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Highly Selective Enolization Method for Heteroatom Substituted Esters; Its Application to the Ireland Ester Enolate Claisen Rearrangement

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Abstract: A method for the stereoselective synthesis of silyl ketene acetals from α-siloxy esters, β-hydroxy esters, and α-amino esters is described. Internal quench with excess trimethylsilyl chloride of the lithium enolate at -100 °C, which is generated using a hindered base, LTMP, leads to the selective formation of *E*-silyl ketene acetal. In contrast, the deprotonation at -100 °C using LHMDS in THF-HMPA (4:1), followed by treatment with *tert*-butyldimethyisilyl chloride affords the *Z*-silyl ketene acetal selectively. The method can be applied to the stereoselective reaction of the Ireland ester enolate Claisen rearrangement.

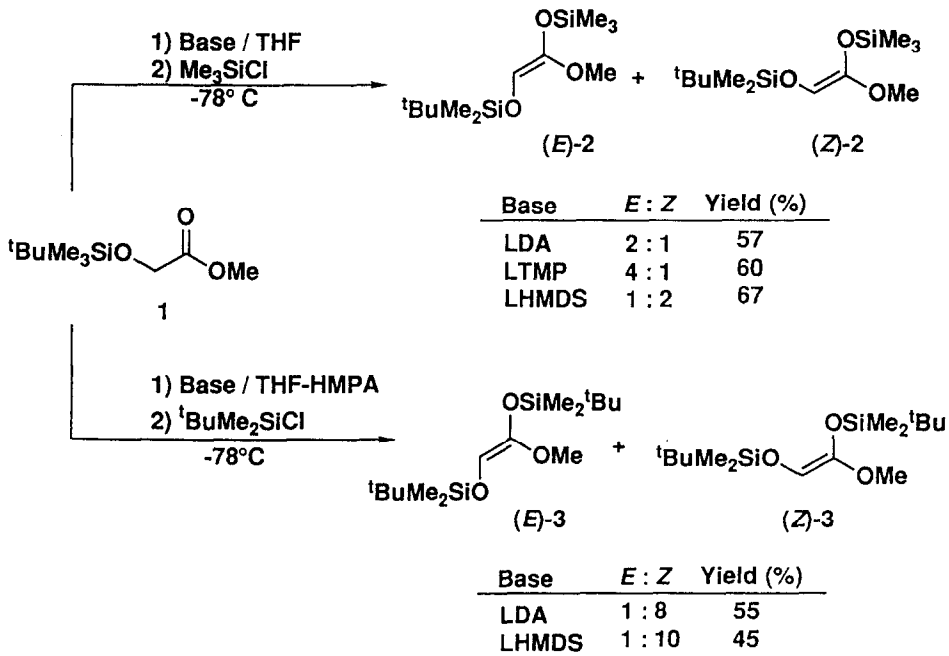
Lithium ester enolates have been shown to be of great importance as reactive intermediate in organic chemistry, where the stereochemistry of the enolates strongly influences the stereochemical outcome of the products.[1] Recently, extensive studies by Ireland and co-workers have demonstrated that the stereochemistry of ester enolates can be successfully controlled by changing the solvent system.[2] The lithium ester enolates created by the deprotonation in THF afford *E*-silyl ketene acetals as a major product, while in THF-23% HMPA the production of *Z*-silyl ketene acetals is predominant. Further, selective enolization has been successfully applied to the ester enolate Claisen rearrangement.

Silyl ketene acetals of α-hydroxy esters in particular become very valuable synthetic intermediates: they become an important component of a method for positioning hydroxy function on α–carbonyl group with stereochemical control. A number of groups have therefore investigated the enolization of α-hydroxy esters and subsequent Claisen rearrangement or its variants.[3,4] Unfortunately, however, there is no general technique for the stereoselective formation of a given silyl ketene acetal from α-hydroxy ester. In fact, since the enolization of α-hydroxy esters is strongly controlled by chelation between α- and carbonyl oxygen, changes in solvent or reaction conditions are known to be ineffective in changing the stereochemical course of the reaction. We describe here the stereoselective formation of both *E*- and *Z*-isomers of silyl ketene acetals from α-siloxy esters and relative esters.

Effect of the base on stereoselectivity in silyl ketene acetal formation. First, we examined the effect of the base in the formation of silyl ketene acetal from *tert*-butyldimethylsilyloxy ester **1** as shown in Scheme I. Deprotonation of ester **1** with 1.1 equiv of LDA in THF at -78 °C then silylation with TMSCl, gave 2:1 ratio of the silyl ketene acetals (*E*)-**2** and (*Z*)-**2**. The use of a hinder base, lithium 2,2,6,6-tetramethylpiperidide (LTMP)[5] led to an increase in the *E*:*Z* ratio to 4:1, whereas the use of lithium 1,1,1,3,3,3-hexamethyldisilylamide (LHMDS)[6] resulted in a reversal in selectivity, *E*:Z=1:2.

In THF-23 % HMPA solvent system,[2] the degree of stereoselectivity in the formation of the *Z*-silyl ketene acetal was increased. LHMDS was slightly more efficient for this selectivity than LDA, 1:10 *vs.* 1:8. However, the results confirmed that the usual conditions are totally ineffective for such selective enolization of α-siloxy esters.[7]

Scheme I

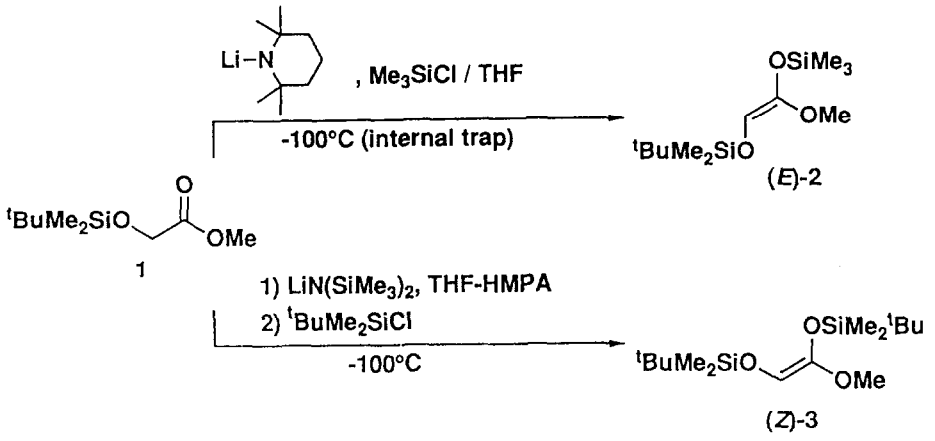


Base	*E* : *Z*	Yield (%)
LDA	2 : 1	57
LTMP	4 : 1	60
LHMDS	1 : 2	67

Base	*E* : *Z*	Yield (%)
LDA	1 : 8	55
LHMDS	1 : 10	45

Selective formation of both *E*- and Z-silyl ketene acetals from α-siloxy esters.

Scheme II

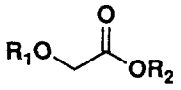


After further optimization in this study, we developed a new method which led to new levels of stereoselectivity in the generation of silyl ketene acetals under kinetic control. *tert*-Butyldimethylsiloxy ester **1** was added to a mixture of LTMP in the presence of excess trimethylsilyl chloride (TMSCl) at -100 °C in THF. After usual workup, the silyl ketene acetal was isolated by distillation (method A). This internal quench method[8] led to high selectivity of *E*-silyl ketene acetal (*E*:Z=96:4). In contrast, the ester **1** was added to a solution of LHMDS at -100 °C in THF-HMPA (4:1), and then treated with *tert*-butyldimethylsilyl chloride (TBDMSCl) at the same low temperature (method B).[9] Z-Silyl ketene acetal was obtained with almost complete stereoselectivity (*E*:Z= <1:99). The ratio and geometry were determined by ^{1}H-NMR and NOESY spectroscopic experiments.[10] Additional results concerning the stereocontrolled formation of silyl ketene acetals are shown in Table I. Generally, the *E*-selectivity slightly decreased as R_2 became larger (entries 1-10). The size of silyl group as a protective group on the hydroxy ester was known to be closely related to the chelation effect.[11] Therefore, sterically demanding silyl groups such as triisopropylsilyl or *tert*-butyldiphenylsilyl inhibited chelation and should have given a high level of *E*-silyl ketene acetal. Meanwhile, the selective formation of Z-silyl ketene acetal proceeded smoothly in all cases studied under method B.

Table I. *E*- and *Z*-Stereoselective Preparation of Silyl Ketene Acetals from Various α-Siloxy Esters

Entry	Ester[a]	Method[b]	Yield (%)[c]	*E* : *Z*[d]
1	**1**	A	82	96 : 4
2		B	61	1 : 99
3	**5**	A	81	96 : 4
4		B	64	2 : 98
5	**6**	A	79	95 : 5
6		B	73	5 : 95
7	**7**	A	84	95 : 5
8		B	68	2 : 98
9	**8**	A	76	90 : 10
10		B	67	<1 : 99
11	**9**	A	71	44 : 56
12		B[e]	69	<1 : 99
13	**10**	A	82	88 : 12
14		B	62	1 : 99
15	**11**	A	74	>99 : 1
16		B	63	3 : 97
17	**12**	A	96[f]	>99 : 1
18		B	98[f]	2 : 98

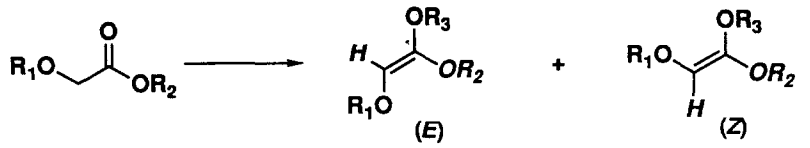
[a]Structures are given below. [b]See text. [c]Yield was determined after isolation by distillation. [d]Ratio was determined by ^{1}H-NMR. The ratios did not change after distillation. [e]THF was used as a solvent and TMSCl was used to trap enolate. [f]Yield was determined by ^{1}H-NMR of the crude product.



1: R_1 = TBDMS, R_2 = Me
5: R_1 = TBDMS, R_2 = Et
6: R_1 = TBDMS, R_2 = *i*-Pr
7: R_1 = TBDMS, R_2 = *n*-Bu
8: R_1 = TBDMS, R_2 = Ph
9: R_1 = TMS, R_2 = Me
10: R_1 = TES, R_2 = Me
11: R_1 = TIPS, R_2 = Me
12: R_1 = TBDPS, R_2 = Me

Mechanism of ester enolate control. It seems very likely that these remarkable enolization-silylations of α-siloxy esters arise from geometric constraints in the relevant transition states. One intriguing possibility is that there may be a preferred pericyclic transition state of **13** for proton abstraction by LTMP. Thus, formation of the enolate anion would presumably require removal of a pseudoaxial hydrogen, the large repulsion of TMP and ^{t}BuMe$_2$SiO dominant caused this pathway to be favored, which would lead to *E* enolate

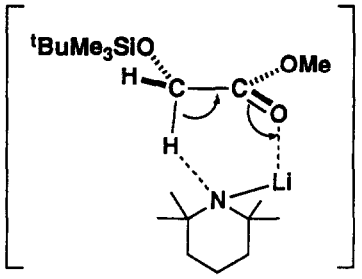
Table II. NMR Data for R_2 and Vinyl Proton of *E*- and *Z*-Silyl Ketene Acetals (δ in ppm)[a]



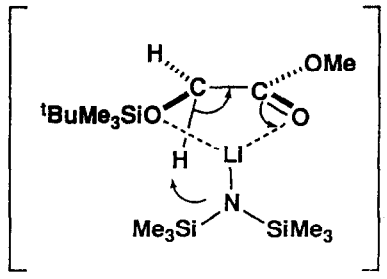
ester	silyl ketene acetal			(*E*)		(*Z*)	
	R_1	R_2	R_3	*R_2*	*vinyl H*	*R_2*	*vinyl H*
1	TBDMS	Me	TMS	3.64(3H, s)	5.45(1H, s)	3.47(3H, s)	5.52(1H, s)
1	TBDMS	Me	TBDMS	3.62(3H, s)	5.41(1H, s)	3.47(3H, s)	5.50(1H, s)
5	TBDMS	Et	TMS	1.28(3H, t)[b] 3.93(2H, q)[b]	5.49(1H, s)		5.55(1H, s)
5	TBDMS	Et	TBDMS		5.47(1H, s)	1.22(3H, t)[b] 3.71(2H, q)[b]	5.53(1H, s)
6	TBDMS	*i*-Pr	TMS	1.22(6H, d)[c] 4.2-4.4(1H, m)	5.52(1H, s)		5.59(1H, s)
6	TBDMS	*i*-Pr	TBDMS		5.52(1H, s)	1.17(6H, d)[c] 4.2-4.4(1H, m)	5.58(1H, s)
7	TBDMS	*n*-Bu	TMS	0.92(3H, t)[d] 1.3-1.7(4H, m) 3.87(2H, t)[e]	5.47(1H, s)		5.51(1H, s)
7	TBDMS	*n*-Bu	TBDMS		5.45(1H, s)	1.3-1.7(4H, m) 3.63(2H, t)[f]	5.51(1H, s)
8	TBDMS	Ph	TMS	6.7-7.4(5H, m)	5.83(1H, s)		5.88(1H, s)
8	TBDMS	Ph	TBDMS		5.80(1H, s)	6.9-7.3(5H, m)	5.90(1H, s)
9	TMS	Me	TMS	3.62(3H, s)	5.40(1H, s)	3.48(3H, s)	5.50(1H, s)
10	TES	Me	TMS	3.65(3H, s)	5.47(1H, s)	3.49(3H, s)	5.56(1H, s)
10	TES	Me	TBDMS	3.63(3H, s)	5.47(1H, s)	3.47(3H, s)	5.48(1H, s)
11	TIPS	Me	TMS	3.67(3H, s)	5.55(1H, s)		
11	TIPS	Me	TBDMS	3.65(3H, s)	5.43(1H, s)	3.38(3H, s)	5.52(1H, s)
12	TBDPS	Me	TMS	3.69(3H, s)	5.48(1H, s)		
12	TBDPS	Me	TBDMS	3.68(3H, s)	5.46(1H, s)	3.31(3H, s)	5.46(1H, s)

[a] Samples were dissolved in $CDCl_3$ and discerned from the mixture. [b] J = 7.2 Hz. [c] J = 6.2 Hz. [d] J = 7.0 Hz. [e] J = 7.4 Hz. [f] J = 6.6 Hz.

(*deprotonation control*). Because of the much weaker base of LHMDS with less reactive TBDMSCl, the complexation step would be more important in method B. Thus, chelation (see **14**) would take place to generate the *Z*-enolate selectively (*complexation control*).[12,13]



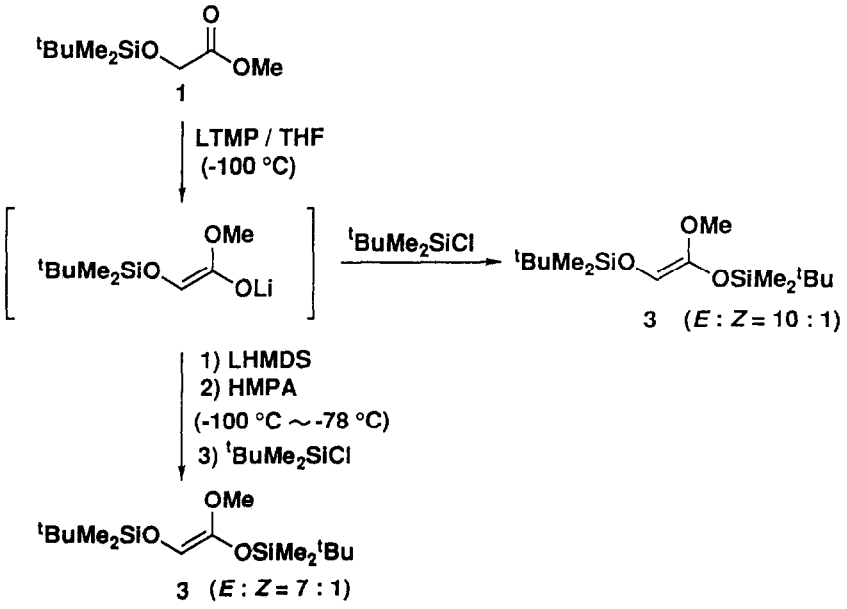
13



14

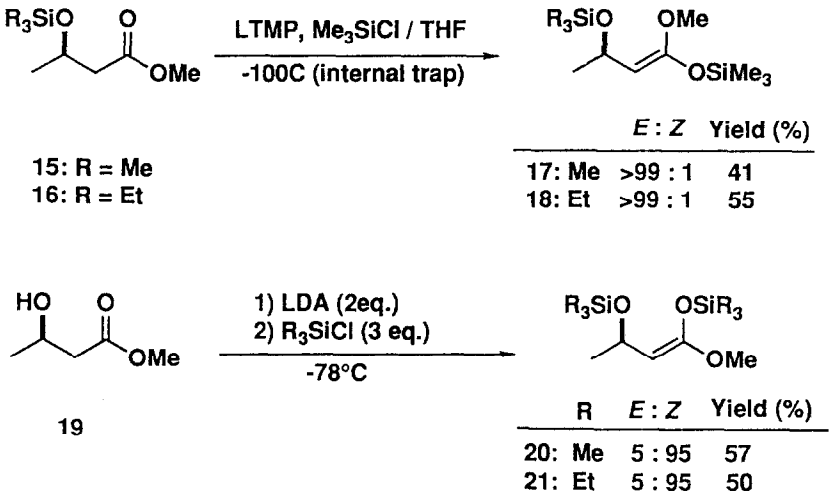
In both methods, *Z*- and *E*- enolates may be formed under kinetic control, and solvation of the lithium cation by HMPA may only minimally promote equilibration of the enolates. Actually, when HMPA and hexamethyldisilazane were added to a solution of lithium enolate of ester **1** in THF before being treated with TBDMSCl, little change in the *E*/*Z* ratio was observed (Scheme III). Treatment of the lithium enolate prepared from LTMP in THF at -100 °C with TBDMSCl gave a 10:1 ratio of the silyl ketene acetals (*E*)-**3** and (*Z*)-**3**. To the same enolate in THF was added HMPA (25% of THF) and hexamethyldisilazane (1.2 equiv) at -100 °C and this solution was then warmed up to -78 °C over 30 min. Treatment of the solution with TBDMSCl at -78 °C gave a 7:1 ratio of the silyl ketene acetals. These results suggest that ester enolate are not prone to rapid equilibration.

Scheme III



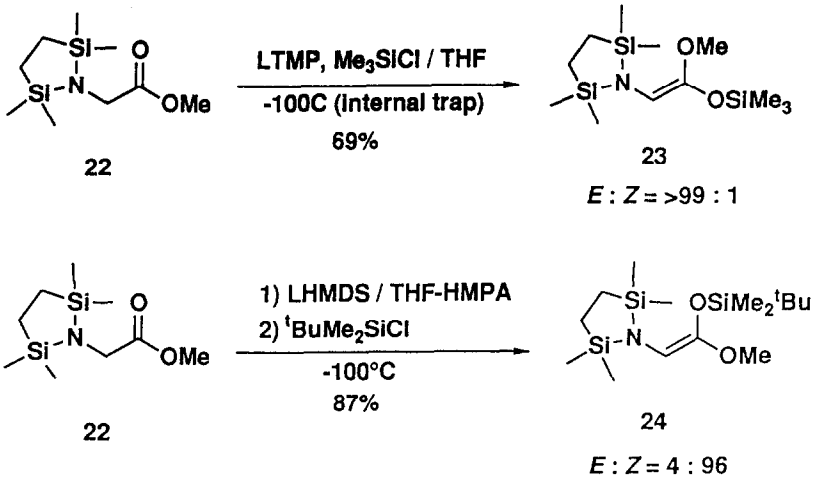
Selective formation of both *E*- and *Z*-silyl ketene acetals from β-hydroxy esters. As an extension of this method, we turned to enolization of β-hydroxy esters, which is also known to be controlled by the similar chelation. Treatment of β-trimethylsilyloxy ester **15** and β-triethylsilyloxy ester **16** with LDA under normal conditions easily replaced the β-elimination so that the desired silyl ketene acetal could not be obtained. A remarkable finding, however, was that our process using the internal quench method with LTMP enabled production of the selective *E*-silyl ketene acetal. Addition of the protected esters **15** and **16** to a mixture of LTMP and TMSCl at -78 °C stereoselectively furnished the pure *E*-silyl ketene acetal, respectively, in 41-55% yield after distillation (Scheme IV).[14] In contrast, *Z*-silyl ketene acetals could be obtained through double deprotonation of β-hydroxy ester **19** with 2 equiv of LDA by chelation control.[15]

Scheme IV



Selective formation of both *E*- and *Z*-silyl ketene acetals from α-amino esters. Both *E*- and *Z*-silyl ketene acetals of protected α-amino esters were also prepared by the procedure in Scheme V. When protected glycinate **22**[16] was treated in the same internal quench manner, *E*-silyl ketene acetal **23** was selectively obtained in 69% yield.[14] Treatment of the same substrate **22** with a solution of LHMDS in THF-HMPA at -100 °C and then with TBDMSCl afforded *Z*-silyl ketene acetal **24** (*E*:*Z*=4:96, 87% yield).

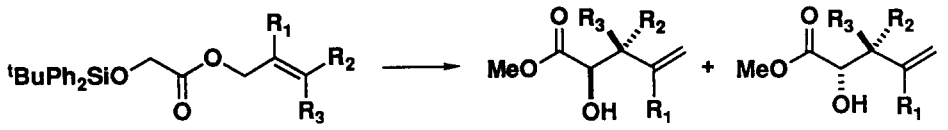
Scheme V



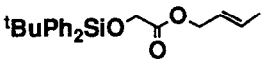
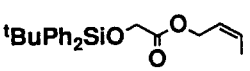
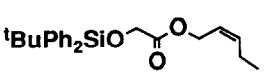
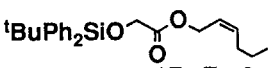
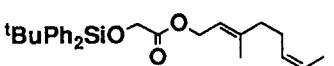
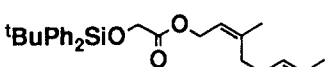
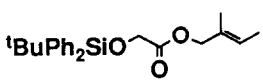
Diastereoselective reaction in ester enolate Claisen rearrangement. Finally, we demonstrated the effectiveness of this approach in the Ireland ester enolate Claisen rearrangement.[17] Table III summarizes the results obtained for the reaction of some allyl glycolates. When *tert*-butyldiphenylsiloxy esters **25** were exposed to a mixture of LTMP and excess TMSCl in THF at -100 °C (method A) and then at room temperature for 4 h, the hydroxy methyl esters were isolated in 82-98% yield, after esterification with diazomethane and desilylation with tetrabutylammonium fluoride. GLC and NMR analysis of the products showed the formation of isomer **26**.[18] In contrast, when the same substrate was treated with a solution of LHMDS in THF-HMPA (4:1) at -100 °C and then with TMSCl (method B) and warmed to room temperature, the diastereomerically pure isomer **27** was produced in 80-87% yield. In acyclic systems, Claisen rearrangements were obviously proposed to proceed *via* chairlike transition states. Regarding the allylic bond configuration, *trans*-allyl glycolates gave slightly lower selectivity than *cis*-compounds in the reaction through *E*-enolate by method A (entries 1 *vs.* 2, 5 *vs.* 6, and 7 *vs.* 8). In a cyclic system, cyclohexenyl glycolate **28** was smoothly reacted under method A in 75% yield to a 78:22 ratio of the rearrangement products **29** and **30** (Scheme VI).[18] Under method B, **28** was rearranged in 81% yield to a 13:87 ratio of **29** and **30**. With both *E*-and *Z*-enolates the major isomer was therefore formed *via* a boatlike transition state. Thus, the formation of both enolates was controlled and the relative stereochemistry of the Claisen product was consistent with the stereochemistry of the derived enolate.

In conclusion, complementary conditions are now available for stereoselective generation of *E*- and *Z*-silyl ketene acetals from α-siloxy esters, β-hydroxy esters, and α-amino esters under a kinetically controlled enolization. Thermodynamic equilibration does not seem to take place even when THF-HMPA solvent system is used for enolization. The simplicity and high selectivity of the procedure make it a very practical approach for the synthesis of stereochemically homogeneous silyl ketene acetals (or enolates) which have vast potential in ester enolate Claisen rearrangement and various organic syntheses.

Table III. Diastereoselective Ester Enolate Claisen Rearrangement of Allyl Glycolates

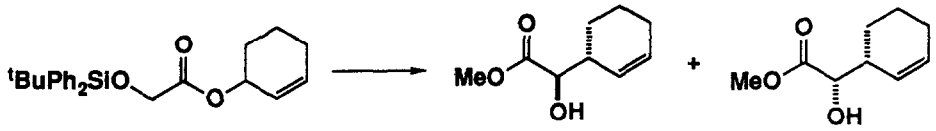


25 *26* *27*

Entry	Ester[a]	Method[b]	Yield (%)	Ratio[c] *26* : *27*	
1	25a:  ($E:Z = 95:5$)	A	82	80 : 20	(85 : 15)[d]
		B	87	10 : 90	(5 : 95)[d]
2	25b:  ($E:Z = 2:98$)	A	86	95 : 5	(97 : 3)[d]
		B	80	3 : 97	(1 : 99)[d]
3	25c:  ($E:Z = 3:97$)	A	85	95 : 5	(98 : 2)[d]
		B	80	4 : 96	(1 : 99)[d]
4	25d:  ($E:Z = 2:98$)	A	93	96 : 4	(98 : 2)[d]
		B	85	3 : 97	(1 : 99)[d]
5	25e:  ($E:Z = >99:1$)	A	98	91 : 9[e]	
		B	80	3 : 97	
6	25f:  ($E:Z = <1:99$)	A	94	94 : 6	
		B	81	4 : 96	
7	25g:  ($E:Z = >99:1$)	A	97	89 : 11	
		B	87	3 : 97	
8	25h:  ($E:Z = <1:99$)	A	86	94 : 6	
		B	80	1 : 99	

[a] *E-Z* ratio was determined by ^{1}H-NMR or HPLC. [b] See text. [c] Determined by ^{1}H-NMR and GLC analyses as described in ref 18. [d] Corrected ratio for starting impurities.
[e] The relative configuration of *27* was determined by X-ray structural analysis.

Scheme VI



28 29 30

	Yield	29 : 30
Method A:	75%	78 : 22
Method B:	81%	13 : 87

Experimental Section[19]

Preparation of silyl ketene acetal from α-siloxy ester.

General Procedure for Method A: A solution of tetramethylpiperidine (0.50 mL, 2.9 mmol) in THF (12 mL) was cooled to 0 °C and *n*-BuLi in hexane (1.7 mL, 2.7 mmol) was added slowly under argon. This mixture was stirred for 15 min at 0 °C and subsequently cooled to -100 °C (cooling bath temp). TMSCl (0.40 mL, 3.2 mmol) was added and then a solution of the ester **1** (0.5 g, 2.5 mmol) in THF (2 mL) was added slowly over 5 min. The reaction mixture was stirred for 10 min at the same temperature and subsequently allowed to warm up to room temperature. After stirring for 1 h, the solution was diluted with hexane (100 mL). The mixture was filtered using suction through a Celite pad, and concentrated *in vacuo*. Distillation of the residue under reduced pressure gave the silyl ketene acetal (0.55 g, 82% yield).

General Procedure for Method B: A solution of hexamethyldisilazane (1.2 mL, 6.0 mmol) in THF (20 mL) was cooled to 0 °C and *n*-BuLi in hexane (3.4 mL, 5.5 mmol) was added slowly under argon. This mixture was stirred for 15 min at 0 °C, subsequently cooled to -78 °C, and HMPA (5 mL) was added dropwise. After 5 min, the solution was cooled to -100 °C (cooling bath temp). A solution of the ester **1** (1.0 g, 5.0 mmol) in THF (2 mL) was added slowly over 5 min followed by a solution of TBDMSCl (1.0 g, 6.5 mmol) in THF (1 mL). The reaction mixture was stirred for 10 min at the same temperature and subsequently allowed to warm up to room temperature. After stirring for 1 h, the solution was quenched with a sat. solution of $NaHCO_3$ (50 mL) and cold hexane (150 mL). The organic layer was washed with water (50 mL) 3 times, dried over $MgSO_4$, filtered, and concentrated. Distillation of the residue under reduced pressure gave the silyl ketene acetal (0.89 g, 61% yield).

Preparation from β-siloxy ester and β-hydroxy ester.

(*E*)-(3*R*)-Triethylsilyloxy-1-methoxy-1-trimethylsilyloxy-1-butene 18: A solution of tetramethylpiperidine (0.87mL, 5.2 mmol) in THF (25 mL) was cooled to 0°C and n-BuLi in hexane (3.0 mL, 4.7 mmol) was added slowly under argon. This mixture was stirred for 15 min at 0°C and subsequently cooled to -100°C (cooling bath temp). TMSCl (0.71 mL, 5.6 mmol) was added and then a solution of the methyl triethylsiloxybutyrate **16** (1.0 g, 4.3 mmol) in THF (2 mL) was added slowly over 5 min. The reaction mixture

was stirred for 10 min at the same temperature and subsequently allowed to warm up to room temperature. After stirring for 1 h, the solution was diluted with hexane (125 mL). The mixture was filtered using suction through a Celite pad, and concentrated. Distillation of the residue under reduced pressure gave **18** (720 mg, 55%): bp. 115-118 °C / 8 mmHg; NMR($CDCl_3$) δ 0.26(9H, s), 0.5-0.8(6H, m), 0.8-1.0(9H, m), 1.22(3H, d, J = 6.2 Hz), 3.53(3H, s), 3.80(1H, d, J = 8.8 Hz), 4.5-4.7(1H, m).

(*E*)-(3*R*)-Trimethylsilyloxy-1-methoxy-1-trimethylsilyloxy-1-butene 17: The reaction was carried out in the same manner from **15** (41%). bp. 84-87 °C / 7 mmHg; NMR($CDCl_3$) δ 0.13(9H, s), 0.25(9H, s), 1.22(3H, d, J = 6.2 Hz), 3.54(3H, s), 3.79(1H, d, J = 8.8 Hz), 4.5-4.8(1H, m).

(*Z*)-(3*R*)-Trimethylsilyloxy-1-methoxy-1-trimethylsilyloxy-1-butene 20: *Z*-Silyl ketene acetal was prepared from **19** according to the procedure in the literature.[15] yield 57%; bp. 82-88 °C / 7 mmHg; NMR($CDCl_3$) δ 0.13(9H, s), 0.23(9H, s), 1.24(3H, d, J = 6.4 Hz), 3.52(3H, s), 3.64(1H, d, J = 8.8 Hz), 4.5-4.8(1H, m).

(*Z*)-(3*R*)-Triethylsilyloxy-1-methoxy-1-triethylsilyloxy-1-butene 21: yield 50%; bp. 110-115 °C / 5 mmHg; NMR($CDCl_3$) δ 0.4-0.8((12H, m), 0.9-1.1(18H, m), 1.20(3H, d, J = 6.2 Hz), 3.46(3H, s), 3.57(1H, d, J = 8.8 Hz), 4.5-4.7(1H, m).

Preparation from α-amino ester.

(*E*)-2-Amino-1-methoxy-1-trimethylsilyloxyethylene 23: Method A from **22**; yield 69%, bp. 160-170°C(7 mmHg); NMR($CDCl_3$) δ 0.02–0.07(12H, m), 0.18(9H, s), 0.68(4H, s), 3.46(3H, s), 4.62(1H, s).

(*Z*)-2-Amino-1-*tert*-butyldimethylsilyloxy-1-methoxyethylene 24: Method B from **22**; yield 87%, bp. 175-180°C(7 mmHg); NMR($CDCl_3$) δ 0.02(12H, m), 0.12(6H, s), 0.69(4H, s), 0.90(9H, s), 3.48(3H, s), 4.30(1H, s).

Effect of LHMDS and HMPA (in Scheme III).

[1] A solution of tetramethylpiperidine (0.5 mL, 3.0 mmol) in THF (10 mL) was cooled to 0 °C and *n*-BuLi in hexane (1.7 mL, 2.8 mmol) was added slowly under argon. After the mixture was stirred for 15 min at 0 °C, subsequently cooled to -100 °C (cooing bath temp), a solution of the ester **1** (0.5 g, 2.5 mmol) in THF (2 mL) was added slowly over 5 min. To this solution of enolate was added a solution of TBDMSCl (0.48 g, 3.2 mmol) in THF (1 mL), followed by HMPA (3 mL) at -100 °C. The reaction mixture was stirred for 10 min at the same temperature and subsequently allowed to warm up to room temperature. After stirring for 1 h, the solution was quenched with sat. solution of $NaHCO_3$ and cold hexane. The organic layer was washed with water, dried over $MgSO_4$, filtered, and concentrated. Distillation of the residue under reduced pressure gave the silyl ketene acetal (0.48 g, 62% yield; ratio *E*:*Z*=9:1).

[2] To the same enolate in THF were added hexamethyldisilazane (0.62 mL, 3.0 mmol) and HMPA (3 mL) at -100 °C, and this solution was warmed up to -78 °C over 30 min. After treatment with a solution of TBDMSCl (0.48 g, 3.2 mmol) in THF(1 mL) at -78 °C, the mixture was warmed up to room temperature, and treated again in the same manner (0.41 g, 53%; ratio *E*:*Z*=7:1).

Ester Enolate Claisen Rearrangement

General procedure of Claisen rearrangement.

Method A: A solution of tetramethylpiperidine (0.31 mL, 2.0 mmol) in THF (12 mL) was cooled to 0 °C and *n*-BuLi in hexane (1.1 mL, 1.8 mmol) was added slowly under argon. This mixture was stirred for 15 min at 0 °C and subsequently cooled to -100 °C (cooling bath temp). TMSCl (0.26 mL, 2.1 mmol) was added and then a solution of the allyl ester (1.6 mmol) in THF (2 mL) was added slowly over 5 min. The reaction mixture was stirred for 10 min at the same temperature and subsequently allowed to warm up to room temperature. After stirring for 4 h, the solution was poured into a mixture of ether and 1N hydrochloric acid solution. The organic layer was washed with brine, dried over $MgSO_4$, and then the filtrate was concentrated. The residue was dissolved in a mixture of benzene (15 mL) and MeOH (3 mL) and trimethylsilyldiazomethane (2-3 mL, 10% in hexane) was added to the solution at room temperature. After stirring for 1h, the solvent was removed *in vacuo*. The residue was dissolved in THF (5 mL) and tetrabutylammonium fluoride (2.4 mL, 1M solution in THF) was added at room temperature. After further stirring for 4h, the solution was diluted with ether. The mixture was washed with 1N hydrochloric acid, sat. $NaHCO_3$, and brine. The organic solution was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel by eluting with a mixture of hexane/ether to give the pure Claisen products.

Method B: A solution of hexamethyldisilazane (0.41 mL, 2.0 mmol) in THF (12 mL) was cooled to 0 °C and *n*-BuLi in hexane (1.1 mL, 1.8 mmol) was added slowly under argon. This mixture was stirred for 15 min at 0 °C, subsequently cooled to -78 °C, and HMPA (3 mL) was added dropwise. After 5 min, the solution was cooled to -100 °C (cooling bath temp). A solution of the allyl ester (1.6 mmol) in THF (2 mL) was added slowly over 5 min followed by a solution of TMSCl (0.26 mL, 2.1mmol). The reaction mixture was subsequently treated as described in method A.

***erythro*-Methyl 2-hydroxy-3-methyl-4-pentenoate 26b:** NMR($CDCl_3$) δ 1.02(3H, d, J = 6.8 Hz), 2.6-2.8(1H, m), 2.84(1H, d, J = 5.4 Hz), 3.80(3H, s), 4.20(1H, br.t, J = 5.4 Hz), 5.1-5.3(2H, m), 5.7-6.0(1H, m); IR (neat) 3400, 1734 cm^{-1}; Anal. Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39. Found: C, 58.38; H, 8.71.

***threo*-Methyl 2-hydroxy-3-methyl-4-pentenoate 27b:** NMR($CDCl_3$) δ 1.17(3H, d, J = 7.0 Hz), 2.6-2.8(1H, m), 2.76(1H, d, J = 6.2 Hz), 3.79(3H, s), 4.15(1H, dd, J = 3.4, 6.2 Hz), 5.0-5.2(2H, m), 5.6-6.0(1H, m); IR (neat) 3400, 1734 cm^{-1}; Anal. Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39. Found: C, 58.21; H, 8.72.

***erythro*-Methyl 2-hydroxy-3-ethyl-4-pentenoate 26c:** NMR($CDCl_3$) δ 0.88(3H, t, J = 7.6 Hz), 1.2-1.7(2H, m), 2.2-2.4(1H, m), 2.81(1H, d, J = 7.2 Hz), 3.78(3H, s), 4.17(1H, dd, J = 4.4, 7.2 Hz), 5.0-5.3(2H, m), 5.5-5.8(1H, m); IR (neat) 3450, 1734 cm^{-1}; Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.69; H, 9.30.

***threo*-Methyl 2-hydroxy-3-ethyl-4-pentenoate 27c:** NMR($CDCl_3$) δ 0.94(3H, t, J = 7.4 Hz), 1.4-1.7(2H, m), 2.2-2.5(1H, m), 2.73(1H, d, J = 6.0 Hz), 3.80(3H, s), 4.26(1H, dd, J = 3.0, 6.0 Hz), 5.0-5.3(2H, m), 5.6-5.8(1H, m); IR (neat) 3450, 1734 cm^{-1}; Anal. Calcd for $C_7H_{12}O_3$: C, 60.74; H, 8.92. Found: C, 60.76; H, 9.31.

***erythro*-Methyl 2-hydroxy-3-propyl-4-pentenoate 26d:** NMR($CDCl_3$) δ 0.89(3H, t, J = 6.2 Hz), 1.1-1.6(4H, m), 2.35-2.55(1H, m), 2.78(1H, d, J = 7.2 Hz), 3.79(3H, s), 4.16(1H, dd, J = 6.2, 7.2 Hz), 5.07-5.25(2H, m), 5.56-5.80(1H, m); IR (neat) 3500, 1734, 1640 cm^{-1}; Anal. Calcd for $C_9H_{16}O_3$: C, 62.99; H, 9.86. Found: C, 63.34; H, 9.99.

***threo*-Methyl 2-hydroxy-3-propyl-4-pentenoate 27d:** NMR($CDCl_3$) δ 0.92(3H, t, J = 7.0 Hz), 1.2-1.7(4H, m), 2.35-2.55(1H, m), 2.85(1H, d, J = 5.8 Hz), 3.77(3H, s), 4.22(1H, dd, J = 3.0, 5.8 Hz), 4.95-5.20(2H, m), 4.97-5.12(1H, m); IR (neat) 3500, 1740, 1640 cm^{-1}; Anal. Calcd for $C_9H_{16}O_3$: C, 62.99; H, 9.86. Found: C, 63.30; H, 9.97.

***erythro*-Methyl 2-hydroxy-3-methyl-3-(4-methyl-3-pentenyl)-4-pentenoate 26f:** NMR($CDCl_3$) δ 1.02(3H, s), 1.3-1.5(2H, m), 1.54(3H, s), 1.63(3H, s), 1.7-2.0(2H, m), 2.70(1H, d, J = 8.6 Hz), 3.70(3H, s), 3.92(1H, d J = 8.6 Hz), 4.9-5.2(3H, m), 5.74(1H, dd, J = 11.0, 17.6 Hz); IR (neat) 3500, 1734 1640 cm^{-1}; Anal. Calcd for $C_{13}H_{22}O_3$: C, 69.00; H, 9.80. Found: C, 69.00; H, 10.21.

***threo*-Methyl 2-hydroxy-3-methyl-3-(4-methyl-3-pentenyl)-4-pentenoate 27f:** NMR($CDCl_3$) δ 1.00(3H, s), 1.3-1.7(2H, m), 1.59(3H, s), 1.67(3H, s), 1.8-2.0(2H, m), 2.73(1H, d, J = 7.4 Hz), 3.78(3H, s), 3.97(1H, d J = 7.4 Hz), 5.0-5.3(3H, m), 5.79(1H, dd, J = 10.8, 17.4 Hz); IR (neat) 3500, 1732, 1640 cm^{-1}; Anal. Calcd for $C_{13}H_{22}O_3$: C, 69.00; H, 9.80. Found: C, 68.94; H, 10.18.

***erythro*-Methyl 2-hydroxy-3, 4-dimethyl-4-pentenoate 26h:** NMR($CDCl_3$) δ 1.03(3H, d, J = 7.0 Hz), 1.81(3H, s), 2.5-2.7(1H, m), 2.66(1H, d, J = 6.0 Hz), 3.80(3H, s), 4.30(1H, m), 4.8-5.0(2H, m); IR (neat) 3500, 1740, 1646 cm^{-1}; Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.69; H, 9.16.

***threo*-Methyl 2-hydroxy-3, 4-dimethyl-4-pentenoate 27h:** NMR($CDCl_3$) δ 1.16(3H, d, J = 7.0 Hz), 1.73(3H, s), 2.5-2.8(1H, m), 2.62(1H, d, J = 7.0 Hz), 3.78(3H, s), 4.15(1H, m), 4.8-5.0(2H, m); IR (neat) 3500, 1740, 1646 cm^{-1}; Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.71; H, 9.23.

Methyl 2-(2-cyclohexenyl)-2-hydroxyacetate 29: Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.51; H, 8.65. The spectral data were identical with those described in ref 18.

Methyl 2-(2-cyclohexenyl)-2-hydroxyacetate 30: Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.65. Found: C, 63.49; H, 8.76. The spectral data were identical with those described in ref 18.

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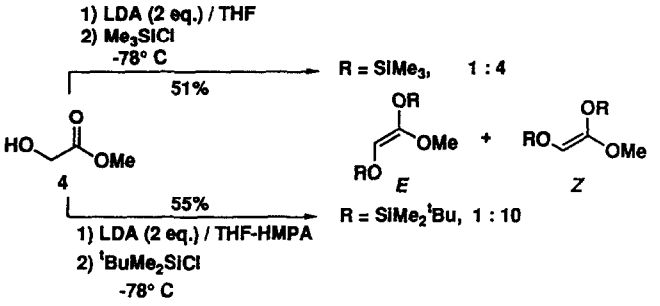

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(19) **General.** Infrared (IR) spectra were recorded on a Shimadzu FTIR-8100 spectrometer. ^{1}H-NMR spectra were measured on a Varian Gemini-200 spectrometer. Gas liquid phase chromatographic (GLC) analyses were performed on Shimadzu 8A instrument equipped with 25 m PEG-HT capillary column and a flame ionization detector, using nitrogen as a carrier gas. High-performance liquid chromatography (HPLC) analysis was carried out on a Shimadzu LC-6A instrument with a SPD-6A UV detector. All experiments were performed under an atmosphere of dry argon unless otherwise specified. The products were purified by preparative column chromatography on silica gel E. Merck 9385. Elemental analysis, mass spectra, and X-ray analysis were performed at the analysis laboratories of Fujisawa Pharmaceutical Co..

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