

## CHEMOSELECTIVITY OF THE INTRAMOLECULAR RADICAL ADDITION BETWEEN TRIPLE AND DOUBLE BOND.<sup>1</sup>

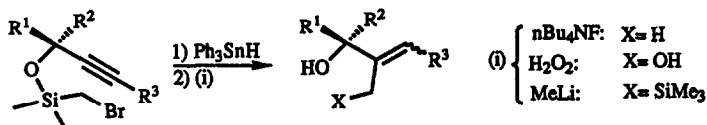
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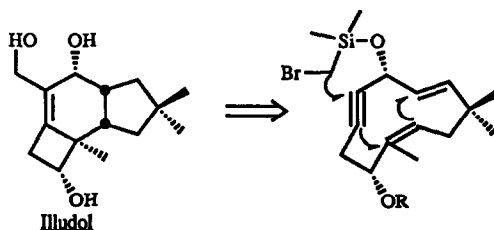
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**Abstract:** Intramolecular radical cyclization of (bromomethyl)dimethylsilyl propargyl ethers containing both double and triple bond at the  $\alpha$  and  $\alpha'$  positions is chemoselective at the triple bond.

We have recently reported a new radical cyclization of (bromomethyl)dimethylsilyl propargyl ethers leading regio- and stereoselectively to the construction of functionalized di- and trisubstituted double bonds.<sup>2,3</sup>



We are currently investigating the possibilities of using this reaction to initiate, via the generation of a vinyl radical intermediate, transannular radical cyclizations with the aim of building up in one step the basic tricyclic skeleton of the sesquiterpene diol illudol.<sup>4</sup>

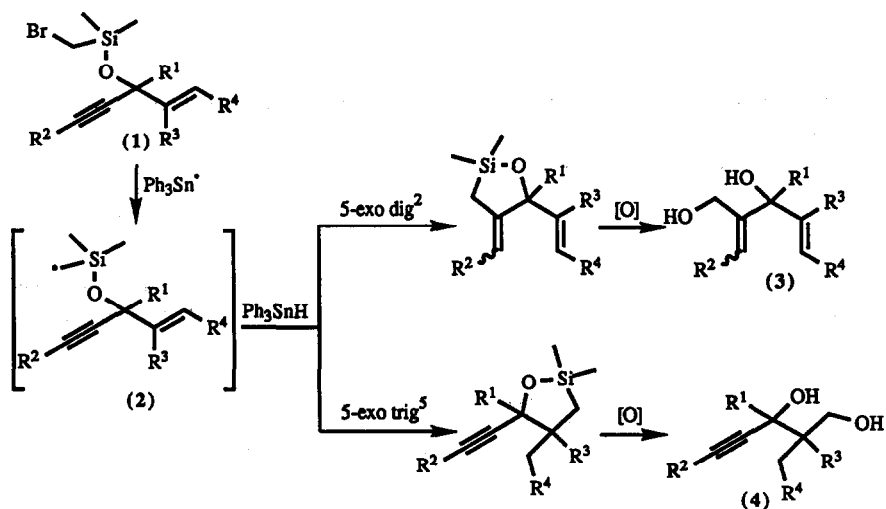


For this purpose, we needed to start from a compound containing both double and triple bond at the  $\alpha$  and  $\alpha'$  positions. In such a system, several modes of cyclization processes may occur either at the double bond or the triple bond.<sup>5</sup> For the success of our synthetic plan, the initial cyclization of the  $\alpha$ -silyl radical (2) must occur

totally chemoselective at the triple bond. We have now studied this chemoselectivity with variously substituted substrates (1).<sup>6</sup>

The reaction was carried out in refluxing benzene using triphenyltin hydride as chain transfer agent and azobisisobutyronitrile as radical initiator; after completion of the reaction the mixture of very sensitive heterocycles was in situ oxidized according to the Tamao procedure.<sup>7</sup>

The representative results are summarized in Table. Compound (1a) led to a mixture of (3a) and (4a) in a 65/35 ratio indicating a slight selectivity in favor of the triple bond when no substituent is present on the unsaturated framework. This result was surprising since intermolecular additions to isolated alkenes and alkynes either show no selectivity or are faster with the alkenes.<sup>8</sup>



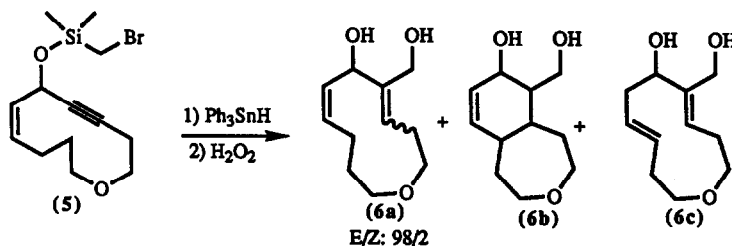
Moreover, the presence of substituents like phenyl or trimethylsilyl, either on the terminal position of the triple or the double bonds, able to stabilize an  $\alpha$  radical, does not change significantly the selectivity (entries 1b, 1d, 1e). These results showed clearly this reaction not to be under thermodynamic control. In contrast, when alkyl chain substituents are present at the terminal carbon of both unsaturations (R<sup>2</sup> and R<sup>4</sup>), the chemoselectivity was very slightly increased to a 76:24 ratio showing a steric influence in the orientation of the cyclization (entry 1c). Finally, the chemoselectivity was dramatically increased in the case of (1f) and (1g) where a methyl substituent is present on the internal position of the double bond (R<sup>3</sup>), whatever was the substitution of the triple bond. The steric hindrance of the methyl group is sufficient to suppress the approach of the  $\alpha$ -silyl radical toward the double bond. Even in that case, no product resulting from a 6-endo trig process was detected,<sup>5</sup> (3f) and (3g) were the only compounds isolated. These results showed that the stabilization of the radical intermediates was without influence on the orientation of the cyclization. The fair chemoselectivity observed can only be explained by a steric control on the approach of the initial radical to the unsaturations.

Entries	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	(3) (%) <sup>9i</sup>	(4) (%) <sup>9</sup>	yield (%) <sup>ii</sup>
1a	Me	H	H	H	65	35	69
1b	H	Ph	H	Ph	66	34	61
1c	H	nC <sub>5</sub> H <sub>11</sub>	H	nC <sub>4</sub> H <sub>9</sub>	76	24	63
1d	Me	SiMe <sub>3</sub>	H	H	64	36	42 <sup>9</sup>
1e	H	Ph	(-CH <sub>2</sub> ) <sub>4</sub> -		70	30	67
1f	H	Ph	Me	H	100	0	67
1g	H	nC <sub>5</sub> H <sub>11</sub>	Me	H	100	0	67

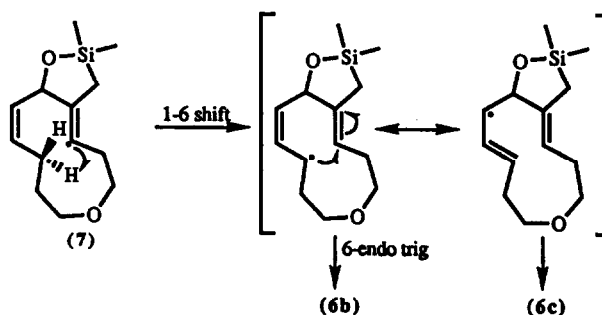
i) E/Z ratio of the newly formed double bond for (3b) to (3g) ranged from 7/3 to 9/1.

ii) Isolated yield after flash chromatography over silica gel with diethylether as eluent.

As in our synthetic plan the enyne framework is part of an eleven membered ring we then decided to study the influence of such a situation in a model compound. The heterocycle (5) was efficiently prepared<sup>10</sup> and was submitted under the radical cyclization condition. Three products were isolated (6a) (56%), (6b) (16%) and (6c) (9%), all resulting from an initial addition to the triple bond.<sup>9</sup>



To explain the formation of (6b) and (6c), we must invoke a 1,6-hydrogen shift involving the vinyl radical intermediate (7) to give an allyl radical intermediate which either reacts with Ph<sub>3</sub>SnH to yield (6c) or gives a 6-endo cyclization process leading finally to (6b).



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## References and Notes:

1. Part IV; Part III: M.Journet, E.Magnol, M.Malacria, submitted for publication.
2. E.Magnol, M.Malacria, *Tetrahedron Lett.*, **27**, 2255 (1986).
3. G.Agnel, M.Malacria, *Synthesis*, 687 (1989).
4. (a) T.Matsumoto, K.Miyamo, S.Kawaga, S.Yu, J.I.Ogawa, A.Ichihara, *Tetrahedron Lett.*, 3521 (1971).  
 (b) M.F.Semmelhack, S.Tomada, K.M.Hurst, *J. Am. Chem. Soc.*, **102**, 7567 (1980).  
 (c) M.F.Semmelhack, S.Tomada, H.Nagaoka, S.D.Boettger, K.M.Hurst, *J. Am. Chem. Soc.*, **104**, 747 (1982).
5. (a) H.Nishiyama, T.Kitajima, M.Matsumoto, K.Itoh, *J. Org. Chem.*, **49**, 2298 (1984).  
 (b) G.Stork, M.Kahn, *J. Am. Chem. Soc.*, **107**, 500 (1985).  
 (c) G.Stork, M.J.Sofia, *J. Am. Chem. Soc.*, **108**, 6826 (1986).  
 (d) G.Stork, R.Mook, *Tetrahedron Lett.*, **30**, 3609 (1989).
6. Alcohols are prepared by reaction of the lithium acetylide with various  $\alpha,\beta$  ethylenic aldehydes in THF at  $-78^\circ\text{C}$ . Yields ranging from 85 to 98%.  
 Silylated ethers are obtained following the Stork procedure (4a). Yields ranging from 67 to 98%.
7. K.Tamao, N.Ishida, T.Tanaka, M.Kumada, *Organometallics*, **2**, 1694 (1983).
8. (a) G.Stork, R.Mook, *Tetrahedron Lett.*, **27**, 4529 (1986).  
 (b) G.Stork, R.Mook, *J. Am. Chem. Soc.*, **109**, 2829 (1987).  
 (c) C.A.Broka, D.E.C.Reichert, *Tetrahedron Lett.*, **28**, 1503 (1987).  
 (d) K.Nazaki, K.Oshima, K.Utimoto, *J. Am. Chem. Soc.*, **109**, 2547 (1987).  
 (e) Y.Watanabe, M.Mitani, T.Morita, S.Ozaki, *J. C. S. Chem. Comm.*, 482 (1989).  
 (f) B.Giese, S.Lachein, *Angew. Chem. Int. Ed. Engl.*, **21**, 768 (1982).  
 (g) B.Giese, J.Meixner, *Angew. Chem. Int. Ed. Engl.*, **20**, 965 (1981).  
 (h) B.Giese, S.Lachein, J.Meixner, *Tetrahedron Lett.*, **21**, 2505 (1980).
9. All the compounds were fully characterized by  $^1\text{H}$  and  $^{13}\text{C}$  NMR, infrared and mass spectroscopy. As an exemple we give a full description of (3c) and (4c).  
 (3c): IR(neat): 3350, 3020, 2980, 1660, 1470, 1380, 970.  $^1\text{H}$ -NMR( $\text{CDCl}_3$ , TMS, 300 MHz): Z isomer: 0.80-0.92(m, 6H); 1.23-1.40 (m, 6H); 1.49-1.67(m, 4H); 2.07-2.24(m, 4H); 4.32(s, 2H); 5.80(t, J=7.0 Hz, 1H); 6.03(d, J=10.1 Hz, 1H); 6.27-6.37(m, 2H). E isomer: 0.80-0.92(m, 6H); 1.23-1.40(m, 6H); 1.49-1.67(m, 4H); 2.07-2.24(m, 4H); 4.30(s,2H); 5.75(t, J=7.0 Hz, 1H); 6.03(d, J=10.1 Hz, 1H); 6.27-6.37(m, 2H).  $^{13}\text{C}$ -NMR( $\text{CDCl}_3$ , TMS: 75.5 MHz): Z isomer: 14.1; 14.3; 22.5; 22.8; 25.9; 31.6; 32.0; 32.9; 36.1; 58.2; 77.5; 123.1; 124.2; 135.2; 140.4. E isomer: 14.1; 14.3; 22.5; 22.8; 25.9; 31.6; 32.0; 32.9; 35.9; 58.4; 77.4; 125.2; 129.8; 138.0; 138.4. MS(70 eV, m/e(%)): 240 ( $\text{M}^+$ , 2); 41(100).  
 (4c): IR(neat): 3350, 2980, 2200, 1470, 1380.  $^1\text{H}$  NMR( $\text{CDCl}_3$ , TMS, 300 MHz): 0.81-0.92(m, 6H); 1.18-1.41(m, 14H); 1.47-1.54(m, 2H); 1.87-1.99(m,1H); 2.23(dt, J=7.0 and 2.0 Hz, 2H); 3.72(dd, J= 10.8 and 3.5 Hz, 1H); 3.91(dd, J= 10.8 and 8.9 Hz, 1H); 4.57(s, 1H).  $^{13}\text{C}$ -NMR( $\text{CDCl}_3$ , TMS, 75.5 MHz): 13.7; 13.8; 18.5; 21.9; 22.3; 26.7; 27.2; 28.2; 30.8; 31.8; 44.8; 64.4; 66.3; 78.5; 86.9. MS(70 eV, m/e (%)): 169 ( $\text{M}^+$ , 1); 55(100).
10. In that case, the non-isolated intermediary oxasilanes are not oxidized but treated by MeLi in THF at  $-78^\circ\text{C}$  to give this mixture of  $\gamma$ -trimethylsilylalcohols.

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