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Highly Stereoselective 6-Exo Ring-Closure of 5-Substituted Hept-6-enyl Radicals

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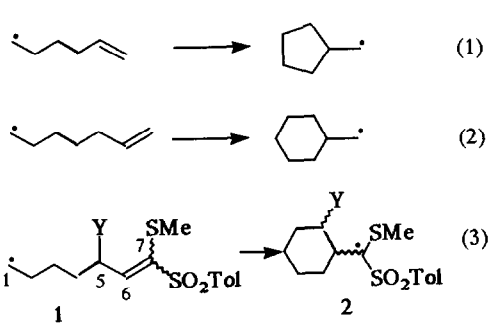
Abstract: 5-Substituted 7-methylthio-7-(*p*-tolylsulfonyl)-6-heptenyl radicals (1) and their 4-oxa derivatives cyclized in 6-exo manner with extremely high 1,2-asymmetric induction leading to trans ring-closure. Transition states for the ring closure are discussed by the experimental results and MO calculations.

Free-radical reactions to form C-C bonds have become important in organic synthesis.[1] Among all the free-radical reactions, hex-5-enyl radical cyclization (eq 1) is the most well-known,[2] and Beckwith proposed general guidelines for the stereochemical outcome of the reaction of simple hex-5-enyl radicals.[3,4] Ring formation by radical cyclizations is not restricted to five-membered rings, but 6-exo closure of hept-6-enyl radicals (eq 2) receives little attention. This is probably because it is slower than the ring closure of hex-5-enyl radicals and because intramolecular abstraction of allylic hydrogen atom occurs via a six-membered transition state. Since introduction of activating groups on the alkene part makes the 6-exo cyclizations efficient[5] and 1-methylthio-1-(*p*-tolylsulfonyl)-1-alkene is a good acceptor of various radicals,[6] our investigation was started on the 6-exo cyclization (eq 3) of 5-substituted 7-methylthio-7-(*p*-tolylsulfonyl)-6-heptenyl radicals (**1**).



To our surprise, no report appeared on substituent effects on the stereochemical course in the 6-exo closure of simple hept-6-enyl radicals except for one special case.[5c] Here we wish to report highly efficient 1,2-asymmetric induction in 6-exo closure of 5-substituted ones (**1**; Y = hydroxyl or alkoxyl) and its related compounds.

A radical precursor, 7-bromo-3-methoxy-1-methylthio-1-(*p*-tolylsulfonyl)-1-heptene (**3a**),[7] was subjected to the usual "tin hydride" method: Treatment of (*E*)-**3a** with tributyltin hydride (1.20 mol equiv) and

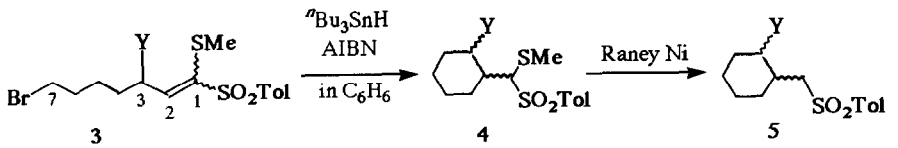
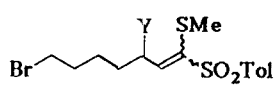
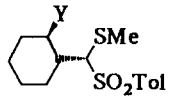
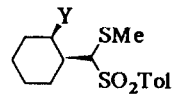
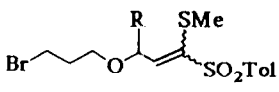
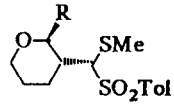
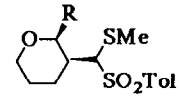
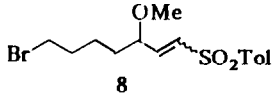
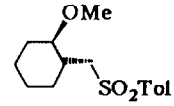
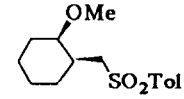
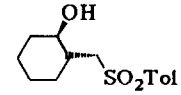


Table 1. Radical Cyclization

entry	starting material			product yield/% (diastereomeric ratio)		selectivity of ring closure
				 + 		
	3			*trans*-4	*cis*-4	
1	**3a**	Y=OMe	E only	81 (73:27)	---	trans only
2	**3a**	Y=OMe	Z only	82 (74:26)	---	trans only
3	**3a**	Y=OMe	E : Z = 45 : 55	99 (75:25)	---	trans only
4	**3b**	Y=O^{i}Pr	Z only	78 (71:29)	---	trans only
5	**3c**	Y=OAc	E : Z = 67 : 33	85 (78:22)	6 [a]	96 : 4
6	**3d**	Y=OH	E : Z = 46 : 54	68 (54:46) [b]	7 (ca. 1 : 1)	92 : 8
7	**3e**	Y=Me	E : Z = 60 : 40	70 (61:39)	---	trans only
				 + 		
	6			*trans*-7	*cis*-7	
8	**6a**	R=Me	E only	97 (60:40)	---	trans only
9	**6b**	R=Ph	Z only	82 (74:26)	---	trans only
				 + 		
	8			*trans*-9	*cis*-9	
10		**8**	E only	50	50	50 : 50
11		**8**	Z only	93	5	94 : 6

[a] Formation of a single isomer was observed.

[b] Desulfurization product (**10**) was also obtained in 9% yield.

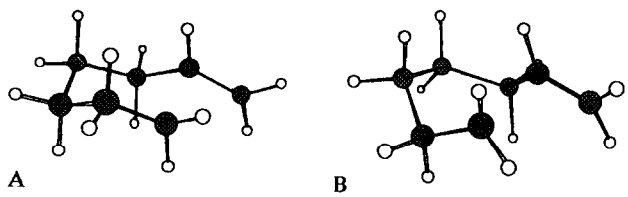


(10)

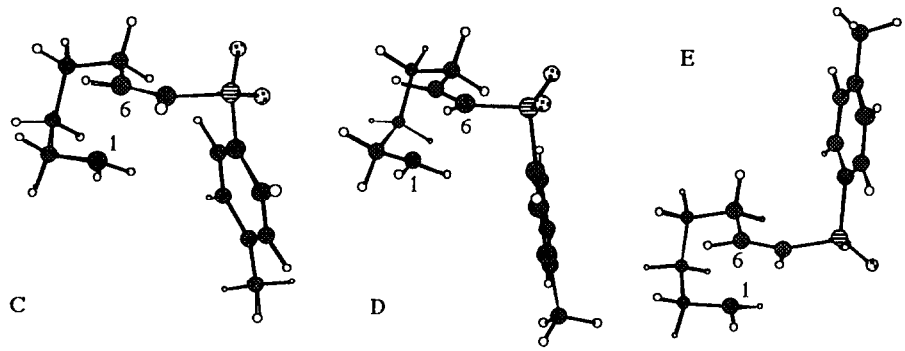
AIBN (0.10 mol equiv) in refluxing benzene formed a six-membered ring product (**4a**) in 81% yield. The product consists of two diastereomers (73:27) though four diastereomers are possible. Desulfurization of the product with Raney Ni-W2 in ethanol gave only one isomer (**5a**), whose stereochemistry was determined by the Ha-Hb coupling constant (J =10.4 Hz) in ^{1}H NMR to be trans. The similar result was obtained on similar treatment of (*E*)-**3a** or a mixture of (*Z*)- and (*Z*)-**3a**, (see Table 1), showing that the geometrical isomerism of

3a does not affect the extremely high stereoselectivity. The results for radical cyclization of **3b-d** having various Y are summarized in Table 1. The stereoselectivity is always high. Notably, it remains high even when Y is less-hindered OH or OAc. Similarly, 7-bromo-3-methyl (or phenyl)-1-methylthio-1-(*p*-tolylsulfonyl)-4-oxa-1-heptene (**6**) also afforded the corresponding trans ring-closure product (**7**). Thus, intramolecular radical cyclization of 3-substituted 7-bromo-1-methylthio-1-(*p*-tolylsulfonyl)-1-alkenes (**3**) and their related compounds (**6**) exhibited a highly efficient 1,2-asymmetric induction to cause trans ring-closure.

By the following experiments and MO calculations, the 1*Z*-substituent of **3** or **6** was revealed to be crucial to the high 1,2-asymmetric induction in their radical cyclization. As shown in Table 1 (entries 10 and 11), (*Z*)-7-bromo-3-methoxy-1-(*p*-tolylsulfonyl)-1-heptene [(*Z*)-**8**] gave *trans*-1-methoxy-2-[(*p*-tolylsulfonyl)-methyl]cyclohexane (*trans*-**9**) as a predominant product, while (*E*)-**8** gave a 1:1 mixture of *trans*-**9** and *cis*-**9**. The transition state of 6-exo closure of 6-heptenyl radical was estimated by MNDO/PM3 calculation.[9] In both of chair-like and boat-like forms, the radical center approaches toward the C6 carbon and, in the transition states,[10] the distance between C1 and C6 atoms is 2.13 Å. The chair-like transition state (**A**) is more stable by 2.96 kcal/mol in energy than the boat-like one (**B**).



In the cyclization of (*Z*)-7-(*p*-tolylsulfonyl)-5-heptenyl radical (**11**) in a chair form, three transition states (**C**, **D**, and **E**) were calculated. It is noteworthy that, in the transition state **C** with the lowest energy, *p*-tolylsulfonyl group is very close to the pseudoaxial H of the 5-position. Another calculation for the transition state of (*E*)-**11** cyclization also revealed that *p*-tolylsulfonyl group is too remote from the protons of the 5-position to affect each other. These imply that the 1-substituent of (*Z*)-**8** takes an important role in its highly stereoselective cyclization leading to trans-**9**.



rel. energy /kcal mol^{-1}	0.00	0.94	1.08
C_1-C_6 distance/Å	2.13	2.13	2.14

In conclusion, 5-substituted 7-methylthio-7-(*p*-tolylsulfonyl)-6-heptenyl radicals (**1**) and their 4-oxa derivatives cyclize in 6-exo manner via the favorable transition state avoiding the repulsion between the 5-substituent and 7*Z*-substituent to attain extremely high selectivity of trans ring-closure. This conclusion provides a useful and general concept for stereoselective construction of 1,2-disubstituted cyclohexane derivatives.

References and Notes

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7. 3-Substituted 7-bromo-1-methylthio-1-(*p*-tolylsulfonyl)-1-heptenes (**3**) were prepared by the following sequence: (Methylthio)methyl *p*-tolyl sulfone was condensed with 6-bromohexanal using *n*-butyllithium (2.2 mol equiv) and trimethylsilyl chloride (2.2 mol equiv) in THF to afford 7-bromo-1-methylthio-1-(*p*-tolylsulfonyl)-1-heptene (**i**) in 76% yield.[8] Bromination of **i** with *N*-bromosuccinimide (1.0 mol equiv) and benzoyl peroxide (10 mol%) gave 3,7-dibromo-1-methylthio-1-(*p*-tolylsulfonyl)-1-heptene (**ii**) in 85% yield. Further conversion of **ii** to **3a**,**b** was attained by treatment (room temperature) with Ag_2O in the corresponding alcohol. Hydrolysis of **ii** occurred in a mixture of water and acetone in the presence or absence of Ag_2O. An acetoxyl derivative (**3c**) was obtained on treatment of with Ag_2O in acetic acid at room temperature.
8. Yahata, N.; Fujita, M.; Ogura, K. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 3601.
9. With MOPAC (Version 5.0) molecular orbital package: Stewart, J. J. P. *QCPE* **1989**, Program 455.
10. The transition states were estimated by the use of the appropriate reaction coordinate analysis[11] and the SADDLE routine. Further refinement of the transition state geometries was carried out with the use of the NLLSQ algorithm.
11. The attacking 1-carbon was fixed at an appropriate distance (a Å) from the 6-carbon and the remaining atoms were optimized for all bonds and atoms except for the distance between C1 and C6 to give an energy-minimized structure having an energy (heat of formation: b kcal mol^{-1}). A reaction energy profile of the cyclization was obtained by plotting the energy (b kcal mol^{-1}) vs the distance (a Å).

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