Atom Transfer Cyclization Reactions of α-Iodo Esters, Ketones, and Malonates: Examples of Selective 5-Exo, 6-Endo, 6-Exo, and 7-Endo Ring Closures

Dennis P. Curran*[1] and Chi-Tai Chang

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

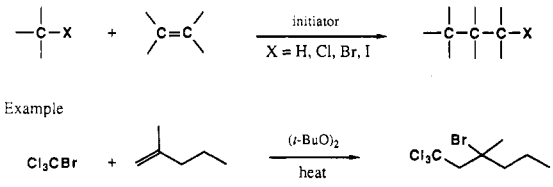
Received January 13, 1989

The preparation and free-radical cyclization reactions of unsaturated α-iodo esters, ketones, and malonates have been investigated. For example, sunlamp irradiation of methyl 2-iodo-6-heptenoate in benzene in the presence of 10 mol % hexabutylditin produces methyl 2-(iodomethyl)cyclopentanecarboxylate (cis and trans) and methyl 3-iodocyclohexanecarboxylate in a ratio of 93/7 in a combined yield of 86%. The γ-iodo carbonyl products can either be isolated (in most cases) or converted in situ to deiodinated products (with Bu_3SnH) or lactones (by heating). Five-, six-, or seven-membered rings selectively form, depending on chain length and alkene substitution. Terminal alkene substituents favor exo cyclization while internal alkene substituents promote endo cyclization. A preference for endo closure is also observed when there is a carbonyl group "inside" the forming ring. A detailed analysis of reaction rates indicates that these isomerizations proceed by an iodine atom transfer chain mechanism, and thus the observed selectivities are due to the kinetic substituent effects. The results contrast the thermodynamically controlled hydrogen atom transfer cyclizations of Julia. A new procedure for the removal of tin byproducts is described.

Introduction

The increasing application of free-radical reactions to problems in organic synthesis is a testament to the diverse types of transformations that can be accomplished.[2] This diversity notwithstanding, there are relatively few methods by which free-radical reactions can be conducted. For synthetic application,[2a] a method is required that (1) generates an initial radical with site selectivity, (2) permits this radical (and other intermediate radicals) some lifetime to undergo reactions, and (3) converts the final radical to a stable product before it can be consumed by radical–radical reactions, radical–solvent reactions, or undesired radical–reagent reactions. Certain chain reactions can meet these requirements, and methods based on the chemistry of organotin hydrides (the tin hydride method), allyl- and vinyltins (the fragmentation method), and thiohydroxamate esters (the Barton method[3]) have greatly expanded the repertoire of bond-forming reactions that is at the disposal of the synthetic organic chemist.[2] The use of halogen atom transfer to mediate free-radical reactions is rapidly emerging as a powerful, often complementary, alternative to the above methods.[2a,4,5] Herein, we report the details of an investigation on the atom transfer cyclization reactions of α-iodo esters, ketones, and malonates.[6] The atom-transfer method is particularly suited for mediating the reactions of these electrophilic radicals,[7] and much of their basic cyclization chemistry (regioselectivity, stereoselectivity) is presented herein.

The atom transfer addition of a C–X bond (where X is a univalent atom) across a double bond is a fundamental reaction of organic free radicals (eq 1), the scope and underlying principles of which were pioneered by Kharasch.[8] The addition of polyhalomethanes and related molecules across carbon–carbon double bonds is a well studied, if infrequently used, method for the formation of C–C bonds. The scope of this reaction is greatly expanded by the addition of certain metals,[9-11] although it is not always clear whether organometallic intermediates, metal-complexed radicals, or free radicals (with the metal acting only as an initiator) are involved as intermediates.[12]



(1) Recipient of a Sloan Foundation Fellowship, 1985–87. Dreyfus Teacher–Scholar, 1985–89. Eli Lilly Grantee, 1985–87. Merck Faculty Development Awardee, 1986–87. NIH Research Carrer Development Awardee, 1987–92.

(2) (a) Curran, D. P. *Synthesis* **1988**, 417 and 489. (b) Giese, B. *Radicals in Organic Synthesis; Formation of Carbon–Carbon Bonds*; Pergamon Press: Oxford, 1986. (c) Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541. (d) Neumann, W. P. *Synthesis* **1987**, 665. (e) Hart, D. J. *Science* **1984**, *223*, 883.

(3) Crich, D. *Aldrichimica Acta* **1987**, *20*, 35.

(4) (a) Curran, D. P.; Chen, M.-H.; Kim, D. *J. Am. Chem. Soc.* **1986**, *108*, 2489. (b) Curran, D. P.; Kim, D. *Tetrahedron Lett.* **1986**, *27*, 5821. (c) Curran, D. P.; Chen, M.-H. *J. Am. Chem. Soc.* **1987**, *109*, 6558.

(5) Iodine atom transfer is a key step in a series of new redox chain additions to protonated heteroaromatic bases: Fontana, F.; Minisci, F.; Vismara, E. *Tetrahedron Lett.* **1987**, *28*, 6373. It is probably also an important step in recent triethylborane-promoted additions of iodides to enones: Nozaki, K.; Oshime, K.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 1041.

(6) Portions of this work have been reported in preliminary form. Curran, D. P.; Chang, C.-T. *Tetrahedron Lett.* **1987**, *28*, 2477 and Section 5.2.2 of ref 2a.

(7) Electrophilic (carbonyl-substituted) radicals have frequently been formed by the addition of nucleophilic radicals to activated alkenes but have rarely been used to form C–C bonds in cyclization reactions. For examples, see: Curran, D. P.; Kuo, S.-C. *Tetrahedron* **1987**, *43*, 5653. Feldman, K. S.; Romanelli, A. L.; Ruckle, R. E., Jr.; Miller, R. F. *J. Am. Chem. Soc.* **1988**, *110*, 3300. See also ref 4c.

(8) (a) Walling, C.; Huyser, E. S. *Org. React.* **1963**, *13*, 91. (b) Stacy, F. W.; Harris, J. F. *Org. React.* **1963**, *13*, 150.

(9) Review: Bellus, D. *Pure Appl. Chem.* **1985**, *57*, 1827.

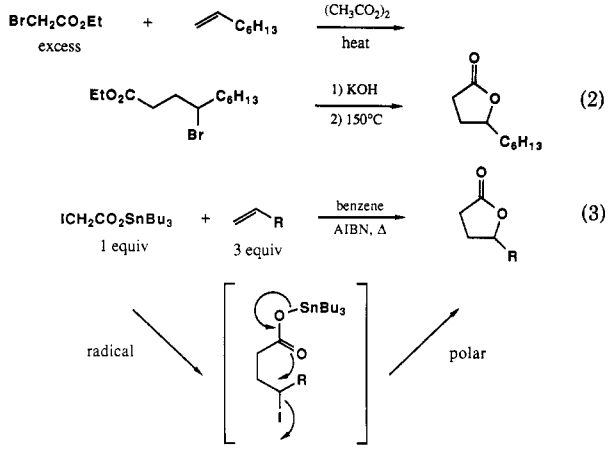
(10) Examples of addition reactions: (a) Maruaka, K.; Sano, H.; Fukatani, Y.; Yamamoto, H. *Chem. Lett.* **1985**, 1689. (b) Tsuji, J.; Sato, K.; Nagashima, H. *Tetrahedron* **1985**, *41*, 5003, 5645. (c) Fields, D. L., Jr.; Shechter, H. *J. Org. Chem.* **1986**, *51*, 3369.

(11) Examples of cyclization reactions: (a) Takano, S.; Nishizawa, S.; Akiyama, M.; Ogasawara, K. *Synthesis* **1984**, 949.. (b) Mori, M.; Kanda, N.; Ban, Y. *J. Chem. Soc., Chem. Commun.* **1986**, 1375. (c) Mori, M.; Kanda, N.; Oda, I.; Ban, Y. *Tetrahedron* **1985**, *41*, 5465. (d) Mori, M.; Kubo, Y.; Ban, Y. *Tetrahedron Lett.* **1985**, *26*, 1519. (e) Mori, M.; Kubo, Y.; Ban, Y. *Tetrahedron* **1988**, *44*, 4321. (f) Nagashima, H.; Ara, K.; Watamakstu, H.; Itoh, K. *J. Chem. Soc., Chem. Commun.* **1985**, 518. (g) Hayes, T. K.; Freyer, A. J.; Parvez, M.; Weinreb, S. M. *J. Org. Chem.* **1986**, *51*, 5501. (h) Hayes, T. K.; Villani, R.; Weinreb, S. M. *J. Am. Chem. Soc.* **1988**, *110*, 5533. This reference contains a good bibliography of related reactions.

(12) Grigg, R.; Devlin, J.; Ramasubbu, A.; Scott, R. M.; Stevenson, P. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1515.

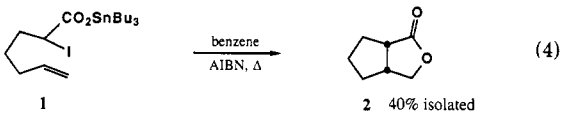
0022-3263/89/1954-3140$01.50/0

That polyhalogenated derivatives were not required for such reactions was reported as early as 1948 in a seminal paper by Kharasch, Skell, and Fisher[13] which described the addition of ethyl bromoacetate to 1-octene (eq 2). Sporadic developments in this area[14] were punctuated by an important report by Kraus and Landgrebe[15] in 1984 of a convenient new synthesis of lactones from alkenes (eq 3). Based on the Kharasch precedent and concurrent



developments in our lab,[4a] we were convinced that the new lactone annulation must proceed by atom transfer addition across the double bond and subsequent polar lactonization (facilitated by the nucleophilicity of the stannyl ester). Early in our study, the mechanism outlined in eq 3 was both proposed and confirmed by Kraus and Maillard.[16] Believing that the key halogen atom transfer[17] step was greatly facilitated by the use of iodine as the donor rather than bromine, we undertook a general study of the synthetic potential of this iodine atom transfer reaction as a method to mediate free-radical cyclizations of such carbonyl-substituted radicals.

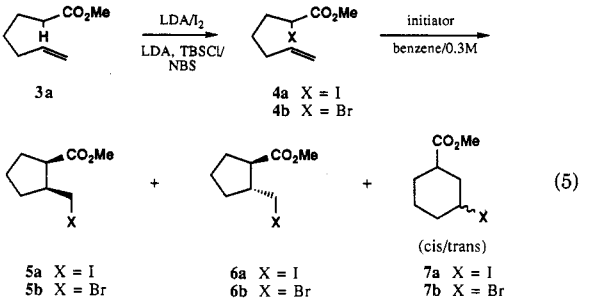
Atom Transfer Cyclizations of α-Iodo Esters and Ketones. Initial Studies. An intriguing example from the work of Kraus and Landgrebe[15b] served as a starting point for our studies (eq 4). When iodo stannyl ester **1** was refluxed for 4 h in benzene containing 5% AIBN, lactone **2** was isolated in 40% yield. We considered three explanations for the isolation of only the 5-exo cis isomer **2**: (1) the radical cyclization is irreversible and gives mainly the 5-exo cis product, (2) the radical cyclization is reversible but only the 5-exo cis product lactonizes, or (3) the radical cyclization is neither highly selective nor reversible but products derived from cyclization in a 5-exo trans fashion (or a 6-endo fashion) are not isolated because they cannot readily lactonize. The latter two explanations are conceivable because trans bicyclo[3.3.0] lactones are difficult to form due to ring strain.[18] A series of experiments quickly demonstrated that the third proposal was correct.



1 2 40% isolated

Iodination of methyl 6-heptenoate[19] was accomplished by the method of Rathke.[20] Deprotonation of **3a** with LDA, followed by addition to molecular iodine, gave **4a** in 80% yield after purification by flash chromatography. Other iodo esters and ketones were prepared similarly and were typically isolated as yellow oils that were >95% pure according to NMR and GC analysis. Although sensitive to light, these iodides could be stored in the freezer for extended periods; however, most were reacted soon after their preparation.

The atom transfer cyclization reaction of **4a** was investigated with several different initiators (see eq 5). Heating of **4a** in refluxing benzene in the presence of 10% tri-*n*-butyltin hydride and 10% AIBN gave cyclic iodides **5a/6a/7a** in 48% combined yield after isolation by flash chromatography. Heating of **4a** for 24 h with 10 mol %



Halide	Initiator	Time	5 / 6 / 7(cis/trans)	Yield
4a	10% Bu_3SnH/AIBN	5h	48 45 7(1/2.1)	48%
4a	10% AIBN	24h	49 43 8(1/2)	78%
4a	$Me_3SnSnMe_3$/heat	16h	53 40 7(1/1.9)	83%
4b	$Bu_3SnSnBu_3$/hv	24h	50 40 10(1/1.9)	42%

AIBN alone or with 10 mol % AIBN and 10 mol % hexamethylditin (added in two portions at 1-h intervals) gave better yields (78%, 83%) of products but required longer reactions times (16–24 h) for complete conversion. For comparison purposes, bromide **4b** was also prepared; however, attempted isomerization of **4b** under each of the above reaction conditions produced only traces of isomerized products **5b–7b** accompanied by large amounts of unreacted starting bromide **4b**. Attempted initiations with dibenzoyl peroxide and di-*tert*-butyl peroxide were also not successful. In contrast, irradiation of **4b** with a 275-W sunlamp in the presence of 10% hexabutylditin for 24 h did produce significant amounts of isomerized products **5b–7b** (42%, combined), although unreacted bromide was still present. Clearly the bromide is much less reactive than the iodide.

The products from the cyclization of **4a** could be separated by flash chromatography to provide **5a**, **6a**, and **7a** (as a cis/trans mixture). Structures were assigned by a combination of methods. Reduction of the mixture of iodocyclohexanecarboxylates **7a** provided methyl cyclohexanecarboxylate. The gross structure of the (iodomethyl)cyclopentanecarboxylates was readily discerned from the ^1H NMR spectra. The stereochemistry was assigned by chemical transformations (eq 6). Treatment of the major isomer **5a** with iodotrimethylsilane produced the derived carboxylic acid, which readily lactonized on

(13) Kharasch, M. S.; Skell, P. S.; Fisher, P. *J. Am. Chem. Soc.* **1948**, *70*, 1055.

(14) (a) Kharasch, N.; Lewis, P.; Sharma, R. K. *J. Chem. Soc., Chem. Commun.* **1967**, 435. (b) Nakano, T.; Kayama, M.; Matsumoto, H.; Nagai, Y. *Chem. Lett.* **1981**, 415. (c) Nakano, T.; Kayama, M.; Nagai, Y. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1049. (d) Ghodoussi, V.; Gleicher, G. J.; Kravetz, M. *J. Org. Chem.* **1986**, *51*, 5007.

(15) (a) Kraus, G. A.; Landgrebe, K. *Tetrahedron Lett.* **1984**, *25*, 3939. (b) Kraus, G. A.; Landgrebe, K. *Tetrahedron* **1985**, *41*, 4039. (c) For a recent application, see: Pezechk, M.; Brunetiere, A. P.; Lallemand, J. Y. *Tetrahedron Lett.* **1986**, *27*, 3715.

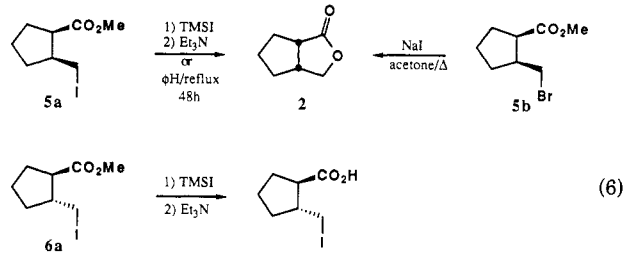
(16) Degueil-Castaing, M.; De Jeso, B.; Kraus, G. A.; Landgrebe, K.; Maillard, B. *Tetrahedron Lett.* **1986**, *27*, 5927.

(17) For reviews of halogen atom abstraction, see: Danen, W. C. In *Methods in Free Radical Chemistry*; Huyser, E. S., Ed.; Marcel Dekker: New York, 1974; Vol. 5, pp 1–100. Also, Poutsma, M. *Free Radicals*; Kochi, J. K., Ed.; Wiley: New York, 1973; Vol. II, p 23.

(18) Paquette, L. A. *Top. Curr. Chem.* **1979**, 41.

(19) Most cyclization precursors were prepared by simple malonate alkylation followed by standard decarboxylation. Full details are contained in the Ph.D. Thesis of C.-T. Chang, University of Pittsburgh, 1989.

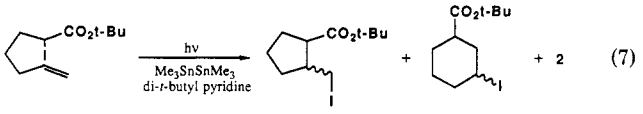
(20) Rathke, M. W.; Lindert, A. *Tetrahedron Lett.* **1971**, 3995.



(6)

basification to give **2**. Under the same conditions, the acid derived from **6a** resisted lactonization. Heating of **5a** in refluxing benzene for 48 h also gave **2** in 80% yield while **6a** did not react. The structures of the bromides were assigned similarly. To confirm the stereochemical assignment, **5b** was heated with sodium iodide in acetone to provide **2**. These transformations are representative of the methods of structure assignment that were used throughout this work.[21]

The behavior of the *tert*-butyl ester **8** was next investigated (eq 7). The ditin initiation was attempted first because it was the only successful procedure for the relatively unreactive bromide. Iodide **8** was completely consumed after only 10 min of irradiation in the presence of 10% hexamethylditin. In addition to the isomerized products, **9-cis/trans** and **10-cis/trans**, a substantial amount of lactone **2** was already present. Control experiments showed that **2** was not a primary product but arose from the facile thermal reaction of **9-cis**. The product ratios reported in eq 7 were obtained by conducting the

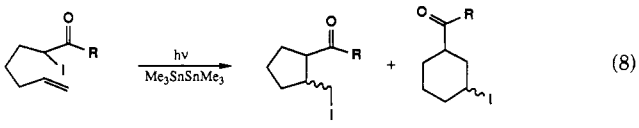


(7)

8	9-cis/9-trans	10(cis/trans)	Yield
	44/49	6(1/2.2)	74%

isomerization in the presence of a catalytic amount of di-*tert*-butylpyridine which suppressed, but did not completely eliminate, the formation of lactone **2**. The ratio of **9-cis** is corrected for the small amount of lactone (~5%) that formed from it. The *tert*-butyl ester **9-cis** lactonized much more readily than the methyl ester **5a**, and the Kraus stannyl esters (eq 3) may be so reactive that lactonization becomes faster than atom-transfer cyclization.[16]

The behavior of two simple α-iodo ketones was also investigated. Compounds **11a/b** were selected to avoid potential regiochemical problems in the iodination of the enolates. Irradiation of either **11a** or **11b** in the presence of AIBN resulted in their decomposition over several hours without formation of identifiable products. However, irradiation with 10 mol % hexamethylditin resulted in rapid consumption of both starting iodides (10 min). The cyclic iodides that were produced are summarized in eq 8. With

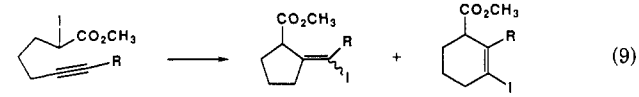


(8)

	12-cis/12-trans	13(cis/trans)	Yield
11a R = *t*-Bu	20/54	26(1/2.0)	63%
11b R = Ph	21/54	25(1/2.2)	68%

these ketones, significantly more 6-endo products **13a/b** formed (5-exo/6-endo = 3/1). Chromatography of the respective crude reaction mixtures effected separation, and pure **12a/b-trans**, **13a/b-cis**, and **13a/b-trans** were isolated in combined isolated yields of 63 and 68%, respectively. Neither **12a-cis** nor **12b-cis** could be isolated; both apparently decomposed during chromatography. However, their presence in the crude reaction mixture was easily discerned by the characteristic NMR peaks of the iodomethyl protons.[21] Thus, the lower yields in these two cases reflect the loss of 20% of the products on the chromatography columns.

The cyclization reactions of two alkynyl α-iodo esters were also investigated (eq 9). Irradiation of terminal acetylene **14** with ditin gave a 94/6 ratio of **15** (5-exo) and **16** (6-endo) in 85% combined isolated yield. Similar treatment of (trimethylsilyl)alkyne **17** gave only the 5-exo product **18**. The 6-endo isomer **19** could not be detected.



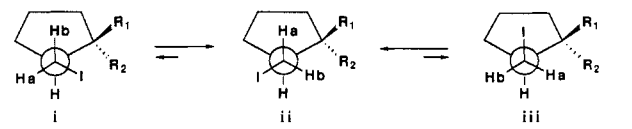
(9)

				yield
14 R = H	15	94/6	16	85%
17 R = TMS	18	>97/3	19	81%

The photolytic initiation method with ditin was so rapid and effective relative to the other methods that it was adopted as the standard procedure. In general, a 0.3 M solution of iodide containing 10 mol % hexabutylditin or hexamethylditin was dissolved in benzene (or benzene-d_6) in a standard Pyrex flask or NMR tube. The mixture was irradiated with a 275-W sunlamp for 10–60 min. In most cases, the starting iodide was consumed as indicated by TLC, GC, or NMR. If starting iodide remained, an additional portion of ditin was added and irradiation was continued. The sunlamp was placed at a distance that maintained the reaction temperature below the reflux point of benzene. This distance varied from 5 to 10 cm depending on the size of the reaction vessel. Since small reaction vessels were used in many experiments (NMR tubes were particularity convenient for following reaction progress and obtaining product ratios), the precise reaction temperatures were not often determined. We estimate that most reaction temperatures climbed rapidly due to the heat of the lamp to 70–85 °C. In the successful reactions, the cyclic iodides were the major reaction products. However, in nearly every reaction, traces of reduced starting material (<5%) could be detected along with small amounts of what we assumed to be oligomeric products.[22]

The iodide products could be isolated by direct chromatography of the crude reaction mixture after removal of the benzene. In many cases, the reductively deiodinated products were formed by adding 1.1 equiv of tri-*n*-butyltin hydride and a catalytic amount of AIBN directly to the reaction mixture. After continued heating for 1–4 h, the tin products were substantially removed by a new workup

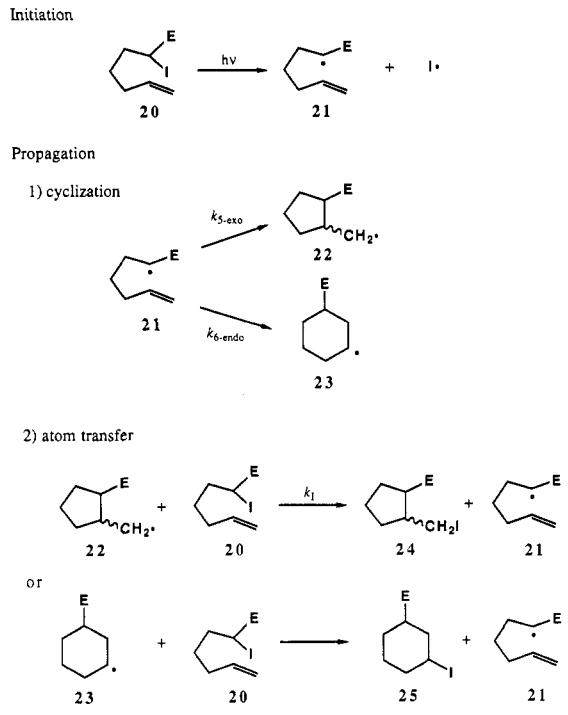
(21) The coupling constants of the iodomethyl protons (H_a, H_b) were diagnostic of the stereochemistry. In the trans isomer, both protons always appeared as doublets of doublets. In the cis isomer, one proton (H_b) was always a doublet of doublets but the other (H_a) was always a triplet ($J_{vicinal} \approx J_{geminal}$). We believe that this is due to the conformation behavior illustrated in the Newman projections below. Conformer iii is the highest in energy for either the cis or trans isomer. In the trans isomer, two conformers (i and ii) are comparable in energy. In the cis isomer, conformer i is disfavored due to interaction between R_1 and CH_2I. Conformer ii has a large coupling constant between H and H_a that approximately equals the vincinal coupling constant (J_{AB}).



cis R_1 = COR, R_2 = H
trans R_1 = H, R_2 = COR

(22) A broad, weak absorption in the alkene region was observed in virtually every crude ^1H NMR spectrum. Products containing this resonance were never isolated.

Scheme I



procedure employing 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The resulting crude products were further purified by chromatography. Several workup procedures for the removal of tin halides are commonly used.[23] This convenient and practical procedure with DBU is described briefly at the end of the paper.

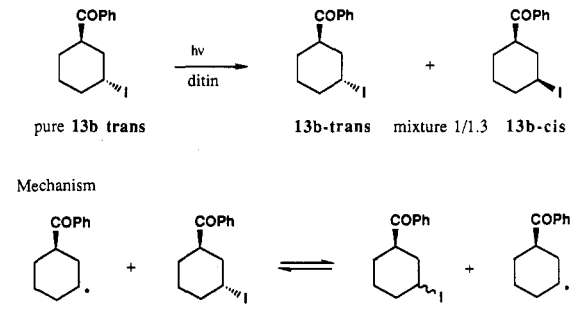
Mechanism. The proposed mechanism for these isomerization reactions is outlined in Scheme I. The initiation is believed to involve photolytic cleavage of a carbon–iodine bond of **20** to give stabilized radical **21** and atomic iodine. The ditin functions to rapidly consume either atomic or molecular iodine, both of which react rapidly with radicals and suppress chain reactions.[24]

The name "atom transfer cyclization" derives from the two propagation steps and thus describes the overall transformation. Cyclization of **21** in a 5-exo mode gives **22-cis/trans** and closure in a 6-endo mode gives **23**. Despite the conversion of a resonance-stabilized radical to an alkyl radical, this cyclization is significantly exothermic because of the gain in energy in the conversion of a carbon–carbon π-bond to a carbon–carbon σ-bond. As a result, both **22** and **23** are more reactive than the starting radical **21** and either can abstract iodine from the starting iodide **20** in a rapid, exothermic step. This gives the products (**24** and **25**) and regenerates the starting radical **21**.

The exothermic transfer of iodine atoms from organic iodides to radicals is a very fast reaction.[25,26] Indeed we believe that virtually any time an exothermic addition, cyclization, or fragmentation reaction converts a more resonance stabilized radical to a less resonance stabilized counterpart, iodine atom transfer will rapidly follow and a viable chain will result.[2a] Because bromine transfer is much slower than iodine transfer, the chain process is significantly less efficient with bromo esters.[27] Chain reactions incorporating an endothermic iodine atom transfer are not likely to succeed. As we will illustrate, this atom-transfer method to conduct radical reactions can have significant advantages over other radical chain reactions.

A central question in the mechanism involves the possibility of reversible cyclization. Although it is well known from the pioneering work of Julia[28] that stabilizing groups such as carbonyls can allow radical cyclizations to be reversible, very little is known about how rapid such reverse cyclization reactions are.[29] A series of control experiments was undertaken to determine if the product ratios that were observed were kinetically controlled. The reduction of several of the iodide products (both pure and as crude reaction mixtures) was conducted with Bu_3SnH at 0.02 M.[30] In no case was any evidence for crossover detected (that is, the 5-cis/5-trans and 5-exo/6-endo ratios of the reduced products always reflected the ratios of the starting iodides). This indicates that ring opening is slower than reduction of alkyl radicals by tin hydride at 0.02 M.

Several attempts to isomerize products by resubjecting them to the reaction conditions led to the following conclusions: (1) the 5-exo products were completely stable to the reaction conditions, and (2) the 6-endo products could equilibrate with each other but were not converted to 5-exo products. For example, the resubjection of **5a** to irradiation with or without an initiator resulted in lactonization to **2** with no evidence for isomerization to **6a** or **7**. Isomer **6a** did not lactonize, nor form **5a** or **7**, but slowly decomposed. However, irradiation of pure 6-endo product **13b-trans** resulted in interconversion with **13b-cis** without formation of **12b-cis** or **12b-trans**. After 30 min or irradiation starting with pure **13b-trans**, a 1/1.3 ratio of **13b-cis/13b-trans** was formed. There is no indication that equilibrium had been reached. In this case, interconversion does not involve a reversible cyclization but only the exchange of iodine atoms between alkyl radicals (eq 10).[4b,25]



(10)

That both iodide **4a** and bromide **4b** gave (within experimental error) the same product ratios also supports the proposed irreversible closure. If cyclization had been

(23) The most popular workup involves treatment of the reaction mixture with fluoride: Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636. Leibner, J. E.; Jacobus, J. *J. Org. Chem.* **1979**, *44*, 449.

(24) A detailed discussion of the initiation and the role of the ditin is provided in the following full paper: Curran, D. P.; Chen, M.-H.; Kim, D. *J. Am. Chem. Soc.*, in press.

(25) (a) Newcomb, M.; Curran, D. P. *Acc. Chem. Res.* **1988**, *21*, 206. (b) Newcomb, M.; Sanchez, R. M.; Kaplan, J. *J. Am. Chem. Soc.* **1987**, *109*, 1195.

(26) Curran, D. P.; Bosch, E.; Kaplan, J.; Newcomb, M. *J. Org. Chem.* **1989**, *54*, 1826.

(27) Another problem with chains based on bromine transfer could be inefficient initiation. Photolytic cleavage of the C–Br bond of **4b** with a sunlamp is not likely.

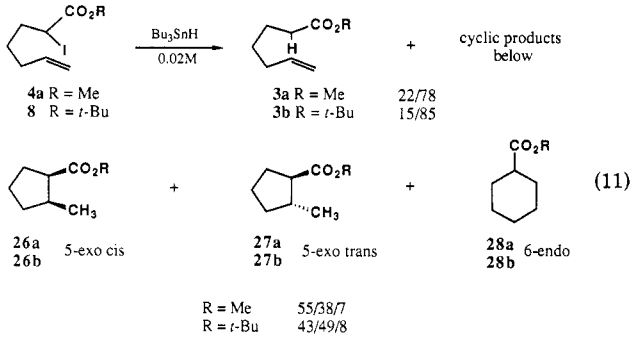
(28) Julia, M. *Acc. Chem. Res.* **1971**, *4*, 386; *Pure Appl. Chem.* **1974**, *40*. 553. A nice discussion of the contributions from the Julia group is given by Surzur, J. M. In *Reactive Intermediates*; Abramovitch, R. A., Ed.; Plenum Press: New York, 1982; Vol. 2, Chapter 3.

(29) (a) Equilibration via benzyl radicals: Pines, H.; Sih, N. C.; Rosenfeld, D. B. *J. Org. Chem.* **1966**, *31*, 2235. Walling, C.; Cioffari, A. *J. Chem. Soc.* **1972**, *94*, 6064. (b) Possible equilibration via ester-, ketone-, and nitrile-substituted radicals: Julia, M.; Maumy, M. *Bull. Soc. Chim. Fr.* **1969**, 2415 and 2427.

(30) For example, reduction of pure **12b-trans** at 0.02 M gave *trans*-2-methyl-1-benzoylcyclopentane as the only detectable product.

reversible, more equilibration should have occurred with the bromide because the intermediate radicals **22** and **23** have a longer lifetime (bromine transfer is slower than iodine transfer).[26]

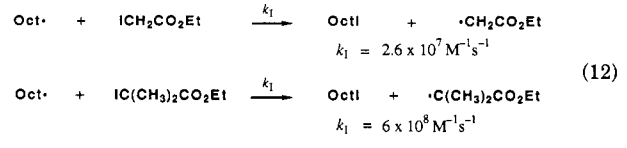
Additional evidence came from the reduction of both the methyl ester **4a** and the *tert*-butyl ester **8** with 1.1 equiv of tri-*n*-butyltin hydride at 85 °C (eq 11). The ratios of



(11)

reduced cyclic products **26a/b–28a/b** produced in these reactions (at 0.02 M) were very similar to the ratios of isomerized products from eq 5 and 7. In addition to reduced cyclic products, significant amounts of reduced acyclic products **3a/b** (22 and 15%, respectively) resulted from these experiments. The trapping of radicals by hydrogen abstraction from the reagent before cyclization is a common problem in the tin hydride method. With substrates **4a** and **8**, concentrations lower than 0.02 M are required to decrease the amount of direct reduction. Since no tin hydride is present during isomerization by the atom-transfer method, these reactions can be conducted at relatively high concentrations (0.3 M). If the reduced cyclized products are desired, tin hydride can be added after the cyclization is complete to effect reductive deiodination at high concentration. With radicals that will propagate a chain by the atom-transfer method, we suggest that this two-stage method (isomerization/reduction) at high concentration will be comparable to the direct reduction with tin hydride at very low concentration when ring opening is slow relative to ring closure. It will be superior to tin hydride when ring opening is competitive with ring closure.[31] Several examples of this technique will be provided below.

These results provide strong circumstantial evidence indicating that the cyclizations of these substrates are not reversible. That ring opening cannot possibly compete with iodine atom transfer was rigorously established by measuring rate constants for the reaction of octyl radical with ethyl iodoacetate and ethyl iodoisobutyrate.[26] These rate constants (at 50 °C) are listed in eq 12. It is safe to assume that the rate of a secondary iodo ester such as **4a** will fall about halfway in between these numbers.



(12)

(31) The atom-transfer method is convenient because it is rapid and does not require large solvent volumes. With reactive halides such as iodocarbonyls, very good results can probably be obtained with very low tin hydride concentrations (either syringe pump addition or catalytic tin hydride/sodium cyanoborohydride). However, at the low concentrations required for cyclization, the kinetic product may not always be trapped with tin hydride. By providing a long lifetime for the initial radical to permit cyclization, tin hydride also provides a long lifetime for the cyclic radical (equilibration may occur). The atom-transfer method provides a long lifetime for the initial radical and permits cyclization but rapidly traps the cyclic radical to insure the formation of kinetic products.

Figure 1. Orientation of the carbonyl.

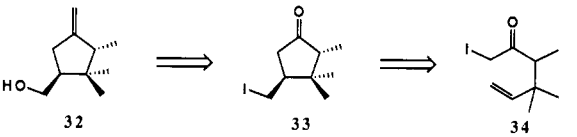
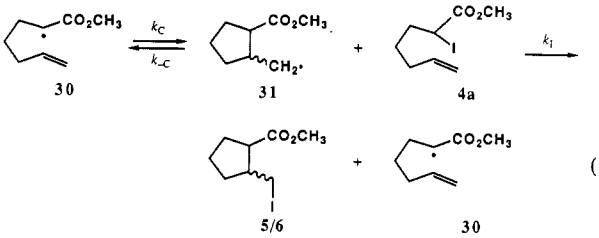


Figure 2.

With this estimate and the known rate constant for reaction of primary alkyl radicals with tin hydride,[32] we are now in a position to quantitatively evaluate the fate of a cyclic radical such as **31** arising form the kinetic closure of **30** (eq 13).



(13)

The maximum rate of disappearance of **31** by reverse cyclization can be estimated from the tin hydride control experiments as

$$k_{-c} \leq k_H[Bu_3SnH](0.1)$$

The factor 0.1 assumes that 10% crossover could readily have been detected by GC. This is a conservative estimate since no crossover products were observed. Substituting the values for k_H and $[Bu_3SnH]$ leads to

$$k_{-c} < 4 \times 10^3\ s^{-1}$$

The rate of disappearance of **31** to give **5/6** is

$$d31/dt = k_I[4a]$$

Substituting an estimate of the rate constant for iodine atom transfer for a secondary iodo ester (based on the rates of eq 12) and the initial concentration gives

$$d31/dt \approx 3 \times 10^8\ M^{-1}\ s^{-1} \times [0.3]$$

$$\approx 1 \times 10^8\ s^{-1}$$

Thus the initial rate of iodine transfer of **31** ($\sim 1 \times 10^8$ s^{-1}) is more than 4 orders of magnitude faster than the maximum rate of reverse cyclization (4×10^3 s^{-1}). We conclude that reverse cyclization cannot compete with iodine atom transfer in any of the examples presented and that all of the observed product ratios are the result of kinetic control.

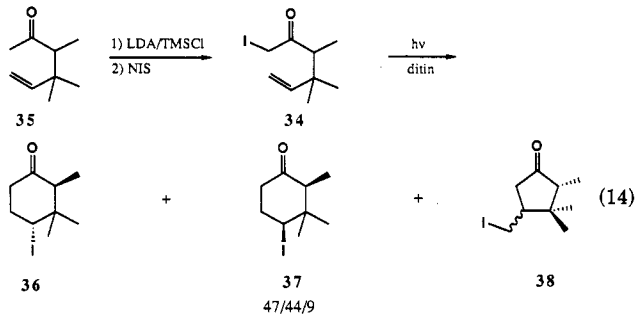
Regiochemistry of Cyclizations. A common feature in all of the previous substrates is the orientation of the carbonyl group outside (exo to) the forming ring (see Figure 1). A projected synthesis of the simple natural product necrodol (**32**)[33] provided the opportunity to study the cyclization of a substrate with a carbonyl group inside (endo to) the forming ring. The plan (Figure 2) called for

(32) Chatgilialogu, C.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 7739.

(33) Isolation: Jacobs, R.; Feutrill, G.; Meinwald, J. *Tetrahedron Lett.* **1983**, *24*, 2441. Meinwald, J. *Ann. N. Y. Acad. Sci.* **1986**, *471*, 197. Synthesis: Oppolzer, W.; Schneider, P. *Helv. Chim. Acta* **1986**, *69*, 1817. Trost, B. M.; Braslau, R. *Tetrahedron Lett.* **1988**, *29*, 1231.

isomerization of iodo ketone **34** to **33**. However, the synthesis did not proceed according to plan!

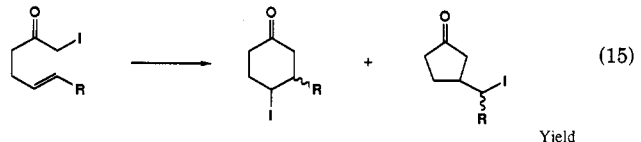
Ketone **35** is readily available from 3-methyl-2-buten-1-ol by Johnson–Claisen rearrangement with 2,2-dimethoxybutane.[34] Iodination of the kinetic enol silyl ether derived from **35** provided **34** (eq 14). Irradiation of **34**



(14)

under the usual conditions provided four isomeric cyclized products in 82% yield.[35] The two major products **36** and **37** (91% of the cyclic products) were readily identified as resulting from 6-endo cyclization because each produced 2,3,3-trimethylcyclohexanone on reduction with tin hydride. The minor products (9% of the cyclic products) were assigned as stereoisomers of the (iodomethyl)cyclopentanone **38** (unassigned 3/1 ratio of stereoisomers).

Although the synthesis of necrodol was foiled by this (at the time surprising) regiochemical outcome, we were encouraged to investigate the effect of an "endo-oriented" carbonyl group as a potential route to formation of products derived from the larger of the two possible rings in a radical cyclization. Both Clive and Cheshire[36] (in simple systems related to those below) and Porter et al.[37] (in transannular cyclizations of macrocycles) have recently reported similar observations, and this effect appears to be quite general. A brief survey of substitution patterns that have been investigated is illustrated in eq 15–17. Isomerization of unsubstituted iodo ketone **39** gave only the 6-endo product, 4-iodocyclohexanone (**40**), in 56% yield. 3-(Iodomethyl)cyclopentanone (**41**) could not be detected. Cyclization of disubstituted alkene **42** (eq 15) gave a 75/25 mixture of 6-endo products **43** and 5-exo products **44** (each was a 1/1 mixture of stereoisomers). Thus, a significant preference for 6-endo cyclization remains even when the alkene substitution pattern is equal at both ends.

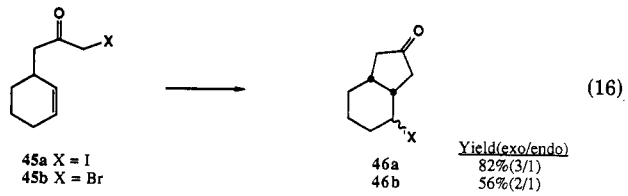


(15)

				Yield
39 R = H	**40**	>97/3	**41**	56%
42 R = CH_3	**43**	75/25	**44**	73%

This preference for endo cyclization can be overriden by competing 6-endo closure to form a bridged ring with 5-exo closure to form a fused ring (eq 16). Isomerization of iodide **45a** provided **46a** as a mixture of stereoisomers in 82% yield. As in the simple case above (eq 5), isomerization of the related bromide **45b** provided the cyclic product **46b** but at a much slower rate and in lower yield.

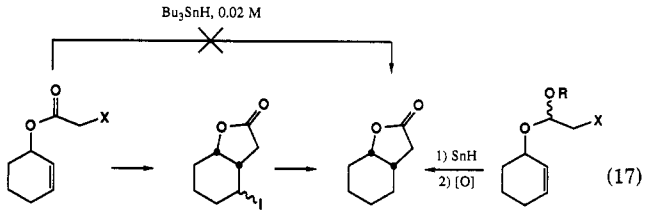
Cyclization of the related iodoacetate **47a** provided an illustration of the power of the atom-transfer method (eq



(16)

		Yield(exo/endo)
45a X = I	**46a**	82%(3/1)
45b X = Br	**46b**	56%(2/1)

17). It was discovered some time ago that the tin hydride mediated cyclization of halo esters such as **47a** was not a viable route to cyclic lactones.[38] Indeed, we observed that reduction of **47a** with tri-*n*-butyltin hydride at 0.02 M gave only cyclohexenyl acetate **47b**. None of the lactone **49** was



(17)

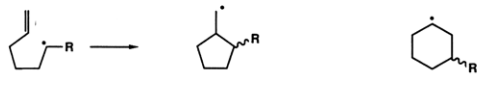
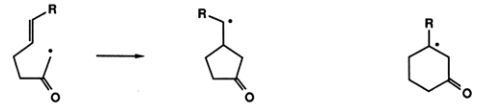
47a X = I
47b X = H
48
49
Stork and Ueno

present according to GC analysis of the crude reaction mixture. Stork[38a] and Ueno[38b] solved this problem by removing the offending ester. The resulting tin hydride cyclization of haloacetals is one of the most powerful and commonly applied free-radical methods. By using the atom transfer method, ester **47a** becomes a viable precursors for **49**. Isomerization of **47a** under the standard conditions was unusually slow and required the addition of a second portion of ditin to consume starting material. After chromatography, lactone **48** and reduced ester **47b** were isolated in 53 and 7% yields, respectively. We believe that the modest yield of **48** and the presence of relatively large amounts (7%) of reduced product **47b** (even in the absence of tin hydride) reflect the very slow cyclization of the intermediate radical (cyclization is competitive with hydrogen atom abstraction from the medium and other reactions).[39] Nonetheless, the result is remarkable when compared to the attempted tin hydride cyclization.[31] In a separate preparative experiment, **47a** was isomerized with ditin (0.3 M), and the crude reaction mixture was then treated with 1.1 equiv of tri-*n*-butyltin hydride (0.3 M). After flash chromatography, lactone **49** was isolated in 55% yield.

Although important exceptions exist, most radical cyclizations proceed kinetically in an exo fashion to provide the smaller of the two possible rings.[28,40] For example, the simple 5-hexenyl radical gives a 50/1 ratio of exo/endo products. The control experiments of Clive,[36] combined with the ability of the iodine atom transfer method to trap kinetic cyclization products, demonstrate that the products from the cyclizations of endo-oriented ketones form under kinetic control. The ability of a carbonyl group inside the forming ring to promote cyclization in an endo fashion is

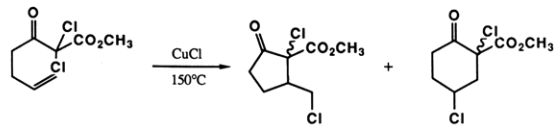
(34) Wohl, R. A. *Synthesis* **1974**, 38.
(35) We thank Tina Morgan for conducting this series of experiments.
(36) Clive, D. L. J.; Cheshire, D. R. *J. Chem. Soc., Chem. Commun.* **1987**, 1520.
(37) Porter, N. A.; Chang, V. H.-T.; Magnin, D. R.; Wright, B. T. *J. Am. Chem. Soc.* **1988**, *110*, 3554.
(38) (a) Stork, G.; Sher, P. M.; Chen, H.-L. *J. Am. Chem. Soc.* **1986**, *108*, 6384. Stork, G.; Mook, R., Jr.; Biller, S. A.; Rychnovsky, S. D. *Ibid.* **1983**, *105*, 3741. (b) Ueno, Y.; Moriya, O.; Chino, K.; Watanabe, M.; Okawara, M. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1351.
(39) A potentially useful modification of our conditions that provides better yields with unreactive substrates has recently been communicated. Jolly, R. S.; Livinghouse, T. *J. Am. Chem. Soc.* **1988**, *110*, 7536.
(40) (a) Reviews of cyclizations: Beckwith, A. L. J.; Ingold, K. U. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic Press: New York, 1980; Vol. 1, pp 162–283. (b) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073. Theoretical treatments of cyclizations: (c) Houk, K. N.; Paddon-Row, M. N.; Spellmeyer, D. C.; Rondan, N. G.; Nagase, S. *J. Org. Chem.* **1986**, *51*, 2874. Spellmeyer, D. C.; Houk, K. N. *Ibid.* **1987**, *52*, 959. (d) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron Lett.* **1985**, *26*, 373; *Tetrahedron* **1985**, *41*, 3925.

Table I. Regioselectivities in Closure of Electrophilic Hexenyl Radicals

entry	precursor	5-exo product	6-endo product
			
			5-exo/6-endo
1		R = H, alkyl	>95/5
2		R = CO_2R	~93/7
3		R = COalkyl, COPh	~75/25
			
4		R = H	<3/97
5		R = Me	25/75

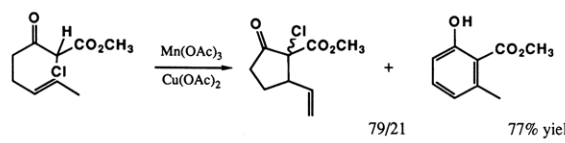
powerful synthetic tool. Recently, Weinreb[11h] and Snider[41] have provided several examples where unusually high amounts of 6-endo cyclization products were formed (eq 18). Although the interpretation is not completely straightforward (metals are present and free radicals may not be involved), it is possible that the ketone substituent inside the forming ring promotes endo cyclization in such cases.

Weinreb



69/31 77% yield

Snider



79/21 77% yield (18)

A summary of the regioselectivities of ring closure for these electrophilic hexenyl radicals is contained in Table I. The cyclization of simple nucleophilic radicals to terminal alkenes usually shows excellent 5-exo selectivity (entry 1, 98/2 when R = H). This selectivity is particularly impressive when one considers that there is an inherent bias for any radical to add to the less substituted end of an alkene. The stereoelectronic rationale of Beckwith[40] provides a basis for understanding this selectivity: the ideal SOMO–LUMO overlap (attack angle ≈ 109°) is accommodated much better in the 5-exo transition state than in the 6-endo. In addition, because the transition state (TS) is so early, the torsional strain in the 5-exo TS resembles that of a six-membered ring while the torsional strain of the 6-endo TS resembles that of a seven-membered ring.

Progressive substitution by an ester and a ketone outside the forming ring (entries 2 and 3) gives a noticeable increase in the amount of 6-endo product. Several explanations may be advanced for this trend. (1) Since the carbonyl-substituted radicals are more stable than their alkyl-substituted counterparts, the transition state may occur later on the reaction coordinate and the stability of the product radical may be more important. (2) Alternatively, ester- and ketone-substituted radicals are usually regarded as electrophilic.[2b] Thus, to the extent that positive charge is developed in the transition state, the 6-endo product will be favored. (3) Again because of the

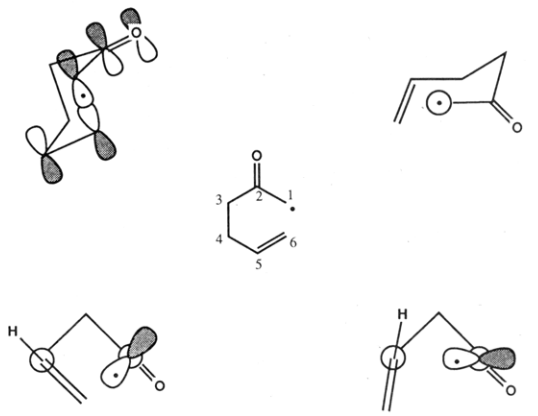


Figure 3. Left: transition state for 6-endo cyclization maintains resonance overlap. Right: transition state for 5-exo cyclization partially sacrifices resonance overlap.

electrophilic nature of the radicals, the $SOMO_{radical}$–$HOMO_{alkene}$ interaction should be more important than with alkyl radicals. This interaction should be maximized at approximately a 90° attack angle, not 109° as for the SOMO–LUMO interaction. Calculations show the angle of attack in the 6-endo transition state to be much smaller than the 5-exo, and so this effect should also favor 6-endo attack.[40c,d] Nonetheless, the sum of these possible effects is not sufficient to overcome the usual bias for the 5-exo product when the carbonyl group is outside the forming ring. Indeed, in "unbiased" systems where the alkene possesses a terminal alkyl substituent, it is certain that an even higher 5-exo selectivity would be observed.

The stereoselectivity in the 5-exo cyclizations of these electrophilic radicals is poor: esters (Table I, entry 2) give nearly a 1/1 mixture of cis/trans stereoisomers while ketones (Table I, entry 3) show a slight preference for the trans isomer. The effects of temperature on the stereoselectivity have not yet been studied. For comparison, alkyl groups (Table I, R = alkyl) show a modest preference for the cis isomer while ether substituents (R = *O*-alkyl) often provide a slight excess of the trans isomer.[42] The stereochemistry of the 6-endo products (also a mixture) is not controlled by cyclization but by atom transfer (see eq 10).

Carbonyl substitution inside the forming ring causes a significant reversal in regioselectivity. It is appropriate to compare entries 3 and 4, which have the same alkene substitution. Only the endo product is formed in entry 4. Even where an equally substituted alkene is used to provide an "unbiased" example (entry 5), the 6-endo product still prevails. On the surface, these results contradict the Beckwith model; however, an in-depth look shows that this is not the case. Both Clive[36] and Porter[37] have cited possible stereoelectronic effects arising from resonance interactions in these types of radicals. Due to the overlap between the radical and the ketone,[43] the geometries of transition states for cyclization are severely restricted (Figure 3). Atoms 1–3 and 4–6 are in separate planes which are connected by the C3–C4 bond. The "chair" transition state for 6-endo cyclization resembles that often proposed for Claisen and Cope rearrangements[44] (a "boat" TS may also be considered). Overlap for the

(41) Snider, B. B.; Patricia, J. J.; Kates, S. A. *J. Org. Chem.* **1988**, *56*, 2137.

(42) Curran, D. P.; Kim, D.; Liu, H. T.; Shen, W. *J. Am. Chem. Soc.* **1988**, *110*, 5900.

(43) Birkhofer, H.; Beckhaus, H.-D.; Ruchardt, C. In *Substituent Effects in Radical Chemistry*; Viehe, H. G., Janousek, Z., *Merenyi*, R., Eds.; Reidel: Boston, 1986; p 199. Sustmann, R. *Ibid.* p 143.

(44) Hill, R. K. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, 1984; Chapter 7.

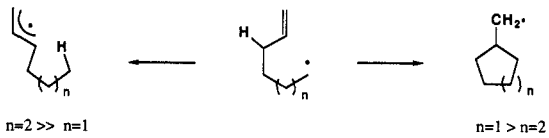


Figure 4. Problems with 6-exo cyclizations.

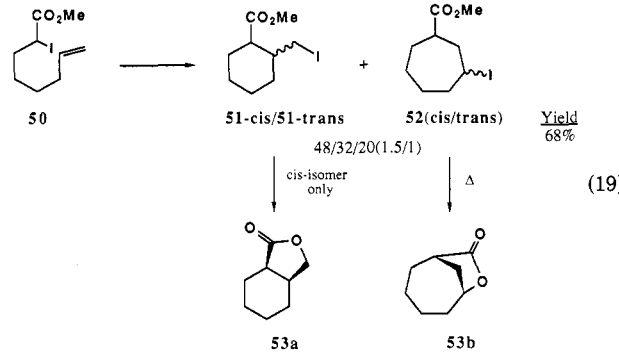
formation of the 6-endo product is acceptable if not ideal. Rotation about the C3–C4 bond approaches the 5-exo transition state; however, overlap to form the 5-exo product is very poor because it is difficult to get the outside atom of one plane (C1) to approach the central atom of the other plane (C5) without rotating the C1–C2 bond and sacrificing resonance.[45] If resonance is maintained, angle and torsional strain are introduced instead. This is best illustrated by the double Newman projections in Figure 3.

Interestingly, nucleophilic radicals that possess a stabilizing heteroatom inside the forming ring (such as α-acylamino[46a] and α-oxy radicals[46b]) also cyclize slowly and provide unusually large amounts of 6-endo products. The geometric constraints imposed by resonance and the introduction of sp^2 centers inside the forming ring may also be important control elements in the reactivity profile of these radicals.[46b]

6-Exo/7-Endo Cyclizations. The formation of six-membered rings by 6-exo cyclizations of nucleophilic radicals is hampered by two problems (Figure 4).[2a] First, 6-exo cyclization is significantly slower than its lower homologue (5-exo).[28,40] In the tin hydride method, reductive trapping of radicals before ring closure is a serious problem. Second, many cyclization substrates contain an allylic hydrogen which is subject to kinetically rapid and thermodynamically favorable 1,5-hydrogen shift. In the lower homologue, the analogous 1,4-hydrogen shift is strongly disfavored on kinetic grounds. This hydrogen-transfer reaction is particularly damaging because the partitioning between cyclization and allylic H atom abstraction is not affected by the tin hydride concentration. Fortunately, the introduction of activating groups on the alkene acceptor can often simultaneously solve both problems.[47]

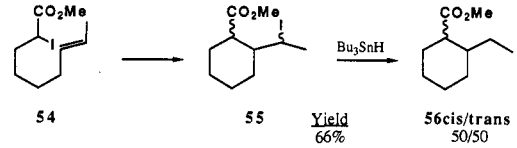
We felt that the cyclization of electrophilic radicals by the atom-transfer method might be advantageous because: (1) slow cyclizations can be conducted without resort to high dilution, and (2) the cyclization precursors are stabilized radicals and should be less prone to allylic hydrogen transfer due to the reduced exothermicity. As shown in eq 19–21, these expectations were borne out by the experiments.

Isomerization of **50** under the standard conditions provided 6-exo products **51-cis/51-trans** and the 7-endo products **52** in a ratio of 80/20. The combined isolated yield of these iodides was 68%. The major 6-exo product was assigned as the cis stereoisomer because it readily formed lactone **53a** on warming (the trans isomer was recovered under these conditions). The stereochemistry of the 7-endo products **52** was also tentatively assigned by lactonization. Upon warming the mixture, the minor stereoisomer was rapidly converted to bridged lactone **53b**. The major stereoisomer was also converted to **53b** if tetra-*n*-butylammonium iodide was added to the reaction mixture. We assume that the trans isomer can undergo direct S_N2 substitution to provide **53b** while the cis isomer requires inversion by iodide ion. The exo/endo ratio in this example (80/20) is very similar to the ratio for the unsubstituted heptenyl radical (85/15).[48,49]



(19)

Isomerization of **54** gave a mixture of four products in nearly equal amounts. To facilitate identification, the crude reaction mixture was reductively deiodinated to give **56-cis** and **56-trans** in a ratio of 50/50 in 66% yield. The authentic 7-endo product (methyl 2-methylcycloheptane carboxylate) was independently prepared for comparison purposes.[50] This product could not be detected in the capillary GC or ^1H NMR spectra of the crude reaction mixture. Thus, to the extent of our ability to detect, this cyclization gave exclusively the 6-exo product.



(20)

In sharp contrast, the isomeric methyl-substituted alkene **57** gave only the products of 7-endo cyclization. In this case, the presumed intermediate tertiary iodide **58** was

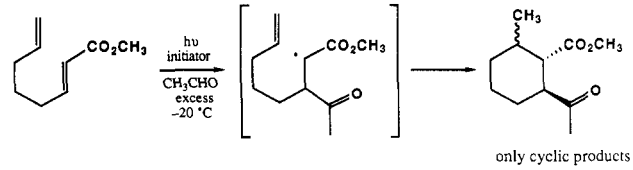
(45) This rationale predicts that the origin of the effect is a decrease in the rate of 5-exo closure not an increase in 6-endo closure. Support for this comes from the observations of Porter (ref 37).

(46) (a) Burrnett, D. A.; Choi, J.-K.; Hart, D. J.; Tsai, Y.-M. *J. Am. Chem. Soc.* **1984**, *106*, 8201. Hart, D. J.; Tsai, Y.-M. *J. Am. Chem. Soc.* **1982**, *104*, 1430. Hart, D. J.; Tsai, Y.-M. *J. Am. Chem. Soc.* **1984**, *106*, 8209. Choi, J.-K.; Hart, D. J. *Tetrahedron* **1985**, *41*, 3959. Padwa, A.; Nimmegern, H.; Wong, G. S. K. *J. Org. Chem.* **1985**, *50*, 5620; *Tetrahedron Lett.* **1985**, *26*, 957. Padwa, A.; Dent, W.; Nimmesgern, H.; Venkatramanan, M. K.; Wong, G. S. K. *Chem. Ber.* **1986**, *119*, 813. Bachi, M. D.; Frolow, F.; Hoornaert, C. *J. Org. Chem.* **1983**, *48*, 1841. Bachi, M. D.; Hoornaert, C. *Tetrahedron Lett.* **1981**, *22*, 2689, 2693; **1982**, *23*, 2505. Bachi, M. D.; De Mesmaeker, A.; Stevenart-De Mesmaeker, N. *Tetrahedron Lett.* **1987**, *28*, 2637 and 2887. (b) Beckwith, A. L. J.; Glover, S. A. *Aust. J. Chem.* **1987**, *40*, 157.

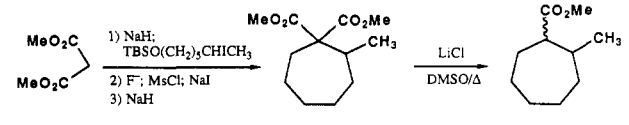
(47) For some successful 6-exo cyclizations, see: Beckwith, A. L. J.; Pigou, P. E. *J. Chem. Soc., Chem. Commun.* **1986**, 85. Stork, G.; Krafft, M. E.; Biller, S. A. *Tetrahedron Lett.* **1987**, *28*, 1035. Ladlow, M.; Pattenden, G. *Tetrahedron Lett.* **1985**, *26*, 4413. Hanessian, S.; Dhanoa, D. S.; Beaulieu, P. L. *Can. J. Chem.* **1987**, *65*, 1859. Chuang, C.-P.; Gallucci, J. C.; Hart, D. J.; Hoffman, C. *J. Org. Chem.* **1988**, *53*, 3218.

(48) Beckwith, A. L. J.; Moad, G. *J. Chem. Soc., Chem. Commun.* **1974**, 472.

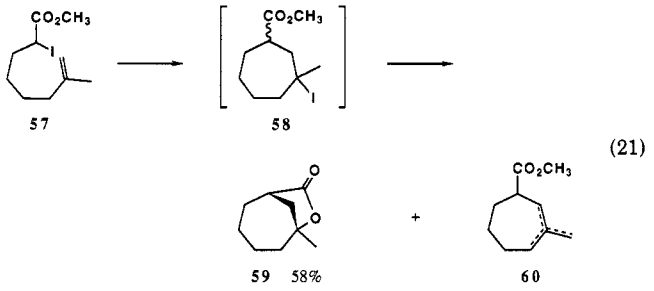
(49) Neckers has recently reported a related cyclization that is shown below. Only 6-exo products were reported. At present it is not clear whether this is because equilibration can occur under these conditions (this seems unlikely) or whether substituent or temperature effects kinetically favor 6-exo closure over 7-endo. Gottschalk, P.; Neckers, D. C. *J. Org. Chem.* **1985**, *50*, 3498.



(50) The following sequence was employed (Chang, C.-T. Ph.D. Thesis, University of Pittsburgh, 1989):



not observed in the reaction mixture.[51] The major reaction product was lactone **59**, which could be isolated in 58% yield. Also present was a mixture of alkenes tentatively assigned as isomers **60**. We think it likely that all of these products resulted from ionic reactions of the presumed intermediate **58**.[51] In a separate experiment, treatment of the crude **59**/**60** mixture with *p*-toluenesulfonic acid (*p*TSA) appeared (by TLC and NMR) to convert the alkenes **60** to the lactone **59**; however, the isolated yield of **59** after chromatography was virtually unchanged.



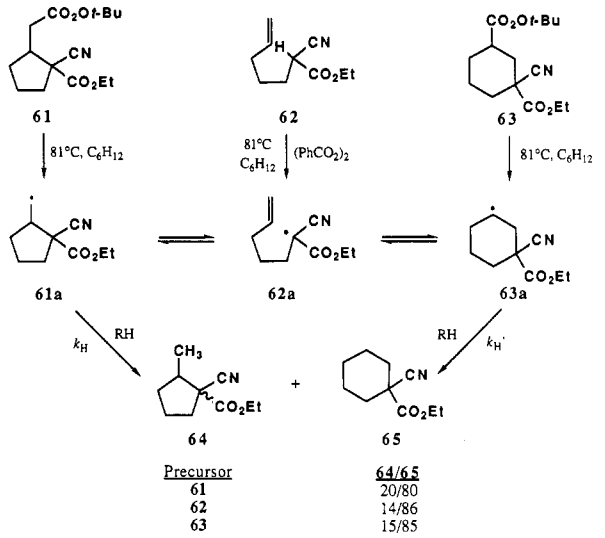
(21)

The isolated yields in these 6-exo/7-endo examples were consistently lower than in the similarly substituted 5-exo/6-endo systems. One reason for this was the presence of increased amounts of reduced–uncyclized products derived from the starting iodoesters (I = H in **50**, **54**, **57**; yields ~10%). The source of the hydrogen atom is not presently known. In addition, the sizes of the broad peaks in the alkene region[22] of the crude products (tentatively assigned to oligomeric or polymeric products) were noticeably larger. We believe that the cyclizations of these radicals are slow enough that reactions of the radicals with the medium (and possibly with each other) can compete. However, the observed yields are acceptable (55–60%), and it is well known that the placement of substituents on the chain often increases the rate of cyclization.[2,40] More complex examples for synthetic application may actually give better yields than these simple unsubstituted substrates.

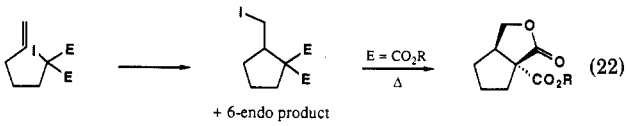
The trend of the directing effects of the methyl groups in eq 20 and 21 is not surprising. However, it is particularly pleasing that the isomer **57** provided exclusively the 7-endo product **59** in reasonable yield. Indeed, there are very few examples of selective 7-endo radical cyclizations.[52] These preliminary results indicate that it will be possible to dictate regiochemistry by olefin substitution pattern, a useful asset for synthetic application.

Atom Transfer Cyclizations of α-Iodomalonates Background and Initial Studies: The cyclizations of α-iodo esters, ketones, and related substrates by the atom-transfer method show promise as mild reactions to form rings the size of which are dictated by substituents. One obvious shortcoming is the lack of inherent stereoselectivity. Most of the 5-exo cyclizations presented above gave cis/trans ratios not far from unity. Enolate chemistry offers the possibility to use both isomers to form one

Scheme II



product (for example, by base-catalyzed epimerization or by cyclopropanation by intramolecular cyclization[53]). In more complex systems, interplay between the various substituents may impose stereocontrol. A different approach involves the cyclization of a substrate bearing two identical radical-stabilizing groups (eq 22). The 5-exo

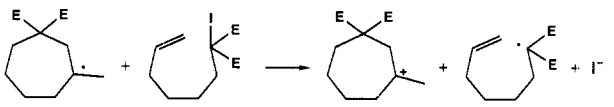


(22)

products would then be devoid of stereochemistry at the radical center, and differentiation of the two groups (which are identical in the starting material but not in the product) would be required. The cyclization reactions of iodomalonates are attractive for this purpose because the differentiation of the two esters will readily be accomplished by lactonization. Furthermore, iodomalonates should be even better iodine atom donors than iodo esters and ketones. Indeed, bromomalonates[54] and bromomalononitriles[55] have been shown to participate in atom-transfer addition reactions.[56]

The hydrogen atom transfer reactions of malonyl and related stabilized radicals were systematically investigated by the Julia group about 20 years ago.[28] This pioneering body of work provided clear evidence that radical cyclizations could be reversible. An illustrative example which summarizes key aspects of Julia's work is present in Scheme II.[57] Heating of cyanomalonate **62** with excess benzoyl peroxide in refluxing cyclohexane provided 5-exo product **64** and 6-endo product **65** in a 14/86 ratio (58% yield). That this was not the kinetic ratio was proven by decomposition of the peresters **61** and **63** under the same conditions. The same two products were produced in the same ratio (within experimental error). Under these Curtin–Hammett conditions,[58] radicals **61a** and **63a** are

(51) When the product iodides cannot be observed, the possibility arises that outer sphere electron transfer (see below) is occurring rather than atom transfer followed by solvolysis (a net inner sphere electron transfer). As the radical becomes more easily oxidized (tertiary, heteroatom-substituted), this possibility becomes more likely.



(52) Bachi, M. D.; Frolow, F.; Hoornaert, C. *J. Org. Chem.* **1983**, *48*, 1841.

(53) Mori, M.; Kanda, N.; Ban, Y.; Aoe, K. *J. Chem. Soc., Chem. Commun.* **1988**, 12.

(54) Giese, B.; Horler, H.; Leising, M. *Chem. Ber.* **1986**, *119*, 444.

(55) Riemenschneider, K.; Bartels, H. M.; Dornow, R.; Dreschel-Grau, E.; Eichel, W.; Luthe, H.; Matter, Y. M.; Michaelis, W.; Boldt, P. *J. Org. Chem.* **1987**, *52*, 205. Bartels, H. M.; Boldt, P. *Justus Liebigs Ann. Chem.* **1981**, 40.

(56) For a related reaction, see: Yoshida, J.; Yamamoto, M.; Kawabata, N. *Tetrahedron Lett.* **1985**, *26*, 6217.

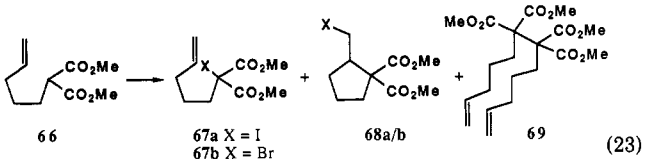
(57) Julia, M.; Maumy, M.; Mion, L. *Bull. Chim. Soc. Fr.* **1967**, 2641. See also ref 29b.

(58) Review, Seeman, J. *Chem. Rev.* **1983**, *83*, 84.

in equilibrium with each other via the open radical **62a**. The ratio of products depends on the ratio of **61a/63a** (equilibrium constant) and the relative rates of hydrogen abstraction (k_H and $k_{H'}$). The most likely hydrogen donor (RH) is the solvent cyclohexane.[59] One can safely conclude that the primary radical **61a** must abstract a hydrogen somewhat faster than a secondary radical ($k_H > k_{H'}$). Thus, the ratio of the products **64/65** is probably higher than the ratio of their respective radical precursors **61a/63a**.

With terminal alkenes, other stabilizing groups gave higher 5-exo/6-endo ratios, and it was not easy to demonstrate if equilibrium had been reached. Malonates with alkyl groups on the internal position of the alkene gave 6-endo products regardless of the nature of the stabilizing groups. Due to the lack of a trap which was much more rapid than reverse cyclization, little was learned about the kinetic partitioning between the 5-exo and 6-endo pathways.[60]

We felt that atom-transfer cyclizations of iodomalonates could provide a compliment to the classic work of Julia by providing access to kinetic products. Iodomalonates are a little known class of compounds,[61] and research began with the development of a general method for their preparation by iodination of malonate anions (eq 23).



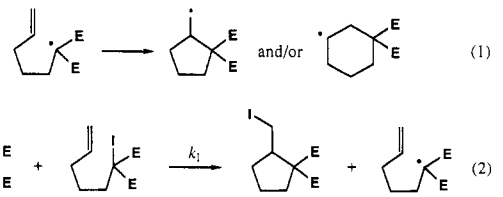
(23)

Conditions	Products(Isolated Yield)
LDA/I_2	**68a**, (60%); **69**, (28%)
NaH/I_2	**67a**, (20%); **68a**, (16%); **69**, (50%)
KH/NIS	**67a**, (90%)
KH/NBS	**67b**, (84%)

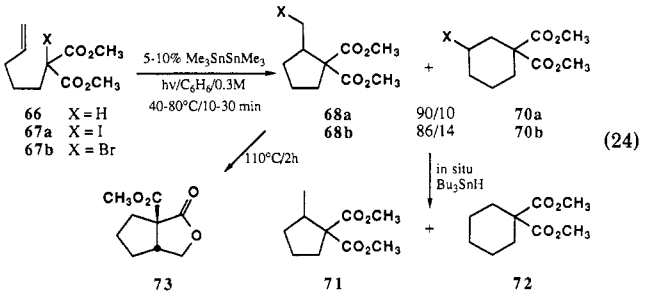
Deprotonation of **66** with LDA in THF, followed by addition of molecular iodine, gave none of the desired iodomalonate **67a**. Instead the cyclic product **68a**[62] and the oxidatively coupled product **69**[63] were isolated. Use of sodium hydride as a base gave some of the iodomalonate **67a** (20%) along with **68a** and **69**. In contrast, deprotonation of **66** with potassium hydride and addition of *N*-iodosuccinimide to a cold (−78 °C) solution of the resulting anion gave **67a** as the sole detectable crude product in 90% yield. Sodium hydride could be substituted for potassium hydride if desired. Quenching of the anion with NBS provided the bromomalonate **67b** in 84% yield after chromatographic purification.

Halogenation of the malonate anion with NIS or NBS proved to be a very general procedure, and it was used for the preparation of all of the subsequent cyclization precursors. The iodomalonates were stable if protected from light and could be stored in the freezer. They decomposed on prolonged exposure to ordinary tungsten room light. In general, the crude iodomalonates were >95% pure as estimated by ^{1}H NMR analysis. Although purification by flash chromatography was possible, it was not usually necessary. Irradiation of the crude iodomalonate gave the highest overall yields.

Scheme III

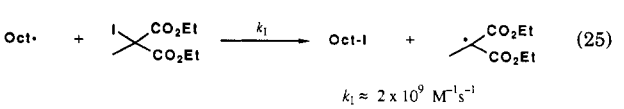


When irradiated under the standard reaction conditions, iodomalonate **67a** was rapidly consumed (<10 min) and an inseparable mixture of 5-exo (**68a**) and 6-endo (**70a**) products was isolated in 86% yield. The ratio of **68a/70a** in the crude reaction mixture was 90/10. The structures were easily assigned by in situ tin hydride reduction after isomerization to give a 90/10 mixture of **71** and **72**. In addition, heating of the mixture converted the major component **68a** to lactone **73**, thus differentiating the two esters in the product.



(24)

Mechanism. Experiments to address the issue of reversibility were an immediate concern. Isomerization of bromide **67b** gave a very similar product mixture of **68b/70b** (86/14, 84% yield)—circumstantial evidence for kinetic control. In addition, it appears that bromomalonates (in contrast to bromo esters) are sufficiently reactive to initiate and maintain a chain. Reduction of **67a** with tri-*n*-butyltin hydride at 0.02 M (85 °C) gave **71** and **72** in a ratio of 89/11. Thus, reverse cyclization must be slower than hydrogen transfer from tin hydride at 0.02 M. The cyclic products **71** and **72** accounted for 79% of the reduced products, the remainder (21%) being reduced uncyclized product **66**. As before, the formation of **71/72** is best accomplished by isomerization followed by in situ tin hydride reduction at high concentration (0.3 M) rather than by direct tin hydride reduction at low concentration.[31] Conclusive evidence that cyclization was kinetically controlled came from the measurement of the rate constant for reaction of octyl radical with iodomalonate **74** (eq 25): $k_I \approx 2 \times 10^9$ M^{-1} s^{-1} (at 50 °C).[26]



(25)

From this evidence, we conclude that the mechanism proposed in Scheme III is operative. Irreversible cyclization (step 1) is followed by rapid iodine atom transfer (step 2). By using a similar analysis to that for the esters (Scheme I), one can show that ring opening is several orders of magnitude slower than step 2 at the concentrations employed.

(59) Donation of a hydrogen atom by the starting malononitrile **62** is a chain transfer step. It seems that this is not an efficient reaction because such a large amount of "initiator" is required.

(60) Low-temperature oxidation of an anion provided evidence for kinetic 5-exo closure in one example. Julia, M.; Barreau, M. C. R. *Acad. Sci. Ser. C* **1975**, *280*, 957.

(61) Bell, R. P.; Engel, P. *J. Chem. Soc.* **1957**, 247. D'Auria, M.; D'Onofrio, F.; Piancatelli, G.; Scettri, A. *Synth. Commun.* **1982**, 1127. Doleschall, G.; Toth, G. *Tetrahedron* **1980**, *36*, 1649.

(62) The mechanistic origin of the cyclic product is not presently known. Free radicals may be formed by oxidation of the anion. Also, normal iodination may occur, followed by initiation of the chain isomerization. The high 5-exo selectivity may be a temperature effect. An ionic mechanism may even be envisioned. The direct conversion of malonate anions to cyclic iodides has not been developed but it appears to hold potential as a one-step alternative to form cyclic products.

(63) The oxidative coupling of anions with molecular iodine is a known reaction. For recent synthetic advances, see: Belletire, J. L.; Spletzer, E. G. *Tetrahedron Lett.* **1986**, *27*, 131; *Synth. Commun.* **1986**, 16, 575.

Scheme IV

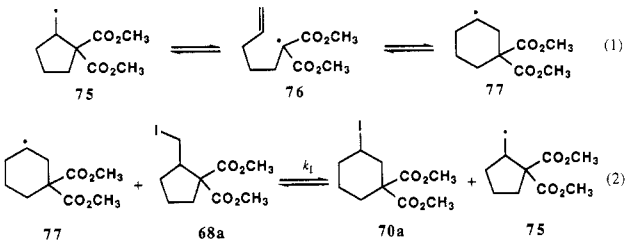
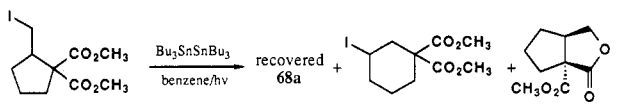
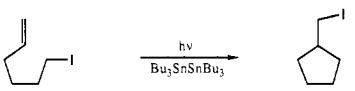


Table II. Irradiation of 5-Exo Product 68a



irradiation time	% 68a	% 70a	% 73	combined mass balance
15 min	82	~0	18	98
30 min	80	3	17	97
1 h	76	5	19	74
3 h	60	12	28	66
4 h	62	7	31	58
8 h	55	10	35	48

There is an important caveat! That iodine atom transfer (step 2) is faster than reverse cyclization does not rigorously demonstrate that the ratio of products is kinetically controlled. It is known that alkyl iodides can be equilibrated via iodine atom transfer between alkyl radicals.[4b,d,25,64] For example, irradiation of 5-iodo-1-hexene under the standard reactions conditions gives significant amounts (up to 75%) of (iodomethyl)cyclopentane (eq 26).[4b,d] Reversible iodine atom transfer provides a con-



(26)

stant source of radicals while irreversible cyclization provides the driving force for this transformation. Because the malonate group facilitates ring opening, the mechanism for equilibration outlined in Scheme IV must now be considered. Only the productive iodine transfer step for the conversion of the 5-exo product **68a** to the more stable 6-endo product **70a** is shown. This mechanism can only operate after the consumption of the starting iodomalonate because the equilibration (step 1) cannot occur in its presence. Reversible cyclization provides a path for equilibration of radical **75** to **77** via the open form **76**. The productive iodine atom transfer (step 2) provides isomerized iodide **70a** and the starting radical **75**. This iodine transfer is slightly endothermic but still possible. In effect, all the alkyl iodides will be in equilibrium if reverse cyclization is sufficiently rapid.

In order to study the possible equilibration of cyclic products via the Scheme IV mechanism, pure 5-exo product **68a** was irradiated under the usual reaction conditions in the presence of hexabutylditin. 1,3-Dichlorobenzene was added as an internal standard, and the yields of starting iodide **68a**, 6-exo product **70a**, and lactone **73** were measured by GC against the internal standard. The results are summarized in Table II. The results show that isomerization of **68a** to **70a** is possible but not particularly rapid. As the ratio of **68a**/**70a** begins to decrease, the mass balance begins to decrease. The reaction is still far from equilibrium after 8 h. The ratio of **68a**/**70a** is about 5.5/1 but only 48% of the products can be accounted for. It is likely that the chains in the Scheme IV mechanism are very short because the iodine transfer is nearly thermoneutral and because the ring opening is slow. Thus, isomerization is competitive with the various possible decomposition pathways of the intermediate radicals. In the iodomalonate cyclizations, we conclude that isomerization of the kinetically formed products is not an important reaction while starting iodomalonate remains and it is a possible, but relatively slow, reaction after the iodomalonate is consumed. Irradiation should be terminated as soon as possible after consumption of the starting material.

(64) Hiatt, R.; Benson, S. W. *J. Am. Chem. Soc.* **1972**, *94*, 25. Castelhano, A. L.; Griller, D. *Ibid.* **1982**, *104*, 3655.

Table III. Atom Transfer Cyclization Reactions of Iodomalonates: 5-Exo/6-Endo

entry	iodomalonate yield[a]	cyclic products ratio	purified derivatives combined yields[b]	regiochemistry
1)	**78** 87%	**79** 1/1 mixture of stereoisomers	**80** 84%	5-exo
2)	**81** 86%	**82**[d]	**83** 84%	6-endo
3)	**84** 58%[c]	**85**	**86** 76%	5-exo
4)	**87** 62%[c]	**88**	**89** 61%	5-exo

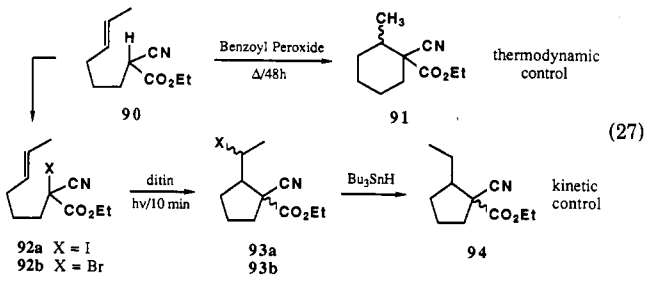
[a] Yield of crude iodomalonate which was used without further purification. [b] Isolated yield from iodomalonate. [c] Yield of iodomalonate after purification by flash chromatography. [d] Observed by ^{1}H NMR but not isolated.

5-Exo/6-Endo Examples. Substituent effects were briefly probed in a series of substituted systems where 5-exo/6-endo cyclizations were possible. The results are contained in Table III. In each case, the intermediate iodide products were directly reduced (**80, 83**) or lactonized (**86, 89**) for the purposes of structure confirmation and yield. The three secondary iodide products (entries 1, 3, and 4) could be isolated in comparable yields to those indicated for reduction or lactonization. The tertiary iodide **82** (entry 2) could be observed in the ^{1}H NMR of the crude reaction spectrum but was not stable to chromatography.

In each of the examples, only a single regioisomeric product was formed. Introduction of a terminal methyl group in **78** gave only the 5-exo product **79** (entry 1) while the placement of an internal methyl group in **81** gave only the 6-endo product **82** (entry 2). Based on the above experiments, there can be little doubt that this latter product is formed under kinetic control. As in the case of the esters, the placement of an alkyl substituent on the internal position of the alkene promotes the complete reversal of regiochemistry. Cyclization of **84** (entry 3) gave exclusively a fused 5-exo product **85** over a possible bridged 6-endo product as expected, but entry 4 (**87** → **88**) showed that

bridged rings can be formed in reasonable yield.[65] In both cases, a single stereoisomeric iodide was formed, resulting from iodine abstraction from the less hindered face of the bicyclic system. Substituent effects should provide a valuable and predictable tool to control ring size in these cyclizations.

The original hydrogen atom transfer method of Julia has potential synthetic utility and is inherently complementary to the iodine atom transfer method. These points are illustrated by the direct comparisons in eq 27. The cyclization of malononitrile **90** is an *Organic Synthesis* preparation[66] that is reported to give only the 6-endo product **91** in 75% isolated yield (1/1 mixture of stereoisomers). Attempted iodination of **90** by the usual method gave on workup not the expected iodomalononitrile **92a** but instead the cyclic product **93a**.[62,67] The bromide **92b** behaved in a normal fashion and could be isolated and characterized spectroscopically. Irradiation of **92b** for 10 min resulted in formation of **93b** (four stereoisomers). In situ tin hydride reduction of **93b** gave exclusively the 5-exo product **94** in 78% yield (~7/3 mixture of stereoisomers). Although exactly the same intermediate radicals must be involved in each cyclization reaction, there is no good trap for the kinetic 5-exo product in the Julia method; cyclization becomes reversible and equilibration ensues. In the halogen atom transfer method, the lifetime of the cyclic radical is very short because it rapidly abstracts a halogen from the starting material (Scheme III, step 2).[26] The kinetic cyclization product is trapped. This is a particularly favorable example where the kinetic and thermodynamic products are opposite (in the case of internal alkene substitution these products will be the same) and where complete equilibration of intermediate radicals in the Julia method is possible. Nonetheless, it shows the potential for the generation of different ring systems from the same precursor (**90**) by simply altering the atom donor (H versus Br or I).



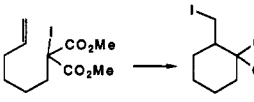
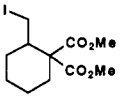
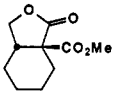
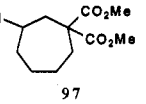
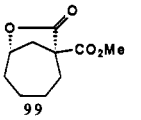
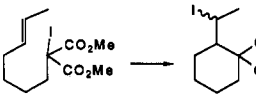
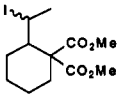
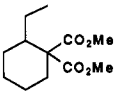
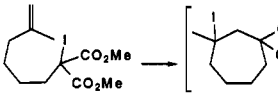
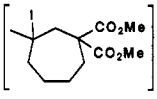
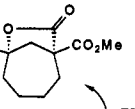
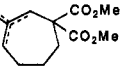
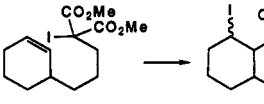
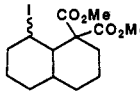
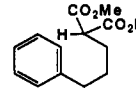
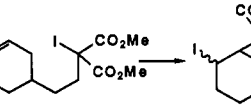
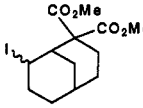
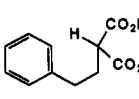
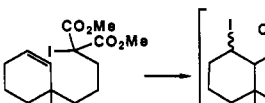
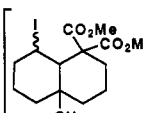
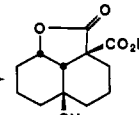
(27)

6-Exo/7-Endo Examples. A series of homologous substrates was prepared to investigate the potential for 6-exo versus 7-endo cyclization. These substrates are shown in Table IV. The simple alkene **95** (entry 1) gave a 60/40 mixture of 6-exo and 7-endo products **96**/**97**. This represents a significant increase in the percentage of 7-endo product when compared to the monoester **50** (eq 19). On heating of the mixture, the 7-endo iodide **97** lactonized very rapidly to give **99** while the 6-exo product **96** lactonized more slowly to **98**. The separable lactones were isolated in a combined yield of 66%.

The same alkyl-directing effects operate as in the lower homologues. That is, an external methyl group directs exclusively for 6-exo cyclization **100** → **101** (entry 2), while an internal methyl group directs exclusively for 7-endo closure, **103** → **104** (entry 3). In the later case, the tertiary iodide **104** was not observed at any time in the crude reaction by ^{1}H NMR. The major products were the lactone **105** and a regioisomeric mixture of alkenes **106** in roughly equal proportions. Treatment of the crude mixture with *p*TSA, followed by chromatographic purification, gave the lactone **105** in 71% isolated yield. We believe that all of these mixtures represent kinetic cyclization products.

As in the case of the iodo esters, the yields of in the 6-exo/7-endo series were 13–22% lower than the 5-exo/6-endo series. Increased amounts of reduced/uncyclized products and other (oligomeric?) products were present. This implies that these 6-exo/7-endo cyclizations are slow

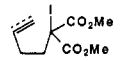
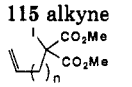
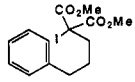
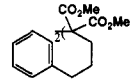
Table IV. Atom Transfer Cyclization Reactions of Iodomalonates: 6-Exo/7-Endo

entry	iodomalonate yield[a]	cyclic products ratio	purified derivatives combined yields[b]
1)	 95 98%	 96 + 60/40	 98 + 66%
		 97	 99
2)	 100 87%	 101 1/1 mixture of stereoisomers	 102 62%
3)	 103 80%	 104	 105 71% +  106
4)	 107 91%	 not found	 108 44%
5)	 109 61%[c]	 110 trace(<10%)	 111
6)	 112 91%		 113 42%

[a] Yield of crude iodomalonate which was used without further purification. [b] Isolated yield from iodomalonate. [c] Yield of iodomalonate after purification by flash chromatography. [d] The presumed intermediate iodide was not actually observed. Instead, a mixture of elimination products and the lactone were produced. Brief heating with *p*TSA converted the alkenes to the lactone. [e] The presumed intermediate iodide was not actually observed.

(65) We thank Dr. Eric Spletzer for performing this experiment.
(66) Julia, M.; Maumy, M. *Org. Synth.* **1976**, *55*, 57.
(67) It is uncertain whether **92a** is an intermediate that undergoes very rapid isomerization when exposed to light or heat. Nitriles appears to facilitate halogen atom transfer greatly with respect to esters. Iodoacetonitrile is a better halogen donor than ethyl iodoacetate by about 2 orders of magnitude (see ref 26).

Table V. Unsuccessful Cyclizations of Iodomalonates

substrate	possible ring sizes	products
		
(1) **114** alkene	4-exo/5-endo	reduced malonate
(2) **115** alkyne	4-exo/5-endo	+ unidentified
		
(3) **116** n = 5	7-exo/8-endo	reduced SM + unidentified
(4) **117** n = 11	13-exo/14-endo	reduced SM + unidentified
(5) **118** n = 15	17-exo/18-endo	reduced SM + unidentified
(6)  **119**	"6-exo"	 **120** + reduced SM + unidentified

enough to be competitive with other pathways of reaction for the intermediate malonyl radicals. Indeed, two of the homologous cyclizations failed to give significant yields of expected products. Attempted closure of **107** to the fused decalin system (entry 4) gave no detectable bicyclic products. The aromatic malonate **108** was the only readily identifiable product aside from the reduced starting material. A similar result was obtained with the bridged ring precursor **109** (entry 5). While resonances consistent with the bicyclic product **110** could be detected in the crude ^1H NMR, the amount of this product was quite small (estimated <10%).[68] Again, a significant amount of the aromatized product **111** was present.

We suspected that the aromatized products **108** and **111** might ultimately result from 1,5-transfer of an allylic hydrogen to the malonyl radical.[69] Some support for this suspicion is provided in entry 6; replacement of the offending hydrogen with a methyl group gives a modest yield of the cyclic lactone (**112** → **113**). We caution that substituent effects may also operate to accelerate the cyclization in entry 6 relative to entry 4.

Several other cyclizations that were unsuccessful are collected in Table V. Not surprisingly, attempted 4-exo/5-endo cyclization failed with either the alkene **114** or the alkyne **115** (entries 1 and 2). The simple substrate **116** for 7-exo/8-endo cyclization also failed (entry 3) as did two precursors (**117**, **118**) for possible macrocyclization (entries 4 and 5). These last two substrates were irradiated at a variety of concentrations (0.3–0.001 M) without success. The macrocyclization of nucleophilic radicals to activated alkenes under high dilution has been developed with great success by Porter,[70] and it is not presently clear why these counterparts with reversed electronic requirements are not successful. In all of these cases, starting material is consumed, albeit more slowly than in the successful cyclizations (sometimes additional ditin was added). From the above reactions, complex product mixtures resulted in which the reduced malonate was the only readily identified product. Placement of appropriate substituents on the chain to facilitate closure may provide viable cyclization substrates in some of these cases. Finally, an attempted intramolecular addition to an aromatic ring **119** (entry 6) was also not successful. In this case, the coupled malonate **120** was isolated in 42% yield. At present we do not understand why this particular substrate produces such a large amount of dimer relative to the other systems.

Conclusions

The cyclization of electrophilic radicals by the atom transfer method should provide a powerful means for construction of five-, six-, and seven-membered rings. The size of the ring formed is dictated by chain length and substituent effects. Further variations will no doubt emerge in more complex systems, and the chemistry exhibited by the simple systems in this study can now serve as a basis for prediction and understanding of related cyclizations. Since many (but not all) chain substituents accelerate radical cyclizations, it can be anticipated that more functionalized substrates will actually cyclize more rapidly that their unfunctionalized models. Unfortunately, nothing is presently known about the absolute rates of any of the cyclizations presented in this paper.[71]

It is appropriate to compare this atom-transfer method with related overall transformations including tin hydride cyclizations and manganese(III) oxidations. In principle, all of the cyclizations presented in this paper could be conducted by stoichiometric tin hydride cyclization. Of course, this method is restricted to formation of the reduced/cyclized products. Atom transfer cyclization can also give iodides and lactones—useful functional groups for subsequent synthetic transformations. Further, competitive reduction before cyclization can be a serious problem with tin hydride.[31] An easy way to form reduced cyclized products is to conduct an atom transfer cyclization followed by in situ reduction. If ring opening is competitive with closure, this may be the only way to trap kinetic products.[31] Manganese(III) oxidation of malonates, acetoacetates, and related functional groups has emerged as a powerful method for the formation of lactones[72] (and more recently alkenes and alkyl chlorides[73]). Simple esters and ketones are not efficiently cyclized by Mn(III). The atom-transfer cyclization provides a powerful and versatile complement to the manganese(III) chemistry. Because manganese(III) cyclizations may not always involve free radicals[74] and because it is not clear if cyclizations under such conditions are irreversible, it is presently not safe to assume that these two methods will produce the same type of products from appropriate precursors of the same radical. The atom-transfer reactions, which involve free-radical intermediates and trap kinetic products, may provide appropriate "model" substrates to investigate the mechanisms of the manganese(III) cyclizations and other possible free-radical reactions involving metal additives.

DBU Workup Procedure

The use of stoichiometric tin hydride or catalytic ditin reagents with organic halides requires the separation of the organotin compounds from the desired products. Depending on relevant R_f values, direct chromatography

(68) A related (and equally unsuccessful) application of our method toward the synthesis of upial has recently been attempted. Paquette, L. A.; Schaefer, A. G.; Springer, J. P. *Tetrahedron* **1987**, *43*, 5657.

(69) Disproportionation of the resulting allylic radical would give a cyclohexadiene that might subsequently behave as a hydrogen atom source.

(70) Porter, N. A.; Chang, V. H-T. *J. Am. Chem. Soc.* **1987**, *109*, 4976.

(71) Rate constants can be estimated from the tin hydride reductions if one assumes that the malonyl radical abstracts hydrogen from tin hydride with about the same rate as an alkyl radical. It is not clear that this assumption is justified. Given this precaution, $k_{5\text{-exo}}$ for the radicals derived from both **4a** and **67a** $\approx 8 \times 10^4\ M^{-1}\ s^{-1}$. This number should be regarded as very approximate. Detailed kinetic studies are warranted.

(72) See, Heiba, E. I.; Dessau, R. M.; Rodewald, P. G. *J. Am. Chem. Soc.* **1974**, *96*, 7977. Fristad, W. E.; Peterson, J. R.; Ernst, A. B.; Urbi, G. B. *Tetrahedron* **1986**, *42*, 3429. Corey, E. J.; Kang, M. *J. Am. Chem. Soc.* **1984**, *106*, 5384. Corey, E. J.; Ghosh, A. K. *Tetrahedron Lett.* **1987**, *28*, 175; *Chem. Lett.* **1987**, 223. Snider, B. B.; Mohan, R.; Kates, S. A. *J. Org. Chem.* **1985**, *50*, 3659.

(73) Snider, B. B.; Domroski, M. A. *J. Org. Chem.* **1987**, *52*, 5487.

(74) Fristad, W. E.; Petersen, J. R. *J. Org. Chem.* **1985**, *50*, 10.

of the reaction mixture is a viable approach. Often special workup techniques[23] are applied to remove most of the tin products before chromatography. One of us (C.-T.C.) has developed a procedure based on diazabicycloundecene (DBU), which has been used for both the tin hydride and ditin experiments discussed in this paper and in other systems as well. This workup procedure is described in detail in the Experimental Section and involves: (1) dilution of the reaction mixture with reagent grade (undried) ether, (2) addition of a slight excess of DBU (a crystalline precipitate appears), (3) dropwise addition of an ethereal solution of iodine until the iodine color just persists, (4) rapid filtration of the mixture through a short column of silica gel eluting with ether. After concentration, a crude product is obtained that is usually free of >90% of tin-containing products (as observed by NMR). In the best cases, the product is virtually tin-free. This crude product is then purified by standard techniques (usually flash chromatography).

A brief study showed that DBU does not form a precipitate with a pure trialkyltin chloride in anhydrous benzene. The precipitate appears on addition of undried reagent grade ether but not anhydrous ether. Addition of 1 equiv of water to the anhydrous solution also forms the precipitate, which was isolated and identified as DBU hydrochloride. All of the tin residue remained in the solution phase and consisted of trimethyltin hydroxide or hexabutyldistannoxane.

From these experiments, we can formulate the workup procedure as in eq 28. Molecular iodine rapidly converts both hexaalkylditins and trialkyltin hydrides to trialkyltin iodides. DBU hydrolyzes the tin halides to tin hydroxides with concomitant formation of DBU hydrohalide. This

$$R_3SnX + DBU + H_2O \longrightarrow DBU{\cdot}HX + R_3SnOH \rightleftharpoons R_3SnOSnR_3 + H_2O \quad (28)$$

solid is retained at the head of the column. Any excess DBU is also retained by the column. It is known that the tin hydroxides are in rapid equilibrium at room temperature with the distannoxanes. The tin hydroxide is favored with trimethyltin, but the stannoxane is favored with tributyltin.[75] Apparently, the position of this equilibrium is of no consequence and a substantial portion these species is retained on silica gel with ether as the eluent.[76] Perhaps the tin rapidly exchanges with free hydroxyl groups on the silica gel? It is anticipated that tin compounds that are not converted to tin halides and hydroxides by this procedure will not be removed. In any case, the procedure is fast, convenient, and efficient for removing the bulk of the tin products from a reaction mixture.

Experimental Section

Preparation of the Atom Transfer Cyclization Products. Method A. The iodide (or bromide) precursor was dissolved in benzene (0.3 M), and the initiator (0.05 equiv) was added. The mixture was placed into a preheated (85 °C) oil bath and heated at reflux for 1 h. Another equal portion of the initiator was then added, and the mixture was heated until completion as monitored by GC. After the reaction was complete, the solvent was removed, leaving a brown oil. The product was purified by medium-pressure liquid chromatography (hexanes/ethyl acetate = 40/1 for ester cases, 8/1 for malonate cases).

Method B. The precursor was dissolved in benzene to give a 0.3 M solution, and the hexaalkyl ditin (0.07–0.1 equiv) was added. The solution was placed 6–10 cm in front of a GE 275-W sunlamp. The mixture was irradiated with sunlamp at 60–80 °C (estimated final temperature) for 5–30 min. For less reactive substrates an additional portion of ditin was added, and irradiation was continued. Appearance of the characteristic iodine color indicates that the ditin is consumed. After evaporation of the solvent and treatment with DBU as discribed at the end of the Experimental Section, the residue was purified by medium-pressure liquid chromatography.

***cis*- and *trans*-Methyl 2-(Iodomethyl)cyclopentanecarboxylate (5a, 6a) and *cis*- and *trans*-Methyl 3-Iodocyclohexanecarboxylate (7a-cis, 7a-trans).** Compounds **5a**, **6a**, and **7a** were prepared by method A using iodo ester **4a** (298 mg, 1.119 mmol) and AIBN (4.6 mg, 0.028 mmol). Purification via MPLC gave in order of elution **5a** (124 mg, 41.6%), **6a** (98 mg, 32.8%), **7a-cis** and **-trans** (18 mg, 6%), and lactone **2** (4 mg, 2.8%), all oils (hexanes/EtOAc = 40/1 to 3/1). **5a**: ^{1}H NMR ($CDCl_3$) δ 3.68 (3 H, s), 3.28 (1 H, dd, J = 6.6, 9.5 Hz), 3.09 (1 H, t, J = 9.5 Hz), 2.94 (1 H, m), 2.53 (1 H, m), 2.04–1.83 (4 H, m), 1.53 (2 H, m); IR (thin film) 2952, 2970, 1732, 1435, 1373, 1198, 1163 cm^{-1}; MS (m/z) 237 (M – OMe), 209, 162, 141, 109, 81, 69; high-resolution MS calcd for $C_7H_{10}IO_2$ 236.9776, found 236.9771. **6a**: ^{1}H NMR ($CDCl_3$) δ 3.28 (3 H, s), 2.98 (1 H, dd, J = 4.8, 9.7 Hz), 2.85 (1 H, dd, J = 6.7, 9.7 Hz), 2.25 (1 H, m), 2.11 (1 H, m), 1.80–1.57 (3 H, m), 1.43–1.29 (2 H, m), 1.06 (1 H, m); IR (thin film) 2952, 2872, 1732, 1435, 1397, 1335, 1306, 1203, 1161 cm^{-1}; MS (m/z) 268, 251, 237, 162, 141, 109, 87, 82, 67, 59; high-resolution MS calcd for $C_8H_{13}IO_2$ 267.9960, found 267.9931. **7a-cis** and **7a-trans** as a mixture: ^{1}H NMR ($CDCl_3$) assigned to cis δ 4.07 (1 H, tt, J = 4.0, 12.3 Hz), 3.66 (3 H, s), 2.67 (1 H, m); assigned to trans 4.8 (1 H, m), 3.67 (3 H, s), 2.83 (1 H, tt, J = 3.9, 13.8 Hz); overlapping 2.43–1.25 (8 H, m); IR (thin film) 2945, 2858, 1734, 1435, 1371, 1323, 1244, 1189, 1095 cm^{-1}; MS (m/z) 237 (M – OMe), 209, 141, 109, 74, 79, 67, 59; high-resolution MS calcd for $C_8H_{13}IO_2$ 267.9960, found 267.9962.

***cis*-2-(Iodomethyl)cyclopentane-1-carboxylic Acid.** To a solution of **5a** (26 mg, 0.097 mmol) in chloroform (0.5 mL) was added iodotrimethylsilane (52.2 mg, 0.28 mmol). The mixture was heated at 50 °C under argon for 24 h and diluted with ether. After washing with $NaHSO_4$, the organic layer was dried over $MgSO_4$. Evaporation of the solvent under reduced pressure yielded the acid (23 mg): ^{1}H NMR (C_6D_6) δ 3.17 (1 H, dd, J = 5.5, 9.5 Hz), 2.83 (1 H, t, J = 9.5 Hz), 2.55 (1 H, m), 2.06 (1 H, m), 1.75 (1 H, m), 1.64–1.15 (5 H, m).

***trans*-2-(Iodomethyl)cyclopentane-1-carboxylic Acid.** *trans*-2-(Iodomethyl)cyclopentane-1-carboxylic acid was prepared following the procedure for *cis*-2-(iodomethyl)cyclopentane-1-carboxylic acid with iodo ester **6a** (24.5 mg, 0.091 mmol) and iodotrimethylsilane (56.2 mg, 0.28 mmol). A clear oil (22 mg) was obtained after workup: ^{1}H NMR (C_6D_6) δ 2.94 (1 H, dd, J = 4.9, 9.8 Hz), 2.81 (1 H, dd, J = 5.9, 9.8 Hz), 2.24 (1 H, m), 2.05 (1 H, m), 1.78–1.50 (3 H, m), 1.37–1.21 (2 H, m), 1.03–0.98 (1 H, m); IR (thin film) 2500–3500 (broad), 2959, 2874, 1699, 1456, 1423, 1290, 1232, 1032, 937 cm^{-1}; MS (m/z) 237 (M – OMe), 192, 160, 127, 109, 81, 69, 55, 43; high-resolution MS calcd for $C_{12}H_{10}IO$ 236.9776, found 236.9744.

***cis*-Dihydrocyclopenta[*c*]furan-1(3*H*)-one (2). Method I.** To a solution of *cis*-2-(iodomethyl)cyclopentanecarboxylic acid (21 mg, 0.082 mmol) in benzene (0.5 mL) was added triethylamine (15 mg, 0.14 mmol) at room temperature. The reaction mixture was stirred for 10 min. During this time, triethylammonium iodide precipitated. Filtration of the mixture and concentration in vacuo afforded lactone **2** as a clear oil (8.4 mg, 82%).

Method II. A solution of iodo ester **5a** (8 mg, 0.03 mmol) in benzene was placed into an oil bath and heated to 85 °C. After refluxing for 60 h, the solvent was removed under reduced pressure to yield lactone **2** (3 mg, 80%): ^{1}H NMR ($CDCl_3$) δ 4.47 (1 H, dd, J = 8.7, 9.4 Hz), 4.99 (1 H, dd, J = 3.1, 9.4 Hz), 3.04–2.91 (2 H, m), 2.08 (1 H, m), 1.98–1.53 (3 H, m); IR (thin film) 2959, 2909, 2870, 1770, 1576, 1481, 1452, 1377, 1184, 1140 cm^{-1}; MS (m/z) 126, 120, 105, 74, 67, 59, 45, 43, 41.

***cis*- and *trans*-Methyl 2-(Bromomethyl)cyclopentanecarboxylate (5b and 6b) and *cis*- and *trans*-Methyl 3-Bromocyclohexanecarboxylate (7b-cis and 7b-trans).** Compounds **5b**, **6b**, and **7b** were prepared by method B using bromo ester **4b** (90 mg, 0.407 mmol) and hexabutylditin (24 mg, 0.04

(75) Brown, J. M.; Chapman, A. C.; Harper, R.; Mowthorpe, D. J.; Davies, A. G.; Smith, P. J. *J. Chem. Soc., Dalton Trans.* **1972**, 338.

(76) In a sample experiment, 0.5 mmol (417 mg) of tributyltin iodide was generated by the titration of hexabutylditin in ether with iodine. After addition of 0.5 mmol of DBU and 0.5 mmol of water, the mixture was loaded on to 3 g of silica gel and eluted with 50 mL of ether. The eluent contained only 8 mg of residue after evaporation.

mmol). Purification by MPLC (hexanes/EtOAc = 40/1) gave **5b** (20 mg, 22%) and a mixture of **6b** and **7b-cis** and **-trans** (18 mg, 20%). **5b**: ^{1}H NMR ($CDCl_3$) δ 3.68 (3 H, s), 3.50 (1 H, dd, J = 6.9, 9.8 Hz), 3.33 (1 H, dd, J = 8.5, 9.8 Hz), 2.95 (1 H, m), 2.56 (1 H, m), 1.85–1.79 (4 H, m), 1.70–1.59 (2 H, m); IR (thin film) 2953, 2873, 1732, 1435, 1371, 1308, 1201, 1165, 1011 cm^{-1}; MS (m/z) 189 (M – OMe), 179, 158, 141, 109, 91, 87, 81; high-resolution MS calcd for $C_7H_{10}{}^{79}BrO$ 188.9915, found 188.9913. Mixture of **6b** and **7b**: ^{1}H NMR ($CDCl_3$) assigned to **7b-trans** δ 4.64 (1 H, m), 3.66 (3 H, s), 2.89 (1 H, tt, J = 4.4, 10.8 Hz); assigned to **7b-cis** 3.96 (1 H, tt, J = 4.6, 11.5 Hz), 3.66 (3 H, s); assigned to **6b** 3.68 (3 H, s), 3.55 (1 H, dd, J = 4.6, 9.5 Hz), 3.47 (1 H, dd, J = 6.0, 9.4 Hz); overalpping 2.64–1.35 (8 H, **6b** and **7b-trans**, 9 H **7b-trans**, m); IR (thin film) 2935, 2870, 1732, 1435, 1733, 1333, 1253, 1161, 1022 cm^{-1}; MS (m/z) 189 (M – OMe), 179, 141, 109, 87, 81, 67, 59, 53; high-resolution MS calcd for $C_7H_{10}{}^{79}BrO$ 188.9915, found 188.9922.

***cis*- and *trans*-*tert*-Butyl 2-(Iodomethyl)cyclopentanecarboxylate (9-cis, 9-trans) and *cis*- and *trans*-*tert*-Butyl 3-Iodocyclohexanecarboxylate (10-cis, 10-trans).** Compounds **9** and **10** were prepared by method B using iodo ester **8** (294 mg, 0.95 mmol), 2,6-di-*tert*-butylpyridine (190 mg, 0.993 mmol), and hexamethylditin (1.15 M, 21 μL, 0.024 mmol) in benzene. Purification by MPLC gave a mixture of **9-cis** and **-trans** (151 mg, 51%), pure **9-trans** (51 mg, 17%), **10-cis** and **-trans** (16 mg, 5%), and lactone **2** (11 mg, 8%). **9-cis**: ^{1}H NMR ($CDCl_3$) δ 3.34 (1 H, dd, J = 6.6, 9.4 Hz), 3.14 (1 H, t, J = 9.4 Hz), 2.82 (1 H, m), 2.50 (1 H, m), 1.46 (9 H, s), 2.08–1.34 (6 H, m); IR (thin film) 2967, 2870, 1722, 1478, 1454, 1391, 1368, 1254, 1215, 1150, 1036 cm^{-1}; MS (m/z) 267 (M – C_3H_7), 254, 237, 209, 127, 109, 81, 67, 57; high-resolution MS calcd for $C_8H_{12}IO_2$ 266.9881, found 266.9891. **9-trans**: ^{1}H NMR ($CDCl_3$) δ 3.41 (1 H, dd, J = 4.7, 9.6 Hz), 3.25 (1 H, dd, J = 6.9, 9.6 Hz), 2.37 (1 H, m), 2,23 (1 H, m), 2.08–1.85 (4 H, m), 1.73–1.60 (2 H, m), 1.45 (9 H, s); IR (thin film) 2968, 2870, 1725, 1454, 1391, 1368, 1283, 1215, 1150, 1036 cm^{-1}; MS (m/z) 267 (M – C_3H_7), 254, 237, 209, 127, 109, 81, 67, 57; high-resolution MS calcd for $C_8H_{12}IO_2$ 266.9881, found 266.9867. Mixture of **10-cis** and **10-trans**: ^{1}H NMR ($CDCl_3$) assigned to **10-trans** δ 4.80 (1 H, m), 1.44 (9 H, s); assigned to **10-cis** 4.07 (1 H, tt, J = 3.8, 8.4 Hz), 1.43 (9 H, s); overlapping 2.74–1.30 (9 H, m); IR (thin film) 2975, 2936, 2860, 1727, 1447, 1391, 1283, 1246, 1151, 1055, 1011 cm^{-1}; MS (m/z) 267 (M – C_3H_7), 254, 237, 209, 183, 127, 109, 81, 67, 57; high-resolution MS calcd for $C_8H_{12}IO_2$ 266.9981, found 266.9914.

***trans*- and *cis*-2,2-Dimethyl-1-(2-(iodomethyl)cyclopentan-1-yl)propanone (12a-trans and 12a-cis) and *cis*- and *trans*-2,2-Dimethyl-1-(3-iodocyclohexan-1-yl)propanone (13a-cis, 13a-trans).** Compounds **12a** and **13a** were prepared by method B using iodo ketone **11a** (294 mg, 1.00 mmol) and hexamethylditin (1.15 M, 70 μL, 0.08 mmol) in benzene. Purification by MPLC (hexanes/EtOAc = 20/1) gave **12a-trans** (122 mg, 41%), **13a-cis** (28 mg, 10%), and **13a-trans** (34 mg, 12%). **12a-trans**: ^{1}H NMR ($CDCl_3$) δ 3.28 (1 H, dd, J = 4.4, 9.8 Hz), 3.11 (1 H, dd, J = 6.0, 9.8 Hz), 3.01 (1 H, td, J = 9.4, 9.4 Hz), 2.35 (1 H, m), 2.07–1.88 (2 H, m), 1.78–1.36 (4 H, m), 1.16 (9 H, s); IR (thin film) 2961, 2869, 1698, 1478, 1464, 1425, 1395, 1366, 1281, 1073, 1001, 936 cm^{-1}; MS (m/z) 237 (M – t-Bu), 209, 167, 85, 79, 67, 57; high-resolution MS calcd for $C_7H_{10}IO$ 236.9776, found 236.9739. **13a-cis**: ^{1}H NMR ($CDCl_3$) δ 4.14 (1 H, tt, J = 4.5, 12.4 Hz), 2.95 (1 H, tt, J = 3.3, 11.6 Hz), 2.46–1.23 (8 H, m); IR (thin film) 2936, 2861, 1701, 1478, 1462, 1449, 1395, 1366, 1323, 1285, 1244, 1207, 1159, 1100, 1061, 1003, 967 cm^{-1}; MS (m/z) 237 (M – t-Bu), 209, 167, 85, 81, 67, 57; high-resolution MS calcd for $C_7H_{10}IO$ 236.9776, found 236.9774. **13a-trans**: ^{1}H NMR ($CDCl_3$) δ 4.93 (1 H, m), 3.47 (1 H, tt, J = 3.1, 11.3 Hz), 2.08–1.40 (8 H, m), 1.16 (9 H, s); IR (thin film) 2697, 2940, 2865, 1701, 1478, 1467, 1428, 1395, 1368, 1329, 1285, 1254, 1235, 1152, 1092, 1059, 1005, 967 cm^{-1}; MS (m/z) 237 (M – t-Bu), 209, 85, 81, 74, 59; high-resolution MS calcd for $C_7H_{10}IO$ 236.9776, found 236.9775.

***trans*-1-Phenyl-1-(2-(iodomethyl)cyclopentan-1-yl)-methanone (12b-trans) and *cis*- and *trans*-1-Phenyl-1-(3-iodocyclohexan-1-yl)methanone (13b-cis, 13b-trans).** Compounds **12b** and **13b** were prepared by method B using iodo ketone **11b** (100 mg, 0.318 mmol) and hexamethylditin (1.15 M, 23 μL, 0.026 mmol) in benzene. Purification by MPLC (hexanes/EtOAc = 20/1) gave **12b-trans** (46 mg, 46%), **13b-cis** (15 mg, 15%), and **13b-trans** (7 mg, 7%). **12b-trans**: ^{1}H NMR ($CDCl_3$) δ 8.00–7.97 (2 H, m), 7.60–7.45 (3 H, m), 3.52 (1 H, m), 3.36 (1 H, dd, J = 5.3, 9.8 Hz), 3.28 (1 H, dd, J = 5.99, 9.8 Hz), 2.63 (1 H, m), 2.16 (1 H, m), 1.99 (1 H, m), 1.84–1.48 (4 H, m); IR (thin film) 3060, 2953, 2869, 1678, 1597, 1580, 1447, 1425, 1370, 1275, 1000, 698 cm^{-1}; MS (m/z) 314, 273, 219, 187, 169, 131, 119, 105, 77, 69; high-resolution MS calcd for $C_{13}H_{15}IO$ 314.0167, found 314.0153. **13b-cis**: ^{1}H NMR ($CDCl_3$) δ 7.92–7.90 (2 H, m), 7.60–7.45 (3 H, m), 4.24 (1 H, tt, J = 4, 12.4 Hz), 3.37 (1 H, tt, J = 3.2, 11.7 Hz), 2.62–2.47 (2 H, m), 2.26–1.46 (6 H, m); IR (thin film) 3061, 2936, 1680, 1597, 1582, 1460, 1447, 1370, 1277, 1077, 69, cm^{-1}; MS (m/z) 237 (M – C_6H_5) 187, 105, 77; high-resolution MS calcd for $C_7H_{10}IO$ 236.9776, found 236.9792. **13b-trans**: ^{1}H NMR ($CDCl_3$) δ 8.00–7.97 (2 H, m), 7.60–7.41 (3 H, m), 5.99 (1 H, m), 3.88 (1 H, tt, J = 3.3, 10.9 Hz), 2.31–1.53 (8 H, m); IR (thin film) 3061, 2938, 2861, 1682, 1579, 1578, 1446, 1373, 1335, 1319, 967, 911, 698 cm^{-1}; MS (m/z) 237 (M – C_6H_5), 187, 151, 105, 77; high-resolution MS calcd for $C_{13}H_{15}IO$ 314.0167, found 314.0146.

***(E)*- and *(Z)*-Methyl 2-(Iodomethylidene)cyclopentanecarboxylate (15E and 15Z) and Methyl 3-Iodo-2-cyclohexenecarboxylate (16).** Compounds **15E**, **15Z**, and **28** were prepared by method B using iodo ester **14** (21 mg, 0.08 mmol) and hexamethylditin (1.15 M, 9 μL, 0.011 mmol). Purification by MPLC (hexanes/EtOAc = 40/1) yielded **15E** (12 mg, 57%) and a mixture of **15Z** and **16** (6 mg, 29%) (**15E**/**15Z** = 2.4/1). **15E**: ^{1}H NMR ($CDCl_3$) δ 6.24 (1 H, td, J = 2.4, 2.2 Hz), 3.71 (3 H, s), 3.36 (1 H, td, J = 2.3, 7.5 Hz), 2.39–2.34 (2 H, m), 2.22–1.66 (4 H, m); IR (thin film) 2952, 2874, 1734, 1624, 1163 cm^{-1}; MS (m/z) 213 (M – C_4H_7), 207, 151, 139, 107, 84, 79, 59, 49; high-resolution MS calcd for $C_8H_{11}IO_2$ 265.9803, found 265.9839. Mixture of **15Z** and **16**: ^{1}H NMR ($CDCl_3$) assigned to **16** δ 6.45 (1 H, m), 3.70 (3 H, s), 3.14 (1 H, m); assigned to **15Z** 6.17 (1 H, td, J = 1.7, 1.8 Hz) 3.72 (3 H, s) 3.37 (1 H, m); overlapping 2.54–2.43 (2 H, m), 2.20–1.71 (2 H, m); IR (thin film) 2950, 2870, 2838, 1736, 1628, 1433, 1335, 1308, 1246, 1163, 1028 cm^{-1}; MS (m/z) 266, 235, 207, 201, 157, 139, 107, 79, 67, 59; high-resolution MS calcd for $C_8H_{11}IO_2$ 265.9803, found 265.9804.

***(E)*- and *(Z)*-Methyl 2-[Iodo(trimethylsilyl)-methylidene]cyclopentanecarboxylate (18E and 18Z).** Compounds **18E** and **18Z** were prepared by method B using iodo ester **17** (30 mg, 0.087 mmol) and hexamethylditin (1.15 M, 7 μL, 0.008 mmol). Purification by MPLC (hexanes/EtOAc = 40/1) yielded **18E** and **18Z** (24.2 mg, 81%) (**18E**/**18Z** = 1/1). The isomers were separable but the stereochemistry was not assigned. **18** (less polar): ^{1}H NMR ($CDCl_3$) δ 3.68 (3 H, s), 3.61 (1 H, d, J = 7.9 Hz), 2.64 (1 H, m), 2.47–2.29 (2 H, m), 2.02 (1 H, m), 1.83–1.72 (2 H, m), 0.25 (9 H, s); IR (thin film) 2953, 2896, 1734, 1605, 1248, 1192, 1163, 880, 841 cm^{-1}; MS (m/z) 323 (M – Me), 279, 265, 211, 201, 185, 89, 73, 59; high-resolution MS calcd for $C_{11}H_{19}IO_2Si$ 338.0199, found 338.0177. **18** (more polar): ^{1}H NMR ($CDCl_3$) δ 3.70 (3 H, s), 3.55 (1 H, m), 2.55–2.39 (2 H, m), 2.15–1.80 (4 H, m), 0.26 (9 H, s); IR (thin film) 2953, 2897, 1736, 1599, 1433, 1311, 1159, 883, 841 cm^{-1}; MS (m/z) 338, 323, 279, 265, 211, 201, 185, 109, 85, 73, 59; high-resolution MS calcd for $C_{11}H_{19}IO_2Si$ 338.0199, found 338.0136.

4-Iodo-2,3,3-trimethylcyclohexan-1-one (36 and 37) and 3-(Iodomethyl)-4,4,5-trimethylcyclopentan-1-one (38).[35] A solution of **34** (146 mg, 0.546 mmol), deuterated benzene (1.83 mL), and Me_6Sn_2 (18 mg, 0.055 mmol, 0.1 equiv) was placed in a thin, flat-faced photochemical flask. The reaction mixture was irradiated for 15 min with a GE 275-W sunlamp at 10-cm distance. The solvent was then evaporated in vacuo. The product was purified by flash column chromatography (EtOAc/hexanes = 1/20) to yield **36** and **37** (75%) and **38** (7%). **36**: ^{1}H NMR ($CDCl_3$) δ 4.61 (1 H, dd, J = 5, 2 Hz), 2.80 (2 H, m), 2.35 (4 H, m), 1.16 (3 H, s), 1.00 (3 H, d, J = 7 Hz), 0.98 (3 H, s); IR (thin film) 2972, 2945, 2920, 2360, 2341, 1714, 1714, 1450, 1178 cm^{-1}; MS (m/z) 266, 251, 209, 205, 139 (M – I), 111, 97, 83, 69, 55; high-resolution MS calcd for $C_9H_{15}OI$, 266.0168, found 266.0168. **37**: ^{1}H NMR ($CDCl_3$) δ 4.55 (1 H, dd, J = 14, 4 Hz), 2.70 (1 H, m), 2.42 (4 H, m), 2.24 (1 H, m), 1.21 (3 H, s), 1.12 (3 H, d, J = 7 Hz), 0.85 (3 H, s); IR (thin film) 2970, 1717, 1650, 1560 cm^{-1}; MS (m/z) 139 (M – I), 121, 11, 97, 83, 69, 55; high-resolution MS calcd for $C_9H_{15}O$ 139.1123, found 139.1124. **38** (major): ^{1}H NMR ($CDCl_3$) δ 3.46 (1 H, dd, J = 10, 4 Hz), 3.0 (1 H, dd, J = 12, 10 Hz), 2.74 (1 H, dd, J = 19, 8 Hz), 2.35 (1 H, m), 2.10 (1 H, q, J = 7 Hz), 1.91 (1

H, dd, J = 19, 12 Hz), 1.18 (3 H, s), 0.95 (3 H, d, J = 7 Hz), 0.65 (3 H, s). **38** (minor): ^{1}H NMR ($CDCl_3$) δ 3.54 (1 H, dd, J = 10, 4 Hz), 3.04 (1 H, dd, J = 12, 10 Hz), 2.60 (1 H, dd, J = 19, 8 Hz), 2.43 (1 H, m), 2.28 (1 H, dd, J = 19, 1 Hz), 2.16 (1 H, q, J = 7 Hz), 1.05 (3 H, s), 0.98 (3 H, d, J = 7 Hz), 0.96 (3 H, s); IR (thin film) **38** (mixture) 2964, 2933, 1741, 1462, 1309, 1200, 1183 cm^{-1}; MS (m/z) **38** (mixture) 266, 251, 209, 167, 139, 111, 97, 83, 69, 55; high-resolution MS calcd for $C_9H_{15}IO$ 266.0168, found 266.0168.

4-Iodocyclohexanone (40). Compound **40** was prepared following the standard cyclization procedure using 1-iodo-5-hexen-2-one (**39**) (60 mg, 0.27 mmol) and hexamethylditin (9 mg, 0.027 mmol). After purification by MPLC (hexane/EtOAc = 25/1), 4-iodocyclohexanone (34 mg, 56%) was obtained as a white solid (mp 62 °C): ^{1}H NMR ($CDCl_3$) δ 4.71 (1 H, m), 2.67–2.58 (2 H, m), 2.40–2.06 (6 H, m); ^{13}C NMR 208.5, 40.8, 38.1, 27.5 ppm; IR (thin film) 2955, 2901, 1713, 1431, 1348, 1318 cm^{-1}; MS (m/z) 224, 154, 127, 97, 69, 55; high-resolution MS calcd for C_6H_9IO 223.9698, found 223.9683.

4-Iodo-3-methylcyclohexanone (43) and 3-(1-Iodoethyl)-cyclopentanone (44). Compounds **43** and **44** were prepared via standard cyclization procedure B using 1-iodo-5-hepten-2-one (**42**) (70 mg, 0.29 mmol) and hexamethylditin (10 mg, 0.03 mmol). Purification by MPLC (hexanes/EtOAc = 15/1) gave 4-iodo-3-methylcyclohexanone (**43**) (cis and trans) (38 mg, 54%) and 3-(1-iodoethan-1-yl)cyclopentanone (two diastereomers) (18 mg, 19%). **43**: ^{1}H NMR ($CDCl_3$) assigned to one isomer δ 4.68 (1 H, s), 1.01 (3 H, d, J = 6.4 Hz); assigned to the other isomer 4.21 (1 H, s), 1.16 (3 H, d, J = 6.7 Hz); overlapping 2.75–2.08 (7 H, m). **44**: ^{1}H NMR ($CDCl_3$) δ 4.31–4.18 (1 H, m), 2.53–2.02 (6 H, m), 1.98 (3 H, d, J = 6.8 Hz); assigned to one diastereomer 1.96 (3 H, d, J = 4.7 Hz); assigned to the other diastereomer 1.60 (1 H, m).

4α- and 4β-(3aα,7aα)-4-Iodobicyclo[3.4.0]nonan-3-one (46a-exo and 46a-endo). Compounds **46a-exo** and **46a-endo** were prepared by method B using iodo ketone **45a** (30 mg, 0.11 mmol) and hexamethylditin (1.15 M, 6.7 μL, 0.008 mmol). Purification by MPLC (hexanes/EtOAc = 20/1) gave a mixture of **46a-exo** and **46a-endo** (24.6 mg, 82%) (**46a-exo/46a-endo** = 3/1): ^{1}H NMR ($CDCl_3$) assigned to **46a-endo** δ 4.49 (1 H, td, J = 4.7, 12.8 Hz); assigned to **46a-exo** 4.21 (1 H, m); overlapping 2.92–1.08 (12 H, m); IR (thin film) 2928, 2855, 1742, 1447, 1404, 1308, 1161, 1113, 1098, 1078 cm^{-1}; MS (m/Z) 264, 137, 119, 109, 95, 79, 67, 55; high-resolution MS calcd for $C_9H_{13}IO$ 264.0011, found 264.0012.

4α- and 4β-(3aα,7aα)-4-Bromobicyclo[3.4.0]nonan-3-one (46b-exo and 46b-endo). Compounds **46b-exo** and **46b-endo** were prepared by method B using bromo ketone **45b** (18 mg, 0.083 mmol) and hexabutylditin (4.8 mg, 0.008 mmol). Purification by flash chromatography (hexanes/EtOAc = 8/1) gave a mixture of **46b-exo** and **46b-endo** (10 mg, 56%) (**46b-exo/46b-endo** = 2/1): ^{1}H NMR ($CDCl_3$) assigned to **46b-endo** δ 4.36 (1 H, td, J = 4.7, 12.4 Hz), 2.92 (1 H, m); assigned to **46b-exo** 4.06 (1 H, m); overlapping 2.81–1.14 (11 H endo, 12 H exo, m); IR (thin film) 2934, 2859, 1744, 1449, 1310, 1242, 1225, 1157, 1080, 1015, 912 cm^{-1}; MS (m/z) 216, 137, 119, 109, 95, 79, 76, 55; high-resolution MS calcd for $C_9H_{13}{}^{79}BrO$ 216.0150, found 216.0150.

4α- and 4β-(3aα,7aα)-Hexahydro-4-iodo-2(3*H*)-benzofuranone (48-exo and 48-endo). Compounds **48-exo** and **48-endo** were prepared by method B using iodo ester **47a** (48 mg, 0.18 mmol) and hexabutylditin (10.8 mg, 0.019 mmol). Purification by flash chromatography (hexanes/EtOAc = 15/1) gave a mixture of **48-exo** and **48-endo** (28 mg, 58%) (**48-exo/48-endo** = 4/1) and **47b** (3 mg, 7%). Mixture of **48-exo** and **48-endo**: ^{1}H NMR ($CDCl_3$) assigned to **48-endo** δ 4.53 (1 H, m), 4.28 (1 H, td, J = 5.1, 12.9 Hz), 3.18 (1 H, m); assigned to **48-exo** 4.47 (1 H, m), 3.88 (1 H, ddd, J = 4.0, 4.5, 11.8 Hz), 2.86 (1 H, m); overlapping 2.76–1.27 (8 H, m); IR (thin film) 2940, 2863, 1773, 1447, 1306, 1233, 1148, 1015 cm^{-1}; MS (m/z) 266, 213, 162, 139, 121, 93, 79, 67, 61, 55; high-resolution MS calcd for $C_8H_{11}IO_2$ 265.9802, found 265.9798.

***cis*-Hexahydro-2(3*H*)-benzofuranone (49).** A solution of **47a** (100 mg, 0.375 mmol) and hexamethylditin (12 mg, 0.038 mmol) in benzene (1.25 mL) was irradiated with a GE 275-W sunlamp for 30 min. To the reaction mixture was added a spatula tip of AIBN and tri-*n*-butyltin hydride (122 mg, 0.42 mmol). This mixture was heated at reflux for 4 h. Concentration and purification by MPLC (hexanes/EtOAc = 5/1) gave lactone **49** as a clear oil (52.8 mg, 55%): ^{1}H NMR ($CDCl_3$) δ 4.5 (1 H, q, J = 4.3 Hz), 2.61 (1 H, dd, J = 6.8, 16.7 Hz), 2.38 (1 H, m), 2.25 (1 H, dd, J = 2.6, 16.7 Hz), 2.09 (1 H, m), 1.76–1.22 (7 H, m); IR (thin film) 2932, 2859, 1773, 1173, 1142 cm^{-1}; MS (m/z) 140, 96, 81, 67, 55.

***cis*- and *trans*-Methyl 2-(Iodomethyl)-1-cyclohexanecarboxylate (51-cis, 51-trans) and *cis*- and *trans*-Methyl 3-Iodo-1-cycloheptanecarboxylate (52-cis, 52-trans).** The preparation of **51-cis**, **51-trans**, **52-cis**, and **52-trans** followed the standard cyclization procedure B using methyl 2-iodo-7-octenoate (**50**) (120 mg, 0.42 mmol) and hexamethylditin (13 mg, 0.04 mmol). DBU workup and purification by MPLC (hexanes/EtOAc = 38/1) afforded **51-cis** (29 mg, 24%), **51-trans** (33 mg, 28%), and a mixture of **52-cis** and **52-trans** (19 mg, 16%). **51-cis**: ^{1}H NMR ($CDCl_3$) δ 3.68 (3 H, s), 3.32 (1 H, dd, J = 7.4, 9.7 Hz), 3.25 (1 H, t, J = 8.4 Hz), 2.87 (1 H, m), 2.03–1.37 (9 H, m); IR (thin film) 2934, 2857, 1732, 1450, 1433, 1381, 1347, 1306, 1242, 1198, 1225 cm^{-1}; MS (m/Z) 251 (M – OMe), 223, 181, 169, 155, 124, 95, 87, 81; high-resolution MS calcd for $C_8H_{12}IO$ 250.9933, found 250.9932. **51-trans**: ^{1}H NMR ($CDCl_3$) δ 3.70 (3 H, s), 3.24 (1 H, dd, J = 3.1, 10 Hz), 3.13 (1 H, dd, J = 6.5, 10 Hz), 2.23 (1 H, dt, J = 3.7, 10 Hz), 1.91–1.76 (4 H, m), 1.56–1.09 (5 H, m); IR (thin film) 2934, 2857, 1734, 1449, 1435, 1368, 1316, 1294, 1254, 1240 cm^{-1}; MS (m/z) 251 (M – OMe), 223, 181, 167, 155, 123, 95, 87, 81; high-resolution MS calcd for $C_8H_{12}IO$ 250.9933, found 250.9932. **52-cis** and **52-trans**: ^{1}H NMR ($CDCl_3$) assigned to cis δ 4.28 (1 H, m), 2.66 (3 H, s)f assigned to trans 4.73 (1 H, m), 3.68 (3 H, s); overlapping 2.80–2.74 (1 H, m), 2.49–1.46 (10 H, m); IR (thin film) 2934, 2861, 1734, 1443, 1372, 1335, 1294, 1256, 1217 cm^{-1}; MS (m/z) 251 (M – OMe), 223, 155, 123, 95, 78; high-resolution MS calcd for $C_8H_{12}IO$ 250.9933, found 250.9932.

Lactone 53a. The *cis*-methyl 2-(iodomethyl)cyclohexanecarboxylate (15 mg, 0.053 mmol) was heated with benzene at reflux for 12 h. After the solvent was removed, lactone **53a** (6.5 mg, 88%) was obtained as a clear oil: ^{1}H NMR ($CDCl_3$) δ 4.19 (1 H, dd, J = 5, 8.8 Hz), 3.95 (1 H, t, J = 8.8 Hz), 2.63 (1 H, m), 2.46 (1 H, m), 2.10 (1 H, m), 1.81 (1 H, m), 1.66–1.57 (2 H, m), 1.27–1.16 (4 H, m); IR (thin film) 2932, 2857, 1773, 1445, 1375, 1211, 1188, 1159, 1128, 1096 cm^{-1}; MS (m/z) 140, 105, 91, 81. 67.

Lactone 53b. A mixture of *cis*- and *trans*-methyl 3-iodocycloheptanecarboxylate **51-cis/trans** (10 mg, 0.05 mmol) was heated in benzene at reflux for 2 h. Only *trans*-iodo ester was converted to lactone **53b**. After treatment of the reaction mixture with a catalytic amount of tetrabutylammonium iodide in refluxing benzene for another 2 h, lactone **53b** (4 mg) was isolated in 81% by MPLC (hexanes/EtOAc = 3/1) as a white solid (mp 53 °C): ^{1}H NMR ($CDCl_3$) δ 4.89 (1 H, m), 2.74 (1 H, m), 2.44 (1 H, m), 2.04–1.96 (3 H, m), 1.80–1.54 (6 H, m); IR (thin film) 2928, 1757, 1368, 1211, 1157 cm^{-1}; MS (m/z) 140, 112, 98, 81, 67; high-resolution MS calcd for $C_8H_{12}O_2$ 140.0837, found 140.0838.

Methyl 2-(1-Iodoethyl)-1-cyclohexanecarboxylate (55) (four diastereomers). γ-Iodo esters **55** were prepared following standard cyclization procedure B using *trans*-methyl 2-iodo-7-nonenoate (**54**) (110 mg, 0.37 mmol) and hexamethylditin (1/ mg, 0.03 mmol). γ-Iodo ester **55-cis** (two diastereomers) (39 mg 35%) and **55-trans** (two diastereomers) (34 mg, 31%) were obtained as clear oils. **55-cis**: ^{1}H NMR ($CDCl_3$) assigned to one diastereomer δ 4.52 (1 H, m), 3.67 (3 H, s), 3.21 (1 H, m), 2.01 (3 H, d, J = 6.7 Hz); assigned to the other diastereomer δ 4.41 (1 H, m), 3.66 (3 H, s), 3.03 (1 H, m), 1.95 (3 H, d, J = 6.9 Hz); overlapping δ 2.04–1.20 (9 H, m); IR (thin film) 2967, 2880, 1740, 1227 cm^{-1}; MS (m/z) 265 (M – OMe), 237, 169, 137, 128, 109, 95.81; high-resolution MS calcd for $C_9H_{14}IO$ 265.0089, found 265.0089. **55-trans**: ^{1}H NMR ($CDCl_3$) assigned to one diastereomer δ 4.40 (1 H, m), 3.69 (3 H, s), 1.74 (3 H, d, J = 7.1 Hz); assigned to the other diastereomer δ 4.32 (1 H, m), 3.69 (3 H, s), 1.90 (3 H, d, J = 7.1 Hz); overlapping 2.41–2.27 (1 H, m), 2.07–1.16 (9 H, m); IR (thin film) 2934, 2857, 1734, 1449, 1435, 1372, 1331, 1298, 1254, 1239, 1194 cm^{-1}; MS (m/Z) 265 (M – OCH_3), 237, 169, 137, 109, 81; high-resolution MS calcd for $C_9H_{14}IO$ 265.0089, found 265.0089.

Lactone 59 was prepared following standard cyclization procedure using methyl 2-iodo-7-methyl-7-ocenoate (40 mg, 0.14 mmol) and hexamethylditin (3 mg, 0.09 mmol). After purification by MPLC (hexane/EtOAc = 4/1), **59** (12 mg, 58%) was obtained as a white solid (mp 63 °C): ^{1}H NMR ($CDCl_3$) δ 2.80 (1 H, m), 2.15–1.92 (4 H, m), 1.84–1.49 (6 H, m), 1.47 (3 H, s); IR (thin film)

2936, 2865, 1752, 1460, 1306, 1231, 1196, 1140, 1107 cm^{-1}; MS (m/z) 154, 111, 97, 81; high-resolution MS calcd for $C_9H_{14}O_2$ 154.0994, found 154.0998.

Dimethyl 2-(Iodomethyl)cyclopentane-1,1-dicarboxylate (68a) and Dimethyl 3-Iodocyclohexane-1,1-dicarboxylate (70a). Compounds **68a** and **70a** were prepared by method A using iodo ester **67a** (84 mg, 0.258 mmol) and AIBN (4.6 mg, 0.018 mmol). Purification by MPLC (hexanes/EtOAc = 8/1) afforded **68a** (65 mg, 77%) and **70a** (7 mg, 8%). **68a**: ^1H NMR ($CDCl_3$) δ 3.74 (3 H, s), 3.72 (3 H, s), 3.54 (1 H, dd, J = 3.2, 9.0 Hz), 2.99 (1 H, dd, J = 9.0, 11.4), 2.89 (1 H, m), 2.48 (1 H, m), 2.29–2.14 (2 H, m), 1.90–1.54 (3 H, m); IR (thin film) 2953, 2874, 1730, 1433, 1333, 1269, 1198, 1127, 1082, 1034 cm^{-1}; MS (m/z) 294 (M – MeOH), 198, 138, 107, 79, 67, 59; high-resolution MS calcd for $C_9H_{11}O_3$ 293.9753, found 293.9754. **70a**: ^1H NMR ($CDCl_3$) 4.27 (1 H, tt, J = 4.0, 12.4 Hz), 3.76 (3 H, s), 2.71 (3 H, s), 3.03 (1 H, m), 2.43–2.34 (2 H, m), 2.24 (1 H, t, J = 12.8 Hz), 1.97–1.29 (4 H, m)f IR (thin film) 2951, 2863, 1734, 1451, 1435, 1310, 1294, 1252, 1211, 1152, 1121, 1098, 1061, 1036 cm^{-1}; MS (m/z) 295 (M – OMe), 267, 235, 199, 167, 139, 107, 79, 59; high-resolution MS calcd for $C_9H_{12}IO_3$ 294.9831, found 294.9832.

Dimethyl 2-(Bromomethyl)cyclopentane-1,1-dicarboxylate (68b) and Dimethyl 3-Bromocyclohexane-1,1-dicarboxylate (70b). Compounds **68b** and **70b** were prepared by method B using bromomalonate **67b** (88 mg, 0.315 mmol) and hexabutylditin (15 mg, 0.026 mmol). Purification by MPLC (hexanes/EtOAc = 8/1) produced **68b** (63 mg, 72%) and **70b** (10.8 mg, 12%). **68b**: ^1H NMR ($CDCl_3$) δ 3.74 (3 H, s), 3.72 (3 H, s), 3.71 (1 H, dd, J = 3.9, 10.1 Hz), 3.26 (1 H, t, J = 10.1 Hz), 2.94 (1 H, m), 2.43 (1 H, m), 2.22–2.13 (2 H, m), 1.86 (1 H, m), 1.67–1.56 (2 H, m); IR (thin film) 2.53, 2876, 1732, 1435, 1271, 1225, 1200, 1177, 1136, 1086, 1022 cm^{-1}; MS (m/z) 249 (M – OMe), 239, 205, 199, 167, 139, 113, 95, 79, 69; high-resolution MS calcd for $C_9H_{12}{}^{79}BrO_3$ 246.9970 found 246.9969. **70b**: ^1H NMR ($CDCl_3$) δ 4.17 (1 H, tt, J = 4.1, 11.5 Hz), 3.76 (3 H, s), 3.72 (3 H, s), 2.71 (1 H, m), 2.33–2,23 (2 H, m), 2.09 (1 H, dd, J = 11.8, 13.7 Hz), 1.83–1.68 (3 H, m), 1.40 (1 H, m); IR (thin film) 2953, 2867, 1732, 1452, 1435, 1310, 1296, 1254, 1159, 1130, 1065, 1003, 912 cm^{-1}; MS (m/z) 262 (M – Me), 247, 199, 167, 139, 113, 79, 67, 59; high-resolution MS calcd for $C_9H_{12}{}^{79}BrO_3$ 246.9970, found 264.9971.

(3aα,6aα)-Dihydro-6a-carbomethoxycyclopenta[*c*]furan-1(3*H*)-one (73). A solution of iodomalonate **68a** (16 mg, 0.055 mmol) in toluene was heated at reflux for 8 h, and was then filtered through silica gel. Evaporation of the solvent afforded a clear oil of **73** (8.5 mg, 84%): ^1H NMR ($CDCl_3$) δ 4.55 (1 H, dd, J = 7.6, 9.3 Hz), 4.07 (1 H, dd, J = 2.4, 9.3 Hz), 3.77 (3 H, s), 3.09 (1 H, m), 2.42–2.26 (2 H, m), 2.06 (1 H, m), 1.82 (1 H, m), 1.68–1.60 (2 H, m); IR (thin film) 2957, 2874, 1773, 1742, 1448, 1435, 1379, 1256, 1204, 1146, 1116, 1055, 1013, 978 cm^{-1}; MS (m/z) 153 (M – OMe), 140, 125, 109, 95, 81, 67, 53.

Dimethyl 2-Ethylcyclopentane-1,1-dicarboxylate (80). Malonate **80** was prepared following the procedure for lactone **49** using iodomalonate **78** (70 mg, 0.21 mmol), hexamethylditin (6 mg, 0.02 mmol), tri-*n*-butyltin hydride (80 mg, 0.28 mmol), and AIBN (1 mg, 0.006 mmol). After purification by MPLC (hexanes/EtOAc = 8/1), malonate **80** (37 mg, 84%) was isolated as a clear oil: ^1H NMR ($CDCl_3$) δ 3.71 (3 H, s), 3.69 (3 H, s), 2.50–2.38 (2 H, m), 2.02–1.96 (2 H, m), 1.82 (1 H, m), 1.66–1.52 (2 H, m), 1.36 (1 H, m), 1.03 (1 H, m), 0.92 (2 H, t, J = 6.9 Hz); ^{13}C NMR δ 173.2, 172.1, 63.6, 52.4, 52.0, 48.2, 34.5, 30.3, 24.3, 22.9, 13.7 ppm; IR 2959, 2876, 1732, 1435, 1266, 1194, 1169 cm^{-1}; MS (m/z) 214, 183, 154, 145, 132, 113, 95; high-resolution MS calcd for $C_{10}H_{15}O_3$ 183.1021, found 183.1021.

Dimethyl 3-Methylcyclohexane-1,1-dicarboxylate (83). Compound **83** was prepared following the procedure for lactone **49** using iodomalonate **81** (100 mg, 0.29 mmol), hexamethylditin (9.6 mg, 0.029 mmol), and tri-*n*-butyltin hydride (100 mg, 0.35 mmol). Purification by MPLC (hexanes/EtOAc = 6/1) gave **83** (52 mg, 84%) as a clear oil: ^1H NMR ($CDCl_3$) δ 3.75 (3 H, s), 3.68 (3 H, s), 2.38–2.27 (2 H, m), 1.75–1.26 (7 H, m), 0.91 (3 H, d, J = 5.5 Hz); IR (thin film) 2953, 2870, 1734, 1453, 1314, 1252, 1215, 1183, 1148 cm^{-1}; MS (m/z) 214, 183, 154, 145, 133, 122, 133, 94; high-resolution MS calcd for $C_{11}H_{18}O_4$ 214.1191, found 214.1198.

(2aα,4aα,7aα,7bα)-Octahydro-2-carbomethoxyindeno[7,1-*bc*]furan-2-one (86). Compound **86** was prepared following method B using iodomalonate **84** (22 mg, 0.06 mmol) and hexamethylditin (1.5 mg, 0.0045 mmol) to give the crude cyclized product **85**. The crude reaction mixture was then heated to 80 °C for 2 h. Compound **86** was obtained as a clear oil after purification by medium-pressure liquid chromatography (hexanes/EtOAc = 5/1) (10.2 mg, 76%): ^1H NMR ($CDCl_3$) δ 4.81 (1 H, m), 3.76 (3 H, s), 2.81 (1 H, dd, J = 6.7, 10.0 Hz), 2.41–2.05 (4 H, m), 1.75–1.36 (7 H, m); IR (thin film) 2942, 2870, 1773, 1744, 1435, 1368, 1356, 1264, 1223, 1200, 1167, 1148, 978 cm^{-1}; MS (m/z) 193 (M – OMe), 180, 148, 138, 121, 93, 79, 67.

1,1-(Dicarbomethoxy)-6-iodobicyclo[3.2.1]octane (88)[65] was prepared by method B with iodide **87** (217 mg, 0.61 mmol) and hexamethylditin (23 mg, 0.07 mmol) in C_6D_6 (2 mL). After flash chromatography (EtOAc/hexanes = 20/1), **88** was obtained as a clear oil (142 mg, 65%): ^1H NMR ($CDCl_3$) δ 4.63 (1 H, b s), 3.77 (3 H, s), 3.73 (1 H, m), 3.70 (3 H, s), 3.15 (1 H, t, J = 4.0 Hz), 2.48 (1 H, dd, J = 2.2, 14.1 Hz), 2.35–1.75 (7 H,m); IR (thin film) 2951, 2859, 1733, 1433, 1240 cm^{-1}; MS (m/z) 321 (M – OMe), 293, 225, 193, 165, 137, 133, 113, 107, 93, 79; high-resolution MS calcd for $C_{11}H_{14}IO_3$ (M – HOMe) 320.9988, found 320.9988.

Methyl 2-Ethyl-1-cyanopentane-1-carboxylate (94). This was prepared following the procedure for lactone **49** with *trans*-methyl-2-bromo-2-cyano-6-octenoate **92b** (60 mg, 0.23 mmol), hexamethylditin (7 mg, 0.023 mmol), tri-*n*-butyltin hydride (80 mg, 0.28 mmol), and AIBN (1 mg, 0.006 mmol). Purification by MPLC (hexanes/EtOAc = 2.5/1) gave **94** (32 mg, 78%) as a clear oil: ^1H NMR ($CDCl_3$) major isomer δ 3.82 (3 H, s), 0.93 (3 H, t, J = 7.5 Hz); minor isomer δ 3.79 (3 H, s), 0.98 (3 H, t, J = 7.6 Hz), 2.5–1.7 (7 H, m); IR (thin film) 2963, 2878, 2242, 1743, 1450, 1435, 1383, 1250, 1200 cm^{-1}; MS (m/z) 180 (M – H), 127, 112, 84, 74, 59; high-resolution MS calcd for $C_{10}H_{14}NO_2$ 180.1024, found 180.1025.

Dimethyl 2-(Iodomethyl)cyclohexane-1,1-dicarboxylate (96) and Dimethyl 3-Iodocycloheptane-1,1-dicarboxylate (97). Compounds **96** and **97** were prepared by method B using iodomalonate **95** (98 mg, 0.288 mmol) and hexabutylditin (7 mg, 0.021 mmol). Purification by MPLC (hexanes/EtOAc = 8/1) yielded **96** (28 mg, 29%) and **97** (18 mg, 18%). **96**: ^1H NMR ($CDCl_3$) δ 3.75 (3 H, s), 3.74 (3 H, s), 3.39–3.32 (2 H, m), 2.32 (1 H, m), 2.25–2.08 (2 H, m), 1.78–1.25 (6 H, m); IR (thin film) 2946, 2861, 1732, 1451, 1435, 1356, 1337, 1283, 1252, 1173, 1138, 1069 cm^{-1}; MS (m/z) 309 (M – OMe), 281, 213, 153, 142, 121, 93; high-resolution MS calcd for $C_{10}H_{14}O_3I$ 308.9988, found 308.9986. **97**: ^1H NMR ($CDCl_3$) δ 4.43 (1 H, tt, J = 2.7, 11.0 Hz), 3.75 (3 H, s), 3.70 (3 H, s), 3.16 (1 H, m), 2.54 (1 H, dd, J = 11.0, 14.7 Hz), 2.46 (1 H, m), 2.26–1196 (3 H, m), 1.75–1.36 (4 H, m); IR (thin film) 2938, 2865, 1775, 1734, 1456, 1435, 1364, 1260, 1210, 1154, 1078, 1061, 968 cm^{-1}; MS (m/z) 309 (M – OMe), 281, 249, 213, 167, 156, 139, 122, 111, 97, 95; high-resolution MS calcd for $C_{10}H_{14}IO_3$ 308.9988, found 308.9988.

(3aα,7aα)-Hexahydro-7a-carbomethoxyisobenzofuran-1(3*H*)-one (98). Compound **98** was prepared via the procedure for lactone **2** (method II) using **96** (5 mg, 0.0147 mmol). Purification by MPLC (hexanes/EtOAc = 5/1) afforded **98** a clear oil of (2.3 mg, 79%): ^1H NMR ($CDCl_3$) δ 4.30 (1 H, dd, J = 3.9, 8.9 Hz), 3.99 (1 H, dd, J = 4.3, 8.9 Hz), 3.77 (3 H, s), 2.94 (1 H, m), 2.06–1.83 (3 H, m), 1.61–1.52 (2 H, m), 1.44–1.26 (3 H, m); IR (thin film) 2938, 2861, 1779, 1734, 1437, 1374, 1111, 1062, 1022, 995 cm^{-1}; MS (m/z) 198, 170, 167, 154, 139, 122, 111, 95, 87, 79, 67, 59.

Methyl 8-Oxo-7-oxabicyclo[4.2.1]nonanecarboxylate (99). Compound **99** was prepared following the procedure for lactone **2** (method II) with iodomalonate **97** (5 mg, 0.0147 mmol). Purification by MPLC (hexanes/EtOAc = 5/1) afforded **99** (2.5 mg, 86%) as a clear oil: ^1H NMR ($CDCl_3$) δ 4.94 (1 H, m), 3.77 (3 H, s), 2.95 (1 H, dd, J = 8.7, 13.0 Hz), 2.32 (1 H, m), 2.24 (1 H, d, J = 13.0 Hz), 2.08–2.01 (2 H, m), 1.81–1.59 (5 H, m); IR (thin film) 2938, 2867, 1773, 1437, 1368, 1335, 1304, 1262, 1194, 1123, 1078, 1061, 967 cm^{-1}; MS (m/z) 167 (M – OMe) 154, 139, 122, 111, 95, 91, 87, 81, 77, 67, 59, 55.

Dimethyl 2-Ethylcyclohexane-1,1-dicarboxylate (102). Compound **102** was prepared following the procedure for lactone **49** using iodomalonate **100** (20 mg, 0.056 mmol), hexamethylditin (1.5 mg, 0.005 mmol), and tri-*n*-butyltin hybride (21 mg, 0.072 mmol). Purification by MPLC (hexanes/EtOAc = 10/1) gave **102** (7.8 mg) in 61% yield: ^1H NMR ($CDCl_3$) δ 3.71 (3 H, s), 7.30 (3 H, s), 2.13–1.74 (4 H, m), 1.57–1.21 (7 H, m), 0.88 (3 H, t, J

= 7.4 Hz); ^{13}C NMR 172.7, 171.7, 59.7, 52.1, 42.4, 30.6, 25.5, 23.1, 22.9 ppm; IR (thin film) 2952, 2863, 1732, 1452, 1433, 1242, 1217, 1204, 1146 cm^{-1}; MS (m/z) 228, 196, 164, 145, 132, 113, 94; high-resolution MS calcd for $C_{12}H_{20}O_4$ 228.1361, found 228.1359.

Methyl 8-Oxo-6-methyl-7-oxabicyclo[4.2.1]nonanecarboxylate (105). Iodomalonate **103** was placed in a 5-mm NMR tube. Benzene (0.43 mL) and hexamethylditin (4 mg, 0.012 mmol) were added. The solution was irradiated for 10 min at a distance of 6 cm from a GE 275-W sunlamp. The reaction mixture was then heated with *p*TSA (20 mg, 0.11 mmol) at reflux for 12 h. After purification by MPLC (hexanes/EtOAc = 3/1), lactone **105** (19 mg, 71%) was isolated as a clear oil: ^1H NMR ($CDCl_3$) δ (3 H, s), 2.58 (1 H, d, J = 13 Hz), 2.48 (1 H, d, J = 13 Hz), 2.30–1.94 (3 H, m), 1.75–1.55 (5 H, m), 1.52 (3 H, s); IR (thin film) 2936, 1769, 1740, 1437, 1302, 1271, 1209, 1190, 1080 cm^{-1}; MS (m/z) 180 (M – MeOH), 168, 153, 132, 109; high-resolution MS calcd for $C_{10}H_{12}O_3$ 180.078, found 180.0787.

(2aα,5aα,8aα,8bα)-Decahydro-2a-carbomethoxy-5a-methylnaphthaleno[8,1-*bc*]furan-2-one (113). Compound **113** was prepared following method B. Iodomalonate **112** was obtained as a clear oil (42%) after purification by medium-pressure liquid chromatography (hexanes/EtOAc = 5/1): ^1H NMR ($CDCl_3$) δ 4.68 (1 H, m), 3.75 (3 H, s), 2.46 (1 H, d, J = 5.8 Hz), 2.25 (1 H, m), 2.12 (1 H, m), 1.93 (1 H, m), 1.70–1.51 (7 H, m), 1.14–1.07 (2 H, m), 1.06 (3 H, s); IR (thin film) 2950, 2876, 1775, 1734, 1464, 1435, 1356, 1007 cm^{-1}.

DBU Workup Procedure. After irradiation with a GE 275-W sunmlamp, the reaction mixture was diluted with reagent grade (undried) ether (10–20 mL). DBU (0.2 equiv, for 0.1 equiv hexaalkylditin) was added to the reaction mixture and then titrated with 0.1 M iodine solution. During this time, DBU–hydroiodide precipitated as a white solid. After the iodine color just persisted, the solution was transferred to a short column (SiO_2); after elution with ether (30 mL), the solvent was removed. The residue was almost tin-free. If dehalogenated products were desired, the procedure was applied following tin hydride (1.2 equiv) treatment. Excess DBU (1.5 equiv) was used in order to remove all tin halide. The sequence of addition of DBU followed by titration with iodine solution can be inversed.

Acknowledgment. We thank the National Institutes of Health (Grant GM 33372) for funding of this work and we also thank Hoffman-La Roche for support. We are particularly grateful to Dr. Eric Spletzer and Tina Morgan for their experimental contributions and to Dr. Craig Jasperse for his helpful comments on the manuscript.

Registry No. **2**, 113428-55-0; **3a**, 1745-17-1; **3b**, 120790-76-3; **4a**, 113335-69-6; **4b**, 113335-70-9; **5a**, 113335-78-7; **5a** (acid), 120790-18-3; **5b**, 113428-53-8; **6a**, 113335-79-8; **6a** (acid), 120790-19-4; **6b**, 113428-54-9; *cis*-**7a**, 113335-86-7; *trans*-**7a**, 113335-87-8; *cis*-**7b**, 113335-97-0; *trans*-**7b**, 113335-88-9; **8**, 113335-71-0; *cis*-**9**, 113335-80-1; *trans*-**9**, 113335-81-2; *cis*-**10**, 113335-98-1; *trans*-**10**, 113335-89-0; **11a**, 113335-73-2; **11a** (de-iodo ketone), 120790-73-0; **11b**, 113335-72-1; **11b** (de-iodo ketone), 15177-05-6; *trans*-**12a**, 113335-85-6; *trans*-**12b**, 113335-83-4; *cis*-**13a**, 113335-92-5; *trans*-**13a**, 113335-93-6; *cis*-**13b**, 113335-90-3; *trans*-**13b**, 113335-91-4; **14**, 113335-76-5; **14** (2-fluoro analog), 120790-78-5; (*E*)-**15**, 110550-93-1; (*Z*)-**15**, 110550-94-2; **16**, 110550-95-3; **17**, 113335-77-6; **17** (de-iodo ester), 120790-74-1; (*E*)-**18**, 110550-96-4; (*Z*)-**18**, 110550-97-5; **19**, 120790-17-2; **26a**, 80926-05-2; **26b**, 120790-96-7; **27a**, 63649-24-1; **27b**, 120790-97-8; **28a**, 4630-82-4; **28b**, 16537-05-6; **34**, 120790-20-7; **35**, 54678-05-6; **36**, 120790-21-8; **37**, 120790-22-9; *cis*-**38**, 120790-23-0; *trans*-**38**, 120790-47-8; **39**, 120790-24-1; **39** (de-iodo ketone), 109-49-9; **39** (de-iodo trimethylsilyl enol ether), 57711-32-7; **40**, 31053-10-8; **42**, 120790-25-2; **42** (de-iodo ketone), 1071-94-9; *cis*-**43**, 120790-26-3; *trans*-**43**, 120829-05-2; *cis*-**44**, 120790-27-4; *trans*-**44**, 120790-61-6; **45a**, 113335-74-3; **45b**, 120790-64-9; **45** (X = H), 18955-93-6; **45** (X = H, trimethylsilyl enol ether), 120790-79-6; *exo*-**46a**, 113335-94-7; *endo*-**46a**, 113358-63-7; *exo*-**46b**, 120790-62-7; *endo*-**46b**, 120790-63-8; **47a**, 113335-75-4; **47b**, 14447-34-8; **47** (X = Cl), 66928-67-4; *exo*-**48**, 113335-95-8; *endo*-**48**, 120790-65-0; **49**, 24871-12-3; **50**, 120790-28-5; **50** (de-iodo ester), 15766-90-2; *cis*-**51**, 120790-29-6; *trans*-**51**, 120790-66-1; *cis*-**52**, 120790-30-9; *trans*-**52**, 120790-67-2; **53a**, 6939-71-5; **53b**, 18543-37-8; **54**, 120790-31-0; **54** (de-iodo ester), 62472-89-3; **55** (isomer 1), 120790-32-1; **55** (isomer 2), 120851-24-3; **55** (isomer 3), 120851-25-4; **55** (isomer 4), 120851-26-5; **57**, 120790-33-2; **57** (de-iodo ester), 120790-75-2; **59**, 120790-34-3; **66**, 93185-10-5; **67a**, 120790-35-4; **67b**, 120790-70-7; **68a**, 120790-36-5; **68b**, 120790-68-3; **70a**, 120790-37-6; **70b**, 120790-69-4; **71**, 120790-38-7; **72**, 72963-31-6; **73**, 120790-39-8; **78**, 120790-40-1; **78** (de-iodo malonate), 85484-83-9; **80**, 120829-04-1; **81**, 120790-41-2; **81** (de-iodo malonate), 120790-80-9; **83**, 61558-99-4; **84**, 120790-42-3; **84** (de-iodo malonate), 120790-81-0; **85**, 120790-43-4; **86**, 120790-44-5; **87**, 120790-45-6; **87** (de-iodo malonate), 120790-82-1; **88**, 120790-46-7; **90**, 25143-86-6; **92b**, 120790-71-8; *cis*-**94**, 120790-48-9; *trans*-**94**, 120790-72-9; **95**, 120790-49-0; **95** (de-iodo malonate), 120790-83-2; **96**, 120790-50-3; **97**, 120790-51-4; **98**, 120790-52-5; **99**, 120790-53-6; **100**, 120790-54-7; **100** (de-iodo malonate, 120790-84-3; **102**, 120790-55-8; **103**, 120790-56-9; **103** (de-iodo malonate), 120790-85-4; **105**, 120790-57-0; **107**, 120790-58-1; **107** (de-iodo malonate), 120790-86-5; **109**, 120790-59-2; **110**, 120790-60-5; **111**, 120790-93-4; **112**, 120790-94-5; **113**, 120790-95-6; **114**, 120790-92-3; **115**, 120790-87-6; **116**, 120790-88-7; **117**, 120790-89-8; **118**, 120829-06-3; **119**, 120790-90-1; **120**, 120790-91-2; $CH_2{=}CH(CH_2)_3CH{=}C(OMe)OSiMe_2Bu\text{-}t$, 120790-77-4.

Supplementary Material Available: Details of the preparation and characterization of all the halide cyclization precursors and copies of the ^1H NMR spectra for 16 representative products (26 pages). Ordering information is given on any current masthead page.