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## Remarkable Effect of a Silicon Group on the Stereoselectivity of Radical *5-exo-*Trig Cyclizations

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Sulfonyl radical mediated 5-exo-trig cyclization of chiral 3-silylhepta-1,6-dienes has been shown to provide cyclopentanes having up to four stereogenic centers with an unexpectedly high level of stereocontrol.

Five-membered-ring carbocycles are a common structural unit in natural products of biological interest and can be assembled in a number of ways (i.e. 1-2, Scheme 1).<sup>1</sup> We



recently started an investigation on the construction of polysubstituted cyclopentane skeletons of type **3**, based on the cyclization of dienes **4** having a chiral allylsilane moiety.

Our strategy relied on a sequential tosyl radical addition, 5-exo-trig cyclization,  $\beta$ -fragmentation. This process is known to provide five-membered-ring skeletons under mild conditions with generally high efficiency.<sup>2</sup> Excellent control of the C1–C2 relative configuration is usually observed but the control of the C2–C3 configuration has remained a challenging task to achieve.<sup>3</sup>

A few examples on the application of this strategy to the synthesis of heterocyclic analogues have been reported, effectively revealing that only low to moderate levels of stereocontrol could be attained.<sup>3</sup> Recent studies on intermolecular radical functionalization of chiral allylsilanes, however, convinced us that a silicon group at the stereogenic center might be a decisive element for the stereocontrol in this radical process.<sup>4</sup> So far, to our knowledge, this issue has not been addressed. We describe here our preliminary

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results on the sulfonyl radical cyclizations of chiral allylsilanes such as **4**, and demonstrate that this approach provides an efficient and highly stereocontrolled access to polysubstituted five-membered-ring carbocycles **3**.

Chiral racemic allylsilanes were easily prepared by using the following sequences. For instance, 1,6-diene **8** was prepared in 6 steps from allylsilane **5** (Scheme 2). Metalation



of **5** and coupling with oxetane afforded an inseparable 2:1  $\alpha/\gamma$  mixture<sup>5</sup> of alcohols **6** which were directly oxidized into the corresponding aldehydes. Separation of the major aldehyde followed by Wittig-Horner olefination and reduction of the resulting  $\alpha,\beta$ -unsaturated ester with DIBAH led to the allylic alcohol, which was protected as its acetate **7**. Palladium-catalyzed sulfonylation<sup>6</sup> of **7** finally led to the required (*E*)-allylic sulfone **8**.

A second model **12**, having an additional stereogenic center, was prepared starting from vinylsilane  $9^7$  (Scheme 3). **9** was submitted to Johnson–Ireland rearrangement to provide the  $\beta$ -silylester **10**.<sup>8</sup> The enolate of **10** was then alkylated with (*E*)-1,4-dibromobut-2-ene to give a unique



diastereomer *anti*-11,<sup>9</sup> which was sulfonylated as above, affording the required allylic sulfone 12 in reasonable yield as a unique stereoisomer.

We first investigated the radical cyclization by treating allylsilane 8 with a catalytic amount of p-TolSO<sub>2</sub>SePh in the presence of AIBN (Table 1, entry 1). A mixture of two





entry	diene	solvent	<i>T</i> (°C)	time (h)	$13/14^{d}$	yield <sup>e</sup> (%)
1	8	C <sub>6</sub> H <sub>6</sub>	<b>80</b> <sup>a</sup>	10	86:14	69
2	8	$C_6H_6$	16	4	96:4	77
3	8	$CCl_4$	-15	2.5	98:2	85
4	8	CHCl <sub>3</sub>	$-50^{b}$	0.5	> <b>99:</b> <1	85
5	12	$CHCl_3$	$-50^{b}$	0.5	95:5	72
6	12	$CH_2Cl_2$	- <b>78</b> <sup>c</sup>	3.5	>99:<1	56

<sup>*a*</sup> AIBN was used as initiator. <sup>*b*</sup> 0.25 equiv of *p*-TolSO<sub>2</sub>SePh. <sup>*c*</sup> 0.5 equiv of *p*-TolSO<sub>2</sub>SePh. <sup>*d*</sup> Ratio estimated from GC analysis of the crude reaction mixture. <sup>*e*</sup> Yield of isolated major diastereomer.

diastereomers **13a** and **14a** was thus obtained in a reasonable yield with moderate diastereocontrol. <sup>1</sup>H NMR (NOESY) of the purified products showed that the major isomer **13a** had the C1–C2–C3 trans-cis stereochemistry, while the minor **14a** had the trans-trans stereochemistry, indicating that, as expected, the C1–C2 relative configuration was totally controlled during the process. A better yield and selectivity was then obtained at room temperature, by irradiation of the mixture with a sunlamp (entry 2). Lowering the temperature and using CHCl<sub>3</sub> or CH<sub>2</sub>Cl<sub>2</sub> as solvents eventually led to a complete control of the stereochemistry of the three stereogenic centers, with only the isomer **13a** detectable by GC analysis (entry 4). Parallel studies were performed on substrate **12** which showed a similar behavior. Cyclopentane

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**13b** having four contiguous stereocenters was obtained as a unique stereoisomer when irradiation was performed at -50 or -78 °C (entries 5 and 6).<sup>10</sup> Interestingly, cyclizations of **8** and **12** were complete within 0.5 h at -50 °C, leading to high yield of the cyclized products, in contrast with literature reports on similar cyclizations, where long reaction times are usually observed (vide infra).

We then extended our study to simple acyclic precursors **15** and **17**,<sup>11</sup> to test the generalization of the strategy to other allylic systems (Scheme 4). Surprisingly, **15** led, after 14 to



24 h, to a mixture of four stereoisomers in good yield but with low stereocontrol.<sup>12</sup> When the reaction was performed at lower temperature (-78 °C), only traces of the cyclized product **16** were observed after 8 h of irradiation. On the opposite side, allylic alcohol **17** afforded, after 2 h at -50 °C, a mixture of cyclopentanes **18a,b** in reasonable yield but again with modest diastereocontrol. Interestingly, the allcis isomer **18a** was obtained as the major isomer, thus providing an access to the complementary stereochemistry to that of the silylated analogues.<sup>13</sup>

We thus noticed that under analogous conditions, cyclization of allylsilanes **8** and **12** was faster than that of analogues having a methyl, a hydroxy, or simply no allylic substituent. This may be mainly attributed to the known reactivity of allylsilanes toward electrophiles.<sup>14</sup> *p*-TolSO<sub>2</sub> radical is electrophilic in nature and is thus likely to react efficiently with electron-rich allylsilanes.

Stereocontrol in these 5-exo-trig cyclizations is usually rationalized by using Beckwith–Houk transition state mod-

els.<sup>15</sup> Applied to our case, these models effectively provide a good basis for understanding the sense of the stereoinduction (Figure 1). The major isomer is likely to be formed



Figure 1. Beckwith–Houk transition state models for 5-exo-trig cyclization of 8, 12, and 17.

through a chairlike transition state A, in which the bulky silicon group prefers the pseudoequatorial position. The minor isomer could then be formed through a boatlike TS **B**, which is higher in energy due to higher torsional strain.<sup>16</sup> Interestingly, the electron-rich C-Si bond is nearly aligned with the incipient C-C bond and is thus able to stabilize the partial positive charge developing at the  $\beta$ -center. This is reminiscent of the well-known  $\beta$ -silicon effect<sup>17</sup> and may explain both the unusual rate and the level of stereocontrol of the process. Steric and electronic effects would thus reinforce one another in cyclizations of models 8 and 12 having an allylic silicon group. Electronic effects are probably operating in the case of alcohol 17. Major cyclopentane 18a is likely to be formed through a TS similar to A, in which the OH group at C2 would prefer the pseudoaxial position to avoid destabilizing interactions between the C2–O bond and the partial positive charge developing at C1.18

Finally, cyclopentanes **13** can be elaborated further in a simple way, using the pendant olefinic moiety and the sulfonyl function. This is illustrated below with the efficient preparation of the tricyclic ketone **19** (Scheme 5). Alkylation

<sup>(10)</sup> Best results were obtained at -50 °C, using 0.25 equiv of *p*-TolSO<sub>2</sub>-SePh (entries 4 and 5). As shown in entry 6, use of 0.5 equiv of *p*-TolSO<sub>2</sub>-SePh at -78 °C slightly increased the diastereoselectivity, but at the expense of the yield.

<sup>(11)</sup> **15** and **17** were prepared in 6 and 4 steps from (R)-(-)-citronellene and hexa-1,5-diene, respectively (see Supporting Information).

<sup>(12)</sup> Cyclization of the achiral analogue of 15, lacking the allylic Me group, provided a 3:1 cis/trans ratio at best, in good agreement with earlier reports.<sup>2</sup>

<sup>(13)</sup> A silicon group may be used as a masked hydroxy group, see: Jones, G. R.; Landais, Y. *Tetrahedron* **1996**, *52*, 7599–7662.

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<sup>(16)</sup> Boatlike conformation  $\mathbf{B}$  with a SiR<sub>3</sub> group in the pseudoequatorial position has been preferred over a chairlike conformation with the bulky silicon group in the pseudoaxial position.

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<sup>(18)</sup> In TS A, a pseudoequatorial  $\sigma_{C2-H}$  bond, which is a better electron donor than the  $\sigma_{C-O}$  bond would be aligned with the incipient C–C bond and thus stabilize more efficiently the developing positive charge at C1.



of **13a** with a TMS-protected propargylic bromide led to the desired enyne as a mixture of two stereoisomers. Pauson–Khand cyclization<sup>19</sup> of the resulting enynes led in turn to ketone **19**, with the stereochemistry as shown (NOESY), as a 3:1 mixture of diastereomers.<sup>20</sup>

In summary, we have demonstrated that tosyl radical sequential addition -5-exo-trig cyclization  $-\beta$ -fragmentation

of allylsilanes such as **8** and **12** provides an efficient and highly stereocontrolled access to polysubstituted cyclopentanes. This work illustrates further the unique role of a silyl group in the control of the stereochemistry of radical processes.<sup>4,21</sup> Cyclizations of related substrates having different substituents on the chain are currently underway. Application of this methodology to the synthesis of natural products is also in progress and will be reported in due course.

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**Supporting Information Available:** Representative experimental procedures including product characterization, preparation, and cyclizations of precursors **8**, **12**, **15**, and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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<sup>(20)</sup> Removal of the sulfonyl group led to a single isomer, indicating that stereochemistry at the ring junction is totally controlled during the Pauson–Khand reaction.

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