Asymmetric Syntheses Based on 1,3-Oxathianes. 1. Scope of the Reaction

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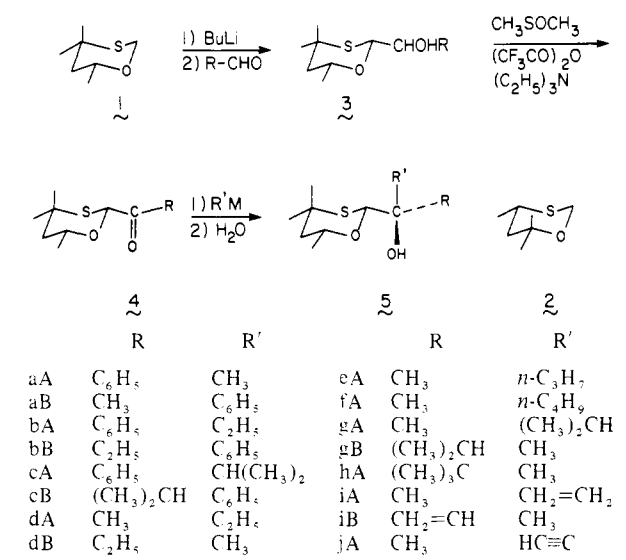
Abstract: The stereoselectivity of the reactions of 2-acyl- and 2-aroyl-4,4,6-trimethyl-1,3-oxathianes and -4,6,6-trimethyl-1,3-oxathianes with organometallic reagents has been studied as a function of the following reaction variables: substitution pattern (4,4,6 or 4,6,6), nature of the 2-acyl or -aroyl group, nature of the organometallic reagent (RLi, RMgX, or R_2Mg), nature of the halide X in the case of RMgX, solvent, and temperature. Optimum conditions for the reaction have been established under which it will yield over 95% of one diastereomer for almost any combination of ketone and Grignard reagent tried.

On the basis of the very high stereoselectivity of the reaction of 2-lithio-1,3-dithianes with electrophiles,[2,3] we devised, in 1978, a highly (nearly 100%) stereoselective synthesis of atrolactic acid methyl ether.[4] The first of two stages of this asymmetric synthesis is the reaction of 4,4,6-trimethyl-1,3-oxathiane (**1**) (or the 4,6,6 analogue **2**) with benzaldehyde to give virtually exclusively the equatorial (cis) substitution product **3** (Scheme I, top, R = C_6H_5), which is subsequently oxidized to the ketone **4**.[5] In the second stage, reaction of this ketone with methyl Grignard reagent (R'M = CH_3MgI) again proceeds with high stereoselectivity, the diastereomeric purity of the product being 95% with the 4,4,6- and nearly 100% with the 4,6,6-trimethyl substitution pattern[4] (Scheme I, **2**, lower right). Methylation of the tertiary carbinol so formed followed by oxathiane cleavage and oxidation gave[4] (S)-(−)-atrolactic acid methyl ether in 92% and nearly 100% optical yield in the two series, respectively.

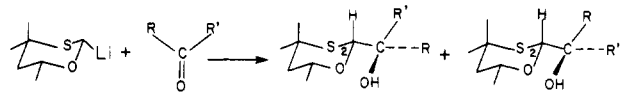
In exploratory work designed to elaborate this reaction sequence into a general asymmetric synthesis of compounds of type RR'C(OH)X (where X = CHO, COOH, CH_2OH, etc.[6-8]) we have now studied the effect of various process variables: substitution pattern of the oxathiane (4,4,6- vs. 4,6,6-trimethyl), nature of the acyl substituent, nature of the alkyl group in the organometallic reagent, nature of the metal, nature of the halide when the organometallic reagent is RMgX, solvent, and temperature.

Scheme I

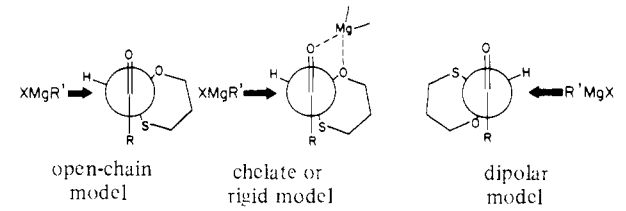


	R	R'		R	R'
aA	C_6H_5	CH_3	eA	CH_3	n-C_3H_7
aB	CH_3	C_6H_5	fA	CH_3	n-C_4H_9
bA	C_6H_5	C_2H_5	gA	CH_3	$(CH_3)_2CH$
bB	C_2H_5	C_6H_5	gB	$(CH_3)_2CH$	CH_3
cA	C_6H_5	$CH(CH_3)_2$	hA	$(CH_3)_3C$	CH_3
cB	$(CH_3)_2CH$	C_6H_5	iA	CH_3	$CH_2=CH_2$
dA	CH_3	C_2H_5	iB	$CH_2=CH$	CH_3
dB	C_2H_5	CH_3	jA	CH_3	$HC\equiv C$

Scheme II



Scheme III



Results

The results of the present study (cf. Scheme I) are summarized in Table I (4,4,6-trimethyloxathiane ketones **4**) and Table II (4,6,6-trimethyloxathiane ketones **6**). The starting ketones were prepared by condensing the 2-lithio derivatives of 1,3-oxathianes **1** and **2** with aldehydes (in good to excellent yields) followed by oxidation of the isomer mixtures so formed with dimethyl sulfoxide, trifluoroacetic anhydride, and triethylamine[5] (in fair to good yields) (Scheme I). Pure equatorial isomers were thus obtained. Direct acylation of the oxathiane by a variety of methods either failed to give the desired ketone or proceeded in unacceptable yield. Diastereomer mixtures of the expected addition products (for spectral comparison) were obtained by condensation of the appropriate 2-lithio-1,3-oxathiane with the appropriate ketone (Scheme II). This reaction was unstereoselective except in the case of acetophenone or pinacolone (Table III).[9] The product mixtures could generally be analyzed by NMR using either the ratios of the NMR singlets due to the C(2) protons of the oxathiane moiety or (where these protons were insufficiently resolved) by ^{13}C NMR analysis using two or three well-resolved pairs of corresponding carbons. [C(2) often displays a shift difference in excess of 1 ppm as between epimers.]

In a number of cases (Table I, entries 1/6, 3/14, 4/28, 5/37, 16/31, 24/36, and 25/32, and Table II, entries 42/49 and 44/53) the oxathianyl carbinols RR'C(OH)oxathia [where oxathia stands

(1) From the Ph.D. Thesis of Susan Morris-Natschke, University of North Carolina, Chapel Hill, NC 1982.

(2) Eliel, E. L.; Hartmann, A. A. *J. Am. Chem. Soc.* **1971**, *93*, 2572. Eliel, E. L.; Hartmann, A. A.; Abatjoglou, A. G. *Ibid.* **1974**, *96*, 1807. Abatjoglou, A. G.; Eliel, E. L.; Kuyper, L. F. *Ibid.* **1977**, *99*, 8262.

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(8) Eliel, E. L.; Lynch, J. E. "Abstracts of Papers", 183rd National Meeting of the American Chemical Society, Las Vegas, NV, March 1983; American Chemical Society: Washington, DC, ORGN 19.

(9) The stereoselectivity observed in these two cases conforms to Scheme II with the keto group eclipsing the ring oxygen (to which it may be tied through chelation involving the lithium moiety of the lithiooxathiane), the large group R'' eclipsing H(2) and the smaller group R' eclipsing sulfur.

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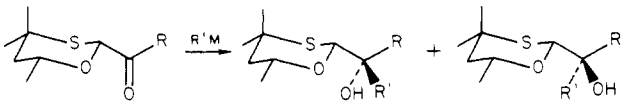
Table I. Reactions of 2-Acyl-4,4,6-trimethyl-1,3-oxathianes with Organometallics

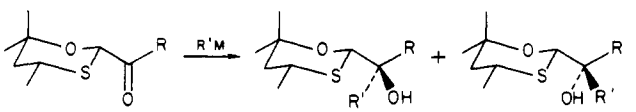


4 5a 5b

entry	compd	R	R′	M	temp, °C	solvent	ratio a:b[a]
1	5a	C_6H_5	CH_3	MgI	reflux	Et_2O	96:4
2	5a	C_6H_5	CH_3	MgI	reflux	Et_2O:THF (3:1)	98:2
3	5a	C_6H_5	CH_3	Li	reflux	Et_2O	86:14
4	5b	C_6H_5	CH_2CH_3	MgI	reflux	Et_2O	>99:<1
5	5c	C_6H_5	$CH(CH_3)_2$	MgI	reflux	Et_2O	99:1
6	5a	CH_3	C_6H_5	MgBr	reflux	Et_2O	89:11
7	5a	CH_3	C_6H_5	MgBr	reflux	Et_2O:THF (2:1)	91:9
8	5a	CH_3	C_6H_5	MgBr	−20	Et_2O	92:8
9	5a	CH_3	C_6H_5	MgBr	−40	Et_2O	93:7
10	5a	CH_3	C_6H_5	MgBr	−78	Et_2O	89:11
11	5a	CH_3	C_6H_5	MgBr	−78	Et_2O[b]	88:12, 88:12[c]
12	5a	CH_3	C_6H_5	Mg[d]	reflux	Et_2O	78:22
13	5a	CH_3	C_6H_5	MgI	reflux	Et_2O	87:13
14	5a	CH_3	C_6H_5	Li	reflux	Et_2O:C_6H_6 (30:1)	88:12
15	5a	CH_3	C_6H_5	Li[e]	reflux	Et_2O:C_6H_6 (35:1)	69:31
16	5d	CH_3	CH_2CH_3	MgI	reflux	Et_2O	90:10
17	5d	CH_3	CH_2CH_3	MgI	−78	Et_2O[b]	97:3
18	5d	CH_3	CH_2CH_3	MgBr	reflux	Et_2O	87:13
19	5e	CH_3	$CH_2CH_2CH_3$	MgI	reflux	Et_2O	90:10[f]
20	5e	CH_3	$CH_2CH_2CH_3$	MgBr	reflux	Et_2O	83:17,[f] 85:15[f,c]
21	5e	CH_3	$CH_2CH_2CH_3$	MgCl	reflux	Et_2O	79:21,[f] 75:25[f,c]
22	5f	CH_3	$(CH_2)_3CH_3$	Mg[g]	reflux	Et_2O	87:13[f]
23	5f	CH_3	$(CH_2)_3CH_3$	Mg[g]	reflux	Et_2O:hexane (5:1)	76:24[f]
24	5g	CH_3	$CH(CH_3)_2$	MgI	reflux	Et_2O	67:33
25	5i	CH_3	$CH=CH_2$	MgBr	reflux	THF	91:9
26	5i	CH_3	$CH=CH_2$	MgBr	−78	Et_2O:THF (3:1)[b]	90:10
27	5j	CH_3	$C\equiv CH$	MgBr	reflux	THF	94:6
28	5b	CH_2CH_3	C_6H_5	MgBr	reflux	Et_2O	83:17
29	5b	CH_2CH_3	C_6H_5	MgBr	reflux	Et_2O[b]	80:20
30	5b	CH_2CH	C_6H_5	MgBr	−78	Et_2O[b]	97:3
31	5d	CH_2CH_3	CH_3	MgI	reflux	Et_2O	80:20
32	5i	$CH=CH_2$	CH_3	MgI	reflux	Et_2O	87:13
33	5i	$CH=CH_2$	CH_3	MgI	−78	Et_2O[b]	≃95:5[h]
34	5g	$CH(CH_3)_2$	CH_3	MgI	reflux	Et_2O	68:32
35	5g	$CH(CH_3)_2$	CH_3	MgI	−78	Et_2O[b]	77:23
36	5g	$CH(CH_3)_2$	CH_3	MgI	reflux	Et_2O[i]	69:31
37	5c	$CH(CH_3)_2$	C_6H_5	MgBr	reflux	Et_2O	85:15
38	5c	$CH(CH_3)_2$	C_6H_5	MgBr	−78	Et_2O[b]	>99:<1
39	5h	$C(CH_3)_3$	CH_3	MgI	reflux	Et_2O	93:7
40	5h	$C(CH_3)_3$	CH_3	MgI	−78	Et_2O[b]	96:4

[a] Ratios >50:50 conform to Cram's rigid model;[11] ratios <50:50 do not. [b] Grignard reagent added to ketone (where not noted, the ketone was added to the Grignard reagent). [c] Duplicate run. [d] $(C_6H_5)_2Mg$ prepared by dioxane precipitation. [e] TMEDA added to alkyllithium solution prior to addition of ketone. [f] Some reduction to 2° alcohol also seen. [g] Commercial solution of $(n\text{-Bu})_2Mg$. [h] Impure product: analysis approximate. [i] $MgBr_2$ added to ketone prior to addition of Grignard reagent.

Table II. Reactions of 2-Acyl-4,6,6-trimethyl-1,3-oxathianes with Organometallics



6 7a 7b

entry	compd	R	R′	M	temp, °C	solvent	ratio a:b[a]
41	7a	C_6H_5	CH_3	MgI	reflux	Et_2O	96:4
42	7a	C_6H_5	CH_3	MgI	reflux	Et_2O:THF (5:1)	>99:<1
43	7a	C_6H_5	CH_3	MgI	reflux	Et_2O:toluene	96:4
44	7a	C_6H_5	CH_3	Li	reflux	Et_2O	75:25
45	7b	C_6H_5	CH_2CH_3	MgI	reflux	Et_2O	94:6, 93:7[b]
46	7b	C_6H_5	CH_2CH_3	MgI	reflux	Et_2O:THF (4:1)	>99:<1
47	7c	C_6H_5	$CH(CH_3)_2$	MgI	reflux	Et_2O:THF (14:1)	93:7[c]
48	7a	CH_3	C_6H_5	MgBr	reflux	Et_2O:THF (2:1)	82:18
49	7a	CH_3	C_6H_5	MgBr	reflux	Et_2O:THF (4:1)	82:18
50	7a	CH_3	C_6H_5	MgBr	reflux	THF	85:15
51	7a	CH_3	C_6H_5	MgBr	reflux	Et_2O	64:36
52	7a	CH_3	C_6H_5	MgI	reflux	Et_2O	64:36
53	7a	CH_3	C_6H_5	Li	reflux	Et_2O:C_6H_6 (30:1)	72:28

[a] Ratios >50:50 conform to Cram's rigid model;[11] ratios <50:50 do not. [b] Duplicate runs. [c] Major product is secondary alcohol (by reduction).

Table III. Reaction of 2-Lithiooxathianes with Ketones, RR'CO

oxathiane	R	R'	product	ratio a/b
2	CH_3	C_6H_5	7a	70:30
2	CH_2CH_3	C_6H_5	7b	65:35
2	$CH(CH_3)_2$	C_6H_5	7c	66:34
1	CH_3	C_6H_5	5a	68:32
1	CH_2CH_3	C_6H_5	5b	68:32
1	$CH(CH_3)_2$	C_6H_5	5c	66:34
1	CH_3	CH_2CH_3	5d	56:44
1	CH_3	$(CH_2)_2CH_3$	5e	56:44
1	CH_3	$(CH_2)_3CH_3$	5f	54:46
1	CH_3	$CH(CH_3)_2$	5g	55:45
1	CH_3	$C(CH_3)_3$	5h	69:31
1	CH_3	$CH=CH_2$	5i	54:46

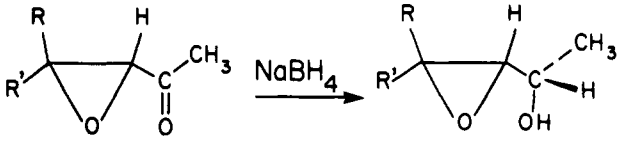
for the 2-linked 4,4,6- or 4,6,6-trimethyloxathianyl moiety (Scheme I)] were obtained both by treatment of the ketone RCOoxathia (**4,6**) with the organometallic R'M and by the reverse process, reaction of R'COoxathia with RM. As expected, the two modes of reaction produce an excess of opposite diastereomers. In other work[4,6-8,10] we have shown that the major diasteromer formed in all cases investigated is that in which the addition of the organometallic to the ketone follows Cram's rule (either the open-chain[11] or rigid[12] model—which in this case lead to the same prediction—but not the dipolar model;[13] cf. Scheme III).

Discussion

A quick survey of Tables I and II indicates that diastereoselectivity in the additions of Grignard reagents to 2-acyl-1,3-oxathianes (**4, 6**) is generally high, the major isomer being formed, with few exceptions, in proportions ranging from 80 to nearly 100%. Since the first step in the reaction sequence depicted in Scheme I—reaction of the 2-lithio-1,3-oxathiane with an aldehyde—also proceeds with high stereoselectivity (only the equatorial addition product is formed), the combination of the two reactions in Scheme I provides the basis of a highly stereoselective asymmetric synthesis, and, in fact, such a synthesis has been accomplished.[7,14,15] Here the question whether the major diastereoisomer (Tables I, II) constitutes 80 or nearly 100% of the product mixture is of vital importance, since it spells the difference between attaining a 60% (probably not practically useful) or near 100% enantiomeric excess in the overall synthesis. We have therefore carried out a detailed study of the process variables in this reaction with a view to being able to establish conditions under which it would proceed reliably with very high stereoselectivity.

(1) Nature of the Oxathiane Backbone: 4,4,6- (1) vs. 4,6,6-Trimethyl-1,3-oxathiane (2) Systems. Comparison of entries 1–5 in Table I with 41–47 in Table II suggests but minor differences in the reaction of the 2-benzoyl derivatives in the two systems, except in the case of the methyllithium reactions (**3** vs. **44**) and the isopropyl Grignard reactions (**5** vs. **47**) in which the 4,4,6 system is superior. (Also, in the case of the isopropyl Grignard reagent, the 4,6,6 system gives as much as 88% reduction and only 12% addition whereas the 4,4,6 system gives only addition; we shall return to this point below.) It must be taken into account, however, that in the range of composition between 96:4 and >99:<1, small changes in composition (which are difficult to measure experimentally) correspond to large changes in activation energy differences for the formation of the two diastereomers; compositions in that range are therefore not suitable for exploring subtle differences in selectivity. Therefore, the less stereoselective reactions of the 2-acetyl-1,3-oxathianes (entries 6–15 in Table I and 48–53 in Table II) with various phenylorganometallic reagents provide a more selective probe of the merits of the two systems. Here it is quite clear that both with phenylmagnesium bromide (entries 6 and 7 vs. 48–51) and phenylmagnesium iodide (entry 13 vs. 52), the 4,4,6 system (Table I) is superior to the 4,6,6 one (Table II) and also less sensitive to solvent variation; superiority of the 4,4,6 system is also seen with phenyllithium (entry 14 vs. 53). In view of these findings, both as to the lower stereoselectivity and the greater tendency to undergo reduction, as opposed to addition, in the 4,6,6 system, all subsequent work was carried out with the 4,4,6-trimethyl-1,3-oxathiane system (Table I).

Scheme IV



predominant isomer, by

R = R' = H	100%
R = R' = Me	86%
R = Me; R' = H	95%
R = H; R' = Me	90%

Two reasons may be suggested for the inferiority of the 4,6,6-trimethyloxathiane backbone. One is that an axial methyl group next to the oxygen (i.e., at C-6) is much closer to the axial hydrogen at C-2 than an axial methyl next to sulfur (i.e., at C-4) because of the much shorter C–O (as compared to C–S) bond length. In this way Me-6a interferes—more than Me-4a—with the preferential approach of the organometallic reagent to the diastereotopic faces of the ketone from the side of the hydrogen rather than from the side of the sulfur, thus reducing selectivity (cf. Scheme III). Another possibility is that the two methyl groups next to oxygen in the 4,6,6-trimethyl compound impede complexing and thus shift the mechanism from a more selective one involving the chelate model (Scheme III) to a less selective one involving the open-chain model (vide infra). An effect similar to that seen here has been reported in 2-acetyloxiranes (Scheme IV).[16]

(2) Nature of the Acyl substituent. When one compares additions of Grignard reagents at reflux, phenyl ketones (entries 1, 2, 4, and 5 in Table I and 41–43 and 45–47 in Table II) are generally more stereoselective than alkyl ketones (entries 6, 7, 13, 16, 18–21, 24, 25, 27–29, 31, 32, 34, 36, 37 in Table I and 48–52 in Table II) although the same does not appear to be true for the few comparisons availabe for alkyllithium reagents (3 vs. 14 in Table I, 44 vs. 53 in Table II). One might surmise that since phenyl ketones are more basic than alkyl ketones, complexing with magnesium is more effective and therefore more of the reaction proceeds via a transition state corresponding to Cram's rigid model[12] and less through one involving the open-chain model[11] (Scheme III). This would enhance stereoselectivity, since reactions proceeding according to the chelate model are known[15] to be more selective than those involving the open-chain one presumably because the transition state in the chelate model is more rigid and its steric preference therefore more compelling. The argument becomes uncertain, however, when one considers the *tert*-butyl ketone (entry 39, Table I) which approaches the phenyl ketone in stereoselectivity, even though, for steric reasons, it might not be particularly well complexed. Perhaps the *tert*-butyl ketone is highly selective even when the transition state is not chelated; cases of this type have been seen elsewhere[17,18] Alternatively, the higher stereoselectivity seen with phenyl and *tert*-butyl ketones may simply be a reflection of their lesser reactivity (for steric reasons in both instances and in the case of the phenyl ketone, also because of resonance); reactions having low activation energy—such as

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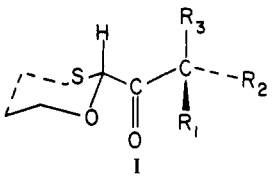
(18) Karabatsos, G. J.; Zioudrou, C.; Moustakali, I. *Tetrahedron Lett.* **1972**, 5289.

the reactions of the alkyl ketones with Grignard reagents—have a lower intrinsic probability of being stereoselective than those with higher activation energy (reactivity–selectivity relationship). Comparison of the reaction of methyl, ethyl, and isopropyl ketones with the phenyl Grignard reagent (entries 6, 28, 37 in Table I) shows little difference in selectivity. However, whereas the stereoselectivity in the reaction of the methyl ketone with ethyl Grignard reagent (entry 16) is quite high, that of the ethyl ketone with the methyl Grignard is only moderate (entry 31) and that of the isopropyl ketone with methyl Grignard (entry 34) is low. A possible interpretation is given in **I**. The ketone function, by



I

virtue of complexing, is eclipsed with the ring oxygen; it is also eclipsed with substituent R_1. Substituent R_2 will thus be eclipsed with the ring sulfur and R_3 with the C(2) hydrogen. For a methyl ketone, all R's are hydrogen. For the ethyl ketone, since methyl/oxygen eclipsing is preferred over hydrogen/oxygen eclipsing,[19] R_1 will be methyl. However, not all molecules are in this conformation and the next most likely one is the one in which R_3 is methyl (since R_2 = Me would engender a syn-axial Me/S interaction with the ring sulfur). In this conformation, the normally facile approach of the alkyl group of the Grignard reagent from the side of the hydrogen (rather than sulfur) will be impeded and stereoselectivity will suffer. This argument assumes that the same conformational considerations that apply to the ground state will also be dominant in the transition state, an assumption which is perhaps reasonable since the reaction of a ketone with a Grignard reagent is quite exothermic (Hammond postulate). When the substituent is isopropyl, two of the R's are methyl, and if one eclipses the carbonyl, the other must eclipse either H or S, and for the reasons indicated above, it is more likely to eclipse H (i.e., $R_1 = R_3$ = Me, R_2 = H). Once again approach from the side of H(2) is impeded and stereoselectivity suffers, but the effect is larger than with ethyl where the most likely conformation is one where $R_2 = R_3$ = H and R_1 = Me, in which no bias is introduced by the R-groups. Finally, in the *tert*-butyl ketone $R_1 = R_2 = R_3$ = Me and so there is no additional bias for or against approach from the side of the hydrogen, which thus remains the preferred mode.

(3) Nature of the Organometallic Reagent: Organolithium Compound, Grignard Reagent, or Organomagnesium Compound. There is extensive work in the literature[15] concerning the relative effectiveness of various organometallic reagents as to the stereoselectivity of their addition to ketones in cases where Cram's rule (chelate model[12]) applies. The results vary depending on the nature of the complexing group Z in the system Z–CRR′–COR″: when Z = $-OCH_3$ Grignard reagents are equally or less selective, but when Z = $CH_3OCH_2CH_2OCH_2-$ Grignard reagents are more selective as addends than organolithium reagents;[12,20,21] dialkylmagnesium reagents are similar in selectivity to Grignard reagents where tried.[20,22] Because of the small magnitude and uncertain direction of these effects, it was deemed essential to probe the effect in the oxathiane system used here. Comparison of entries 1 and 3, 7 and 14 (solvent not identical) in Table I and 41 and 44 in Table II suggests that Grignard reagents are generally more stereoselective in their additions to 2-acyl-1,3-oxathianes than organolithium compounds, though entries 48–53 in Table II indicate that this difference may be overshadowed by a solvent effect. Diorganomagnesium compounds tend to be less stereoselective than organomagnesium halides, as evidenced by entries 12 vs. 6 and 13 in Table I (the evidence from entries 19–23 is less clear-cut because of the simultaneous effect of the nature of the halide, X, in RMgX). In view of the apparent superiority of RMgX over R_2Mg combined with the existence of the Schlenk equilibrium, $2RMgX \rightleftharpoons R_2Mg + MgX_2$, one might expect that the addition of MgX_2 in the reaction would be beneficial by suppressing R_2Mg formation. This was tested in only two cases: in the addition of CH_3MgI to the isobutyroyl compound (entries 34 and 36 in Table I) where it was ineffective and in the addition of vinylmagnesium bromide to a related oxathiane[10] where it was beneficial. The effect may well depend on the equilibrium constant for the Schlenk equilibrium: the larger this constant (for the equilibrium as written above), the more likely MgX_2 is to be of value. No generalizations can be made, but the addition of anhydrous $MgCl_2$ (or of $MgBr_2$ prepared in situ) should be considered in reactions where stereoselectivity is unsatisfactory otherwise.

While the effect of the acyl group (RCO in Scheme I) is important in affecting stereoselectivity, that of the alkyl group of the Grignard reagent (R′) is of much lesser influence. Illustrations are provided by entries 3–5, 13, 16, 19, 25, and 27 in Table I and 41, 46, 47 in Table II. The only exception is the addition of isopropylmagnesium iodide to the methyl ketone (entry 24 in Table I) where little stereoselectivity was achieved (similarly as in the inverse process, viz., addition of methyl Grignard reagent to the isopropyl ketone, entry 34). The addition of the acetylenic Grignard reagent (entry 27, Table I) may be somewhat more selective than other additions.

We had indicated earlier that, whereas addition of isopropylmagnesium bromide to 2-benzoyl-4,4,6-trimethyl-1,3-oxathiane proceeds cleanly and with very high stereoselectivity (entry 5 in Table I), the corresponding reaction in the 4,6,6 system (Table II, entry 47) gives mainly reduction (88%), though the (minor) addition process also proceeds quite stereoselectively. This may suggest that addition proceeds mainly in accordance with the chelate model (hence its high stereoselectivity) but reduction may involve a nonchelated transition state, which, for the reasons already discussed, is more likely to occur in the 4,6,6- than in the 4,4,6-trimethyl system.

(4) Effect of Halide X in RMgX. Only one example was studied systematically: the addition of propylmagnesium halides to 2-acetyl-4,4,6-trimethyloxathiane (entries 19–21 in Table I). Selectivity falls off in the series X = I > Br > Cl. Thus, alkylmagnesium chlorides should be avoided; the situation as between the bromides and iodides is not so clear-cut, however (compare entry 6 with 13 where there is no significant difference). We suggest the following tentative explanation: RMgCl is a halogen-bridged dimer[23] and may therefore be poorly disposed toward bidentate coordination, whereas RMgBr and RMgI exist as equilibrating monomeric and oligomeric species which, in the monomeric form, may coordinate more readily with two oxygen atoms at a time (Scheme III).

(5) Effect of Solvent. Since evidence discussed earlier suggests that stereoselectivity is greater when the transition state corresponds to the chelate (as compared to the open-chain) model, a highly coordinating solvent, by interfering with chelation in the acyloxathiane, should depress stereoselectivity. This effect is very evident in entries 14 and 15 in Table I where addition of tetramethylethylenediamine (TMEDA) in addition of phenyllithium reduces diastereomer excess from 76 to 38%. However, the opposite effect if any seems to emerge in Grignard additions when ether is replaced by a ether–tetrahydrofuran (THF) mixture or pure THF—entries 2 vs. 1 and 7 vs. 6 in Table I and 42 vs. 41 and 50 vs. 48 in Table II—despite the fact that THF is more coordinating than ether. [Entries 25 and 26 point in the same direction; the addition of ether seems to counterbalance the normally beneficial (see below) effect of lowering the temperature.] Clearly the effect of solvent is not just one of favoring or disfavoring chelation; other factors may be a change in the position of the Schlenk equilibrium (vide supra) or in the degree of association (oligomerization) of the Grignard reagent, and a clear

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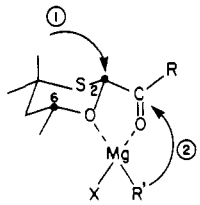
Chart I. Two-Step Asymmetric Synthesis[a]



[a] (1) Equatorial electrophilic substitution in 2-lithio-1,3-oxathiane; (2) stereoselective Grignard addition according to Cram's rule (chelate model).

prediction of the effect of solvent is not possible.

(6) Effect of Temperature. Of the various factors studied, temperature is the one which has the most dramatic effect. Comparison of entries 6–9,[24] 16 and 17, 29 and 30, 32 and 33, 34 and 35, 37 and 38, and 39 and 40 in Table I shows that lowering the temperature from reflux to −78 °C almost invariably causes a marked increase in stereoselectivity to values of 90% or above. This is, of course, what would be expected if the stereoselectivity is due to enthalpy (rather than entropy) differences between the two diastereomeric transition states leading to the epimeric products.

Conclusion

The sequence of an electrophilic substitution at C(2) in a chiral 1,3-oxathiane followed by a Grignard addition, summarized in Chart I leads to an almost stereoisomerically pure tertiary alcohol, with high stereoselectivity in both steps. When the starting oxathiane is enantiomerically pure, this carbinol can be further cleaved to a nearly enantiomerically pure tertiary α-hydroxy aldehyde.[6-8,14] The stereoselectivity of the first step rests on the vastly greater stability of the equatorial over the axial 1,3-oxathiane-2-carbanion. This carbanion undergoes electrophilic substitution with retention of configuration;[1-3,25] the reaction is stereoelectronically controlled. The stereoselectivity of the second step rests on the efficacy of the process proceeding according to Cram's chelate model; other cases of high stereoselectivity involving this model are on record.[12,15,16,20,26,27] The selectivity of this step is probably controlled sterically. The combination of the two steps dependably produces stereoselectivities in excess of 90:10. In processes involving 1,2-induction (Cram's rule), though stereoselectivity tends to be high because of the proximity of the inducing and the induced chiral center, this same proximity normally makes it impossible to carve out both the newly generated chiral center and regenerate the original one. In the present synthesis, while the chiral center at C(2) of the oxathiane is sacrificed, the original one at C(4) or C(6) of the oxathiane can be preserved when the exocyclic one (tertiary carbinol center) is separated from the rest of the molecule. The synthesis thus fulfills the condition[15,28] that the original and the newly generated chiral center must be separated without either of them being destroyed.

Experimental Section

Since large parts of the Experimental Section serve, mainly, to document the results already presented in Tables I–III, most of this material has been relegated to the supplemental material.[29]

4,4,6-Trimethyl-1,3-oxathiane (1).[30] The procedure of Aftalion et al.[31] was followed. A mixture of 15 g (0.112 mol) of 4-mercapto-4-methyl-2-pentanol, 4.8 g (0.193 mol) of paraformaldehyde, 2.8 mL of concentrated sulfuric acid, and 20 mL of water was mixed in a 50-mL round-bottom flask equipped with a downward condenser. The flask was heated so that slow steam distillation occurred. When about half the water had distilled, an additional 9 mL was added and distillation continued, additional increments of water being supplied until no more organic material appeared in the distillate. The organic material was then extracted with two 20-mL portions of ether which were washed once with 10% aqueous potassium carbonate, dried over anhydrous potassium carbonate, filtered, and concentrated. Distillation gave 15 g (92%) of the oxathiane, bp 90 °C/50 mm.

Anal. Calcd for $C_7H_{14}OS$: C, 57.49; H, 9.65. Found: C, 57.64; H, 9.64.

NMR: δ 1.15 (d, J = 7 Hz), 1.25 (s), 1.43 (s), 1.1–1.4 (unresolved m, total integral 11 H), 3.65 (m, 1 H), 4.75 (AB signal, Δ = 0.20 ppm, J = 11 Hz, 2 H).

^{13}C NMR: δ 22.17 (q, Me–6), 26.45 (q, Me–4a), 32.45 (q, Me–4e), 39.57 (s, C-4), 47.48 (t, C-5), 67.48 (t, C-2), 70.54 (d, C-6).

4-Mercapto-2-methyl-2-pentanol.[30] **3-(Benzylthio)butanoic Acid.** A mixture of 100 g (1.16 mol) of crotonic acid, 144 g (1.16 mol) of benzyl mercaptan, and 120 mL of morpholine was boiled at reflux for 14 h. The cooled solution was acidified with concentrated hydrochloric acid (ca. 100 mL) and extracted three times with 150-mL portions of ether. The combined ether layers were extracted with 10% aqueous sodium bicarbonate until free of acid and then discarded; the aqueous layer was acidified with concentrated hydrochloric acid and extracted with two 100-mL portions of ether. The combined ether layers were dried over magnesium sulfate, filtered, concentrated, and distilled to give 260.4 g (93%) of acid, bp 170 °C/0.01 mm (lit.[32] 140–160 °C/10^{-4} mm).

Ethyl 3-(Benzylthio)butanoate. The acid was esterified with ethanol in cyclohexane solvent in the presence of a few drops of sulfuric acid by azeotropic distillation of the water formed. The yield of ester, bp 112–121 °C/0.1–0.7 mm, was 83%.

2-Methyl-4-(benzylthio)-2-pentanol. An ether solution of ca. 0.52 mol of methylmagnesium iodide was prepared from 12.6 g of magnesium (0.52 mol) and 74 g (0.52 mol) of methyl iodide in the usual manner. A solution of 59.5 g (0.25 mol) of ethyl 3-(benzylthio)butanoate in 150 mL of ether was added dropwise over 45 min, the solution refluxed for 1 h and cooled, and the reaction quenched by the addition of 250 mL of saturated ammonium chloride. The ether layer was decanted and the precipitated magnesium salts were dissolved in cold 15% aqueous sulfuric acid. The aqueous layer was extracted three times with 50-mL portions of ether, and the combined ether layers were washed once with 10% aqueous sodium bicarbonate, dried over sodium sulfate, filtered, and concentrated to leave a viscous oil.

NMR: δ 1.02 (s), 1.08 (s), 1.24 (d, J = 6 Hz, altogether 9 H), 1.59 (m, 2 H), 2.72 (sextet, J = 6 Hz, 1 H), 3.00 (s, 1 H), 3.57 (s, 2 H), 7.07 (s, 5 H).

4-Mercapto-2-methyl-2-pentanol. Into a three-necked flask equipped with a mechanical stirrer, dry ice condenser, and ammonia inlet containing 28.8 g (0.128 mol) of 2-methyl-4-(benzylthio)-2-pentanol was passed 500 mL of ammonia. Small pieces of sodium (total ca. 5 g, 0.22 mol) were dropped into the flask with stirring until the ammonia solution turned permanently blue. Then 20 g of solid ammonium chloride was added in small portions and the ammonia was allowed to evaporate overnight. Residual ammonia was removed in a stream of nitrogen passed through the flask, the remaining solid was dissolved in 100 mL of water, and the solution was acidified with 15% sulfuric acid and extracted four times with 100-mL portions of ether. The ether was washed with brine, dried over magnesium sulfate, filtered, and concentrated to give 17.5 g of liquid. Distillation at 92 °C/22 mm yielded 13.2 g (81%) of the desired mercapto alcohol.

Anal. Calcd for $C_6H_{14}OS$: C, 53.68; H, 10.51. Found: C, 53.78; H, 10.53.

NMR: δ 1.23 (s, 6 H), 1.37 (d, J = 6 Hz, 3 H), 1.74 (apparent doublet, J = 6.5 Hz, 3 H), 2.8 (s, 1 H), 3.05 (sextet, J = 6 Hz, 1 H).

4,6,6-Trimethyl-1,3-oxathiane (2).[30] Condensation of 9.64 g (64.7 mmol) of 2-methyl-4-mercapto-2-pentanol, 2.83 g (94 mmol) of paraformaldehyde, 20 mL of concentrated sulfuric acid, and 10 mL of water was effected as described for **1** above. The yield, after distillation, bp 102 °C/53 mm, was 8.09 g (85%): n^{26}_D 1.4794.

(24) In entries 10 and 11, crystallization of phenylmagnesium bromide seems to have occurred at −78 °C but not at −40 °C.

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Anal. Calcd for $C_7H_{14}OS$: C, 57.49; H, 9.65. Found: C, 57.64; H, 9.64.

***cis*-2-(1-Hydroxybenzyl)-4,4,6-trimethyl-1,3-oxathiane (3, R = C_6H_5).** To a solution of 2.02 g (0.0138 mol) of 4,4,6-trimethyl-1,3-oxathiane (**1**) in 40 mL of THF at −78 °C under nitrogen was added 6.3 mL of 2.2 M butyllithium (0.0139 mol) in hexane. The mixture was allowed to warm (removal of cooling bath) for 20 min and was then recooled to −78 °C. Benzaldehyde (1.148 g, 0.0140 mol) was added with a syringe. The solution was stirred at −78 °C for 1 h, then at room temperature overnight, and quenched into 40 mL of saturated aqueous ammonium chloride. The mixture was twice extracted with 40-mL portions of ether. The combined extracts were dried over sodium sulfate and concentrated, and the residue was distilled, bp 100–120 °C/0.5 mm, yield 2.12 g (61%) of a mixture of diastereomers.

NMR: δ 1.1–1.5 (overlapping signals, total 11 H), 3.05 and 3.35 (broad s, total 1 H), 3.75 (sextet, 1 H), 4.5–5.1 (overlapping d of d, total 2 H), 7.3 (s, 5 H).

***cis*-2-Benzoyl-4,4,6-trimethyl-1,3-oxathiane (4, R = C_6H_5). A. By Oxidation of the Alcohol 3, R = C_6H_5.** To a solution of 0.57 mL (8.0 mmol) of dimethyl sulfoxide (Me_2SO, previously dried over calcium hydride) in 8 mL of methylene chloride in a three-necked, round-bottom flask under a nitrogen atmosphere, cooled to −78 °C in a dry ice–acetone bath, was added, dropwise, a solution of 0.85 mL (6.0 mmol) of trifluoroacetic anhydride (TFAA) with stirring which was continued for 20 min, when a white precipitate formed. Compound **3**, R = C_6H_5, 940 mg, 3.7 mmol in 10 mL of methylene chloride, was added dropwise with stirring while the temperature was maintained at −78 °C. After 1 h triethylamine (1.6 mL, 12.5 mmol; previously dried over calcium hydride) was added slowly; the precipitate disappeared. The solution was allowed to warm to 0 °C over 1 h and then poured into 40 mL of a 1:1:2 mixture of ether/hexane/saturated sodium bicarbonate solution. The organic layer was separated, washed wih 20 mL of 3 N hydrochloric acid followed by aqueous sodium bicarbonate and brine (3 × 20 mL), dried over Na_2SO_4, and concentrated to give 470 mg (50%) of product, mp 88–90 °C.

B. By Benzoylation of the Oxathiane 1. The compound was also obtained[30] from 2-lithio-4,4,6-trimethyl-1,3-oxathiane (lithium derivative of **1**) and ethyl benzoate but was admixed with the axial isomer, probably obtained by translithiation. Equilibration in ether with a Nafion XR resin over 2 days gave the equatorial isomer, which was purified by crystallization from ether–petroleum ether, yield 36%, mp 88–90 °C.

Anal. Calcd for $C_{14}H_{18}O_2S$: C, 67.16; H, 7.24. Found: C, 66.92; H, 7.19.

NMR: δ 1.33 (d, 3 H), 1.35 (s, 3 H), 1.61 (s, 3 H), 1.8–2.0 (m, 2 H), 3.90 (m, 1 H), 6.15 (s, 1 H), 7.5 (m, 3 H), 8.1 (m, 2 H).

^{13}C NMR spectrum: Table IV.[29]

***cis*-2-(1-Hydroxy-1-phenylethyl)-4,4,6-trimethyl-1,3-oxathiane (5a). A. Mixture of Diastereomers.** To 1.94 g (13.3 mmol) of **1** dissolved in 50 mL of dry THF cooled to −78 °C (dry ice–acetone bath) in a 100-mL round-bottom flask equipped with stirring bar and nitrogen inlet and capped with a rubber septum was added 6.1 mL (13.7 mmol) of *n*-butyllithium in hexane (2.25 M) with a syringe. The solution was allowed to warm for 20 min with stirring and was then recooled to −78 °C. Acetophenone (1.60 g, 13.3 mmol) was added with a syringe and the solution was stirred at −78 °C for 1 h and then at room temperature overnight. It was poured into 50 mL of saturated ammonium chloride and extracted twice with 40-mL portions of ether. The combined ether extracts were washed with brine, dried over sodium sulfate, and concentrated. The residue was distilled at 0.15 mm to remove excess acetophenone (bp up to 100 °C) and the residue distilled at 100–120 °C/0.05 mm to give 2.07 g (58.7%) of product containing the two diastereomers in a 30:70 ratio (**5aA**:**5aB**).

Anal. Calcd for $C_{15}H_{22}O_2S$: C, 67.63; H, 8.32. Found: C, 67.81; H, 8.29.

NMR: δ 1.06–1.28 (overlapping signals, 6 H), 1.34 (s, 3 H), 1.3–1.5 (m, 2 H), 1.62 and 1.64 (s, total 3 H), 3.22 (broad s, 1 H), 3.72 (m, 1 H), 4.98 and 5.05 (s, total 1 H, ratio 7:3), 7.2–7.6 (m, 5 H).

^{13}C NMR spectrum: Table V.[29]

B. From Phenyl Ketone and Methylmagnesium Iodide. A solution of 419 mg (1.68 mmol) of **4**, R = C_6H_5, in 5 mL of ether was added slowly to 7.5 mL of an ether solution of 6.8 mmol of methylmagnesium iodide prepared in the usual way. The solution was refluxed for 30 min, cooled, and hydrolyzed with saturated ammonium chloride. The layers were separated, the aqueous layer was extracted with 25 mL of ether, and the combined organic layers were washed with saturated aqueous sodium bicarbonate and then sodium chloride, dried over sodium sulfate, and concentrated to give 410 mg of crude product which distilled at 110–130 °C/0.3 mm, yield 379 mg (84.8%). The diastereomer ratio was 96:4 with the minor isomer from procedure A (**5aA**) being the principal one obtained here.

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Supplementary Material Available: Improved preparation of 4-mercapto-4-methyl-2-pentanol, preparation of alcohols **3** (Scheme I), R = CH_3, CH_2=CH, $(CH_3)_2CH$, $(CH_3)_3C$, and of *cis*-2-(1-hydroxybenzyl)–4,6,6-trimethyl-1,3-oxathiane, preparation of ketones **4** (Scheme I), R = CH_3, CH_2=CH, C_2H_5, $(CH_3)_2CH$, $(CH_3)_3C$, and **6** (Table II) R = C_6H_5 and CH_3, reaction of **4** (Scheme I), R = C_6H_5, with CH_3Li and **4**, R = CH_3, with C_6H_5MgX, C_6H_5Li, and $(C_6H_5)_2Mg$, and various preparations of diastereomer mixtures of **7a**, **7b**, and **7c** (Table II) and of **5b**, **5c**, **5d**, **5e**, **5f**, **5g**, **5h**, **5i**, and **5j** (Scheme I), and ^{13}C NMR spectra (Tables IV and V) (24 pages). Ordering information is given on any current masthead page.