Highly Selective Generation and Application of (*E*)- and (*Z*)-Silyl Ketene Acetals from α-Hydroxy Esters

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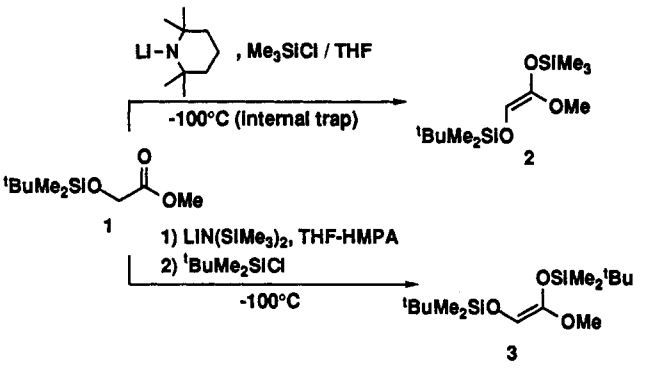
Summary: A method for the stereoselective synthesis of silyl ketene acetals from α-hydroxy esters is described. Internal quench with excess TMSCl of the lithium enolate at −100 °C, which is generated using a hindered base, LTMP, leads to the selective formation of (*E*)-silyl ketene acetal. In contrast,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

Silyl ketene acetals of α-hydroxy esters are very valuable synthetic intermediates. Their importance is attributable to the fact that, together with the ester enolate Claisen rearrangement or its variants, they become an important component of a method for positioning hydroxy function on the α-carbonyl group with complete stereochemical control.[1] 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 condition are known to be ineffective in changing the stereochemical course of the reaction. The significance of the work reported here is that it achieves the formation of both *E*- and *Z*-isomers of silyl ketene acetal from α-hydroxy ester stereoselectively. The new method has now 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 hindered base, lithium 2,2,6,6-tetramethylpiperidide (LTMP),[2] in the presence of excess trimethylsilyl chloride (TMSCl) at −100 °C in THF (method A).[3] After usual workup, the silyl ketene acetal was isolated by distillation. The ratio and geometry were determined by ^{1}H-NMR and NOESY spectroscopic experiments.[4] This effective internal quench method[5] led to high selectivity of (*E*)-silyl ketene acetal (*E*:*Z* = 96:4). In contrast, the ester **1** was

Scheme I



added to a solution of lithium 1,1,1,3,3,3-hexamethyldisilylamide (LHMDS)[6] at −100 °C in THF–HMPA (4:1), and then treated with *tert*-butyldimethylsilyl chloride (TBSCl) at the same low temperature (method B).[7] (*Z*)-Silyl ketene acetal was obtained with almost complete stereoselectivity (*E*:*Z* = <1:99). Additional results concerning the stereocontrolled formation of silyl ketene acetals are shown in Table I.

It should be noted that the use of a lithium diisopropylamide (LDA) under the usual conditions[8] was totally ineffective for such selective enolization (entries 3, 4, 13, 20, and 21). Generally, the *E*-selectivity slightly decreased as R_2 became larger (entries 5–12). The size of silyl group as a protective group on the hydroxy ester was known to

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(1) (a) For the ester enolate Claisen rearrangement, showing the reaction was controlled under chelation control of enolate. Panek also applied the kinetic enolate to the reaction with moderate selectivity (4:1): Sparks, M. A.; Panek, J. S. *J. Org. Chem.* **1991**, *56*, 3431. Barrish, J. C.; Lee, H. L.; Baggiolini, E. G.; Uskokvic, M. R. *J. Org. Chem.* **1987**, *52*, 1372. Gould, T. J.; Balestra, M.; Wittmann, M. D.; Gary, J. A.; Rossano, L. T.; Kallmerten, J. *J. Org. Chem.* **1987**, *52*, 3889. Sato, T.; Tsunekawa, H.; Kohama, H.; Fujisawa, T. *Chem. Lett.* **1986**, 1553. Fujisawa, T.; Tajima, K.; Sato, T. *Chem. Lett.* **1984**, 1669. Burke, S. D.; Fobare, W. F.; Pacofsky, G. J. *J. Org. Chem.* **1983**, *48*, 5221. Kallmerten, J.; Gould, T. J. *Tetrahedron Lett.* **1983**, *24*, 5177. (b) For aldol reaction, showing *anti*- and *syn*-products were stereocontrolled by using the proper benzyloxy ester and *tert*-butyldimethylsiloxy ester: Annunziata, R.; Cinquini, M.; Cozzi, F.; Borgia, A. L. *J. Org. Chem.* **1992**, *57*, 6339. Mukaiyama, T.; Shiina, I.; Kobayashi, S. *Chem. Lett.* **1991**, 1901. Mukaiyama, T.; Uchiro, H.; Shiina, I.; Kobayashi, S. *Chem. Lett.* **1990**, 1019. (c) For Michael reaction, showing *syn*-selectivity was obtained using thermodynamic enolate: Kanemasa, S.; Nomura, M.; Wada, E. *Chem. Lett.* **1991**, 1735.

(2) Nakamura, E.; Hashimoto, K.; Kuwajima, I. *Tetrahedron Lett.* **1978**, 2079.

(3) 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 (cold bath temperature). 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 to room temperature. After being stirred 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).

(4) The chemical shift of vinyl proton, C*H*OSi, generally appears at a lower field in (*Z*)-silyl ketene acetal than in the *E*-isomer.

(5) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495.

(6) Ireland, R. E.; Wipf, P.; Armstrong, J. D., III. *J. Org. Chem.* **1991**, *56*, 650.

(7) 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 and subsequently cooled to −78 °C, and HMPA (5 mL) was added dropwise. After 5 min, the solution was cooled to −100 °C (cold bath temperature). 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 TBSCl (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 to room temperature. After being stirred for 1 h, the solution was quenched with a saturated solution of $NaHCO_3$ (50 mL) and cold hexane (150 mL). The organic layer was washed with water (50 mL) three 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).

(8) Method C: Standard procedure by sequential treatment of **1** with LDA (1.1 equiv) at −78 °C in THF and then with TMSCl. Method D: Ireland method by sequential treatment of **1** with LDA in 23% THF–HMPA and then with TBSCl as described in ref 5. Method E: Same as method D except using LDA (2.1 equiv) and TBSCl (2.3 equiv).

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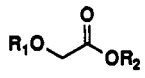
Table I. *E*- and *Z*-Stereoselective Preparation of Silyl Ketene Acetals from Various α-Hydroxy Esters



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

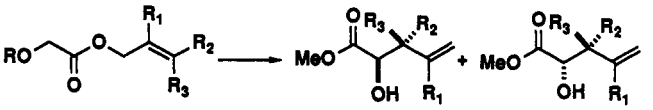
entry	ester[a]	method[b]	yield[c] (%)	*E*:*Z*[d]
1	1	A	82	96:4
2		B	61	1:99
3		C	57	67:33
4		D	55	11:89
5	4	A	81	96:4
6		B	64	2:98
7	5	A	79	95:5
8		B	73	5:95
9	6	A	84	95:5
10		B	68	2:98
11	7	A	76	90:10
12		B	67	<1:99
13	8	E[e]	55	9:91
14	9	A	71	44:56
15		B[f]	69	<1:99
16	10	A	82	88:12
17		B	62	1:99
18	11	A	74	>99:1
19		B	63	3:97
20		C	54	75:25
21		D	56	15:85
22	12	A	96[g]	>99:1
23		B	98[g]	2:98

[a] Structures are shown above. [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] The silyl ketene acetal of 8 under the similar method B was not obtained. [f] THF was used as a solvent, and TMSCl was used to trap enolate. [g] Yield was determined by ^{1}H-NMR of the crude product.

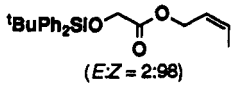
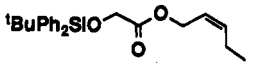
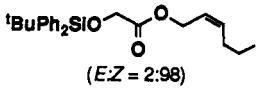
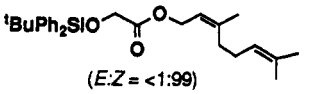
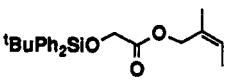
be closely related to the chelation effect.[9] Therefore, sterically demanding silyl groups such as triisopropylsilyl or *tert*-butyldiphenylsilyl inhibited chelation and should have given a high level of (*E*)-silyl ketene acetal. Meanwhile, the selective formation of (*Z*)-silyl ketene acetal proceeded smoothly in all cases studied under method B.

We now demonstrate the effectiveness of this approach in the Ireland ester enolate Claisen rearrangement.[10] Table II summarizes the results obtained for the reaction of (*Z*)-allyl glycolates.[11] When *tert*-butyldiphenylsiloxy esters **13** 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 85–94% yield, after esterification with diazomethane and desilylation with tetrabutylammonium fluoride. GLC and NMR analysis of the products showed the formation of *erythro* isomer **14**.[12] 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 *threo* isomer **15** was produced in 80–87% yield. Thus, the formation of both *E*- and *Z*-enolates was controlled, and the relative stereochemistry

Table II. Diastereoselective Ester Enolate Claisen Rearrangement of Allyl Glycolate



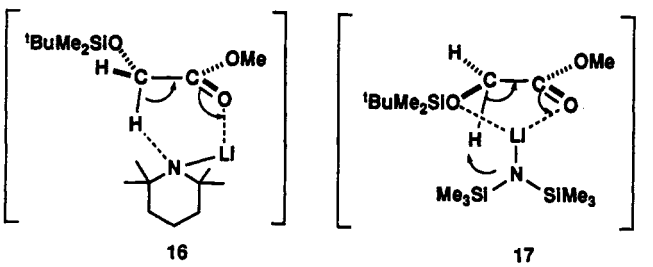
13 14 15

ester 13	method[a]	yield[b] (%)	ratio[c] 14:15
 (*E*:*Z* = 2:98)	A	86	95:5 (97:3)[d]
	B	80	3:97 (1:99)[d]
 (*E*:*Z* = 3:97)	A	85	95:5 (98:2)[d]
	B	80	4:96 (1:99)[d]
 (*E*:*Z* = 2:98)	A	93	96:4 (98:2)[d]
	B	85	3:97 (1:99)[d]
 (*E*:*Z* = <1:99)	A	94	94:6[e]
	B	81	4:96[e]
 (*E*:*Z* = <1:99)	A	86	94:6
	B	80	1:99

[a] See text. [b] Isolated yield of 14 and 15. [c] Determined by ^{1}H-NMR and GLC analyses as described in ref 12. [d] Corrected ratio for starting impurities. [e] The relative configuration of 15 was determined by X-ray structural analysis.

of the Claisen product was consistent with the stereochemistry of the derived enolate.

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 **16** for proton abstraction by LTMP.



16 17

Thus, formation of the enolate anion would presumably require removal of a pseudoaxial hydrogen, and the large repulsion of TMP and ^{t}BuMe$_2$SiO dominant caused this pathway to be favored, which would lead to *E* enolate (*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 would take place to generate the *Z*-enolate selectively (*complexation control*).[13,14]

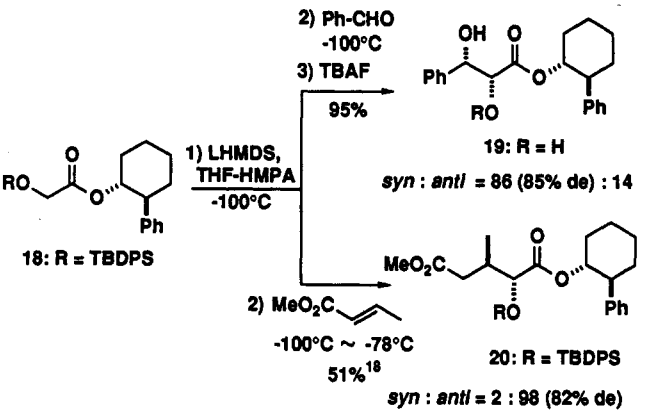
(9) Chen, X.; Hortelano, E. R.; Elier, E. L. *J. Am. Chem. Soc.* **1990**, *112*, 6130.
(10) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. Ireland, R. E.; Wipf, P.; Xiang, J.-N. *J. Org. Chem.* **1991**, *56*, 3572.
(11) (*E*)-Allyl glycolates gave slightly lower selectivity with method A.
(12) Snider, B. B.; van Straten, J. W. *J. Org. Chem.* **1979**, *44*, 3567.
(13) Goodman, J. M.; Paterson, I. *Tetrahedron Lett.* **1992**, *33*, 7223. Reference 6.
(14) To a solution of lithium enolate prepared from LTMP in THF at −100 °C were added HMPA and hexamethyldisilazane before being treated with TBDMSCl, but little change in value of the *E*–*Z* ratio was observed: Treatment of the enolate in THF with TBDMSCl gave the corresponding silyl ketene acetal (*E*:*Z* = 10:1). To the same enolate in THF was added HMPA (25% of THF) and hexamethyldisilazane (1.2 equiv) at −100 °C, and this was then warmed to −78 °C over 30 min. Treatment of the solution with TBDMSCl at −78 °C gave the silyl ketene acetal (*E*:*Z* = 7:1).

The utility of the present system in the asymmetric aldol was also investigated with interesting results: (1*R*,2*S*)-2-phenyl-1-cyclohexyl ester **18** was treated with LHMDS under the *complexation control* condition to generate the *Z*-enolate which was exposed either with benzaldehyde or methyl crotonate to give the corresponding condensation products with useful levels of diastereoselection.[15,16]

In conclusion, the complementary conditions are now available for stereoselective generation of *E*- and *Z*-enolization from α-hydroxy esters. 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 various organic syntheses.[17]

Acknowledgment. Support of this research by the Ministry of Education, Science and Culture of the Japanese Government is greatly appreciated. We thank Mr. A. Sato and Mr. T. Azuma of Fujisawa Pharmaceutical Co. for NOE experiments.

Scheme II



(15) The absolute configuration of **19** was ascertained by converting to the known (2*R*,3*S*)-methyl 2,3-dihydroxy-3-phenylpropionate (Denis, J.-N. *J. Org. Chem.* **1990**, *55*, 1957).

(16) The absolute configuration of **20** was ascertained by converting to the known [4*S*-(1*S*)]-4-(3-hydroxy-1-methylpropyl)-2,2-dimethyl-1,3-dioxolane (Boeckman, R. K., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 5337).

(17) For our previous report for the Lewis acid catalyzed reaction of imine with the silyl ketene acetal prepared from the corresponding ester, see: Hattori, K.; Miyata, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 1151.

(18) 92% yield based on recovered **18**.

Supplementary Material Available: Claisen experimental procedure and characterization data for silyl ketene acetals and aldol products (4 pages). This material is contained in 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.