pK_a values were measured spectrophotometrically using standard perchloric acid solutions of known H_0 value.

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Supplementary Material Available: ^{1}H NMR spectra for compounds **14**, **18–20**, and **22–28** (11 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.

Convenient Synthesis of α-Hetero-Substituted Acyloxathianes

Xu Bai[†] and Ernest L. Eliel*

W. R. Kenan Jr. Laboratories, Department of Chemistry, University of North Carolina, Chapel Hill, North Carolina 27599-3290

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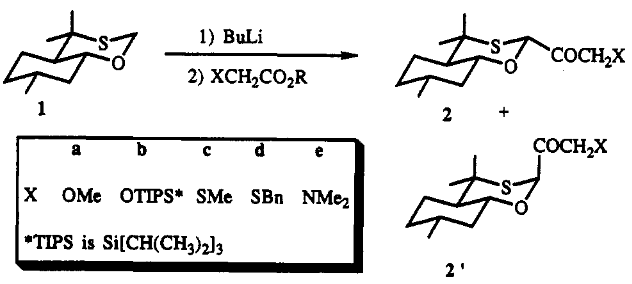
In contrast to simple esters, α-alkoxy, α-alkylthio, and α-dimethylamino esters react with lithiooxathiane **1**-Li in good yield to give the corresponding α-functionalized 2-acetylhexahydro-4,4,7-trimethyl-4*H*-1,3-benzoxathiin **2**. In some cases, mixtures of diastereomers (**2**, **2′**) are obtained. The reaction has been extended to α-methoxy- and α-[(triisopropylsilyl)oxy]propanoyl and α-(methylthio)butanoyl homologs which have chiral centers at C(α).

Introduction and Results

In connection with another problem[1] we had occasion to prepare chiral 2-acyloxathianes (**2**) with α-alkoxy, α-alkylthio, and α-dialkylamino substituents. In previous syntheses of corresponding 2-acyloxathianes devoid of α-substituents, we had found the reaction of 2-lithiooxathiane (**1**-Li) with esters to proceed in poor yield at best;[2] the preferred way of preparing these compounds (X = H or alkyl in Scheme I) was condensation of **1**-Li either with aldehydes followed by Swern oxidation[3] or with nitriles followed by hydrolysis.[4] In contrast, the α-substituted acyloxathianes have now been synthesized in good yield and generally high conversion (see Table I) by condensation of esters with **1**-Li (Scheme I). An interesting aspect of this reaction, not reported previously, is the isolation of the axial ketone **2′** along with the equatorial one (**2**) in the case of the α-alkoxy compounds (entries 1, 2 in Table I). Evidently, because of the greater acidity of the acylated products at C(2), proton transfer from the product **2** to the starting material **1**-Li takes place, with formation of the more stable[5] equatorial anion of **2′**; this process will be discussed in more detail below. In the case of the (triisopropylsilyl)oxy ("O-TIPS") compound, **2b′** was actually the major product, but was converted to **2b** by (slow) silica gel chromatography, indicating that, as expected, free **2b** is more stable than **2b′**. In the case of the synthesis of the alkylthio compounds (**2c**, **2d**, entries 3 and 4 in Table I) only a small amount of the axial isomers (**2c′**, **2d′**) was formed (as indicated by NMR spectroscopy) but not isolated; no axial isomer (**2e′**) was observed in the case of the dimethylamino compound (entry 5 in Table I).

Scheme I



1 2 2′

	a	b	c	d	e
X	OMe	OTIPS*	SMe	SBn	NMe_2

*TIPS is $Si[CH(CH_3)_2]_3$

Table I. Reactions of 2-Lithiooxathiane with Substituted Acetates

entry	series	X	$2/2'/1^a$	2^b	$2'^b$	1^c
1	a	OMe	61/22/17	54	17	*d*
2	b	OTIPS	36/64/*e*	39	52*f*	*d*
3	c	SMe	85/*e*/15	76	*d*	13
4	d	SBn	74/*e*/26	55	*g*	17
5	e	NMe_2	*h*	82	*i*	*d*

[a] Ratio of crude product mixture determined by proton NMR. [b] Isolated yield. [c] Recovered yield. [d] Not isolated. [e] Too little material present, not calculated. [f] Converted to **2b** on silica gel. [g] Impure. [h] Almost complete conversion to **2e**. [i] Not observed.

Table II. Chemical Shifts (ppm) of the Geminal Ring Methyl Protons[a]

compd	2a	2a′	2b	2b′	2c	2d	2d′	2e
a-Me	1.43	1.25	1.43	1.25	1.44	1.43	1.23	1.44
e-Me	1.26	1.20	1.25	1.19	1.27	1.26	1.20	1.27

[a] **a.** Methoxy ketone. **b.** Triisopropylsiloxy ketone. **c.** Methylthio ketone. **d.** Benzylthio ketone. **e.** *N*,*N*-Dimethylamino ketone.

Table III. C=O Frequencies (cm^{-1}) in the IR spectrum

compd	IR (C=O)
2a	1740
2a′	1731
2b	1740
2b′	1729

Assignment of Configuration. Compound **2b** has been previously described.[6] That **2b′** is the diastereomer at C(2) of **2b** follows from its epimerization to the latter. In the other cases, **2a**/**2a′**, **2c**/**2c′**, **2d**/**2d′**, and **2e**, the assignment of the major isomer as the equatorial one was confirmed by comparison of the proton chemical shifts of the axial and equatorial methyl groups in the oxathiane moiety (Table II): corresponding protons resonate at higher field in the 2-axial (primed) series, presumably because of the shielding effect of the axial carbonyl moiety;

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

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Table IV. CI-MS (Isobutane) of Methoxymethyl Ketones

compd	273	241	200	138
2a	100[a]	2	20	6
2a′	100[b]	19	42	13

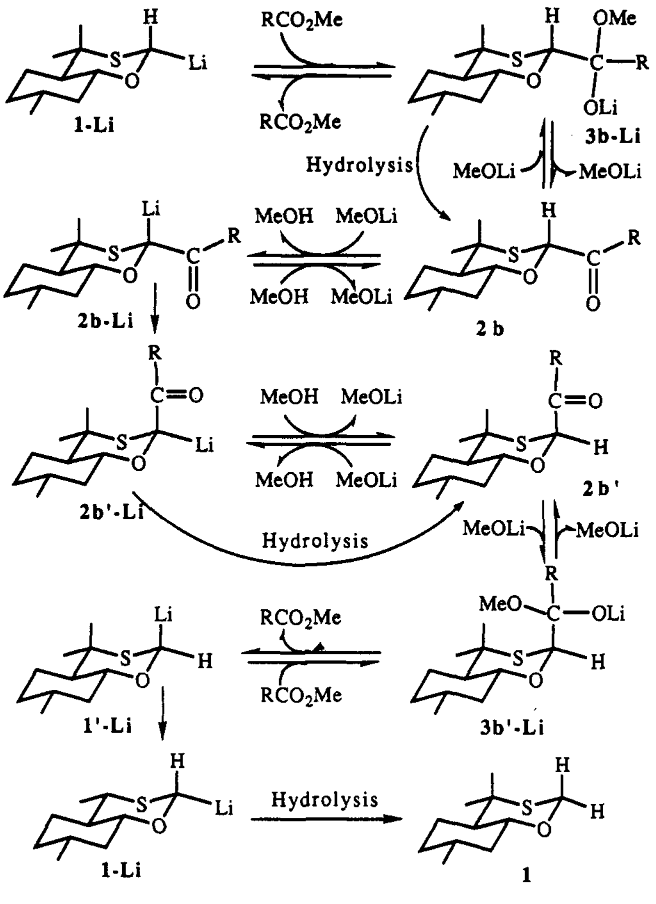
[a] 78% of sum of the four peaks shown. [b] 57% of sum of the four peaks shown.

Table V. Kinetic Studies[a]

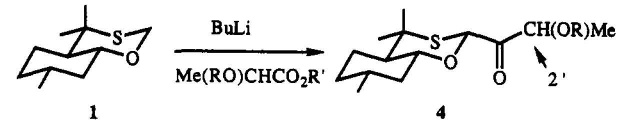
entry	T (°C)	time (h)	1:2b:2b′
1	-78	0.25	57:43:0
2	-78	4	56:44:0
3	-78	9 (0)[b]	66:26:8
4	-22	25	65:8:27
5	-22	43.5 (0)[c]	73:4:23
6	rt	3	72:6:22
7	rt	8.5	81:7:12

[a] This experiment was performed as follows. Ester **2b** ($TIPSOCH_2CO_2Me$) was added to a solution of the lithiated oxathiane **1** in THF. Then, the reaction mixture was stirred for 9 h at -78 °C, and then 43.5 h at -22 °C, and finally 8.5 h at room temperature. At intervals, an aliquot of reaction mixture was taken out and hydrolyzed by saturated aqueous NH_4Cl. The ^1H NMR of each crude sample was recorded immediately. [b] The temperature was raised to -22 °C at this time, and the time count starts at zero again. [c] Temperature raised to room temperature; new time count.

Scheme II



Scheme III



Scheme IV

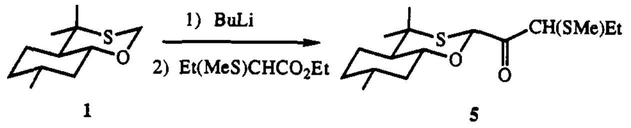


Table VI. Reactions of Optically Active Lactates

	protected lactate			4	
series	config	R	R′	C-2′ config	yield (%)
a[a]	*S*	Me	Et	*S*	72[b]
b	*R*	Me	Me	*R*	50[c]
c	*S*	TIPS	Et	*S*	74[b]
d	*R*	TIPS	Me	*R*	63[d]

[a] Starting material of 80% ee yielded **4a** with 80% de. [b] Isolated yield based on oxathiane **1** converted. [c] Isolated yield without recovery of **1**, 66% conversion of **1** based on ^1H NMR of the crude material. [d] Isolated yield without recovery of **1**, 80% conversion of **1** based on ^1H NMR of the crude material.

predictably, the differential is larger for the (more proximate) axial methyl group. In the case of the alkoxy (**a**) and TIPS-O (**b**) analogs, there is, in addition, a characteristic difference in the C=O stretching frequency in the infrared (Table III). Comparison of the CI-MS spectra of **2a** and **2a′** (Table IV) is also of interest: the less stable axial isomer clearly shows more fragmentation of the M + 1 peak than the equatorial.

Interconversion of 2b and 2b′. The results of a time- and temperature-dependent analysis of the reaction of **1**-Li with $TIPSOCH_2CO_2Me$ are shown in Table V. The ester was added to a stirred solution of **1**-Li in THF at -78 °C. After 9 h, the temperature was raised to -22 °C and after 52.5 h to room temperature. At -78 °C, reaction is incomplete and little epimerization of the initially formed **2b** occurs. In terms of the interpretation of Scheme II, it would appear that **1**-Li, the starting ester, and **3b**-Li are in equilibrium. Since the ketone is largely in form of its adduct, no double addition occurs. Hydrolysis (work up) of **3b**-Li at this point produces **2b**. When the temperature is raised to -22 °C, **3b**-Li partly reverts to **1**-Li (whose proportion increases) and in part loses MeOLi to give **2b** which, being quite acidic, is converted by either MeOLi or **1**-Li to **2b**-Li; the latter spontaneously epimerizes to **2b′**-Li. Hydrolysis at this stage generates **2b′** as well as **1** and an amount of **2b** which decreases with time. Evidently, however, both **2b** and **2b′** and MeOLi are in equilibrium with **3b**-Li and **3b′**-Li which revert to **1**-Li and MeOLi. As the temperature is raised, the proportion of **1**-Li at equilibrium increases, presumably because dissociation is entropically favored.

Apparently the adducts of lithiooxathiane to simple esters do not persist as **3b**-Li but decompose spontaneously to **2b** which then undergoes a second addition of **1**-Li to give a tertiary carbinol. Presumably, α-alkoxy, α-alkylthio, and α-dialkylamino substituents stabilize **3b**-Li, perhaps by providing chelation sites for Li additional to that provided by the oxathiane ring. Admittedly this interpretation is speculative, in particular, since it is not known to what extent the lithio derivatives resemble enolates.

Reaction of 1-Li with Higher α-Alkoxy and α-Alkylthio Esters. As an extension of the reactions discussed

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above, reactions of lithiooxathiane **1**-Li with O-protected lactates (Scheme III) and with 2-(methylthio)butyrate (Scheme IV) were investigated. The results with (*S*)- and (*R*)-*O*-methyl and *O*-triisopropylsilyl lactates (Scheme III) are summarized in Table VI. Enantiomeric starting esters of 80% and 100% ee (enantiomer excess) were used. The optical yield of the product in all cases is near 100%; i.e., except for entry 1 where the ee of the starting material was only 80%, diastereomerically and enantiomerically pure products resulted. No epimerization occurred in the condensation at −78 °C, even though **4** (R = Me) very slowly epimerizes on silica gel.

In the case of the 2-(methylthio)butyrate (Scheme IV), since only racemic starting material was available, two diastereomeric products were obtained in nearly equal yield at −78 °C, indicating the absence of kinetic resolution. The products were partially separated (in the head and tail fractions) by rapid chromatography on silica gel. Attempts at more quantitative separation failed, since slower and more careful chromatography led to epimerization.

When the reaction mixture (Scheme IV) was allowed to stand overnight at −22 °C before quenching, the epimer ratio changed to 76:24 with the α-*R* isomer (see below) predominating. Equilibration at 20 °C indicated a 58:42 ratio; evidently the α-*R* diastereomer is the more stable one. (The configurational assignment of these ketones rests on that of the phenyllithium adduct of one of them effected by X-ray diffraction analysis; see the accompanying paper[1]).

Conclusion

In contrast to simple esters, α-alkoxy-, α-alkylthio-, and α-dimethylamino-substituted esters react cleanly with lithiooxathiane **1**-Li to give the corresponding 2-acyloxathianes. Under certain conditions, axial 2-acyl compounds are formed. When there is a chiral center at C(α), the method can be used to obtain individual diastereomers by chromatographic separation. The products are useful for the synthesis of diastereomerically pure, functionalized tertiary carbinols.[1]

Experimental Section

Proton NMR spectra were recorded at 200.1 MHz and ^{13}C NMR spectra at 50.3 MHz, both in CDCl$_3$. The TIPS protection of the hydroxyl group of the corresponding lactates with triisopropylsilyl chloride according to the previously described procedure[6,7] gives the desired products in excellent yields and apparently without racemization.

The diastereomer ratio and/or the ratio of the product to starting oxathiane in the crude materials below was calculated on the basis of integration of the C(2) proton signal of the oxathiane ring. Phenyllithium in cyclohexane/ether (Aldrich) was used as received. Oxathiane **1** was prepared as described in the literature.[8] All the compounds described were chemically over 95% pure based on ^{1}H NMR analysis.

2-(2′-Methoxyacetyl)hexahydro-4,4,7-trimethyl-4*H*-1,3-benzoxathiins 2a and 2a′. To a solution of 200 mg (1.00 mmol) of oxathiane **1** in 6 mL of THF at −78 °C under N$_2$ was added, dropwise, 0.8 mL of butyllithium (1.6 M in hexanes). After being stirred for 10 min, the mixture was allowed to warm to 0 °C and then recooled to −78 °C. Methyl methoxyacetate (0.30 mL, 3.00 mmol) was rapidly added dropwise, and the mixture was stirred for another 0.5 h at −78 °C and then stored in a freezer (−22 °C) overnight. It was quenched with saturated aqueous NH$_4$Cl and extracted with diethyl ether (Et$_2$O). The organic layer was separated, washed with 10 mL of brine, dried (Na$_2$SO$_4$), and concentrated to yield 297 mg of crude products with a ratio of **2a** to **2a′** to **1** of 61:22:17. Purification by flash column chromatography on silica gel with 8% ethyl acetate (EtOAc) in hexanes gave 129 mg (54% yield) of crystalline product **2a** and 47 mg (17% yield) of an oily material, **2a′**. An analytical sample of **2a** was obtained by recrystallization from pentane, mp 87.5–88 °C.

Equatorial epimer **2a**. ^{1}H NMR: δ 0.91 (d, J = 6.4 Hz, 3 H), 1.26 (s, 3 H), 1.43 (s, 3 H), 3.40 (s, 3 H), 3.41 (dt, J = 4.4, 10.4 Hz, 1 H), 4.41, 4.45 (AB, J = 18.8 Hz, 2 H), 5.54 (s, 1 H) and others. ^{13}C NMR: δ 22.0 (CH$_3$), 22.4 (CH$_3$), 24.3 (CH$_2$), 29.2 (CH$_3$), 31.4 (CH), 34.6 (CH$_2$), 41.5 (CH$_2$), 44.1 (C), 50.4 (CH), 59.4 (CH$_3$), 74.4 (CH$_2$), 77.1 (CH), 81.5 (CH), 202.3 (C). IR: 1740 cm^{-1} (C=O). MS (CI, isobutane) *m/e*: 273 (100), 241 (2), 200 (20), 138 (6). Anal. Calcd for C$_{14}$H$_{24}$O$_3$S: C, 61.74; H, 8.88. Found: C, 61.60, 61.63; H, 8.94, 9.00.

Axial epimer **2a′**. ^{1}H NMR: δ 0.89 (d, J = 6.6 Hz, 3 H), 1.20 (s, 3 H), 1.25 (s, 3 H), 3.38 (s, 3 H), 4.12 (dt, J = 4.5, 10.4 Hz, 1 H), 4.20, 4.30 (AB, J = 16.8 Hz, 2 H), 5.25 (s, 1 H), and others. ^{13}C NMR: δ 22.0 (CH$_3$), 23.8 (CH$_3$), 24.1 (CH$_2$), 29.9 (CH$_3$), 31.2 (CH), 34.6 (CH$_2$), 41.7 (CH$_2$), 43.3 (C), 50.2 (CH), 59.4 (CH$_3$), 71.5 (CH), 74.8 (CH$_2$), 75.9 (CH), 207.0 (C). IR: 1731 cm^{-1} (C=O). MS (CI, isobutane) *m/e*: 273 (100), 241 (9), 200 (42), 138 (13).

Methyl (Triisopropylsiloxy)acetate. A mixture of 1.51 mL (20 mmol) of methyl glycolate, 4.28 mL (20 mmol) of triisopropylsilyl chloride, and 3.4 g (50 mmol) of imidazole in 6 mL of DMF was stirred for 72 h at rt. The solution was diluted with 20 mL of Et$_2$O, and 20 mL of saturated aqueous NH$_4$Cl was added. The organic layer was separated, washed twice with 10 mL of 2 N aqueous HCl, dried (MgSO$_4$), and concentrated to yield 4.50 g of crude product which was chromatographed on silica gel with EtOAc/hexanes (4/96) to give 3.60 g (73%) of pure liquid product.

^{1}H NMR: δ 1.00–1.16 (m, 21 H), 3.72 (s, 3 H), 4.31 (s, 2 H). ^{13}C NMR: δ 11.9 (CH), 17.8 (CH$_3$), 51.6 (CH$_3$), 61.9 (CH$_2$), 172.0 (C).

2-[2′-(Triisopropylsiloxy)acetyl]hexahydro-4,4,7-trimethyl-4*H*-1,3-benzoxathiins 2b and 2b′. By the procedure described for **2a**, 2.54 g of a crude mixture of **2b** and **2b′** in a ratio of 36:64 was obtained from 1.00 g (5.00 mmol) of **1** and 1.85 g (7.50 mmol) of methyl (triisopropylsiloxy)acetate. Separation of this mixture by flash column chromatography on silica gel with EtOAc/hexanes gave 0.817 g (39%) of liquid product **2b** and a fraction of 1.078 g (52%) of a mixture of **2b** and **2b′** in a ratio of 11:89. Slow conversion of **2b′** to **2b** on silica gel was observed. However, nearly pure **2b′** was obtained by fast chromatography. Both ^{1}H and ^{13}C NMR spectra of **2b** were identical to those reported.[7]

Equatorial epimer **2b**. ^{1}H NMR: δ 0.90 (d, J = 6.4 Hz, 3 H), 1.25 (s, 3 H), 1.43 (s, 3 H), 3.40 (dt, J = 4.3, 10.5 Hz, 1 H), 4.58, 4.60 (AB, J = 18.5 Hz, 2 H), 5.69 (s, 1 H), and others. ^{13}C NMR: δ 11.9 (CH), 17.9 (CH$_3$), 22.0 (CH$_3$), 22.4 (CH$_3$), 24.3 (CH$_2$), 29.2 (CH$_3$), 31.4 (CH), 34.6 (CH$_2$), 41.4 (CH$_2$), 44.0 (C), 50.4 (CH), 66.8 (CH$_2$), 77.1 (CH), 80.7 (CH), 202.8 (C). IR: 1740 cm^{-1} (C=O).

Axial epimer **2b′**. ^{1}H NMR: δ 0.89 (d, J = 6.4 Hz), 1.04 (s), 1.19 (s), 1.25 (s), 4.28 (dt, J = 4.4, 10.5 Hz), 4.34, 4.56 (AB, J = 16.6 Hz), 5.51 (s), and others. ^{13}C NMR: δ 11.8 (CH), 17.9 (CH$_3$), 22.0 (CH$_3$), 23.7 (CH$_3$), 24.1 (CH$_2$), 30.1 (CH$_3$), 31.2 (CH), 34.7 (CH$_2$), 41.9 (CH$_2$), 43.2 (C), 50.2 (CH), 67.5 (CH$_2$), 71.3 (CH), 74.4 (CH), 207.3 (C). IR: 1729 cm^{-1} (C=O).

2-[2′-(Methylthio)acetyl]hexahydro-4,4,7-trimethyl-4*H*-1,3-benzoxathiins 2c and 2c′. By the procedure described for **2a** and **2b**, 300 mg of a crude mixture of the desired ketone **2c** and **1** in a 85:15 ratio, apparently also containing a trace amount of ketone **2c′** according to the ^{1}H NMR spectrum (a minor peak at 5.56 ppm indicated the possible presence of axial ketone **2c′**), was obtained from 200 mg (1.0 mmol) of **1** and 0.41 mL (3.0 mmol) of ethyl (methylthio)acetate. Purification by flash column chromatography on silica gel with EtOAc/hexanes gave 208 mg (83% based on **1** converted) of liquid product **2c**, 27 mg (13%) of recovered oxathiane **1** and a trace amount of **2c′**.

Equatorial epimer **2c**. ^{1}H NMR: δ 0.91 (d, J = 6.4 Hz, 3 H), 1.27 (s, 3 H), 1.44 (s, 3 H), 2.08 (s, 3 H), 3.36, 3.48 (AB, J = 14.3 Hz, 2 H), 3.46 (dt, J = 4.3, 10.4 Hz, 1 H), 5.76 (s, 1 H), and others. ^{13}C NMR: δ 15.8 (CH$_3$), 22.0 (CH$_3$), 22.4 (CH$_3$), 24.3 (CH$_2$), 29.2 (CH$_3$), 31.3 (CH), 34.5 (CH$_2$), 38.4 (CH$_2$), 41.5 (CH$_2$), 44.1 (C), 50.3 (CH), 77.3 (CH), 80.7 (CH), 199.3 (C). Anal. Calcd for C$_{14}$H$_{24}$O$_2$S$_2$ (M$^+$): 288.1219. Found: 288.1229.

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(8) Eliel, E. L.; Lynch, J. E.; Kume, F.; Frye, S. V. *Org. Synth.* **1987**, *65*, 215.

Ethyl (Benzylthio)acetate. To a stirred mixture of 1.13 mL (0.01 mol) of ethyl thioacetate and 2.76 g (0.02 mol) of K_2CO_3 in 10 mL of ethanol at rt was added 1.21 mL (0.01 mol) of benzyl bromide dropwise. The mixture was stirred for 30 min and then concentrated, and the residue was dissolved in 15 mL of water and 30 mL of Et_2O. The organic layer was separated, dried (Na_2SO_4), and concentrated to give 2.04 g (98%) of pure liquid product. The ^1H NMR spectrum was identical to that reported in the literature.[9]

^1H NMR: δ 1.27 (t, J = 7.1 Hz, 3 H), 3.05 (s 2 H), 3.81 (s, 2 H), 4.16 (q, J = 7.1 Hz, 2 H), 7.25–7.33 (m, 5 H). ^{13}C NMR: δ 14.1, 32.2, 36.2, 61.2, 127.1, 128.4, 129.1, 137.2, 170.3.

2-[2′-(Benzylthio)acetyl]hexahydro-4,4,7-trimethyl-4*H*-1,3-benzoxathiins 2d and 2d′. By the procedure described for **2a**, reaction of 200 mg of **1** and 273 mg of ethyl (benzylthio)acetate yielded 199 mg (66% based on converted **1**) of the desired liquid **2d**; 34 mg (17%) of **1** was recovered. The chromatogram also yielded a small amount of impure isomer **2d′**.

Major equatorial isomer **2d**. ^1H NMR: δ 0.91 (d, J = 6.4 Hz, 3 H), 1.26 (s, 3 H), 1.43 (s, 3 H), 3.25, 3.39 (AB, J = 14.6 Hz, 2 H), 3.43 (dt, J = 4.4, 10.4 Hz, 1 H), 3.69 (s, 2 H), 5.69 (s, 1 H), 7.21–7.31 (m, 5 H), and others. ^{13}C NMR: δ 21.9 (CH_3), 22.3 (CH_3), 24.2 (CH_2), 29.2 (CH_3), 31.3 (CH), 34.5 (CH_2), 35.0 (CH_2), 41.4 (CH_2), 44.0 (C), 50.2 (CH), 77.2 (CH), 80.9 (CH), 127.1 (CH), 128.4 (CH), 129.1 (CH), 137.2 (C), 199.6 (C). Anal. Calcd for $C_{20}H_{29}O_2S_2$ (MH^+): 365.1609. Found: 365.1608.

Minor axial isomer **2d′**. ^1H NMR: δ 0.91 (d, J = 6.5 Hz, 3 H), 1.20 (s, 3 H), 1.23 (s, 3 H), 3.15, 3.51 (AB, J = 14.6 Hz, 2 H), 3.71 (s, 2 H), 4.11 (dt, J = 4.6, 10.3 Hz, 1 H), 5.45 (s, 1 H) and others.

2-[2′-(*N*,*N*-Dimethylamino)acetyl]hexahydro-4,4,7-trimethyl-4*H*-1,3-benzoxathiin (2e). By the procedure described for **2a**, reaction of 200 mg of **1** and 0.42 mL of ethyl (*N*,*N*-dimethylamino)acetate (Aldrich) yielded 234 mg (82%) of the desired liquid equatorial ketone **2e**. An analytical sample of **2e** (mp 86–87.5 °C) was obtained by flash chromatography on silica gel with EtOAc/hexanes. The axial epimer of this ketone was not observed in ^1H NMR spectrum.

^1H NMR: δ 0.92 (d, J = 6.5 Hz, 3 H), 1.27 (s, 3 H), 1.44 (s, 3 H), 2.63 (s, 6 H), 3.41 (dt, J = 4.4, 10.5 Hz, 1 H), 3.88, 3.98 (AB, J = 19.1 Hz, 2 H), 5.51 (s, 1 H), and others. ^{13}C NMR: δ 21.9 (CH_3), 22.3 (CH_3), 24.1 (CH_2), 29.2 (CH_3), 31.2 (CH), 34.5 (CH_2), 41.4 (CH_2), 43.9 (CH), 45.5 (CH_3), 50.3 (CH), 64.0 (CH_2), 76.9 (CH), 81.8 (CH), 202.3 (3), and others. IR: 1732 cm^{-1} (C=O). Anal. Calcd for $C_{15}H_{27}NO_2S$: C, 63.13; H, 9.54. Found: C, 62.97, H, 9.42.

(*R*)-Methyl 2-Methoxypropanoate.[10] A mixture of 2.23 g of (*R*)-(+)-methyl lactate, 10 mL of iodomethane, and 2.73 g of silver oxide was stirred for 24 h at room temperature. The liquid was filtered, and the residue was washed with Et_2O. Distillation gave 0.90 g of an azeotropic mixture (bp 132 °C) of the desired product and the starting lactate in a ratio of 2:1 identified by ^1H NMR. Flash chromatography on silica gel with Et_2O/pentane (15/85) yielded 0.57 g (21%) of the desired ester free of starting lactate. Its ^1H NMR spectrum was in accord with that reported.[11]

^1H NMR: δ 1.38 (d, J = 6.8 Hz, 3 H), 3.37 (s, 3 H), 3.74 (s, 3 H), 3.87 (q, J = 6.8 Hz, 1 H).

2-[(2′*R*)-2′-Methoxypropanoyl]hexahydro-4,4,7-trimethyl-4*H*-1,3-benzoxathiin (4b). By the procedure described for **2a**, reaction of 400 mg of **1** and 0.47 g of (*R*)-2-methoxypropionate for 30 min at −78 °C yielded a crude product containing the desired ketone **4b** and starting oxathiane **1** in a 66:34 ratio. Chromatographic separation on silica gel with EtOAc/hexanes (5/95) gave 284 mg (50%, 100% de) of liquid product **4b**.

^1H NMR: δ 0.86 (d, J = 6.4 Hz, 3 H), 1.21 (s, 3 H), 1.32 (d, J = 6.8 Hz, 3 H), 1.40 (s, 3 H), 3.28 (s, 3 H), 3.40 (dt, J = 4.3, 10.4 Hz, 1 H), 4.20 (q, J = 6.8 Hz, 1 H), 5.63 (s, 1 H), and others. ^{13}C NMR: δ 17.5 (CH_3), 21.9 (CH_3), 22.0 (CH_3), 24.2 (CH_2), 29.1 (CH_3), 31.3 (CH), 34.5 (CH_2), 41.4 (CH_2), 44.1 (CH), 50.4 (CH), 57.5 (CH_3), 77.2 (CH), 78.9 (CH), 80.2 (CH), 204.9 (C). Anal. Calcd for $C_{15}H_{27}O_3S$ (MH^+): 287.1680. Found: 287.1678.

2-[(2′*S*)-2′-Methoxypropanoyl]hexahydro-4,4,7-trimethyl-4*H*-1,3-benzoxathiin (4a). By the procedure described for **4b**, 261 mg of crude products was obtained from 200 mg of **1** and 396 mg of (*S*)-ethyl 2-methoxypropanoate[12] (80% ee). Rapid chromatographic separation on silica gel with EtOAc/hexanes gave 147 mg (80% de, 72% yield based on **1** converted) of liquid product **4a**; 58 mg (29%) of **1** was recovered. In another run, very slow epimerization was observed on a silica gel plate during separation.

^1H NMR: δ 0.89 (d, J = 6.4 Hz, 3 H), 1.24 (s, 3 H), 1.30 (d, J = 6.8 Hz, 3 H), 1.42 (s, 3 H), 3.29 (s, 3 H), 3.40 (dt, J = 4.3, 10.4 Hz, 1 H), 4.30 (q, J = 6.8 Hz, 1 H), 5.66 (s, 1 H), and others. ^{13}C NMR: δ 16.7 (CH_3), 21.9 (CH_3), 22.4 (CH_3), 24.2 (CH_2), 29.2 (CH_3), 31.3 (CH), 34.5 (CH_2), 41.4 (CH_2), 44.0 (C), 50.3 (CH), 57.6 (CH_3), 77.1 (CH), 78.6 (CH), 81.0 (CH), 205.2 (C).

(*S*)-Ethyl 2-(Triisopropylsiloxy)propanoate. By the procedure described above for the lower homolog, 1.99 g (90%) of pure liquid product was obtained from 0.91 mL (8.0 mmol) of (*S*)-ethyl lactate, 1.71 mL (8.0 mmol) of triisopropylsilyl chloride, and 1.36 g of imidazole.

^1H NMR: δ 1.04 (s, 21 H), 1.24 (t, J = 7.1 Hz, 3 H), 1.39 (d, J = 6.7 Hz, 3 H), 4.15 (q, J = 7.1 Hz, 2 H), 4.38 (q, J = 6.7 Hz, 1 H). ^{13}C NMR: δ 12.1 (CH), 14.2 (CH_3), 17.8 (CH_3), 21.7 (CH_3), 60.6 (CH_2), 68.5 (CH), 174.2 (C).

(*R*)-Methyl 2-(Triisopropylsiloxy)propanoate. By the procedure described above, 1.18 g (91%) of the desired liquid product was obtained from 0.48 mL (5.0 mmol) of (*R*)-methyl lactate, 1.07 mL (5.0 mmol) of triisopropylsilyl chloride, and 0.75 g of imidazole.

^1H NMR: δ 1.04 (s, 21 H), 1.40 (d, J = 6.7 Hz, 3 H), 3.70 (s, 3 H), 4.41 (q, J = 6.7 Hz, 1 H). ^{13}C NMR: δ 12.1 (CH), 17.8 (CH_3), 21.7 (CH_3), 51.6 (CH_3), 68.5 (CH), 174.5 (C).

2-[(2′*S*)-2′-(Triisopropylsiloxy)propanoyl]hexahydro-4,4,7-trimethyl-4*H*-1,3-benzoxathiin (4c). By the procedure described for **4b**, reaction of 400 mg of **1** and 823 mg of (*S*)-ethyl 2-(triisopropylsiloxy)propanoate yielded 509 mg (100% de, 74% yield based on **1** converted) of the desired liquid product **4c**; 80 mg (20%) of **1** was recovered.

^1H NMR: δ 0.91 (d, J = 6.4 Hz, 3 H), 1.06 (bs, 21 H), 1.26 (s, 3 H), 1.38 (d, J = 6.7 Hz, 3 H), 1.42 (s, 3 H), 3.44 (dt, J = 4.3, 10.3 Hz, 1 H), 4.71 (q, J = 6.7 Hz, 1 H), 5.86 (s, 1 H), and others. ^{13}C NMR: δ 12.4 (CH), 18.0 (CH_3), 20.8 (CH_3), 22.0 (CH_3), 22.5 (CH_3), 24.3 (CH_2), 29.4 (CH_3), 31.4 (CH), 34.6 (CH_2), 41.5 (CH_2), 43.7 (C), 50.4 (CH), 72.0 (CH), 77.6 (CH), 80.0 (CH), 205.0 (C). Anal. Calcd for $C_{23}H_{44}O_3SSi$: C, 64.43; H, 10.34. Found: C, 64.06; H, 10.08.

2-[(2′*R*)-2′-(Triisopropylsiloxy)propanoyl]hexahydro-4,4,7-trimethyl-4*H*-1,3-benzoxathiin (4d). By the procedure described for **4b**, reaction of 400 mg of **1** and 781 mg of (*R*)-ethyl (triisopropylsiloxy)propanoate yielded 1.07 g of a crude mixture containing **4d** and **1** in an 80:20 ratio. Chromatographic separation on silica gel with EtOAc/hexanes gave 540 mg (63% yield, 100% de) of the desired liquid product **4d**.

^1H NMR: δ 0.90 (d, J = 6.4 Hz, 3 H), 1.05 (bs, 21 H), 1.26 (s, 3 H), 1.41 (d, J = 6.9 Hz, 3 H), 1.45 (s, 3 H), 3.40 (dt, J = 4.3, 10.3 Hz, 1 H), 4.62 (q, J = 6.9 Hz, 1 H), 5.93 (s, 1 H), and others. ^{13}C NMR: δ 12.2 (CH), 17.9 (CH_3), 18.0 (CH_3), 21.8 (CH_3), 22.0 (CH_3), 22.4 (CH_3), 24.3 (CH_2), 29.2 (CH_3), 31.4 (CH), 34.6 (CH_2), 41.4 (CH_2), 44.2 (C), 50.5 (CH), 72.5 (CH), 77.1 (CH), 78.6 (CH), 205.8 (C). Anal. Calcd for $C_{23}H_{45}O_3SSi$ (MH^+): 429.2860. Found: 429.2840.

2-[2′-(Methylthio)butanoyl]hexahydro-4,4,7-trimethyl-4*H*-1,3-benzoxathiins ((*S*)-5 and (*R*)-5). By the procedure described for **2a**, 550 mg of a crude product mixture was obtained from 400 mg of **1** and 0.87 mL of ethyl 2-(methylthio)butyrate. The ^1H NMR spectrum indicated the presence of the desired ketones (76/24 of *R* to *S* epimer) and starting oxathiane **1** in a 68/32 ratio. Purification by chromatography on silica gel with EtOAc/hexanes returned 102 mg (26%) of **1** and gave 286 mg (61% based on **1** converted) of the desired liquid **5** (mixture). Both (*R*)- and (*S*)-isomers were obtained pure by partial chromatographic separation on silica gel with EtOAc/hexanes. Slow ep-

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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$_2$S$_2$ (MH$^+$): 317.1609. Found: 317.1610.

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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

Xu Bai[†] and Ernest L. Eliel*

W. R. Kenan Jr. Laboratories, Department of Chemistry, University of North Carolina, Chapel Hill, North Carolina 27599-3290

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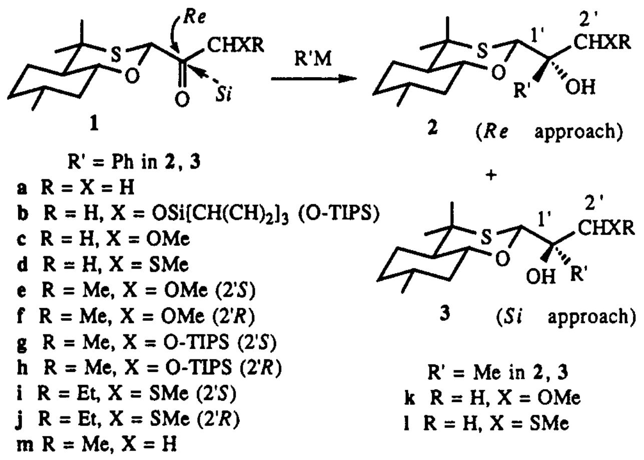
The addition of methyl- and phenylmagnesium bromide and phenyllithium to 2-(methoxyacetyl)-, 2-[(triisopropylsiloxy)acetyl]-, and 2-[(methylthio)acetyl]hexahydro-4,4,7-trimethyl-4*H*-1,3-benzoxathiin and the corresponding 2′-methyl, 2′-(triisopropylsiloxy)propionyl, and 2′-(methylthio)butyryl homologs 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$_2$OBn), 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)$_2$]$_3$ (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.

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