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RADICAL CYCLIZATION OF (BROMOMETHYL)DIMETHYLSILYL PROPARGYL ETHERS REGIOSELECTIVE INTRAMOLECULAR CYCLIZATION OF VINYL RADICALS.[1]

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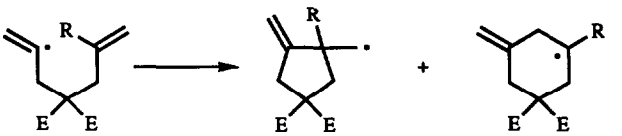
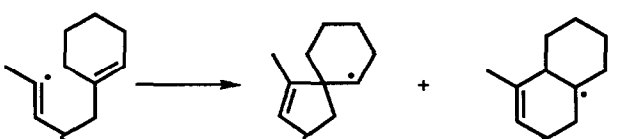
Abstract: Vinyl radical intermediates generated from radical cyclization of (bromomethyl)dimethylsilyl propargyl ethers have been trapped intramolecularly by a double bond leading to functionalized carbocycles with high yield and high regioselectivity.

Radical cyclizations developed in the last ten years represent a new method for C-C bond formation and several reviews have appeared.[2] *External* and *internal* vinyl radical cyclizations have been extensively studied by Stork[3] and Beckwith.[4] Their results clearly demonstrated that a 5-*exo*-cyclization was largely favored over a 6-*endo*-ring closure. Although, this preference may be inverted sterically[3c] (Eq.1,2) or by inducing reversibility[3-6]: high dilution,[3b,4] germanium hydride[5] as mediator or tetramethyl tetrahydrofuran[6] as solvent were found to increase the 6-*endo* product due to rearrangement of the kinetically generated homoallyl radical.



(1)

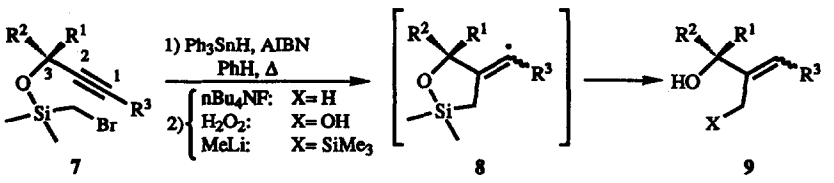
1-*external*	2-*exo*	3-*endo*
1a (R= H)	75%	25%
1b (R= Me)	0%	100%



(2)

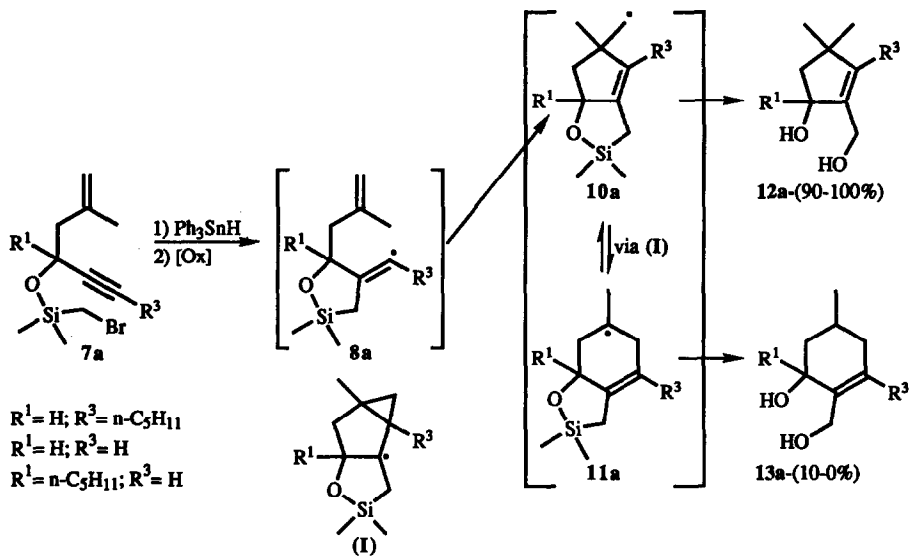
4-*internal*	5-*exo*	6-*endo*
	66%	33%

We have already shown that radical cyclization of different derivatives of 3-[(bromomethyl)dimethylsiloxy]-1-propyne **7** allows the regio- and stereoselective preparation of functionalized double bonds **9** (Scheme 1).[7] The exocyclic vinyl radical **8** involved in this reaction, trapped intramolecularly by a double bond connected to C-1 or to C-3 could be easily used as an access to functionalized carbocycles.



Scheme 1

Radical cyclization of variously substituted derivatives of type **7a** with an alkenyl chain connected to C-3 was studied first (Scheme 2 and Table).



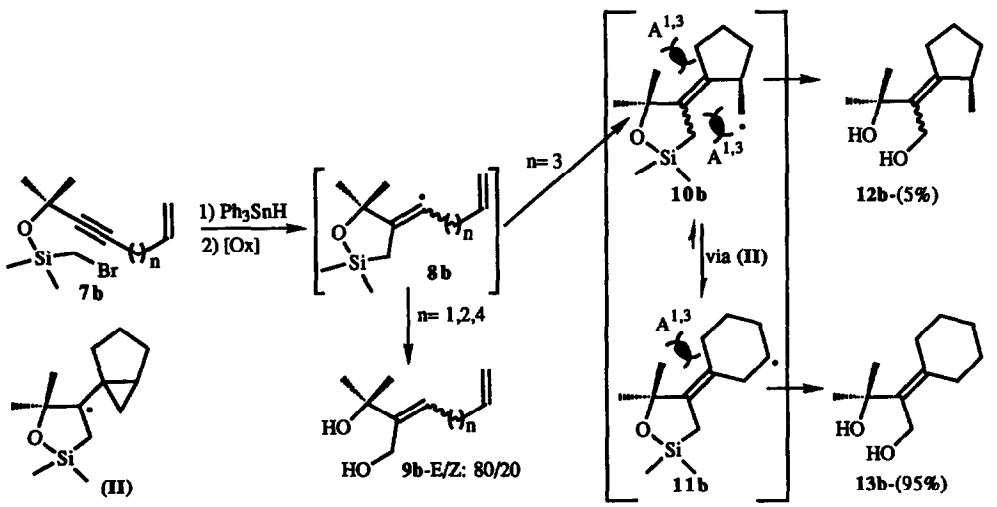
Scheme 2

The best results were observed when a slow addition of the chemical mediator (2.10^{-4}mol/h, 1.1 equiv.) and a catalytic amount of AIBN as initiator were added to the starting material (0.025M) in refluxing benzene. After completion of the reaction, the crude product was subjected to Tamao oxidation (H_2O_2 30%, $KHCO_3$, THF/MeOH 1/1)[8] and the resulting diols were isolated as pure compounds[9] by flash chromatography over silica gel. The radical reactions were conducted at that concentration to avoid the reduction of the stabilized α-silyl radical[10] initially generated. Importantly, when R^1 and R^3 are H or alkyl, the 5-*exo*-ring closure leading to **12a** is 90 to 100% regioselective (entries 1, 2, 3). The steric hindrance of methyl substitution at the site of attack can be completely surmounted. The five-membered transition state with a short carbon-carbon double bond is by far the most favored. Due to shorter C-O versus C-C bond, similar regiocontrol was also observed when radical cyclization afforded an oxygenated membered ring product.[11] In contrast, when R^3=Ph (entry 4), the reaction led to a 42:58 mixture **12a**:**13a**. The increased amount of 6-*endo*-ring closure product **13a** may be due to electronic stabilisation of cyclopropyl radical intermediate (**I**) by the phenyl group since slight faster addition of

the mediator, more concentrated solutions or use of germanium hydride as initiator were without effect on the regioselectivity.

Entries	R^1	R^3	Ratio (%) **12a / 13a**	Overall isolated yield (%)
1	H	$n\text{-}C_5H_{11}$	90 / 10	79
2	$n\text{-}C_5H_{11}$	H	100 / 0	75
3	H	H	100 / 0	65
4	H	Ph	42 / 58	80

Results starting from the (bromomethyl)dimethylsilyl propargyl ethers **7b** with an alkenyl chain connected to C-1 are illustrated in the Scheme 3.



Scheme 3

Radical cyclization of these substrates with an olefinic side chain of various length (n= 1,2,3,4) linked to C-1 afforded cyclic products only from the substrate where n= 3. A 5:95 ratio of the diols **12b**:**13b** has been isolated[9] with 89% overall yield after Tamao oxidation.[8] The selective formation of the rearranged *endo*-compound might be explained by *three* $A^{1,3}$-allylic strains present in intermediate **10b** against only *one* 1,3-allylic interaction in the radical **11b**. This is in our opinion the first example in which the nearly exclusive formation of six-membered ring product is exclusively due to steric hindrance in the transition state. However, when n= 1, 2 and 4 the corresponding (bromomethyl)dimethylsilyl propargyl ethers **7b** only furnish reduction products **9b** with 70% overall isolated yield. These results are in good agreement with the known behavior of α-cyclopropyl, α-cyclobutyl radicals[12] and also with the unfavorable 6-*exo*-*trig*-cyclization process.[13] Furthermore the stereoselective formation of trisubstituted double bonds (E/Z: 80/20) observed for **9b** is in agreement with our previous results.[7]

This study has shown the synthetic utility of system such as **7a** (R^1,R^3= H or alkyl) for the regioselective preparation of functionalized cyclopentenes **12a** in the access to linear and angular triquinanes which is under progress in our laboratory, using tandem cyclizations.

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References and Notes:

1) Part V; Part IV: G. Agnel, M. Malacria, *Tetrahedron Lett.*, in press.

2) (a) B. Giese *"Radicals in Organic Synthesis: Formation of carbon-carbon bonds"* Pergamon Press, Oxford, 1986; (b) D.P. Curran, *Synthesis*, 1988, 417 (part I) and 489 (part II); (c) E.R.Laird, W.L.Jorgensen, *J. Org. Chem.*, 1990, **55**, 9.

3) (a) G. Stork, R. Mook Jr., J. Am. Chem. Soc., 1987, **109**, 2829; (b) G. Stork, R. Mook Jr., *Tetrahedron Lett.*, 1986, **27**, 4529; (c) G.Stok, N.H.Bain, J. Am. Chem. Soc., 1982, **104**, 2321.

4) A.L.J. Beckwith, D.M. O'Shea, *Tetrahedron Lett.*, 1986, **27**, 4525.

5) J. Lusztyk, B. Maillard, S. Deycard, D.A. Lindsay, K.U. Ingold, *J. Org. Chem.*, 1987, **52**, 3509.

6) C.A. Broka, D.E.C. Reichert, *Tetrahedron Lett.*, 1987, **28**, 1503.

7) (a) E. Magnol, M. Malacria, *Tetrahedron Lett.*, 1986, **27**, 2255; (b) G. Agnel, M. Malacria, Synthesis, 1989, 687.

8) K. Tamao, N. Ishida, T. Tanaka, M. Kumada, *Organometallics*, 1983, **2**, 1694.

9) All compounds were fully characterized by ^{1}H and ^{13}C-NMR, infrared, mass spectroscopy and elementary analysis. As an example, we give a full description of **12a** (entry 1) and **13b**.

12a: IR(neat): 3350, 2960, 1660, 1470, 1380, 1100, 1050. ^{1}H-NMR($CDCl_3$, TMS, 300 MHz): 0.88(t, J= 7.0 Hz, 3H); 0.99(s, 3H); 1.12(s, 3H); 1.26-1.35(m, 6H); 1.55(dd, J= 13.1 and 4.8 Hz, 1H); 1.92-1.98(m,2H); 2.07(dd, J= 13.1 and 7.2 Hz, 1H); 4.25(AB, 2H); 4.83(dd, J= 7.2 and 4.8 Hz, 1H). ^{13}C-NMR($CDCl_3$, TMS, 75.5 MHz): 14.1; 22.4; 25.3; 28.4; 28.6; 30.5; 32.5; 45.9; 49.2; 58.2; 76.5; 134.8; 150.9. MS(70 eV, m/e (%)): 212(M^+, 0.36); 29(100). Elementary analysis: calcd: 73.54% C- 11.39% H- found: 73.62% C- 11.44% H.

13b: IR($CHCl_3$): 3600, 2960, 1470, 1380. ^{1}H-NMR($CDCl_3$, TMS, 300 MHz): 1.47(s, 6H); 1.57(br.s, 6H); 2.26-2.34(m, 4H); 4.29(s, 2H). ^{13}C-NMR($CDCl_3$, TMS, 75.5 MHz): 26.8; 28.3; 29.1; 31.4; 32.7; 33.0; 60.1; 74.2; 135.9; 139.8. MS(70 eV, m/e, (%)): 166(M-18, 3.85); 43(100). Elementary analysis: calcd: 71.69% C- 10.94% H- found: 71.74% C- 11.00% H. m.p= 116°C.

10) K. Miura, K. Oshima, K. Utimoto, *Tetrahedron Lett.*, 1989, **30**, 4413.

11) S.P.Munt, E.J.Thomas, *J. Chem. Soc. Chem. Comm.*, 1989,480.

12) (a) F.C. Friedrich, R.L. Holmstead, *J. Org. Chem.*, 1971, **36**, 971; (b) D. Griller, K.U. Ingold, *Acc. Chem. Res.*, 1980, **13**, 317; (c) A.L.J. Beckwith, G. Moad, *J. Chem. Soc. Perkin Trans II*, 1980, 1083.

13) A.L.J. Beckwith, G. Moad, *J. Chem. Soc. Chem. Comm.*, 1974, 472.

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