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Stereoselective Synthesis of *syn,syn*- and *syn,anti*-1,3,5-Triols via Intramolecular Hydrosilylation of Substituted Pent-3-en-1,5-diols

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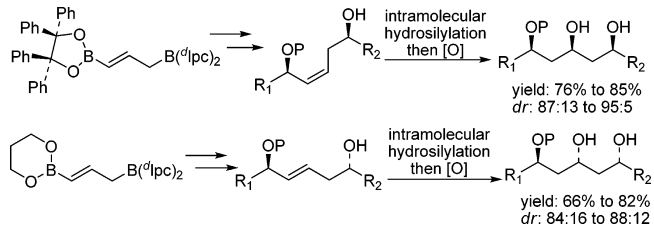
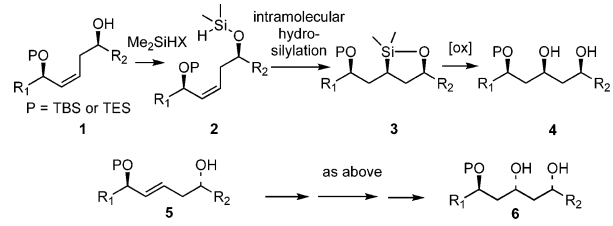
ABSTRACT



A stereoselective method for synthesis of *syn,syn*- and *syn,anti*-1,3,5-triols based on a double allylboration−intramolecular hydrosilylation sequence has been developed. The 1,3-*syn* stereocontrol is achieved in the intramolecular hydrosilylation of monoprotected (*Z*)-1,5-*syn*-diols and (*E*)-1,5-*anti*-diols with 87:13 to 95:5 and 86:14 to 88:12 diastereomeric ratios, respectively, by using 0.5 mol % of Karstedt's catalyst in toluene.

The 1,3,5-triol motif is a common subunit of many biologically active natural products.[1,2] Consequently, the stereoselective synthesis of these units has attracted much interest.[1,3] During the course of our efforts toward the synthesis of polyketide natural products, we became interested in exploring the intramolecular hydrosilylation of substituted pent-3(*Z*)-en-1,5-*syn*- and (*E*)-1,5-*anti*-diol monoethers, **1** and **5**, respectively, which are prepared using our double allylboration methodology,[4] as a strategy for synthesis of *syn,syn*- and *syn,anti*-1,3,5-triols **4** and **6**, respectively (Scheme 1).

Scheme 1. Intramolecular Hydrosilylation of Homoallylic Alcohols **1** and **5**



Intramolecular hydrosilylation of acyclic homoallylic alcohols followed by oxidative cleavage of the resultant carbon−silicon bond presents a mild and efficient way to construct 1,3-diols.[5−7] Several publications by the Tamao group described the regio- and stereocontrolled synthesis of 1,3-diols from allylic and

(1) For a review, see: Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2021.
(2) For several specific examples, see: (a) Hazen, E. L.; Brown, R. *Science* **1950**, *112*, 423. (b) Kobinata, K.; Koshino, H.; Kudo, T.; Isono, K.; Osada, H. *J. Antibiot.* **1993**, *46*, 1616. (c) Dong, L.; Victoria, A. G.; Grange, R. L.; Johns, J.; Parsons, P. G.; Porzelle, A.; Reddell, P.; Schill, H.; Williams, C. M. *J. Am. Chem. Soc.* **2008**, *130*, 15262.
(3) For recent examples and additional reviews, see: (a) Zhang, Z.; Aubry, S.; Kishi, Y. *Org. Lett.* **2008**, *10*, 3077. (b) Bode, S. E.; Wolberg, M.; Muller, M. *Synthesis* **2006**, 557. (c) Schneider, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 1375. (d) Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041.
(4) Flamme, E. M.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 13644.
(5) Tamao, K.; Nakajima, T.; Sumiya, R.; Arai, H.; Higuchi, N.; Ito, Y. *J. Am. Chem. Soc.* **1986**, *108*, 6090.

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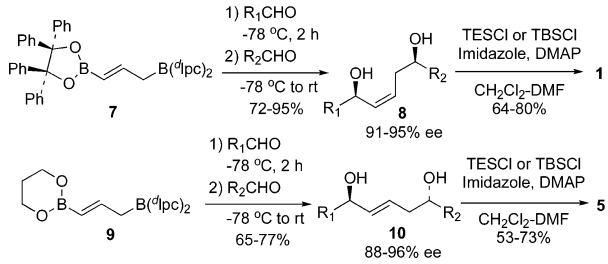
homoallylic alcohols.[5,6a] However, 1,3-stereochemical control was not observed in hydrosilylation reactions of acyclic (*E*)- and (*Z*)-disubstituted homoallylic alcohols by using Speier's catalyst (H_2PtCl_6·$6H_2O$).[5,8] Further investigations of the 1,3-diastereoselective intramolecular hydrosilylation of homoallylic alcohols have not been reported. We report herein our studies of this reaction, using homoallylic alcohols **1** and **5** as the substrates, which demonstrate that *syn*,*syn*-diols **4** and *syn*,*anti*-diols **6** are obtained with 87−95% and 84−88% diastereoselectivity, respectively, by using 0.5 mol % of Karstedt's catalyst[9] in toluene.

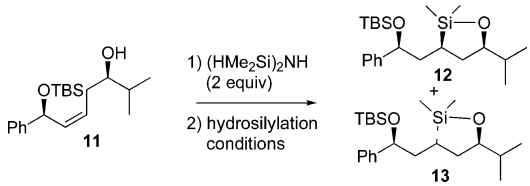
Syntheses of 1,5-diol derivatives **1** and **5** were accomplished as summarized in Scheme 2. Sequential treatment

Scheme 2. Synthesis of Monoprotected 1,5-Diols **1** and **5**

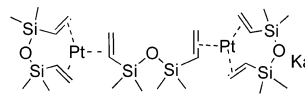


of two aldehydes with γ-borylallylboranes **7** or **9** provided (*Z*)-1,5-*syn*-diols **8** and (*E*)-1,5-*anti*-diols **10**, respectively, with excellent diastereo- and enantioselectivity.[4] Treatment of 1,5-diols **8** and **10** with 1.1 equiv of TES-Cl or TBS-Cl, imidazole, and catalytic DMAP in CH_2Cl_2−DMF furnished the targeted monosilyl ethers **1** and **5** with excellent chemoselectivity and good yield (see Supporting Information for details).[10] We used homoallylic alcohol **11** to screen catalysts and reaction conditions for the intramolecular hydrosilylation reaction. We elected to use Speier's catalyst[8] ($PtCl_6$·$6H_2O$), Karstedt's catalyst[9] (**14**, platinum(0)-1,3-divinyl-1,1,3,3-tetramethyl-disiloxane), and $Pt(PPh_3)_4$,[11] because of their commercial availibility and known utility as catalysts for hydrosilylation reactions. Hence, a mixture of homoallylic alcohol **11** and $(HMe_2Si)_2NH$ (2 equiv) was stirred at room temperature overnight to ensure silylation of the hydroxy group. The excess disilazane was removed under

Table 1. Optimization of Conditions for Intramolecular Hydrosilylation of (*Z*)-1,5-*syn*-Diol Monosilyl Ether **11**



entry	hydrosilylation conditions	dr (*syn*:*anti*)[a]	conversion[a]
1	0.5 mol %, H_2PtCl_6·$6H_2O$ toluene, 60 °C, 12 h	85:15	~100%
2	5 mol %, $Pt(PPh_3)_4$ toluene, 110 °C, 5 h	70:30	~90%
3	0.5 mol %, Karstedt's catalyst, toluene, 0 °C, 3 h	93:7	~100%
4	0.5 mol %, Karstedt's catalyst, hexane, 0 °C, 3 h	93:7	~100%
5	0.5 mol %, Karstedt's catalyst, THF, 0 °C, 3 h	90:10	~100%



[a] Diastereomeric ratio and reaction conversion were determined by ^{1}H NMR analysis of the reaction mixture.

Scheme 3. Synthesis of *syn*-1,3-Diol **15** and Proposal for Origin of 1,3-*syn* Stereocontrol

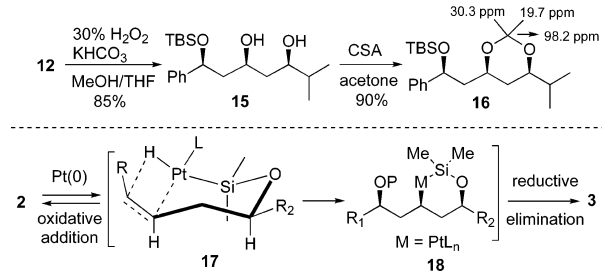
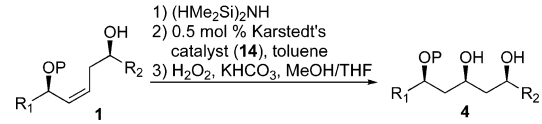
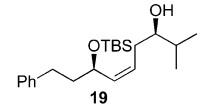
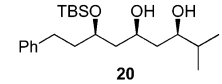
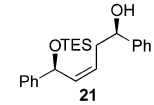
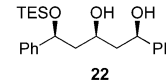
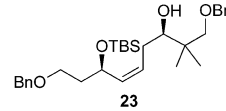
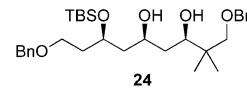
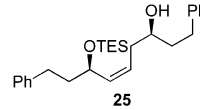
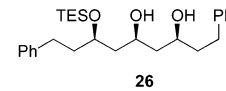


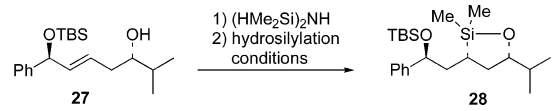
Table 2. Intramolecular Hydrosilylation of (*Z*)-1,5-*syn*-Diol Monosilyl Ethers **19**, **21**, **23**, and **25**



entry	protected 1,5-diols	major product	yield(dr)[a]
1			78% (87:13)
2			76% (95:5)
3			77% (89:11)
4			72% (89:11)

[a] Diastereomeric ratio determined by NMR spectroscopy.

Table 3. Optimization of Intramolecular Hydrosilylation of (*E*)-1,5-*anti*-Diol Monosilyl Ether **27**



27 28

entry	hydrosilylation conditions	dr (*syn*:*anti*)[a]	conversion (%)[a]
1	0.5 mol %, $H_2PtCl_6{\cdot}6H_2O$ toluene, 110 °C, 12 h	69:31	~80
2	5 mol %,$Pt(PPh_3)_4$ toluene, 110 °C, 5 h	82:18	~80
3	0.5 mol %, Karstedt's catalyst (**14**) toluene, 0 °C, 2 h then rt, 2 h	85:15	~100
4	0.5 mol %, Karstedt's catalyst (**14**) THF, 0 °C, 2 h then rt, 2 h	77:23	~100
5	0.5 mol %, Karstedt's catalyst (**14**) hexane, 0 °C, 2 h then rt, 2 h	78:22	~100
6	0.5 mol %, Karstedt's catalyst (**14**) toluene, −40 °C, 10 h, then 0 °C, 2 h and rt, 2 h	85:15	~100

[a] Diastereomeric ratio and reaction conversion were determined by ^{1}H NMR analysis of the crude reaction mixture.

vacuum, and then the silane intermediate was subjected to a range of hydrosilylation conditions as summarized in Table 1.

The results indicated that hydrosilylation of **11** using 0.5 mol % of Karstedt's catalyst (**14**) in toluene proceeded to completion very smoothly at 0 °C in 3 h (entry 3). On the other hand, elevated temperatures and longer reaction times were needed for complete hydrosilylation using Speier's catalyst (0.5 mol %, 60 °C, 12 h, entry 1) and $Pt(PPh_3)_4$ (5 mol %, 110 °C, 5 h, entry 2). More importantly, use of Karstedt's catalyst (**14**) led to superior 1,3-*syn* diastereoselectivity (93:7), compared to the selectivity obtained by using Speier's catalyst (85:15 dr) and $Pt(PPh_3)_4$ (70:30 dr). The stereochemistry of of siloxane **12** was assigned as discussed subsequently. The overall reaction diastereoselectivity was best in toluene and hexanes among the solvents that we examined (entries 3−5).

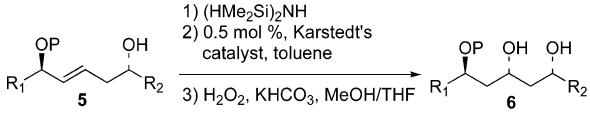
Intermediate **12** was oxidized to 1,3-*syn* diol **15** by treatment with 30% H_2O_2 (20 equiv) and $KHCO_3$ (5 equiv) in THF−MeOH (Scheme 3).[12] The overall yield of **15** was 85% for this three-step sequence starting from **11**.

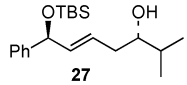
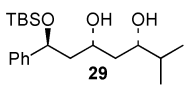
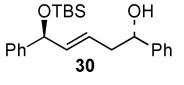
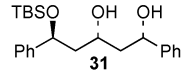
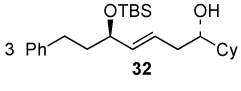
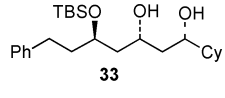
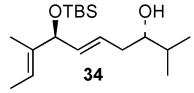
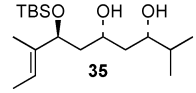
The stereochemistry of **15** was assigned by conversion to acetonide **16** (Scheme 3). ^{13}C NMR analysis of **16** according to Rychnovsky's method[13] established the 1,3-*cis* acetonide stereochemistry. This also confirmed the 1,3-*syn*stereochemistry of hydrosilylation product **12**, since the oxidative cleavage of the C−Si bond is known to proceed with retention of configuration.[12]

Tamao has suggested that the Pt-catalyzed intramolecular hydrosilylation reaction preceeds through an oxidative addition−hydrometalation−reductive elimination sequence.[14] We speculate that the origin of 1,3-*syn* stereocontrol could derive from a chairlike transition state **17** for the 6-*exo* hydrometalation step with the olefin in a pseudoequatorial position (Scheme 3). Intermediate **18** could then undergo reductive elimination to provide the five-membered *syn*-cyclic siloxane **3**.

Having developed suitable conditions for intramolecular hydrosilylation of **11**, we explored the scope of this sequence with additional substrates as summarized in Table 2. The (*Z*)-1,5-*syn*-diol monosilyl ethers **19**, **21**, **23**, and **25** were converted into the corresponding *syn*,*syn*-1,3,5-triol mono-

Table 4. Intramolecular Hydrosilylation of Monoprotected (*E*)-1,5-*anti*-Diols



entry	protected 1,5-diols	major product	yield (dr)[a]
1	 **27**	 **29**	82% (85:15)
2	 **30**	 **31**	81% (84:16)
3	 **32**	 **33**	79% (88:12)
4	 **34**	 **35**	72% (85:15)

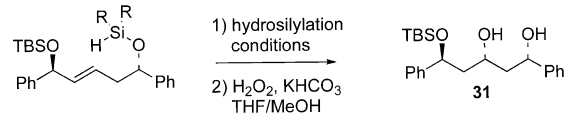
[a] Diastereomeric ratio determined by NMR spectroscopy.

(6) (a) Tamao, K.; Nakagawa, Y.; Arai, H.; Higuchi, N.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 3712. For other examples of intramolecular hydrosilylation of acyclic allylic and homoallylic alcohols (the latter of which are controlled by minimization of allylic interactions), see: (b) Young, D. G. J.; Hale, M. R.; Hoveyda, A. H. *Tetrahedron Lett.* **1996**, *37*, 827. (c) Hoveyda, A. H.; Hale, M. R. *J. Org. Chem.* **1992**, *57*, 1643. (d) Denmark, S. E.; Forbes, D. C. *Tetrahedron Lett.* **1992**, *33*, 5037.

(7) For an example of polyol synthesis via intramolecular silylformation−allylsilylation, see: Zacuto, M. J.; Leighton, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 8587.

(8) Speier, J. L. *Adv. Organomet. Chem.* **1979**, *17*, 407.

Table 5. Effect of Silane Substituents on the Intramolecular Hydrosilylation Reaction



entry	R	hydrosilylation conditions	dr (*syn*:*anti*)	yield (%)
1	Me (36)	0.5 mol %, Karstedt's catalyst toluene, 0 °C, 2 h then rt, 1 h	84:16	81
2	Ph (37)	0.5 mol %, Karstedt's catalyst toluene, rt, 12 h	84:16	80
3	i-Pr (38)	0.5 mol %, Karstedt's catalyst toluene, 110 °C, 12 h		0

ethers **20**, **22**, **24**, and **26**, respectively, in 72−78% yield with 87: 13 to 95: 5 diastereoselectivity. This procedure worked well for the sterically demanding substrate **23** (Table 2, entry 3). Moreover, from a practical standpoint, this reaction can be performed essentially as a one-pot operation without purification of the silyl ether and cyclic siloxane intermediates.

We next turned our attention to the synthesis of the *syn*,*anti* triol unit **6** from monoprotected (*E*)-1,5-*anti*-diols **5**. Optimization of the hydrosilylation conditions was conducted using (*E*)-homoallylic alcohol **27**. Therefore, as summarized in Table 3, alcohol **27** was silylated with $(HMe_2Si)_2NH$ and then subjected to various hydrosilylation catalysts and conditions to form the *syn* hydrosilylation product **28** as a major diastereomer. Again, use of 0.5 mol % Karstedt's catalyst **14** (Table 3, entry 3) in toluene (0 °C, 2 h, then room temperature, 2 h) provided the best reaction diastereoselectivity (*syn*:*anti* = 85:15). Attempts to improve the diastereoselectivity by conducting the reaction in other solvents (entries 4, 5), at lower temperatures (entry 6; only trace amounts of **28** were observed after 12 h at −40 °C), or with other catalysts (entries 1, 2) were unsuccessful.

Further investigation of the scope of the hydrosilylation of (*E*)-1,5-*anti*-diol monoethers was performed as summarized in Table 4. The intramolecular hydrosilylations of **30**, **32**, and **34** in Table 4 proceeded with 84:16 to 88:12 diastereoselectivity favoring the formation of the indicated 1,3-*syn* diols **31**, **33**, and **35** (which were obtained in 72−81% yield for the three-step sequence). It is also worth noting that, as demonstrated by substrate **34** (Table 4, entry 4), the intramolecular hydrosilylation occurs on the proximal internal olefin, leaving the distal trisubstitute olefin intact without any olefin isomerization or intermolecular hydrosilylation products being observed.

We also investigated the effect of greater steric bulk in the silane unit in an attempt to improve the diastereoselectivity of the intramolecular hydrosilylation process. Accordingly, substrates **36**, **37**, and **38** were synthesized and subjected to hydrosilyaltion conditions as summarized in Table 5. The diphenylsilane **37** (Table 5, entry 2) underwent hydrosilylation but required 12 h at room temperature for complete conversion; subsequent oxidation of the intermediate siloxane gave triol **31** in good yield. However, the reaction diasteroselectivity (84:16) was not improved as compared to that of the analogous reaction of dimethylsilane **36** (Table 5, entry 1). On the other hand, diisopropylsilane **38** failed to undergo the intramolecular hyrosilylation, presumely due to steric hindrance. When **38** was heated at 110 °C in toluene for 12 h in the presence of Karstedt's catalyst, an unidentified byproduct began to form.

In summary, we have developed a mild, stereoselective procedure for synthesis of *syn*,*syn*- and *syn*,*anti*-1,3,5-triol derivatives based on the intramolecular hydrosilylation of 1,5-diol monoethers **1** and **5**. By using 0.5 mol % Karstedt's catalyst **14** in toluene, 87:13 to 95:5 *syn* diasteroselectivity was achieved for the intramolecular hydrosilylation of (*Z*)-1,5-*syn*-diol monoethers **1**. Similarly, 84:16 to 88:12 *syn* diasteroselectivity was achieved for the analogous intramolecular hydrosilylation of (*E*)-1,5-*anti*-diol monoethers **5**. In all cases, the *syn*-1,3-diol derivatives were obtained in 72−85% yields for the simple three-step silyl ether formation−hydrosilylation−oxidative cleavage sequence. Applications of this method in natural products synthesis will be reported in due course.

Acknowledgment. We acknowledge the NIH (GM038436 and GM027682) for support of this research.

Supporting Information Available: Experimental procedures and copies of ^{1}H NMR and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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