

Figure 2. Plot of bond length  $r$  versus external angle in tricyclopentanes ( $r = 0.998$ ).

angle  $\phi$ . The inverse relationship between the bridging bond length  $r$  and the bridgehead substituent angle  $\phi$  (C1-C5-C6 and C5-C1-C7 for 1) is apparent in the linear correlation ( $r = 0.998$ ) between the length of the bridging C1-C5 bond  $r$  and the angle  $\phi$  shown in Figure 2. This plot constitutes clear and direct confirmation of the theoretical prediction<sup>3</sup> and the qualitative suggestion<sup>6</sup> that the angle  $\phi$  is a direct determinant of the bridging bond length in bicyclobutanes.

**Acknowledgment.** We acknowledge financial support by the Fonds der Chemischen Industrie, by the Deutsche Forschungsgemeinschaft, and by the U.S. National Science Foundation. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

**Supplementary Material Available:** Table I, atomic coordinates and thermal parameters of 1; Table II, interatomic angles of 1; Table III, anisotropic thermal parameters for 1; Table IV, atomic coordinates and thermal parameters of H-atoms (3 pages); Table V, structure amplitudes (26 pages). Ordering information is given on any current masthead page.

## Free Radical Ring Expansion by Three and Four Carbons

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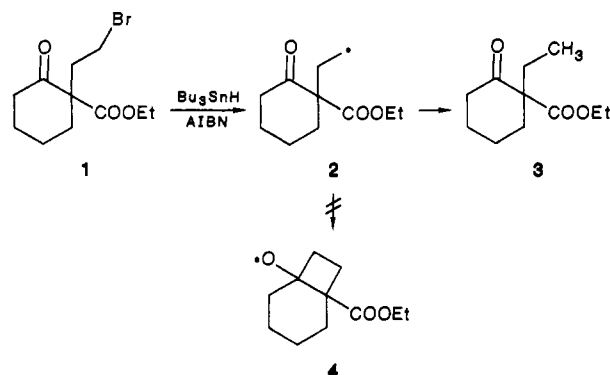
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Received July 10, 1987

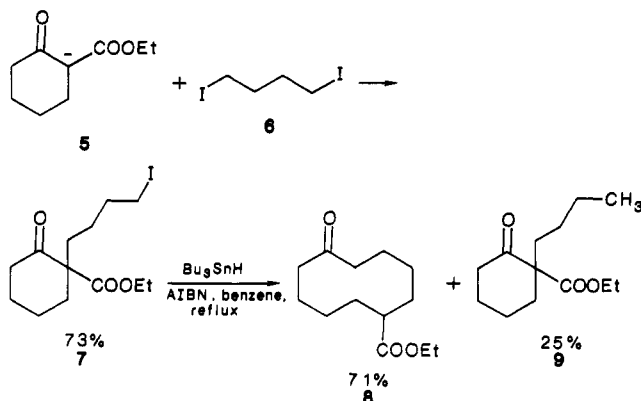
Organic synthesis<sup>1</sup> requires efficient and flexible access to functionalized medium-sized rings. In this paper, we describe a new route to medium-sized rings based upon free radical promoted insertion of a three- or four-carbon chain into a cyclic  $\beta$ -keto ester system. The new reaction is an extension of the recently discovered one-carbon ring expansion reaction of  $\alpha$ -(bromomethyl)- $\beta$ -keto esters with tri-*n*-butyltin hydride as the promoting reagent,<sup>2-4</sup> but

the new reaction is itself unique among ring expansion methods.

We doubted that a two-carbon ring expansion could be carried out. Indeed, when the bromoethyl-substituted  $\beta$ -keto ester 1 is treated with tri-*n*-butyltin hydride in the presence of AIBN in refluxing benzene, no ring-expanded product is observed; only the ethyl-substituted  $\beta$ -keto ester 3 is obtained. Apparently, formation of the four-membered intermediate 4 required for ring-expansion is not competitive with chain transfer reduction of the initially formed radical 2.



By contrast, the three-carbon and four-carbon ring expansions appear to be very promising. When the bromo- or iodopropyl or the bromo- or iodobutyl derivatives are treated with tri-*n*-butyltin hydride,<sup>5</sup> smooth ring expansion occurs to yield the enlarged ring together with a small amount of reduction product. To illustrate: ethyl cyclohexanone-2-carboxylate (5) was treated with 1,4-diiodobutane (6) in the presence of sodium hydride yielding the



2-iodobutyl adduct 7 (73%). When 7 was treated with tri-*n*-butyltin hydride, ethyl cyclodecanone-6-carboxylate (8) was produced in 71% yield together with the direct reduction product ethyl 2-butylcyclohexanone-2-carboxylate (9) (25%).

Further examples are presented in Table I. The ring expansion product is readily separated from the direct reduction product by column chromatography since the large ring products elute significantly more slowly than do the direct reduction products.

Iodides undergo more efficient chain transfer with the tri-*n*-butyl radical than do the corresponding bromide; therefore, iodides give higher yields of ring-expansion product, in accord with the observations of Porter.<sup>6</sup>

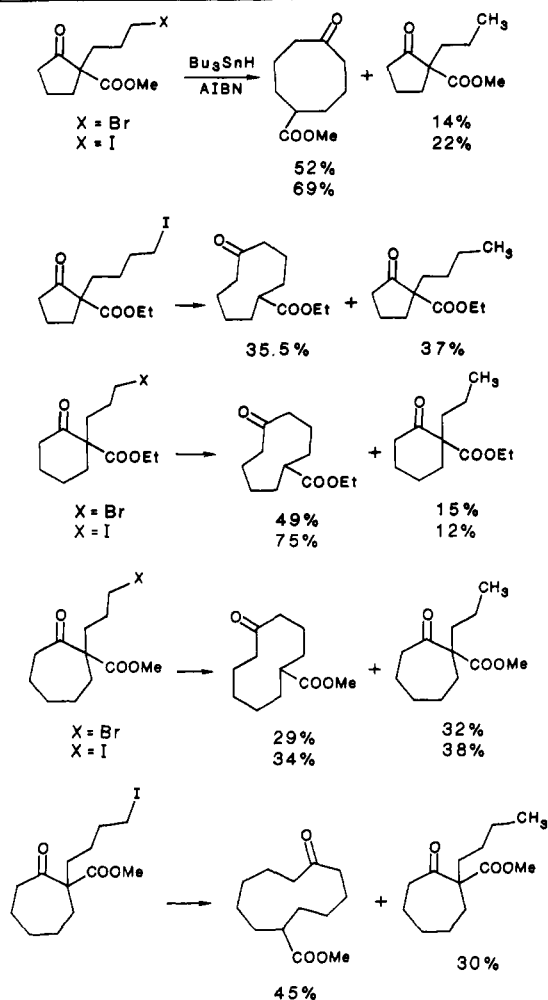
(3) A similar transformation, carried out simultaneously with our work,<sup>2</sup> was reported very recently by Beckwith, A. L. J.; O'Shea, D. M.; Gerba, S.; Westwood, S. W. *J. Chem. Soc., Chem. Commun.* **1987**, 666. This paper also contains an example in which a phenyl radical undergoes intramolecular insertion into a  $\beta$ -keto ester resulting in formation of a benzocyclodecanone as one of the products. See, also: Okabe, M.; Osawa, T.; Tada, M. *Tetrahedron Lett.* **1981**, 1899. Tada, M.; Miura, K.; Okabe, M.; Seki, S.; Mizukauni, H. *Chem. Lett.* **1981**, 33. Best, W. M.; Cook, A. P. F.; Russell, J. J.; Widdowson, D. A. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1139.

(4) A tri-*n*-butyltin hydride based ring expansion of a penam to a cepham has been reported very recently by Baldwin et al. (Baldwin, J. E.; Adlington, R. M.; Kang, T. W.; Lee, E.; Schofield, C. J. *J. Chem. Soc., Chem. Commun.* **1987**, 104).

(5) The tri-*n*-butyltin hydride is delivered in low concentration by using a syringe pump.

(1) For leading references to recent work on the formation of carbon-carbon bonds using free radical intermediates, see: Stork, G.; Baine, N. H. *J. Am. Chem. Soc.* **1982**, *104*, 2321. Hart, D. J.; Tsai, Y.-M. *J. Am. Chem. Soc.* **1982**, *104*, 1430. Curran, D. P.; Rakiewicz, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 1448. Koreeda, M.; George, I. A. *J. Am. Chem. Soc.* **1986**, *108*, 8098.

(2) Dowd, P.; Choi, S.-C. *J. Am. Chem. Soc.* **1987**, *109*, 3493.

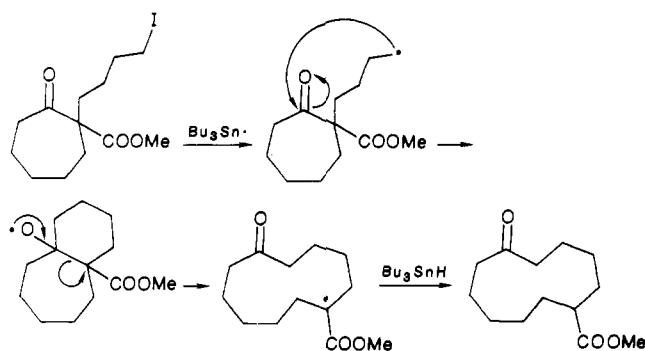
Table I. Three- and Four-Carbon Ring Expansion of  $\beta$ -Keto Esters<sup>a,b</sup>

<sup>a</sup> All new substances had satisfactory carbon-13 and proton NMR, IR, and mass spectra. <sup>b</sup> % isolated yields.

In the one-carbon ring expansion described earlier,<sup>2-4</sup> there were two possible reaction paths. The reaction could have proceeded by addition of the primary radical to the ketone carbonyl<sup>7</sup> followed by fragmentation-ring enlargement of the oxy radical, as we had (tentatively) formulated the mechanism.<sup>2</sup> Alternatively, the primary radical might have fragmented to an acyl radical and an acrylate.<sup>8</sup> The reaction would be completed by addition of the acyl radical to the  $\beta$ -carbon of the acrylate. Of these two mechanistic alternatives the fragmentation pathway is untenable in the present work. A possible mechanism is suggested in Scheme I.

Since Beckwith<sup>9</sup> has shown that treatment of 2-(4-bromobutyl)cyclohexanone with tri-*n*-butyltin hydride yields little or no ring expansion product, it is clear that the ester plays a critical

Scheme I



role in the rearrangement described above, perhaps in activating the ketone and certainly in providing a driving force for the ring expansion.

To summarize, we have described a novel method to enlarge the normal 5-, 6-, and 7-membered  $\beta$ -keto esters in a strictly regioselective reaction to the more difficultly accessible 8-, 9-, 10-, and 11-membered rings.<sup>10</sup>

**Acknowledgment.** This research was generously supported by Institute of General Medical Sciences of the National Institutes of Health under Grant GM 19906.

(10) **Added in Proof:** We have recently learned in a private communication from Professor A. L. J. Beckwith that he has also observed free radical mediated insertion of three and four carbons in cyclic  $\beta$ -keto esters.

## A Receptor for the Oriented Binding of Uric Acid Type Molecules

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Received May 11, 1987

Host-guest chemistry to date has focussed primarily on binding interactions which involve at least one charge-bearing partner (e.g., metal and alkylammonium ions).<sup>1</sup> With rare exceptions,<sup>2a-c</sup> those

(6) Cf. Porter et al. (Porter, N. A.; Magnin, D. R.; Wright, B. T. *J. Am. Chem. Soc.* **1986**, *108*, 2787) where the free radical cyclization of alkyl iodides on unsaturated ketones was very effectively used in the synthesis of medium and large rings.

(7) Competitive addition to carbonyl groups and double bonds has recently been examined by Tsang et al. (Tsang, R.; Dickson, J. K., Jr.; Pak, H.; Walton, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1987**, *109*, 3484). See also: Tsang, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1986**, *108*, 8102. Nickon, A.; Iwadare, T.; Maguire, F. J.; Mahajan, J. R.; Narang, S. A.; Umezawa, B. *J. Am. Chem. Soc.* **1970**, *92*, 1688. Spero, G. B.; Thompson, J. L.; Schneider, W. P.; Kagan, F. *J. Org. Chem.* **1963**, *28*, 755. Sugimoto, H.; Sato, N.; Masumune, T. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 215. Sugimoto, H.; Sato, N.; Masumune, T. *Tetrahedron Lett.* **1967**, 1557. Heusler, K.; Kalvoda, J. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 525.

(8) Cf. Riemann, H.; Capomaggi, A. S.; Strauss, T.; Oliveto, E. P.; Barton, D. H. R. *J. Am. Chem. Soc.* **1961**, *83*, 4481.

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