

## Stereoselective Tandem Aldol-Tishchenko Reaction with Acylsilanes

Mitsunori Honda,\* Ryota Iwamoto, Yoshie Nogami, and Masahito Segi  
 Division of Material Sciences, Graduate School of Natural Science and Technology,  
 Kanazawa University, Kakuma-machi, Kanazawa 920-1192

(Received December 22, 2004; CL-041582)

The treatment of acetyltrimethylsilane with LDA, followed by reaction of the resulting enolate with the excess amount of aldehydes gave the corresponding 1,3-diol derivatives in moderate yields with perfect diastereoselectivity as a single regioisomer via tandem aldol-Tishchenko reaction, whereas the reaction with  $\alpha$ -branched aldehydes under similar conditions gives a mixture of two regioisomers. The reaction using benzyl trimethylsilyl ketone afforded the corresponding 1,3-diol monoesters having three contiguous stereogenic centers with perfect levels of stereochemical control in one-pot.

Acylsilanes have received considerable attention due to their unusual spectroscopic properties, novel chemical reactivity, and their utility as useful synthons in organic synthesis.<sup>1,2</sup> Several procedures using acylsilanes have been developed for the asymmetric synthesis.<sup>2</sup> In late years we were interested in the Lewis acid mediated aldol reaction using silyl enol ethers derived from simple acylsilanes that gave the corresponding acylsilanes having the contiguous stereogenic centers,<sup>3</sup> and then examined nucleophilic addition reaction to the acylsilanes obtained by the above aldol reaction that led to the construction of three contiguous stereogenic centers with high stereoselectivity.<sup>4</sup> In the course of this work we recently found that the lithium enolate of acylsilane reacted with aldehydes to give the 1,3-diol monoester derivatives via tandem aldol-Tishchenko reaction.<sup>5</sup> This reaction affords the corresponding *anti*-diol monoesters with excellent levels of stereochemical control. The resulting 1,3-diol monoesters would be useful synthetic intermediates as valuable building blocks for the construction of polyoxy compounds, since the silyl group in the product would be converted to other substituents.<sup>1a</sup> Although Kuwajima<sup>6</sup> and Schinzer<sup>7</sup> have also reported the reaction using lithium enolate of acylsilanes with aldehydes, the reaction products were  $\gamma$ -hydroxy- $\alpha$ -siloxy ketone via the Brook rearrangement<sup>1a</sup> or  $\beta$ -hydroxyacylsilane as a usual aldol product respectively. On the other hand, Utimoto et al. have reported the formation of the 1,3-diol monoester by the reaction using lithium enolate of acylsilane with benzaldehyde, without a detailed description.<sup>8</sup> Here we wish to report our findings on the tandem aldol-Tishchenko reaction using lithium enolates of acylsilanes with various aldehydes and the details regarding diastereoselectivity of this reaction. Furthermore, the reaction using benzyl trimethylsilyl ketone that affords the corresponding 1,3-diol monoesters having three contiguous stereogenic centers and its stereochemistry are described.

The reaction of lithium enolates of acylsilanes **1** with various aldehydes was examined. The results are summarized in Table 1. The lithium enolates were formed by the treatment of **1** with LDA in THF for 0.5 h at  $-40^\circ\text{C}$ . Benzaldehyde (2.5 equiv.) was added to this solution and stirring was continued for 1 h at  $0^\circ\text{C}$ , which gave rise to the 1,3-*anti*-diol monoester

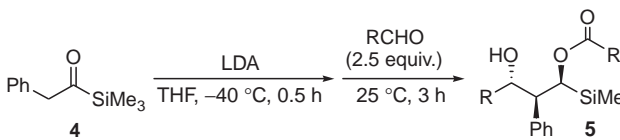
**Table 1.** Reaction of acetyl silane enolates with various aldehydes

Entry	R	Si	Yield <sup>a</sup> /%	2:3 <sup>b</sup>
1	Ph	SiMe <sub>3</sub>	62	>99:1
2 <sup>c</sup>	Ph	SiMe <sub>3</sub>	33	>99:1
3	1-Naphthyl	SiMe <sub>3</sub>	45	>99:1
4	<i>p</i> -NCC <sub>6</sub> H <sub>4</sub>	SiMe <sub>3</sub>	58	>99:1
5	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	SiMe <sub>3</sub>	Complex mixture	
6	C <sub>2</sub> H <sub>5</sub>	SiMe <sub>3</sub>	81	>99:1
7	C <sub>2</sub> H <sub>5</sub>	SiMe <sub>2</sub> Ph	32	>99:1
8	C <sub>2</sub> H <sub>5</sub>	SiMe <sub>2</sub> <sup>t</sup> Bu	Complex mixture	
9	<i>n</i> -C <sub>7</sub> H <sub>15</sub>	SiMe <sub>3</sub>	64	>99:1
10	<i>c</i> -C <sub>6</sub> H <sub>11</sub>	SiMe <sub>3</sub>	48	68:32
11	<i>t</i> -C <sub>4</sub> H <sub>9</sub>	SiMe <sub>3</sub>	34	75:25

<sup>a</sup>Isolated yield. <sup>b</sup>Determined by <sup>1</sup>H NMR analysis (270 MHz). <sup>c</sup>An equimolar amount of benzaldehyde was used.

**2** in 62% yield as a single regio- and diastereoisomer (Entry 1). With an equimolar amount of benzaldehyde, the reaction of **1** resulted in the lower yield for product **2**, and the formation of usual aldol type product was not observed at all (Entry 2). Similarly, the reaction with 1-naphthaldehyde or 4-cyanobenzaldehyde proceeded smoothly to give the corresponding aldol-Tishchenko products in moderate yields with an excellent diastereoselectivity (Entries 3 and 4). On the other hand, the desired product was not obtained in the reaction with *p*-anisaldehyde (Entry 5).

The reaction with various aliphatic aldehydes was carried out under similar conditions as above (Entries 6–11). The reaction with propionaldehyde exhibited high yield rather than that with benzaldehyde (Entry 6). Additionally, in an effort to study the influence of substituents bonded with silicon atom on the reactivity, 1-(dimethylphenylsilyl)ethanone and 1-(*tert*-butyldimethylsilyl)ethanone were prepared as a reactant, and subjected to the enolization followed by the reaction with propionaldehyde (Entries 7 and 8). In these reactions, when the steric bulk adjacent to the carbonyl moiety was increased, the reactivity was decreased. In particular, the desired product was not yielded in the reaction of 1-(*tert*-butyldimethylsilyl)ethanone (Entry 8). With *n*-octanal as a straight-chain aldehyde, the reaction also gave the corresponding 1,3-*anti*-diol monoester **2** in 64% yield with an excellent diastereoselectivity as a single regioisomer (Entry 9). On the other hand, the reaction with  $\alpha$ -branched aldehydes

**Table 2.** Aldol-Tishchenko reaction using benzyl trimethylsilyl ketone **4** with aldehydes<sup>a</sup>


Entry	R	Yield <sup>b</sup> /%	d.e. <sup>c</sup> /%
1	Ph	62	>99
2	1-Naphthyl	24	>99
3	<i>p</i> -NCC <sub>6</sub> H <sub>4</sub>	15	>99
4	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	31	>99
5	3-Furyl	42	>99
6	C <sub>2</sub> H <sub>5</sub>	77	>99
7	<i>n</i> -C <sub>7</sub> H <sub>15</sub>	58	>99
8	<i>i</i> -C <sub>3</sub> H <sub>7</sub>	58	>99
9	<i>c</i> -C <sub>6</sub> H <sub>11</sub>	46	>99
10	<i>t</i> -C <sub>4</sub> H <sub>9</sub>	No reaction	

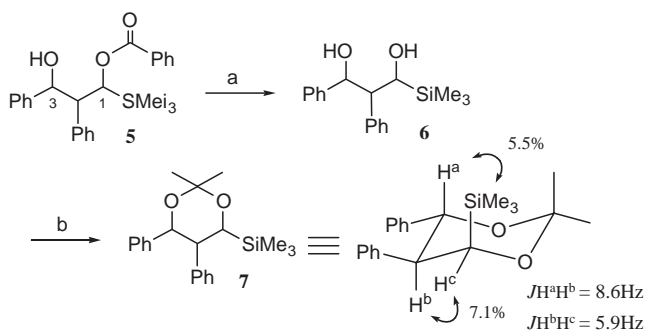
<sup>a</sup>For *E/Z* ratio of enolate of benzyl silyl ketone, see Ref. 9.<sup>b</sup>Isolated yield. <sup>c</sup>Determined by <sup>1</sup>H NMR analysis (270 MHz).

under similar conditions gave a mixture of two regioisomers of 1,3-*anti*-diol monoesters (**2** and **3**) with preference of isomer **2** in moderate yields due to slower rearrangement of ester moieties (Entries 10 and 11).

The reaction using benzyl trimethylsilyl ketone **4** as an acylsilane with various aldehydes was carried out under similar conditions as above. The results are summarized in Table 2.

The reaction with aromatic aldehydes proceeded to give the corresponding aldol-Tishchenko products **5** having three contiguous stereogenic centers in moderate yields with perfect regio- and diastereoselectivity (Entries 1–5). The reaction with various aliphatic aldehydes was also carried out, and the perfect diastereoselectivity was observed as with the reaction with aromatic aldehydes (Entries 6–9). The reaction with propionaldehyde exhibited high yield rather than that with aromatic aldehydes (Entry 6). With *n*-octanal as a straight-chain aldehyde or  $\alpha$ -branched aldehydes, the reaction also gave the corresponding 1,3-diol monoesters **5** in moderate yields (Entries 7–9). However, the desired product was not obtained in the reaction with pivalaldehyde (Entry 10).

Stereochemical assignment of the resulting aldol-Tishchenko adduct **5** was performed by conversion into the corresponding acetone ketal (Scheme 1). The adduct **5** obtained by the reaction

**Scheme 1.** Reagents and conditions: a) LiAlH<sub>4</sub>, ether, rt, 82%; b) (CH<sub>3</sub>)<sub>2</sub>C(OMe)<sub>2</sub>, acetone, cat. PTSA, rt, 94%.

of benzyl trimethylsilyl ketone **4** with benzaldehyde (Table 2, Entry 1) was converted to a single 1,3-diol **6** by the reaction with LAH in ether.<sup>10</sup> Treatment of diol **6** and acetone dimethyl acetal with catalytic amounts of *p*-toluenesulfonic acid gave the corresponding 4-silyl-1,3-dioxane derivative **7**.<sup>11</sup> The vicinal coupling constants observed between the protons on C-1, C-2, and C-3 in the <sup>1</sup>H NMR spectrum and the NOE experiments clearly indicated an axial-equatorial-equatorial arrangement of silyl group and two phenyl groups in the chair conformation of **7**, which is correlated to 1,2-*syn*-2,3-*anti*-configuration in aldol-Tishchenko product **5**. Thus, the stereoconfiguration of other products was predicted by comparing with the chemical shifts and coupling constants.

In summary, aldol-Tishchenko reaction using acylsilanes has been described. The reaction of benzyl trimethylsilyl ketone affords the corresponding 1,3-diol monoesters having three contiguous stereogenic centers with perfect levels of stereochemical control in one-pot. Application of this method to the synthesis of complex products is in progress.

## References and Notes

- For recent reviews on synthesis and reaction of acylsilanes, see: a) M. A. Brook, in "Silicon in Organic, Organometallic, and Polymer Chemistry," John Wiley & Sons, New York (2000). b) B. F. Bonini, M. Comes-Franchini, M. Fochi, G. Mazzanti, and A. Ricci, *J. Organomet. Chem.*, **567**, 181 (1998). c) H. Qi and D. P. Curran, in "Acyl Silicon, Germanium, or Boron Functions. Comprehensive Organic Functional Group Transformations: Synthesis: Carbon with Two Attached Heteroatoms with at Least One Carbon-to-Heteroatom Multiple Link," ed. by A. R. Katritzky, O. Meth-Cohn, C. W. Rees, and C. J. Moody, Pergamon Press, Oxford (1995), Vol. 5, Chap. 5.09, p 409. d) P. F. Cirillo and J. S. Panek, *Org. Prep. Proced. Int.*, **24**, 553 (1992).
- a) P. C. B. Page, S. S. Klair, and S. Rosenthal, *Chem. Soc. Rev.*, **19**, 147 (1990). b) A. Ricci and A. Degl'Innocenti, *Synthesis*, **1989**, 647. c) I. Fleming, A. Barbero, and D. Walter, *Chem. Rev.*, **97**, 2063 (1997). d) C. S. Hau, A. N. Jarvis, and J. B. Sweeney, *Contem. Org. Synth.*, **3**, 65 (1996).
- M. Honda, W. Oguchi, M. Segi, and T. Nakajima, *Tetrahedron*, **58**, 6815 (2002).
- M. Honda, N. Ohkura, S. Saisyo, M. Segi, and T. Nakajima, *Tetrahedron*, **59**, 8203 (2003).
- For recent reports about aldol-Tishchenko reaction: a) C. Schneider and M. Hansch, *Synlett*, **2003**, 837. b) C. Schneider and M. Hansch, *Chem. Commun.*, **2001**, 1218. c) C. M. Mascarenhas, S. P. Miller, P. S. White, and J. P. Morken, *Angew. Chem., Int. Ed.*, **40**, 601 (2001). d) C. Delas and C. Moïse, *Synthesis*, **2000**, 251. e) C. M. Mascarenhas, M. O. Duffey, S.-Y. Liu, and J. P. Morken, *Org. Lett.*, **1**, 1427 (1999).
- I. Kuwajima, K. Matsumoto, and S. Sugahara, *Chem. Lett.*, **1980**, 525.
- D. Schinzer, *Synthesis*, **1989**, 179.
- Y. Horiuchi, M. Taniguchi, K. Oshima, and K. Utimoto, *Tetrahedron Lett.*, **36**, 5353 (1995).
- The treatment of benzyl silyl ketone with LDA at 25 °C gave the corresponding enolate (*E/Z* = 82/18). On the other hand, the same reaction carried out at -78 °C indicated *Z*-selectivity (*E/Z* = 11/89). For the enolation of acylsilanes and trapping of resulting enolates with trimethylsilyl chloride, see Ref. 3.
- J. Kossanyi, B. Furth, and P. Morizur, *Tetrahedron*, **26**, 395 (1970).
- P. Huber, S. Bratovanov, S. Bienz, C. Syldatk, and M. Pietzsch, *Tetrahedron: Asymmetry*, **7**, 69 (1996).