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Addition of TMS-Substituted Oxiranyl Anions to Acylsilanes. A Highly Stereoselective Approach to Tetrasubstituted (*Z*)-β-Hydroxy-α-TMS Silyl Enol Ethers

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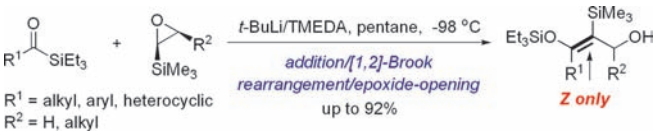
ABSTRACT



A highly stereoselective approach to novel tetrasubstituted (*Z*)-β-hydroxy-α-TMS silyl enol ethers is described. The reaction proceeds via a sequential addition/[1,2]-Brook rearrangement/epoxide-opening process of TMS-substituted oxiranyl anions with acylsilanes.

Silyl enol ethers as important building blocks have shown wide utility in many synthetic transformations.[1] As the configuration of double bonds is crucial for high facial selectivity, preparation of geometrically defined silyl enol ethers has been in long-standing demand in organic synthesis.[2] Although good configurational control has been achieved in the formation of di- and trisubstituted silyl enol ethers, stereoselective accessibility of the *acyclic tetrasubstituted one*, which possesses great potential in the construction of various stereogenic quaternary carbon centers,[3] still remains quite a challenging task.[4]

Silyl-substituted oxiranyl anion **2**, first introduced by Eisch and Galle, has presented good nucleophilicity to various electrophiles.[5] However, to our knowledge, no addition of this species to acylsilanes **1**[6] has been

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(1) For reviews, see: (a) Brownbridge, P. *Synthesis* **1983**, 1. (b) Kuwajima, I.; Nakamura, E. *Acc. Chem. Res.* **1985**, *18*, 181. (c) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063. (d) Kobayashi, S.; Manabe, K.; Ishitani, H.; Matsuo, J.-I. *Sci. Synth.* **2002**, *4*, 317.

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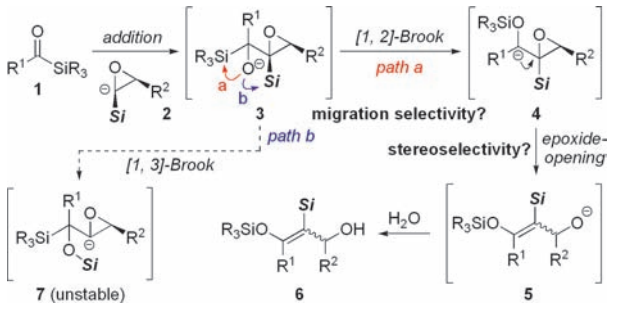
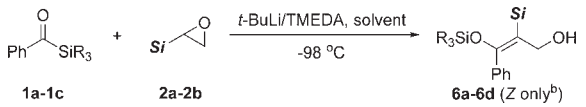
Scheme 1



investigated. Additionally, despite the preparation of silyl enol ethers from acysilanes having been reported,[7] there are only limited examples describing the synthesis of tetrasubstituted one. We envisioned that such an addition might initiate an efficient approach to tetrasubstituted β-hydroxy-α-TMS silyl enol ethers **6** based on the consideration of the following selectivity issues (Scheme 1). First, for the potential two C_{sp^3} to O silyl migration paths of alkoxide intermediate **3**, we presumed that the desired [1,2]-Brook rearrangement[8] (path a) should be energetically more favorable due to the relief of epoxide ring strain.[9] Moreover, despite the fact that the competitive [1,3]-Brook rearrangement has been used in other systems as a dominant direct path to vinylsilane,[10] formation of the unstable oxiranyl anion **7** would render path b rather unfavorable here. On the other hand, for the potential stereoselectivity in [1,2]-Brook path a, we anticipated the sterically hindered $SiMe_3$ group might have some key impacts on the conformation of siloxy carbanion **4**, thus providing reasonable configurational control during formation of the double bond. Herein, we report the realization of this sequential addition/[1,2]-Brook rearrangement/epoxide-opening process.

Table 1. Screening of Reaction Conditions



entry[a]	acylsilane (R_3Si)	epoxide	solvent	product	yield[c]
1	**1a** (Et_3Si)	**2a** (*Si* = Me_3Si)	Et_2O	**6a**	18%
2	**1a** (Et_3Si)	**2a** (*Si* = Me_3Si)	pentane	**6a**	63%
3	**1b** (*t*-$BuMe_2Si$)	**2a** (*Si* = Me_3Si)	pentane	**6b**	42%
4	**1c** ($PhMe_2Si$)	**2a** (*Si* = Me_3Si)	pentane	**6c**	23%
5	**1a** (Et_3Si)	**2b** (*Si* = Ph_3Si)	pentane	**6d**	50%

[a] Reaction conditions: acylsilane **1** (1.0 equiv), epoxide **2** (2.0 equiv), *t*-BuLi (2.0 equiv), TMEDA (2.4 equiv); 0.12 M at −98 °C. [b] The stereoselectivity was determined by ^1H NMR spectroscopy, and the configuration was determined by NOE experiments of **6a**. [c] Isolated yield after purification by silica gel column chromatography.

To establish feasibility, the reaction of acylsilane **1a**[11] with epoxide **2a** was examined initially. Deprotonation of **2a** by *t*-BuLi/TMEDA complex in Et_2O at −98 °C and the following addition to **1a** afforded the desired silyl enol ether **6a**, although in 18% yield, as a single *Z*-diastereomer (Table 1, entry 1). To our delight, using *nonpolar* solvents such as pentane then led to a much higher yield (63%, entry 2). The alkoxide intermediate **5** showed good stability even at room temperature for several hours, and no further 1,3-C_{sp^2} to O silyl migration occurred.[12] The result is consistent with Takeda's observation that such silyl migrations are not active in less polar solvents due to the covalent character of the Li−O bond.[13] Acylsilanes containing the more hindered *t*-$BuMe_2Si$ and $PhMe_2Si$ group proved to

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(7) (a) Reich, H. J.; Rusek, J. J.; Olson, R. E. *J. Am. Chem. Soc.* **1979**, *101*, 2225. (b) Reich, H. J.; Olson, R. E.; Clark, M. C. *J. Am. Chem. Soc.* **1980**, *102*, 1423. (c) Kato, M.; Mori, A.; Oshino, H.; Enda, J.; Kobayashi, K.; Kuwajima, I. *J. Am. Chem. Soc.* **1984**, *106*, 1773. (d) Enda, J.; Kuwajima, I. *J. Am. Chem. Soc.* **1985**, *107*, 5495.

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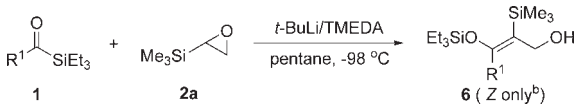
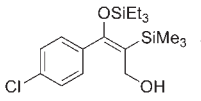
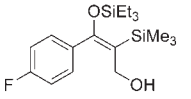
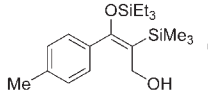
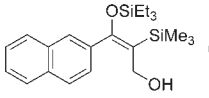
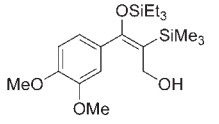
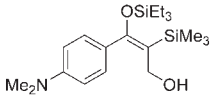
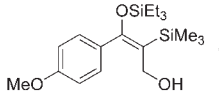
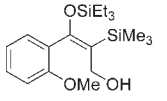
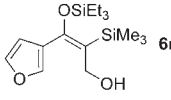
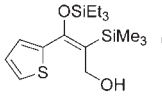
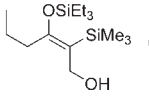
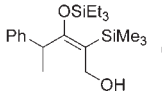
(11) Xin, L. H.; David, A. N.; Johnson, J. S. *Org. Lett.* **2002**, *4*, 2957.

(12) Further 1,3-C_{sp^2} to O silyl migration of **6a** or **6b** and the following alkylation with alkyl halides would potentially generate various tetrasubstituted silyl enol ethers. Investigations on this transformation are still ongoing. For recent studies on C_{sp2} to O silyl migration, see: (a) Moser, W. H.; Endsley, K. E.; Colyer, J. T. *Org. Lett.* **2000**, *2*, 718. (b) Taguchi, H.; Ghoroku, K.; Tadaki, M.; Tsubouchi, A.; Takeda, T. *Org. Lett.* **2001**, *3*, 3811. (c) Moser, W. H.; Zhang, J.; Lecher, C. S.; Frazier, T. L.; Pink, M. *Org. Lett.* **2002**, *4*, 1981. (d) Tsubouchi, A.; Itoh, M.; Onishi, K.; Takeda, T. *Synthesis* **2004**, *9*, 1504. (e) Taguchi, H.; Takami, K.; Tsubouchi, A.; Takeda, T. *Tetrahedron Lett.* **2004**, *45*, 429. (f) Devarie-Baez, N. O.; Shuhler, B. J.; Wang, H.; Xian, M. *Org. Lett.* **2007**, *9*, 4655. (g) Smith, A. B., III; Kim, W. S.; Wuest, W. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 7082. (h) Devarie-Baez, N. O.; Kim, W. S.; Smith, A. B., III; Xian, M. *Org. Lett.* **2009**, *11*, 1861. (i) Smith, A. B., III; Kim, W. S.; Tong, R. B. *Org. Lett.* **2010**, *12*, 588.

(13) Tsubouchi, A.; Kira, T.; Takeda, T. *Synlett* **2006**, 2577.

Table 2. Scope of Acylsilanes



entry[a]	acylsilane (R^1)	product		yield[c]
1	**1d** (*p*-Cl-C_6H_4)		**6e**	63%
2	**1e** (*p*-F-C_6H_4)		**6f**	48%
3	**1f** (*p*-Me-C_6H_4)		**6g**	62%
4	**1g** (2-Np)		**6h**	80%
5	**1h** (*m*, *p*-$(MeO)_2$-C_6H_3)		**6i**	90%
6	**1i** (*p*-Me_2N-C_6H_4)		**6j**	92%
7	**1j** (*p*-MeO-C_6H_4)		**6k**	70%
8	**1k** (*o*-MeO-C_6H_4)		**6l**	55%
9	**1l** (3-Furyl)		**6m**	51%
10	**1m** (2-Thienyl)		**6n**	71%
11	**1n** (n-C_3H_7)		**6o**	—
12	**1o** (PhMeCH)		**6p**	50%

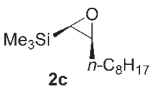
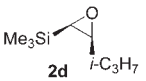
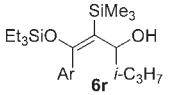
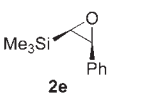
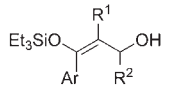
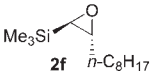
[a] Reaction conditions: acylsilane **1** (1.0 equiv), epoxide **2a** (2.0 equiv), *t*-BuLi (2.0 equiv), TMEDA (2.4 equiv); 0.12 M in pentane at −98 °C. [b] The stereoselectivity was determined by ^{1}H NMR spectroscopy. [c] Isolated yield after purification by silica gel column chromatography.

be poor substrates in giving **6b** and **6c**, respectively, in 42% and 23% yield (entries 3 and 4). Additionally, although the electron-deficient triphenylsilyl group is expected to make the oxiranyl anion of **2b** more stable than that of **2a**, its bulkiness appears to prohibit further addition partially with giving **6d** in the moderate 50% yield.

With the optimal conditions identified, the scope of this approach was examined. As summarized in Table 2, the reaction is suitable for a wide range of aryl acylsilanes (entries 1−8). Compared to the one bearing an electron-deficient phenyl group (entry 1 and 2), electron-rich phenyl acylsilanes appear to undergo the process more efficiently with higher yields (entries 5−7). Probably, the lower stability of siloxy carbanion **4** attached to an electron-rich phenyl group might accelerate the epoxide-opening step and thus make the overall process more facile. The steric effects of an aryl ring also present certain impacts on the efficiency, as reaction of *para*-methoxy phenyl acylsilane **1j** gave a higher yield (70%, entry 7) than that of *ortho*-methoxy-substituted one **1k** (55%, entry 8). The process is tolerant of heterocyclic acysilanes **1l** and **1m** as well (entries 9 and 10). The potential deprotonation of a heterocycle ring by an oxiranyl anion appeared not to interfere with the course. However, reaction of unbranched alkyl acylsilane **1n** suffered a lot from the deprotonation at the α-position of the carbonyl group and led to a very complex mixture (entry 11). A successful example was achieved when **1o** containing a sterically more hindered PhMeCH group was employed (50%, entry 12). This success also implies that relief of epoxide ring strain, to a large extent, drives the [1,2]-Brook rearrangement since the C_{sp^2}-stabilization of a silyloxy carbanion does not exist in this case.[9b]

With acylsilane **1j**, multisubstituted epoxides were further evaluated under the same condition. For *cis*-disubstituted epoxide **2c**[5c] bearing an unbranched chain and **2d**[14] bearing a more bulky isopropyl group, reactions proceeded quite smoothly to give the desired silyl enol ether **6q** and **6r**, respectively, in 92% and 64% yield (Table 3, entries 1 and 2). Poor regioselectivity of deprotonation of

Table 3. Scope of TMS-Substituted Epoxides

entry	epoxide	product[c]	yield[d]
1[a]	 **2c**	 **6q**	92%
2[a]	 **2d**	 **6r**	64%
3[a]	 **2e**	 **6s** (R^1 = $SiMe_3$, R^2 = Ph) **6t** (R^1 = Ph, R^2 = $SiMe_3$)	50% (**6s**:**6t** = 1:1)
4[b]	 **2f**	—	N.R.

[a] Reaction conditions: acylsilane **1j** (1.0 equiv), epoxide **2c**−**2e** (2.0 equiv), *t*-BuLi (2.0 equiv), TMEDA (2.4 equiv); 0.12 M in pentane at −98 °C. [b] Deprotonation was performed at −116 °C for 3.0 h. [c] The stereoselectivity was determined by ^{1}H NMR spectroscopy. Ar = *p*-MeOPh. [d] Isolated yield after purification by silica gel column chromatography.

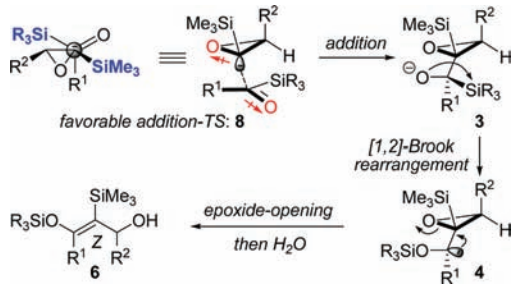


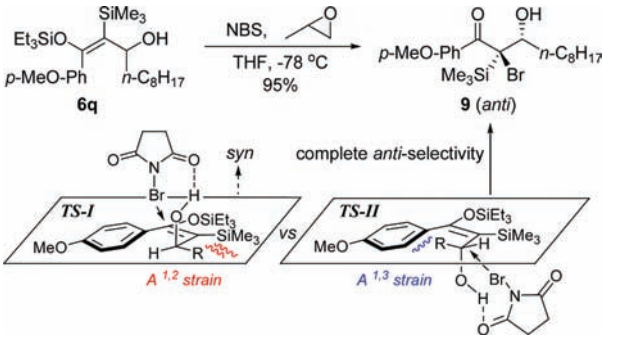
Figure 1. Model analysis for the high *Z*/*E*-stereoselectivity.

epoxide **2e**[14] containing a *cis*-phenyl group was found to give **6s** and **6t** as an inseparable mixture and in 50% yield (entry 3). Additionally, no reaction occurred when *trans*-disubstituted epoxide **2f**[5c] was employed. Imaginably, the formed *trans*-oxiranyl anion increases the difficulty of its approach to bulky acylsilane (entry 4).[15]

Rationalization for the high *Z*/*E* selectivity is proposed as follows. The initial addition is expected to proceed through the favorable transition state **8**, in which the two bulky silyl groups are oriented *anti* to each other to avoid the potential steric interaction, and the two oxygen atoms are also oriented in such a setup to minimize the dipole moment in the nonpolar solvent (Figure 1). Thus, alkoxide **3** would be formed diastereoselectively and further transformed via C to O-silyl migration to siloxy carbanion **4** with retention of the stereochemistry. Due to the fact that the sp^3 hybridized orbital containing a negative charge is aligned antiperiplanar to the cleaved C−O bond, **4** could undergo smooth epoxide opening to provide the observed (*Z*)-silyl enol ether **6** predominantly.[16]

The stereochemical course of the electrophilic addition of silyl enol ether **6q** was further examined with NBS (Scheme 2). Based on the proposed formation of a hydrogen bond between the hydroxyl group and NBS,

Scheme 2



two transition states **TS-I** and **TS-II** involving conflicting $A^{1,2}$ strain (between *n*-C_8H_{17} and $SiMe_3$ groups) and $A^{1,3}$ strain (between *n*-C_8H_{17} and aryl groups) would be expected to give different facial selectivities. In fact, we found that only the *anti*-isomer of *β*-hydroxy ketone **9**[17] containing a quaternary carbon center was formed in 95% yield. This result suggests that $A^{1,2}$ strain in **TS-I** is much stronger than $A^{1,3}$ strain in **TS-II**; thus **TS-II** would be more favorable in leading to the complete *anti*-selectivity.

In conclusion we have described a sequential addition/[1,2]-Brook rearrangement/epoxide-opening process of TMS-substituted oxiranyl anions with acylsilanes. This route provides a direct and stereoselective entry to novel tetrasubsitituted (*Z*)-*β*-hydroxy-α-TMS silyl enol ethers. Further applications of these useful building blocks are ongoing in our group.

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Supporting Information Available. Experimental procedures and spectra data for products. This material is available free of charge via the Internet at http://pubs.acs.org.

(14) (a) Burford, C.; Cooke, F.; Roy, G.; Magnus, P. *Tetrahedron* **1983**, *39*, 867. (b) Burford, C.; Cooke, F.; Ehlinger, E.; Magnus, P. *J. Am. Chem. Soc.* **1977**, *99*, 4536.

(15) Similar sluggish reactivity was also found in the reaction of trisubstituted epoxide $Me_3SiCHOC(CH_2)_5$, in which only the reduced product of acylsilane **1j** was obtained via a proposed successive SET process.

(16) The authors thank referees' helpful suggestions on proposing this mechanism. In addition, despite formation of the corresponding *β*-silyloxy ketone being possible for the *E*-isomer via O to O silyl transfer, no such compounds were observed after isolation.

(17) The stereochemistry of **9** was determined by NOE experiments of α-bromo enone **10**, which was obtained in 79% yield through a Peterson olefination protocol of **9** with NaH in DMF.