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Six- versus five-membered ring formation in radical cyclization of 1-vinyl-5-methyl-5-hexenyl radicals

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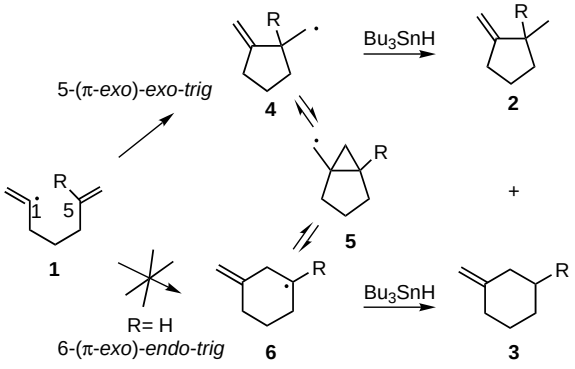
Abstract—Radical cyclization of 1-vinyl-5-methyl-5-hexenyl radicals (radical numbering) affords six-membered ring products prevailing over the isomeric five-membered ring compounds; the former are generated through two reaction pathways: 6-*endo–trig* ring closure and rearrangement of intermediate methylenecyclopentyl radicals obtained by 5-*exo–trig* cyclization.

Since their introduction in 1982,[1] vinyl radical cyclizations have proved to be extremely popular in organic synthesis.[2] Seminal studies by Beckwith and Stork's groups[3,4] have shown that, under tin hydride mediated reaction conditions, vinyl radical cyclization gives a mixture of both 5-*exo* and 6-*endo* products **2a** and **3a**, respectively (Scheme 1). More recently, Crich's group reported the preferential formation of 5-*exo* products when the reaction was conducted in the presence of PhSeSePh.[5] The work by Beckwith and O'Shea[3] revealed that formation of the more stable methylenecyclohexane derivative **3a** is not due to a competing 6-*endo* [6-(π-*exo*)-*endo–trig*][6] cyclization (**1a→6a**), but it is the result of a rapid rearrangement of the methylenecyclopentyl radical, **4a**, via a reversible 3-*exo–trig* cyclization (**4a→5a→6a**). As such, the 5-*exo*:6-*endo* ratio is a function of tin hydride concentration with higher concentrations favoring the kinetic 5-*exo* product **2a**.



Scheme 1.

On the other hand, it is well established that 5-alkyl substituents retard radical cyclization of related 5-hexenyl radicals, so that 6-*endo* cyclization becomes an effective competing reaction (see Scheme 2).[2a,7]

In this communication we describe experiments to answer the question whether the formation of methylenecyclohexane derivative **3b** takes place via 'direct' 6-*endo–trig* cyclization (**1b→6b**) or via the intermediates **4b**, **5b** and **6b** ('formal' 6-*endo* mode[5]).[2b,8]

The yields of products **8**, **9** and **10** (Scheme 3) obtained when bromide, **7**, was heated in toluene in the presence of tributyltin hydride and 2,2′-azobisisobutyronitrile (AIBN) at 80°C are given in Table 1.[9] The same products were also obtained by tin radical-mediated cyclization[10] of 1,6-enyne **11**, followed by protiodestannylation (4:2:1; AcOH, THF, H_2O) (Table 1, entries 2, 5, 8, 11 and 14).[11] The above-mentioned results have been compared with literature data for the cyclization of the corresponding unsubstituted analog, **12**.[4]

Stork and Mook reported cyclization of enyne **12** with 0.02 M Bu_3SnH to give a 1:4 ratio of 5-*exo* and 6-*endo* products **13** and **14**, respectively (Table 1, entry 1). Analogous cyclization of **7** and **11** (0.02 M Bu_3SnH) yielded methylenecyclohexane **9**[12] as the sole observed

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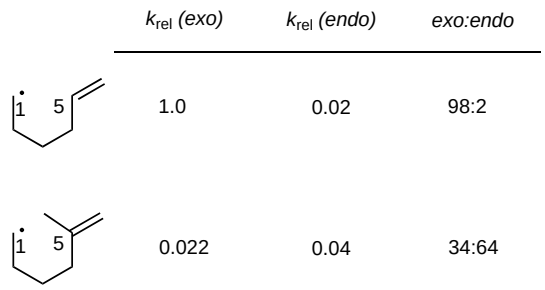
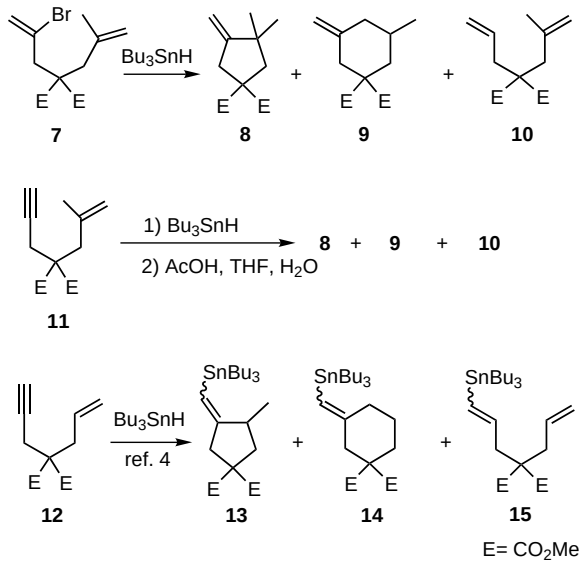


Scheme 2.



Scheme 3.

product (Table 1, entries 2 and 3). Literature data for cyclization of **12** with 0.25 M Bu_3SnH showed a reversal in the regiochemistry, and methylenecyclopentane **13** was obtained as the major isomer (Table 1, entry 4).[4] Conversely, bromide **7**, and enyne **11**, cyclize under similar, or even higher, tin hydride concentration (0.25 and 0.50 M) to give methylenecyclohexane **9** as the major product[13] (Table 1, entries 5 and 6). Radical cyclization of **7** and **11** with 2.2 M Bu_3SnH provided a mixture of **9** and **8**, with the former prevailing (Table 1, entries 11 and 12), whereas cyclization of **12** with the same Bu_3SnH concentration had been reported to yield exclusively the 5-*exo* product, **13** (Table 1, entry 10).

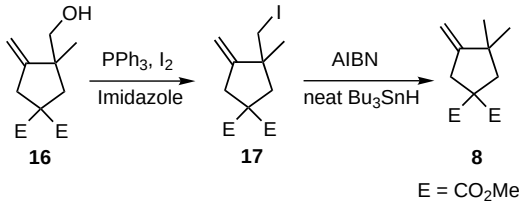
It was also reported that vinyl radical cyclization of **12** took place, even, in neat Bu_3SnH leading to five-membered ring compound, **13**, along with acyclic product, **15** (Table 1, entry 13).[4] When a similar ring closure reaction (neat Bu_3SnH) was conducted on 5-methyl analogs, **7** and **11**, the six-membered ring product, **9**, was obtained as the major isomer (Table 1, entries 14 and 15).

These results (Table 1, entries 13–15) indicate that radical cyclization of methyl substituted compounds **7** and **11** gives predominant 6-*endo* cyclization whereas the hydrogen-substituted analog, **12**, gives only 5-*exo* cyclization. This observation could be interpreted in two different ways: (a) that formation of methylenecyclohexane **9** takes place, partially or completely, by *direct* 6-*endo–trig* cyclization (i.e. **1b→6b**) of **7** and **11**, or (b) that 3-*exo* cyclization of **4b** is significantly faster than 3-*exo*-cyclization of the unsubstituted analog **4a** (R = H) and therefore a pathway, **4b→5b→6b**, could be responsible for the formation of **9**. In the first case the rate of 6-*endo–trig* cyclization of radical **1b** would be faster than the rate of tin hydride transfer, and in the latter the rate of 3-*exo* cyclization of **4b** would prevail over tin hydride transfer.

In order to shed some light on this issue we prepared iodide, **17** (Scheme 4), as a precursor of radical, **4b**, by iodination[14] of hydroxy compound **16**.[15] Treatment of iodide, **17**, under the reaction conditions used in entries 14 and 15 (neat Bu_3SnH), resulted in the exclusive formation of methylenecyclopentane **8**.[16]

This result shows that 3-*exo* radical cyclization of radical **4b** is slower than hydride transfer in neat Bu_3SnH, and by corollary that formation of methylenecyclohexane, **9** (Table 1, entries 14 and 15), had to be explained by *direct* 6-*endo–trig* radical cyclization of radical **1b** (**1b→6b**). In addition, the fact that methylenecyclohexane **9** prevailed over **8**, when the cyclization was conducted in neat Bu_3SnH, seems to indicate that 6-*endo–trig* cyclization of 5-methyl vinyl radicals is slightly faster than the corresponding 5-*exo–trig* ring closure. Under lower tin hydride concentrations the rearrangement **4b→5b→6b** might also take place, therefore it could be assumed that methylenecyclohexane formation in the cyclization of 1-vinyl-5-methyl-5-hexenyl radicals would take place by two different reaction pathways, the *formal* 6-*endo* mode and a *direct* 6-*endo–trig* mode.

In summary, we have shown that in the vinyl radical ring closure of 5-methyl hexenyl radicals, unlike vinyl radical cyclization of 5-unsubstituted substrates, a 'direct' 6-*endo–trig* ring closure is responsible, to a considerable extent, for the regiochemical outcome of the reaction. It is, however, to be emphasized that the regioselectivity control does not rely exclusively in the presence of the methyl group, but that the tin hydride concentration plays an essential role in the observed regiochemistry. From a synthetic standpoint, these results are of interest since they reveal that substituted cyclohexanes can be efficiently prepared by cyclization of 5-alkyl-vinyl radicals. This process is currently being applied to the synthesis of carbasugars[18,19] from carbohydrates and the results will be reported in due course.

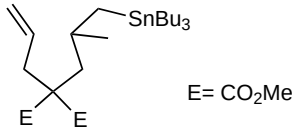


Scheme 4.

Table 1. Radical cyclization of compounds **7**, **11** and **12** under different tin hydride concentrations[4,9,11]

Entry	Substrate	Molar concentration of substrate	Molar concentration of tributyltin hydride	Product ratio, 5-*exo*:6-*endo*	Acyclic products (% yield)	Yield (%)[a]
1 (lit.)[4]	**12**	0.02	0.02	20:80		
2	**11**	0.02	0.02	0:100	–	72
3	**7**	0.02	0.02	0:100	–	65
4 (lit.)[4]	**12**	0.3	0.25	80:20		
5	**11**	0.25	0.5	16:84	–	59
6	**7**	0.3	0.25	15:85	–	75
7 (lit.)[4]	**12**	0.7	0.6	95:5	–	
8	**11**	0.5	0.75	19:81	–	58
9	**7**	0.5	0.75	28:72	14[b]	63
10 (lit.)[4]	**12**	1.9	2.2	100:0		
11	**11**	1.9	2.2	30:70	21[c]	54
12	**7**	1.9	2.3	38:62	13[b]	65
13 (lit.)[4]	**12**	Neat Bu_3SnH	Neat Bu_3SnH	100:0	16	
14	**11**	Neat Bu_3SnH	Neat Bu_3SnH	43:57	28[c]	72
15	**7**	Neat Bu_3SnH	Neat Bu_3SnH	45:55	24[b]	58

[a] Based on isolated compounds.
[b] Yield of isolated **10**.
[c] Compound **10** was not detected but instead a mixture of tin containing products were isolated. The structure shown below had been tentatively assigned to one of the products.



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6. (π-Exo)-vinyl radical cyclizations were defined as vinyl radical cyclization in which the vinyl radical is exocyclic to the ring formed; see: Crich, D.; Fortt, S. M. *Tetrahedron Lett.* **1987**, *28*, 2895.
7. Beckwith, A. L. J.; Ingold, K. U. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic Press: New York, 1980.
8. It has been shown, however, how vinyl radical cyclization may be directed to give a high preference for 6-*endo* cyclization by substituting the 5-position of the alkene with radical stabilizing groups: (a) Urabe, H.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 1355; (b) Munt, S. P.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1989**, 480; (c) Maguire, R. J.; Munt, S. P.; Thomas, E. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2853.
9. *General experimental procedure:* A thoroughly degassed (argon) soln of bromide **7** (85 mg, 0.28 mmol) in toluene (appropriate concentration) was heated to 80°C under argon. A soln of Bu_3SnH (1.6 equiv.) and AIBN (0.1 equiv.) in toluene (appropriate concentration) was then added and the reaction mixture was kept at that temperature over 6 h. After cooling, the organic solvent was evaporated, the residue treated with CCl_4 (0.2 mL) and a dilute soln of iodine in ether until a faint color persisted. The organic solvent was then removed in vacuo, the residue taken up in ethyl acetate, washed with a satd aq. soln of potassium fluoride, dried and evaporated. The reaction mixture was then evaporated, the residue chromatographed (hexane/ethyl acetate; 98:2) and the products ratio determined by ^1H NMR.
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11. *General experimental procedure:* A thoroughly degassed (argon) soln of enyne **11** (224 mg, 1.0 mmol) in toluene was heated at 110°C under argon. A soln of Bu_3SnH (1.5

equiv.) and AIBN (0.1 equiv.) in toluene (to reach the final concentration given in Table 1) was then added and the reaction mixture was kept at that temperature over 6 h. After cooling, the organic solvent was evaporated, the residue was dissolved in a mixture of AcOH/THF/H_2O (4:2:1) (4 mL) and warmed at 85°C, with stirring for 1 h. The reaction mixture was then evaporated and the residue chromatographed (hexane–ethyl acetate; 7:3).

12. The spectral data obtained for compound **9** are in complete agreement with known literature values. See: Ozaki, S.; Horiguchi, I.; Matsushita, H.; Ohmori, H. *Tetrahedron Lett*. **1994**, *35*, 725.
13. The ratio of products (**8**:**9**) was determined by ^{1}H NMR ($CDCl_3$); **9**: 4.74 (s, 2H, =C$\underline{H}_2$), 3.71 (s, 3H, OCH_3), 2.91 (dt, J=13.4, 2.0 Hz, 1H, C$\underline{H}_2$CHCH$_3$); **8**: 4.88 (t, J=2.2 Hz, 1H, =C$\underline{H}_2$), 3.74 (s, 3H, OCH_3), 3.09 (t, J=2.2, 1H, C$\underline{H}$CH$_3$).
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16. An analytical sample of **8** was prepared by deiodination (Zn dust, aq. AcOH, 100°C)[17] of **17**: ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 4.88 (t, 1H, J=2.2 Hz), 4.79 (t, 1H, J=2.2 Hz), 3.74 (s, 6H), 3.09 (t, 2H, J=2.2 Hz), 2.31 (s, 2H), 1.10 (s, 6H). Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.96; H, 8.16.
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