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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. 1,3-*Syn* stereocontrol is achieved in the intramolecular hydrosilylation of mono-protected (*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*- (**1**) 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).

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 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 ($\text{H}_2\text{PtCl}_6 \cdot 6\text{H}_2\text{O}$).^{5,8} Further investigations of the

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 catalyst⁹ in toluene.

Syntheses of 1,5-diol derivatives **1** and **5** were accomplished as summarized in Scheme 2. Sequential treatment 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 CH₂Cl₂-DMF furnished the targeted mono-silyl ethers **1** and **5** with good chemoselectivity and 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 catalyst⁸ (PtCl₆•6H₂O), Karstedt's catalyst⁹ (**14**, platinum(0)-1,3-divinyl-1,1,3,3-tetramethyl-disiloxane) and Pt(PPh₃)₄,¹¹ due to their commercial availability and known utility as catalysts for hydrosilylation reactions. Hence, a mixture of homoallylic alcohol **11** and (HMe₂Si)₂NH (2 equiv) was stirred at room temperature overnight to ensure silylation of the hydroxy group. The excess disilazane was removed under vacuum, 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(PPh₃)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 d.r.) and Pt(PPh₃)₄ (72 : 18 d.r.). The stereochemistry 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% H₂O₂ (20 equiv) and KHCO₃ (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). ¹³C NMR analysis of **16** according to Rychnovsky's method¹³ established the *syn*-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 proceeds through an oxidative addition-hydrometalation-reductive elimination sequence.¹⁴ We speculate that the origin of 1,3-*syn*-stereocontrol could derive from a chair-like transition state **17** for the 6-*exo*-hydrometalation step with the olefin in a pseudo-equatorial 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 monoethers **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 mono-protected (*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 (HMe₂Si)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 72-82% yield for the three-step sequence). It is also worth noting that, as demonstrated by substrate **34** (Table 4, entry 4), the intramolecular hydrosilylation occur 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 hydrosilylation 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 diastereoselectivity (84 : 16) was not improved as compared to the analogous reaction of dimethylsilane **36** (Table 5, entry 1). On the other hand, diisopropylsilane **38** failed to undergo the intramolecular hydrosilylation, presumably 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 by-product 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*-diastereoselectivity was achieved for the intramolecular hydrosilylation of (*Z*)-1,5-*syn*-diol monoethers **1**. Similarly, 84:16 to 88:12 *syn* diastereoselectivity 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

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

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

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

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

entry	hydrosilylation conditions	dr (<i>syn:anti</i>) ^a	conversion ^a
1	0.5 mol %, $\text{H}_2\text{PtCl}_6 \cdot 6\text{H}_2\text{O}$ toluene, 60 °C, 12 h	85:15	~100%
2	5 mol %, $\text{Pt}(\text{PPh}_3)_4$ 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%

^aDiastereomeric ratio and reaction conversion were determined by ^1H NMR analysis of the reaction mixture.

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

entry

protected 1,5-diols

1

entry

protected 1,5-diols

n

2

3

entry	protected 1,5-diols	n
4	25	26

^aDiastereomeric ratio determined by NMR spectroscopy.

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

entry	hydrosilylation conditions	dr (<i>syn:anti</i>) ^a	conversion ^a
1	0.5 mol %, $\text{H}_2\text{PtCl}_6 \cdot 6\text{H}_2\text{O}$ toluene, 110 °C, 12 h	69:31	~80%
2	5 mol %, $\text{Pt}(\text{PPh}_3)_4$ 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%

^aDiastereomeric ratio and reaction conversion were determined by ^1H NMR analysis of the crude reaction mixture.

Table 4Intramolecular Hydrosilylation of Mono-protected (*E*)-1,5-anti-Diols

entry

protected 1,5-diols

1

2

entry

protected 1,5-diols

3

4

^aDiastereomeric ratio determined by NMR spectroscopy.

Table 5

Effect of Silane Substituents on the Intramolecular Hydrosilylation Reaction

entry	R	hydrosilylation conditions	dr (<i>syn:anti</i>)	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>i</i> -Pr(38)	0.5 mol %, Karstedt's catalyst toluene, 110 °C, 12 h		0%