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DIASTEREOSELECTIVE SYNTHESIS OF α-ALKYL-β-HYDROXY THIOACETALS BY CHELATION-CONTROLLED ADDITION TO α-HYDROXY KETENE THIOACETALS

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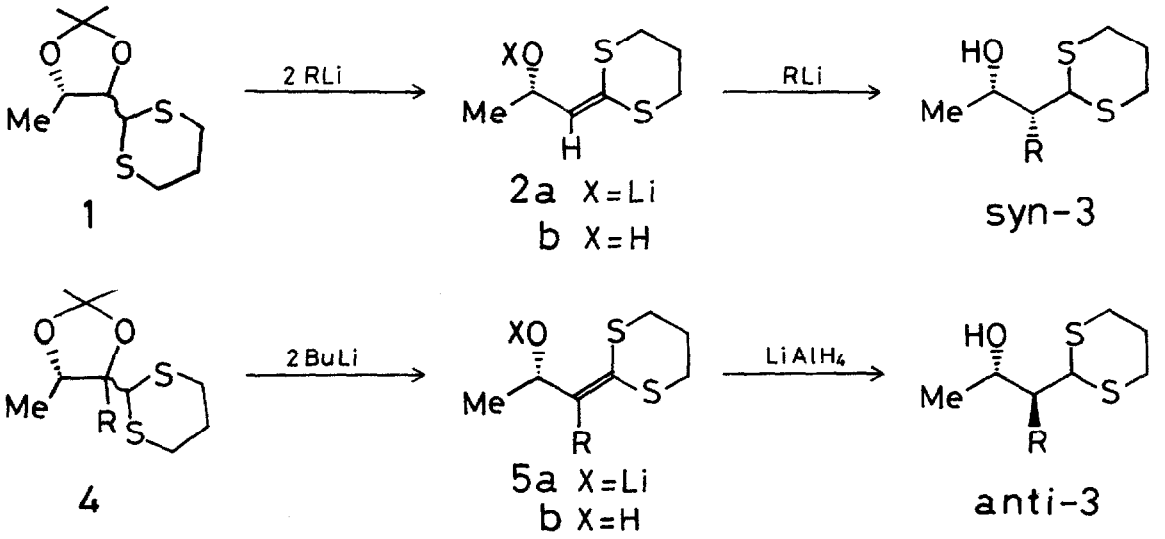
Summary: *Addition of alkyllithiums to (S)-2-(2-hydroxypropylidene)-1,3-dithiane and reduction of (S)-2-(2-hydroxy-1-alkylpropylidene)-1,3-dithianes with lithium aluminum hydride gave optically active syn- and anti-2-(2-hydroxy-1-alkylpropyl)-1,3-dithianes with high diastereoselectivity, respectively.*

Syn- and *anti*-β-alkyl alcohol functionalities are characteristic structural elements which are frequently found in macrolide[1a] and ionophore[1b,c] antibiotics as well as pheromones.[2] The conjugate addition of organometallics towards γ-alkoxy-α,β-unsaturated carbonyl compounds[3] provides one of the useful methods for the construction of the above stereochemically defined structure. Although the *syn*- and *anti*-stereochemistry in the conjugate addition is controlled by chelation[3a~e] or non-chelation (modified Felkin-Anh)[3e~h] in the transition state, respectively, the stereoselectivity is puzzling and not high in some cases. Recently the conjugate addition to vinyl sulfones possessing α-alkoxy- or β-hydroxyl group has been reported to provide an effective way of acyclic stereoselection by chelation control for natural product synthesis.[4] In this communication, we wish to describe highly diastereoselective synthesis of both *syn*- and *anti*-2-(2-hydroxy-2-alkylpropyl)-1,3-dithianes (3) by chelation-assisted addition of alkyllithiums and lithium aluminum hydride to 2-(2-hydroxypropylidene)-1,3-dithiane derivatives (2 and 5).[5]



The optically active ketene thioacetal **2b** was prepared by the reaction of 2.5 equiv. of butyllithium with 1,2-*O*-isopropylidene-1-(1,3-dithian-2-yl)-1,2-propanediol (**1**), which was easily available from methyl (S)-lactate or furnished by the bakers' yeast reduction of 1-(1,3-dithian-2-yl)-1,2-propanedione.[6] Although pure **2b** could be isolated by silica-gel TLC, the reactions of **2a** with alkyllithium were carried out in one pot from **1** without isolation of **2b** due to its instability. A representative reaction of **2a** with alkyllithiums is as follows (method A): To a solution of **1** (0.5 mmol) in THF (1.5 ml) and hexamethylphosphoric triamide (HMPA) (1.5 ml) was added 4 equiv. of methyllithium[7] (ca. 1M ether solution) at -50 °C. The mixture was allowed to warm to -25 °C during 2.5 h. Two equiv. of methyllithium was further added and stirred at the same temperature for 19 h and at 0 °C for 3 h. After addition of water, extractive workup and purification on silica-gel TLC (hexane : AcOEt = 5 : 1) gave an oil of diastereomerically pure *syn*-**3** (R=Me) (67%).

Addition of HMPA is necessary for the present addition reaction. Without HMPA alkyllithium caused only the abstraction of the proton at C_2 of 1,3-dithiane to give **2a**[8] and no *syn*-**3**. The *syn*-stereochemistry of **3** was confirmed by comparison of ^{1}H NMR and GLPC (FFAP 50 m) with those of authentic samples prepared from ethyl (2R,3S)- and (2S,3S)-3-hydroxy-2-methylbutanoates.[9,10] ^{1}H NMR analysis of the MTPA ester of *syn*-**3** with Eu(fod)$_3$ also proved absence of the enantiomer. It should be noted that alkyllithium generally abstracts the α-hydrogen of ketene thioacetal to produce stable allylic anion,[11] however, the α-oxygen anion of **2a** seems not only to prevent the hydrogen abstraction but also to assist the addition of alkyllithium to **2a**.

The results of the addition of several alkyllithiums to **2a** are summarized in Table 1. Although the yields are not satisfactory,[12] the complete stereoselection of *syn*-preference illustrates the efficiency of chelation

Table 1. Diastereoselective synthesis of α-alkyl-β-hydroxy thioacetals **3**

Entry	R	Method[a]	Yield/%	*syn* : *anti*	$[\alpha]_D^{25}$ /°(c EtOH)
1	Me	A	67	100 : 0[b]	-21 (0.96)
2	Me	B	71	0.5 : 99.5[b]	+24 (0.93)
3	Et	A	18	100 : 0[b]	-27 (0.38)
4	Et	B	55	4.0 : 96.0[b]	-6.3 (0.44)
5	n-Bu	A	32	97.5 : 2.5[c]	-20 (0.75)
6	n-Bu	B	59	0.6 : 99.4[c]	+9.3 (0.99)
7	i-Pr	A	16	95.6 : 4.4[b]	-37 (0.36)
8	Ph	A	50	100 : 0[d]	+26 (0.83)[e]
9	Ph	B	34	0 : 100[d]	+8.9 (0.97)[e]

[a] See the text. [b] Determined by a capillary GLPC (FFAP 50 m). [c] Determined by HPLC (JASCO Finepak SIL 25 cm, hexane : isopropyl alcohol = 50 : 1). [d] No isomer was detected by ^{1}H NMR and isolated by TLC. [e] Measured in $CHCl_3$.

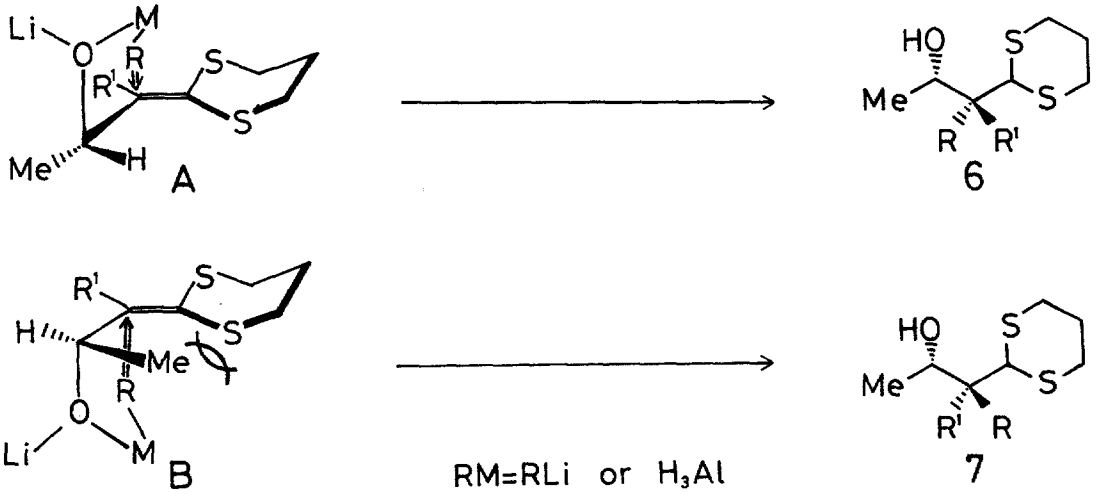
control in the addition of alkyl- and phenyllithiums (entries 1, 3, and 8) except butyllithium (97.5%) and isopropyllithium (95.6%) (entries 5 and 7).

Next, expecting non-chelation (modified Felkin-Anh type) control to obtain *anti*-**3**, the reaction of *O*-t-butyldimethylsilyl-protected **2b** with methyllithium was examined, however, resulting in formation of a complex mixture. Then, addition of hydride, instead of alkyllithium, to **5b** possessing alkyl group R was explored on the basis of the result of the diastereoselective reduction of α-oxo ketene thioacetals with lithium aluminum hydride.[13]

Acetonide **4**, the precursor of **5** was readily available from methyl (*S*)-lactate *via* addition of alkyllithium to 2-t-butyldimethylsiloxy-1-(1,3-dithian-2-yl)-1-propanone.[14] Treatment of **4** with 2 equiv. of butyllithium at -70 °C to -50 °C for 1.5 h, followed by addition of aqueous NH_4Cl and extractive workup gave **5b**, which was immediately subjected to the reduction. Thus, **5b** was added to lithium aluminum hydride (1 equiv.) in THF at -25 °C and then heated under reflux for 3 h (method B).

High *anti*-diastereoselectivity of over 96% was achieved as shown in Table 1 (entries 2, 4, 6, and 9). One-pot synthesis of *anti*-**3** without isolation of **5b** was possible as similar to that of *syn*-**3** (method A), however, the diastereoselectivity decreased compared to method B, for example, from 100% to 78% in the synthesis of *anti*-**3** (R = Ph) (entry 9). This result suggests that intermediate aluminate-complex formation by the reaction of **5b** with lithium aluminum hydride is more favorable than that of **5a**.

The high diastereoselectivity observed in the above addition can be rationalized by the following transition state of A and B with the carbon-oxygen bond perpendicular to the double bond of the ketene thioacetal and with coordination of the oxygen anion to alkyllithium or aluminum hydride. Transition state A is more stable than B having the steric repulsion between the methyl and dithiane groups, which leads to the predominant formation of **6**



rather than 7, *i.e.*, the addition of alkyllithiums (R^1 = H, R = alkyl) gave *syn*-3 and lithium aluminum hydride (R^1 = alkyl, R = H) furnished *anti*-3.

Thus, nucleophilic addition to α-hydroxy ketene thioacetals can provide a novel method for the diastereoselective synthesis of *syn*- and *anti*-β-alkyl alcohols with 1,3-dithiane which is synthetically useful synthon of aldehyde.[11,15]

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