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INTRAMOLECULAR [2 + 2] CYCLOADDITION AND SEQUENTIAL RING EXPANSION

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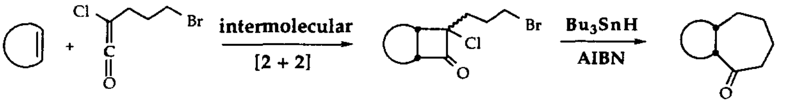
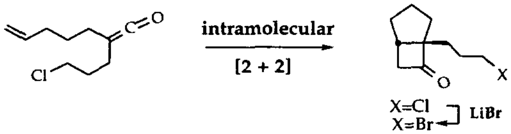
Abstract: *Free radical ring expansion of fused-cyclobutanones gives bicyclic ketones expanded by three and four carbons, with the carbonyl group β to the ring junction. Four-carbon ring expansion shows stereoselectivity favoring the trans-fused product* ***6-trans****. The radical precursor cyclobutanones are readily prepared by intramolecular [2 + 2] cycloaddition of ketenes or keteniminium salts to olefins.*

In our continuing exploration of ring expansion reactions,[1a] we earlier reported an intermolecular [2 + 2] cycloaddition, followed by a cyclobutanone ring expansion sequence (eq 1).[2,3] Cyclobutanones with the exo side chain undergo smooth ring expansion to form *cis*-fused bicyclic ketones. An extension of this strategy (eq 2), takes advantage of the higher yields of intramolecular [2 + 2] cycloadditions[4] compared with those of the intermolecular series, generating the cyclobutanone as a single isomer with the side chain at the fused carbon. Sequential ring expansion provides a new fused ring system with the ketone β to the ring junction, complementary to the earlier synthetic strategy,[2] where the carbonyl group is deployed α to the ring junction. The intramolecular route provides a useful addition to the free radical synthesis of fused rings.



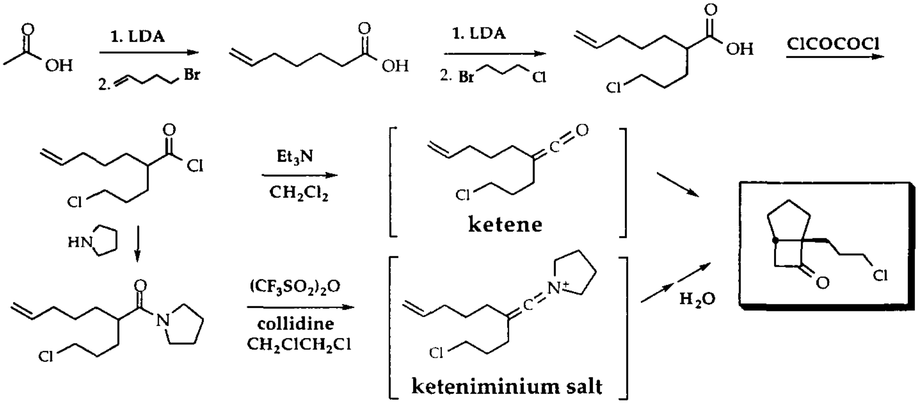
(1)



(2)

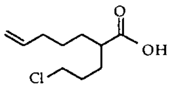
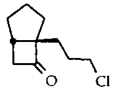
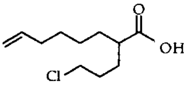
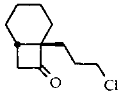
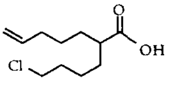
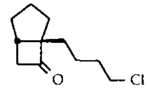
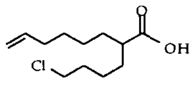
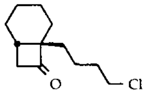
Preparation of the radical precursors is straightforward (Scheme 1). In the first step of a one-pot dialkylation, the dianion of acetic acid is generated using 3.2 eq of LDA in THF and HMPA at 0 °C, then quenched by sequential addition of the appropriate bromides at -78 °C. The resulting dialkylation products are quantitatively transformed to the corresponding acid chlorides by treatment with oxalyl chloride in benzene at room temperature. Reaction of the acid chloride with triethylamine in CH_2Cl_2 at 40 °C leads to *in situ* formation of the ketene, which then undergoes intramolecular cycloaddition to the olefin to form the fused-cyclobutanone.[5] An

Scheme 1



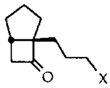
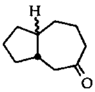
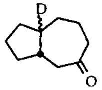
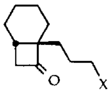
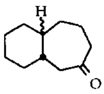
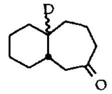
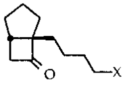
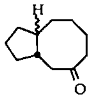
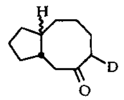
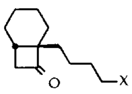
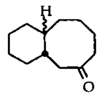
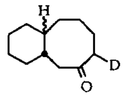
alternative method for preparing cyclobutanones makes use of the hydrolysis of [2 + 2] adducts from keteniminium salts. The keteniminium salt is generated by treatment of an amide with trifluoromethanesulfonic anhydride and 2,4,6-collidine in 1,2-dichloroethane.[6] Cycloaddition of keteniminium salts generally gives better yields than does cycloaddition of ketenes.[7] The difference is especially evident in the formation of the bicyclo[4.2.0] ring system (Table 1).[5]

Table 1. Dialkylation and Cycloaddition

Dialkylation of acetic acid	Intramolecular [2 + 2] cycloaddition
	
61%	37%^{a} 40%^{b}
	
70%	<5%^{a} 35%^{b}
	
65%	30%^{a} 68%^{b}
	
51%	45%^{b}

^{a} ketene cycloaddition. ^{b} keteniminium salt cycloaddition.

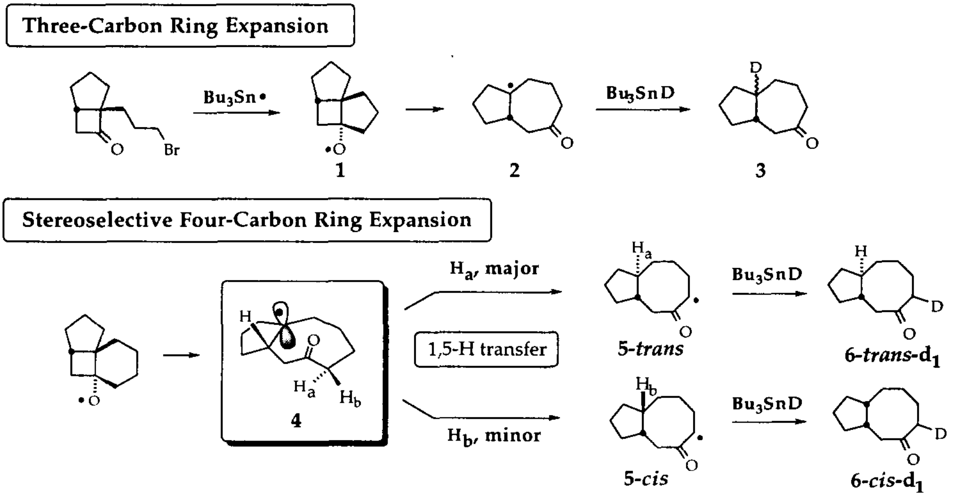
Table 2. Ring Expansion of Cyclobutanones[8]

Cyclobutanone	Ring expansion and ratio (trans:cis) Bu$_3$SnH/AIBN	Bu$_3$SnD/AIBN
		
X=Br	88% (60:40)	
X=I	91% (64:36)	86% (63:37)
		
X=Br	87% (56:44)	
X=I	86% (51:49)	73% (54:46)
		
X=Br	43% (86:14)	
X=I	67% (88:12)	34% (80:20)
		
X=Br	57% (80:20)	46% (78:22)
X=I	57% (77:23)	

The intramolecular [2 + 2] cycloadducts are readily transformed to bromides or iodides by treatment of the chlorides with LiBr or NaI in refluxing acetone. Free radical ring expansion of bromoalkyl and iodoalkyl cyclobutanones is carried out in refluxing benzene solution by slow addition of 1.5 eq of tributyltin hydride with a catalytic amount of AIBN. Small amounts of direct reduction product are detected in the four-carbon ring expansion reaction. Examples in Table 2 show the preparation of 5,7-, 6,7-, 5,8-, and 6,8-fused bicyclic ketones[9] by three- or four-carbon ring expansion. Stereochemical control over the ring-junction is lost because one of the ring-junction carbons becomes a radical center during the ring expansion. Three-carbon ring expansion (Table 2, entries 1 and 2) gives a mixture of the two diastereomers in the ratio of 60:40 with little stereoselectivity. However, the four-carbon ring expansion (Table 2, entries 3 and 4) does exhibit stereoselectivity. The ratio of the diastereomers **6-*trans*** and **6-*cis*** (Scheme 2) is 85:15 favoring the trans isomer.[8]

In order to better understand the reaction sequence, tributyltin deuteride experiments were carried out. The deuterium labeling experiments show that in the three-carbon ring expansion (Scheme 2), the ring-expanded radical **2** from β-scission of alkoxy radical **1** is reduced by tributyltin deuteride to give bicyclic ketone **3** with the deuterium atom at the bridgehead carbon. Reduction of radical **2** by tributyltin deuteride has low selectivity forming a mixture of cis and trans isomers. However, the four-carbon ring-expanded radical **4** undergoes intramolecular 1,5-hydrogen transfer forming the stabilized α-acyl radicals **5-*trans*** and **5-*cis***, which are then reduced by tributyltin deuteride to give bicyclic ketones **6-*trans*-d$_1$** and **6-*cis*-d$_1$** with the deuterium atom adjacent to the carbonyl. A model of radical **4** shows that 1,5-hydrogen transfer of H_a to form the trans isomer is more favorable than H_b transfer to form the cis isomer.[8] That the deuterium atom is adjacent to the carbonyl was established by ^1H NMR and ^{13}C NMR. The deuterium at this position is readily exchanged upon treatment with H_2O under basic conditions (DBU/ether).

Scheme 2



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(1) Reviews of free radical ring expansion: (a) Dowd, P.; Zhang, W. *Chem. Reviews*, **1993**, *93*, 2091 and references there in. (b) Hesse, M. *Ring Enlargement in Organic Chemistry*; VCH: Weinheim, 1991.

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(4) For an excellent review of intramolecular [2 + 2] cycloadditions, see (a) Snider, B. B. *Chem. Rev.* **1988**, *88*, 793. See also (b) Hyatt, J. A.; Raynolds, P. W. *Org. React.* **1994**, *45*, 159. (c) Carruthers, W. in *Cycloaddition Reaction in Organic Synthesis* Pergamon: Oxford, 1990, pp 332-369. (d) Ghosez, L.; O'Donnell, M. J. *Pericyclic Reactions;* Marchand, A. P.; Lehr, R. E., Eds., Academic: New York, **1977**, Vol. II, pp 79-140. (e) Brady, W. T. in *The Chemistry of Ketenes, Allenes and Related Compounds*; Patai, S., Eds., Interscience: New York, 1980, pp 278-308.

(5) For intramolecular ketene cycloaddition procedures, see: Marko, I.; Ronsmans, B.; Hesbain-Frisque, A.-M.; Dumas, S.; Ghosez, L. *J. Am. Chem. Soc.* **1985**, *107*, 2192.

(6) For intramolecular keteniminium salt cycloaddition procedures, see: L. Gobeaux, B.; Ghosez, L. *Heterocycles* **1989**, *28*, 29.

(7) The low yields for the ketene reactions might be improved by carrying out the reactions at higher temperatures, see: Snider, B. B.; Allentoff, A. J.; Walner, M. B. *Tetrahedron* **1990**, *46*, 8031.

(8) In most cases, the diastereomeric ring expansion products could not be separated by column chromatography. The **6-*trans*** to **6-*cis*** product ratio was determined by GC-MS analysis. An 82:18 mixture of authentic **6-*trans*** and **6-*cis*** was prepared following Winkler's procedure.[9a] In addition, an 82:18 mixture of **6-*trans*** and **6-*cis*** was prepared by reduction of bicyclo[6.3.0]undec-1-en-3-one[9c] using Li in liquid NH_3, followed by PCC oxidation. Authentic **6-*cis*** was prepared by hydrogenation of bicyclo[6.3.0]undec-1-en-3-one[9c] in EtOH using Pd/C as catalyst.

(9) For alternative approaches to the preparation of bicyclo[6.3.0]undecan-3-ones by free radical annulation and ring expansion, see: (a) Winkler, J.; Sridar, V. *Tetrahedron Lett.* **1988**, *29*, 6219. (b) Ellwood, C. W.; Pattenden, G. *Tetrahedron Lett.* **1991**, *32*, 1591. (c) Nishida, A.; Takahashi, H.; Takeda, H.; Tekada, N.; Yonemitsu, O. *J. Am. Chem. Soc.* **1990**, *112*, 902.

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