Exploration of Versatile Geminal Bis(silane) Chemistry

Lu Gao, Yuebao Zhang, Zhenlei Song*

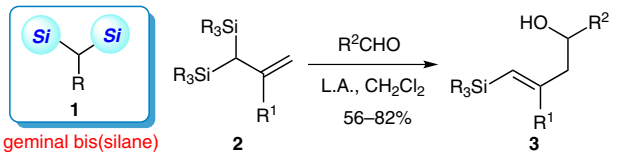
Key Laboratory of Drug-Targeting of Education Ministry and Department of Medicinal Chemistry, West China School of Pharmacy, Sichuan University, Chengdu, 610041, P. R. of China
E-mail: zhenleisong@scu.edu.cn

Received: 03.09.2012; Accepted after revision: 01.11.2012

Abstract: Geminal bis(silyl) compounds, a special type of organosilane, are attractive synthons because of their great potential for bifunctional reactivity. This article outlines our recent efforts to develop a practical method to synthesize geminal bis(silane) compounds and to explore their interesting bifunctionality.

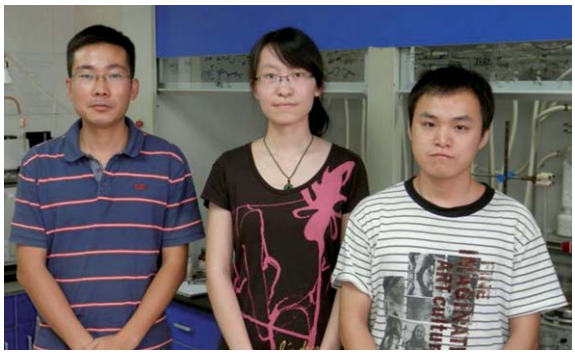
Key words: organosilane, geminal bis(silane), bifunctional reactivity, silyl migration, Prins cyclization

Organosilane chemistry[1] has remained an active and important area of research for organic chemists in recent decades. Studies describing new organosilane species and exploring their unique reactivity and efficient use in natural product synthesis have led to many significant developments in this field. For example, some well-known name reactions such as the Brook rearrangement,[2] Danheiser cyclopentene annulation,[3] Fleming–Tamao oxidation,[4] Hiyama coupling,[5] Peterson olefination,[6] and Sakurai allylation[7] have been widely used in organic synthesis. Geminal bis(silane) compounds **1**,[8] featuring the attachment of two silyl groups to one carbon center, are a special type of organosilane (Scheme 1). Similar to other geminal bimetallic species,[9] which are useful coupling reagents, bis(silyl) compounds also possess great potential because of their bifunctional reactivity. For example, Lautens[10] and Williams[11] reported the Sakurai reaction of allyl bis(silane) **2** with aldehyde to generate homo allylic alcohols **3** (Scheme 1). Elimination of one silyl group left the second group in the form of vinylsilane, which could be used as a functional group for the next transformation.



Scheme 1 General structure of geminal bis(silane) (left) and the Sakurai reaction of allyl bis(silane) with aldehyde (right)

Despite their attractiveness as synthons, studies on geminal bis(silane) have been very limited, presumably as a result of steric considerations. Indeed, the attachment of two large silyl groups to one carbon center is quite challenging in such a sterically bulky system. In this SynPact article, we wish to outline our recent efforts to develop a practical method to synthesize geminal bis(silane) and to explore their interesting bifunctional reactivity.

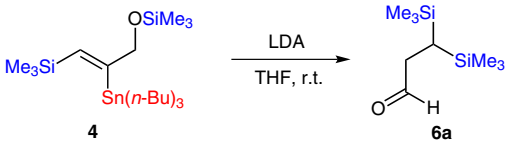


Zhenlei Song (left) was born in Jiangsu Province, China, in 1978. He obtained his PhD in organic chemistry from Lanzhou University with Professor Yongqiang Tu in 2005. From 2005 to 2008, he was a postdoctoral associate in Professor Richard P. Hsung's group at the University of Wisconsin at Madison. Currently he is Associate Professor at West China School of Pharmacy, Sichuan University. His research program focuses on organosilane chemistry, total syntheses of natural products, and medicinal chemistry.
Lu Gao (center) was born in Xinjiang Province, China, in 1987. She attended Sichuan University, where she received her BA in 2009. Currently she is pursuing doctoral studies with Prof. Zhenlei Song at West China School of Pharmacy, Sichuan University. Her research projects focus on silyl migration to form useful organosilane species.
Yuebao Zhang (right) was born in Henan Province, China, in 1988. He received his BA from Henan University in 2011. Currently he is a second-year master's student in Prof. Zhenlei Song's group at West China School of Pharmacy, Sichuan University. His research projects focus on the application of bis(silyl) chemistry in natural product synthesis.

In 1997, Mitchell developed a lithium amide induced retro-[1,4] Brook rearrangement[12] of 2-tributylstannyl-3-silyl allyloxysilane **4** to create 3,3-bis(trimethylsilyl) aldehyde **6a** directly (Scheme 2).[13] Nevertheless, the substrate containing a vinyl (n-Bu)$_3$Sn group, which is required to facilitate the silyl migration, is toxic and difficult to prepare. In addition, the reaction is only feasible when the less bulky trimethylsilyl group is involved, which limits the usefulness of this approach.

Inspired by this work, our group developed an improved method in 2010.[14] Using s-BuLi as base, and HMPA as cosolvent to reduce aggregation of the initially formed allyl anion, a smooth silyl group migration of 3-silyl allyloxysilanes **5** was achieved (Scheme 3). Through base-mediated hydrolysis of lithium enolate, a wide range of 3,3-bis(silyl) aldehydes **6** were formed in good to excel-

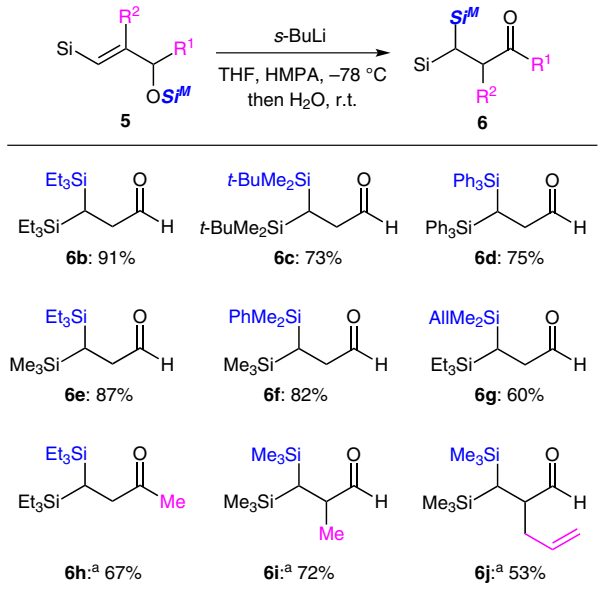
SYNLETT 2013, 24, 0139–0144
Advanced online publication: 28.11.2012
DOI: 10.1055/s-0032-1317706; Art ID: ST-2012-P0739-SP



4 6a

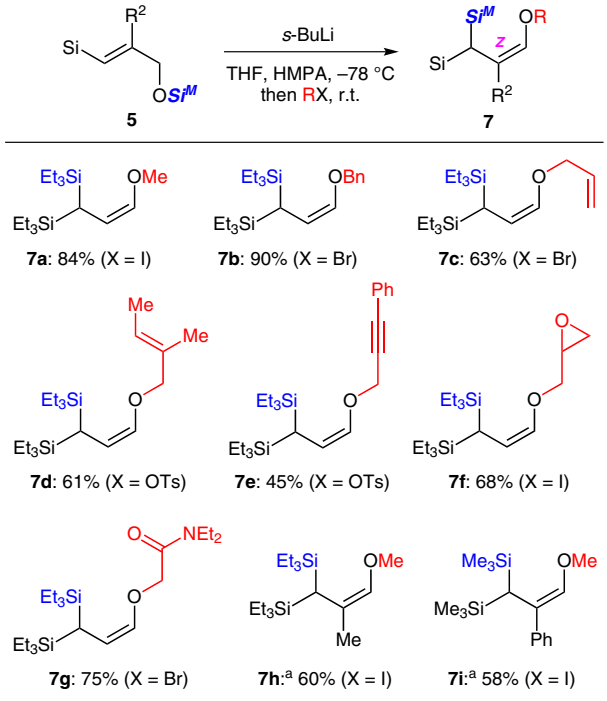
Scheme 2 Mitchell's LDA-induced retro-[1,4] Brook rearrangement of **4** to synthesize 3,3-bis(trimethylsilyl) aldehyde **6a**

lent yield, including products containing the much more sterically bulky geminal bis(silyl) group (**6c** and **6d**) and compounds containing two different silyl groups (**6e**–**g**). The approach was also applicable to substrates with a substituent at the 1- or 2-position, which readily produced the corresponding 3,3-bis(silyl) ketone **6h** and 2-substituted 3,3-bis(silyl) aldehydes **6i** and **6j**.

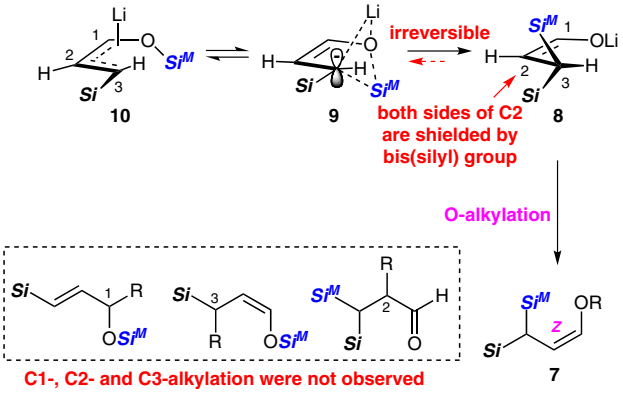


Scheme 3 *s*-BuLi-induced retro-[1,4] Brook rearrangement of 3-silyl allyloxysilanes to synthesize various 3,3-bis(silyl) aldehydes and ketones. *Reagents and conditions*: **5** (0.15 M), *s*-BuLi (1.5 equiv), HMPA (1.2 equiv), THF, –78 °C, then H_2O (10 equiv), warmed to r.t., 3 h. [a] TMEDA (1.5 equiv) was added to facilitate the initial deprotonation step.

We obtained a particularly notable result when trapping 3,3-bis(silyl) enolate **8** with alkyl halides. All reactions proceeded through selective O-alkylation and provided the corresponding *Z*-enol ethers exclusively, with no C-alkylated products detected at all (Scheme 4). This interesting selectivity provided a deeper mechanistic insight, especially into the unique properties of the 3,3-bis(silyl) enolate. We proposed that the enolate adopts the *Z*-configuration and that its most favorable conformation is that shown in **8**, which minimizes allylic strain and nonbonded interactions and which benefits from a double-hyperconjugation effect between the two C–Si bonds and the enol double bond (Scheme 5). This would prevent reverse silyl migration via the pentacoordinated silicate **9** to give allyl anion **10**, as well as further C1- and C3-alkylation of **10**. At the same time, the bulky geminal bis(silyl) moiety shields both sides of the 2-position in **8**, making C2-alkylation more difficult. As a result, halides are forced to react with the oxygen anion, generating exclusively O-alkylated products **7**.



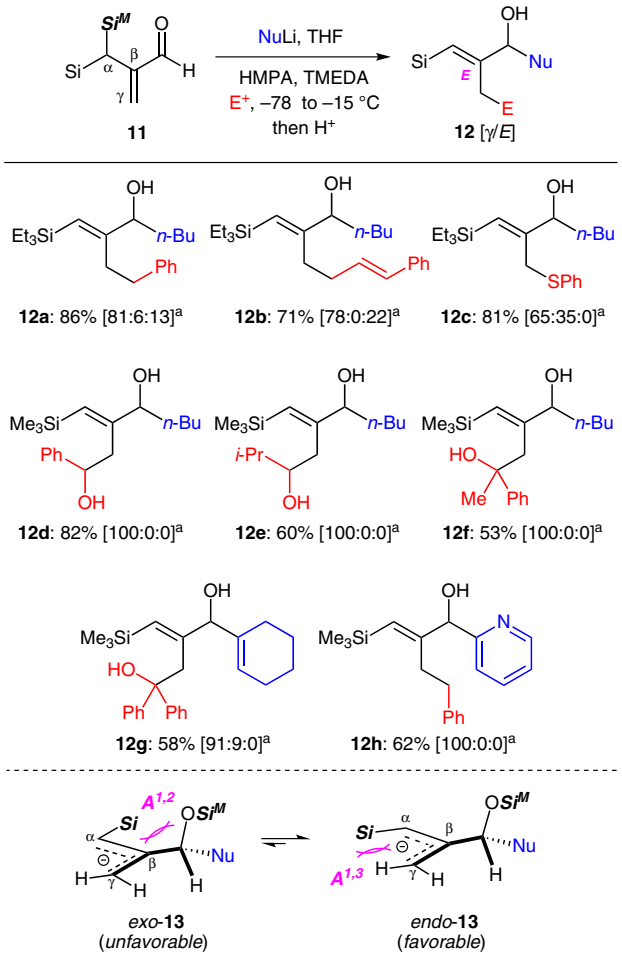
Scheme 4 Selective O-alkylation with alkyl halides to generate 3,3-bis(silyl) enol ethers. *Reagents and conditions*: **5** (0.15 M), *s*-BuLi (1.5 equiv), HMPA (1.2 equiv), THF, –78 °C, then RX (3.0 equiv), warmed to r.t., 4 h. [a] TMEDA (1.5 equiv) was added to facilitate the initial deprotonation step.



Scheme 5 Model to explain the exclusive O-alkylation of 3,3-bis(silyl) enolate with alkyl halides

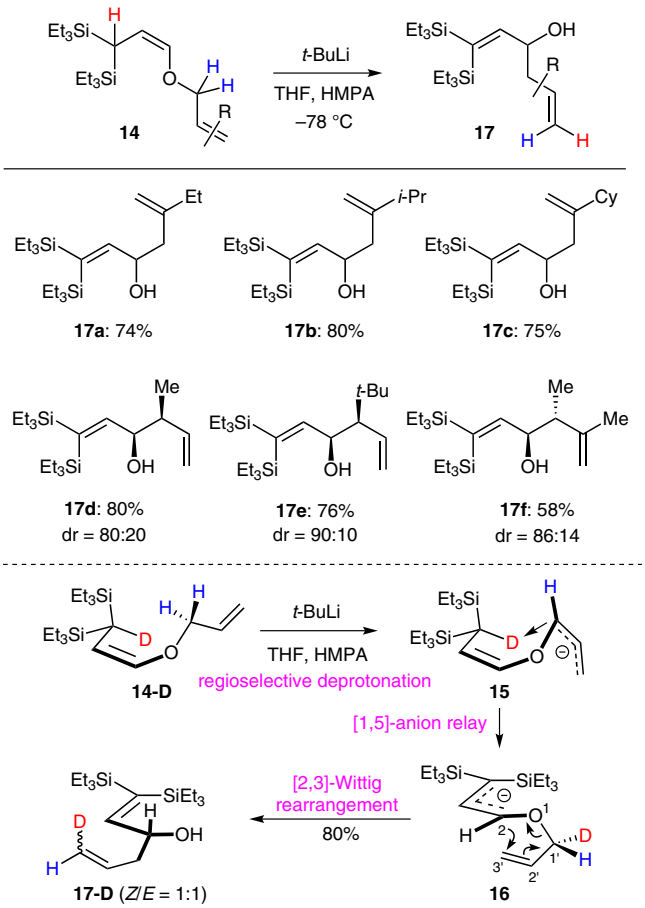
The easy accessibility of 3,3-bis(silyl) aldehyde and enol derivatives allowed us to explore the more diverse reactivity of geminal bis(silanes). We discovered that bis(silyl) enal **11**,[15] prepared by a Mannich reaction of aldehyde **6** with formaldehyde, proved to be a useful linchpin in an efficient three-component coupling process involving anion relay chemistry (Scheme 6).[16] The reaction features a [1,4]-Brook rearrangement, which is triggered by the ad-

dition of organolithium to aldehyde, to generate the silicon-stabilized allyl anion **13**. It is noteworthy that this process provides a new method for forming silyl allyl anions, which is generally accessed by deprotonation of allyl silane. Two transition states seem possible: *endo*-orientated *endo*-**13** features tolerable $A^{1,3}$ strain between the silyl group and γ-H, so it appears to be more favorable than *exo*-**13**, which involves severe $A^{1,2}$ strain between the silyl group and the 2-substituent. Thus, addition of electrophiles to *endo*-**13** at the more accessible γ-position gave various *E*-vinylsilanes **12** both regio- and stereoselectively in good yields.



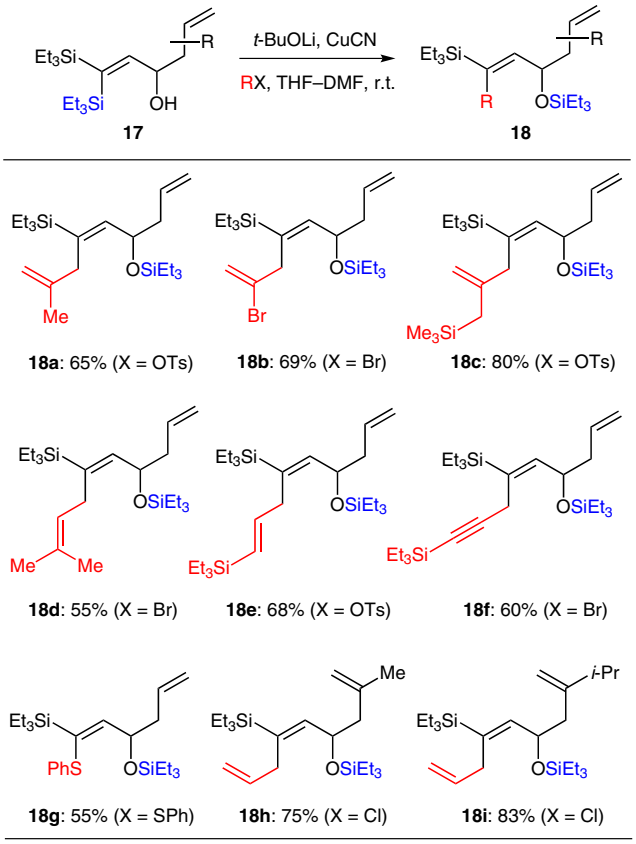
Scheme 6 Geminal bis(silyl) enal as the linchpin in the synthesis of vinylsilane species by anion relay chemistry. *Reagents and conditions*: **11** (1.0 equiv), NuLi (1.1 equiv), THF, –78 °C, then TMEDA (1.1 equiv), warm to –15 °C, then electrophile (3.0 equiv) and HMPA (4.0 equiv); crude products were treated with *p*-TsOH (0.2 equiv) in MeOH. [a] The ratio γ/*E*:γ/Z:α.

As part of our studies on the reactivity of 3,3-bis(silyl) enol ethers, we focused on the deprotonation of the extremely bulky bis(silyl) group. Because initial attempts based on either intermolecular deprotonation or directed metalation proved unsuccessful, a conceptually new strategy was designed and verified using deuterium-labeling experiments (Scheme 7).[17] The entire process is initiated by regioselective deprotonation of enol allyl ether **14-D** to form allyl anion **15**, which quickly undergoes a [1,5]-anion relay via a boat-shaped transition state with a six-membered ring to generate the thermodynamically more stable geminal bis(silyl) allyl anion **16**. Next, [2,3]-Wittig rearrangement of **16** occurs to continuously drive the reaction to give bis(silyl) allylic alcohol **17-D**. The reaction is generally suitable for enol allyl ethers with a substituted allyl chain, and it delivers the products in good yields. When a substrate with one substitution at the 3-position was used, the *syn*-isomer was obtained as a major product (**17d** and **17e**). When enol allyl ether substituted at both the 2- and 3-positions was used, the *anti*-isomer formed predominantly (**17f**).



Scheme 7 Regioselective deprotonation/[1,5]-anion relay/[2,3]-Wittig rearrangement of 3,3-bis(silyl) allyl enol ethers. *Reagents and conditions*: **14** (1.0 equiv), *t*-BuLi (3.0 equiv) and HMPA (3.0 equiv), THF, –78 °C.

Geminal bis(silyl) allylic alcohols **17** can be further transformed into the more functionalized trisubstituted vinylsilanes **18** (Scheme 8). The process features a sequential [1,4]-Brook rearrangement/alkylation reaction promoted by *t*-BuOLi/CuCN in THF and DMF as co-solvents.[18] The reaction is suitable for a wide range of allylic and propargyl electrophiles, and the leaving group can be one of several species, such as halides and tosylate.

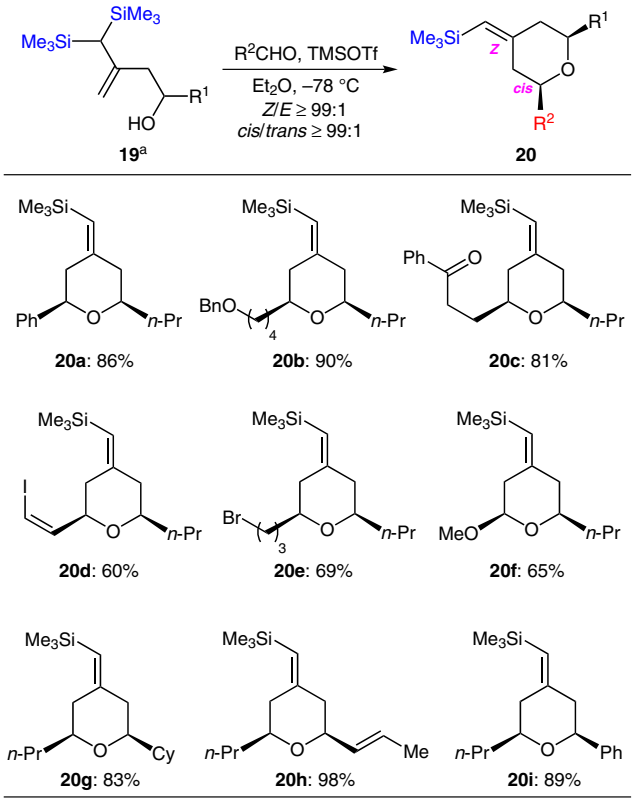


Scheme 8 Application of the [1,4]-Brook rearrangement/alkylation protocol with geminal bis(silyl) allylic alcohols to synthesize trisubstituted vinylsilanes. *Reagents and conditions*: **17** (1.0 equiv), RX (2.0 equiv), *t*-BuOLi (3.0 equiv), CuCN (3.0 equiv), DMF–THF (5:3) as cosolvent at 25 °C.

Our latest investigations have shown that bis(silyl) chemistry may also play a key role in the synthesis of complex natural products such as bryostatins.[19] This family of molecules has shown remarkable biological activity against a range of cancers, and has been used extensively in clinical trials against these diseases. The main challenge presented by the bryostatins is the construction of *cis*-tetrahydropyran rings B and C containing geometrically defined exocyclic methyl enoates. Inspired by the bifunctionality of geminal bis(silyl) compounds, we developed a new strategy to form ring B of bryostatins.[20]

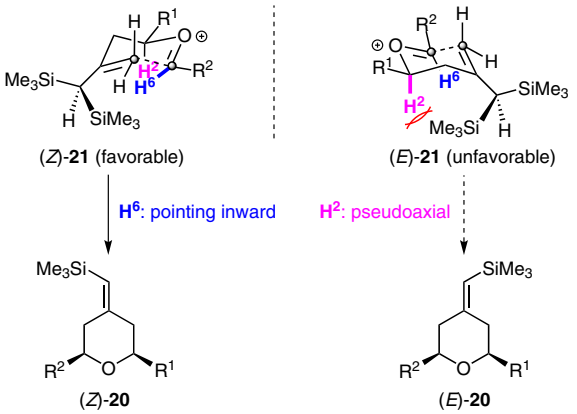
The key reaction lies in a TMSOTf-promoted Prins cyclization[21] of geminal bis(silyl) homoallylic alcohols **19**[22] with aldehydes to generate 2,6-*cis*-tetrahydropyrans **20** containing an exocyclic *Z*-vinylsilane (Scheme 9). This approach is not only widely applicable to a variety of aldehydes and homo allylic alcohols, but is also remarkable in that configurational control of the exocyclic vinylsilane is independent of both the R^1 and R^2 groups. Thus, reliable *Z*-selectivity can be achieved when the silyl group falls on the same side as the incorporated aldehyde.

A rationalization of this interesting stereoselectivity is tentatively proposed in Scheme 10. Two chair-like transition states (*Z*)-**21**- and (*E*)-**21**, in which both R^1 and R^2

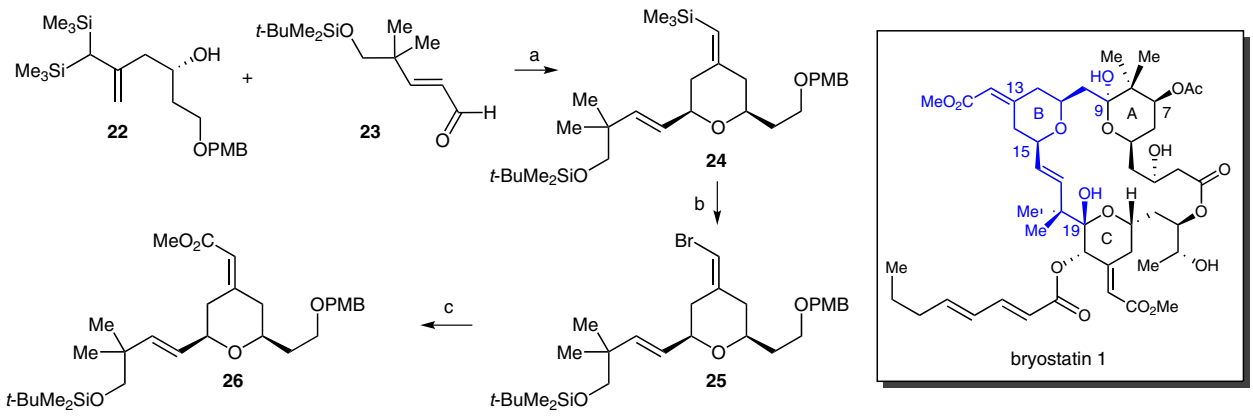


Scheme 9 The Prins cyclization of geminal bis(silyl) homoallylic alcohols with aldehydes to generate 2,6-*cis*-tetrahydropyrans containing an exocyclic *Z*-vinylsilane. *Reagents and conditions*: **19** (0.1 M), R^2CHO (2.0 equiv), TMSOTf (1.5 equiv), Et_2O, –78 °C, 20 min.

groups lie in the pseudoequatorial position, could be expected to give (*Z*)-**20** and (*E*)-**20**, respectively. Although both feature antiperiplanar arrangements, the second silyl group adopts a different orientation. Whereas transition state (*E*)-**21** suffers from a steric interaction between the silyl group and H-2 in the pseudoaxial position, a similar interaction between the silyl group and H-6 in transition state (*Z*)-**21** appears to be tolerated because H-6 points inward. Thus, transition state (*Z*)-**21** should be energetically more favorable and should lead to the observed exclusive *Z*-selectivity.



Scheme 10 A model to explain the exclusive *Z*-selectivity observed during formation of exocyclic vinylsilane



Scheme 11 Synthesis of the ring B of bryostatins. *Reagents and conditions*: (a) **23** (2.0 equiv), TMSOTf (1.5 equiv), Et_2O, –78 °C, 92%; (b) NBS (5.0 equiv), DMF, 0 °C, 88%; (c) $[PdCl_2(MeCN)_2]$ (10 mol%), dppf (30 mol%), CO, MeOH, Et_3N, DMF, 80 °C, 73%.

This methodology was then applied to the synthesis of ring B of bryostatins to show the bifunctional role of the bis(silyl) group (Scheme 11). Prins cyclization of bis(silyl) homoallylic alcohol **22** with aldehyde **23** under standard conditions generated the desired *cis*-tetrahydropyran **24** in 92% yield with exclusive *Z*-selectivity. Bromination of the exocyclic vinylsilane in **24** with *N*-bromosuccinimide (NBS) gave **25** in 88% yield and with retention of the *Z*-configuration. A final carbonylation step led to formation of methyl enoate and generated **26** as the C9–C19 fragment of bryostatins in 73% yield.

In summary, we have described our recent progress in studies of geminal bis(silane) chemistry. Our research has involved developing practical methods to synthesize functionalized geminal bis(silanes), discovering new reactions involving these compounds, and applying them to natural product synthesis. This interesting chemistry shows the attractive versatility of geminal bis(silyl) species, especially their bifunctional reactivity in several transformations. We are optimistic that research in this field will grow and some breakthroughs can be expected. For example, enantioselective silyl migration to generate chiral 3,3-bis(silyl) aldehydes containing two different silyl groups would be an extremely useful advance. These compounds should be useful in all kinds of asymmetric transformations involving selective desilylation. In addition, the steric bulk of the bis(silyl) group may be a unique way to achieve regio- and stereoselectivity under challenging circumstances. Encouraged by the construction of ring B of bryostatins, we expect that geminal bis(silane) chemistry will, as additional reactivities are discovered, play further key roles and find more efficient applications in natural product synthesis.

Acknowledgment

We thank the National Natural Science Foundation of China (21172150, 21021001), the National Basic Research Program of China (973 Program, 2010CB833200), and Sichuan University (Distinguished Young Scientist Program, 2011SCU04A18; 985 project – Science and Technology Innovation Platform for Novel Drug Development) for financial support.

References and Notes

(1) For selective 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) Langkopf, E.; Schinzer, D. *Chem. Rev.* **1995**, *95*, 1375. (d) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063.

(2) For reviews on the Brook rearrangement, see: (a) Brook, A. G. *Acc. Chem. Res.* **1974**, *7*, 77. (b) Moser, W. H. *Tetrahedron* **2001**, *57*, 2065.

(3) (a) Danheiser, R. L.; Carini, D. J.; Basak, A. *J. Am. Chem. Soc.* **1981**, *103*, 1604. (b) Danheiser, R. L.; Kwasigroch, C. A.; Tsai, Y. M. *J. Am. Chem. Soc.* **1985**, *107*, 7233. (c) Danheiser, R. L.; Fink, D. M.; Tsai, Y. M. *Org. Synth.* **1988**, *66*, 8. (d) Danheiser, R. L.; Stoner, E. J.; Koyama, H.; Yamashita, D. S.; Klade, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 4407. (e) Danheiser, R. L.; Dixon, B. R.; Gleason, R. W. *J. Org. Chem.* **1992**, *57*, 6094.

(4) (a) Tamao, K.; Akita, M.; Kumada, M. *J. Organomet. Chem.* **1983**, *254*, 13. (b) Fleming, I.; Henning, R.; Plaut, H. *J. Chem. Soc., Chem. Commun.* **1984**, 29. (c) For the latest review on Fleming–Tamao oxidation, see: Jones, G. R.; Landais, Y. *Tetrahedron* **1996**, *52*, 7599.

(5) (a) Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 918. (b) For the latest review on Hiyama coupling, see: Denmark, S.; Regens, C. S. *Acc. Chem. Res.* **2008**, *41*, 1486.

(6) (a) Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780. (b) For the latest review on Peterson olefination, see: van Staden, L. F.; Gravestock, D.; Ager, D. J. *Chem. Soc. Rev.* **2002**, *31*, 195.

(7) (a) Hosomi, A.; Endo, M.; Sakurai, H. *Chem. Lett.* **1976**, 941. For reviews on Sakurai allylation, see: (b) Fleming, I. *Allylsilanes, Allylstannanes and Related Systems*, In *Comp. Org. Synth.*; Vol. 6; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, **1991**, 563–593. (c) Schinzer, D. *Synthesis* **1988**, 263. (d) Fleming, I.; Dunogues, J.; Smithers, R. *Org. React.* **1989**, *37*, 57.

(8) For studies on geminal bis(silyl) species, see: (a) Fleming, I.; Floyd, C. D. *J. Chem. Soc., Perkin Trans. 1* **1981**, 969. (b) Ahlbrecht, H.; Farnung, W.; Simon, H. *Chem. Ber.* **1984**, *117*, 2622. (c) Brook, A. G.; Chrusciel, J. J. *Organometallics* **1984**, *3*, 1317. (d) Klumpp, G. W.; Mierop, A. J. C.; Vrielink, J. J.; Brugman, A.; Schakel, M. *J. Am. Chem. Soc.* **1985**, *107*, 6740. (e) Lautens, M.; Delanghe, P. H. M.; Goh, J. B.; Zhang, C. H. *J. Org. Chem.* **1995**, *60*, 4213. (f) Lautens, M.; Ben, R. N.; Delanghe, P. H. M. *Tetrahedron* **1996**, *52*, 7221. (g) Princet, B.; Anselme, G.; Pornet, J. *Synth. Commun.* **1999**, *29*, 3326. (h) Princet, B.; Gariglio, H. G.; Pornet, J. *J. Organomet. Chem.* **2000**, *604*, 186.

(i) Hodgson, D. M.; Barker, S. F.; Mace, L. H.; Moran, J. R. *Chem. Commun.* **2001**, 153. (j) Onyeozili, E. N.; Maleczka, R. E. *Tetrahedron Lett.* **2006**, *47*, 6565.

(9) For reviews on geminal bimetallic species, see: (a) Marek, I.; Normant, J. F. *Chem. Rev.* **1996**, *96*, 3241. (b) Marshall, J. A. *Chem. Rev.* **1996**, *96*, 31. (c) Marek, I. *Chem. Rev.* **2000**, *100*, 2887.

(10) Lautens, M.; Ben, R. N.; Delanghe, P. H. M. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2448.

(11) Williams, D. R.; Morales-Ramos, Á. I.; Williams, C. M. *Org. Lett.* **2006**, *8*, 4393.

(12) For recent studies on the retro-[1,4] Brook rearrangement, see: (a) Simpkins, S. M. E.; Kariuki, B. M.; Arico, C. S.; Cox, L. R. *Org. Lett.* **2003**, *5*, 3971. (b) Nahm, M. R.; Xin, L. H.; Potnick, J. R.; Yates, C. M.; White, P. S.; Johnson, J. S. *Angew. Chem. Int. Ed.* **2005**, *44*, 2377. (c) Yamago, S.; Fujita, K.; Miyoshi, M.; Kotani, M.; Yoshida, J. *Org. Lett.* **2005**, *7*, 909. (d) Mori, H.; Matsuo, T.; Yoshioka, Y.; Katsumura, S. *J. Org. Chem.* **2006**, *71*, 9004. (e) Mori, Y.; Futamura, Y.; Horisaki, K. *Angew. Chem. Int. Ed.* **2008**, *47*, 1091.

(13) (a) Mitchell, T. N.; Schütze, M.; Giebelmann, F. *Synlett* **1997**, 187. (b) Mitchell, T. N.; Schütze, M. *Tetrahedron* **1999**, *55*, 1285.

(14) Song, Z. L.; Lei, Z.; Gao, L.; Wu, X.; Li, L. J. *Org. Lett.* **2010**, *12*, 5298.

(15) Gao, L.; Lin, X. L.; Lei, J.; Song, Z. L.; Lin, Z. *Org. Lett.* **2012**, *14*, 158.

(16) For reviews on anion relay chemistry (ARC), see: (a) Smith, A. B. III.; Adams, C. M. *Acc. Chem. Res.* **2004**, *37*, 365. (b) Smith, A. B. III.; Wuest, W. M. *Chem. Commun.* **2008**, 5883. For the latest advances, see: (c) Smith, A. B. III.; Kim, W. S. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 6787. (d) Smith, A. B. III.; Tong, R. B.; Kim, W. S.; Maio, W. A. *Angew. Chem. Int. Ed.* **2011**, *50*, 8904. (e) Smith, A. B. III.; Han, H.; Kim, W. S. *Org. Lett.* **2011**, *13*, 3328. (f) Smith, A. B. III.; Hoye, A. T.; Martinez-Solorio, D.; Kim, W.-S.; Tong, R. B. *J. Am. Chem. Soc.* **2012**, *134*, 4533.

(17) Sun, X. W.; Lei, J.; Sun, C. Z.; Song, Z. L.; Yan, L. J. *Org. Lett.* **2012**, *14*, 1094.

(18) (a) Taguchi, H.; Ghoroku, K.; Tadaki, M.; Tsubouchi, A.; Takeda, T. *Org. Lett.* **2001**, *3*, 3811. (b) Smith, A. B. III.; Kim, W. S.; Tong, R. B. *Org. Lett.* **2010**, *12*, 588.

(19) For reviews on the bryostatins, see: (a) Hale, K. J.; Hummersone, M. G.; Manaviazar, S.; Frigerio, M. *Nat. Prod. Rep.* **2002**, *19*, 413. (b) Kortmansky, J.; Schwartz, G. K. *Cancer Invest.* **2003**, *21*, 924. (c) Wender, P. A.; Baryza, J. L.; Hilinski, M. K.; Horan, J. C.; Kan, C.; Verma, V. A. *Beyond Natural Products: Synthetic Analogues of Bryostatin 1*, In *Drug Discovery Research: New Frontiers in the Post-Genomic Era*; Huang, Z., Ed.; Wiley-VCH: Weinheim, **2007**, 127–162. (d) Hale, K. J.; Manaviazar, S. *Chem.–Asian J.* **2010**, *5*, 704.

(20) Lu, J.; Song, Z. L.; Zhang, Y. B.; Gan, Z. B.; Li, H. Z. *Angew. Chem. Int. Ed.* **2012**, *51*, 5367.

(21) For the latest review on Prins cyclization, see: Crane, E. A.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2010**, *49*, 8316.

(22) The geminal bis(silyl) homoallylic alcohols **19** were synthesized in 55–60% yield by a zinc-promoted Barbier reaction of aldehyde with bis(silyl) allyl bromide, which was prepared from bis(silyl) enal **11** in three steps. See the Supporting Information of ref. 15 for details.

