Preparation of optically active bicyclodihydrosiloles by a radical cascade reaction

Koichiro Miyazaki¹, Yu Yamane¹, Ryuichiro Yo¹, Hidemitsu Uno² and Akio Kamimura*¹

Abstract
Bicyclodihydrosiloles were readily prepared from optically active enyne compounds by a radical cascade reaction triggered by tris(trimethylsilyl)silane ((Me₃Si)₃SiH). The reaction was initiated by the addition of a silyl radical to an α,β-unsaturated ester, forming an α-carbonyl radical that underwent radical cyclization to a terminal alkyne unit. The resulting vinyl radical attacked the silicon atom in an S⁻Hi manner to give dihydrosilole. The reaction preferentially formed trans isomers of bicyclosiloles with an approximately 7:3 to 9:1 selectivity.

Introduction
Radical cyclization occupies a unique position in organic synthesis because it is a useful reaction for the construction of cyclic molecules [1-10]. The radical cascade cyclization process is also an interesting synthetic reaction that often provides an efficient method [11-13]. Recently, we reported a new type of higher-order radical cascade reaction between chiral enyne compounds and Bu₃SnH, which is recognized as a useful reagent in radical reactions [14]. In this reaction, radical addition–cyclization cascade followed by intramolecular radical substitution (S⁻Hi) occurred in one-pot to give optically active bicyclostannolanes in good yields [15]. We are interested in whether such a cascade S⁻Hi process might occur with other radical species. We have found that a methylthiyl radical also undergoes such a radical cascade reaction to stereoselectively give bicyclic dihydrothiophenes [16]. We expected that tris(trimethylsilyl)silane ((Me₃Si)₃SiH) [17], which is a well-known alternative to Bu₃SnH in radical reactions [18-22], would be a good promoter of a similar cascade S⁻Hi reaction, because there were several reports so far that show such S⁻Hi reaction on silicon atoms progressing efficiently [23-28]. In this
paper, we report a new synthesis of chiral bicycldihydrosiloles through an addition–cyclization–S_{H}i cascade reaction in one-pot treatment of chiral enyne compounds. A good trans-selectivity was observed in the reaction.

**Results and Discussion**

We examined the cascade process using optically active enyne precursor 1a, which was prepared by a Michael/aldol domino reaction to chiral sulfinimines followed by thermal elimination and N-propargylation [29,30]. We first optimized the reaction conditions. The results are summarized in Table 1.

Treatment of 1 with (Me_3Si)_3SiH in the presence of catalytic amounts of AIBN at 110 °C resulted in the formation of the desired bicycldihydrosilole 2a in 14% yield (Table 1, entry 1). The use of one equivalent of AIBN improved the yield of 2a to 39% (Table 1, entry 2). These results suggest that the radical chain reaction insufficiently progressed during the reaction initiated by AIBN. The product contained two diastereomers, which were separated by chromatography. The use of Et_3B/air as an initiator enhanced the yield of 2a to 58% (Table 1, entry 3). The enantiomeric excess of trans-2a was estimated to be 95% by HPLC analysis, which was the same ee level of precursor 1a. Thus, no epimerization at the C3 chiral center occurred during the reaction. The stereoselectivity was improved to 8:2. The stereoselectivity was sensitive to the reaction temperature, and an 86/14 mixture of trans-2a and cis-2a was obtained when the reaction was performed at 0 °C, although the yield was less than that obtained when the reaction was performed at room temperature (Table 1, entry 4).

Having determined the optimized reaction conditions, we examined the generality of the reaction. The results are summarized in Table 2.

For example, the reaction of 1b smoothly occurred, giving bicyclic dihydrosilole 2b in 60% yield. HPLC analysis of the reaction mixture revealed that the diastereomeric ratio of 2b was 84/16. Dihydrosiloles 2c–2j were isolated in good yields from other precursors in a trans-selective manner (Table 2, entries 2–9). Their diastereomeric ratios ranged from 9/1 to 7/3. Although we could not determine the enantiomeric excesses for some compounds of 2 because of insufficient separation by chiral HPLC analyses using ChiralPak ID and IC (Table 2, entries 1, 2, and 4), the enantiomeric excesses of most of products 2 were high, and their original values were maintained (Table 2, entries 3, 5, 6, 8, and 9). Interestingly, significant epimerization occurred during the reaction of 1h; the enantiomeric excess of 2h was only 68% ee (Table 2, entry 7).

The configuration of 2 was determined in the following manner: The major isomer of 2a was highly crystalline, which allowed the performance of X-ray crystallography. The observed data clearly showed a trans-2a structure [31]. The ORTEP structure of major 2a, which unambiguously indicates a trans configuration, is shown in Figure 1. The ^1H NMR spectra of trans-2a and other major 2 showed similar trends, and trans configurations for other major 2 were determined unambiguously.

Unfortunately, none of the minor 2 formed suitable crystals, which precluded X-ray analysis of the minor isomers. However, their ^1H NMR spectra showed several diagnostic points. For example, the tert-butyl group in the ester at the C3a position in minor 2a appeared at 1.17 ppm; this peak was substantially shifted toward higher field than that of trans-2a. Compared with X-ray data for the sulfur analogue of cis-2a, the tert-butyl ester group is located above the aromatic ring at C3, and expected to introduce an anisotropic effect that subsequently causes a high-field

<table>
<thead>
<tr>
<th>Entry</th>
<th>Initiator (equiv)</th>
<th>Temp (°C)</th>
<th>2a: Yield (%)(^a)</th>
<th>trans/cis(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AIBN (0.1)</td>
<td>110</td>
<td>14</td>
<td>n/a</td>
</tr>
<tr>
<td>2</td>
<td>AIBN (1.0)</td>
<td>110</td>
<td>39</td>
<td>69/31</td>
</tr>
<tr>
<td>3</td>
<td>Et_3B (3.0)</td>
<td>25</td>
<td>58</td>
<td>80/20 (95)%</td>
</tr>
<tr>
<td>4</td>
<td>Et_3B (3.0)</td>
<td>0</td>
<td>48</td>
<td>86/14</td>
</tr>
</tbody>
</table>

\(^a\)Isolated yield. \(^b\)Determined by HPLC analyses. \(^c\)Enantiomeric excess for trans-2a. Determined by chiral HPLC analysis using ChiralPak ID.
Table 2: Preparation of pyrrolidinodihydrosiloles 2.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>Product</th>
<th>Yield (^a) (%)</th>
<th>trans/cis (^b)</th>
<th>ee for trans-2 (^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-MeC₆H₄</td>
<td>2b</td>
<td>60</td>
<td>84/16</td>
<td>nd (^d)</td>
</tr>
<tr>
<td>2</td>
<td>4-MeC₆H₄</td>
<td>2c</td>
<td>53</td>
<td>91/9</td>
<td>nd (^d)</td>
</tr>
<tr>
<td>3</td>
<td>4-MeOC₆H₄</td>
<td>2d</td>
<td>42</td>
<td>86/14</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td>3-ClC₆H₄</td>
<td>2e</td>
<td>42</td>
<td>71/29</td>
<td>nd (^d)</td>
</tr>
<tr>
<td>5</td>
<td>4-ClC₆H₄</td>
<td>2f</td>
<td>51</td>
<td>81/19</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>4-FC₆H₄</td>
<td>2g</td>
<td>61</td>
<td>80/20</td>
<td>97</td>
</tr>
<tr>
<td>7</td>
<td>4-CF₃C₆H₄</td>
<td>2h</td>
<td>61</td>
<td>80/20</td>
<td>68</td>
</tr>
<tr>
<td>8</td>
<td>2-thienyl</td>
<td>2i</td>
<td>48</td>
<td>75/25</td>
<td>98</td>
</tr>
<tr>
<td>9</td>
<td>2-naphthyl</td>
<td>2j</td>
<td>51</td>
<td>81/19</td>
<td>99</td>
</tr>
</tbody>
</table>

\(^a\)Isolated yield. \(^b\)Determined by HPLC analyses. \(^c\)Determined by HPLC analyses with a Chiral-Pak-ID. \(^d\)Not determined owing to insufficient separation by chiral HPLC analyses with ChiralPak ID and IC.

Figure 1: ORTEP structure of trans-2a.

To explore the reaction mechanism, we examined the reaction of 1a without additional solvents (Scheme 1).
The treatment of 1a, (Me$_3$Si)$_3$SiH, and Et$_3$B in hexane under an air atmosphere gave 2a in 72%. To our surprise, this yield was better than that of the reaction performed under the usual conditions. We expected that *exo*-methylenepyrrrolidine 4 would be a side product under these conditions, and we indeed detected an *exo*-methylene compound in 5% yield in the reaction mixture. However, NMR spectra and HRMS results indicated that the isolated product was compound 3, which contained a Me$_3$SiCH$_2$- group instead of a (Me$_3$Si)$_3$SiCH$_2$- group. These results suggest that Me$_3$Si radicals were generated during the cascade reaction, and that a small part of the radical was subsequently trapped by 1 under such conditions.

We believe this process progressed in a similar manner to our previously investigated reaction that involved tributyltin radicals [15]. A plausible reaction mechanism is depicted in Scheme 2.

The (Me$_3$Si)$_3$Si radical attacks the β-carbon of the α,β-unsaturated ester in 1, and α-carbonyl radical A is generated. Intermediate A undergoes radical cyclization in a 5-*exo-dig* mode giving vinyl radical intermediate B, which is potentially reactive for attacking the silyl group in an S$_{hi}$ manner to give a Me$_3$Si radical and 2. The process from B to 2 should be very rapid. Giese and co-workers have reported that the reaction rate for a similar S$_{hi}$ process reaches 2.4 × 10$^5$ s$^{-1}$ at 80 °C [25]. Although most of the Me$_3$Si radicals undergo hydrogen abstraction from (Me$_3$Si)$_3$SiH to yield a new (Me$_3$Si)$_3$Si radical and Me$_3$SiH, a small fraction of the Me$_3$Si radicals compete to attack 1; a similar cascade reaction progresses consequently, and compound 3 is formed in 5% yield under very high concentration conditions. We assume that compound 4 was not detected in the reaction product under such conditions for two reasons: first, as previously mentioned, the S$_{hi}$ process from intermediate B to 2 is very rapid, and the process occurs faster than intermolecular hydrogen abstraction from (Me$_3$Si)$_3$SiH, even under high concentration conditions. Second, the addition rate of (Me$_3$Si)$_3$Si radicals to alkenes should be relatively slow; the rate competes with the addition rate of Me$_3$Si radicals to alkenes. This reason is supported by the results that indicated the yield of 2a to be much improved under high (Me$_3$Si)$_3$SiH concentration conditions because the addition rate should be accelerated as the concentration of (Me$_3$Si)$_3$SiH increased.

We examined whether a germyl radical might undergo a similar reaction with 1. Treatment of 1 with Et$_3$GeH in the presence of Et$_3$B, however, failed in the formation of the corresponding compound 5. This failure was probably because a carbon–germanium bond, which is supposed to be stronger than a Si–Si bond, was never cleaved under these conditions (Scheme 3). Another possibility of this failure might be that the addition rate of a triethylgermyl radical to enyne 1a was slow and less efficient.

**Conclusion**

In conclusion, we have successfully converted chiral enyne compounds 1, which were readily available from an asymmetric aza-Morita–Baylis–Hillman equivalent reaction, into
bicyclic pyrrolidinodihydrosiloles 2 in good yields. These reactions progressed in a highly stereoselective manner. Further application of the present silole synthesis is now underway in our laboratory.

**Experimental**

**General methods:** All $^1$H and $^{13}$C NMR spectra were recorded on a JEOL JNM-ECA500 Delta2 (500 MHz for $^1$H, 126 MHz for $^{13}$C) spectrometer. All the reactions in this study were performed under nitrogen atmosphere unless otherwise noted. CH$_2$Cl$_2$ was dried over CaH$_2$, and distilled under nitrogen before use. High-resolution mass spectra (HRMS) were measured at the Tokiwa Instrumentation Analysis Center, Yamaguchi University.

**Preparation of (3$S$)-**-**tert-**-**butyl 3-phenyl-2-tosyl-5,5-bis(trimethylsilyl)-1,2,3,3a,4,5-hexahydrosilolo[3,4-c]pyrrole-3a-carboxylate (2a).** A solution of 1a (85 mg, 0.201 mmol, 95% ee), (Me$_3$Si)$_2$SiH (0.06 mL, 0.195 mmol), and Et$_2$B (1.0 M in hexane, 0.60 mL, 0.60 mmol) in toluene (20 mL) was stirred at room temperature under air for 15 min. Et$_3$B (3 equiv), air, 25 °C to be 95% ee; 1$^\alpha$c,2,3,3a,4,5-hexahydrosilolo[3,4-c]pyrrole-3a-carboxylate (2a). Pale yellow oil; [$\alpha$]$_D$ +97.3 (c 0.27, CHCl$_3$); $^1$H NMR (500 MHz, CHCl$_3$) $\delta$ 7.63 (d, $J = 7.8$ Hz, 2H), 7.75–7.50 (m, 2H), 7.33–7.22 (m, 5H), 5.51 (s, 1H), 4.60 (d, $J = 14.3$ Hz, 1H), 4.23 (s, 1H), 4.11 (dd, $J = 14.3$, 1.6 Hz, 1H), 2.39 (s, 3H), 2.00 (d, $J = 12.8$ Hz, 1H), 1.17 (s, 9H), 0.92 (d, $J = 15.0$ Hz, 1H), 0.04 (s, 9H), −0.11 (s, 9H); $^{13}$C NMR (126 MHz, CHCl$_3$) $\delta$ 169.5, 157.8, 143.8, 138.1, 133.1, 129.9 (2C), 128.0 (2C), 127.7 (2C), 127.7, 127.1 (br, 2C), 122.8, 82.1, 75.2, 72.5, 53.7, 27.9 (3C), 21.6, 17.4, 0.3 (3C), −1.4 (3C); HRMS–ESI (positive mode; M + Na) $m/z$ 622.2292, calcd for C$_{30}$H$_{45}$NaO$_4$SSi$_3$, 622.2275.

**Preparation of 2a under no solvent conditions (Scheme 3, near condition).** A solution of 1a (85 mg, 0.201 mmol), (Me$_3$Si)$_2$SiH (0.07 mL, 0.228 mmol), and Et$_2$B (1.0 M in hexane, 0.60 mL, 0.60 mmol) was stirred at room temperature for 15 min under air. The reaction mixture was concentrated in vacuo, and the yellow residue was purified by flash chromatography (silica gel/hexane–EtOAc 15/1 to 10/1, v/v) to give 2a in 58% yield (70.2 mg, 0.117 mmol). The two diastereomers, trans-2a and cis-2a, were separated by further careful chromatography.

(3$S$,3aR)-**tert-**-**butyl 3-phenyl-2-tosyl-5,5-bis(trimethylsilyl)-1,2,3,3a,4,5-hexahydrosilolo[3,4-c]pyrrole-3a-carboxylate (trans-2a).** White solid; mp 144–145 °C; [$\alpha$]$_D$ −31.8 (c 0.68, CHCl$_3$); the enantiomeric purity was determined by HPLC analysis, $t_R$ 10.0 min (major), $t_R$ 11.5 min (minor) [CHIRALPAK ID (0.46 cm × 25 cm), hexane/iPrOH, 95/5, 40 °C, 1.0 mL/min] to be 95% ee; $^1$H NMR (500 MHz, CHCl$_3$) $\delta$ 7.32 (d, $J = 8.2$ Hz, 2H), 7.26 (s, 3H), 7.24–7.07 (m, 2H), 7.03 (d, $J = 7.8$ Hz, 2H), 5.86 (s, 1H), 5.23 (s, 1H), 4.42 (d, $J = 13.0$ Hz, 1H), 3.95 (d, $J = 13.0$ Hz, 1H), 2.32 (s, 3H), 1.51 (s, 9H), 1.15 (d, $J = 14.9$ Hz, 1H), 0.50 (d, $J = 14.8$ Hz, 1H), 0.07 (s, 9H), −0.20 (s, 9H); $^{13}$C NMR (126 MHz, CHCl$_3$) $\delta$ 173.9, 157.6, 142.6, 138.6, 137.1, 129.1 (2C), 128.3 (br, 4C), 127.5, 127.0 (2C), 124.2, 82.3, 71.1, 69.7, 50.5, 28.0 (3C), 21.5, 12.2, −0.3 (3C), −0.9 (3C); HRMS–ESI (positive mode; M + Na) $m/z$ 622.2282, calcd for C$_{30}$H$_{45}$NaO$_4$SSi$_3$, 622.2275.

(3$S$,3aS)-**tert-**-**butyl 3-phenyl-2-tosyl-5,5-bis(trimethylsilyl)-1,2,3,3a,4,5-hexahydrosilolo[3,4-c]pyrrole-3a-carboxylate (cis-2a).** Pale yellow oil; [$\alpha$]$_D$ +3.0 (c 0.01, CHCl$_3$); $^1$H NMR (500 MHz, CHCl$_3$) $\delta$ 7.20–7.09 (m, 5H), 7.00–6.94 (m, 4H), 5.36 (s, 1H), 5.21 (t, $J = 1.8$ Hz, 1H), 5.14 (dd, $J = 2.7$, 1.5 Hz, 1H), 4.36 (dt, $J = 13.0$, 2.5 Hz, 1H), 3.90 (dt, $J = 13.0$, 1.5 Hz, 1H), 2.29 (s, 3H), 1.50 (s, 9H), 0.90 (d, $J = 14.6$ Hz, 1H), 0.48 (d, $J = 14.7$ Hz, 1H), −0.13 (s, 9H); $^{13}$C NMR (126 MHz, CHCl$_3$) $\delta$ 172.4, 148.8,
142.4, 138.2, 136.7, 129.0 (4C), 128.1 (2C), 127.8, 127.0 (2C),
110.0, 82.4, 70.2, 61.0, 51.5, 27.9 (3C), 21.5, 19.6, 0.7 (3C);
HRMS–ESI (positive mode; M + Na) m/z 522.2108, calcd for
C_{27}H_{37}NNaO_2S_{11}, 522.2110.

Supporting Information

Supporting Information File 1
Experimental procedures and \(^1\)H and \(^{13}\)C NMR spectra.
[http://www.beilstein-journals.org/bjoc/content/
supplementary/1860-5397-9-149-S1.pdf]

Supporting Information File 2
CIF data for trans-2a.
[http://www.beilstein-journals.org/bjoc/content/
supplementary/1860-5397-9-149-S2.cif]

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31. Crystallographic data (excluding structure factors) for the structures of trans 2a have been deposited with the Cambridge Crystallographic Data Centre under supplementary publication numbers CCDC 931894. Copies of the data can be obtained, free of charge, upon request from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or email: deposit@ccdc.cam.ac.uk].