$) ∂ 4.83 (d, J = 6.7 Hz, 1 H), 3.86 (m, 1 H), 3.84 (m, 2 H), 3.44 (dt, J = 4.2, 10.5 Hz, 1 H), 2.71 (br s, 2 H), and others; ^{13}C NMR (50.3 MHz, $CDCl_3$) ∂ 81.7, 77.2, 73.3, 60.8, 50.8, 42.9, 41.6, 34.6, 34.3, 31.4, 29.6, 24.4, 22.9, 22.0.

Anal. Calcd for $C_{14}H_{26}O_3S$: C, 61.28; H, 9.55. Found: C, 61.08; H, 9.47.

Oxathianylcarbinol 21 (n = 1; R = CH_2Ph). To ketone **7** (0.290 g, 0.83 mmol) in absolute THF (10 mL) at −78 °C under N_2 was added, dropwise, 3.2 M methylmagnesium bromide (0.6 mL, 1.9 mmol) in ether. The reaction mixture was stirred for 4 h and quenched with saturated NH_4Cl, ether (10 mL) was added, the layers were separated, and the organics were washed with saturated NaCl (10 mL), dried ($MgSO_4$), and concentrated to give 0.307 g (100% crude) of **21** as a mixture of epimers: 33% de of the *R* epimer (anti-Cram chelate product). Flash chromatography (10% EtOAc/hexanes) provided an analytical sample.

***S* epimer**: ^{1}H NMR (250 MHz, $CDCl_3$) ∂ 7.34 (m, 5 H), 5.06 (s, 1 H), 4.59 (A of AB, J_{AB} = 12.3 Hz, 1 H), 4.55 (B of AB, J_{AB} = 12.3 Hz, 1 H), 3.62 (d, J = 10.9 Hz, 1 H), 3.38 (d, J = 10.9 Hz, 1 H), 3.33 (dt, J = 4.3, 10.5 Hz, 1 H), 2.55 (br s, 1 H), and others; ^{13}C NMR (62.9 MHz, $CDCl_3$) ∂ 138.4, 128.2, 127.6, 127.5, 83.3, 82.4, 77.5, 74.1, 73.4, 50.9, 42.8, 41.6, 34.7, 31.5, 29.8, 24.4, 22.8, 22.1, 20.5.

***R* epimer**: ^{1}H NMR (250 MHz, $CDCl_3$) ∂ 7.34 (m, 5 H), 5.09 (s, 1 H), 4.58 (A of AB, J_{AB} = 12.4 Hz, 1 H), 4.52 (B of AB, J_{AB} = 12.4 Hz, 1 H), 3.54 (d, J = 10.5 Hz, 1 H), 3.38 (d, J = 10.5 Hz, 1 H), 3.37 (dt, J = 4.3, 10.5 Hz, 1 H), 2.55 (br s, 1 H), and others; ^{13}C NMR (62.9 MHz, $CDCl_3$) ∂ 138.4, 128.2, 127.6, 127.5, 83.3, 82.4, 77.5, 74.1, 73.4, 50.9, 43.0, 41.6, 34.7, 31.5, 29.7, 24.4, 22.8, 22.1, 21.0.

Anal. Calcd for $C_{21}H_{32}O_3S$: C, 69.19; H, 8.85. Found: C, 69.14; H, 8.81.

Oxathianylcarbinol 22 (n = 1; R = TIPS). By the procedure given above ketone **8** gave 0.745 g (100% crude) of **22** as a mixture of epimers: 95% de of the *S* epimer. Carbinol **22** was also prepared by addition of methyllithium to **8** at room temperature under similar conditions to the procedure given above to give **22** as a mixture of epimers: 56% de of the *R* epimer.

***S* epimer**: ^{1}H NMR (200 MHz, $CDCl_3$) ∂ 5.13 (s, 1 H), 3.85 (d, J = 9.3 Hz, 1 H), 3.49 (d, J = 9.3 Hz, 1 H), 3.35 (dt, J = 4.3, 10.5 Hz, 1 H), 2.75 (br s, 1 H) and others; ^{13}C NMR (50.3 MHz, $CDCl_3$) ∂ 82.4, 77.4, 74.0, 67.5, 50.8, 42.4, 41.7, 34.7, 31.4, 29.8, 24.3, 22.6, 22.1, 19.3, 17.9, 11.9.

***R* epimer**: ^{1}H NMR (200 MHz, $CDCl_3$) ∂ 5.12 (s, 1 H), 3.74 (d, J = 9.1 Hz, 1 H), 3.54 (d, J = 9.1 Hz, 1 H), 3.42 (dt, J = 4.3, 10.5 Hz, 1 H), 2.70 (br s, 1 H) and others; ^{13}C NMR (50.3 MHz, $CDCl_3$) ∂ 81.8, 77.5, 74.5, 67.5, 50.8, 42.7, 41.7, 34.7, 31.4, 29.7, 24.3, 22.7, 22.1, 20.8, 17.9, 11.9.

Oxathianylcarbinol 23 (n = 1; R = H). (a) From 22. Carbinol **22** [46% de of the *S* epimer (prepared from mixing 54 mg of **22**, obtained from the treatment of **8** with CH_3MgBr, with 15 mg of **22** obtained from the treatment of **8** with CH_3Li)] was deprotected as described above for **16** to give crude **23** for NMR analysis.

(b) From 21. Carbinol **21** (23% de of the *R* epimer) was deprotected as described above for **15** to give crude **23** for NMR analysis.

***S* epimer**: ^{1}H NMR (200 MHz, $CDCl_3$) ∂ 4.98 (s, 1 H), 3.93 (d, J = 11.8 Hz, 1 H), 3.39 (d, J = 11.8 Hz, 1 H), 3.40 (dt, J = 4.3, 10.5 Hz, 1 H), 3.22 (br s, 1 H) and others.

***R* epimer**: ^{1}H NMR (200 MHz, $CDCl_3$) ∂ 5.01 (s, 1 H), 3.66 (d, J = 11.8 Hz, 1 H), 3.49 (d, J = 11.8 Hz, 1 H), 3.43 (dt, J = 4.3, 10.5 Hz, 1 H), 2.60 (br s, 1 H) and others.

Oxathianylcarbinol 24 (n = 2; R = CH_2Ph). Methylmagnesium bromide was added to ketone **9** (as described above for **7**) to give, after flash chromatography (7% EtOAc/hexanes), 0.611 g (64%) of **24** as a mixture of epimers: 17% de of the *R* epimer (determined by integration of ^{13}C signals).

***S* epimer**: ^{1}H NMR (400-MHz, CDCl3) ∂ 7.34 (m, 5 H), 4.84 (s, 1 H), 4.51 (s, 2 H), 3.72 (m, 2 H), 3.34 (dt, J = 4.4, 10.5 Hz, 1 H), 2.91 (br s, 1 H), and others; ^{13}C NMR (100.6 MHz, $CDCl_3$) ∂ 138.1, 128.2, 127.7, 127.6, 86.0, 77.5, 73.8, 73.1, 67.1, 50.8, 42.8, 41.7, 36.9, 34.6, 31.4, 29.8, 24.3, 23.8, 22.7, 22.1.

***R* epimer**: ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 7.34 (m, 5 H), 4.84 (s, 1 H), 4.51 (s, 2 H), 3.72 (m, 2 H), 3.37 (dt, J = 4.4, 10.5 Hz, 1 H), 2.91 (br s, 1 H), and others; ^{13}C NMR (100.6 MHz, $CDCl_3$) ∂ 138.1, 128.3, 127.7, 127.6, 85.3, 77.5, 73.7, 73.0, 66.6, 50.7, 42.9, 41.6, 37.3, 34.6, 31.4, 29.7, 24.3, 23.5, 22.7, 22.1.

Anal. Calcd for $C_{22}H_{34}O_3S$: C, 69.80; H, 9.05. Found: C, 69.30; H, 8.94.

Oxathianylcarbinol 25 (n = 2; R = TIPS). Methylmagnesium bromide was added to ketone **10** (as described above for **7**) to give, after flash chromatography (10% EtOAc/hexanes), 0.251 g (91%) of **25** as a mixture of epimers: 95% de of the *S* epimer. Carbinol **25** was also prepared by addition of methyllithium to **10** at room temperature under conditions similar to the procedure given above to give **25** as a mixture of epimers: 38% de of the *S* epimer. In addition carbinol **25** was prepared by treatment of **10** with dimethylmagnesium at −78 °C under conditions similar to those given above to yield **25** as a mixture of epimers: 96% de of the *S* epimer.

***S* epimer**: ^{1}H NMR (250 MHz, $CDCl_3$) ∂ 4.92 (s, 1 H), 4.00 (m, 2 H), 3.87 (s, 1 H), 3.39 (dt, J = 4.3, 10.5 Hz, 1 H), and others; ^{13}C NMR (62.9 MHz, $CDCl_3$) ∂ 86.0, 77.4, 74.1, 60.7, 50.9, 42.6, 41.8, 39.2, 34.7, 31.4, 29.8, 24.3, 23.5, 22.7, 22.0, 17.9, 11.8.

***R* epimer**: ^{1}H NMR (250 MHz, $CDCl_3$) ∂ 4.89 (s, 1 H), 3.98 (m, 2 H), 3.74 (s, 1 H), 3.43 (dt, J = 4.3, 10.5 Hz, 1 H), and others; ^{13}C NMR (62.9 MHz, $CDCl_3$) ∂ 85.8, 77.6, 74.1, 60.4, 51.0, 42.8, 41.7, 39.2, 34.7, 31.4, 29.8, 24.3, 23.4, 22.7, 22.0, 17.9, 11.8.

Oxathianylcarbinol 26 (n = 2; R = CPh_3). Methylmagnesium bromide was added to ketone **11** (as described above for **7**) to give, after flash

chromatography (12% EtOAc/hexanes), 0.600 g (85%) of **26** as a mixture of epimers: 72% de of the *S* epimer (Cram chelate product).

***S* epimer**: ^{1}H NMR (250 MHz, $CDCl_3$) ∂ 7.35 (m, 15 H), 4.71 (s, 1 H), 3.29 (m, 5 H), 3.16 (br s, 1 H), and others; ^{13}C NMR (62.9 MHz, $CDCl_3$) ∂ 144.0, 128.6, 127.9, 127.8, 127.2, 126.9, 87.3, 85.3, 77.5, 73.8, 60.3, 50.7, 42.9, 41.6, 37.7, 34.7, 31.4, 29.7, 24.3, 23.4, 22.4, 22.1.

***R* epimer**: ^{1}H NMR (250 MHz, $CDCl_3$) ∂ 7.35 (m, 15 H), 4.70 (s, 1 H), 3.29 (m, 5 H), 3.16 (br s, 1 H), and others; ^{13}C NMR (62.9 MHz, $CDCl_3$) ∂ 144.0, 128.6, 127.9, 127.8, 127.2, 126.9, 87.3, 85.8, 77.5, 73.8, 60.3, 50.8, 42.9, 41.6, 37.7, 34.7, 31.4, 29.7, 24.3, 23.5, 22.7, 22.1.

Oxathianylcarbinol 27 (n = 2; R = H). Dimethylmagnesium was added to ketone **13** (as described above for **10**) to give, after acidic workup (desilylation), **27** as a mixture of epimers: 46% de of the *S* epimer. (Treatment of **13** with methylmagnesium bromide was found to cause extensive decomposition.)

From 25. Carbinol **25** (38% de of the *S* epimer) was deprotected as described above for **16** to give crude **27** for NMR analysis: 39% de of the *S* epimer.

From 24. Carbinol **24** (17% de of the*R* epimer) was deprotected as described above for **15** to give crude **27** for NMR analysis: 17% de of the *R* epimer.

***S* epimer**: ^{1}H NMR (200 MHz, $CDCl_3$) ∂ 4.84 (s, 1 H), 3.86 (m, 2 H), 3.44 (dt, J = 4.3, 10.5 Hz, 1 H), 3.02 (br s, 1 H), and others.

***R* epimer**: ^{1}H NMR (200 MHz, $CDCl_3$) ∂ 4.90 (s, 1 H), 3.86 (m, 2 H), 3.45 (dt, J = 4.3, 10.5 Hz, 1 H), 3.02 (br s, 1 H), and others.

Oxathianylcarbinol 28 (n = 3; R = CH_2Ph). Methylmagnesium bromide was added to ketone **14** (as described above for **7**) to give, after flash chromatography (10% EtOAc/hexanes), 0.530 g (98%) of **28** as a mixture of epimers: 62% de of the presumed *S* epimer (Cram chelate product). Carbinol **28** was also prepared by addition of 3-benzyloxy-1-propylmagnesium bromide to acyloxathiane **29**[12e] to give, after flash chromatography (10% EtOAc/hexanes), **28** as a mixture of epimers: 60% de of the presumed *R* epimer.

***S* epimer**: ^{1}H NMR (250 MHz, $CDCl_3$) ∂ 7.34 (m, 5 H), 4.81 (s, 1 H), 4.51 (s, 2 H), 3.49 (t, J = 6.7 Hz, 2 H), 3.41 (dt, J = 4.3, 10.5 Hz, 1 H), 2.47 (br s, 1 H), and others; ^{13}C NMR (62.9 MHz, $CDCl_3$) ∂ 138.5, 128.3, 127.5, 127.4, 86.1, 77.5, 73.6, 72.7, 70.8, 50.8, 42.9, 41.6, 34.6, 34.2, 31.4, 29.7, 24.3, 23.8, 23.2, 22.7, 22.0.

***R* epimer**: ^{1}H NMR (200 MHz, $CDCl_3$) ∂ 7.34 (m, 5 H), 4.81 (s, 1 H), 4.51 (s, 2 H), 3.49 (t, J = 6.7 Hz, 2 H), 3.41 (dt, J = 4.3, 10.5 Hz, 1 H), 2.47 (br s, 1 H), and others; ^{13}C NMR (50.3 MHz, $CDCl_3$) ∂ 138.5, 128.3, 127.5, 127.4, 86.1, 77.5, 73.8, 72.7, 70.7, 50.8, 42.9, 41.6, 35.1, 34.6, 31.4, 29.7, 24.3, 23.5, 22.9, 22.7, 22.0.

(*S*)-(+)-2-Methyl-1,2-dihydroxy-4-(triisopropylsiloxy)butane (30). Carbinol **25** (0.492 g, 0.96 mmol) in CH_3CN (1 mL) and ether (2 mL) was added to 80% CH_3CN/H_2O (15 mL) which contained $AgNO_3$ (0.508 g, 3.0 mmol) and *N*-chlorosuccinimide (0.400 g, 3.0 mmol). A grey-white precipitate (AgCl) formed immediately, and the mixture was stirred for 10 min and quenched by addition of Na_2SO_3, and Na_2CO_3, and NaCl (1 mL each, all saturated solutions) at ca. 1 min intervals. The material was then filtered, the filter cake washed with CH_3CN (20 mL), the layers separated, aqueous extracted with ether (10 mL), the combined organics placed in a flask, and $NaBH_4$ (0.40 g, 13 mmol) added slowly with vigorous foaming and black precipitate (Ag) formation. The mixture was stirred for 1.5 h and acetone (5 mL) was added. After 1 h the material was filtered through Celite, ether (10 mL) added, the layers separated, and the organic solutions dried ($MgSO_4$), concentrated, and flash chromatographed (25% EtOAc/hexane) to give 200 mg (76%) of **30** as an oil: $[\alpha]^{20}_D$ +7.95° (*c* 4.001, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) ∂ 4.03 (A of ABXY, J_{AB} = 10.7 Hz, J_{AX} = 8.9 Hz, J_{AY} = 3.1 Hz, 1 H), 3.92 (B of ABXY, J_{AB} = 10.7 Hz, J_{BX} = 4.0 Hz, J_{BY} = 5.7 Hz, 1 H), 3.48 (A of AB, J_{AB} = 11.1 Hz, 1 H), 3.42 (B of AB, J_{AB} = 11.1 Hz, 1 H), 3.15 (br s, 2 H), 1.91 (X of ABXY, J_{AX} = 8.9 Hz, J_{BX} = 4.0, J_{XY} = 14.7 Hz, 1 H), 1.63 (Y of ABXY, J_{AY} = 3.1 Hz, J_{BY} = 5.7 Hz, J_{XY} = 14.7 Hz, 1 H), 1.22 (s, 3 H), 1.10 (m, 21 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) ∂ 72.6, 70.1, 60.5, 39.8, 24.3, 17.9, 11.7.

(*S*)-(−)-3-Hydroxy-3-methyl-5-(triisopropylsiloxy)pentanonitrile (31). TsCl (0.180 g, 0.94 mmol) in pyridine (2 mL) was added to the optically active diol **30** (0.200 g, 0.72 mmol) in pyridine (2 mL) at 0 °C under N_2. This solution was stirred for 0.5 h and then placed in a refrigerator overnight. Next the solution was poured into ice water (15 mL), the water extracted with ether (4x15 mL), and the combined ether layers washed with 0 °C 4 N HCl (2x20 mL), H_2O (10 mL), and saturated $NaHCO_3$ (10 mL), dried ($MgSO_4$), and concentrated to give 0.340 g (100% crude) of the desired tosylate. Next, the tosylate was dissolved in ether (1 mL) and 60% $EtOH/H_2O$ (7 mL) at 0 °C, KCN (0.260 g, 4 mmol) was added, and the solution was allowed to warm to room temperature. After being stirred for 10 h the solution was concentrated, brine was added (5 mL), the liquid was extracted with CH_2Cl_2 (4 × 20 mL) and ether (10 mL), and the combined organic extracts were dried ($MgSO_4$), concentrated, and flash chromatographed (15% EtOAc/hexanes) to give 0.126 g [74% based on reacted **30** (34 mg of **30** recovered)] of the hydroxynitrile **31** as an oil: $[\alpha]^{20}_D$ -2.86° (*c* 1.050, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) ∂ 4.51 (s, 1 H), 4.07 (m, 2 H), 2.60 (s, 1 H), 1.91 (m, 2 H), 1.43 (s, 3 H), 1.09 (m, 21 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) ∂ 85.9, 71.3, 60.8, 40.4, 31.0, 26.9, 17.9, 11.6; IR (neat) 3600–3200 (br m), 2940 (s), 2865 (s), 2250 (w), 1100 (m) cm^{-1}.

(*S*)-(+)-Mevalolactone. Nitrile **31** (92 mg, 0.32 mmol) was dissolved in 3 N NaOH (1.6 mL), 30% H_2O_2 (0.7 mL), and 95% ethanol (1 mL) and the resulting mixture stirred at 90 °C for 14 h, cooled to 0 °C, acidified with concentrated HCl (pH = 3), and let stir overnight. Next the solution was extracted with CH_2Cl_2 (3 × 20 mL) and ether (20 mL) and the combined organics dried ($MgSO_4$), concentrated, and purified by preparative TLC (100% EtOAc) to give 36 mg (87%) of (*S*)-(+)-Mevalolactone. The ^{1}H NMR of this compound was identical with that of a sample of racemate purchased from the US Biological Corp. A chiral shift experiment[12e] following the method of Wilson, Scallen, and Morrow[27] revealed the material to be the *S* isomer of mevalolactone and to be of 94% enantiomeric excess. This sequence established the configuration of the tertiary alcohol center of **24**, **25**, and **27**.

Oxathianylcarbinol 32. Oxathianyl carbinol **23** (46% de of the isomer produced in excess by the addition of CH_3MgBr to **8**) was tosylated as described above and treated with PhLi in THF (reflux for 30 min) to give **32** (44% de of the *S* epimer) of known configuration.[12g] (In order to exclude the possibility of kinetic resolution, the crude reaction material was checked by NMR after each step to ensure that either the reaction was complete or the unreacted starting material was of the same diastereomeric composition as before the reaction.) Comparison of the TLC (20% EtOAc/hexanes, the *S* epimer is more polar) and the ^{1}H NMR spectra [in particular, the C(2) proton of the *S* epimer resonates at 4.75 ppm while that of the *R* epimer resonates at 4.61 ppm] of the material produced here to that of the two pure epimers of **32**[12g] allowed assignment of the absolute configuration of the tertiary alcohol center of the epimers of **21**, **22**, and **23**.

Oxathianylcarbinol 33. Oxathianyl carbinol **17** (12% de of the isomer epimeric to the one produced in excess by the L-Selectride reduction of **8**) was tosylated as above and reduced with $LiAlH_4$ in refluxing THF to give **33** (10% de of the *R* epimer, overall yield 85%) of known configuration.[13] (The fact that no kinetic resolution of the two diastereomers occurred was evidenced byNMR analysis of the crude reaction products in each case to establish that the reaction was complete.) Comparison of the ^{1}H NMR spectra [in particular, the C(2) proton of the *S* epimer resonates at 4.91 ppm while that of the *R* epimer resonates at 4.68 ppm] of the material produced hereto that of the epimers of known configuration of **33**[13] allowed assignment of the absolute configuration at the secondary alcohol center of **15**, **16**, and **17**.

Oxathianylcarbinol 34. Oxathianylcarbinol **20** (65% de of the isomer produced in excess by the L-Selectride reduction of **10**) was tosylated and reduced as above to give **34** (65% de of the *S* epimer) of known configuration.[13] Precautions to avoid kinetic resolution (see above) were taken. Comparison of the ^{1}H NMR spectra [in particular, the C(2) proton of the *S* epimer resonates at 4.95 ppm while that of the *R* epimer resonates at 4.77 ppm] of the material produced here to that of the epimers of known configuration of **34**[13] allowed assignment of the absolute configuration at the secondary alcohol center of **18**, **19**, and **20**.

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