Acid-Catalyzed Cyclization of Vinylsilanes Bearing a Hemiacetal Group[1]

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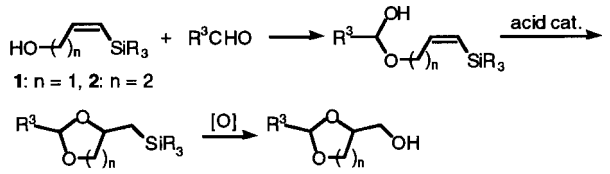
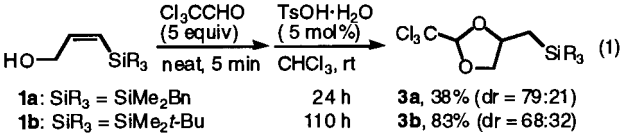
In the presence of a catalytic amount of $TsOH \cdot H_2O$, hemiacetals derived from (*Z*)-4-trialkylsilyl-3-buten-1-ols and chloral were cyclized to 2-trichloromethyl-4-trialkylsilylmethyl-1,3-dioxanes in good to high yields. The substrates bearing an allylic substituent achieved high levels of 1,2-asymmetric induction. When the silyl group was a benzyldimethylsilyl group, the products could be efficiently converted to 1,2,4-triol derivatives by oxidative cleavage of the silicon–carbon bond.

The stereo-controlled synthesis of polyols has been intensively studied in synthetic organic chemistry because of their prevalence in biologically active natural products.[2,3] In connection with this subject, the use of organosilicon reagents is recognized to be considerably valuable for the stereoselective introduction of a hydroxy group.[4] Previously, we have reported the acid-catalyzed cyclization of vinylsilanes bearing a hydroxy group to 2-silylmethylated cyclic ethers, which can be easily converted into the corresponding alcohols by oxidative cleavage of the silicon–carbon bond.[5,6] We herein disclose that the silicon-directed cyclization is applicable to the synthesis of cyclic acetals and protected triols using vinylsilanes with a hemiacetal group (Scheme 1).[7,8]



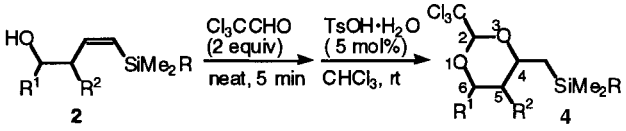
Scheme 1.

Since chloral (Cl_3CCHO) is known to readily react with alcohols to give hemiacetals,[9] vinylsilanes **1** and **2** were treated with chloral to introduce a hemiacetal moiety. The resultant vinylsilanes were subjected to an acid catalyst without isolation in the same flask.[10] The successive reaction of vinylsilane **1a** using chloral (5 equiv) and a catalytic amount of $TsOH \cdot H_2O$ (5 mol%) gave 1,3-dioxolane **3a** in 38% yield (eq 1). Protodesilylation and isomerization to 3-silylpropanal competed with the desired cyclization. The former side reaction may inactivate the acid catalyst. The use of $TiCl_4$ or $TiCl_2(O\,i\text{-}Pr)_2$ as an acid catalyst was not effective in the present cyclization. The change of the silyl group to a TBDMS group suppressed the protodesilylation to improve the cyclization efficiency as expected from our previous result.[5d]



The annulation of vinylsilane **2a** with chloral gave a diastereomeric mixture of 1,3-dioxane **4a** in good yield in marked contrast to the case with **1a** (entry 1 in Table 1). The Prins-type cyclization forming a dihydropyran was not observed.[11] The use of **2b** led to a nearly quantitative formation of **4b** (entry 2). Vinylsilanes **2c**–**f**, bearing a homoallylic substituent (R^1), were converted to four possible diastereomers of 2,4,6-trisubstituted 1,3-dioxanes (entries 3–6). In the major isomers, the silylmethyl group was determined to be *trans* to the other substituents by ^{1}H NMR analysis including NOE experiments (Figure 1). The second major isomers were proved to have 2,4-*cis*- and 4,6-*cis*-configurations. Thus, the present reaction showed low levels of 1,3-asymmetric induction between R^1 and the silylmethyl group. The annulation of vinylsilanes **2g**–**i**, bearing an allylic substituent (R^2), afforded diastereomeric mixtures of 2,4,5-trisubstituted 1,3-dioxanes (entries 7–9). In both major and second major diastereomers of **4g**–**i**, R^2 was assigned to be *trans* to the silylmethyl group on the basis of ^{1}H NMR analysis (Figure 1). These results indicate that the levels of 1,2-asymmetric induction are considerably high.

Table 1. Annulation of vinylsilanes **2** with chloral[a]



Entry	Vinylsilane				Time	Yield	Product	Isomeric
	R^1	R^2	R		/h	/%		Ratio[b]
1	H	H	Bn	**2a**	24	73	**4a**	58:42
2	H	H	*t*-Bu	**2b**	49	95	**4b**	55:45
3	Ph	H	Bn	**2c**	48	75	**4c**	68:22:7:3[c]
4	Ph	H	*t*-Bu	**2d**	96	93	**4d**	64:23:7:6[c]
5	*i*-Pr	H	Bn	**2e**	24	73	**4e**	75:16:5:4[c]
6	*i*-Pr	H	*t*-Bu	**2f**	36	90	**4f**	74:16:6:4[c]
7	H	Ph	Bn	**2g**	118	53	**4g**	67:33[d,e]
8	H	Ph	*t*-Bu	**2h**	113	69	**4h**	66:32:2[d,e]
9	H	Pr	Bn	**2i**	69	74	**4i**	64:27:7:2[d]

[a]All reactions were carried out with 0.50 mmol of **2** in $CHCl_3$ (2.5 mL). [b]Determined by ^{1}H NMR analysis. [c]Relative configuration: 2,4-*trans* and 4,6-*trans* for the major isomer; 2,4-*cis* and 4,6-*cis* for the second major isomer. [d]Relative configuration: 2,4-*trans* and 4,5-*trans* for the major isomer; 2,4-*cis* and 4,5-*trans* for the second major isomer. [e]Other diastereomers were not detected.

Some common aldehydes other than chloral were also usable for the present cyclization (Table 2). The annulation with 4-nitrobenzaldehyde achieved higher reaction efficiency than that with benzaldehyde or 4-methoxybenzaldehyde (entries 1–3). This result is probably due to the ease of hemiacetaliza-

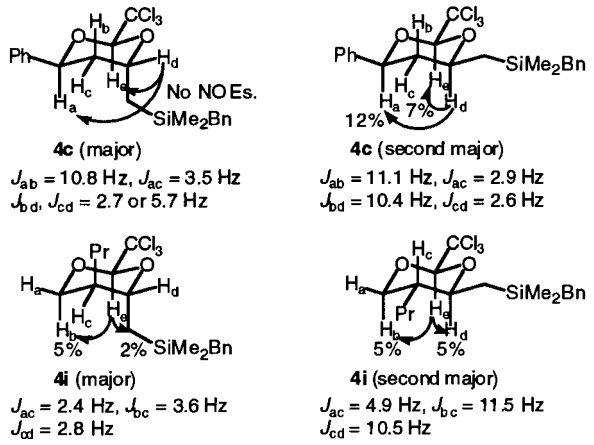
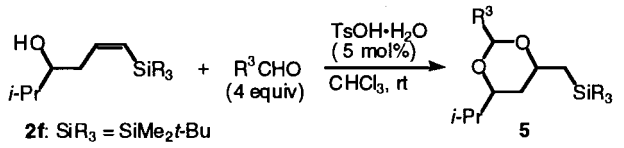


Figure 1.

Table 2. Annulation of vinylsilane **2f** with aldehydes[a]

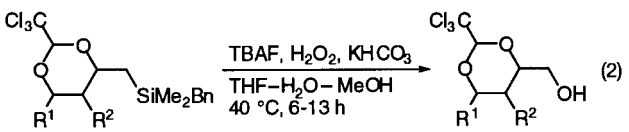


Entry	R	Time /h	Yield /%[b]	Product	Isomeric Ratio[b]
1	4-$O_2NC_6H_4$	96	68	**5a**	55:27:18:<1[d]
2	Ph	120	44	**5b**	76:16:8:<1[d]
3	4-$MeOC_6H_4$	120	36[c]	**5c**	99:<1:<1:<1[d]
4	*i*-Pr	120	74	**5d**	45:21:17:17

[a]See footnote a in Table 1. [b]The yield and isomeric ratio were determined by ^{1}H NMR analysis using benzyl acetate as an internal standard. [c]Isolated yield. [d]The major isomer has 2,4-*cis*- and 4,6-*cis*-configurations.

tion with the electron-deficient aldehyde. Interestingly, the major isomers of **5a–c** were determined to possess 2,4-*cis*- and 4,6-*cis*-configurations unlike the case with chloral. In particular, the annulation with 4-methoxybenzaldehyde showed high diastereoselectivity although the origin is not clear. Under the same conditions, **2f** reacted with isobutyraldehyde as well to afford **5d** in good yield with rather low stereoselectivity (entry 4).

The cyclized products bearing a benzyldimethylsilyl group could be efficiently converted into partly protected 1,2,4-triols with stereochemical retention by oxidative cleavage of the silicon–carbon bond using TBAF, $KHCO_3$, and H_2O_2 (modified Tamao method).[5d,7a,12]



Substrate, Yield of Alcohol (%): **4a**, 91; **4c**, 91; **4e**, 75; **4g**, 81; **4i**, 80

In summary, we have demonstrated that the TsOH-catalyzed cyclization of hemiacetals derived from (*Z*)-4-trialkylsilyl-3-buten-1-ols (**2**) and aldehydes is available for the synthesis of certain 1,3-dioxanes. The present cyclization provides a new stereoselective route to 1,2,4-triols.

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Dedicated to Prof. Hideki Sakurai on the occasion of his 70th birthday.

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10 Typical procedure: A mixture of chloral (147 mg, 1.00 mmol) and **2a** (110 mg, 0.50 mmol) was stirred for 5 min at room temperature under N_2. Chloroform (2.5 mL) and $TsOH·H_2O$ (4.8 mg, 0.025 mmol) were added to the mixture. After being stirred for 24 h, the mixture was poured into saturated aqueous $NaHCO_3$. The extract with *t*-BuOMe (3 × 15 mL) was dried over Na_2SO_4 and evaporated. Purification by column chromatography (SiO_2, hexane–AcOEt 20:1) gave **4a** (134 mg) in 73% yield.
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