imerization on silica gel made complete separation impossible.

In another run in which the reaction proceeded for 2.5 h at −78 °C, the diastereomer ratio of the desired (*R*)- to (*S*)-ketone was determined as 49/51 as based upon their C(2) ^{1}H signals in the NMR spectrum of the crude product.

2-[(2′*R*)-2′-(Methylthio)butanoyl]hexahydro-4,4,7-trimethyl-4*H*-1,3-benzoxathiin ((*R*)-5). ^{1}H NMR: δ 0.90 (d, *J* = 6.5 Hz, 3 H), 0.94 (t, *J* = 7.5 Hz, 3 H), 1.26 (s, 3 H), 1.43 (s, 3 H), 1.86 (s, 3 H), 3.47 (dt, *J* = 4.3, 10.4 Hz, 1 H), 3.77 (t, *J* = 7.5 Hz, 1 H), 5.83 (s, 1 H), and others. ^{13}C NMR: δ 10.6 (CH_3), 11.4 (CH_3), 20.7 (CH_3), 22.0 (CH_3), 22.5 (CH_3), 24.3 (CH_2), 29.3 (CH_3), 31.3 (CH), 34.6 (CH_2), 41.5 (CH_2), 43.5 (C), 47.0 (CH), 50.4 (CH), 77.6 (CH), 80.8 (CH), 199.5 (C).

2-[(2′*S*)-2′-(Methylthio)butanoyl]hexahydro-4,4,7-trimethyl-4*H*-1,3-benzoxathiin ((*S*)-5). ^{1}H NMR: δ 0.90 (d, *J* = 6.2 Hz, 3 H), 0.93 (t, *J* = 7.5 Hz, 3 H), 1.27 (s, 3 H), 1.45 (s, 3 H), 1.89 (s, 3 H), 3.45 (dt, *J* = 4.3, 10.4 Hz, 1 H), 3.49 (t, *J* = 7.5 Hz, 1 H), 5.86 (s, 1 H), and others. ^{13}C NMR: δ 10.8 (CH_3), 11.6 (CH_3), 21.2 (CH_3), 22.0 (CH_3), 22.4 (CH_3), 24.4 (CH_2), 29.3 (CH_3), 31.4 (CH), 34.6 (CH_2), 41.4 (CH_2), 44.7 (C), 48.0 (CH), 50.2 (CH), 77.2 (CH), 80.1 (CH), 197.4 (C). Anal. Calcd for $C_{16}H_{29}O_2S_2$ (MH^+): 317.1609. Found: 317.1610.

Acknowledgment. We acknowledge support of this work by NSF grant CHE-8703060.

Supplementary Material Available: ^{1}H NMR spectra of **2a′**, **2b′**, **2c**, **2d**, **4a**, **4b**, **4c**, **4d**, (*R*)-**5**, (*S*)-**5**, methyl (triisopropylsiloxy)acetate, methyl (*R*)-2-(triisopropylsiloxy)propionate, and ethyl (*S*)-2-(triisopropylsiloxy)propionate (14 pages). This material is contained in many 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.

Addition of Organometallic Reagents to Acyloxathianes. Diastereoselectivity and Mechanistic Consideration

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Received October 22, 1991

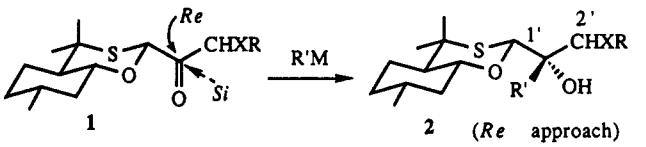
The addition of methyl- and phenylmagnesium bromide and phenyllithium to 2-(methoxyacetyl)-, 2-[(triisopropylsiloxy)acetyl]-, and 2-[(methylthio)acetyl]hexahydro-4,4,7-trimethyl-4*H*-1,3-benzoxathiin and the corresponding 2′-methyl, 2′-(triisopropylsiloxy)propionyl, and 2′-(methylthio)butyryl homologs has been studied. Depending on the 2′-substituent, the reagent and (in case of the higher homologs) the configuration at C(2′), these reactions may or may not be highly diastereoselective and may or may not yield the product of Cram's chelate rule involving the oxygen moiety of the oxathiane ring. Explanations for the different stereochemical outcome of the various reactions are suggested.

Introduction

In previous papers,[1] we have described the generally highly stereoselective addition of Grignard reagents to 2-acyloxathianes (Scheme I, X = H or alkyl). An essential determinant of the high stereoselectivity observed appears to be chelation, involving the magnesium atom of the Grignard reagent (hard acid),[2] the carbonyl oxygen of the ketone function, and the (hard) oxygen rather than the (soft) sulfur atom of the oxathiane ring. Thus, if competing chelation is introduced in the form of an alkoxy group in the side chain (R = H, X = OBn or CH_2OBn), not only is stereoselectivity severely reduced,[3] but the steric course is actually reversed.[4] The fact that the transfer of the alkyl moiety R′ of the Grignard reagent is intramolecular—as evidenced by second-order kinetics in the reaction of α-alkoxy ketones, R″COCHXR (X = OMe or OBn) with dimethylmagnesium[5]—may contribute to the face-selective addition of R′ once rotation about the C(2)–CO bond is frozen by chelation.

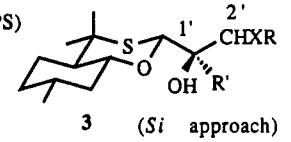
Chelation to an α- or β-alkoxy moiety in the ketone can be obviated by replacing the alkoxy by a triisopropylsiloxy (TIPSO) group[4,5] (smaller silyloxy groups are much less effective), presumably for steric reasons. Encouraged by these earlier studies,[6] we have undertaken a broader study of the addition of Grignard and alkyllithium reagents to 2-acyloxathianes functionalized with oxygen (methoxy, triisopropylsiloxy) and sulfur (methylthio) moieties at C(2′) and, in some instances, having a chiral center at C(2′).

Scheme I



R′ = Ph in **2**, **3**

a R = X = H
b R = H, X = OSi[CH(CH$_3$)$_2$]$_3$ (O-TIPS)
c R = H, X = OMe
d R = H, X = SMe
e R = Me, X = OMe (2′*S*)
f R = Me, X = OMe (2′*R*)
g R = Me, X = O-TIPS (2′*S*)
h R = Me, X = O-TIPS (2′*R*)
i R = Et, X = SMe (2′*S*)
j R = Et, X = SMe (2′*R*)
m R = Me, X = H



R′ = Me in **2**, **3**

k R = H, X = OMe
l R = H, X = SMe

Clearly, if high stereoselectivity can be achieved in these reactions, they will provide an approach to trifunctional chiral synthons of the type RCHXCR′(OH)CHO (X =

†From the Ph.D. dissertation of X. Bai, University of North Carolina, Chapel Hill, NC, 1990.

(1) (a) Lynch, J. E.; Eliel, E. L. *J. Am. Chem. Soc.* **1984**, *106*, 2943. (b) For a review see: Eliel, E. L. *Phosphorus Sulfur* **1985**, *24*, 73.
(2) For a recent reference, see: Ho, T.-L. *Chem. Rev.* **1975**, *75*, 1.
(3) Frye, S. V.; Eliel, E. L. *Tetrahedron Lett.* **1985**, *26*, 3907.
(4) Frye, S. V.; Eliel, E. L. *J. Am. Chem. Soc.* **1988**, *110*, 484.
(5) (a) Chen, X.; Hortelano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1990**, *112*, 6130. (b) Chen, X.; Hortelano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1992**, *114*, 1778. Dimethylmagnesium was used in the kinetic studies in preference to a Grignard reagent to avoid complications due to the Schlenk equilibrium.
(6) See also the review by: Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1531.

0022-3263/92/1957-5166$03.00/0

Table I. Additions of Organometallics to Acyloxathianes[a]

entry	1	X	R	C(2')	R'M	2:3[b]
1	a	H	H		PhMgBr	78:22
2	a	H	H		PhLi	50:50
3	b	OTIPS	H		PhMgBr	100:0
4[c]	c	OMe	H		PhMgBr	16:84
5[c]	c	OMe	H		PhLi	12:88
6[c]	c	OMe	H		MeMgBr	18:82[f]
7[c]	d	SMe	H		PhMgBr	80:20[d]
8	d	SMe	H		PhMgBr	87:13
9	d	SMe	H		PhLi	NR[e]
10[c]	d	SMe	H		PhLi	23:77
11	d	SMe	H		MeMgBr	60:40[f]
12	e	OMe	Me	*S*	PhMgBr	79:21
13	e	OMe	Me	*S*	PhLi	22:78
14	f	OMe	Me	*R*	PhMgBr	0:100
15	f	OMe	Me	*R*	PhLi	0:100
16	g	OTIPS	Me	*S*	PhMgBr	100:0
17	g	OTIPS	Me	*S*	PhLi	59:41
18	h	OTIPS	Me	*R*	PhMgBr	100:0
19	h	OTIPS	Me	*R*	PhLi	100:0
20	i	SMe	Et	*S*	PhMgBr	100:0
21	i	SMe	Et	*S*	PhLi	9:91
22	j	SMe	Et	*R*	PhMgBr	100:0[f]
23	j	SMe	Et	*R*	PhLi	53:47[f]

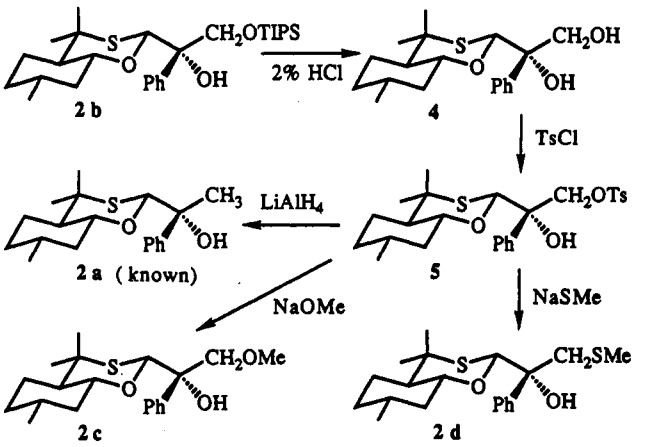
[a] At −78 °C unless otherwise indicated. [b] Determined on the basis of the integrated C(2) proton signals of the ^{1}H NMR spectrum of the crude product; a 100:0 or 0:100 ratio means the signals corresponding to the minor diastereomer were not seen in the ^{1}H NMR spectrum. [c] R'M was added to the ketone; in all other cases, ketone was added to R'M. [d] At 0 °C. [e] The desired product was not obtained, and the starting ketone was recovered. [f] Configuration of the major product was not proved.

OR'' or SR'') previously available only indirectly. As described in the accompanying paper,[7] the precursor ketones (1, X = OR'', SR'', NMe_2) are readily available by reaction of the lithium derivatives of hexahydro-4,4,7-trimethyl-4*H*-1,3-benzoxathiin[8] with appropriately functionalized esters.

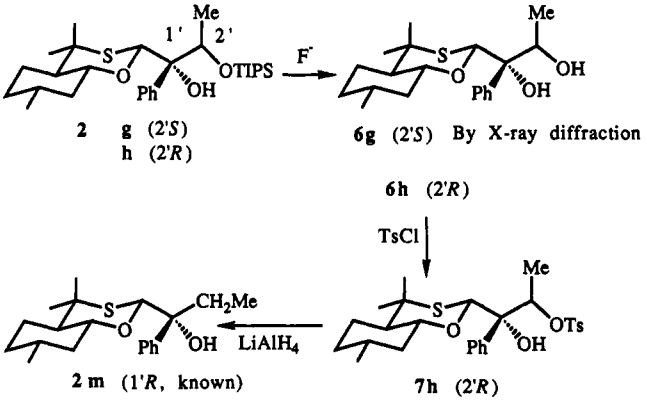
Results

Configurations. The stereochemical outcome of the addition of phenylmagnesium bromide and phenyllithium to 2-acyloxathianes 1 without and with α-heterosubstituents is shown in Table I.[9] Entry 1, which provides a "base line", shows that the reaction of the parent acetyloxathiane **1a** with a Grignard reagent is less stereoselective than corresponding reactions of higher acyloxathianes,[1] a fact already known from earlier work.[10] Likewise, entry 2 confirmed earlier observations[11] that the reaction of **1a** with alkyllithium reagents is much less stereoselective than corresponding reactions with alkylmagnesiums. This may result from less effective chelation of Li^+ as compared to Mg^{2+}; additional factors may be greater competition of chelation with sulfur (vide infra) and lesser face selectivity (once the chelate is formed) in the alkyl transfer from R'Li, which may not be intramolecular. Compound **2a** (from *Re*-face approach) is the major product of the Grignard addition (entry 1). The configuration of the accompanying minor isomer **3a** (from *Si*-face approach) rests on its being identical with the major product of addition of CH_3MgI to the corresponding 2-benzoyloxathiane (1, C_6H_5 in place

Scheme II



Scheme III



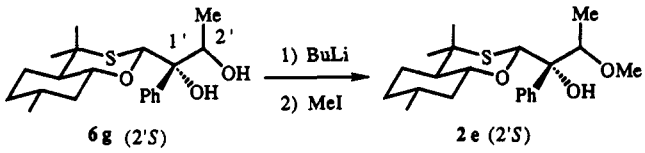
of RCHX), previously shown to be 1'*S* by cleavage to (*S*)-atrolactic acid.[1] Thus, the major product **2a** is the one corresponding to Cram's chelate rule.[1,12,13] Not surprisingly,[4] this is also true a fortiori (entry 3) for the ketone where X = TIPSO (**1b**). The configuration of the product **2b** as 1'*S* was proved by cleaving the TIPS group with acid, converting the resulting diol to the primary monotosylate, and reducing the latter to **2a** as shown in Scheme II.

Addition of either PhMgBr (entry 4) or PhLi (entry 5) to the (methoxyacetyl)oxathiane **1c** gave, as the major product, **3c** formed contrary to Cram's chelate rule (assuming chelation with ring oxygen). The configuration of the minor product **2c** was correlated with that of the TIPS compound as shown in Scheme II. MeMgBr (entry 6) yielded two products in a ratio essentially identical to that in the PhMgBr addition; the configuration of the major product as 1'*R* (**3k**) was assigned by analogy.

The results of addition of PhMgBr or PhLi to the (methylthio)acetyl compound **1d** are shown in Table I, entries 7–10. Addition of the phenyl Grignard reagent (entries 7 and 8) yields mainly the Cram chelate product **2d** whose configuration (1'*S*) was proved by correlation with the corresponding products with R' = H, X = H or TIPSO as shown in Scheme II. In the case of the corresponding addition of PhLi, it was important to add PhLi to **1d**, and not vice versa, to avoid abstraction of the fairly acidic α-hydrogen taking the place of nucleophilic addition. The product (entry 10) was mainly stereoisomer **3d**, different from that predominating in Grignard addition. Entry 11 shows rather low stereoselectivity in the addition

(7) Bai, X.; Eliel, E. L. *J. Org. Chem.*, preceeding paper in this issue.
(8) Eliel, E. L.; Lynch, J. E.; Kume, F.; Frye, S. V. *Org. Synth.* **1987**, *65*, 215.
(9) Unfortunately, simple addition products could not be isolated in the reaction of 1 (X = NMe_2) with Grignard reagents. For other work on the addition of Grignard reagents to amino ketones, see ref 6.
(10) Eliel, E. L.; Alvarez, M. T.; Lynch, J. E. *Nouv. J. Chim.* **1986**, *10*, 749.
(11) Eliel, E. L.; Morris-Natschke, S. *J. Am. Chem. Soc.* **1984**, *106*, 2937.
(12) Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 2748.
(13) Eliel, E. L. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 2, p 125.

Scheme IV



of MeMgBr to **1d**; the configuration of the major addition product in this case is uncertain, but by analogy with other cases is probably **21**.

In Table I, entries 12–19 are the results of addition of PhMgBr and PhLi to 2-lactoyloxathianes, both methyl (**1e,f**) and TIPS (**1g,h**) protected, with the configuration of the lactoyl group being either *S* or *R*. The configuration at C(2′) follows from that of the lactate precursor. To determine the configuration at C(1′) of the 2′*R* TIPS compound **2h**, the product of addition of PhMgBr and PhLi (entries 18 and 19) was converted to (1′*R*)-**2m** (R = CH_3, X = H) by the sequence of reactions shown in Scheme III. Authentic (1′*R*)-**2m** was obtained by addition of PhMgBr to the 2-propionyloxathiane 1 (R = CH_3, X = H); it is different (see Experimental Section) from the known[1a] (1′*S*)-**2m**. It follows that addition of PhMgBr to **1h** (entry 18) proceeds by the normal *Re* approach (front-side approach in Scheme III) to give the 1′*S* product **2h**. (That **2h** is 1′*S*, whereas **2m**, with which it was correlated, is 1′*R*, is a fortuitous consequence of the Cahn–Ingold–Prelog nomenclature system.) PhLi addition to **1h** (entry 19) takes the same stereochemical course. Addition of PhMgBr to the *S* stereoisomer at C(2′), **1g** (entry 16), also gives the 1′*S* isomer **2g**. In this case, the configuration was established by cleavage to **6g** (Scheme III) followed by X-ray diffraction analysis of the latter; see Figure 1 of the supplementary material. The same major isomer was obtained in PhLi addition to **1g** (entry 17), but with very low stereoselectivity. The configuration of the major product of PhMgBr addition to the methyl ether **1e**, entry 12, was established to be **2e**, *S* at C(1′) as shown in Scheme IV; by default the major product of the corresponding PhLi addition (entry 13) is **3e**, *R* at C(1′). The configuration of the sole reaction product of **1f** with PhLi (entry 15) was established to be **3f** (2′*R*,1′*R*) by X-ray diffraction analysis (Figure 2 of supplementary material); addition of PhMgBr to **1f** (entry 14) gives the same product exclusively.

The results of addition of PhMgBr and PhLi to the two diastereomeric (2′*R* and 2′*S*) [2′-(methylthio)butanoyl]-oxathianes (**1i, 1j**)[7] are shown in Table I, entries 20–23. In the case of the 2′*S* isomer **1i**, the two organometallics give products of opposite configuration at C(1′). The major product of PhLi addition to the 2′*S* compound **1i** (entry 21) was shown, by X-ray diffraction analysis (cf. Figure 3 of supplementary material), to be **3i**, i.e., to have the 1′*R*,2′*S* configuration; since a diastereomeric product was obtained in the addition of PhMgBr to the same substrate (entry 20), this compound must be the 1′*S*,2′*S* isomer. By analogy, and based on mechanistic considerations (see below), the product of addition of PhMgBr to the 2′*R* diastereomer **1j** (entry 22) was assumed to be **2j** (R = C_2H_5, X = SCH_3) also, i.e., to have the 1′*S*,2′*R* configuration. The addition of PhLi to the same substrate (entry 23) is essentially stereorandom.

Discussion

Addition of PhMgBr. Previous work[1,4,5] had shown that in the absence of competing chelation Grignard reagents (Lewis acids) add to 2-acyloxathianes according to Cram's chelate rule,[12,13] with the oxygen rather than the sulfur of the oxathiane ring acting as the chelating moiety,

Chart I

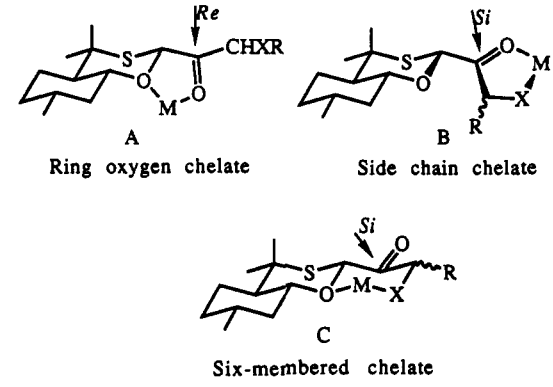
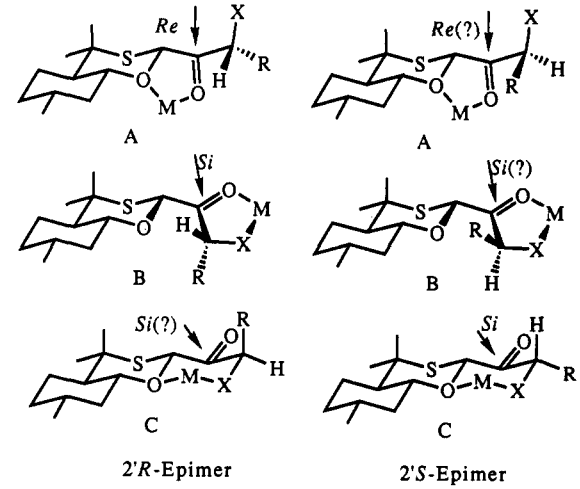


Chart II



to give the product of *Re* addition **2** as the principal adduct (A, Chart I). This generalization serves to explain the results in entries 1, 3, 7, 8, and (probably) 11 (a case of low stereoselectivity), as well as 16, 18, 20, and (assuming correct configurational assignment) 22 in Table I. Competing chelation, e.g., with an alkoxy moiety in the side-chain, B (Chart I), is known to interfere with this outcome:[4] predominant approach of the nucleophile is now from the *Si* face, perhaps because of the tendency of the ring C—O and C=O dipoles to be antiparallel (Cornforth rule[14]). Approach according to B leads to product **3** and explains the results of entries 4, 14, and probably 6 in Table I. However, the result of entry 12 contravenes this explanation. Chart II suggests a possible reason: chelate B in the case of the 2′*S* epimer **1e** (R = Me, X = OMe, right) rigidly places the 2′-methyl substituent over the normally approached *Si* face of the ketone inhibiting approach of the nucleophile to that face. As a result, either approach to the normally less open *Re* face occurs or else reaction proceeds via the otherwise less favored chelate A in which facile rotation about the OC–C(2′) bond allows the nucleophile to approach from the *Re* face. In contrast, in the 2′*R* diastereomer (Chart II, left) both chelate A and chelate B are open to nucleophile approach and B wins out, as it does with the lower homolog (entries 4 and 6). As one might perhaps have expected, approach to the unhindered *Si* face in the 2′*R* epimer leads to high stereoselectivity (entry 14) whereas potential competition between two or more faces or transition states in the 2′*S* epimer (entry 12) depresses the diastereomer preference.

(14) Cornforth, J. W.; Cornforth, R. H.; Mathew, K. K. *J. Chem. Soc.* 1959, 112.

Addition of PhLi. Organomagnesium compounds, being hard acids, coordinate poorly with the soft sulfur atom as evidenced, for example, by the fact that it is the oxygen rather than the sulfur atom in 1 that coordinates with Grignard reagents (A, Chart I). In contrast, the softer lithium atom of organolithium reagents does coordinate effectively to sulfur,[15,16] as documented, inter alia, by the dimeric nature of 2-lithio-2-methyl-1,3-dithiane in the solid state.[15] It is therefore not surprising that the stereochemistry of PhLi is frequently opposite to that of PhMgBr addition when the latter involves *Re* approach (Scheme I) (e.g., entry 10 vs 7/8, 13 vs 12, and 21 vs 20) and that stereoselectivity in addition of PhLi is often quite low (entries 2, 17, and 23), possibly because of competing chelation with the oxygen and sulfur atom of the oxathiane ring. However, this cannot be the whole explanation, in as much as heteroatoms at C(2′) in the side chain generally bias the stereochemical outcome of PhLi addition toward product **3** (*Si* approach); compare entry 2 to 5, 10, 13, 15, and 21. (Entry 19 is exceptional in that only **2**, the product of *Re* approach, is observed.)

The simplest explanation is to assume that chelate B (Chart I) is favored not only with Grignard reagents when X = O (but not when X = S) but also with alkyllithium reagents if X = O or S. Approach of the nucleophile to the (less hindered) *Si* face of the carbonyl moiety in B will then give predominantly product **3** in addition of PhLi (cf. entries 15 and 21). However, the above explanation is not satisfactory in accounting for some of the results in Table I. Thus (entries 12 and 13), if the methyl group in chelate B (R = Me, X = OMe, Chart II) in the 2′*S* isomer prevents *Si* attack of PhMgBr (entry 12, vide supra), why does it not do the same for PhLi (entry 13)?

An alternative postulate of a lithium chelate intermediate is C (Chart I) with a six-membered chelate ring[17] involving the single-bonded oxygen or sulfur atom at C(2′). Equatorial (*Si*) approach to this chelate will normally give **3**, as observed in entries 5, 10, 13, 15, and 21. This explanation, in modified form, may also explain the low stereoselectivity in entry 23 (addition of PhLi to **1j**). Contemplation of transition state C (R = Et, X = SMe, Chart II) for this 2′*R* isomer shows possible hindrance to *Si* approach by the adjacent axial ethyl group. This may depress stereoselectivity in model C or it may mean that **1j** reverts to transition state A which is inherently unselective for PhLi addition (cf. entry 2).

Since OTIPS does not chelate, **1g** and **1h** (entry 17 and 19) must react through transition state A (Charts I and II). The question then is why is **1h** (2′*R*) (entry 19) so unusually stereoselective for *Re* approach while **1g** (2′*S*) (entry 17) is not. Referral to model A (R = Me, X = OTIPS) in Chart II may provide the answer. If one assumes the O=C—C—OTIPS moiety to be antiparallel, in the 2′*R* isomer, the *Si* face in A (upper left) is blocked, whether chelation is to oxygen or to sulfur, by the 2′-methyl substituent in **1h**. This causes a favorable situation for oxygen chelation, which anyway favors *Re* approach, and an unfavorable situation for sulfur chelation (which normally produces *Si* approach).[18] The opposite situation would seem to apply to the 2′*S* isomer **1g** which corresponds to model A, upper right, in Chart II; PhLi addition to this stereoisomer is unselective. (One might, perhaps, have expected more *Si* approach in this case.)

Conclusion

In summary, the addition of phenyl Grignard reagents to 2-acyl-1,3-oxathianes functionalized at C(2′) with ether or thioether moieties is generally quite stereoselective (Table I, entries 3, 4, 7, 8, 14, 16, 18, 20, 22), and the stereochemical outcome can usually be predicted. In the addition of phenyllithium, stereoselectivity is often less (entries 10, 13, 17, 23) and the stereochemical course of the reaction is less easy to predict or even to rationalize, perhaps in part because of the oligomeric nature of the organolithium reagents and their lesser tendency to form chelates, in addition to the possibility of multiple transition states. However, in some cases even addition of PhLi is quite stereoselective (entries 5, 15, 19, 21). In several cases, addition can be directed to either the *Re* or *Si* face, depending on reagent and protective group (cf. entries 3 vs 4 or 5, 12 or 16 vs 13, 14 or 15 vs 18 or 19, and 20 vs 21). These findings expand the scope of the previously described[1] highly stereoselective syntheses based on hexahydro-4,4,7-trimethyl-4*H*-1,3-benzoxathiin.

Experimental Section

^{1}H NMR spectra were recorded at 200.1 MHz, ^{13}C NMR spectra at 50.3 MHz, and both in $CDCl_3$ solvent. CH_3, CH_2, CH, and C carbon signals were distinguished by the DEPT technique.[19] All reactions were performed in THF solution at −78 °C unless stated otherwise. The diastereomer ratio of the products was calculated based on integration of the C(2) proton signals of the oxathiane ring unless mentioned otherwise. The concentration of the organometallic reagents was taken as indicated by the supplier.

2-(1′-Hydroxy-2′-methoxy-1′-phenylethyl)hexahydro-4,4,7-trimethyl-4*H*-1,3-benzoxathiins (2c, 1′*S*) and (3c, 1′*R*). (i) To 54 mg (0.20 mmol) of 2-(methoxyacetyl)oxathiane **1c** in 5 mL of dry THF under N_2 at −78 °C was added, dropwise, 0.13 mL (0.4 mmol) of 3.0 M PhMgBr in Et_2O. After being stirred for 4 h at −78 °C, the mixture was quenched with 5 mL of saturated aqueous NH_4Cl and extracted with 10 mL of Et_2O. The organic layer was washed with 5 mL of brine, dried (Na_2SO_4), and concentrated to give 76 mg of a crude mixture of diastereomers **3c** and **2c** in an 86:14 ratio. Purification by flash column chromatography on silica gel with 8% EtOAc in hexanes gave 38 mg (54%) of solid product **3c** and 6 mg of impure isomer **2c**. An analytical sample of **3c** was prepared by recrystallization from pentane, mp 91.5–92.0 °C.

(ii) By the procedure described above, 70 mg of a crude mixture of **3c** and **2c** in an 88:12 ratio was obtained from reaction of 54 mg (0.20 mmol) of **1c** in 5 mL of THF and 0.20 mL (0.4 mmol) of 2.0 M PhLi in cyclohexane/Et_2O (70/30).

(iii) A solution of 18 mg of 2-[(1′*S*)-1′-hydroxy-1′-phenyl-2′-(tosyloxy)ethyl]oxathiane **5** (see below) in 0.5 mL of THF was added to a solution of excess NaOMe in 1 mL of MeOH at rt and stirred overnight. The solvent was evaporated, and the residue was dissolved in 10 mL of Et_2O, washed with 3 mL of water, followed by 3 mL of brine, dried ($MgSO_4$), and concentrated to give 11 mg of the desired product **2c**. The (1′*R*)-epimer **3c** ws not observed.

Major isomer **3c**. ^{1}H NMR: δ 0.91 (d, *J* = 6.4 Hz, 3 H), 1.19 (s, 3 H), 1.33 (s, 3 H), 3.14 (bs, 1 H), 3.29 (s, 3 H), 3.43 (dt, *J* = 4.2, 10.4 Hz, 1 H), 3.66, 3.88 (AB, *J* = 9.3 Hz, 2 H), 5.28 (s, 1 H), 7.21–7.37 (m, 3 H), 7.51–7.56 (m, 2 H), and others. ^{13}C NMR: δ 22.0 (CH_3), 22.6 (CH_3), 24.3 (CH_2), 29.5 (CH_3), 31.4 (CH), 34.6 (CH_2), 41.6 (CH_2), 43.0 (C), 50.5 (CH), 59.6 (CH_3), 76.5 (C), 76.7 (CH_2), 77.5 (CH), 83.1 (CH), 125.9 (CH), 127.3 (CH), 127.7 (CH), 141.3 (C). Anal. Calcd for $C_{20}H_{30}O_3S$: C, 68.55; H, 8.63. Found: C, 68.57; H, 8.62.

Minor isomer **2c**. ^{1}H NMR: δ 0.90 (d, *J* = 6.4 Hz, 3 H), 1.18 (s, 3 H), 1.37 (s, 3 H), 3.36 (s, 3 H), 3.39 (dt, *J* = 4.2, 10.4 Hz, 1

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H), 3.65, 3.85 (AB, J = 9.6 Hz, 2 H), 5.23 (s, 1 H), 7.24–7.40 (m, 3 H), 7.53–7.59 (m, 2 H), and others. ^{13}C NMR: δ 22.1, 23.0, 24.4, 29.6, 31.4, 34.7, 41.7, 43.1, 50.8, 59.6, 76.1, 77.0, 77.8, 83.9, 126.4, 127.4, 127.6, 140.9. The sample contained a small amount of starting ketone **1c**.

2-(1′-Hydroxy-2′-methoxy-1′-methylethyl)hexahydro-4,4,7-trimethyl-4*H*-1,3-benzoxathiins (2k, 1′*S*) and (3k, 1′*R*). By the procedure described above, reaction of 54 mg (0.20 mmol) of **1c** in 5 mL of THF and 0.4 mL of MeMgBr (1.5 M in THF/toluene (75/25) yielded 61 mg of a crude mixture of diastereomers **3k** and **2k** in an 82:18 ratio. Purification by flash chromatography on silica gel with EtOAc/hexanes (15/85) gave 48 mg (83%) of chemically pure liquid products in a diastereomeric ratio of 83:17. FAB$^+$ MS for $C_{15}H_{28}O_3S$ (M^+) found: m/e 288.1763. Calcd: m/e 288.1760.

Major isomer **3k**. ^{1}H NMR: δ 0.88 (d, J = 6.5 Hz, 3 H), 1.18 (s, 3 H), 1.24 (s, 3 H), 1.38 (s, 3 H), 2.69 (s, 1 H), 3.23–3.49 (m, 6 H), 4.98 (s, 1 H), and others. ^{13}C NMR: δ 20.9, 22.1, 22.7, 24.3, 29.7, 31.4, 34.6, 41.6, 43.0, 50.8, 59.5, 73.9, 76.6, 77.5, 82.4.

Minor isomer **2k**. ^{1}H NMR: δ 2.58 (bs, 1 H), 3.35 (s, 3 H), 4.95 (s, 1 H), and others (identified as a minor set in the above spectrum).

2-[1′-Hydroxy-2′-(methylthio)-1′-phenylethyl]hexahydro-4,4,7-trimethyl-4*H*-1,3-benzoxathiins (2d, 1′*S*) and (3d, 1′*R*). (i) By the procedure described above, reaction of 58 mg (0.20 mmol) of 2-[(methylthio)acetyl]oxathiane **1d** in 5 mL of THF and 0.13 mL (0.39 mmol) of PhMgBr (3.0 M in Et_2O) yielded 68 mg of a crude mixture of diastereomers **2d** and **3d** in an 80:20 ratio. Purification by flash chromatography on silica gel with EtOAc/hexanes (5/95) gave 43 mg of constitutionally pure liquid products in a diastereomer ratio of 83:17. FAB$^+$ MS for $C_{20}H_{30}O_2S_2$ (M^+) found: m/e 366.1685. Calcd: m/e 366.1689.

(ii) A crude mixture of diastereomers **2d** and **3d** in an 87:13 ratio was obtained by adding **1d** in 5 mL of THF to PhMgBr at −78 °C.

(iii) Addition of 0.3 mL (0.6 mmol) of PhLi (2.0 M) to a solution of 58 mg (0.20 mmol) of **1d** in 5 mL of THF at −78 °C yielded 90 mg of a crude mixture of diastereomers **3d** and **2d** in a 77:23 ratio. Purification by flash chromatography on silica gel with EtOAc/hexanes gave 34 mg of a chemically pure liquid product mixture **3d** and **2d** in a 75:25 ratio.

(iv) When PhLi was added to **1d**, no desired product was obtained; the starting material **1d** was recovered.

(v) A solution of 18 mg of tosylate **5** in 0.5 mL of THF was added to a solution of excess NaSMe in 1 mL of MeOH at rt. After the solution was stirred overnight, the solvent was evaporated and the residue was dissolved in 10 mL of Et_2O, washed with 3 mL of water, followed by 3 mL of brine, dried ($MgSO_4$), and concentrated to give 11 mg of **2d** as a liquid. The NMR spectra of this material were identical to those of **2d** obtained as described above.

2d. ^{1}H NMR: δ 0.89 (d, J = 6.4 Hz, 3 H), 1.19 (s, 3 H), 1.36 (s, 3 H), 1.94 (s, 3 H), 3.14, 3.18 (AB, J = 13.8 Hz, 2 H), 3.40 (dt, J = 4.3, 10.4 Hz, 1 H), 5.22 (s, 1 H), 7.20–7.37 (m, 3 H), 7.45–7.58 (m, 2 H), and others. ^{13}C NMR: δ 17.5, 22.0, 22.6, 24.3, 29.6, 31.4, 34.6, 41.6, 43.2, 44.1, 50.7, 77.3, 77.8, 85.3, 126.4, 127.4, 127.7, 142.0.

3d. ^{1}H NMR: δ 0.91 (d, J = 6.4 Hz, 3 H), 1.19 (s, 3 H), 1.34 (s, 3 H), 1.80 (s, 3 H), 3.21 (s, 2 H), 3.43 (dt, J = 4.3, 10.4 Hz, 1 H), 5.26 (s, 1 H), 7.21–7.37 (m, 3 H), 7.45–7.56 (m, 2 H), and others. ^{13}C NMR: δ 17.4, 22.0, 22.7, 24.3, 29.5, 31.4, 34.6, 41.6, 43.2, 44.6, 50.5, 77.5, 77.8, 84.8, 126.0, 127.5, 127.9, 141.9.

A general procedure was adopted for the following reactions: Addition of the carbonyl compound **2** in THF to the organometallic reagent in THF solution at −78 °C, stirring for 4 h, followed by the usual workup described above.

2-[1′-Hydroxy-2′-(methylthio)-1′-methylethyl]hexahydro-4,4,7-trimethyl-4*H*-1,3-benzoxanthiins (2l, 1′*S*) and (3l, 1′*R*). By the procedure described above, reaction of 58 mg (0.20 mmol) of **1d** in 1 mL of THF and 0.4 mL of MeMgBr (1.5 M in THF) in 4 mL of THF yielded 64 mg of a crude mixture of diastereomers **3l** and **2l** in a 60:40 ratio which also contained 11% of recovered **1d** identified by proton NMR. Purification by flash chromatography on silica gel with EtOAc/hexanes (8/92) gave 41 mg (67%) of chemically pure liquid products in a diastereomeric ratio of 59:41. FAB$^+$ MS for $C_{15}H_{28}O_2S_2$ (M^+) found: m/e 304.1537; calcd m/e 304.1532.

Major isomer **3l**. ^{1}H NMR: δ 0.89 (d, J = 6.4 Hz, 3 H), 1.25 (s, 3 H), 1.28 (s, 3 H), 1.39 (s, 3 H), 2.14 (s, 3 H), 2.63, 2.91 (AB, J = 13.7 Hz, 2 H), 3.37 (dt, J = 4.3, 10.3 Hz, 1 H), 4.93 (s, 1 H), and others.

Minor isomer **2l**. ^{1}H NMR: δ 3.42 (dt, J = 4.3, 10.0 Hz, 1 H), 5.05 (s, 1 H), and others (identified as a minor set in the above spectrum).

2-[(1′*S*)-1′-Hydroxy-1′-phenyl-2′-(triisopropylsiloxy)-ethyl]hexahydro-4,4,7-trimethyl-4*H*-1,3-benzoxathiin (2b). Reaction of 349 mg (0.84 mmol of oxathiane **1b** in 2 mL of THF and 0.84 mL of PhMgBr (3.0 M in Et_2O) in 14 mL of THF yielded 485 mg of crude product which was purified by flash chromatography on silica gel with EtOAc/hexanes (10/90) to give 240 mg of pure liquid **2b** (100% de).

^{1}H NMR: δ 0.90 (d, J = 6.4 Hz, 3 H), 1.02–1.06 (TIPS), 1.17 (s, 3 H), 1.40 (s, 3 H), 3.28 (bs, 1 H), 3.38 (dt, J = 4.0, 10.0 Hz, 1 H), 3.62 (d, J = 9.3 Hz, 1 H), 4.26 (d, J = 9.3 Hz, 1 H), 5.39 (s, 1 H), 7.24–7.46 (m, 3 H), 7.56–7.61 (m, 2 H), and others. ^{13}C NMR: δ 12.1 (CH), 18.0 (CH_3), 22.3 (CH_3), 22.6 (CH_3), 24.5 (CH_2), 29.8 (CH_3), 31.6 (CH), 34.8 (CH_2), 41.9 (CH_2), 42.7 (C), 50.9 (CH), 67.6 (CH_2), 77.2 (C), 77.8 (CH), 83.0 (CH), 126.5 (CH), 127.3 (CH), 127.5 (CH), 140.8 (C).

2-(1′-Hydroxy-1′-phenylethyl)hexahydro-4,4,7-trimethyl-4*H*-1,3-benzoxathiins (2a, 1′*R*) and (3a, 1′*S*). (i) Reaction of 48 mg of acetyloxathiane **1a** in 1 mL of THF and 0.2 mL of PhMgBr (3.0 M) in 4 mL of THF yielded 64 mg of a crude mixture of diastereomers **2a** and **3a** in a ratio of 78:22. The proton NMR of this material agreed with that reported.[20]

(ii) Reaction of 74 mg of **1a** in 2 mL of THF and 0.5 mL of PhLi (1.8 M in Et_2O) in 10 mL of THF yielded 117 mg of a crude mixture of **2a** and **3a** in a ratio of 50:50.

(iii) To a dispersion of 100 mg of $LiAlH_4$ in 5 mL of THF was added, dropwise, 69 mg of compound **5** in 5 mL of THF. After being stirred for 12 h at ambient temperature, the mixture was hydrolyzed with 1 mL of 1 N NaOH and 10 mL of water and then extracted twice with Et_2O. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated to give 32 mg of clean liquid product **2a**. The NMR spectra of this material were identical to those of **2a**, the major product described above.

2a. ^{1}H NMR: δ 0.88 (d, J = 6.5 Hz, 3 H), 1.22 (s, 3 H), 1.32 (s, 3 H), 1.59 (s, 3 H), 3.16 (bs, 1 H), 3.38 (dt, J = 4.3, 10.4 Hz, 1 H), 5.01 (s, 1 H), 7.20–7.36 (m, 3 H), 7.44–7.50 (m, 2 H), and others. ^{13}C NMR: δ 22.0 (CH_3), 22.7 (CH_3), 24.3 (CH_2), 24.5 (CH_3), 29.6 (CH_3), 31.4 (CH), 34.6 (CH_2), 41.5 (CH_2), 43.2 (C), 50.7 (CH), 75.7 (C), 77.6 (CH), 86.2 (CH), 125.7 (CH), 127.1 (CH), 127.6 (CH), 144.8 (C).

3a. ^{1}H NMR: δ 0.93 (d, J = 6.4 Hz), 1.19 (s), 1.63 (s), 5.09 (s) and others, identified in the ^{1}H NMR spectrum of the crude mixture of **2a** and **3a**.

2-[(1′*S*)-1′,2′-Dihydroxy-1′-phenylethyl]hexahydro-4,4,7-trimethyl-4*H*-1,3-benzoxathiin (4). A mixture of 240 mg (0.49 mmol) of **2b** in 6 mL of 2% HCl (in 95% EtOH) was stirred for 24 h. The mixture was neutralized with 5 mL of saturated aqueous Na_2CO_3 and 10 mL of water and extracted three times with Et_2O (10 mL each). The etheral extracts were washed with 10 mL of brine, dried ($MgSO_4$), and concentrated to yield 226 mg of crude product which was purified by flash chromatography on silica gel with EtOAc/hexanes to give 94 mg of **4**, pure according to NMR spectra.

^{1}H NMR: δ 0.90 (d, J = 6.5 Hz, 3 H), 1.20 (s, 3 H), 1.31 (s, 3 H), 3.41 (dt, J = 4.1, 10.5 Hz, 1 H), 3.56 (bs, 1 H), 3.79 (d, J = 11.5 Hz, 1 H), 4.26 (d, J = 11.5 Hz, 1 H), 5.16 (s, 1 H), 7.25–7.37 (m, 3 H), 7.48–7.55 (m, 2 H), and others. ^{13}C NMR: δ 22.0 (CH_3), 22.4 (CH_3), 24.3 (CH_2), 29.5 (CH_3), 31.3 (CH), 34.5 (CH_2), 41.6 (CH_2), 43.4 (C), 50.8 (CH), 66.7 (CH_2), 76.8 (C), 77.9 (CH), 85.2 (CH), 126.1 (CH), 127.7 (CH), 127.9 (CH), 140.2 (C).

2-[(1′*S*)-1′-Hydroxy-1′-phenyl-2′-(tosyloxy)ethyl]hexahydro-4,4,7-trimethyl-4*H*-1,3-benzoxathiin (5). To a solution of 94 mg (0.28 mmol) of **4** in 0.5 mL of dry pyridine was added dropwise 80 mg (0.42 mmol) of *p*-toluenesulfonyl chloride in 0.5 mL of pyridine. The mixture was stirred for 30 min at 0 °C and then stored in a refrigerator (4 °C) for 24 h. Ice–water (5 mL) was added with brief stirring, and then the reaction mixture was

(20) Lynch, J. E. Ph.D. Thesis; University of North Carolina at Chapel Hill, 1982; p 59.

extracted twice with Et_2O. The extracts were washed four times with 2 N HCl (5 mL each) and brine, dried ($MgSO_4$), and concentrated to yield 85 mg of crude product. It was purified by flash chromatography on silica gel with EtOAc/hexanes (20/80) to give 69 mg of **5**, pure according to NMR spectra.

^1H NMR: δ 0.90 (d, J = 6.4 Hz, 3 H), 1.15 (s, 3 H), 1.33 (s, 3 H), 2.41 (s, 3 H), 2.93 (bs, 1 H), 3.35 (dt, J = 4.3, 10.4 Hz, 1 H), 4.20, 4.52 (AB, J = 9.9 Hz, 2 H), 5.19 (s, 1 H), 7.25–7.30 (m, 5 H), 7.44–7.49 (m, 2 H), 7.70 (d, J = 8.2, 2 H), and others. ^{13}C NMR: δ 21.6, 22.0, 22.4, 24.2, 29.5, 31.3, 34.6, 41.4, 43.4, 50.7, 72.5, 76.3, 77.9, 83.2, 126.4, 127.8, 127.9, 129.7, 132.8, 138.4, 144.7.

2-(1′-Hydroxy-2′-methoxy-1′-phenylpropyl)hexahydro-4,4,7-trimethyl-4*H*-1,3-benzoxathiins. (i) Reaction of a diastereomeric mixture of 2-[(2′*S*)-2′-methoxypropanoyl]oxathiane **1e** and 2-((2′*R*)-2′-methoxypropanoyl)oxathiane **1f** (56/44) in 0.5 mL of THF and 0.45 mL of PhMgBr (1.0 M in THF) in 1.5 mL of THF yielded a crude mixture of three diastereomers **2e**, **3e**, **3f** in a ratio of 47:11:42 as analyzed by ^1H NMR spectroscopy. Chromatographic purification on silica gel with EtOAc/hexanes (5/95) provided pure samples of **2e** (oil, 14 mg) and **3f** (colorless crystals, mp 143.5–145.5 °C, 12 mg).

(ii) Reaction of 29 mg of a diastereomeric mixture of **1e** and **1f** (90/10) in 0.5 mL of THF and 0.2 mL of THF and 0.2 mL of PhLi (2.0 M in Et_2O) in 1.5 mL of THF yielded 44 mg of a diastereomeric mixture of **2e**, **3e**, and **3f** in a ratio of 20:70:10. Chromatographic purification on silica gel with EtOAc/hexanes (5/95) provided a slightly impure sample of **3e** (oil, 11 mg).

(iii) Similar reaction of 86 mg of **1f** (100% de) and 0.5 mL of PhLi (1.8 M) yielded 124 mg of crude product **3f** free of **2e** and **3e**.

(iv) To a solution of 22 mg of **6g** in 1 mL of THF was added 0.06 mL of butyllithium (1.2 M in hexanes) followed by 0.05 mL of iodomethane. The mixture was stirred for 15.5 h at room temperature. The precipitate was filtered, and the solvent was evaporated to give 23 mg of the crude product containing **6g** and **2e** in an 85:15 ratio determined by ^1H NMR. The epimers of **2e** were not observed.

2-[(1′*R*,2′*S*)-1′-Hydroxy-2′-methoxy-1′-phenylpropyl]hexahydro-4,4,7-trimethyl-4*H*-1,3-benzoxathiin (**3e**). ^1H NMR: δ 0.89 (d, J = 6.8 Hz, 3 H), 1.01 (d, J = 6.4 Hz, 3 H), 1.18 (s, 3 H), 1.38 (s, 3 H), 3.40 (s, 3 H), 3.44 (dt, J = 4.4, 10.4 Hz, 1 H), 3.45 (s, 1 H), 3.80 (q, J = 6.4 Hz, 1 H), 5.47 (s, 1 H), 7.20–7.31 (m, 3 H), 7.44 (d, J = 8.0 Hz, 2 H), and others. ^{13}C NMR: δ 13.8 (CH_3), 22.1 (CH_3), 22.5 (CH_3), 24.3 (CH_2), 29.6 (CH_3), 31.4 (CH), 34.6 (CH_2), 41.5 (CH_2), 43.4 (C), 50.6 (CH), 57.8 (CH_3), 78.0 (CH), 79.1 (C), 80.3 (CH), 83.7 (CH), 126.5 (CH), 127.2 (CH), 127.4 (CH), 140.6 (C).

2-[(1′*S*,2′*S*)-1′-Hydroxy-2′-methoxy-1′-phenylpropyl]hexahydro-4,4,7-trimethyl-4*H*-1,3-benzoxathiin (**2e**). ^1H NMR: δ 0.83 (d, J = 6.4 Hz, 3 H), 0.99 (d, J = 6.2 Hz, 3 H), 1.23 (s, 3 H), 1.44 (s, 3 H), 2.91 (bs, 1 H), 3.21 (s, 3 H), 3.31 (dt, J = 4.2, 10.4 Hz, 1 H), 3.71 (q, J = 6.2 Hz, 1 H), 5.49 (s, 1 H), 7.22–7.34 (m, 3 H), 7.52–7.58 (m, 2 H), and others. ^{13}C NMR: δ 13.2 (CH_3), 22.0 (CH_3), 22.9 (CH_3), 24.4 (CH_2), 29.8 (CH_3), 31.4 (CH), 34.7 (CH_2), 41.6 (CH_2), 43.0 (C), 51.0 (CH), 57.2 (CH_3), 77.8 (CH), 79.2 (C), 80.2 (CH), 84.4 (CH), 126.7 (CH), 126.8 (CH), 127.2 (CH), 141.9 (C). FAB$^+$ MS for $C_{21}H_{33}O_3S$ (MH^+) found: m/e 365.2154. Calcd: m/e 365.2150.

2-[(1′*R*,2′*R*)-1′-Hydroxy-2′-methoxy-1′-phenylpropyl]hexahydro-4,4,7-trimethyl-4*H*-1,3-benzoxathiin (**3f**). ^1H NMR: δ 0.83 (d, J = 6.3 Hz, 3 H), 0.94 (d, J = 6.4 Hz, 3 H), 1.15 (s, 3 H), 1.36 (s, 3 H), 2.85 (s, 1 H), 3.38 (s, 3 H), 3.56 (dt, J = 4.3, 10.4 Hz, 1 H), 3.77 (q, J = 6.3 Hz, 1 H), 5.69 (s, 1 H), 7.23–7.33 (m, 3 H), 7.49–7.54 (m, 2 H), and others. ^{13}C NMR: δ 13.3 (CH_3), 22.1 (CH_3), 22.8 (CH_3), 24.3 (CH_2), 29.5 (CH_3), 31.5 (CH), 34.7 (CH_2), 41.9 (CH_2), 43.1 (C), 50.7 (CH), 57.5 (CH_3), 77.3 (CH), 79.1 (C), 79.5 (CH), 82.3 (CH), 126.6 (CH), 127.3 (CH), 127.4 (CH), 138.6 (C).

2-[1′-Hydroxy-2′-(triisopropylsiloxy)-1′-phenylpropyl]-hexahydro-4,4,7-trimethyl-4*H*-1,3-benzoxathiins 2g and 3g. (i) By the general procedure, 86 mg (85%, 100% de) of liquid **2g** was prepared from reaction of 86 mg of 2-[(2′*S*)-2′-(triisopropylsiloxy)propanoyl]oxathiane **1g** (100% de) in 0.5 mL of THF and 0.6 mL of PhMgBr (1.0 M in THF) in 1.5 mL of THF.

(ii) Similar reaction of 86 mg of **1g** and 0.33 mL of PhLi (1.8 M in Et_2O) yielded a crude mixture of diastereomers **2g** and **3g** in a ratio of 62:38. Chromatographic separation on silica gel with EtOAc/hexanes gave 63 mg (62%) of a chemically pure liquid mixture of diastereomers in a 59:41 ratio.

2-[(1′*S*,2′*S*)-1-Hydroxy-2′-(triisopropylsiloxy)-1′-phenylpropyl]hexahydro-4,4,7-trimethyl-4*H*-1,3-benzoxathiin (**2g**). ^1H NMR: δ 0.85 (d, J = 6.4 Hz, 3 H), 0.92 (s, 21 H), 1.13 (d, J = 6.1 Hz, 3 H), 1.18 (s, 3 H), 1.42 (s, 3 H), 3.09 (s, 1 H), 3.32 (dt, J = 4.3, 10.5 Hz, 1 H), 4.42 (q, J = 6.1 Hz, 1 H), 5.45 (s, 1 H), 7.20–7.31 (m, 3 H), 7.56–7.61 (m, 2 H), and others. ^{13}C NMR: δ 12.8 (CH), 18.1 (CH_3), 18.2 (CH_3), 22.0 (CH_3), 22.9 (CH_3), 24.3 (CH_2), 29.8 (CH_3), 31.4 (CH), 34.7 (CH_2), 41.6 (CH_2), 42.8 (C), 50.9 (CH), 73.0 (CH), 77.4 (CH), 79.2 (C), 84.1 (CH), 126.7 (CH), 127.0 (2CH), 142.2 (C).

2-[(1′*R*,2′*S*)-1-Hydroxy-2′-(triisopropylsiloxy)-1′-phenylpropyl]hexahydro-4,4,7-trimethyl-4*H*-1,3-benzoxathiin (**3g**). ^1H NMR: δ 1.38 (s), 3.43 (dt, J = 4.3, 10.3 Hz), 3.44 (s), 4.51 (q, J = 6.4 Hz), 5.51 (s), and others identified on the basis of the spectrum of a diastereomeric mixture. ^{13}C NMR: δ 13.1, 18.9, 19.1, 22.1, 22.6, 29.5, 31.4, 43.2, 50.4, 72.8, 77.9, 83.3, 126.9, 127.1, 140.6, others overlapped with those of the epimer **2g**.

2-[(2′*R*,1′*S*)-1-Hydroxy-2′-(triisopropylsiloxy)-1′-phenylpropyl]hexahydro-4,4,7-trimethyl-4*H*-1,3-benzoxathiin (2h). (i) By the general procedure, 75 mg (100% de) of liquid **2h** was prepared from reaction of 86 mg of 2-[(2′*R*)-2′-(triisopropylsiloxy)propanoyl]oxathiane **1h** (100% de) in 0.5 mL of THF and 0.6 mL of PhMgBr (1.0 M in THF) in 1.5 mL of THF.

(ii) Similar reaction of 86 mg (100% de) of **1h** and 0.33 mL of PhLi (1.8 M in Et_2O) yielded 71 mg of pure **2h**.

^1H NMR: δ 0.81 (d, J = 6.3 Hz, 3 H), 0.92 (d, J = 6.4 Hz, 3 H), 1.12 (s, 3 H), 1.13 (s, 21 H), 1.38 (s, 3 H), 3.11 (s, 1 H), 3.40 (dt, J = 4.2, 10.5 Hz, 1 H), 4.79 (q, J = 6.3 Hz, 1 H), 5.44 (s, 1 H), 7.22–7.33 (m, 3 H), 7.52–7.57 (m, 2 H), and others. ^{13}C NMR: δ 13.0 (CH), 17.9 (CH_3), 18.2 (CH_3), 18.3 (CH_3), 22.2 (CH_3), 22.4 (CH_3), 24.4 (CH_2), 29.6 (CH_3), 31.5 (CH), 34.7 (CH_2), 41.9 (CH_2), 42.2 (C), 50.9 (CH), 70.3 (CH), 77.4 (CH), 78.9 (C), 83.3 (CH), 126.7 (CH), 127.0 (CH), 127.2 (CH), 139.9 (C). FAB$^+$ MS for $C_{29}H_{51}O_3SSi$ (MH^+) found: m/e 507.3376. Calcd: m/e 507.3330.

2-[(2′*R*,1′*S*)-1′,2′-Dihydroxy-1′-phenylpropyl]hexahydro-4,4,7-trimethyl-4*H*-1,3-benzoxathiin (6h). A mixture of 72 mg of **2h** (100% de) and 1 mL of 1.0 M tetrabutylammonium fluoride in THF was stirred overnight at ambient temperature. It was extracted with 20 mL of Et_2O, and the etheral extract was washed with 3 mL of water, followed by 3 mL of brine, dried ($MgSO_4$), and concentrated to yield 62 mg (100% de) crude product which was chromatographed on silica gel to yield 35 mg of pure solid **6h**, mp 82.5–84.0 °C. FAB$^+$ MS for $C_{20}H_{31}O_3S$ (MH^+) calcd: m/e 351.1995. Found: m/e 351.1975.

^1H NMR: δ 0.90 (d, J = 6.3 Hz, 3 H), 0.91 (d, J = 6.4 Hz, 3 H), 1.21 (s, 3 H), 1.30 (s, 3 H), 2.70 (bs, 1 H), 3.30 (bs, 1 H), 3.41 (dt, J = 4.2, 10.4 Hz, 1 H), 4.60 (q, J = 6.4 Hz, 1 H), 5.12 (s, 1 H), 7.23–7.35 (m, 3 H), 7.49–7.54 (m, 2 H), and others. ^{13}C NMR: δ 16.8 (CH_3), 22.0 (CH_3), 22.5 (CH_3), 24.3 (CH_2), 29.5 (CH_3), 31.4 (CH), 34.6 (CH_2), 41.7 (CH_2), 43.5 (C), 51.0 (CH), 70.3 (CH), 78.3 (CH), 78.4 (C), 86.1 (CH), 126.4 (CH), 127.3 (CH), 127.6 (CH), 140.2 (C).

2-[(1′*S*,2′*S*)-1′,2′-Dihydroxy-1′-phenylpropyl]hexahydro-4,4,7-trimethyl-4*H*-1,3-benzoxathiin (6g). A mixture of 73 mg of **2g** (100% de) and 3 mL of 2% HCl (in 95% ethanol) was stirred over 10 days at ambient temperature to lead to 42 mg of a crude product with 38% conversion to **6g**. This product was added to 1 mL of 1.0 M tetrabutylammonium fluoride in THF, stirred overnight, and worked up to give 35 mg of clean product **6g**. Slow evaporation of the solvent of a hexane solution gave a crystal for X-ray analysis (mp 152–153 °C).

^1H NMR: δ 0.86 (d, J = 6.5 Hz, 3 H), 1.07 (d, J = 6.2 Hz, 3 H), 1.22 (s, 3 H), 1.43 (s, 3 H), 2.04 (bd, 1 H), 2.97 (s, 1 H), 3.37 (dt, J = 4.2, 10.4 Hz, 1 H), 4.23 (bq, 1 H), 5.41 (s, 1 H), 7.27–7.35 (m, 3 H), 7.60 (d, J = 7.2 Hz, 2 H), and others. ^{13}C NMR: δ 16.8 (CH_3), 22.0 (CH_3), 22.7 (CH_3), 24.4 (CH_2), 29.7 (CH_3), 31.4 (CH), 34.6 (CH_2), 41.6 (CH_2), 43.3 (C), 51.0 (CH), 71.7 (CH), 78.0 (CH), 78.9 (C), 84.5 (CH), 126.8 (CH), 127.3 (CH), 127.7 (CH), 141.1 (C).

2-[(2′*R*,1′*S*)-1′-Hydroxy-1′-phenyl-2′-(tosyloxy)propyl]-hexahydro-4,4,7-trimethyl-4*H*-1,3-benzoxathiin (7h). A mixture of 35 mg of **6h** and 38 mg of *p*-toluenesulfonyl chloride in 1 mL of pyridine was stirred for 30 min at 0 °C and then stored

in a refrigerator (ca. 4 °C) for 3 days. The usual workup led to 45 mg of a crude mixture of **6h** and **7h** in a 54:46 ratio. Chromatographic separation on silica gel with EtOAc/hexanes (20/80) gave 19 mg (100% de) of the desired **7h** and 15 mg of recovered **6h**.

^{1}H NMR: δ 0.91 (d, J = 6.5 Hz, 3 H), 0.93 (d, J = 6.4 Hz, 3 H), 1.12 (s, 3 H), 1.35 (s, 3 H), 2.36 (bs, 1 H), 2.43 (s, 3 H), 3.28 (dt, J = 4.2, 10.4 Hz, 1 H), 5.31 (s, 1 H), 5.54 (q, J = 6.5 Hz, 1 H), 7.25–7.34 (m, 5 H), 7.53–7.58 (m, 2 H), 7.80–7.86 (m, 2 H), and others. ^{13}C NMR: δ 14.8, 21.6, 22.1, 22.5, 24.3, 29.6, 31.3, 34.7, 41.4, 43.3, 50.8, 77.6, 78.5, 81.1, 83.3, 126.6, 127.5, 127.7, 127.8, 129.8, 135.5, 138.6, 144.4.

2-[(1′*R*)-1′-Hydroxy-1′-phenylpropyl]hexahydro-4,4,7-trimethyl-4*H*-1,3-benzoxathiin (2m). (i) To a suspension of 0.07 g of $LiAlH_4$ in 2 mL of THF was added 19 mg of **7h** (100% de). After being stirred for 6.5 h at ambient temperature, the mixture was quenched by 1 mL of 1 N NaOH and extracted with 15 mL of Et_2O. The etheral layer was washed with 3 mL of brine, dried ($MgSO_4$), and concentrated to lead to 8 mg of a crude product containing 10% of the uncoverted intermediate, presumably 2-(1′2′-epoxy-1′-phenylpropyl)hexahydro-4,4,7-trimethyl-4*H*-1,3-benzoxathiin, identified by NMR. No epimerization was observed.

^{1}H NMR: δ 0.71 (t, J = 7.4 Hz, 3 H), 0.86 (d, J = 6.5 Hz, 3 H), 1.23 (s, 3 H), 1.34 (s, 3 H), 1.95 (q, J = 7.4 Hz, 2 H), 2.93 (bs, 1 H), 3.35 (dt, J = 4.3, 10.5 Hz, 1 H), 5.06 (s, 1 H), 7.18–7.57 (m), and others. A minor set of signals at 1.21 (s), 1.40 (s), 1.52 (d, J = 5.5 Hz), 2.97 (q, J = 5.5 Hz), 5.11 (s) and others seems to correspond to 2-(1′,2′-epoxy-1′-phenylpropyl)hexahydro-4,4,7-trimethyl-4*H*-1,3-benzoxathiin. ^{13}C NMR: δ 7.5, 22.0, 22.7, 24.4, 29.7, 29.9, 31.4, 34.7, 41.6, 43.2, 50.8, 78.0, 78.3, 86.2, 126.3, 126.9, 127.7, 142.8. The minor set: 13.8, 22.4, 24.3, 29.6, 41.7, 41.9, 50.1, 62.9, 70.4, 77.6, 81.7, 126.8, 127.6, 149.6, and others overlapped with the major signals.

(ii) Reaction of 183 mg (0.71 mmol) of 2-propanoyloxathiane **1** and 1.4 mL of 1.0 M PhMgBr (THF) in 8 mL of dry THF at −78 °C gave 167 mg (69%) of colorless oil, (1′*R*)-**2m**.

^{1}H NMR (because of a referencing difference, 0.05 ppm is added to each shift): δ 0.71 (t, J = 7.4 Hz, 3 H), 0.86 (d, J = 6.5 Hz, 3 H), 1.23 (s, 3 H), 1.33 (s, 3 H), 1.94 (q, J = 7.4 Hz, 2 H), 2.93 (s, 1 H), 3.34 (dt, J = 4.3, 10.5 Hz, 1 H), 5.06 (s, 3 H), 7.19–7.46 (m, 5 H) and others. ^{13}C NMR: δ 7.5, 22.0, 22.7, 24.3, 29.6, 29.7, 31.3, 34.6. 41.5, 43.1, 50.7, 77.6, 78.2, 86.1, 126.3, 126.7, 127.6, 142.7. In the ^{1}H spectrum, faint signals of the diastereomer (1′*S*) were seen at ca. 3.5 and 5.12 ppm.

The salient differences of this authentic 1′*R* and the 1′*S*[1a] isomer and comparison with **2m** obtained from **7h** (Scheme III) are shown in the following comparison of δ's (ppm). 1′*R*: (^{1}H) 3.34 5.06, (^{13}C) 29.6 29.7 31.3 34.6 142.7. **2m**: (^{1}H) 3.35 5.06; (^{13}C) 29.7 29.9 31.4 34.7 142.8. 1′*S*: (^{1}H) 3.51 5.15; (^{13}C) 29.4 31.3 32.0 35.6 141.5.

2-[1′-Hydroxy-2′-(methylthio)-1′-phenylbutyl]hexahydro-4,4,7-trimethyl-4*H*-1,3-benoxathiins. (i) Reaction of 20 mg of 2-[2′-(methylthio)butyl]oxathiane **1i** (84% de) in 0.5 mL of THF and 0.06 mL of PhMgBr (3.0 M in Et_2O) in 1.5 mL of THF yielded 22 mg of crude product **2i** (100% de). Chromatographic separation on silica gel with 2–5% EtOAc/hexanes provided 13 mg of pure **2i**. FAB$^+$ MS for $C_{22}H_{34}O_2S_2$ (M^+) found: m/e 394.1968. Calcd: m/e 394.2000.

(ii) Reaction of 66 mg of **1i** (88% de) in 1 mL of THF and 0.41 mL of PhLi (2.0 M) in 3 mL of THF yielded 92 mg of a crude mixture containing diastereomers **2i** and **3i** in a ratio of 9:91. Chromatographic separation on silica gel with EtOAc/hexanes gave 53 mg of colorless crystalline product **3i**, mp 123–124 °C. Slow evaporation of the solvent of a petroleum ether solution of this product led to a crystal for X-ray analysis.

(iii) To 0.29 mL of PhMgBr (1.0 M in THF) in 1 mL of THF was added 31 mg of 2-[(2′*R*)-2′-(methylthio)butyl]oxathiane **1j** (80% de) in 0.5 mL of THF at −78 °C. After stirring was continued for 4 h at −78 °C, the reaction mixture was quenched with 0.2 mL of D_2O, and saturated aqueous NH_4Cl was added in about 30 s to prevent **1j** from epimerizing in the basic solution. The product was extracted with Et_2O, and the etheral solution was washed with brine, dried (Na_2SO_4), and concentrated to 41 mg of crude products. The ^{1}H NMR spectrum indicated partial conversion of **1j** (62%) to **2j** in 100% de and no deuterium incorporation in the unreacted ketone. A sample of 11 mg of oil **2j** was obtained by preparative TLC on silica gel with EtOAc/hexanes. FAB$^+$ MS for $C_{22}H_{34}O_2S_2$ (M^+) found: m/e 394.1992. Calcd: m/e 394.2000.

(iv) Reaction of 33 mg of **1j** (92% de) in 0.5 mL of THF and 0.2 mL of PhLi (2.0 M) in 1 mL of THF yielded 64 mg of a crude mixture of **2j**, **3j**, and **1j** in a ratio of 42:37:21. Separation by preparative TLC on silica gel with EtOAc/hexanes gave a sample of 6 mg of not quite pure **3j**.

2-[(1′*R*,2′*S*)-1′-Hydroxy-2′-(methylthio)-1′-phenylbutyl]hexahydro-4,4,7-trimethyl-4*H*-1,3-benzoxathiin (**3i**). ^{1}H NMR: δ 0.91 (d, J = 6.4 Hz, 3 H), 1.04 (t, J = 7.1 Hz, 3 H), 1.17 (s, 3 H), 1.39 (s, 3 H), 1.83 (s, 3 H), 3.04 (dd, J = 2.5, 11.4 Hz, 1 H), 3.49 (dt, J = 4.3, 10.4 Hz, 1 H), 3.64 (s, 1 H), 5.68 (s, 1 H), 7.26–7.34 (m, 3 H), 7.41–7.45 (m, 2 H), and others. ^{13}C NMR: δ 12.7 (CH_3), 15.3 (CH_3), 22.1 (CH_3), 22.5 (CH_3), 23.5 (CH_2), 24.4 (CH_2), 29.5 (CH_3), 31.5 (CH), 34.7 (CH_2), 41.6 (CH_2), 43.5 (C), 50.7 (CH), 58.5 (CH_3), 78.2 (CH), 80.2 (C), 84.2 (CH), 126.6 (CH), 127.3 (CH), 127.5 (CH), 141.0 (C). IR: 3420 (OH) cm^{-1}.

2-[(1′*S*,2′*S*)-1′-Hydroxy-2′-(methylthio)-1′-phenylbutyl]hexahydro-4,4,7-trimethyl-4*H*-1,3-benzoxathiin (**2i**). ^{1}H NMR: δ 0.86 (d, J = 6.5 Hz, 3 H), 1.22 (s, 3 H), 1.46 (s, 3 H), 1.71 (s, 3 H), 2.84–2.91 (m, 1 H), 3.10 (bs, 1 H), 3.41 (dt, J = 4.2, 10.4 Hz, 1 H), 5.76 (s, 1 H), 7.22–7.33 (m, 3 H), 7.57–7.62 (m, 2 H), and others. ^{13}C NMR: δ 12.3 (CH_3), 16.6 (CH_3), 22.0 (CH_3), 22.7 (CH_3), 23.2 (CH_2), 24.4 (CH_2), 29.8 (CH_3), 31.4 (CH), 34.7 (CH_2), 41.7 (CH_2), 43.3 (C), 51.0 (CH), 58.3 (CH_3), 78.0 (CH), 79.8 (C), 84.9 (CH), 126.8 (CH), 127.0 (CH), 127.3 (CH), 142.3 (C). IR: 3563 (OH) cm^{-1}.

2-[(2′*R*,1′*S*)-1′-Hydroxy-2′-(methylthio)-1′-phenylbutyl]hexahydro-4,4,7-trimethyl-4*H*-1,3-benzoxathiin (**2j**). ^{1}H NMR: δ 0.91 (d, J = 6.4 Hz, 3 H), 0.92 (t, J = 7.0 Hz, 3 H), 1.14 (s, 3 H), 1.43 (s, 3 H), 2.19 (s, 3 H), 2.52 (s, 1 H), 3.10 (dd, J = 5.0, 8.9 Hz, 1 H), 3.46 (dt, J = 4.3, 10.4 Hz, 1 H), 5.72 (s, 1 H), 7.24–7.33 (m, 3 H), 7.50–7.55 (m, 2 H), and others. ^{13}C NMR: δ 12.4 (CH_3), 16.0 (CH_3), 22.1 (CH_3), 22.6 (CH_3), 22.8 (CH_2), 24.4 (CH_2), 29.7 (CH_3), 31.5 (CH), 34.7 (CH_2), 41.8 (CH_2), 43.1 (C), 50.9 (CH), 57.9 (CH_3), 77.7 (CH), 80.4 (C), 85.6 (CH), 126.4 (CH), 127.1 (CH), 127.4 (CH), 141.9 (C). IR: 3549 (OH) cm^{-1}.

2-[(1′*R*,2′*R*)-1′-Hydroxy-2′-(methylthio)-1′-phenylbutyl]hexahydro-4,4,7-trimethyl-4*H*-1,3-benzoxathiin (**3j**). ^{1}H NMR: δ 0.92 (d, J = 6.7 Hz, 3 H), 0.99 (t, J = 7.2 Hz, 3 H), 1.16 (s, 3 H), 1.42 (s, 3 H), 2.09 (s, 3 H), 2.83 (dd, J = 2.5, 11.6 Hz, 1 H), 3.07 (s, 1 H), 3.59 (dt, J = 4.3, 10.4 Hz, 1 H), 6.13 (s, 1 H), 7.25–7.30 (m, 3 H), 7.55–7.60 (m, 2 H), and others. ^{13}C NMR: δ 12.4, 17.7, 22.1, 22.9, 24.0, 24.3, 29.4, 31.5, 34.7, 41.9, 43.1, 50.7, 59.1, 77.3, 80.9, 83.2, 126.5, 127.3, 127.4, 139.0. IR: 3565 (OH) cm^{-1}.

Acknowledgment. This work was supported by NSF grant CHE-8703060. We are indebted to Dr. Peter S. White for the X-ray diffraction analyses.

Supplementary Material Available: X-ray structural information for compounds **6g**, **3f**, and **3i** (atomic parameters, bond distances, bond angles, torsion angles, anisotropic thermal parameters) and proton NMR spectra of **2a**, **2b**, **2c**, **2d**, **2e**, **2g**, **2h**, **2i**, **2j**, **2m**, **3d**, **3e**, **3f**, **2g/3g** mixture, **3i**, **3j**, **2k/3k** mixture, **2l/3l** mixture, **4**, **5**, **6g**, **6h**, **7h** (53 pages). This material is contained in many 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.