Stereoselective Synthesis of (*E*)- or (*Z*)-α-Alkylidene-γ-butyrolactone from γ-Butyrolactone and Bis[ethoxy(thiocarbonyl)] Disulfide and Mechanistic Studies of the Effect of Metal Complexes on the Stereoselection

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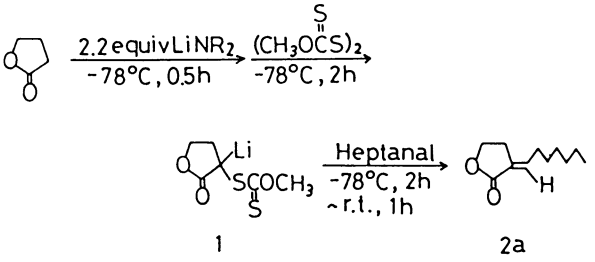
Treatment of γ-butyrolactone with bis[ethoxy(thiocarbonyl)] disulfide in the presence of 2.2 equiv of lithium diisopropylamide (LDA) produced lithium enolate of *O*-ethyl *S*-(tetrahydro-2-oxo-3-furanyl) dithiocarbonate, which reacted with an aldehyde to afford exclusively (*E*)-α-alkylidene-γ-butyrolactone. Interestingly, when the reaction was quenched below −20 °C or when it was carried out in the presence of metal complex such as zinc chloride, copper(I) iodide, or tributyltin chloride, (*Z*)-α-alkylidene-γ-butyrolactone was obtained as the major product. The stereoselectivity of this reaction was sensitive to the reaction temperature and the metal cation employed.

Much attention has been focused on the stereocontrolled synthesis of α-alkylidene-γ-butyrolactones (3-alkylidenedihydro-2(3*H*)-furanone) since these compounds serve as useful intermediates in organic synthesis[1] and constitute the biologically active natural products.[2] In particularly, the general stereoselective synthesis of (*Z*)-α-alkylidene-γ-butyrolactones has been attractive since these compounds can serve as important intermediate in the synthesis of obtusilactone isolated from *Lindela obtusiloba*[3] as cytotoxic natural product. Although several methods have been reported for the direct introduction of an alkylidene group to α position of a γ-butyrolactone.[2,4] there has been no general method for the stereoselective introduction. Recently, the stereoselective synthesis of (*E*)-α-alkylidene-γ-butyrolactones using the monoanion of *O*-ethyl *S*-(tetrahydro-2-oxo-3-furanyl) thiocarbonate, or the dianion of α-mercapto-γ-butyrolactone has been reported by Tanaka et al.[5a] (*E*)- or (*Z*)-α-Alkylidene-γ-butyrolactones can also be synthesized with high stereoselectivity, starting with easily available γ-butyrolactone and bis[methoxy-(thiocarbonyl)] disulfide.[5b] The observation that the presence of metal complex such as zinc chloride, copper(I) iodide, or tributyltin chloride causes a dramatic alternation in the stereoselectivity of the reaction is very interesting.

In this paper the mechanistic aspects of these reaction and the effect of metal complexes on the stereoselection are described in greater detail.

Results and Discussion

One Pot Synthesis of α-Alkylidene-γ-butyrolactones (2) from γ-Butyrolactone. Treatment of γ-butyrolactone with bis[methoxy(thiocarbonyl)] disulfide in the presence of 2.2 equiv of lithium amide at −78 °C in THF gave the lithium enolate **1** which reacted with heptanal to give exclusively (*E*)-α-heptylidene-γ-butyrolactone (**2a**). Among the various lithium amides examined, lithium diisopropylamide (LDA) is the most efficient base for converting γ-butyrolactone into the enolate **1** as shown in Table 1.



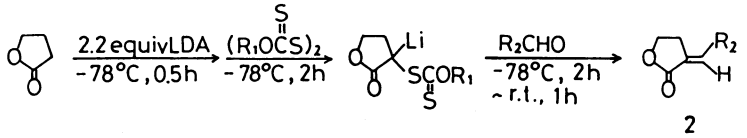
Generality of this new methodology is apparent from the results summarized in Table 2. In all cases examined, (E)-isomers were obtained exclusively. The E/Z ratio of product **2** was determined in same manner as reported previously.[5a] For example, the ^{1}H NMR spectrum of **2a** shows the vinyl proton β to the carbonyl at δ 6.58 for (E)-isomer and at δ 6.06 for (Z)-isomer, respectively.[6] Integration showed a 96:4 mixture of (*E*)-**2a** and (*Z*)-**2a**, being identical with the ratio obtained by GLC analysis (E/Z=95/5). (Z)-Isomer could be readily separated from (E)-isomer, which eluted more slowly than (Z)-isomer.

Table 1. Effect of Lithium Amide in the Reaction of γ-Butyrolactone with Heptanal

Lithium amide	Yield[a] of **2a** %	E/Z[b]
(*i*-Pr)$_2$NLi	65	96/4
i-PrN(Li)-⟨⟩	54	87/13
(Me$_3$Si)$_2$NLi	38	92/8
⟨⟩NLi	49	83/17
(⟨⟩-)$_2$NLi	31	93/7

a) Isolated yields. b) Determined by ^{1}H NMR and GLPC analyses of the isolated product.

Table 2. Stereoselective Synthesis of (*E*)-α-Alkylidene-γ-butyrolactones (**2**) from γ-Butyrolactone and Carbonyl Compounds

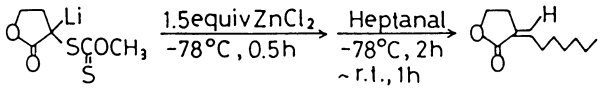


2

$R_1OCSSCOR_1$ (S, S) R_1	Carbonyl compound	Product **2**	Yield[a] %	E/Z[b]
CH_3	Heptanal	(**2a**)	65	96/4
CH_3	Benzaldehyde	(**2b**)	52	100/0
CH_3	Pentanal	(**2c**)	58	96/4
CH_3	Propanal	(**2d**)	37	96/4
CH_3	Butanal	(**2e**)	57	96/4
CH_3	Cyclohexanecarbaldehyde	(**2f**)	65	89/11[c]
C_2H_5	Heptanal	**2a**	71	95/5[d]
C_2H_5	Heptanal	**2a**	60	93/7[c]
C_2H_5	Benzaldehyde	**2b**	59	100/0[c]
$(CH_3)_2CH$	Heptanal	**2a**	58	100/0[c]
$(CH_3)_2CH$	Butanal	**2e**	54	90/10[c]

a) Isolated yields. b) Determined by ^1H NMR and GLPC analyses of the isolated product. c) Triethyl phosphite was added before adding carbonyl compound as a desulfurization agent. d) Ethyl bromide was added before adding carbonyl compound.

In contrast, when the reaction was carried out in the presence of metal complex such as anhydrous zinc chloride, copper(I) iodide, or tributyltin chloride, (*Z*)-α-alkylidene-γ-butyrolactone was obtained as the major product as shown in Table 3. For example, the reaction of the lithium enolate **1** with heptanal in the presence of 1.5 equiv of zinc chloride afforded predominantly (*Z*)-α-heptylidene-γ-butyrolactone in 68% (E/Z=17/83) isolated yield.



1 2a

As can be seen from the data listed in Tables 2 and 3, the alternation of substituent R of disulfide ROCSSCOR gave little significant improvement in the yield and the stereoselectivity of **2**. The effect of solvent on the yield and E/Z ratio of **2a** has been examined in the reaction of **1** with heptanal in the presence of 1.5 equiv of copper(I) iodide. The results (Table 4) indicate that among the solvents examined, tetrahydrofuran is the most efficient solvent for converting γ-butyrolactone into **2a** and the stereoselectivity of (*Z*)-**2a** is correlative with the solubility of metal complex in solvent.

One Pot Synthesis of α-Alkylidene-γ-valerolactone (4) from γ-Valerolactone. (*E*)- or (*Z*)-α-Alkylidene-γ-valerolactones (**4**) were also synthesized with high stereoselectivity according to the following route.

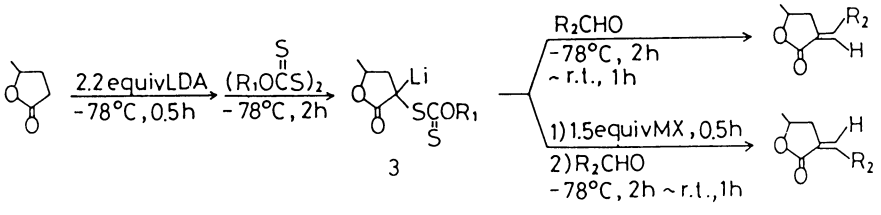


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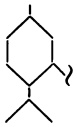
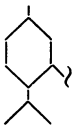
Table 3. Stereoselective Synthesis of (*Z*)-α-Alkylidene-γ-butyrolactones (**2**) from γ-Butyrolactone and Carbonyl Compounds in the Presence of Metal Complex (MX)

$R_1OCSSCOR_1$ (S, S; R_1)	Carbonyl compound	MX	Product **2**	Yield[a] %	E/Z[b]
CH_3	Heptanal	$ZnCl_2$	**2a**	68	17/83
CH_3	Heptanal	$ZnCl_2$	**2a**	67	15/85[c]
CH_3	Heptanal	$(n\text{-Bu})_3SnCl$	**2a**	68	19/81
CH_3	Heptanal	CuI	**2a**	70	25/75[d]
CH_3	Heptanal	CuI	**2a**	67	19/81[e]
CH_3	Pentanal	$ZnCl_2$	**2c**	65	11/89
CH_3	Butanal	$ZnCl_2$	**2e**	58	9/91
C_2H_5	Heptanal	$ZnCl_2$	**2a**	67	15/85[c]
C_2H_5	Heptanal	$MgCl_2$	**2a**	66	92/8
C_2H_5	Heptanal	$HgCl_2$	**2a**	52	37/63[d]
C_2H_5	Heptanal	$ZnCl_2$	**2a**	68	11/89
C_2H_5	Heptanal	$(i\text{-Pro})_3TiCl$	**2a**	38	45/55[d]
$(CH_3)_2CH$	Heptanal	$ZnCl_2$	**2a**	67	23/77
	Heptanal	$ZnCl_2$	**2a**	59	28/72
	Heptanal	$ZnCl_2$	**2a**	68	9/91[e]

a) Isolated yields. b) Determined by ^1H NMR and GLPC analyses of the isolated product. c) Metal complex was added before treating with disulfide. d) Triethyl phosphite was added before adding carbonyl compound as a desulfurization agent. e) 100 ml of THF was used for the reaction of 20 mmol of γ-butyrolactone with aldehyde.

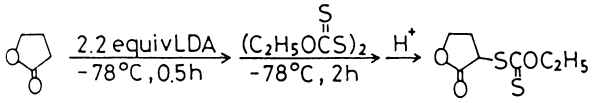
Table 4. Effect of Solvent on the Yields and E/Z Ratios of **2a**

Solvent	Yield[a] of **2a** %	E/Z[b]
THF	69	16/84[c]
THF	61	33/67[d]
DEE	0	—
DME	47	20/80[c]
THF-HMPA[e]	35	15/85[c]

a) Isolated yields. b) Determined by ^1H NMR and GLPC. c) 60 ml of solvent was used for the reaction of 20 mmol of γ-butyrolactone with heptanal. d) 40 ml of solvent was used for the reaction of 20 mmol of γ-butyrolactone with heptanal. e) A mixture of THF and HMPA (8 : 1, v/v) was used as a solvent.

The results were summarized in Table 5. Thus, the observations presented here represent a new and general method for the stereoselective introduction of alkylidene functionality on the α-position of γ-butyrolactone or γ-valerolactone by one pot procedure. These procedures are synthetically significant in respect of utilizing easily available γ-butyrolactone or γ-valerolactone as the starting material.

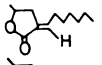
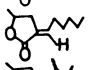
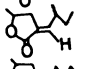
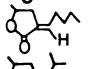
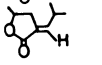
The Reaction of Lithium Enolate of *O*-Ethyl *S*-(tetrahydro-2-oxo-3-furanyl) Dithiocarbonate (5a) and Thiocarbonate (5b) with Carbonyl Compounds. When γ-butyrolactone was treated with bis[ethoxy(thiocarbonyl)] disulfide in the presence of 2.2 equiv of LDA at −78 °C for 2 h and followed by quenching with saturated aqueous ammonium chloride solution, *O*-ethyl *S*-(tetrahydro-2-oxo-3-furanyl) dithiocarbonate (**5a**) was obtained in 72% isolated yield.



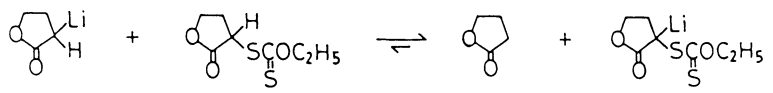
5a

On the other hand, when the reaction was carried out in the presence of 1.1 equiv of LDA, lactone **6** was obtained in the place of **5a** as the major product in 41% (82% based on disulfide) isolated yield and γ-butyrolactone (37%) was recovered. The formation of **6** appears to involve a deprotonation of **5a**, followed by an attack toward disulfide.[7]

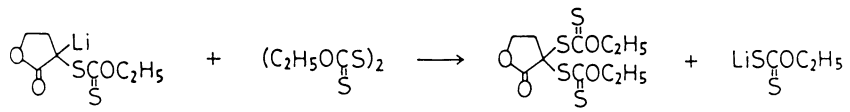
Table 5. Stereoselective Synthesis of α-Alkylidene-γ-valerolactones (**4**) from γ-Valerolactone and Carbonyl Compounds

$R_1OCSSCOR_1$ (S S; R_1)	Carbonyl compound	MX	Product **4**	Yield[a] %	E/Z[b]
CH_3	Heptanal	—	 (**4a**)	58	91/9
CH_3	Hexanal	—	 (**4b**)	65	89/11[c]
CH_3	2-Methylbutanal	—	 (**4c**)	64	89/11
CH_3	Pentanal	—	 (**4d**)	62	94/6
CH_3	2-Methylpropanal	—	 (**4e**)	60	94/6
C_2H_5	Hexanal	—	**4b**	57	96/4
CH_3	Hexanal	$(n\text{-Bu})_3SnCl$	**4b**	92	9/91[c]
CH_3	Pentanal	$ZnCl_2$	**4d**	76	16/84
CH_3	2-Methylbutanal	$ZnCl_2$	**4c**	54	12/88
CH_3	2-Methylpropanal	$ZnCl_2$	**4e**	62	11/89
C_2H_5	Heptanal	CuI	**4a**	68	21/79
C_2H_5	Butanal	$ZnCl_2$	 (**4f**)	70	27/73

a) Isolated yields. b) Determined by ^1H NMR and GLPC analyses of the isolated product. c) Triethyl phosphite was added before adding carbonyl compound as a desulfurization agent.



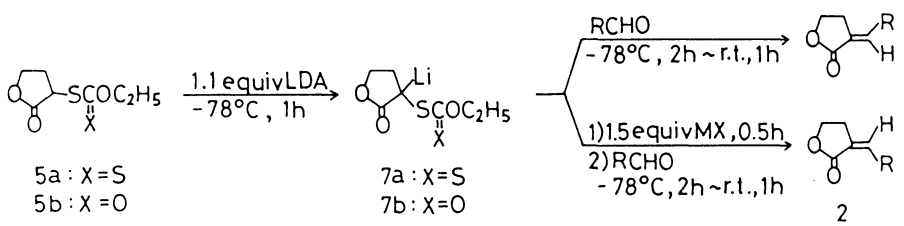
5a



6

Above observation suggests that the reaction of lithium enolate of γ-butyrolactone with aldehydes in the presence of bis[ethoxy(thiocarbonyl)] disulfide to give α-alkylidene-γ-butyrolactone (**2**) proceeds via *O*-ethyl *S*-(tetrahydro-2-oxo-3-furanyl) dithiocarbonate (**5a**) as intermediate. In this paper the author has examined the effect of the starting material **5a** or **5b**, the reaction temperature and time, and metal complex (MX) added on the yields and E/Z ratios of **2** produced in the following reactions, and studied the mechanistic aspects of these reactions.

The geometrical compositions of **2** obtained under various conditions are summarized in Table 6. When the reaction of lithium enolate **7** with aldehyde was carried out in the presence of metal complex (MX) such as $ZnCl_2$, CuI, or $(n\text{-Bu})_3SnCl$, (*Z*)-**2** was obtained as major product, whereas these reactions in the absence of metal cations other than Li^+ gave exclusively (*E*)-**2**. However, $MgBr_2$ was less effective. An increase in the proportion of (*Z*)-product using



5a : X=S
5b : X=O

7a : X=S
7b : X=O

2

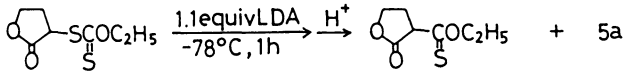
Table 6. Stereoselective Synthesis of α-Alkylidene-γ-Butyrolactones (**2**) from *O*-Ethyl *S*-(Tetrahydro-2-oxo-3-furanyl)dithiocarbonate (**5a**) or Thiocarbonate (**5b**) and Carbonyl Compounds

Starting material	Carbonyl compound	MX	Product **2**	Yield[a] %	E/Z[b]
5a	Heptanal	—	**2a**	63	95/5
5a	Heptanal	—	**2a**	87	97/3[c]
5a	Hexanal	—	**2g**	58	92/8
5a	Benzaldehyde	—	**2b**	60	94/6
5a	Benzaldehyde	CuI	**2b**	90	15/85[c]
5a	Heptanal	CuI	**2a**	76	28/72
5a	Heptanal	$ZnCl_2$	**2a**	56	18/82
5a	Heptanal	$ZnCl_2$	**2a**	94	23/77[c]
5a	Heptanal	$(n\text{-Bu})_3SnCl$	**2a**	60	20/80
5a	Heptanal	$MgBr_2$	**2a**	64	45/55
5a	Hexanal	$ZnCl_2$	**2g**	64	20/80
5a	Hexanal	$ZnCl_2$	**2g**	70	28/72[d]
5b	Heptanal	—	**2a**	48	100/0
5b	Heptanal	$ZnCl_2$	**2a**	46	50/50
5b	Heptanal	$ZnCl_2$	**2a**	63	47/53[e]
5b	Heptanal	$(i\text{-PrO})_2TiCl_2$	**2a**	67	45/55[d,e]
5b	Hexanal	$(EtO)_3Al$	**2g**	85	67/33[e]
5b	Pentanal	$MgBr_2$	**2c**	89	37/63[d,e]

a) Isolated yields. b) Determined by ^1H NMR and GLPC analyses of the isolated product. c) Carbonyl compound was instantly added after **5a** was treated with 1.1 equiv of LDA for 1 min. d) Triethyl phosphite was added before adding carbonyl compound as a desulfurization agent. e) *n*-BuLi was used as a base and THF-HMPA (v/v, 16/1) was used as a co-solvent.

metal complex, but to a lesser extent than for **5a**, was also observed for the reaction of **5b** with aldehyde. Therefore, the common mechanism is taken into cosideration for the reactions of **5a** and **5b** with aldehyde to afford **2**.

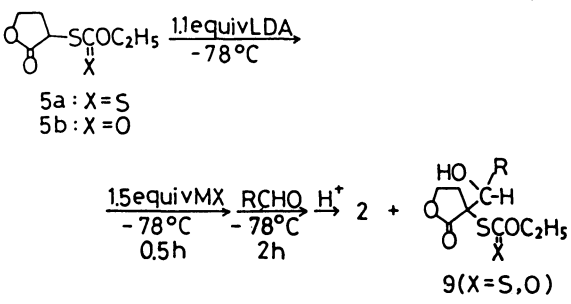
In order to examine the stability of lithium enolate **7a**, **5a** was treated with 1.1 equiv of LDA in THF at −78 °C for 1 h, and then quenched with saturated aqueous ammonium chloride solution. Upon work-up, lactone **8** was isolated in 18% yield in addition to 68% recovery of **5a**. The transformation of **7a** to **8** appears to involve the formation of a thiirane by intramolecular cyclization, followed by expulsion of sulfur.



5a 8

As is apparent from Table 6, when the treating time of **5a** with 1.1 equiv of LDA was shortened to 1 min from 1 h, the yield of **2a** was enhanced to 87% from 63% in the reaction of **5a** with heptanal. The result suggests that the self-rearrangement of lithium enolate **7a** takes place competitively.

The Generation of Aldol Adducts 9. As shown in Table 7, when the reactions of **7a** with aldehydes were carried out at −78 °C for 2 h and then quenched with dilute hydrochloric acid, aldol adduct **9** (X=S) were isolated in good yields but **2** was not detected.



On the other hand, in the reactiion of **7b** with butanal, **2e** was isolated in 23—28% yields but the aldol adduct (X=O) was little isolated. These results may be attributed to the difference in the amount of polarization between thiocarbonyl (C=S) and carbonyl group (C=O) of **9**, that is, in the reaction of **7a** with aldehydes, the small amount of polarization of thiocarbonyl group may reduce the rearrangement of the adduct **10** to **11** (described later).

The aldol adduct **9** should consist of a mixture of diastereomers (erythro and threo isomers).

The stereoselectivity of the resulting α-alkylidene-γ-butyrolactone (**2**) may be closely correlated with the stereo-structure of the aldol adduct **9** from which it is formed. The aldol adduct **9** was separated into the

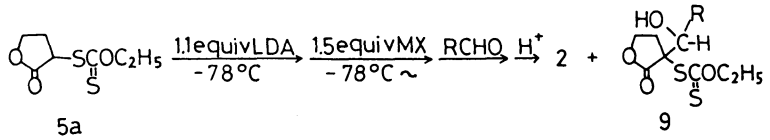
e-9(erythro) t-9(threo)

Table 7. Aldol Condensations of **5** with Carbonyl Compounds at −78 °C

Starting material	Carbonyl compound	MX	**2** %	E/Z[a]	**9** %	erythro/threo[b]	**5** %
5a	Propanal	—	0	—	70	52/48	19
5a	Propanal	$ZnCl_2$	0	—	84	54/46	11
5a	Butanal	—	0	—	65	53/47	21
5a	Butanal	$ZnCl_2$	0	—	84	55/45	9
5b	Butanal	—	28	58/42	Trace	—	42
5b	Butanal	$ZnCl_2$	23	52/48	Trace	—	45
5a	Heptanal	—	0	—	67	55/45	26
5a	Heptanal	$ZnCl_2$	0	—	74	58/42	19

a) Determined by ^{1}H NMR and GLPC analyses of the isolated product. b) Determined by ^{1}H NMR and MPLC (LiChroprep Si60 column, 2:1 hexane-ethyl acetate eluent, Flow rate 1 ml min^{-1}).

Table 8. Effects of Reaction Temperature and Time After Adding Carbonyl Compound on the Yields and Stereoselectivities of **2** and **9**



5a 9

Carbonyl compound	MX	Reaction conditions	**2** %	E/Z[a]	**9** %	erythro/threo[b]	**5a** %
Butanal	—	−78 °C, 1 min	0	—	57	48/52	28
Butanal	—	−78 °C, 15 min	0	—	70	49/51	19
Butanal	—	−78 °C, 2 h	0	—	65	53/47	21
Butanal	—	−78 °C, 6.5 h	0	—	77	56/44	7
Heptanal	—	−78 °C, 2 h	0	—	67	55/45	26
Heptanal	—	−78 °C, 2 h——50 °C,[c] 1 h	26	28/72	58	67/33	10
Heptanal	—	−78 °C, 2 h——40 °C,[c] 1 h	51	37/63	36	62/38	4
Heptanal	—	−78 °C, 2 h——20 °C,[c] 1 h	71	41/59	19	66/34	0
Heptanal	—	−78 °C, 2 h—0 °C,[c] 1 h	83	91/9	0	—	0
Heptanal	—	−78 °C, 2 h—r.t.,[c] 1 h	87	97/3	0	—	0
Heptanal	—	−78 °C, 2 h 25 °C,[d] 4 min	70	56/44	0	—	0
Heptanal	$ZnCl_2$	−78 °C, 2 h	0	—	74	58/42	19
Heptanal	$ZnCl_2$	−78 °C. 2 h——40 °C,[c] 1 h	23	10/90	61	55/45	7
Heptanal	$ZnCl_2$	−78 °C, 2 h—r.t.,[c] 1 h	94	23/77	0	—	0

a) Determined by ^{1}H NMR and GLPC analyses of the isolated product. b) Determined by ^{1}H NMR and MPLC (LiChroprep Si60 column, hexane-ethyl acetate eluent, Flow rate 1 ml min^{-1}). c) The reaction temperature was gradually raised to room temperature from −78 °C by removing cooling bath. d) The reaction temperature was immediately raised by dipping the reaction mixture in water bath maintained at 25 °C.

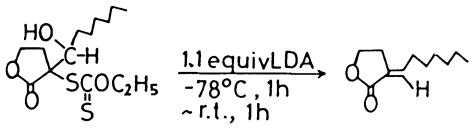
faster-eluting diastereomer and the slower-eluting diastereomer by column chromatography on silica gel with 3:1 hexane–ethyl acetate as eluent. The ^{1}H NMR spectrum of **9a** derived from heptanal shows the hydroxymethine proton at δ 3.70 for the faster-eluting isomer and at δ 4.04 for the slower-eluting isomer. The slightly major isomer resulting from the aldol condensation was in all instances the slower-eluting diastereomer which was assigned erythro form (**e-9**), whereas the slightly minor and mobile isomer was assigned threo form (**t-9**).[8] The stereochemical compositions (**e-9**/**t-9**) of the aldol adducts obtained from various aldehydes were determined by ^{1}H NMR and/or MPLC (medium-pressure liquid chromatography) system, and summarized in Table 7. These results show that the metal enolate of **5a** condensed with aldehydes to exhibit consistently low diastereoselectivity, regardless of the metal cation employed.

Effects of Reaction Temperature and Time. Effects of reaction temperature and time after adding aldehyde on the yields and stereoselectivities of **2** and **9** were next examined. These results under the various conditions were summarized in Table 8. When the reaction of **5a** with heptanal was carried out at −78 °C for 2 h and at −50 °C for 1 h, 58% of aldol adduct **9a** was isolated in addition to 26% of **2a**. Interestingly, the geometry selectivity of **2a** was Z-selective (E/Z=28/72) in spite of absence of metal cation other than Li^+. With only the lithium cation present, as the reaction temperature before quenching was raised gradually to 0 °C or above the yields and E-selectivity of **2a** increased. On the other hand, in the

presence of $ZnCl_2$ Z-selectivity of **2a** was observed even if the reaction temperature before quenching was raised gradually to room temperature. Next, in the reaction of **7a** with butanal at −78 °C, the effect of reaction time on the yields and the erythro/threo ratios of aldol adducts **9e** was examined but it was little observed. It is reasonable to consider that the aldol-type reacition of **7a** with an aldehyde is so rapid that the equilibrium described later is reached almost instantly.

The satisfactory yield of the aldol adduct **9** was obtained only at low temperature (−78 to −20 °C).

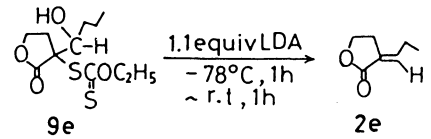
The Retro-Aldolization of 9. The results listed in Tables 7 and 8 predict the retro-aldolization of **9** to the lithium enolate **7a** and aldehyde, since the diastereomer ratios of aldol adducts **9** do not correspond to the E/Z ratios of the final product **2**. When the purified adduct **9a** (erythro/threo=45/55) was lithiated with 1.1 equiv of LDA at −78 °C, and followed by warming to room temperature, α-alkylidene-γ-butyrolactone (**2a**) was obtained in 73% (E/Z=94/6) isolated yield.



9a 2a

erythro/threo=45/55 73%(E/Z=94/6)

The same reaction for the adduct **9e** afforded (*E*)-**2e** with high stereoselectivity, regardless of the stereochemistry of **9e**.

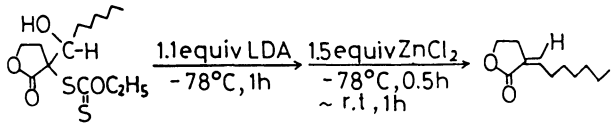


9e 2e

erythro/threo = 20/80 → 63%(E/Z=97/3)

=73/27 → 71%(E/Z=100/0)

On the other hand, when the same reaction for the nearly erythro **9a** (erythro/threo=91/9) was carried out in the presence of $ZnCl_2$, (*Z*)-**2a** was obtained as the major product (E/Z=27/73) in 78% isolated yield.

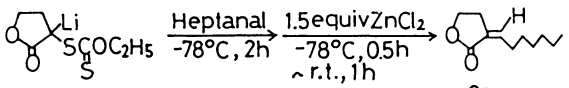


9a 2a

erythro/threo=91/9 78%

(E/Z=27/73)

Furthermore, in the reaction of **7a** with heptanal, even when $ZnCl_2$ was added after treating with heptanal at −78 °C for 2 h, (*Z*)-**2a** was obtained as major product as well as the results listed in Table 6.

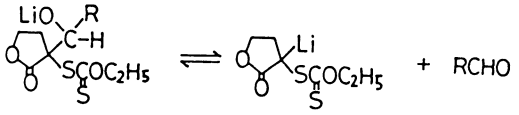


7a 2a

65%

(E/Z=22/78)

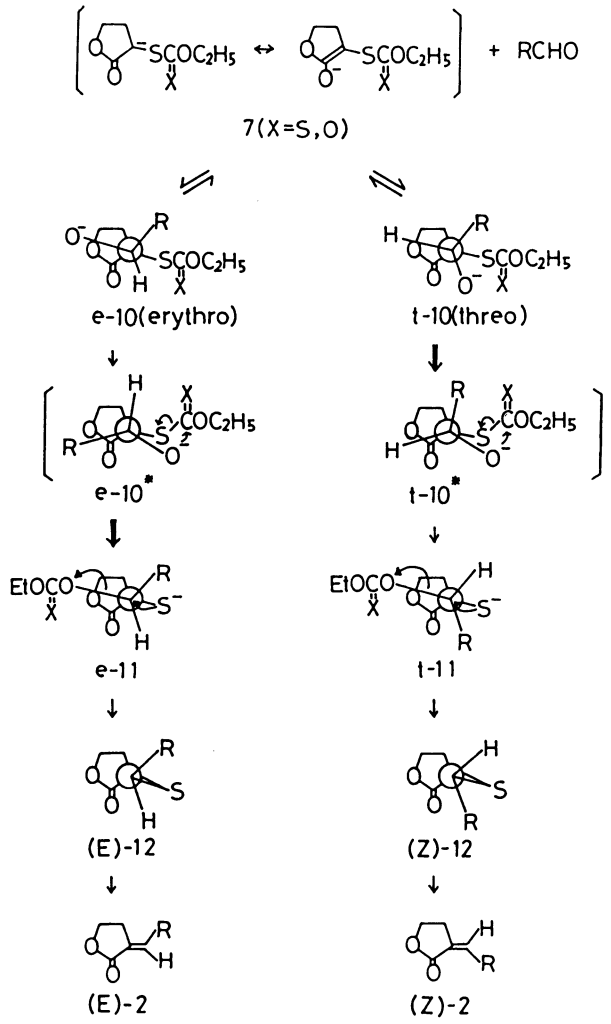
From these results, it is reasonable to consider that **10** is in equilibrium with **7a** as follows, and that the effect of the metal complex employed is exhibited in the conversion of the aldol adduct **10** to the final product **2**.



10 7a

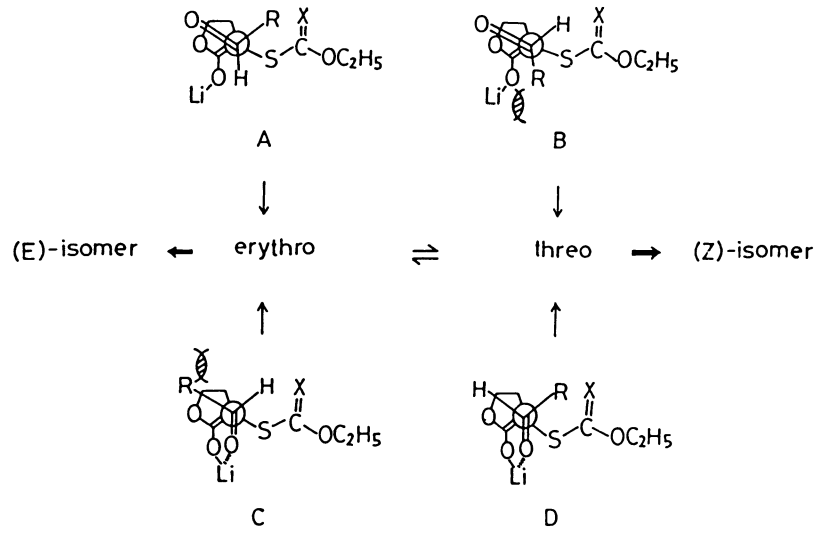
Mechanistic Aspects. As reported previously,[5a,9] it is reasonable to assume that the mechanism of this reaction involves aldol condensation of **7** with carbonyl compound, rearrangement of an adduct **10** to **11**, subsequent conversion of **11** to thiirane species **12**, and elimination of sulfur to give α-alkylidene-γ-butyrolactone (**2**) (Scheme 1). The equilibrium between (*E*)-**2** and (*Z*)-**2** was not observed even after allowding to stand at room temperature for several days. The elimination of sulfur from **12** to give **2** is explained by a stereospecific mechanism.[10] Furthermore, it is reasonable to consider that **e-11** is not in equilibrium with **t-11**, since, in both conformations, the intramolecular rearrangement of COC_2H_5 group (X) is already occured. Thus, the aldol adduct **e-10** (erythro) and **t-10** (threo) should convert to (*E*)- and (*Z*)-**2** stereospecifically, respectively. It is considered that the geometry of final product **2** is dependent on whether the aldol condensation proceeds via erythro or threo isomer as intermediate. However, as is apparent from Tables 7 and 8, the aldol-type reactions of **7** with aldehydes at low temperature have exhibited low diastereoselectivity regardless of metal cation employed. That is, the diastereomer ratio of aldol adduct **9** does not correspond to the geometry of **2**. It is documented that, in the kinetically controlled aldol-type reaction, the appearance of stereoselection is attributed to the form of the transition state.[8g,11] It is generally believed that, when an aldol-type reaction is carried out at relatively low temperature in ethereal solvent, even lithium enolate is satisfactory to stabilize the metal chelate.[8g,12] Recently, acyclic transition states have been also proposed to account for the erythro-selective aldol reaction with enol silyl ethers and acetals,[13] zirconium enolates,[14] and crotyltrialkyltins.[15] Furthermore, Heathcock et al. have reported that the reactions of lithium enolate of dioxolanones

with aldehydes occur through the conventional Zimmerman–Traxler transition state[16] with the hydrogen of the aldehyde RCHO, rather than the R group, over the face of the dioxolanone ring.[17] The transition state models **A**, **B**, **C**, and **D** were proposed for the reactions of **7** with aldehydes (Scheme 2).



Scheme 1.

It is reasonable to consider that , among four possible transition state models (Scheme 2), **A** leading to erythro isomer and **D** leading to threo isomer, in both which the lactone carbonyl group and R group of aldehyde RCHO are anti-oriented, must be favored for the steric reason. Thus, the aldol condensations of **7** with aldehydes under the kinetically controlled reaction conditions occur through the transition states **A** and **D**, giving consistently almost 1:1 mixture of diastereomers of **9**. In these reactions, the effect of metal complex added was little observed for the stereoselection of **9**. The results listed in Table 8 show that, even in the absence of metal cation other than Li^+, when the reaction of **7** with aldehyde was carried out below −20 °C (*Z*)-**2** was obtained as major product, while (*E*)-**2** was exclusively obtained when the reaction was quenched after warming to 0 °C or above. On the contrary, in the presence of metal cation such as Zn^{2+} or Cu^+, Z-selectivity of **2** was observed even when the reaction was quenched after warming to room temperature. The observations presented here can be rationalized by considering that a retro-aldolization of **10** to the starting materials is in competition with the rearrangement of **10** to **11**, that is, the reaction of **7** with aldehyde proceeds via erythro or threo isomer to give **2** is the thermodynamically controlled process, and that the erythro isomer **e-10** become energetically more favorable than the threo isomer **t-10** as the reaction temperature is raised. Since it seems that the cyclic transition state **D** can not be controlled by lithium coordination as the reaction temperature is raised to room temperature.[8g,12] In addition, in two possible stereoisomeric precursors (**e-**



Scheme 2.

11 and **t-11**) leading to **2** as shown in Scheme 1, if the conformer, in which the $OCOC_2H_5$ and S^- groups are

anti-periplanar, is favorable one for the subsequent intramolecular attack of S^- group and elimination of the $OCOC_2H_5$ species, the orientation of R group is

thus represented as **e-11** and **t-11**, respectively. The rearrangement reaction of **e-10** to **e-11** would proceed more smoothly than that of **t-10** to **t-11**, since the steric interaction between a bulky R group and a lactone carbonyl is minimized in **e-11**. On the other hand, the stereoisomer **t-11**, in which the alkyl and carbonyl group are gauche, would exhibit severe interactions. Thus, (*E*)-**2** predominates. However, if a metal complex such as $ZnCl_2$ or CuI is added, the reaction of **7** with aldehyde proceeds via threo isomer **t-10** to give (*Z*)-**2** as major product. Since the threo isomer **t-10**, which seems to exist as structure with the six-membered ring containing coordination to metal cation of an alcoholate anion and a lactone carbonyl oxygen, can become energetically more favorable than the more charged-separated erythro isomer **e-10**. Furthermore, the difference in rotational energy between the conformational conversion of **e-10** to **e-10*** and that of **t-10** to **t-10*** (Scheme 1) is proposed to account for the threo-selective reaction at low temperature (−78 to −20 °C) to give (*Z*)-**2**. That is, the rotation about C–C bond formed by the aldol-type reaction must occur, since the both conformations **e-10*** and **t-10***, in which an alcoholate anion and $SCOC_2H_5$ group are cis or gauche, are favorable for

the subsequent intramolecular attack of O^- group toward $SCOC_2H_5$ group. The conformational

conversion of **t-10** to **t-10*** must be energetically more favorable than that of **e-10** to **e-10*** for the steric interaction between a lactone carbonyl and an alcoholate anion coordinated to a metal cation or a bulky R group.

It is concluded that the stereoselectivity of α-alkylidene-γ-butyrolactone (**2**) results from the aldol-type reaction of **7** with aldehyde which takes a different course as functions of the metal cation employed and the reaction temperature. That is, in the presence of only Li^+, this reaction occurs through erythro adduct **e-10** leading to (*E*)-**2**, whereas the reaction occurs predominantly through threo adduct **t-10** leading to (*Z*)-**2** when it was quenched below −20 °C or when it was carried out in the presence of metal cation such as Zn^{2+}, Cu^+, or Sn^{4+}. Furthermore, the effect of the metal complex employed and the reaction temperature on the stereoselectivity of **2** is exhibited in the rearrangement reaction of aldol adduct **10** to **11**.

Experimental

General. All reactions were performed under a nitrogen atmosphere. The glassware was dried by flaming in a nitrogen stream. Tetrahydrofuran (THF) was dried by distillation from calcium hydride and by subsequent distillation from lithium aluminum hydride under a nitrogen atmosphere. Diisopropylamine were distilled from calcium hydride and stored over molecular sieves. Butyllithium was titrated by the Kofron's method[18] before use. γ-Butyrolactone, γ-valerolactone, triethyl phosphite, and carbonyl compounds were purified by distillation under a nitrogen atmosphere. Zinc chloride was successively fused under reduced pressure and then cooled under nitrogen. Copper(I) iodide and magnesium bromide was prepared by the reported procedure.[8g,19] Magnesium chloride and tributyltin chloride were obtained commercially. Diisopropoxytitanium dichloride and triisopropoxytitanium chloride were prepared from titanium tetrachloride and tetraisopropyl titanate by the Dijkgraaf's method.[20] *O*-Ethyl *S*-(tetrahydro-2-oxo-3-furanyl) dithiocarbonate (**5a**) and thiocarbonate (**5b**) were prepared by the reported procedure.[5a] Melting points were determined with a Yamato Kagaku melting point apparatus and are uncorrected. Boiling points were determined during distillation and are uncorrected. Infrared spectra were determined on a Hitachi Model 260-30 spectrophotometer. Nuclear magnetic resonance spectra were determined on a JEOLCO MH-100 spectrometer. Chemical shifts are given in δ units, part per million relative to tetramethylsilane as an internal standard. Carbon tetrachloride (CCl_4), chloroform-*d* ($CDCl_3$) and benzene-d_6 (C_6D_6) were used as solvent. Gas chromatograms were obtained using a Varian Aerograph Model 920 instrument with a 0.15 cm×120 cm glass column (20% Silicone DC-550 on Celite 545). Silica gel (Wakogel) of the size 100—300 mesh was used for column chromatography. Medium-pressure liquid chromatography (MPLC) was performed on a unit constructed from various commercial components.

Preparation of Disulfides. Bis[methoxy(thiocarbonyl)], bis[ethoxy(thiocarbonyl)], and bis[isopropoxy(thiocarbonyl)] disulfides were prepared by the reported procedure.[21]

Preparation of Bis[menthyl(thiocarbonyl)] Disulfide. To a solution of 6.26 g (40 mmol) of *l*-methol in 50 ml of THF was added dropwise 40 mmol of butyllithium at 0 °C. After stirring for 1 h, 3.2 ml (50 mmol) of carbon disulfide was added dropwise and the reaction mixture was stirred for 1 h. 5.06 g (20 mmol) of iodide in 40 ml of THF was then added dropwise and the reaction mixture was stirred for 1 h. To this was added 10 ml of saturated aqueous ammonium chloride solution and the mixture was extracted four times with ether. The ether extracts were washed with dilute aqueous sodium thiosulfate solution and saturated aqueous sodium chloride solution, dried on anhydrous sodium sulfate, and concentrated under reduced pressure. The recrystallization from ethanol gave 1.31 g (71%) of bis[menthyl(thiocarbonyl)] disulfide: Mp 94.0—95.0 °C; ^1H NMR (CCl_4) δ=5.20—5.48 (m, 2H, 2CHO), 2.04—2.25 (m, 2H, 2CH), 0.72—2.04 (m, 34H, 4CH, $6CH_2$, and $6CH_3$). IR (KBr pellet) 2950, 1050, 630 cm^{-1}. Found: C, 56.94; H, 8.31%. Calcd for $C_{22}H_{38}O_2S_4$: C, 57.10; H, 8.28%.

Reaction of Lithium Enolate of γ-Butyrolactone with Carbonyl Compounds. General Procedure: Lithium diisopropylamide (LDA) (44 mmol) was prepared as usual in 60 ml of THF at −78 °C. After 10 min, a solution of 1.72 g (20 mmol) of γ-butyrolactone in 5 ml of THF was added over a period of 3 min. After stirring for 1 h at −78 °C, a solution of 22 mmol of disulfide in 6 ml of THF was added over a period of 10 min and the reaction mixture was stirred for 2 h at −78 °C. To this was added dropwise a solution of 22 mmol of carbonyl compound in 6 ml of THF over a period of 10 min and the reaction mixture was stirred for 2 h at −78 °C. Usually, the reaction mixture was then warmed gradually to room temperature from −78 °C by removing the cooling bath and it was stirred for 1 h before quenching with saturated aqueous ammonium chloride solution (10 ml). It was then poured into dilute hydrochloric acid and extracted with ether (50 ml×4). The extracts were washed with saturated aqueous sodium chloride solution, dried on anhydrous sodium sulfate, and concentrated under reduced pressure. Product isolation and purification by silica-gel chromatography gave (*E*)-α-alkylidene-γ-butyrolactone as main product.

Reaction of Lithium Enolate of γ-Butyrolactone with Carbonyl Compounds Using Metal Complexes. The preparation of α-heptylidene-γ-butyrolactone (**2a**) using zinc chloride is given here as a typical experiment. To a solution of lithium enolate in THF produced by treatment of γ-butyrolactone with bis[methoxy(thiocarbonyl)] disulfide in the presence of 2.2 equiv of LDA was added a solution of 4.10 g (30 mmol) of zinc chloride in 30 ml of THF. After 30 min, a solution of 2.20 g (22 mmol) of heptanal in 3 ml of THF was added dropwise. After stirring at −78 °C for 2 h, the reaction mixture was warmed gradually to room temperature from −78 °C and it was stirred for 1 h before quenching with saturated aqueous ammonium chloride solution (10 ml). The usual work-up and the purification by silica-gel chromatography (hexane–benzene) gave 2.48 g (68%) of **2a**.

Physical Properties of α-Alkylidene-γ-butyrolactones. The analytical samples were obtained by silica-gel chromatography. The (E)- and (Z)-isomers of **2a** were separated by silica-gel chromatography using hexane–benzene as eluent, and were identified by comparison of ^{1}H NMR and IR spectra with corresponding data reported previously.[5]

(*Z*)-α-Heptylidene-γ-butyrolactone (2a): ^{1}H NMR (CCl_4) δ=6.06 (m, 1H, CH=C), 4.18 (t, *J*=7 Hz, 2H, CH_2O), 2.46—2.92 (m, 4H, $2CH_2$), 1.02—1.50 (m, 8H, $4CH_2$), 0.88 (m, 3H, CH_3). IR (neat) 1758 (COO), 1675 (C=C) cm^{-1}. Found: C, 72.76; H, 9.92%. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95%.

(*Z*)-α-Pentylidene-γ-butyrolactone (2c): ^{1}H NMR (CCl_4) δ=6.00 (m, 1H, CH=C), 4.13 (t, *J*=7 Hz, 2H, CH_2O), 2.44—2.90 (m, 4H, $2CH_2$), 1.00—1.60 (m, 4H, $2CH_2$), 0.88 (m, 3H, CH_3). IR (neat); 1750 (COO), 1670 (C=C) cm^{-1}. Found: C, 69.71; H, 9.22%. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15%.

(*Z*)-α-Butylidene-γ-butyrolactone (2e): ^{1}H NMR (CCl_4) δ=6.12 (m, 1H, CH=C), 4.20 (t, *J*=7 Hz, 2H, CH_2O), 2.88 (m, 2H, CH_2), 2.64 (m, 2H, CH_2), 1.20—1.70 (m, 2H, CH_2), 0.94 (m, 3H, CH_3). IR (neat) 1750 (COO), 1670 (CH=C) cm^{-1}. Found: C, 68.43; H, 8.68%. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63%.

Reaction of Lithium Enolate of γ-Valerolactone with Carbonyl Compounds. The same procedure as above was employed, except using γ-valerolactone instead of γ-butyrolactone.

α-Heptylidene-γ-valerolactone (4a): (E)-Isomer: ^{1}H NMR (CCl_4) δ=6.46 (m, 1H, CH=C), 4.48 (m, 1H, CH-O-), 1.90—3.10 (m, 4H, $2CH_2$), 1.10—1.60 (m, 11H, CH_3 and $4CH_2$), 0.88 (m, 3H, CH_3). IR (neat) 1750 (COO), 1680 (CH=C) cm^{-1}. (Z)-Isomer: ^{1}H NMR (CCl_3) δ=6.02 (m, 1H, CH=C), 4.48 (m, 1H, CH-O-), 2.22—3.10 (m, 4H, $2CH_2$), 1.10—1.62 (m, 11H, CH_3 and $4CH_2$), 0.88 (m, 3H, CH_3). IR (neat) 1750 (COO), 1680 (CH=C) cm^{-1}. Found: C, 73.17; H, 10.40%. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27%.

α-Hexylidene-γ-valerolactone (4b): (E)-Isomer: ^{1}H NMR (CCl_4) δ=6.44 (m, 1H, CH=C), 4.50 (m, 1H, CH-O-), 1.98—3.06 (m, 4H, $2CH_2$), 1.00—1.56 (m, 9H, CH_3 and $3CH_2$), 0.88 (m, 3H, CH_3). IR (neat) 1750 (COO), 1670 (CH=C) cm^{-1}. Found: C, 72.40; H, 10.11%. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95%. (Z)-isomer: ^{1}H NMR (CCl_4) δ=5.94 (m, 1H, CH=C), 4.40 (m, 1H, CH-O-), 2.10—3.00 (m, 4H, $2CH_2$), 1.08—1.60 (m, 9H, CH_3 and $3CH_2$), 0.88 (m, 3H, CH_3). IR (neat) 1750 (COO), 1680 (CH=C) cm^{-1}.

α-(2-Methylbutylidene)-γ-valerolactone (4c): (E)-Isomer: ^{1}H NMR (CCl_4) δ=6.22 (dt, *J*=9.9, 2.7 Hz, 1H, CH=C), 4.52 (m, 1H, CH-O-), 2.00—3.20 (m, 3H, CH_2 and CH), 1.38 (d, *J*=7 Hz, 3H, CH_3), 1.05 (d, *J*=7 Hz, 3H, CH_3), 0.88 (m, 5H, CH_2 and CH_3). IR (neat); 1750 (COO), 1680 (CH=C) cm^{-1}. (Z)-Isomer: ^{1}H NMR (CCl_4) δ=5.72 (dt, *J*=9.8, 2.2 Hz, 1H, CH=C), 4.42 (m, 1H, CH-O-), 3.48 (m, 1H, CH), 2.20—3.20 (m, 2H, CH_2), 1.36 (d, *J*=7 Hz, 3H, CH_3), 0.97 (d, *J*=7 Hz, 3H, CH_3), 0.85 (m, 5H, CH_2 and CH_3). Found: C, 71.15; H, 9.70%. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59%. IR (neat); 1750 (COO), 1670 (CH=C) cm^{-1}.

α-Pentylidene-γ-valerolactone (4d): (E)-Isomer: ^{1}H NMR (CCl_4) δ=6.50 (m, 1H, CH=C), 4.52 (m, 1H, CH-O-), 2.00—3.20 (m, 4H, $2CH_2$), 1.10—1.70 (m, 7H, CH_3 and $2CH_2$), 0.80—1.10 (m, 3H, CH_3). IR (neat) 1750 (COO), 1680 (CH=C) cm^{-1}. Found: C, 71.66; H, 9.70%. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59%. (Z)-Isomer: ^{1}H NMR (CCl_4) δ=6.04 (m, 1H, CH=C), 4.48 (m, 1H, CH-O-), 2.20—3.20 (m, 4H, $2CH_2$), 1.20—1.60 (m, 7H, CH_3 and $2CH_2$), 0.90 (m, 3H, CH_3).

α-(2-Methylpropylidene)-γ-valerolactone (4e): (E)-Isomer: ^{1}H NMR (CCl_4) δ=6.20 (dt, *J*=9.3, 2.6 Hz, 1H, CH=C), 4.44 (m, 1H, CH-O-), 2.20—3.20 (m, 3H, CH_2 and CH), 1.35 (d, *J*=7 Hz, 3H, CH_3), 1.05 (d, *J*=7 Hz, 6H, $2CH_3$). IR (neat) 1750 (COO), 1680 (CH=C) cm^{-1}. Found: C, 70.03; H, 9.38%. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15%. (Z)-Isomer: ^{1}H NMR (CCl_4) δ=5.74 (dt, *J*=9.6, 2.1 Hz, 1H, CH=C), 4.42 (m, 1H, CH-O-), 3.66 (m, 1H, CH), 2.20—3.10 (m, 2H, CH_2), 1.34 (d, *J*=6 Hz, 3H, CH_3), 0.98 (d, *J*=7 Hz, 6H, $2CH_3$). IR (neat) 1750 (COO), 1670 (CH=C) cm^{-1}.

α-Butylidene-γ-valerolactone (4f): (E)-Isomer: ^{1}H NMR (CCl_4) δ=6.36 (m, 1H, CH=C), 4.42 (m, 1H, CH-O-), 1.96—3.00 (m, 4H, $2CH_2$), 1.28—1.60 (m, 5H, CH_2 and CH_3), 0.92 (t, *J*=7 Hz, 3H, CH_3). (Z)-Isomer: ^{1}H NMR (CCl_4) δ=5.96 (m, 1H, CH=C), 4.44 (m, 1H, CH-O-), 2.24—3.04 (m, 4H, $2CH_2$), 1.20—1.56 (m, 5H, CH_3 and CH_2), 0.90 (t, *J*=7 Hz, 3H, CH_3). IR (neat) 1750 (COO), 1680 (CH=C) cm^{-1}. Found: C, 69.95; H, 9.17%. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15%.

Reaction of γ-Butyrolactone with Bis[ethoxy(thiocarbonyl)] Disulfide. To a solution of lithium diisoprop-

ylamide (LDA) (44 mmol) in 60 ml of THF was added a solution of 1.72 g (20 mmol) of γ-butyrolactone in 5 ml of THF at −78 °C. After stirring for 1 h, a solution of 5.32 g (22 mmol) of bis[ethoxy(thiocarbonyl)] disulfide in 5 ml of THF was added and the reaction mixture was stirred at −78 °C for 2 h. The cooling bath was removed and the reaction mixture was quenched with 10 ml of saturated aqueous ammonium chloride solution. The usual work-up and the purification by silica-gel chromatography (benzene) gave 2.97 g (72%) of **5a**. The product was identified by comparison of the ^{1}H NMR spectrum and retention time of GLC with the correponding data from independently synthesized material described above.

On the other hand, the reaction of 20 mmol of γ-butyrolactone treated by 22 mmol of LDA with 22 mmol of bis[ethoxy(thiocarbonyl)] disulfide gave 2.67 g (41%) of **6**: Mp 130.5—131.5 °C. ^{1}H NMR ($CDCl_3$) δ=4.72 (q, *J*=7 Hz, 4H, $2CH_2O$), 4.58 (t, *J*=7 Hz, 2H, CH_2O), 3.21 (t, *J*=7 Hz, 2H, CH_2O), 1.50 (t, *J*=7 Hz, 6H, $2CH_3$). IR (KBr pellet) 2990, 1780 (COO), 1035 cm^{-1}. Found: C, 36.49; H, 3.98%. Calcd for $C_{10}H_{14}O_4S_4$: C, 36.79; H, 4.32%.

Reaction of Lithium Enolate of 5a or 5b with Carbonyl Compounds. The preparation of α-heptylidene-γ-butyrolactone from **5a** and heptanal is given here as a typical experiment. To a solution of lithium diisopropylamide (LDA) (22 mmol) in 60 ml of THF was added 4.13 g (20 mmol) of *O*-ethyl *S*-(tetrahydro-2-oxo-3-furanyl) dithiocarbonate (**5a**) at −78 °C. After 30 min, a solution of 2.51 g (22 mmol) of heptanal in 3 ml of THF was added over 2 min. After stirring at −78 °C for 2 h, the reaction mixture was warmed gradually to room temperature from −78 °C and it was stirred for 1 h before quenching with saturated aqueous ammonium chloride solution (10 ml). The usual work-up and the purification by silica-gel chromatography (benzene) gave 2.22 g (61%) of **2a**.

The procedure using butyllithium instead of LDA as base and THF–HMPA (v/v, 16/1) instead of THF as solvent was also employed for the reaction of lithium enolate of **5b** with carbonyl compounds.

(*Z*)-α-Benzylidene-γ-butyrolactone (2b): Mp 90.5—91.5 °C. ^{1}H NMR ($CDCl_3$) δ=7.50 (m, 2H, aromatic), 7.04 (m, 3H, aromatic), 6.70 (m, 1H, CH=C), 4.20 (t, *J*=7 Hz, 2H, CH_2O), 3.00 (m, 2H, CH_2). IR (KBr pellet); 1740 (COO), 1650 (CH=C) cm^{-1}. Found: C, 75.67; H, 5.88%. Calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79%.

(*Z*)-α-Hexylidene-γ-butyrolactone (2g): ^{1}H NMR (CCl_4) δ=6.22 (m, 1H, CH=C), 4.30 (t, *J*=7 Hz, 2H, CH_2O), 2.60—3.00 (m, 4H, $2CH_2$), 1.00—1.58 (m, 6H, $3CH_2$), 0.92 (m, 3H, CH_3). IR (neat) 1758 (COO), 1675 (CH=C) cm^{-1}. Found: C, 71.20; H, 9.65%. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59%.

Decomposition of Lithium Enolate 7a. The lithium enolate **7a** was prepared as usual from 4.13 g (20 mmol) of **5a** and 22 mmol of LDA in 60 ml of THF. After stirring at −78 °C for 1 h, the reaction mixture was quenched by adding 10 ml of saturated aqueous ammonium chloride solution. The usual work-up and the product isolation gave 2.81 g (68%) of **5a** and 0.63 g (18%) of α-[ethoxy-(thiocarbonyl)]-γ-butyrolactone (**8**): ^{1}H NMR (CCl_4) δ=4.56 (q, *J*=7 Hz, 2H, CH_2O), 4.30 (m, 2H, CH_2O), 3.84 (t, *J*=7 Hz, 1H, CH), 2.72 (m, 2H, CH_2O), 1.44 (t, *J*=7 Hz, 3H, CH_3). Found: C, 47.88; H, 5.91%. Calcd for $C_7H_{10}O_3S$: C, 48.26; H, 5.79%.

Therefore, in the subsequent experiments carbonyl compound was instantly added after treating of **5a** with 1.1 equiv of LDA.

General Procedure for the Preparation of Aldol Adducts 9. To a solution of LDA (22 mmol) in 60 ml of THF was added 4.13 g (20 mmol) of **5a** at −78 °C. When the addition was complete, a solution of 22 mmol of carbonyl compound in 5 ml of THF was added and the reaction mixture was stirred at −78 °C for 2 h. The cooling bath was removed and the reaction mixture was poured into dilute hydrochloric acid, and extracted with ether (50×3 ml). The combined organic layer was washed twice with saturated aqueous sodium chloride solution, dried on anhydrous sodium sulfate, and concentrated under reduced pressure. The chromatography on silica gel (hexane–ethyl acetate 3:1) gave a purified but unseparated diastereomers **9** in high yields. The diastereomers were separated by MPLC system using hexane–ethyl acetate 3:1 as eluent, and the diastereomer ratios were determined.

α-(1-Hydroxyheptyl)-α-[ethoxy(thiocarbonyl)thio]-γ-butyrolactone (9a): Chromatography (hexane–ethyl acetate 3:1) afforded in 67% yield a 45:55 mixture of the faster eluting (assigned threo) and slower eluting (assigned erythro) isomers. The faster eluting diastereomer was obtained as a viscous oil: ^{1}H NMR ($CDCl_3$) δ=4.46 (q, *J*=7 Hz, 2H, CH_2O), 4.20 (m, 2H, CH_2O), 3.70 (bt, 1H, CH), 3.40 (bs, 1H, OH), 2.60 (m, 2H, CH_2), 1.08—1.60 (m, 13H, $5CH_2$ and CH_3), 0.70—0.88 (m, 3H, CH_3). IR (neat) 3402 (OH), 1740 (COO) cm^{-1}.

The slower eluting diastereomer was obtained as crystals: Mp 81.5—82.5 °C. ^{1}H NMR ($CDCl_3$) δ=4.64 (q, *J*=7 Hz, 2H, CH_2O), 4.36 (t, *J*=7 Hz, 2H, CH_2O), 4.04 (m, 1H, CH), 3.68 (bs, 1H, OH), 2.08—2.84 (m, 2H, CH_2O), 1.08—1.60 (m, 13H, $5CH_2$ and CH_3), 0.64—0.84 (m, 3H, CH_3). IR (KBr pellet) 3400 (OH), 1736 (COO) cm^{-1}. Found: C, 52.14; H, 7.17%. Calcd for $C_{14}H_{24}O_4S_2$: C, 52.47; H, 7.55%.

α-(1-Hydroxypropyl)-α-[ethoxy(thiocarbonyl)thio]-γ-butyrolactone (9d): Chromatography (hexane–ethyl acetate 2:1) afforded in 70% yield a 48:52 mixture of the faster eluting (assigned threo) and slower eluting (assigned erythro) isomers. The faster eluting diastereomer was obtained as a viscous oil: ^{1}H NMR ($CDCl_3$) δ=4.58 (q, *J*=7 Hz, 2H, CH_2O), 4.32 (t, *J*=7 Hz, 2H, CH_2O), 4.02 (m, 1H, CH), 3.44 (bs, 1H, OH), 2.12—2.96 (m, 2H, CH_2), 1.06—1.80 (m, 5H, CH_3 and CH_2), 1.02 (t, *J*=7 Hz, 3H, CH_3). IR (neat) 3500 (OH), 1770 (COO) cm^{-1}.

The slower-eluting diastereomer was obtained as a viscous oil: ^{1}H NMR ($CDCl_3$) δ=4.71 (q, *J*=7 Hz, 2H, CH_2O), 4.46 (t, *J*=7 Hz, 2H, CH_2O), 3.74—3.94 (m, 1H, CH), 3.89 (s, 1H, OH), 2.50—3.00 (m, 2H, CH_2), 1.20—1.80 (m, 5H, CH_2 and CH_3), 1.04 (t, *J*=7 Hz, 3H, CH_3). IR (neat) 3480 (OH), 1760 (COO) cm^{-1}. Found: C, 45.20; H, 5.98%. Calcd for $C_{10}H_{16}O_4S_2$: C, 45.43; H, 6.10%.

α-(1-Hydroxybutyl)-α-[ethoxy(thiocarbonyl)thio]-γ-butyrolactone (9e): Chromatography (hexane–ethyl acetate 3:1) afforded in 84% yield a 47:53 mixture of the faster eluting (assigned threo) and slower eluting (assigned erythro) isomers. The faster elutiong diastereomer was obtained as a viscous oil: ^{1}H NMR ($CDCl_3$) δ=4.72 (q, *J*=7 Hz, 2H, CH_2O), 4.44 (t, *J*=7 Hz, 2H, CH_2O), 4.16 (m, 1H, CH), 3.54 (bs, 1H, OH), 2.24—2.96 (m, 2H, CH_2), 1.08—1.64 (m, 7H, $2CH_2$ and CH_3), 0.64—1.08 (m, 3H,

CH_3). IR (neat) 3480 (OH), 1770 (COO) cm^{-1}.

The slower-eluting diastereomer was obtained as a viscous oil: ^1H NMR ($CDCl_3$) δ=4.74 (q, J=7 Hz, 2H, CH_2O), 4.46 (t, J=7 Hz, 2H, CH_2O), 3.78—4.24 (m, 2H, CH and OH), 2.30—3.00 (m, 2H, CH_2), 1.08—1.90 (m, 7H, $2CH_2$ and CH_3), 0.80—1.08 (m,3H, CH_3). IR (neat) 3480 (OH), 1760 (COO) cm^{-1}. Found: C, 47.41; H, 6.70%. Calcd for $C_{11}H_{18}O_4S_2$: C, 47.46; H, 6.52%.

Preparation of α-Heptylidene-γ-butyrolactone (2a) from α-(1-Hydroxyheptyl)-α-[ethoxy(thiocarbonyl)thio]-γ-butyrolactone (9a): Into a solution of 8.10 mmol of LDA in 15 ml of THF, 2.36 g (7.36 mmol) of **9a** in 6 ml of THF was added at −78 °C. After stirring at −78 °C for 1 h and then at room temperature for 2 h, the usual work-up and chromatographic isolation afforded 0.98 g (73%) of **2a**, which was identical by spectroscopic comparison with an authentic sample.

α-Butylidene-γ-butyrolactone (2e): The similar reactions utilizing 2.13 g (7.65 mmol) and 1.61 g (5.80 mmol) of **9e** gave 0.68 g (63%) and 0.58 g (71%) of **2e**, respectively.

Preparation of 2a from 9a Using $ZnCl_2$. Into a solution of 7.21 mmol of LDA in 15 ml of THF, 2.10 g (6.55 mmol) of **9a** in 6 ml of THF was added at −78 °C. After stirring at −78 °C for 1 h, 1.34 g (9.83 mmol) of zinc chloride in 9 ml of THF was added. After stirring at −78 °C for 30 min and then at room temperature for 2 h, the usual work-up and chromatographic isolation afforded 0.93 g (78%) of **2a**.

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