



Practical synthesis of (*E*)- and (*Z*)-2-silyl-3-penten-1-ols with high enantiopurity

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ABSTRACT

Practical methods for the synthesis of the optically active (*E*)- and (*Z*)-2-silyl-3-penten-1-ols are described. The optically pure (*E*)-allylsilane was synthesized from commercially available (*R*)-3-butyne-2-ol in five steps involving hydrozirconation followed by alkylation of the resulting alkenylmetal with BnOCH_2Cl . On the other hand, both enantiomers of the corresponding (*Z*)-allylsilane were prepared from commercially available dimethylphenylvinylsilane through epoxidation, the regioselective epoxide-opening reaction with 1-propynylmagnesium bromide, and the subsequent optical resolution using a lipase.

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Allylsilanes are an important class of compounds as carbon nucleophiles in the regio and stereoselective carbon–carbon bond-forming reactions.¹ In particular, the optically active allylsilanes have found a widespread use² and often played the key role in asymmetric total synthesis of natural products. In this context, the development of practical synthetic methods for chiral allylsilanes has recently been focused.³ We have reported the asymmetric total synthesis of Zincophorin, a unique ionophore antibiotic with a high affinity for Zn(II) cations, based on the key Lewis acid-promoted allylation reaction of tetrahydropyran derivative **2** with chiral allylsilane (*R*)-**1** (Scheme 1).⁴

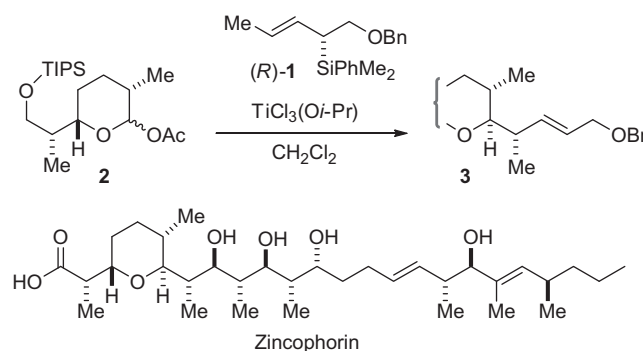
The allyl ether moiety in the product **3** was finally transformed into the polypropionate-derived chain of Zincophorin in a stereoselective manner. These results demonstrate the synthetic potential and utility of the chiral allylsilane (*R*)-**1** which was synthesized from methyl (*R*)-lactate (**4**) in nine steps (Scheme 2).

In the previous synthesis of (*R*)-**1**, the palladium-catalyzed intramolecular silyl transfer reaction of the disilanyl ether **7**, which was developed by Ito and co-workers,⁵ was used as the key step. Preparation of the disilanyl ether **7**, however, required seven steps involving the protection of methyl lactate **4** with a TBS group, which had to be replaced by a $(\text{Me}_2\text{PhSi})\text{Ph}_2\text{Si}$ group at the later stage of the synthesis. To shorten the synthetic route, we prepared the corresponding disilanyl ether of **4**, but subsequent treatment with DIBAL totally caused decomposition.

We report herein the efficient synthetic methods for the optically pure (*E*)-allylsilane (*R*)-**1**⁶ and its (*Z*)-analogs with high enantiomeric purity. The new synthetic plan for the disilanyl ether **7** is shown in Scheme 3. The benzyloxymethyl group in **7** would be introduced through hydrometalation of propargyl ether **8** followed

by a cross-coupling reaction of the resulting alkenylmetal species with benzyl chloromethyl ether (BOMCl).

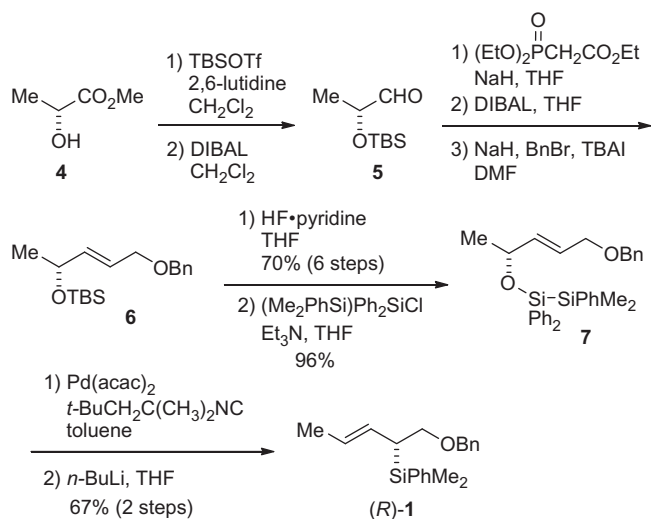
The requisite disilanyl ether **8** was prepared from (*R*)-3-butyne-2-ol, which is commercially available as well as its (*S*)-isomer, by treatment with $(\text{Me}_2\text{PhSi})\text{Ph}_2\text{SiCl}$ ⁷ and triethylamine in THF in 88% yield. Initial attempts to induce the hydroalumination reaction of **8** with DIBAL resulted in a cleavage of the O–Si bond. On the other hand, treatment of **8** with the Schwartz reagent $(\text{Cp}_2\text{Zr}(\text{H})\text{Cl})$ ⁸ followed by an aqueous workup afforded the allyl disilanyl ether **9** in high yield. These results led us to explore the alkylation reaction of the alkenylzirconocene intermediate (Table 1). Since direct addition of BOMCl to the reaction mixture gave none of the desired product **7** (entry 1), transmetalation to enhance the reactivity of the alkenylzirconocene species was examined. Lipshutz has reported that the combined use of methyllithium and cyano(2-thienyl)copper lithium promoted an alkylation reaction of an alkenylzirconocene species through a mixed cuprate.⁹ Although the original procedure was slightly effective in the reaction with



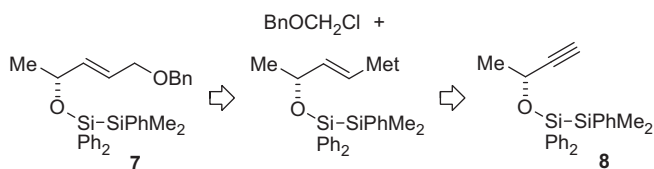
Scheme 1. The key step in the total synthesis of zincophorin.

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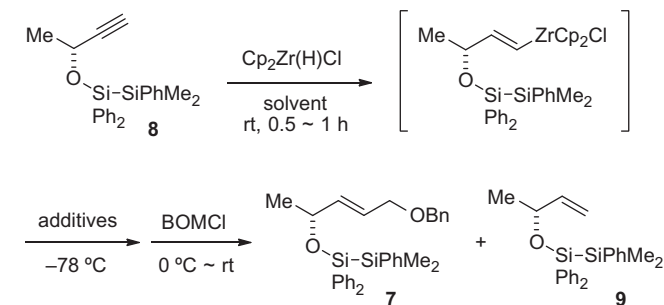


Scheme 2. Previous synthesis of allylsilane (*R*)-1.



Scheme 3. New synthetic plan for disilanyl ether **7**.

Table 1
Preparation of **7** via an alkenylzirconocene species



Entry	Additives	Solvent	Yields ^a (%)	
			7	9
1	None	THF	0	85
2	MeLi, (2-Th)Cu(CN)Li	THF	13	57
3	MeLi, (2-Th)Cu(CN)Li, HMPA	THF	29	—
4	Me ₂ Zn	CH ₂ Cl ₂	30	61
5	Me ₂ Zn, HMPA	CH ₂ Cl ₂	48	47
6	Me ₂ ZnMS4A ^b	CH ₂ Cl ₂	70 (66) ^c	14

^a Yield determined by ¹H NMR analysis of the crude product.

^b Powdered MS4A was suspended in the solution of substrate **8** prior to the addition of Cp₂Zr(H)Cl.

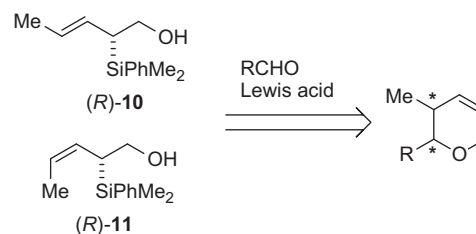
^c Isolated yield of silyl ether **7**.

BOMCl (entry 2), addition of hexamethylphosphoramide (HMPA) led to the formation of **7** in 29% yield (entry 3). Since these reactions gave a rather complex mixture of products, we next focused on the transmetalation by the use of an alkenylzinc intermediate reported by Wipf.¹⁰ Thus, treatment of the alkenylzirconocene species with dimethylzinc followed by the addition of BOMCl afforded

the desired product **7** in 30% yield, along with 61% of the allyl ether **9** (entry 4). Encouraged by the excellent mass balance in this reaction, we investigated the effects of additives. While HMPA brought about somewhat improved yield of **7** (entry 5), addition of molecular sieves 4A (MS4A) was remarkably effective in this particular reaction and gave the best result (entry 6).¹¹

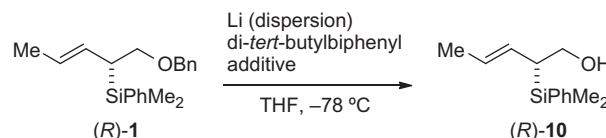
Eventually, the optimum reaction conditions provided multi-grams of the allyl ether **7**, which was subjected to the palladium-catalyzed intramolecular silyl transfer reaction to produce a sufficient amount of the allylsilane (*R*)-**1**. Having established the practical method for the synthesis of the optically pure (*R*)-**1** starting from commercially available (*R*)-3-butyn-2-ol, we carried out the conversion of (*R*)-**1** to the targeted molecule (*E*)-2-silyl-3-pentene-1-ol, (*R*)-**10**, which should be a promising chiral building block for asymmetric synthesis of 3,4-dihydropyran derivatives, as well as the corresponding (*Z*)-isomer (*R*)-**11** (Scheme 4). Indeed, Ito and co-workers reported this type of cyclization reaction for preparing optically active dihydropyran derivatives.¹²

Since removal of the benzyl group in (*R*)-**1** by hydrogenolysis is not applicable, reduction with lithium metal was explored. While the Birch reduction merely caused decomposition of the allylsilane, the combined use of lithium dispersion and di-*tert*-butylbiphenyl¹³ in THF was found to produce the desired alcohol (*R*)-**10**, as shown in Table 2. It should be noted that the reaction produces a lithium alkoxide of (*R*)-**10** in situ, which probably undergoes readily a Peterson-type elimination reaction to afford 1,3-pentadiene. In fact, the initial experiment with no additive resulted in the predominant formation of dimethylphenylsilanol, along with 7% of the desired product (entry 1). Therefore, we examined the reaction in the presence of an appropriate additive so as to reduce the reactivity of the alkoxide species. As a result, while the use of *t*-butanol as a proton source gave the desired alcohol (*R*)-**10** in 29–38% yield (entry 2), weak Lewis acids were found to be more effective (entries 3 and 4). Eventually, the optically pure (*R*)-**10** was obtained in 54% isolated yield by the combination of lithium dispersion and MgBr₂·OEt₂.



Scheme 4. Allylsilanes for asymmetric synthesis of 3,4-dihydropyran derivatives.

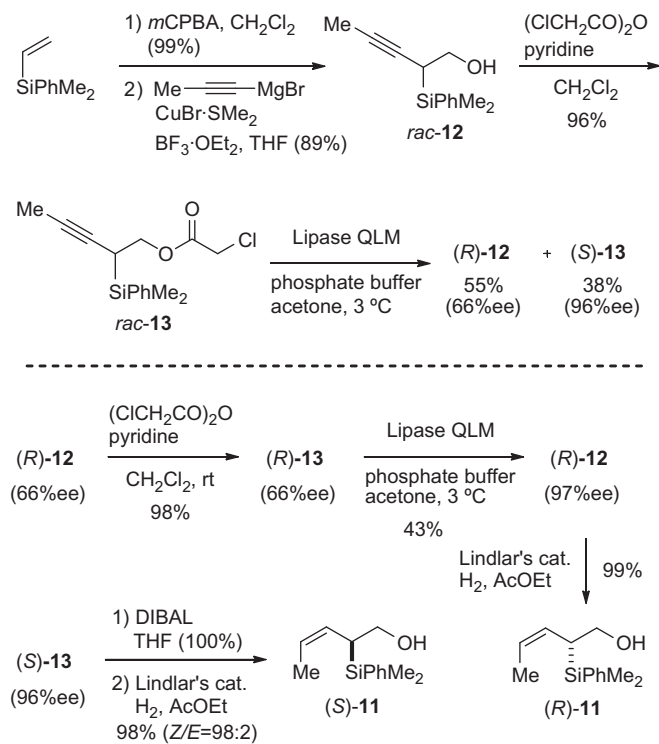
Table 2
Reductive removal of the benzyl group



Entry	Additive	Yield (%) ^a
1	None	7
2	<i>t</i> -BuOH	29–38
3	LiCl	42
4	MgBr ₂ ·OEt ₂	64 (54) ^b

^a Yield determined by ¹H NMR analysis.

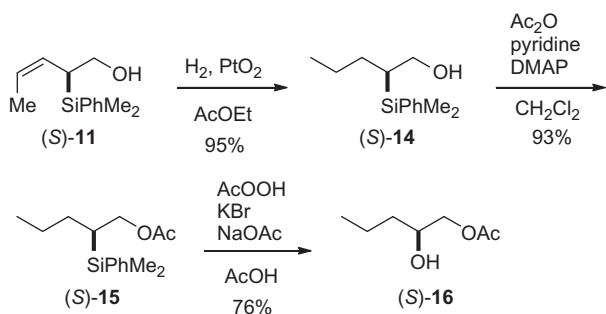
^b Isolated yield of allyl silane (*R*)-**10**.



Scheme 5. Synthesis of the optically active allylsilane **11**.

Next, we turned our attention to the development of practical methods for the synthesis of the optically active (*Z*)-allylsilanes, (*R*)-**11** and (*S*)-**11**. Since the palladium-catalyzed intramolecular silyl transfer reaction is not applicable to a (*Z*)-alkene, we set out to use optical resolution of racemic alcohols by enzyme.¹⁴ To this end, initially, commercially available dimethylphenylvinylsilane was oxidized to the corresponding epoxy silane, which was subjected to the ring-opening reaction with 1-propynylmagnesium bromide in the presence of CuBr·SMe₂ and BF₃·OEt₂ to furnish *rac*-**12** in high overall yield (Scheme 5). The alcohol **12** was then converted to chloroacetate **13** and the subsequent key asymmetric hydrolysis of the acetate was carried out in a phosphate buffer solution in the presence of a lipase.¹⁵ After a number of trials, lipase QLM was found to afford the alcohol (*R*)-**12** with 66% ee in 55% yield, along with 38% of the ester (*S*)-**13** with 96% ee. The optical purity of the products was evaluated by a HPLC analysis using a chiral column.

The alcohol (*R*)-**12** with high enantiomeric purity (97% ee) was obtained by repeating a similar reaction sequence starting from (*R*)-**12** with 66% ee. Finally, hydrogenation of the alcohol (*R*)-**12** over Lindlar's catalyst afforded the targeted allylsilane (*R*)-**11** (97% ee) quantitatively. The corresponding enantiomer (*S*)-**11** with 96% ee was also obtained by the reduction of the ester (*S*)-**13** with



Scheme 6. Determination of the stereochemistry of the allylsilane.

DIBAL followed by the hydrogenation of the resulting alkynyl alcohol over Lindlar's catalyst in 98% overall yield.

The stereochemistry of the allylsilanes was determined as shown in Scheme 6. The hydrogenation of allylsilane (*S*)-**11** followed by acetylation afforded acetate (*S*)-**15** which was subjected to the Tamao oxidation reaction. The optical rotation value of the product (*S*)-**16** was compared with that of the known hydroxy ester,¹⁶ showing that the configuration of the allylsilane as *S*.

In summary, we have developed practical methods for the synthesis of the optically active 2-(dimethylphenylsilyl)-3-penten-1-ols with high enantiopurity. That is, the optically pure (*E*)-allylsilane (*R*)-**10** was synthesized from commercially available (*R*)-3-butyne-2-ol in five steps involving the alkylation reaction of the alkenylzirconocene intermediate with BOMCl as the key step. On the other hand, both enantiomers of (*Z*)-allylsilanes, (*R*)-**11** (97% ee) and (*S*)-**11** (96% ee), were successfully prepared from commercially available dimethylphenylvinylsilane through epoxidation, the regioselective epoxide-opening reaction with 1-propynylmagnesium bromide, and subsequent optical resolution using the lipase QLM. The synthetic potential and utility of these optically active allylsilanes will be described in the following Letter.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures and characterization data for the allylsilanes) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.06.104.

References and notes

- (a) Fleming, I.; Dunoguès, J.; Smithers, R. *Org. React.* **1989**, *37*, 57; (b) Langkopf, E.; Schinzer, D. *Chem. Rev.* **1995**, *95*, 1375; (c) Lambert, J. B. *Tetrahedron* **1990**, *46*, 2677.
- For a review, see: Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293.
- Hayashi, T.; Konishi, M.; Ito, H.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 4962.
- Komatsu, K.; Tanino, K.; Miyashita, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4341.
- (a) Suginoe, M.; Matsumoto, A.; Ito, Y. *J. Am. Chem. Soc.* **1996**, *118*, 3061; (b) Suginoe, M.; Iwanami, T.; Ohmori, Y.; Matsumoto, A.; Ito, Y. *Chem. Eur. J.* **2005**, *11*, 2954.
- This type of allylsilanes have usually been prepared by using an asymmetric Si–H metal carbenoid insertion reaction of α -diazovinylacetates: (a) Bulughapitiya, P.; Landais, Y.; Parra-Rapado, L.; Planchenault, D.; Weber, V. *J. Org. Chem.* **1997**, *62*, 1630; (b) Davies, H. M. L.; Hansen, T.; Rutberg, J.; Bruzinski, P. R. *Tetrahedron Lett.* **1997**, *38*, 1741; (c) Wu, J.; Chen, Y.; Panek, J. S. *Org. Lett.* **2010**, *12*, 2112.
- (a) Tsuji, H.; Fukazawa, A.; Yamaguchi, S.; Toshimitsu, A.; Tamao, K. *Organometallics* **2004**, *23*, 3375; (b) Tamao, K.; Kawachi, A.; Ito, Y. *J. Am. Chem. Soc.* **1992**, *114*, 3989; (c) Murakami, M.; Suginoe, M.; Fujimoto, K.; Nakamura, H.; Anderson, P. G.; Ito, Y. *J. Am. Chem. Soc.* **1993**, *115*, 6487.
- Schwartz, J.; Labinger, J. A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 333.
- Lipshutz, B. H.; Kato, K. *Tetrahedron Lett.* **1991**, *32*, 5647.
- Wipf, P.; Xu, W. *Org. Synth.* **1997**, *74*, 205.
- Since MS4A was suspended in the solution of substrate **8** prior to the addition of Cp₂Zr(H)Cl, it might act as a water scavenger.
- Formal [4+2]-annulation reactions of optically active allylsilanes with an aldehyde: (a) Suginoe, M.; Iwanami, T.; Yamamoto, A.; Ito, Y. *Synlett* **2001**, *SI*, 1042; (b) Roush, W. R.; Dilley, G. J. *Synlett* **2001**, *SI*, 955; (c) Huang, H.; Panek, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9836; (d) Lowe, J. T.; Panek, J. S. *Org. Lett.* **2005**, *7*, 3231.
- Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924.
- Akeboshi, T.; Ohtsuka, Y.; Ishihara, T.; Sugai, T. *Adv. Synth. Catal.* **2001**, *343*, 624. and references cited therein.
- The reactions of the corresponding acetate with lipases in a buffer solution were found to be extremely sluggish.
- Ishihara, K.; Sakai, T.; Tsuboi, S.; Utaka, M. *Tetrahedron Lett.* **1994**, *35*, 4569.