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Sakurai Reaction of 3,3-Bis(silyl) Silyl Enol Ethers with Acetals Involving Selective Desilylation of the Geminal Bis(silane). Concise Synthesis of Nematocidal Oxylipid

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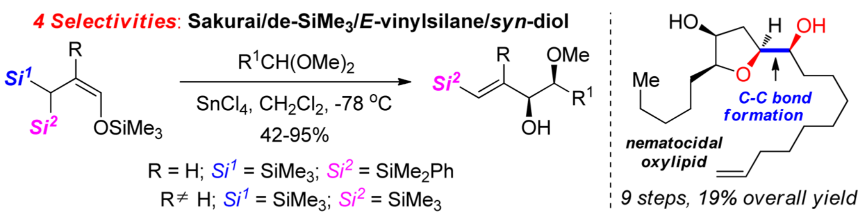
ABSTRACT



3,3-Bis(silyl) silyl enol ethers have been shown to exhibit predominantly Sakurai reactivity, rather than Mukaiyama aldol reactivity, in their Lewis acid promoted reactions with acetals. Starting from a geminal bis(silyl) moiety consisting of two different silyl groups, such as $SiMe_3$ and $SiMe_2Ph$, the $SiMe_3$ is selectively eliminated to give monoprotected *E*- vinylsilyl diols with good to excellent *syn*-diastereoselectivity. This reaction also underpinned a synthesis of the nematocidal oxylipid from *Notheia anomala*, demonstrating the attractive bifunctionality of geminal bis(silanes).

Organosilanes[1] are extremely useful in organic synthesis. Organosilanes with diverse structural features usually possess quite different reactivities, and research into this diverse reactivity has led to many significant achievements in both the areas of synthetic methodology and natural product synthesis. Therefore, the discovery of structurally unique organosilanes could provide important breakthroughs in the development of novel reactions. With this goal in mind, we recently launched a series of studies on geminal bis(silanes) **1**[2,3] that contain two bulky silyl groups attached to a single carbon center (Scheme 1, left).[4] Our recent work, however, has shown that these compounds exhibit unusual behavior that makes them particularly useful as bifunctional synthons,[2] suggesting that they can contribute to a much broader range of reactions than previously thought.

Among the various geminal bis(silanes) that have been described, 3,3-bis(silyl) silyl enol ethers of general structure **2** appear to be particularly interesting (Scheme 1, right).

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(1) For selected reviews on organosilanes, see: (a) Overman, L. E.; Blumenkopf, T. A. *Chem. Rev.* **1986**, *86*, 857. (b) Panek, M.; Masse, C. E. *Chem. Rev.* **1995**, *95*, 1293. (c) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063. (d) Denmark, S. E.; Regens, C. S. *Acc. Chem. Res.* **2008**, *41*, 1486.

(2) (a) Song, Z. L.; Lei, Z.; Gao, L.; Wu, X.; Li, L. J. *Org. Lett.* **2010**, *12*, 5298. (b) Gao, L.; Lin, X. L.; Lei, J.; Song, Z. L.; Lin, Z. *Org. Lett.* **2012**, *14*, 158. (c) Sun, X. W.; Lei, J.; Sun, C. Z.; Song, Z. L.; Yan, L. J. *Org. Lett.* **2012**, *14*, 1094. (d) Gan, Z. B.; Wu, Y.; Gao, L.; Sun, X. W.; Lei, J.; Song, Z. L.; Li, L. J. *Tetrahedron* **2012**, *68*, 6928. (e) Lu, J.; Song, Z. L.; Zhang, Y. B.; Gan, Z. B.; Li, H. Z. *Angew. Chem., Int. Ed.* **2012**, *51*, 5367.

(3) For studies on geminal bis(silanes), see: (a) Fleming, I.; Floyd, C. D. *J. Chem. Soc., Perkin Trans. 1* **1981**, 969. (b) Brook, A. G.; Chrusciel, J. J. *Organometallics* **1984**, *3*, 1317. (c) Klumpp, G. W.; Mierop, A. J. C.; Vrielink, J. J.; Brugman, A.; Schakel, M. *J. Am. Chem. Soc.* **1985**, *107*, 6740. (d) Bellasoued, M.; Majidi, A. *J. Org. Chem.* **1993**, *58*, 2517. (e) Lautens, M.; Delanghe, P. H. M.; Goh, J. B.; Zhang, C. H. *J. Org. Chem.* **1995**, *60*, 4213. (f) Princet, B.; Gariglio, H. G.; Pornet, J. *J. Organomet. Chem.* **2000**, *604*, 186. (g) Hodgson, D. M.; Barker, S. F.; Mace, L. H.; Moran, J. R. *Chem. Commun.* **2001**, 153. (h) Inoue, A.; Kondo, J.; Shinokubo, H.; Oshima, K. *Chem.—Eur. J.* **2002**, *8*, 1370. (i) Williams, D. R.; Morales-Ramos, Á. I.; Williams, C. M. *Org. Lett.* **2006**, *8*, 4393.

(4) (a) Althaus, H.; Breunig, H. J.; Rösler, R.; Lork, E. *Organometallics* **1999**, *18*, 328. (b) Saito, M.; Tokitoh, N.; Okazaki, R. *J. Am. Chem. Soc.* **2004**, *126*, 15572. (c) Agou, T.; Sugiyama, Y.; Sasamori, T.; Sakai, H.; Furukawa, Y.; Takagi, N.; Guo, J. D.; Nagase, S.; Hashizume, D.; Tokitoh, N. *J. Am. Chem. Soc.* **2012**, *134*, 4120.

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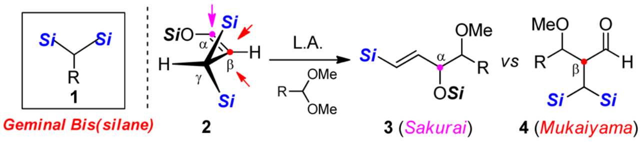
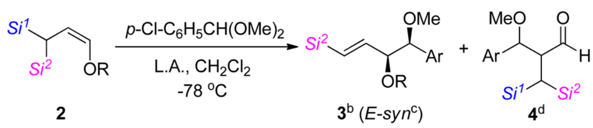
Scheme 1. General Structure of Geminal Bis(silane) (left); Sakurai vs Mukaiyama Adol Reaction of 3,3-Bis(silyl) Silyl Enol Ether with Acetal (right)



In previous work, we proposed the most favorable conformation of 2[2a] is that which minimizes allylic strain and nonbonded interactions, and which also benefits from a double-hyperconjugation effect between the two C–Si bonds and the enol double bond. Since both the silyl enol ether and allyl bis(silane) groups in **2** share the same *Z*-C=C double bond, the compound was expected to participate in two competing pathways in a Lewis acid promoted reaction with an acetal. Such a reaction could either proceed by a Mukaiyama[5] aldol pathway at the *β*-position to give aldehyde **4** or undergo umpolung[6] and proceed by a Sakurai[7] pathway at the α-position to give monoprotected diol **3**. Here we report detailed studies of this reaction and observe that up to four different selectivities can be achieved in a single transformation.

Table 1. Screening of Sakurai Reaction Conditions[a]



entry	2	*Si*[1]	*Si*[2]	R	L.A.	3 (%[e]/*dr*[f])	4 (%[e])
1	**2a**	$SiMe_3$	$SiMe_3$	$SiMe_3$	$TiCl_4$	**3a** (54/≥95:5)	**4a** (21)
2	**2a**	$SiMe_3$	$SiMe_3$	$SiMe_3$	BF_3•OEt_2	**3a** (30/≥95:5)	**4a** (20)
3	**2a**	$SiMe_3$	$SiMe_3$	$SiMe_3$	$SnCl_4$	**3a** (70/≥95:5)	**4a** (23)
4	**2b**	$SiMe_3$	$SiMe_3$	$SiEt_3$	$SnCl_4$	**3a** (40/≥95:5)	**4a** (18)
5	**2c**	$SiMe_3$	$SiMe_3$	Me	$SnCl_4$	**3b** (39/80:20)	**4a** (19)
6	**2d**	$SiMe_3$	$SiMe_3$	COPh	$SnCl_4$	**3c** (41/70:30)	**4a** (0)
7	**2e**	$SiMe_2$*t*-Bu	$SiMe_2$*t*-Bu	$SiMe_3$	$SnCl_4$	**3d** (0)	**4b** (0)
8	**2f**	$SiMe_3$	$SiMe_2Ph$	$SiMe_3$	$SnCl_4$	**3e** (80/≥95:5)	**4c** (10)

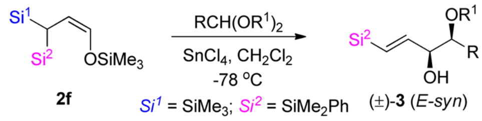
[a] Reaction conditions: 0.15 mmol of **2**, 0.18 mmol of *p*-Cl-PhCH-$(OMe)_2$, and 0.22 mmol of Lewis acid in CH_2Cl_2 (3.0 mL) at −78 °C for 30 min. [b] R = H in **3a** and **3e**. [c] The *E*-configuration was assigned based on J^3_{H-H} vinylic coupling constants ranging from 18 to 20 Hz in **3**. The *syn*-stereochemistry was determined by NOE experiments on the acetonide of desilylated **3a**. [d] Stereochemistry was not determined. [e] Isolated yields after purification by silica gel column chromatography. [f] Ratios were determined by ^1H NMR spectroscopy.

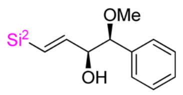
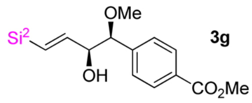
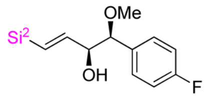
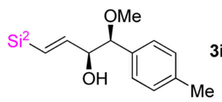
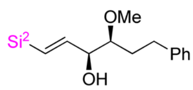
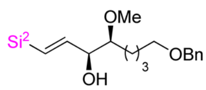
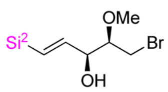
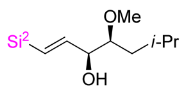
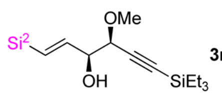
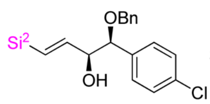
The reaction was initially examined using global $SiMe_3$-substituted **2a** and *p*-Cl-PhCH$(OMe)_2$ in CH_2Cl_2 at −78 °C. $SnCl_4$ appeared to be a better Lewis acid than both $TiCl_4$ and $BF_3\cdot OEt_2$ for leading the reaction predominantly along the Sakurai pathway (Table 1, entries 1–3). With concomitant removal of the $SiMe_3$ group on oxygen, monoprotected *E-syn*-diol **3a** was generated in 70% yield and ≥95:5 *dr*, and Mukaiyama aldol product **4a** was produced in 23% yield. The substrate shows selectivity for Sakurai reactivity probably because the bulky bis(silyl) moiety shields both sides of the *β*-position in **2**, making the competitive Mukaiyama aldol reaction unfavorable. Switching the R group from $SiMe_3$ to the larger $SiEt_3$ or smaller Me group dramatically reduced the yield, and switching to Me also reduced the diastereoselectivity (entries 4 and 5). Switching R to an electron-withdrawing benzoyl group completely suppressed the Mukaiyama aldol pathway, but **3c** formed with only a moderate yield and diastereoselectivity (entry 6). More interesting results were obtained when we examined the effect of geminal bis(silane) on the reaction. When both Si^1 and Si^2 were an $SiMe_2$*t*-Bu group, neither the Sakurai nor Mukaiyama aldol reaction occurred (entry 7). This led us to hypothesize that if the geminal bis(silyl) moiety consisted of a $SiMe_3$ group and a bulkier $SiMe_2$*t*-Bu or $SiMe_2Ph$ group, the more reactive $SiMe_3$ might be selectively eliminated. To the best of our knowledge, few studies have addressed this interesting selectivity issue.[8] As expected, the reaction of **2f** provided **3e** in 80% yield, with only the $SiMe_3$ eliminated (entry 8). Moreover, the ratio of **3** to **4**, in this case, was higher than that in entry 1 due to increased hindrance around the *β*-position in **2f**. Thus, four different selectivities were realized in a single transformation: Sakurai over Mukaiyama aldol reaction, elimination of $SiMe_3$ over $SiMe_2Ph$, *E*- over *Z*-configuration, and *syn*- over *anti*-diastereoselectivity.

The scope of this reaction was then tested using **2f** and various acetals derived from aryl, alkyl, and alkynyl aldehydes. All reactions proceeded predominantly via the Sakurai pathway and gave the monoprotected *E-syn*-diol (±)-**3** in acceptable-to-good yields (Table 2), even though Mukaiyama aldol products were still obtained in some cases in yields around 10%. In all cases, the $SiMe_3$ was reliably eliminated, generating $SiMe_2Ph$-substituted *E*-vinylsilanes selectively. The diastereoselectivity was excellent in most reactions, except for the *dr* of 86:14 for the sterically less

(5) (a) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503. For selected reviews on Mukaiyama aldol and its variants, see: (b) Mukaiyama, T. *Org. React*. **1982**, *28*, 203. (c) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929. (d) Palomo, C.; Oiarbide, M.; Garcia, J. M. *Chem. Soc. Rev.* **2004**, *33*, 65.
(6) For studies on the umpolung of silyl enol ethers, see: (a) Keck, G. E.; Abbott, D. E.; Wiley, M. R. *Tetrahedron Lett.* **1978**, *28*, 139. (b) Marshall, J. A.; Jablonowski, J. A.; Elliott, L. M. *J. Org. Chem.* **1995**, *60*, 2662. (c) Madec, D.; Férézou, J. P. *Tetrahedron Lett.* **1997**, *38*, 6661. (d) Markó, I. E.; Dumeunier, R.; Leclercq, C.; Leroy, B.; Plancher, J. M.; Mekhalfia, A.; Bayston, D. J. *Synthesis* **2002**, *7*, 958. (e) Roush, W. R.; Newcom, J. S. *Org. Lett.* **2002**, *4*, 4739. (f) Greene, M. A.; Prévost, M.; Tolopilo, J.; Woerpel, K. A. *J. Am. Chem. Soc.* **2012**, *134*, 12482. (g) Linclau, B.; Cini, E.; Oakes, C. S.; Josse, S.; Light, M.; Ironmonger, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 1232.
(7) (a) Hosomi, A.; Endo, M.; Sakurai, H. *Chem. Lett.* **1976**, 941. For selected reviews on Sakurai allylation, see: (b) Fleming, I. Allylsilanes, allylstannanes and related systems. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 6, pp 563–593. (c) Fleming, I.; Dunogues, J.; Smithers, R. *Org. React* **1989**, *37*, 57.
(8) (a) Lautens, M.; Ben, R. N.; Delanghe, P. H. M. *Angew. Chem., Int. Ed.* **1994**, *33*, 2448. (b) Lautens, M.; Ben, R. N.; Delanghe, P. H. M. *Tetrahedron* **1996**, *52*, 7221.

Table 2. Scope of Sakurai Reaction of **2f** with Acetals[a]



entry	acetal	product		yield[c]	dr[d]
1[b]	$PhCH(OMe)_2$		**3f**	63%	≥95:5
2[b]	p-CO_2Me-$PhCH(OMe)_2$		**3g**	70%	≥95:5
3[b]	p-F-$PhCH(OMe)_2$		**3h**	58%	≥95:5
4[b]	p-Me-$PhCH(OMe)_2$		**3i**	65%	≥95:5
5[b]	$PhC_2H_4CH(OMe)_2$		**3j**	56%	≥95:5
6[b]	$BnOC_4H_8CH(OMe)_2$		**3k**	70%	≥95:5
7[b]	$BrCH_2CH(OMe)_2$		**3l**	50%	90:10
8	i-$PrCH_2CH(OMe)_2$		**3m**	81%	≥95:5
9	$Et_3SiC{\equiv}CCH(OMe)_2$		**3n**	53%	86:14
10	p-Cl-$PhCH(OBn)_2$		**3o**	64%	≥95:5

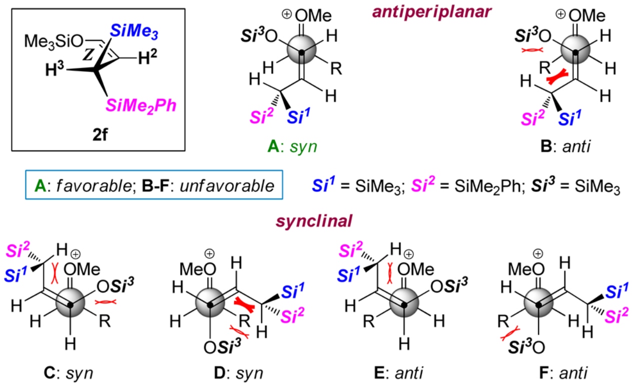
[a] Reaction conditions: 0.15 mmol of **2f**, 0.18 mmol of acetal, and 0.22 mmol of $SnCl_4$ in CH_2Cl_2 (3.0 mL) at −78 °C for 30 min. [b] Mukaiyama aldol products were observed in yields around 10%. [c] Isolated yields after purification by silica gel column chromatography. [d] Ratios were determined by ^{1}H NMR spectroscopy.

demanding diol **3n** (entry 9). This approach is also suitable for acetals derived from benzyl alcohol to provide **3o**, in which the benzyl group would be much easier to remove than the methyl group (entry 10).

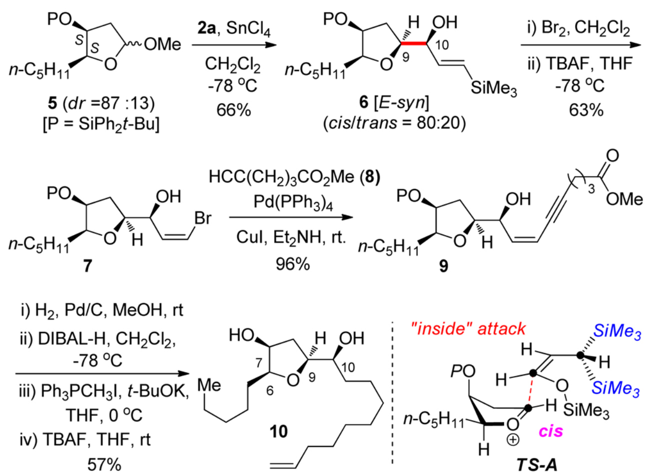
We next examined reactions of various 3,3-bis(trimethylsilyl) silyl enol ethers bearing methyl, phenyl, or allyl substituents at the β-position (Table 3). In all cases, the additional steric hindrance at the β-position completely inhibited the competitive Mukaiyama aldol reaction. Moreover, monoprotected *E-syn*-diol **3** was obtained as the major or only product in all cases, indicating that introduction of a β-substituent had no impact on stereoselectivity. Reaction of **2g** with a cyclic acetal provided an even more attractive result, given the widespread existence of substituted tetrahydropyrans in natural products (entry 3).[9]

The observed *E-syn*-selectivity can be rationalized using non-β-substituted **2f** to simplify the discussion (Scheme 2). The *E*-selectivity can be easily explained as a result of $SiMe_3$ elimination in the most favorable conformation of **2f**. Based on the classical antiperiplanar and synclinal orientations applied to S_E' additions of allylic silanes,[1b,10] the "open" transition states **A**−**F** can be proposed, in which the C−$SiMe_3$ bond to be eliminated is positioned

Scheme 2. Model Analysis to Explain the Observed *E-syn*-Selectivity during Sakurai Reaction of **2f** with Acetal

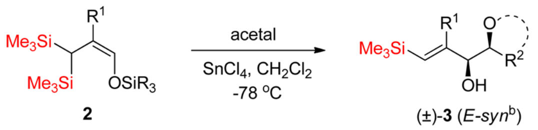


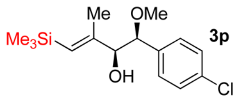
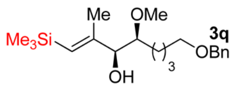
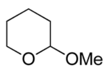
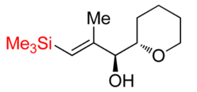
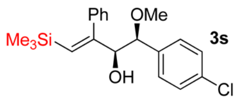
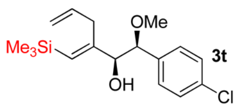
Scheme 3. Synthesis of Nematocidal Oxylipid **10**



(9) For a recent review, see: Fuwa, H. *Heterocycle* **2012**, *85*, 1255.
(10) (a) Yamamoto, Y.; Yatagai, H.; Naruta, Y.; Marutama, K. *J. Am. Chem. Soc.* **1980**, *102*, 7107. (b) Paddon-Row, M. N.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 7162. (c) Denmark, S. E.; Almstead, N. G. *J. Org. Chem.* **1994**, *59*, 5130.

Table 3. Scope of Sakurai Reaction of β-Substituted 3,3-Bis(silyl) Silyl Enol Ethers **2** with Acetals[a]



entry	**2** (R^1,R)	acetal	product		yield[c]	*dr*[d]
1	**2g** (Me,Me)	*p*-Cl-PhCH(OMe)$_2$		**3p**	95%	≥95:5
2	**2g** (Me,Me)	BnOC$_4$H$_8$CH(OMe)$_2$		**3q**	67%	80:20
3	**2g** (Me,Me)			**3r**	80%	90:10
4	**2h** (Ph, Et)	*p*-Cl-PhCH(OMe)$_2$		**3s**	66%	≥95:5
5	**2i**[e] (allyl, Et)	*p*-Cl-PhCH(OMe)$_2$		**3t**	42%	≥95:5

[a] Reaction conditions: 0.17 mmol of **2**, 0.21 mmol of acetal, and 0.26 mmol of $SnCl_4$ in CH_2Cl_2 (3.0 mL) at −78 °C for 30 min. [b] The *E*-configuration was assigned based on NOE experiments on **3p**. The *syn*-stereochemistry was determined by NOE experiments on the acetonide of desilylated **3p**. [c] Isolated yields after purification by silica gel column chromatography. [d] Ratios were determined by ^{1}H NMR spectroscopy. [e] Z/E = 63:37.

anti to the C−C bond to be formed. While the observed stereochemical control may arise from a number of effects, our model assumes that the steric effect predominates. Based on this assumption, transition states **B** and **D** involving severe gauche interaction between bis(silyl) and R groups can be ruled out, as can transition states **C**, **E**, and **F** involving general gauche interactions between bis(silyl) and OMe groups, as well as between $OSiMe_3$ and R groups. The remaining transition state, antiperiplanar **A**, appears to be the most favorable for selective *syn*-addition.

We used this methodology to achieve a concise synthesis of nematocidal oxylipid **10** (Scheme 3), which was isolated from *Notheia anomala* and has shown nematocidal activity comparable to that of commercially available nematocides.[11] The Sakurai reaction of **5**[12] with 2.0 equiv of **2a** proceeded smoothly and gave rise to the desired allylated product **6** in 66% yield, with complete *E*-*syn*-stereochemical control and a *cis*/*trans* ratio of 80:20.[13] Thus, the C9/C10-*syn*-stereochemistry and the entirely *cis*-stereochemistry on the tetrahydrofuran ring was established in a single transformation. The resulting *E*-vinylsilane moiety in **6**, as the second functionality of geminal bis(silane), was then transformed into *Z*-vinyl bromide **7** in 63% yield.[14] Vinyl bromide **7**, in turn, underwent Sonogashira coupling with terminal alkyne **8** to provide **9** in 96% yield. In this way, the long chain was efficiently incorporated on the right side in the target. The final steps of hydrogenation, reduction, Wittig olefination, and deprotection then furnished oxylipid **10** successfully.

To summarize, we have described a Lewis acid promoted reaction of 3,3-bis(silyl) silyl enol ethers with acetals, in which a predominant Sakurai reactivity rather than Mukaiyama aldol reactivity, as well as a selective desilylation of geminal bis(silane), was observed. This reaction also served as a key step in a concise synthesis of nematocidal oxylipid **10** from *Notheia anomala*, demonstrating the attractive bifunctionality of geminal bis(silane). More extensive studies on other applications of this reaction are underway.

(11) Capon, R. J.; Barrow, R. A.; Rochfort, S.; Jobling, M.; Skene, C. *Tetrahedron* **1998**, *54*, 2227. For the latest enantioselective syntheses of **10**, see: Roy, S.; Spilling, C. D. *Org. Lett.* **2012**, *14*, 2230 and references therein.

(12) Acetal **5** was prepared from the known (*S*, *S*)-lactone by two steps and in 85% overall yield. See Supporting Information for details.

(13) The *cis*-facial selectivity on tetrahydrofuran can be explained based on Woerpel's "*inside attack*" model shown as ***TS-A***. For the related references, see: Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Woerpel, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 12208. In addtion, the reaction of **2f** with **5** led to selective elimination of the $SiMe_3$ group to generate the allylated product in 70% yield, with complete *E*-*syn*-selectivity and a *cis*/*trans* ratio of 75:25.

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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) Kobayashi, Y.; Asano, M.; Yoshida, S.; Takeuchi, A. *Org. Lett.* **2005**, *7*, 1533.

The authors declare no competing financial interest.