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Enantio- and Diastereoselective Synthesis of Cyclic β-Hydroxy Allylsilanes via Sequential Aldehyde γ-Silylallylboration and Ring-Closing Metathesis Reactions

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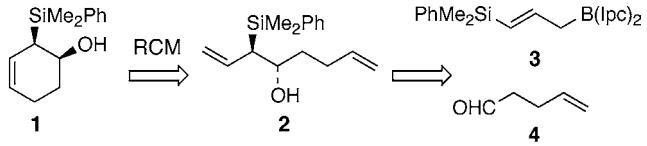
ABSTRACT



Highly enantioenriched cyclic allylsilanes are prepared via stereoselective γ-silylallylboration reactions of β- or γ-unsaturated aldehydes followed by ring-closing metathesis.

Allylsilanes are important intermediates in organic synthesis.[1] Allylsilanes react with a variety of electrophiles, including carbonyl compounds, enones, and imines, to give products with new C−C bonds with high levels of stereoselectivity. The [3 + 2]-annulation reaction[2−5] of allylsilanes with aldehydes is of particular interest in our laboratory,[6] as this process provides facile and highly stereocontrolled access to substituted tetrahydrofurans, which are the key structural elements in a wide range of biologically active natural products.[7] While a number of strategies for synthesis of chiral acyclic allylsilanes have been reported,[1,2,8] relatively few general methods for the synthesis of cyclic, nonracemic allylsilanes are available.[9] Accordingly, we have developed and report herein a flexible strategy for synthesis of highly enantiomerically enriched cyclic allylsilanes.

Previous reports from our laboratory have focused on the asymmetric γ-silylallylboration reactions of aldehydes and the tartrate ester-modified (*E*)-γ-silylallylboronates[10] or the more enantioselective B-diisopinocamphenyl-derived (*E*)-γ-silylallylborane **3**.[8] It was readily apparent that the *anti*-β-hydroxyallylsilane **2** could serve as a substrate for a ring-closing metathesis (RCM) reaction,[11] thereby providing access to the *syn*-β-hydroxycyclohexenylsilane **1** (see Figure 1).[12]

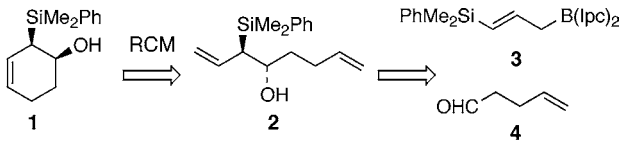


Figure 1. Strategy for Synthesis of Cyclic Allylsilane **1**.

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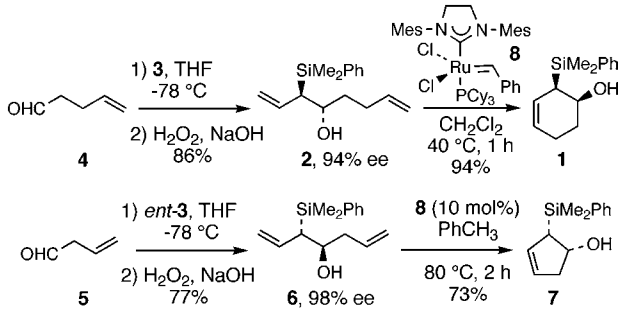
In the event, silylallylboration of 4-penten-1-al (**4**) using γ-silylallylborane **3**, prepared from (+)-Ipc$_2$BOMe, at −78 °C gave *anti*-β-hydroxyallylsilane **2** with good enantioselectivity (94% ee)[13] in 86% yield (Scheme 1). RCM of

Scheme 1. Synthesis of Cyclic Allylsilanes **1** and **7**

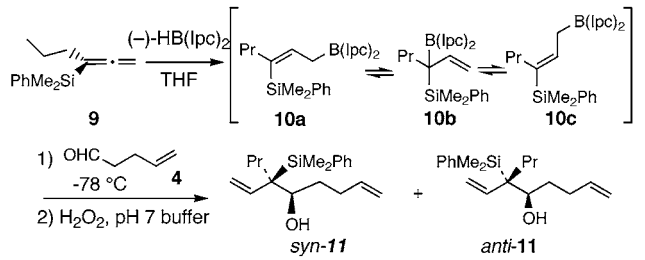


diene **2** using Grubbs' second-generation catalyst **8**[14] (5 mol %) afforded cyclohexenylsilane **1** in excellent yield (94%). This synthetic sequence was also applied to the synthesis of five-membered cyclic allylsilane **7**. In this case, silylallylboration of 3-buten-1-al (**5**)[15] with *ent*-**3** provided *anti*-β-hydroxyallylsilane **6** with 98% enantioselectivity.[13] The RCM cyclization of **6** using 10 mol % **8** at 80 °C then provided **7** in 73% yield.

This two-step allylboration−ring closing metathesis sequence constitutes a highly efficient strategy for the synthesis of cyclic *cis*-β-hydroxyallylsilanes. Previously, such intermediates have been prepared by hydride reduction of 2-silyl-substituted cyclohex-3-enones,[5a] which are prepared by oxidation of *trans*-β-hydroxyallylsilanes deriving from the reactions of cyclohexandienyl epoxides with an appropriate silyllithium nucleophile.[5a,16]

Having successfully demonstrated the synthesis of cyclic *cis*-β-hydroxyallylsilanes **1** and **7**, we turned our attention toward the synthesis of an even more challenging group of cyclic allylsilanes, specifically allylsilanes such as **12** in which the silicon substituent resides at a quaternary center. On the basis of reports by Wang and co-workers,[17] who demonstrated that α-substituted *syn*-β-hydroxyallylsilanes (cf. **11**) could be synthesized selectively via hydroboration of allenylsilanes with 9-BBN−H or HB(Chx)$_2$ followed by addition of the resulting γ-substituted (*Z*)-γ-silylallyboranes to aldehydes, we studied the reaction of allene **9**[18] with (Ipc)$_2$BH. Thus, hydroboration of **9** with (−)-HB(Ipc)$_2$, prepared from (+)-α-pinene,[19] followed by addition of aldehyde **4**, produced *syn*-**11** as the major product via (*Z*)-γ-silylallylborane **10a** (Table 1). The ratio of β-hydroxy-

Table 1. Synthesis of β-Hydroxyallylsilanes **11**



	hydroboration conditions			
entry	temp	time	yield of **11**	**11** (syn:anti)[a]
1	66 °C	6 h	76%	3:1
2	25 °C	6 h	77%	6:1
3	−23 °C	6 h	79%	8:1
4	−50 °C	14 h	67%[b]	10:1

[a] Determined by ^{1}H NMR analysis. [b] Unreacted allenylsilane **9** was recovered (5%).

allylsilane isomers (e.g., *syn*-**11**:*anti*-**11**) was dependent upon the hydroboration reaction temperature; the best selectivity was obtained when the hydroboration was performed at −50 °C, although the reaction was sluggish under these conditions (entry 4). The kinetically formed (*Z*)-γ-silylallylborane **10a** presumably isomerizes to the thermodynamically more stable (*E*)-isomer **10c** via the boron allylic migration intermediate **10b**, a process that is suppressed when the hydroboration is performed at low temperatures.[20] Interestingly, however, *syn*-**11** was obtained as the major product even when the hydroboration of **9** was performed under reflux conditions (entry 1). It is conceivable that, due to the steric bulk of the (Ipc)$_2$B− substituent, intermediate **10b** is much less accessible than in analogous reactions of less highly substituted allylboranes and that the rate of isomerization (**10a** to **10c**) is relatively slow in the present case. Whether the ratio of *syn*-**11**:*anti*-**11** is reflective of kinetic control in the hydroboration step remains to be determined.

(7) (a) Elliot, M. C.; Williams, E. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2303. (b) Elliot, M. C. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1291.

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(12) For olefin metathesis reactions of allylsilanes: (a) Crowe, W. E.; Goldberg, D. R.; Zhang, Z. J. *Tetrahedron Lett.* **1996**, *37*, 2117. (b) Engelhardt, F. C.; Schmitt, M. J.; Taylor, R. E. *Org. Lett.* **2001**, *3*, 2209. (c) Taylor, R. E.; Engelhardt, F. C.; Schmitt, M. J.; Yuan, H. *J. Am. Chem. Soc.* **2001**, *123*, 2964.

(13) Enantioselectivity (% ee) of this reaction was determined by Mosher ester analysis: Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

(14) Prepared by the improved literature method: Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168. (b) For the original report: Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

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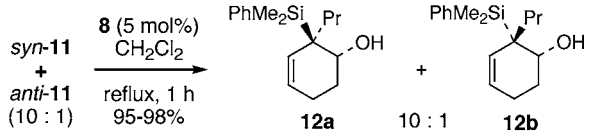
Because the mixture of the *syn*-**11** and *anti*-**11** allylsilane diastereomers was inseparable by column chromatography, a 10:1 mixture of *syn*-**11** and *anti*-**11** was subjected to RCM cyclization. This provided an easily separable 10:1 mixture of cyclohexenylsilanes **12a** and **12b** in 95−98% yield (Scheme 2). The stereochemistry of cyclohexenylsilanes **12a**

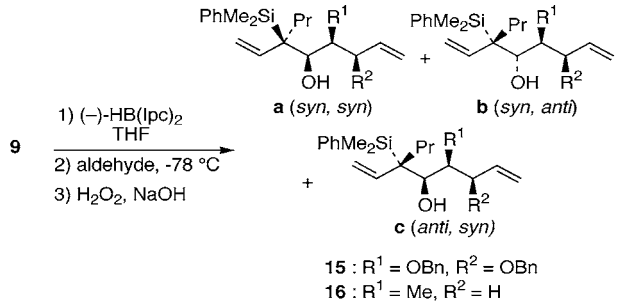
Scheme 2. Synthesis of Cyclohexenylsilane **12a**



and **12b** was assigned via Peterson elimination[21] (KHMDS, THF, −78 °C). Only the *cis*-*β*-hydroxysilane **12b** underwent elimination to 2-propyl cyclohexadiene, while the trans isomer **12a** remained intact and was recovered as a single isomer.

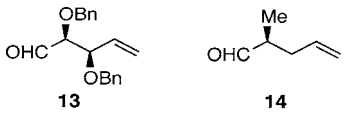
The scope of the *γ*-silylallylboration reactions of **10a** was expanded by using chiral aldehydes such as (2*S*,3*R*)-2,3-dibenzyloxy-4-penten-1-al (**13**)[22] and (*S*)-2-methyl-4-penten-1-al (**14**)[23] (see Table 2). Hydroboration of allenylsilane **9**

Table 2. *γ*-Silylallylboration of Aldehydes **13** and **14**



entry	RCHO	hydroboration temp	product (yield)	ratio (a:b:c)[a]
1	**13**	−30 °C	**15** (90%)	69:19:12
2	**13**	−50 °C	**15** (79%)	77:16:7
3	**14**	−50 °C	**16** (73%)[b]	83:10:7

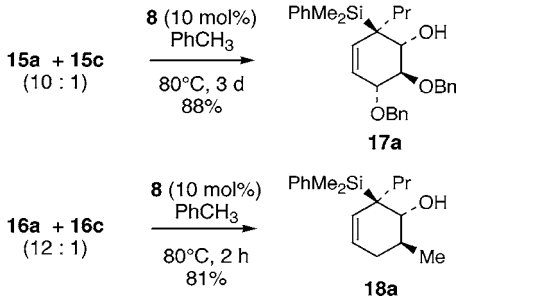
[a] Determined by ^{1}H NMR analysis. [b] Yield of **16a** and **16c**.



at −30 °C, followed by treatment of the in situ-generated *γ*-silylallylborane **10a** with **13** at −78 °C, provided a 69:19:12 mixture of three diastereomeric products **15a**−**c** (entry 1). Diastereomers **15a** (syn,syn) and **15b** (syn,anti) arise from the (*Z*)-silylallylborane **10a**, while **15c** (anti,syn) derives from the (*E*)-isomer **10c**. This result indicated that the selectivity of the hydroboration step was ca. 7:1 (i.e., the ratio of (**10a** + **10b**):**10c**), similar to that realized with the achiral aldehyde **4**, but that the face selectivity of the reaction of **10a** with **13** was 3.6:1 (i.e., the ratio of **15a**:**15b**). When the hydroboration reaction was performed at − 50 °C, the **10a**:**10c** ratio increased to 13:1, and the ratio of **15a**:**15b** increased slightly to 4.8:1 (entry 2). While **15b** was easily separated from the mixture by chromatography, isomers **15a** and **15c** were inseparable. Analogously, the *γ*-silylallylboration of aldehyde **14** provided an 83:10:7 mixture of **16a**−**c** (entry 3). Isomer **16b** could be separated chromatographically, but **16a** and **16c** were obtained as a ca. 12:1 mixture.

Subsequent RCM of a 10:1 mixture of **15a** and **15c** furnished the cyclohexenylsilane **17a** in 88% yield (Scheme 3). A prolonged reaction period (3 days) was required in

Scheme 3. Synthesis of Cyclohexenylsilanes **17a** and **18a**



this case due to the very hindered silyl-substituted quaternary center and the deactivating allylic benzyloxy substituent. RCM of a 12:1 mixture of **16a** and **16c** was straightforward and provided cyclohexenylsilane **18a** also in excellent yield (81%).[24] The stereochemistry of cyclohexenylsilanes **17a** and **18a** (as well as the minor cyclohexenylsilanes derived from **15c** and **16c**)[24] was confirmed by ^{1}H NOE experiments.

This route to highly substituted cyclohexenylsilanes was developed in anticipation that these compounds would be useful intermediates for C−C bond-forming reactions. Accordingly, in an initial test of this hypothesis, the hydroxyl group of **12a** was protected as the TES ether **19** under standard conditions (Scheme 4). Treatment of **19** with α-(benzyloxy)acetaldehyde in the presence of $SnCl_4$ furnished a 9:1 mixture of bicyclic ethers **20** and **21** in 71% yield.[25] The stereochemistry of epimers **20** and **21** was easily assigned by ^{1}H NOE experiments (Scheme 4).

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(22) For synthesis of **13**, see Supporting Information

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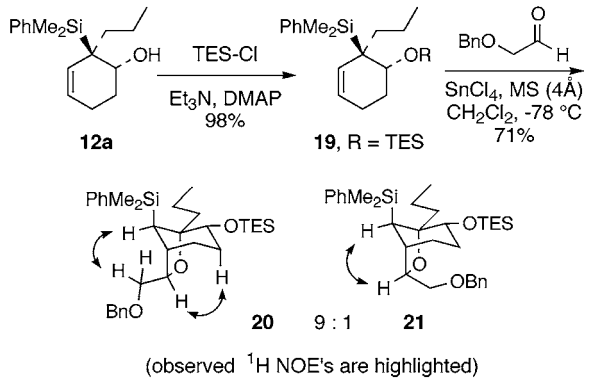
(24) Cyclohexenylsilanes deriving from **15c** and **16c** were also obtained (5−8% yield) but are not shown in Scheme 3.

(25) All attempts using other Lewis acids (BF_3·OEt_2, $TiCl_4$, $ZnCl_2$, or $MgBr_2$) for this reaction failed to give [3 + 2]-annulation products, **20** or **21**.

Scheme 4. [3 + 2]-Annulation Reaction of Cyclohexenylsilane **19**



(observed ^{1}H NOE's are highlighted)

In summary, we have demonstrated that highly functionalized cyclic allylsilanes can be prepared via γ-silylallylboration reactions of β- or γ-unsaturated aldehydes followed by RCM. Applications of this methodology toward the synthesis of representative conduritols and inositols are presented in the accompanying paper.[26] Additional applications of highly functionalized cyclohexenylsilanes in natural product synthesis will be reported in due course.

Acknowledgment. We thank the National Institutes of Health (GM 38907) for generous financial support of this research.

Supporting Information Available: Experimental details and spectroscopic data for compounds **1**, **3**, **6**, **7**, **9**, **11**−**13**, and **15**−**21** plus selected ^{1}H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL034347T

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