Free-Radical Annelation in the Synthesis of Bicyclic β-Lactams. 7.† A One-Pot, Four-Step, Sequential Reaction

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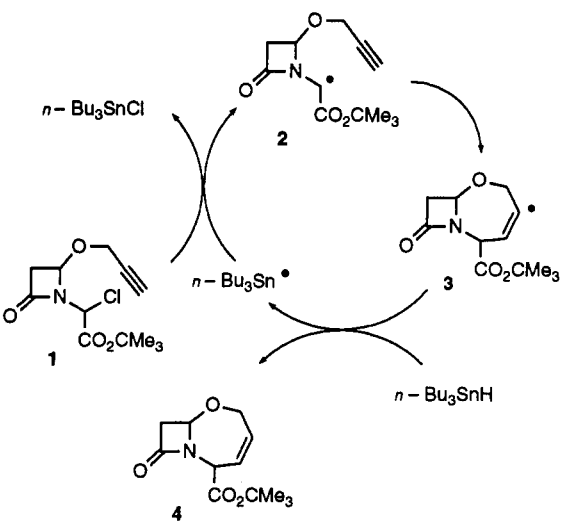
Summary: Nonfused, alkynyl-β-lactams **10** and **18** react with *n*-Bu_3SnH to give *tert*-butyl carbaceph-2-em-4-carboxylate (**11**) and methyl 1-oxahomoceph-3-em-5-carboxylate (**19**), respectively, in a four-step, sequential radical reaction involving homolytic intermolecular addition, intramolecular hydrogen atom transfer, *endo*-intramolecular addition, and β-elimination.

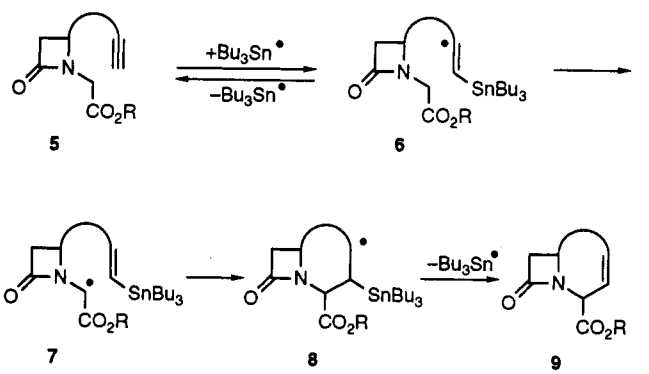
Following the clear delineation of the factors affecting the selectivity of carbon-centered radical cyclization reactions, their value in organic synthesis has been widely recognized.[1] Over the past decade we have presented a variety of approaches to the use of free radicals in the synthesis of bicyclic β-lactams with *n*-Bu_3SnH as a mediator and a chlorine atom, a phenylthio, or phenylseleno group as the pro-radical center.[2-5] In these reactions nonfused β-lactams are converted into fused-bicyclic β-lactams by the intramolecular addition of a carbon-centered radical to a carbon–carbon double bond.[6] It should be noted that contrary to the usual *exo*-cyclization of simple alkenyl radicals,[7] in the absence of otherwise directing groups, radical annelation to fused-bicyclic β-lactams follows preferentially the *endo*-mode.[2-6] Of particular relevance to the present paper is the observation[2a,d] that the acetylenic chloro lactam **1** undergoes exclusive 7-*endo-dig* cyclization to the 1-oxahomoceph-3-em **4** as outlined in Scheme I.

In this paper we present a novel approach to fused-bicyclic β-lactams wherein a terminal alkyne functions as a pro-radical center (Scheme II). A transient vinyl radical **6** is formed on addition of tri-*n*-butyltin radicals to the triple bond of the acetylene lactam **5**. As the reverse reaction, β-elimination of *n*-$Bu_3Sn^•$ from **6**, is a facile process,[8] the key step in this reaction sequence is the intramolecular H-atom transfer to form a more stabilized radical **7**, akin to those which we previously generated in a chemospecific manner by halogen abstraction (*cf.* Scheme I, **1** → **2**). This radical is then well positioned to add to the vinylstannane functionality by the *endo*-mode as observed for the cyclization of **2** to **3** (Scheme I). Subsequent β-elimination of the tri-*n*-butyltin radical from the bicyclic radical **8** would generate the bicyclic β-lactam **9** in a process catalytic with respect to *n*-Bu_3SnH.

Scheme I



Scheme II



In our first attempt to realize this idea, we alkylated 4-propargyl-2-azetidinone[9] with *tert*-butyl bromoacetate forming β-lactam **10**,[3b] which was then treated with *n*-Bu_3SnH under high dilution conditions. Thus, a solution of 1 equiv of *n*-Bu_3SnH and 0.5 equiv of AIBN in benzene was added over 8 h to a boiling 0.003 M solution of **10** in benzene. After the solvent was removed the bicyclic lactam **11** and the stannylated lactam **12** were isolated in 19 and 56% yield, respectively (Scheme III).[10]

† Part 6: see ref 3b.

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(6) For other *n*-Bu_3SnH-mediated cyclizations to bicyclic β-lactams see: (a) Beckwith, A. L. J.; Boate, D. R. *Tetrahedron Lett.* **1985**, *26*, 1761. (b) Beckwith, A. L. J. *Rev. Chem. Intermed.* **1986**, *7*, 143. (c) Knight, J.; Parsons, P. J. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1237. (d) Kametani, T.; Chu, S.-D.; Itoh, A.; Maeda, S.; Honda, T. *J. Org. Chem.* **1988**, *53*, 2683. (e) Girijavallabhan, V. M.; Ganguly, A. K. *Heterocycles* **1989**, *28*, 47.

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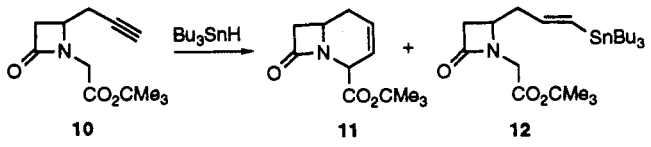
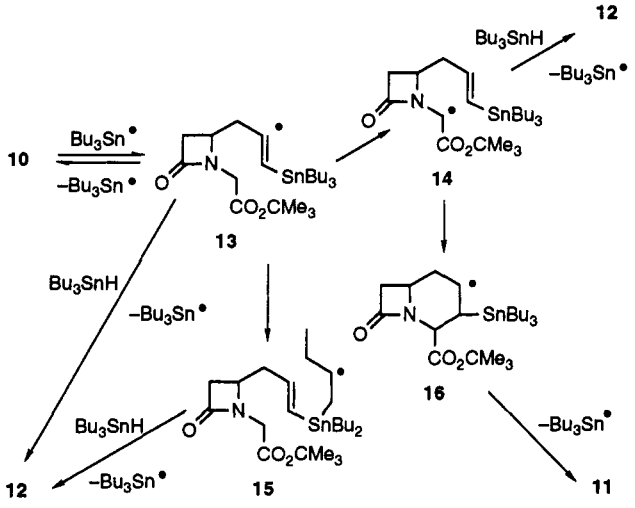
(10) Experimental data available in the supplementary material.

0022-3263/93/1958-5581$04.00/0

Scheme III



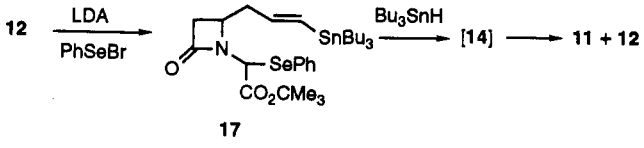
Scheme IV



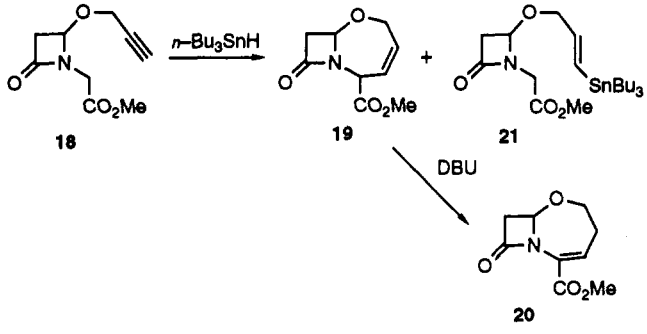
The reasons for the relative low yield in the cyclization process were revealed when the reaction was repeated with *n*-Bu_3SnD in place of *n*-Bu_3SnH. In this reaction the deuterium was incorporated in compound **12**,[11] largely (78%) on the double bond of the side chain, indicating that the desired H-atom transfer was inefficient. A further 16% of the deuterium resided on the acetate moiety, indicating that the cyclization was also inefficient relative to reduction. Surprisingly, 6% of the deuterium was located on the butyl groups of the stannane. On the basis of this we propose the extended reaction mechanism shown in Scheme IV. Thus, reversible addition of tri-*n*-butyltin radicals onto the terminal alkyne generates vinyl radical **13** which is then partitioned between (a) direct reduction by *n*-Bu_3SnH to vinylstannane **12**, (b) intramolecular H-atom transfer forming the desired radical **14**, and (c) intramolecular H-atom transfer from a butyl group forming radical **15**. While radical **15** is reduced to vinylstannane **12**, radical **14** is further partitioned between direct reduction to **12** and cyclization to form bicyclic radical **16**. β-Elimination of tri-*n*-butyltin radical from **16** then forms bicyclic β-lactam **11**. The fact that intramolecular H-atom transfer to form radical **15** competes with 1,5 H-atom transfer to form the more stable radical **14** probably derives from the dominant contribution of steric and steroelectronic factors, rather than thermodynamic factors,[7] on the transformations of the relatively rigid β-lactam radical **13**. After isolation of **12** we were able to verify the path **14** → **11** + **12** by forming radical **14** in an unambiguous manner. Thus, treatment of **12** with LDA followed by phenylselenium bromide formed lactam **17**. Subsequent treatment of **17** with 0.4 equiv of *n*-Bu_3SnH and 0.2 equiv of AIBN under high dilution conditions led to isolation of bicyclic lactam **11** in 44% yield and the reduced lactam **12** in 42% yield (Scheme V). As expected, reaction of **10** with *n*-Bu_3SnH at higher concentration, 0.1 M, led to almost quantitative formation of **12** (92%) and only a trace of **11**.

(11) Determined by ^2H NMR spectra in $CHCl_3$ with $CDCl_3$ as both internal reference and internal standard.

Scheme V



Scheme VI



In view of the particular disposition of alkenyl- and alkynyl-β-lactams to undergo 7-*endo* radical cyclization[2-6] (*cf.* Scheme I) we examined the applicability of our novel methodology to the synthesis of 1-oxahomocephems. Thus, a benzene solution containing *n*-Bu_3SnH (0.6 equiv) and AIBN (0.2 equiv) was added over 6 h to a boiling solution of lactam **18**,[2a,d] 0.024 M in benzene. The residue obtained after evaporation of the solvent was stirred for 2 h with a few drops of DBU in methylene chloride. Flash chromatography of the product afforded methyl 1-oxahomoceph-4-em-5-carboxylate (**20**, 40%) resulting from double-bond migration in the initially formed 1-oxahomoceph-3-em **19** (*cf.* the corresponding *tert*-butyl ester **1**)[2a,d] and the nonfused vinyl lactam **21** (25%).[10]

In summary, we have now added a new array of consecutive reactions to the growing arsenal of potentially useful one-pot sequential radical reactions[1d] which involve *homolytic intermolecular addition, 1,5- or 1,6-intramolecular H-transfer, 6-endo- or 7-endo-intramolecular addition, and β-elimination.* Application of this methodology to the synthesis of other fused bicyclic systems will be investigated.

Supplementary Material Available: Experimental procedures and characterization data for compounds **10–12**, **17**, **18**, **20**, and **21** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.