ORGANIC
LETTERS

2002
Vol. 4, No. 21
3707−3709

Radical Fragmentation of ω-Bromoalkyl Cyclobutanones. A Modular Approach to Eight-Membered Carbocycles

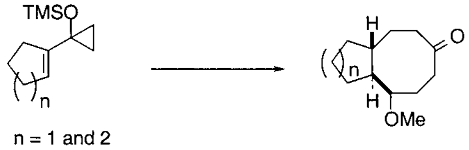
Heong-Sub Oh, Hyoung Ik Lee, and Jin Kun Cha*,†

Department of Chemistry, University of Alabama, Tuscaloosa, Alabama 35487

jcha@bama.ua.edu

Received August 3, 2002

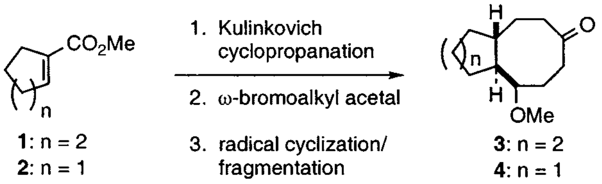
ABSTRACT



An eight-membered ring was conveniently appended onto a cycloalkene carboxylate by employing a facile radical cyclization–fragmentation reaction of an ω-bromoalkyl spirocyclobutanone, which was readily accessible by the Kulinkovich cyclopropanation and subsequent electrophilic addition to a 3-bromoalkyl acetal.

In the past two decades, free radicals have emerged as versatile reaction intermediates in the construction of the carbon−carbon bonds in the presence of other functional groups.[1] Particularly useful is a free radical fragmentation (ring-opening) strategy of spiro- and fused-strained rings to bring about ring expansion for preparing medium-sized carbocycles. For example, sequential application of an inter- or intramolecular [2 + 2] photocycloaddition and a radical fragmentation reaction of the resulting, typically fused cyclobutane derivative has provided a convenient method for generating medium-sized rings.[2] We herein report an expedient annulation of an eight-membered ring onto a cycloalkene carboxylate by relying on facile radical fragmentation of a spiro-cyclobutanone (Scheme 1).

Scheme 1



Our approach to the requisite ω-bromoalkyl-tethered cyclobutanones was built upon the Kulinkovich reaction of cycloalkene carboxylates and subsequent condensation of 1-cycloalkenylcyclopropanols with ω-bromoalkyl acetals (Scheme 2). The original Kulinkovich cyclopropanation[3−5] of methyl cyclohexenecarboxylate (**1**) and methyl cyclopentenecarboxylate (**2**) with ethylmagnesium bromide in the

---

[†] Current address: Department of Chemistry, Wayne State University, Detroit, MI 48202. E-mail: jcha@chem.wayne.edu.

(1) (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon−Carbon Bonds*; Pergamon Press: Oxford, 1986. (b) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237. (c) Motherwell, W. B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*; Academic Press: San Diego, 1992. (d) Fossey, J.; Lefort, D.; Sorba, J. *Free Radicals in Organic Chemistry*; Wiley: Chichester, UK, 1995. (e) *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P. Eds.; Wiley-VCH: Weinheim, Germany, 2001.

(2) For representative examples, see: (a) Dowd, P.; Zhang, W. *J. Org. Chem.* **1992**, *57*, 7163. (b) Dowd, P.; Zhang, W. *Chem. Rev.* **1993**, *93*, 2091. (c) Zhang, W.; Collins, M. R.; Mahmood, K.; Dowd, P. *Tetrahedron Lett.* **1995**, *36*, 2729. (d) Rawal, V. H.; Dufour, C.; Iwasa, S. *Tetrahedron Lett.* **1995**, *36*, 19. (e) Crimmins, M. T.; Huang, S.; Guise-Zawacki, L. E. *Tetrahedron Lett.* **1996**, *37*, 6519. (f) Lange, G. L.; Gottardo, C. *J. Org. Chem.* **1995**, *60*, 2183.

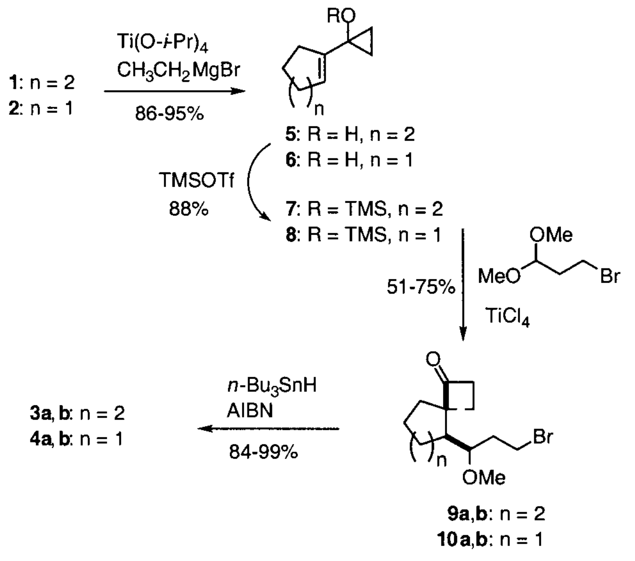
(3) (a) Kulinkovich, O. G.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2789. (b) Sato, F.; Urabe, H.; Okamoto, S. *Chem. Rev.* **2000**, *100*, 2835.

(4) (a) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A.; Pritytskaya, T. S. *Zh. Org. Khim.* **1989**, *25*, 2244. (b) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A.; Savchenko, A. I.; Pritytskaya, T. S. *Zh. Org. Khim.* **1991**, *27*, 294. (c) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A. *Synthesis* **1991**, 234. (d) Kulinkovich, O. G.; Savchenko, A. I.; Sviridov, S. V.; Vasilevskii, D. A. *Mendeleev Commun.* **1993**, 230.

(5) (a) Lee, J.; Kang, C. H.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1996**, *118*, 291. (b) Lee, J.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1996**, *118*, 4198. See also: (c) Kasatkin, A.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 6079. (d) Kasatkin, A.; Kobayashi, K.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1996**, *37*, 1849.

10.1021/ol026666a CCC: $22.00

Scheme 2

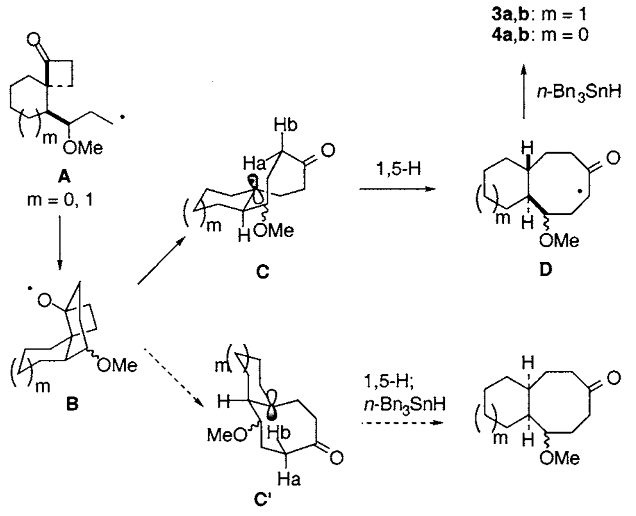


presence of titanium isopropoxide afforded the corresponding cyclopropanols **5** and **6** in 95 and 86% yields, respectively.[6] Vinyl cyclopropanols and silyl ethers can be viewed as vinylogous enols and enol silyl ethers, and their synthetic utility in electrophilic addition reactions was first demonstrated by the Wasserman and Trost groups and, more recently, in our laboratory.[7−9] Following standard silylation (88% yield), a vinylogous Mukaiyama condensation[10] of **7** with 3-bromopropionaldehyde dimethylacetal by the action of $TiCl_4$ gave a 5:3 mixture of **9a** and **9b** (71% yield) that were epimeric at the methoxy stereocenter. The ring junction stereochemistry of **9a** and **9b** was assigned on the basis of the stereoelectronic requirements for electrophilic addition,[8] whereas the relative configuration of the methoxy substituent could not be ascertained. Other Lewis acids such as TMSOTf, BF_3•Et_2O, and Et_2AlCl were ineffective in effecting coupling with an acetal.

Slow addition of *n*-tributyltin hydride and AIBN to a solution (14 M) of **9a** in refluxing benzene afforded cyclooctenone **3a** as a single isomer in 99% yield. Similarly, free radical-mediated cyclization−fragmentation of **9b** also proceeded efficiently to provide **3b** in 91% yield. The identical annulation sequence was also evaluated by starting with **6**, especially because the resultant bicyclo[6.3.0]-undecane skeleton is commonly found in an increasing number of bioactive natural products.[11] In parallel to the above-mentioned results, **10a** and **10b** were obtained in 51% yield in a 1.3:1 ratio from condensation of **8** with 3-bromopropionaldehyde dimethylacetal. Again, free radical-mediated cyclization−fragmentation of **10a** and **10b** took place smoothly to afford **4a** and **4b** (84∼93% yield), respectively, as the sole product in each case.

As outlined in Scheme 3, the reaction sequence is likely to involve 6-exo-cyclization of the initially formed primary radical **A** to the cyclobutanone functionality to generate the alkoxy radical **B**. Ring opening, which is driven by the relief of strain in the four-membered ring, affords the fused bicyclic radical **C**. The ring-annulated radical **C** is anticipated to suffer 1,5-hydrogen transfer leading to the stabilized α-acyl radical **D**, which finally undergoes hydrogen abstraction from tributyltin hydride to furnish the bicyclic ketone products **3a**,**b** and **4a**,**b**. By analogy to a related system examined by Dowd,[2c] the preferential formation of the trans isomers would seem more favorable than the alternate cis ring junction isomers, arising from 1,5-hydrogen transfer of H_a (vs H_b) (i.e., **C** over **C′**). Apparently, the methoxy configuration exerted negligible influences on the stereochemical course, which might be attributable to its small A value.

Scheme 3



To confirm the presumed reaction mechanism involving 1,5-hydrogen transfer, the deuterium labeling experiment using tributyltin deuteride and also the radical allylation reaction by allyltributyltin were undertaken next (Scheme 4). Reduction of **9a** with tributyltin deuteride afforded **11** having the deuterium α to the carbonyl group as a 4:1 diastereomeric mixture (94%). Similarly, separate treatment of **9a** and **9b** with allyltributyltin resulted in grafting an allyl group adjacent to the carbonyl group to give **12** and **13** in 96 and 95% yields, respectively; in both cases, two diastereomers were obtained in a ∼6:1 ratio. The stereochemistry of **9a**,**b** and **11**−**13** was tentatively assigned as shown in Scheme 4 primarily by analogy to **10a**,**b** and **14**−**16** (vide

---

(6) For a previous synthesis of **5** and **6**, see: Salaun, J.; Garnier, B.; Conia, J. M. *Tetrahedron* **1974**, *30*, 1413.

(7) Wasserman, H. H.; Keehn, P. M. *J. Am. Chem. Soc.* **1969**, *91*, 2375.

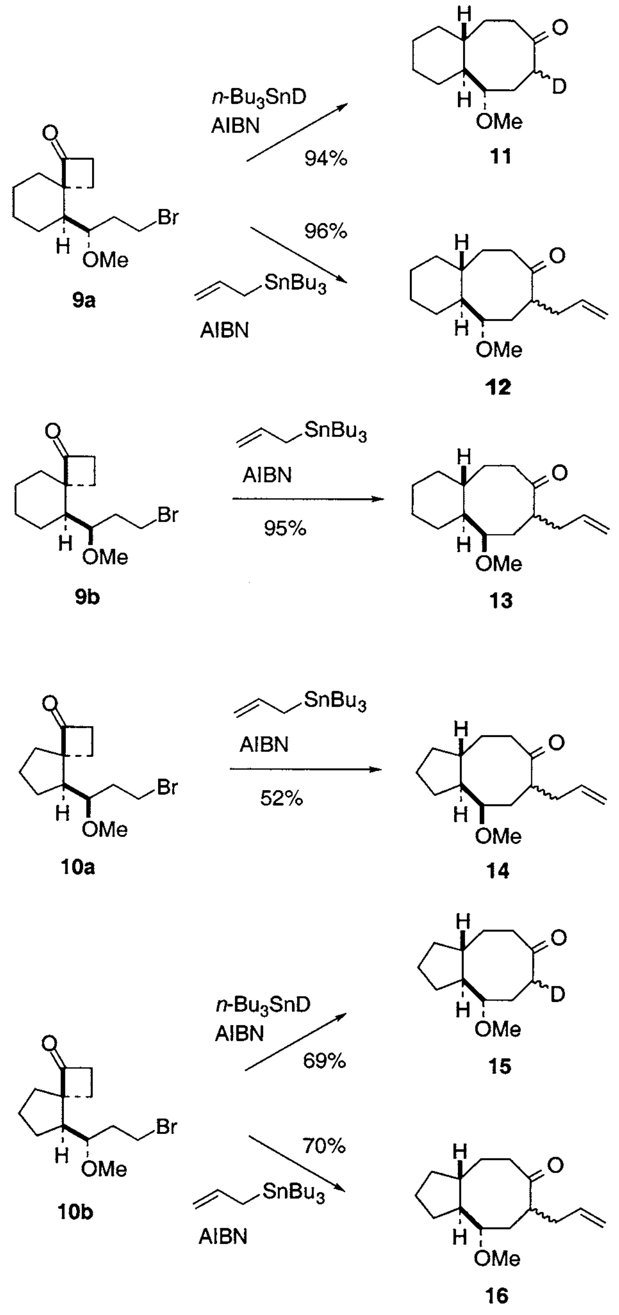
(8) (a) Trost, B. M.; Brandi, A. *J. Am. Chem. Soc.* **1984**, *106*, 5041. (b) Trost, B. M.; Lee, D. C. *J. Am. Chem. Soc.* **1988**, *110*, 6556. For an excellent review, see: (c) Trost, B. M. *Top. Curr. Chem.* **1986**, *133*, 3.

(9) Youn, J.-H.; Lee, J.; Cha, J. K. *Org. Lett.* **2001**, *3*, 2935.

(10) (a) Mukaiyama, T. *Org. React.* **1982**, *28*, 203. (b) Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 3248. See also: (c) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929.

(11) (a) For recent reviews, see: Mehta, G.; Vishwakarma, S. *Chem. Rev.* **1999**, *99*, 881. (b) Yet, L. *Tetrahedron* **1999**, *55*, 9349. For recent examples, see: (c) Aloise, A. D.; Layton, M. E.; Shair, M. D. *J. Am. Chem. Soc.* **2000**, *122*, 12610. (d) Mainetti, E.; Mouriès, V.; Fensterbank, L.; Malacria, M.; Marco-Contelles, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2132.

Scheme 4



infra), along with the $^1H-^1H$ COSY, difference NOE measurements, and mechanistic considerations.[10b]

In the same fashion, treatment of **10b** with tributyltin deuteride furnished **15** as a 2:1 diastereomeric mixture (69%). From individual radical allylation of **10a** and **10b** with allyltributyltin, **14** (as a 5:1 diastereomeric mixture) and **16** (as a 7:1 diastereomeric mixture) were obtained in 52 and 70% yields, respectively. The full stereochemistry of **10a**,**b** and **16** was unequivocally determined by single-crystal X-ray analysis of carbamate **17** that was prepared from the major diastereomer of **16** having the allyl group in the β-configuration by reduction with $NaBH_4$, followed by acylation of the major alcohol with *p*-bromophenylisocyanate. The X-ray structure of **17** is depicted in ORTEP presentation (Figure 1).[12]

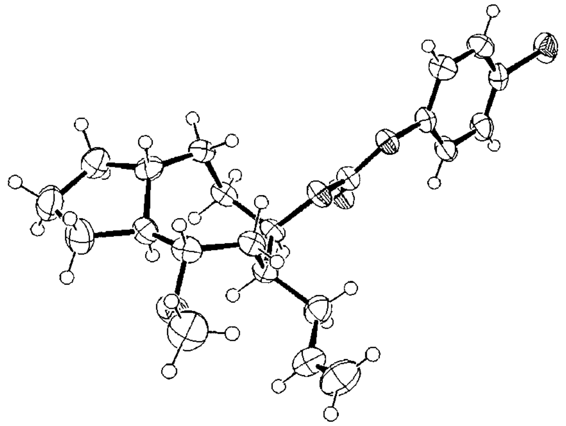


Figure 1.

In summary, a convenient method for appending an eight-membered ring to cycloalkene carboxylates has been developed by employing a facile radical cyclization−fragmentation reaction of bromoalkyl-tethered spirocyclobutanones. The requisite substrates for ring expansion were readily accessible by a modular approach involving the Kulinkovich cyclopropanation of cycloalkene carboxylates and subsequent electrophilic addition of the resulting alkenyl cyclopropanols to a 3-bromoalkyl acetal.

Acknowledgment. We thank the National Institutes of Health (GM35956) and the National Science Foundation (CHE-0209321) for generous financial support.

Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL026666A

---

(12) We thank Dr. Fook Tham (University of California, Riverside) for X-ray analysis.