

Figure 2. Plot of bond length r versus external angle in tricyclo-[2.1.0.0^{2,5}]pentanes ($r = 0.998$).

angle ϕ . The inverse relationship between the bridging bond length r and the bridgehead substituent angle ϕ (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 ϕ shown in Figure 2. This plot constitutes clear and direct confirmation of the theoretical prediction³ and the qualitative suggestion⁶ that the angle ϕ is a direct determinant of the bridging bond length in bicyclobutanes.

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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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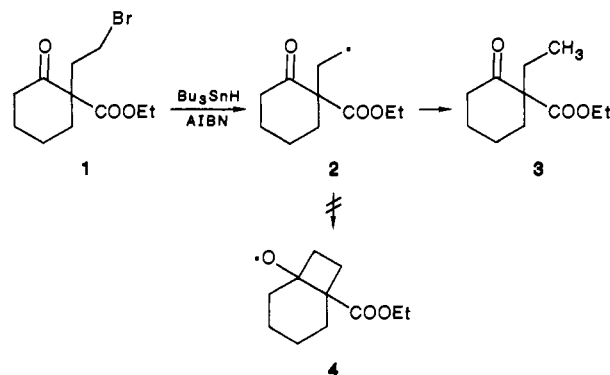
Organic synthesis¹ requires efficient and flexible access to functionalized medium-sized rings. In this paper, we describe a new route to medium-sized rings based upon free radical promoted insertion of a three- or four-carbon chain into a cyclic β -keto ester system. The new reaction is an extension of the recently discovered one-carbon ring expansion reaction of α -(bromomethyl)- β -keto esters with tri-*n*-butyltin hydride as the promoting reagent,²⁻⁴ but

(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.

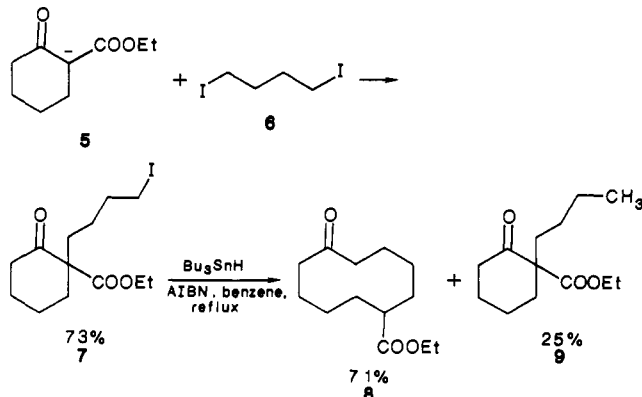
(2) Dowd, P.; Choi, S.-C. *J. Am. Chem. Soc.* **1987**, *109*, 3493.

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 β -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 β -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,⁵ 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%).

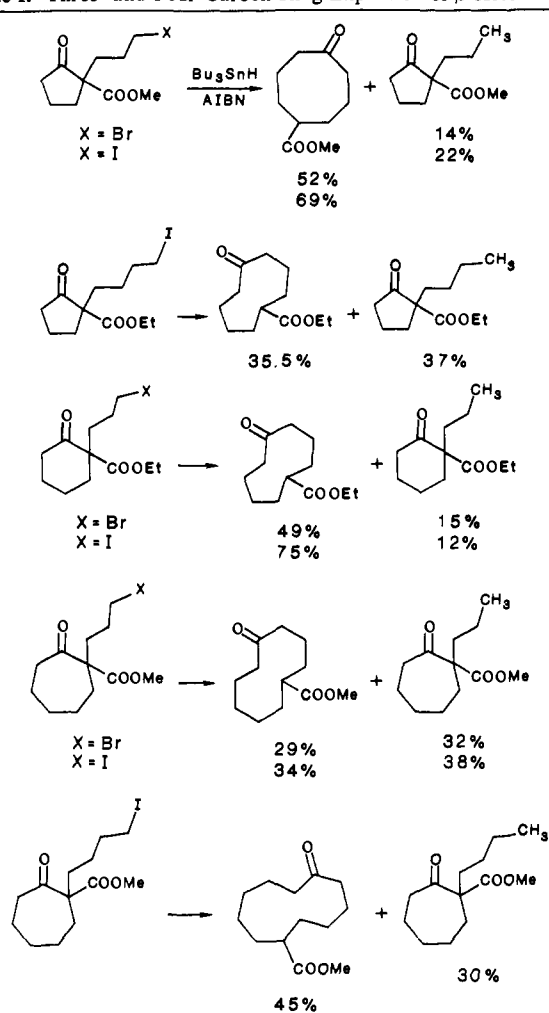
Further examples are presented in Table I. The ring expansion product is readily separated from the direct reduction product by column chromatography since the large ring products elute significantly more slowly than do the direct reduction products.

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.⁶

(3) A similar transformation, carried out simultaneously with our work,² 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 β -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.

Table I. Three- and Four-Carbon Ring Expansion of β -Keto Esters^{a,b}

^aAll new substances had satisfactory carbon-13 and proton NMR, IR, and mass spectra. ^b% isolated yields.

In the one-carbon ring expansion described earlier,²⁻⁴ there were two possible reaction paths. The reaction could have proceeded by addition of the primary radical to the ketone carbonyl⁷ followed by fragmentation-ring enlargement of the oxy radical, as we had (tentatively) formulated the mechanism.² Alternatively, the primary radical might have fragmented to an acyl radical and an acrylate.⁸ The reaction would be completed by addition of the acyl radical to the β -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 Beckwith⁹ 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

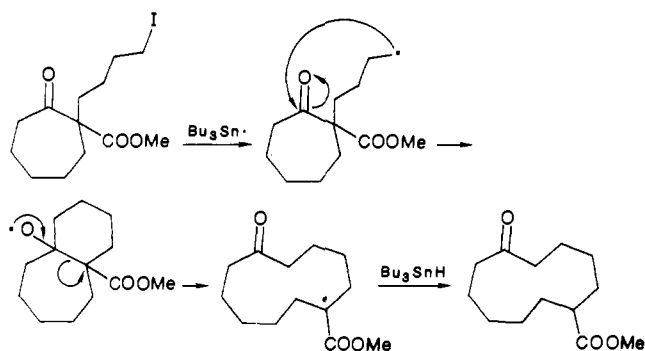
(6) Cf. Porter et al. (Porter, N. A.; Magnin, D. R.; Wright, B. T. *J. Am. Chem. Soc.* **1986**, *108*, 2787) where the free radical cyclization of alkyl iodides on unsaturated ketones was very effectively used in the synthesis of medium and large rings.

(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.

(9) Beckwith, A. L. J.; Kazlauskas, R.; Syner-Lyons, M. R. *J. Org. Chem.* **1983**, *48*, 4718. We thank Professor Dennis P. Curran for this reference.

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 β -keto esters in a strictly regioselective reaction to the more difficultly accessible 8-, 9-, 10-, and 11-membered rings.¹⁰

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(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 β -keto esters.

A Receptor for the Oriented Binding of Uric Acid Type Molecules

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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).¹ With rare exceptions,^{2a-c} those

(1) Among recent leading references see: (a) Cram, D. J. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1039-1057. (b) Colquhoun, H. M.; Stoddart, J. F.; Williams, D. *J. Am. Chem. Soc.* **1986**, *108*, 487-507. (c) Colquhoun, H. M.; Stoddart, J. F.; Williams, D. *J. New Scientist* **1986**, *110* (1 May), 44-48. (d) Vögtle, F.; Löhr, H.-G.; Franke, J.; Worsch, D. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 727-742. (e) Lehn, J. M. *Science (Washington, D.C.)* **1985**, *227*, 849-856. (f) Breslow, R. *Adv. Enzymol.* **1986**, *58*, 1-60. (g) Sheppard, T. J.; Petti, M. A.; Dougherty, D. A. *J. Am. Chem. Soc.* **1986**, *108*, 6085-6087. (h) Bell, T. W.; Firestone, A. *Ibid.* **1986**, *108*, 8109-8111. (i) van Staveren, C. J.; Fenton, D. E.; Reinhoudt, D. N.; van Eerden, J.; Harkema, S. *Ibid.* **1987**, *109*, 3456-3458.

(2) (a) Rebek, J., Jr.; Askew, B.; Islam, N.; Killoran, M.; Nemeth, D.; Wolak, R. *J. Am. Chem. Soc.* **1985**, *107*, 6736-6738. Rebek, J., Jr.; Marshall, L.; Wolak, R.; Parris, K.; Killoran, M.; Askew, B.; Nemeth, D.; Islam, N. *Ibid.* **1985**, *107*, 7476-7481. Rebek, J., Jr.; Nemeth, D. *Ibid.* **1986**, *108*, 5637-5638. Rebek, J., Jr.; Askew, B.; Ballester, P.; Buhr, C.; Jones, S.; Nemeth, D.; Williams, K. *Ibid.* **1987**, *109*, 5033-5035. Rebek, J., Jr. *Science (Washington, D.C.)* **1987**, *235*, 1478-1484. (b) Feibush, B.; Figueroa, A.; Charles, R.; Onan, K. D.; Feibush, P.; Karger, B. L. *J. Am. Chem. Soc.* **1986**, *108*, 3310-3318. (c) Hine, J.; Ahn, K.; Gallucci, J. C.; Linden, S.-M. *Ibid.* **1984**, *106*, 7980-7981. (d) Sheridan, R. E.; Whitlock, H. W., Jr. *Ibid.* **1986**, *108*, 7120-7121. (e) Hamilton, A. D.; Engen, D. V. *Ibid.* **1987**, *109*, 5035-5036. For less oriented binding of neutral guests in nonaqueous solvents see, inter alia: (f) Jarvi, E. T.; Whitlock, H. W. *Ibid.* **1982**, *104*, 7196-7204. (g) Bauer, L. J.; Gutsche, C. D. *Ibid.* **1985**, *107*, 6063-6069. (h) O'Krongly, D.; Denmeade, S. R.; Chiang, M. Y.; Breslow, R. *Ibid.* **1985**, *107*, 5544-5545. (i) Mosier-Boss, P. A.; Popov, A. I. *Ibid.* **1985**, *107*, 6168-6174. (j) Menger, F. M.; Dulany, M. A. *Tetrahedron Lett.* **1985**, *26*, 267-270. (k) Canceill, J.; Lacombe, L.; Collet, A. *J. Am. Chem. Soc.* **1986**, *108*, 4230-4232. (l) Ferguson, S. B.; Diederick, F. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1127-1129. (m) Lutter, H.-D.; Diederick, F. *Ibid.* **1986**, *25*, 1125-1127. (n) Aarts, V. M. L. J.; van Staveren, C. J.; Grootenhuys, P. D. J.; van Eerden, J.; Kruijs, L.; Harkema, S.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1986**, *108*, 5035-5036, and ref 1a.