JOC Article

On the 6-Exo Atom Transfer Radical Cyclization Reactions of 3-Butenyl 2-Iodoalkanoates

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Bis(tributyltin)-initiated atom transfer cyclization reactions of 3-butenyl iodoalkanoates in the presence of $BF_3{\cdot}OEt_2$ as the catalyst afforded the 6-exo cyclization products as a mixture of 3,4-cis- and trans-substituted tetrahydro-2*H*-pyran-2-ones in 53−71% yield with the major isomers being the cis ones. Ab initio calculations at the B3LYP/6-31G* level on the transition states of the radical cyclization and on the cyclized products revealed that the reactions are kinetically controlled and the transition states for the 6-exo radical cyclization are in boat conformations. Moreover, the cis-oriented transition states are of lower energy than the corresponding trans-oriented ones, which are in excellent agreement with experimental results.

Introduction

Tremendous progress in free radical reactions and their applications in organic synthesis have been achieved within the past two decades.[1] Among them, cyclizations of α-carbonyl radicals leading to the formations of lactones, lactams, or cycloalkanones have received enormous attention because of their great potential in natural product synthesis.[1i] Several methods have been developed to carry out these transformations, including the tin hydride method,[2] the halogen atom transfer method[3] with bis(tributyltin) or triethylborane, and the organomercurial method.[4]

Of these cyclization reactions, 5-exo cyclization of α-ester radicals leading to the formation of γ-lactones is the most widely studied type of reaction.[1f,4−6] To have efficient cyclization, fast tautomerism between s-trans and s-cis rotomers of the α-ester radicals is essential because the s-cis rotamers of higher energy are required for the cyclization. The Thorpe−Ingold effect helps the 5-exo cyclization by lowering the energy barriers of the s-trans to s-cis interconversion of the α-ester radicals.[4c,7] High temperature and low concentration also facilitate the cyclization, and the iodine atom transfer annulation method has been proved to be particularly effective in carrying out such transformations as demonstrated by Curran and co-workers.[5n] More recently, the same reactions were carried out in water with higher efficiency, indicating the powerful solvent effect in these radical reactions.[6]

Compared with 5-exo ester cyclization reactions, the corresponding 6-exo ester cyclization reactions are much

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(1) For review articles, see: (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon−Carbon Bonds*; Pergamon: Oxford, UK, 1986. (b) Curran, D. P. *Synthesis* **1988**, 417, 489. (c) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237. (d) Melikyan, G. G. *Synthesis* **1993**, 833. (e) Iqbal, J.; Bhatia, B.; Nayyar, N. K. *Chem. Rev.* **1994**, *94*, 519. (f) Snider, B. B. *Chem. Rev.* **1996**, *96*, 339. (g) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*, VCH: Weinheim, Germany, 1996. (h) Gansauer, A.; Bluhm, H. *Chem. Rev.* **2000**, *100*, 2771. (i) *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001.

(2) Chatgilialoglu, C. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 1, p 28.

(3) Byers, J. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 1, p 72.

(4) (a) Russell, G. A. *Acc. Chem. Res.* **1989**, *22*, 1. (b) Russell, G. A.; Li, C.; Chen, P. *J. Am. Chem. Soc.* **1995**, *117*, 3645. (c) Russell, G. A.; Li, C.; Chen, P. *J. Am. Chem. Soc.* **1996**, *118*, 9831. (d) Russell, G. A.; Li, C. *Synlett* **1996**, 699. (e) Russell, G. A.; Li, C. *Tetrahedron Lett.* **1996**, *37*, 2557.

(5) For other examples, see: (a) Surzur, J.-M.; Bertrand, M. P. *Pure Appl. Chem.* **1988**, *60*, 1659. (b) Curran, D. P.; Chang, C.-T. *Tetrahedron Lett.* **1987**, *28*, 2477. (b) Chuang, C. P.; Gallucci, J. C.; Hart, D. J.; Hoffman, C. *J. Org. Chem.* **1988**, *53*, 3218. (c) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140. (d) Curran, D. P.; Chen, M.-H.; Kim, D. *J. Am. Chem. Soc.* **1989**, *111*, 6265. (e) Oumar-Mahamat, H.; Moustrou, C.; Surzur, J.-M.; Bertrand, M. P. *J. Org. Chem.* **1989**, *54*, 5684. (f) Belletire, J. M.; Mahmoodi, N. O. *Tetrahedron Lett.* **1989**, *30*, 4363. (g) Lee, E.; Ko, S. B.; Jung, K. W. *Tetrahedron Lett.* **1989**, *30*, 827. (h) Clough, J. M.; Pattenden, G.; Wight, P. G. *Tetrahedron Lett.* **1989**, *30*, 7469. (i) Curran, D. P.; Chang, C.-T. *Tetrahedron Lett.* **1990**, *31*, 933. (j) Nagashima, H.; Seki, K.; Ozaki, N.; Wakamatsu, H.; Itoh, K.; Tomo, Y.; Tsuji, J. *J. Org. Chem.* **1990**, *55*, 985. (k) Barth, F.; O-Yang, C. *Tetrahedron Lett.* **1990**, *31*, 1121. (l) Kolt, R. J.; Griller, D.; Wayner, D. D. M. *Tetrahedron Lett.* **1990**, *31*, 7539. (m) Hanessian, S.; Di Fabo, R.; Marcoux, J.-F.; Prud'homme, M. *J. Org. Chem.* **1990**, *55*, 3436. (n) Curran, D. P.; Tamines, J. *J. Org. Chem.* **1991**, *56*, 2746. (o) Pirrung, F. O. H.; Steeman, W. J. M.; Hiemstra, H.; Speckamp, W. N.; Kaptein, B.; Boesten, W. H. J.; Schoemaker, H. E.; Kamphuis, J. *Tetrahedron Lett.* **1992**, *33*, 5141. (p) Lee, E.; Yoon, C. H.; Lee, T. H. *J. Am. Chem. Soc.* **1992**, *114*, 10981. (q) Back, T. G.; Gladstone, P. L. *Synlett* **1993**, 699.

(6) (a) Yorimitsu, H.; Nakamura, T.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **1998**, *63*, 8604. (b) Yorimitsu, H.; Nakamura, T.; Shinokubo, H.; Oshima, K.; Omoto, K.; Fujimoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 11041.

(7) (a) Jung, M. E.; Gervoy, J. *J. Am. Chem. Soc.* **1991**, *113*, 224. (b) Jung, M. E.; Trifunovich, I. D.; Lensen, N. *Tetrahedron Lett.* **1992**, *33*, 6719.

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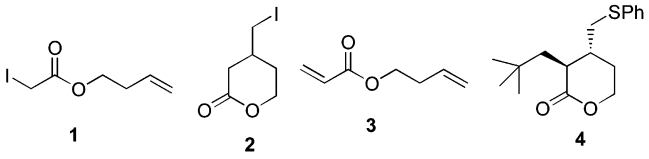
less satisfactory and the reasons are not well understood.[4c,d,5k,m,6] As reported by Barth et al., bis(tributyltin)-initiated cyclization of 3-butenyl iodoacetate (**1**) in benzene (0.008 M) at 80 °C afforded the expected δ-lactone **2** in only 8% yield and gave predominantly oligmers,[5k] indicating the failure of temperature effect and high dilution effect in promoting the 6-exo cyclization. Russell and Li employed *tert*-butylmercury iodide and diphenyl disulfide to react with 3-butenyl acrylate (**3**) to afford the 3,4-trans-substituted δ-lactone **4** in only 9% yield, and an anti-Thorpe−Ingold effect was observed.[4c,d] More recently, Oshima et al. carried out the reaction of **1** in water at room temperature with triethylborane as the initiator and obtained **2** in 42% yield.[6] However, only one example was given and the low solubility of the substrates in water shows a negative impact on the reactions.

To understand the behavior of the 6-exo ester cyclization reactions and to find a general and efficient route to conduct these transformations, we looked into the reactions in detail. We report herein that atom transfer annulation reactions of 3-butenyl 2-iodoalkanoates can be efficiently catalyzed by BF_3·OEt_2 to afford the corresponding 6-exo cyclization products in moderate to good yield with unusual stereoselectivities. Theoretical calculations on the transition states in the radical cyclization and on the cyclized products were performed to help us have a better insight into the cyclization behavior.

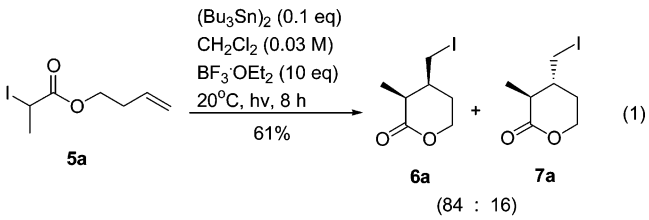


1 **2** **3** **4**

Results

We chose 3-butenyl iodoacetate **1** and 3-butenyl 2-iodopropionate (**5a**) as the model substrates to study the 6-exo ester cyclization. For the ease of comparison, the concentrations of the substrates were all set at 0.03 M in the following experiments. Treatment of **1** or **5a** with $(Bu_3Sn)_2$/*hv* or BEt_3/O_2 in benzene or CH_2Cl_2 at ambient temperature gave mainly oligmers while no expected cyclization products could be isolated, which were in good agreement with Barth's results.[5k] Treatment of **1** with BEt_3/O_2 in water at room temperature for 3 h afforded **2** in 42% yield, which was identical with Oshima's result.[6] On the other hand, reaction of **5a** in water in the same fashion gave only a trace amount of the corresponding cyclization product after 3 days while more than 95% of the starting **5a** remained unchanged.

Aside from temperature effect, high dilution effect, and solvent effect, the participation of Lewis acids is another plausible means to promote free radical reactions and to enhance chemo-, regio-, stereo-, or even enantioselectivities as evidenced in many examples.[8,9] The coordination of Lewis acids to the carbonyl oxygen of the iodoester substrates makes the α-ester radicals more reactive toward electron-rich alkenes because of polar effect. Moreover, it might also help in lowering the energy barrier between s-cis and s-trans rotomers of the α-ester radicals because of the possible increased steric hindrance in the coordinated s-trans rotamers, thus promoting the cyclization. Therefore, various Lewis acids (BF_3·OEt_2, $Zn(OTf)_2$, HgI_2, $Cu(OTf)_2$, $Yb(OTf)_3$, BF_3, BF_3·MeOH, BF_3·H_2O) were screened by photostimulation of **1** or **5a** with $(Bu_3Sn)_2$ (10 mol %) and a Lewis acid (3 equiv) in CH_2Cl_2 at room temperature or 0 °C. In all cases, iodoester **1** failed to give the expected product δ-lactone **2**. Instead, two isomers of 14-membered cyclic dimers were produced as the major products whose structures were confirmed by X-ray diffraction analyses (see Supporting Information). For substrate **5a**, $Zn(OTf)_2$, HgI_2, $Cu(OTf)_2$, and $Yb(OTf)_3$ showed no effect on the cyclization. However, when BF_3·OEt_2 was used, the reaction proceeded slowly to give mainly the expected cyclization products **6a** and **7a** as indicated by TLC monitoring. When a larger amount (10 equiv) of BF_3·OEt_2 was employed, the reaction was faster and TLC monitoring indicated that it was complete within 8 h at 20 °C. After the usual workup, **6a** and **7a** were isolated in 61% yield in the ratio of 84:16 determined by ^{1}H NMR (eq 1).



5a **6a** **7a**

(84 : 16)

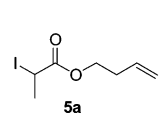
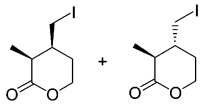
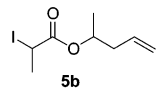
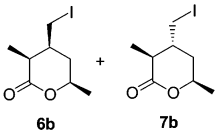
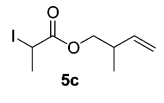
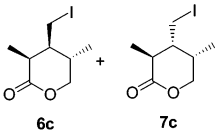
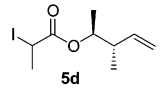
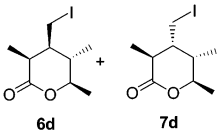
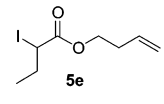
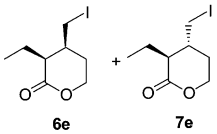
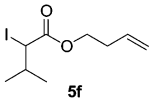
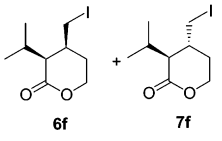
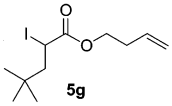
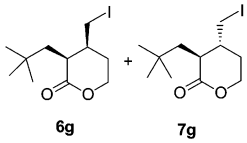
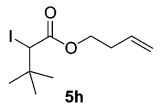
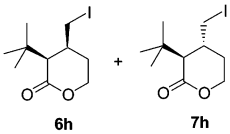
The reaction was also successful in other solvents such as benzene or 1,2-dichloroethane, but CH_2Cl_2 gave the best result. Lowering the reaction temperature to 0 °C resulted in much longer reaction time (90% of **5a** remained after 20 h) although the product selectivity was increased to 90:10. Raising the reaction temperature to 80 °C (in $ClCH_2CH_2Cl$) led to a higher yield (71%) of the products while the ratio was lowered to 73:27.

Other boron trifluoride derivatives showed similar behavior as BF_3·OEt_2. Photostimulation of **5a** in CH_2Cl_2 saturated with BF_3 at room tempeature afforded 55% yield of **6a** and **7a** in a ratio of 87:13. With BF_3·MeOH (3 equiv), 65% yield of **6a** and **7a** was achieved in an 85:15 ratio. When BF_3·H_2O (3 equiv) was used, the starting material **5a** was partially destroyed probably because of the much higher acidity of the catalyst and only 38% yield of expected products could be obtained.

(8) For review articles, see: (a) Renaud, P.; Gerster, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2562. (b) Guerin, B.; Ogilvie, W. W.; Guindon, Y. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 1, p 441.

(9) Fore recent examples, see: (a) Nishida, M.; Nishida, A.; Kawahara, N. *J. Org. Chem.* **1996**, *61*, 3574. (b) Nishida, M.; Ueyama, E.; Hayashi, H.; Ohtake, Y.; Yamaura, Y.; Yanaginuma, E.; Yonemitsu, O.; Nishida, A.; Kawahara, N. *J. Am. Chem. Soc.* **1994**, *116*, 6455. (c) Mero, C. L.; Porter, N. A. *J. Am. Chem. Soc.* **1999**, *121*, 5155. (d) Sibi, M. P.; Ji, J.; Sausker, J. B.; Jaspersse, C. P. *J. Am. Chem. Soc.* **1999**, *121*, 7517. (e) Iserloh, U.; Curran, D. P.; Kanemasa, S. *Tetrahedron: Asymmetry* **1999**, *10*, 2417. (f) Dakternieks, D.; Dunn, K.; Tamara Perchyonok, V.; Schiesser, C. H. *Chem. Commun.* **1999**, 1665. (g) Porter, N. A.; Feng, H.; Kavrakova, I. *Tetrahedron Lett.* **1999**, *40*, 6713. (h) Sibi, M. P.; Rheault, T. R. *J. Am. Chem. Soc.* **2000**, *122*, 8873. (i) Friestad, G. K.; Qin, J. *J. Am. Chem. Soc.* **2000**, *122*, 8329. (j) Munakata, R.; Totani, K.; Takao, K.-I. *Synlett* **2000**, 979. (k) Hayen, A.; Koch, R.; Metzger, J. O. *Angew. Chem., Int. Ed.* **2000**, *39*, 2758. (l) Porter, N. A.; Zhang, G.; Redd, A. D. *Tetrahedron Lett.* **2000**, *41*, 5773. (m) Yang, D.; Ye, X.-Y.; Xu, M.; Pang, K.-W.; Cheung, K.-K. *J. Am. Chem. Soc.* **2000**, *122*, 1658. (n) Kim, K.; Okamoto, S.; Sato, F. *Org. Lett.* **2001**, *3*, 67. (o) Wang, J.; Li, C. *J. Org. Chem.* **2002**, *67*, 1271.

TABLE 1. 6-Exo Cyclization of 5

substrate	products[a]	reaction time (h)	yield (%)[b]	ratio[c] (**6** : **7**)
 **5a**	 **6a** **7a**	8	61	84 : 16
 **5b**	 **6b** **7b**	18	71	88 : 12
 **5c**	 **6c** **7c**	15	70	87 : 13
 **5d**	 **6d** **7d**	29	57	89 : 11
 **5e**	 **6e** **7e**	15	53	93 : 7
 **5f**	 **6f** **7f**	18	61	97 : 3
 **5g**	 **6g** **7g**	20	53	93 : 7
 **5h**	 **6h** **7h**	16	57	87 : 13

[a] Reaction conditions: $BF_3{\cdot}OEt_2$ (10 equiv), $(Bu_3Sn)_2$ (10 mol %), 20 °C, CH_2Cl_2 (0.03 M), *hν*. [b] Isolated yield based on **5**. [c] Determined by 300-MHz ^1H NMR.

Although no detailed work was done to elucidate the different behaviors of the catalysts in the cyclization reactions, we presume that the ineffectiveness of those Lewis acids screened might be ascribed to their poor coordination to the ester substrate **5a** owing to their very low solubility in CH_2Cl_2.

Because of the ready availability and easy handling of $BF_3{\cdot}OEt_2$, we chose it as the catalyst to test other substrates **5b**−**h**. The results are summarized in Table 1.

As shown in Table 1, all the substrates **5a**−**h** gave moderate to good yield of 6-exo cyclization products. Careful characterizations of the δ-lactones revealed that, in all cases, the major products were the 3,4-cis-substituted isomers **6a**−**h**. The ratios of 3,4-cis- to 3,4-trans-substituted products (**6**:**7**) were in the range of 84:16 to 97:3, with the highest stereoselectivity observed in the reaction of **5f** having an isopropyl substituent α to the carbonyl group. The stereochemistry was unambiguously established by X-ray diffraction (Scheme 1) and 2D NMR analyses. Also shown in Scheme 1 are that compounds **6b** and **6f** possess the standard boat conformations in the solid state while the conformations of compounds **6d** and **6h** are slightly distorted from the standard boat conformations. On the other hand, the conformation of compound **7h** in the solid state is half-chair. 2D NOESY experiments along with ^1H NMR analyses indicated that the predominant conformations of **6** and **7** in solution ($CDCl_3$) are very similar to the conformations in the solid states. For example, the NOESY spectra of **6h** exhibited strong NOE between its 3- and 6-protons, indicating the preference of a boat conformation in solution. The 4,5-trans δ-lactones **7h**, however, had no such NOE at all. The ^1H NMR spectrum of **7h** showed that the coupling constant between 3- and 4-protons was only 5.6 Hz, and the quasiequatorial 6-H (δ 4.35) had $J_{gem} = 11.2$ Hz and $J_{vic} = 3.9$ and 2.8 Hz, while the quasiaxial 6-H (δ 4.21) had $J_{vic} = 1.7$ and 11.4 Hz. The coupling constant information could be best analyzed (via Karplus equation) according to a half-chair conformation as in the solid state (Scheme 1).

Calculations and Discussion

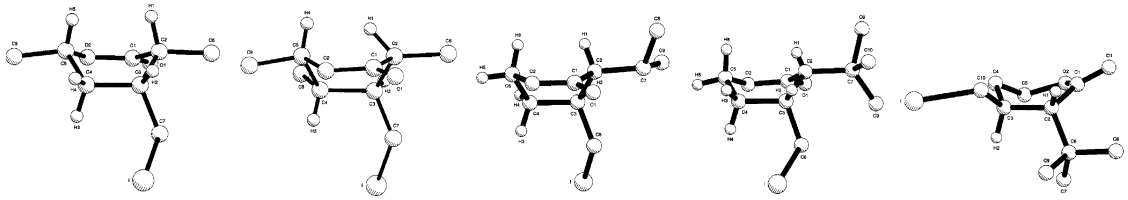
The above high stereoselectivities in favor of the 3,4-cis-substituted lactones are striking because they are in direct contradiction with Russell and Li's results in the photostimulated 6-exo cyclization reactions of organomercurials with diphenyl disulfide affording only the 3,4-trans-substituted δ-lactones such as **4**.[4c,d] Moreover, the trans selectivity was frequently observed in the 6-exo radical carbocyclization reactions leading to the formations of cyclohexane derivatives.[10] To address the differences, the following questions need to be answered: Does $BF_3{\cdot}OEt_2$ affect the stereoselectivity? What are the transition states for the 6-exo cyclization of α-ester radicals? Is the 6-exo cyclization kinetically controlled or thermodynamically controlled? To gain more insight into the 6-exo cyclization behavior, we turned to ab initio calculations for help which have been demonstrated to be an increasingly important tool in modeling radical reactions and mechanisms.[11,12]

Transition States. All the calculations were carried out with the Gaussian98[13] series of programs. The structures of the transition states were searched and pre-optimized by the PM3 semiempirical method[14] using the Spartan program (Version 5.0).[15] All the structures were

(10) For selected examples, see: (a) Bartlett, P. A.; McLaren, K. L.; Ting, P. C. *J. Am. Chem. Soc.* **1988**, *110*, 1633. (b) Marco-Contelles, J.; Martinez-Grau, A.; Bernabe, M.; Martin, N.; Seoane, C. *Synlett* **1991**, 165. (c) Morikawa, T.; Kodama, Y.; Uchida, J.; Takano, M.; Washio, Y.; Taguchi, T. *Tetrahedron* **1992**, *48*, 8915. (d) Marco-Contelles, J.; Pozuelo, C.; Jimeno, M. L.; Martinez, L.; Martinez-Grau, A. *J. Org. Chem.* **1992**, *57*, 2625. (e) Arnone, A.; Bravo, P.; Frigerio, M.; Viani, F.; Cavicchio, G.; Crucianelli, M. *J. Org. Chem.* **1994**, *59*, 3459. (f) Sturino, C.; Fallis, A. G. *J. Am. Chem. Soc.* **1994**, *116*, 7447. (g) Holstein Wagner, S.; Lundt, I. *J. Chem. Soc., Perkin Trans. 1* **2001**, 780.

(11) For review articles on the use of calculations in radical reactions, see: (a) Eksterowicz, J. E.; Houk, K. N. *Chem. Rev.* **1993**, *93*, 2439. (b) Schiesser, C. H.; Skidmore, M. A. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 1, p 337.

SCHEME 1. The X-ray Crystal Structures of 6b,d,f,h and 7h

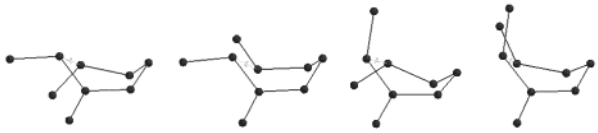


6b **6d** **6f** **6h** **7h**

CHART 1. Calculated Structures of the Transition States for the Cyclization of 1

	C-1	T-1
Total energy (au):	-384.408319	-384.407236
Relative energy (kcal/mol):	0	0.68

CHART 2. Calculated Structures of the Transition States for the Cyclization of 5a



	C-5a	T-5a	T-5a*	C-5a*
Total energy (a.u):	-423.728849	-423.727911	-423.721566	-423.719808
Relative Energy (kcal/mol):	0	0.59	4.57	5.67

optimized with Becke's three-parameter hybrid exchange functional and the Lee−Yang−Parr correlation functional (B3LYP)[16] and the 6-31G* basis sets.[17] Frequency calculations were also performed to characterize the transition states, having only one imaginary frequency.

The calculation results for the cyclization of **1** indicated that there are only two transition states, **C-1** and **T-1**, as shown in Chart 1. All the other possible conformers relaxed to the two conformers when optimized. Both **C-1** and **T-1** are in boat conformations. Moreover, the conformer **C-1** having the carbon−carbon double bond at the pseudoaxial position is 0.68 kcal/mol lower in energy than the conformer **T-1** with the carbon−carbon double bond at the pseudoequatorial position.

For **5a**, the calculated transition states and their relative energies are listed in Chart 2. Only four conformers are obtained and again all possess the boat conformations. Conformers **T-5a*** and **C-5a*** are about 4 to 5 kcal/mol higher in energy than the other two conformers **C-5a** and **T-5a**. This might be attributed to the steric hindrance caused be the pseudoaxial methyl group at the bridgehead carbon. Therefore, we only need to compare **C-5a** and **T-5a**. Conformer **C-5a** has the carbon−carbon double bond at the pseudoaxial position and should lead to the formation of the 3,4-cis-substituted cyclization product **6a**. Conformer **T-5a** has the carbon−carbon double bond at the pseudoequatorial position and should lead to the formation of **7a**. The calculated energy of **C-5a** is about 0.59 kcal/mol lower than that of **T-5a**. This calculated result is in excellent qualitative agreement with the experimental observation that **6a** was the major product. The calculation results for **5a** closely resemble those for **1**.

We also performed the same calculations for the substrates **5d**, **5e**, and **5h**. In all cases, boat transition states similar to **C-5a** and **T-5a** were obtained and the cis-oriented conformers **C-5** are always in lower energies than the corresponding trans-oriented conformers **T-5** (see Supporting Information). The calculated energy differences (ΔE_a) between the two conformers are summarized in Table 2.

It is established that the rate-determining step is the cyclization step in the iodine transfer radical reaction, and iodine transfer is much faster.[18] With the assumption that the cyclization reactions are kinetically controlled,

(12) For recent selected work, see: (a) Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959. (b) Zipse, H.; He, J.; Houk, K. N.; Giese, B. *J. Am. Chem. Soc.* **1991**, *113*, 4324. (c) Beckwith, A. L. J.; Bowry, V. W.; Schiesser, C. H. *Tetrahedron* **1991**, *47*, 121. (d) Damm, W.; Giese, B.; Hartung, J.; Hasskerl, T.; Houk, K. N.; Hueter, O.; Zipse, H. *J. Am. Chem. Soc.* **1992**, *114*, 4067. (e) Myers, A. G.; Condroski, K. R. *J. Am. Chem. Soc.* **1995**, *117*, 3057. (f) Houk, K. N.; Nendel, M.; Wiest, O.; Storer, J. W. *J. Am. Chem. Soc.* **1997**, *119*, 10545. (g) Newcomb, M.; Musa, O. M.; Martinez, F. N.; Horner, J. H. *J. Am. Chem. Soc.* **1997**, *119*, 4569. (h) Curran, D. P.; Lin, C.-H.; DeMello, N.; Junggebauer, J. *J. Am. Chem. Soc.* **1998**, *120*, 342. (i) Lee, E.; Yoon, H. Y.; Lee, T. H.; Kim, S. Y.; Ha, T. J.; Sung, Y.-s.; Park, S.-H.; Lee, S. *J. Am. Chem. Soc.* **1998**, *120*, 7469. (j) Newcomb, M.; Horner, J. H.; Whitted, P. O.; Crich, D.; Huang, X.; Yau, Q.; Zipse, H. *J. Am. Chem. Soc.* **1999**, *121*, 10685. (k) Corminboeuf, O.; Schiesser, C. H.; Renaud, P. *Chimia* **1999**, *53*, 397. (l) Jung, M. E.; Marquez, R.; Houk, K. N. *Tetrahedron Lett.* **1999**, *40*, 2661. (m) Wilsey, S.; Dowd, P.; Houk, K. N. *J. Org. Chem.* **1999**, *64*, 8801. (n) Reference 6b.

(13) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, Revision A. 6; Gaussian, Inc.; Pittsburgh, PA, 1998.

(14) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209.

(15) Wavefunction Inc.: 18401 Von Karman, Suite 370, Irvine, CA 92612, USA, 1997.

(16) (a) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.

(17) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257.

TABLE 2. Calculated Stereoselectivities in the Cyclization Reactions of 5

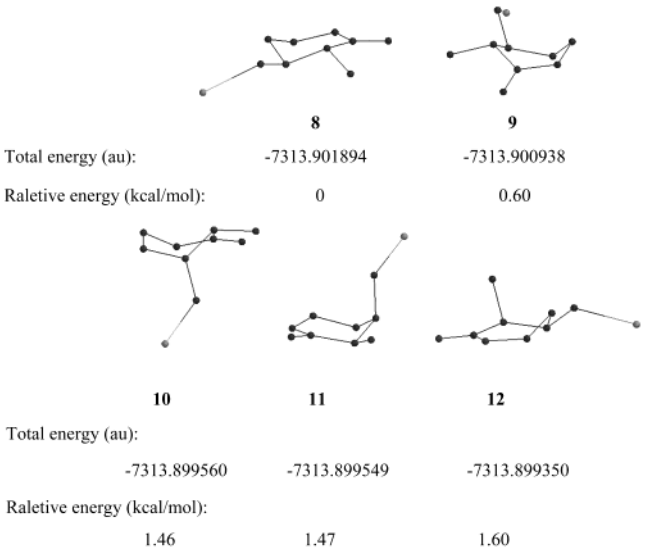
substrate	ΔE_a[a] calcd (kcal/mol)[b]	temp (°C)	6:7 calcd	6:7 expt
1	0.68			
5a	0.59	0	75:25	90:10
		20	73:27	84:16
		80	70:30	73:27
5d	1.54	20	93:7	89:11
5e	2.14	20	98:2	93:7
5h	0.92	20	83:17	87:13

[a] $\Delta E^{\ddagger}$(**T**) − $\Delta E^{\ddagger}$(**C**). [b] B3LYP/6-31G*.

the product ratios can be calculated from the Arrenhius equation based on the activation energy differences between the two transition states, which are also listed in Table 2. As can be seen in Table 2, all the calculations at the B3LYP/6-31G* level give excellent qualitative predictions on the stereoselectivities of the 6-exo ester cyclization reactions. The calculated ratios are in accurate agreement with the experimental data within the experimental error in most cases. The deviation of the observed ratios from the calculated ones might be explained by the influence of the Lewis acid BF_3·OEt_2. Because of the coordination of BF_3·OEt_2 to the substrates, the relative energies between the two transition states might be changed slightly. The temperature effect on the stereoselectivities strongly supports our hypothesis. When the reaction of **5a** was carried out at relatively low temperature (0 °C), the observed ratio (90:10) is significantly deviated from the calculated one (75:25), probably because the coordination of BF_3·OEt_2 to **5a** is strong at low temperature. However, when the reaction temperature was raised to 80 °C, the coordination should become weaker, and the observed ratio (73:27) is almost identical with the calculated ratio (70:30) within the experimental error. The above results unambiguously demonstrate that 3,4-cis-substituted δ-lactones are intrinsically favored in the 6-exo cyclization of α-ester radicals. The presence of BF_3·Et_2O slightly alters the product ratios at room temperature but does not reverse the stereoselectivities. The results also imply that, with the catalysis of a more appropriate Lewis acid, a larger energy difference between the two transition states (**C-5** and **T-5**) might be achieved, which should lead to a better control of stereoselectivity of the cyclization reaction.

The trans selectivity reported by Russell and Li[4c,d] in the 6-exo ester cycliztion by the irradiation of organomercurials with diphenyl disulfide might be attributed to the relatively low reaction rate in the trapping of cyclized radicals by disulfide.[18−20] Curran and coworkers[18c,19] showed that the rate constant for the iodine atom transfer from ethyl iodoacetate or ethyl 2-iodo-2-methylpropionate to a undecyl radical in benzene at 50 °C was about 2.6×10^7 or 6×10^8 M^{-1} s^{-1}, respectively, while the rate constant for the PhS group transfer from diphenyl disulfide to a undecyl radical in benzene at 25 °C was about 2.0×10^5 M^{-1} s^{-1}. Thus, the slow trapping of the cyclized radicals by disulfide might allow the 6-exo cyclization to become reversible.[21] As a result, the thermodynamically more stable trans-substituted cyclized products were formed as the major products. Moreover, relatively low yields were observed in their experiments also because of the low trapping rate with disulfide. It should be mentioned that the boat transition states similar to **T-5a** were also suggested by Russell and Li but their model was apparently incomplete.[4c,d]

CHART 3. Calculated (B3LYP/6-31G*) Structures of 6a and 7a



It should also be noted that the boat transition states presented above are in sharp contrast to the chair transition states involved in the 6-exo radical carbocyclization reactions forming cyclohexane derivatives discussed in the literature.[10,21b] A plausible explanation of the boat conformations might be the requirement to maintain the planarity of the ester function.

Products. In the above discussion we presumed that the iodine atom transfer 6-exo cyclization reactions are kinetically controlled. To gain further evidence for our assumption, we performed energy calculations on the cyclized products **6a**, **7a**, **6h**, and **7h** using the Gaussian98 program at the B3LYP/6-31G* level. The initial structures were generated by molecular dynamics simulation using the CHARMm force field[22] and pre-optimized by the PM3 method. Full geometry optimization was then carried out at the 6-31G* level with the 3-21G basis set[23] for the iodine atom.

The energy calculation on **7a** gave four conformers and the two conformers **8** and **9** of lowest energies are shown in Chart 3. The other two conformers have the two substituents at the quasiaxial positions and are about 1.74 and 4.00 kcal/mol higher in energy than conformer

(18) (a) Newcomb, M.; Curran, D. P. *Acc. Chem. Res.* **1988**, *21*, 206. (b) Newcomb, M.; Sanchez, R. M.; Kaplan, J. A. *J. Am. Chem. Soc.* **1987**, *109*, 1195. (c) Curran, D. P.; Bosch, E.; Kaplan, J. A.; Newcomb, M. *J. Org. Chem.* **1989**, *54*, 1826.

(19) Curran, D. P.; Martin-Esker, A. A.; Ko, S.-B.; Newcomb, M. *J. Org. Chem.* **1993**, *58*, 4691.

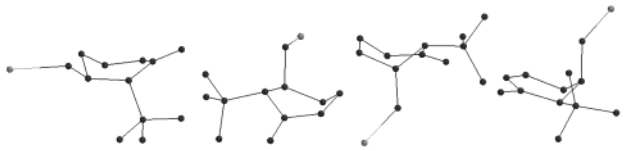
(20) Russell, G. A.; Ngoviwatchai, P.; Tashtoush, H. I.; Pla-Dalmau, A.; Khanna, R. K. *J. Am. Chem. Soc.* **1988**, *110*, 3530.

(21) For a similar discussion on the reversibility of radical cyclizations, see: (a) Beckwith, A. L. J.; Hay, B. P. *J. Am. Chem. Soc.* **1989**, *111*, 2674. (b) Beckwith, A. L. J.; Raner, K. D. *J. Org. Chem.* **1992**, *57*, 4954.

(22) Brooks, B. R.; Bruccoleri, R. E.; Olafson, B. D.; States, D. J.; Swaminathan, S.; Karplus, M. *J. Comput. Chem.* **1983**, *4*, 187.

(23) Binkley, J. S.; Pople, J. A.; Hehre, W. J. *J. Am. Chem. Soc.* **1980**, *102*, 939.

CHART 4. Calculated (B3LYP/6-31G*) Structures of 6h and 7h



	13	14	15	16
Total energy (au):				
	-7431.833288	-7431.830564	-7431.828619	-7431.828806
Relative energy (kcal/mol):				
	0	1.71	2.93	2.81

8, respectively, and therefore need not to be considered further (see Supporting Information). The calculation at the B3LYP/6-31G* level on **6a** gave only three conformers **10**−**12** of close energies. As can be seen in Chart 3, **8** and **9** are the two conformers of lowest energies among **8**−**12**. These results clearly demonstrate that the 3,4-trans-substituted *δ*-lactone **7a** is thermodynamically more stable than the 3,4-cis-substituted *δ*-lactone **6a**, thus indicating that the iodine atom transfer 6-exo cyclization is unlikely to be thermodynamically controlled.

The same calculations were also performed for **6h** and **7h** and the results are presented in Chart 4. Again, both of the two conformers **13** and **14** of **7h** are lower in energy than **15** and **16** of **6h**. Moreover, the half-chair conformer **13** is more stable by about 1.71 kcal/mol in energy than the boat conformer **13**, while the boat conformer **15** is close in energy to the half-chair conformer **16**. The results are in excellent agreement with our experimental data. In fact, the conformers **13** and **15** have almost the identical conformations with the crystal structures of **7h** and **6h**, respectively (Scheme 1). The above calculations provide a strong support to our assumption that the iodine atom transfer 6-exo cyclization reactions are kinetically controlled rather than thermodynamically controlled.

As an extension, the calculations at the B3LYP/6-31G* level on the conformations of *cis*- and *trans*-3,4-dimethyltetrahydro-2*H*-pyran-2-ones were also performed (see Supporting Information) and the results closely resemble those in Charts 3 and 4, indicating that the presence of the iodine atom in **6** or **7** does not show much impact on the relative energies between 3,4-cis- and 3,4-trans-substituted *δ*-lactones.

The conformations of *δ*-lactones have long been the interest of chemists and many works have been carried out experimentally[24,25] and theoretically.[25] All the data available indicate that *δ*-lactones possess two possible conformations, boat and half-chair. Our results closely parallel those in the literature. Moreover, our results also indicate that the relative stabilities between the boat and half-chair conformations strongly depend on the substitution pattern. It is worthy to mention that, despite the numerous experiments and calculations already reported, the crystal structures of **6** and **7** in Scheme 1, combined with the above theoretical calculations, are the first examples to actually "see" that the sterically unconstrained *δ*-lactones possess either boat or half-chair conformations in the solid states.

Conclusion

In conclusion, we have examined experimentally and computationally the atom transfer radical cyclization reactions of 3-butenyl iodoalkanoates and found that the 6-exo cyclization of α-ester radicals requires boat-conformational transition states and the cis-oriented transition states are of lower energy that the corresponding trans-oriented ones, which lead to the high preference of 3,4-cis-substituted tetrahydro-2*H*-pyran-2-ones over the corresponding 3,4-trans-substituted ones. The reactions can be efficiently carried out with the catalysis of $BF_3{\cdot}OEt_2$ to afford the 6-exo cyclization products in moderate to good yield. Ab initio calculations on the transition states at the B3LYP/6-31G* level give accurate predictions on the outcome of the stereoselectivities of the cyclization reactions. The coordination of $BF_3{\cdot}OEt_2$ to the substrates imposes an effect on but does not reverse the stereoselectivities. These results, along with the theoretical calculations on the cyclized *δ*-lactone products at the B3LYP/6-31G* level, indicate that the iodine atom transfer cyclization reactions are kinetically controlled rather than thermodynamically controlled.

Experimental Section

NMR spectra were recorded in $CDCl_3$ (^1H at 300 or 400 MHz and ^{13}C at 75.47 MHz) using TMS as the internal standard. 2D NMR spectra were obtained with a 400-MHz NMR spectrometer. All melting points were uncorrected. Most products were isolated by column chromatography on silica gel with hexane−ethyl acetate in an appropriate ratio as the eluent. Photostimulated reactions utilized a 300 W fluorescent sunlamp. Methylene chloride was dried over CaH_2 and freshly distilled prior to use. Boron trifluoride etherate was distilled and stored under nitrogen. The preparation of substrates **5** that were not commercially available is summarized in the Supporting Information.

General Procedure for the 6-Exo Atom Transfer Cyclization Reactions. To a flask containing 33 mL of anhydrous CH_2Cl_2 under nitrogen atmosphere were added an iodoester **5** (1 mmol), boron trifluoride etherate (1.23 mL, 10 mmol), and bis(tributyltin) (51 μL, 0.1 mmol). The resulting solution was stirred and irradiated at 20 °C with the aid of a 300-W sunlamp. The reaction was monitored by TLC. After the starting **5** was consumed, saturated aqueous $NaHCO_3$ (30 mL) was added and the mixture was stirred at rt for 30 min. The two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic phase was washed with brine (2 × 10 mL). After removal of the solvent, the residue was diluted with wet ether. One equivalent of 1 M DBU ether solution was added followed by the addition of iodine ether solution until the color of iodine just persisted. The mixture was then passed through a short silica column to remove the tin compound. The organic layer

(24) (a) Mathieson, A. M. *Tetrahedron Lett.* **1963**, 81. (b) Cheung, K. K.; Overton, K. H.; Sim, G. A. *J. Chem. Soc., Chem. Commun.* **1965**, 634. (c) Johnson, R. N.; Riggs, N. V. *Tetrahedron Lett.* **1967**, 5119. (d) Carroll, F. I.; Mitchell, G. N.; Blackwell, J. T.; Sobti, A.; Meck, R. *J. Org. Chem.* **1974**, *39*, 3890. (e) Gasic, M. J.; Djarmati, Z. *J. Org. Chem.* **1976**, *41*, 1219. (f) Lambert, J. B.; TeVrucht, M. L. E. *Org. Magn. Reson.* **1984**, *22*, 613.

(25) (a) Allinger, N. L.; Chang, S. H. M. *Tetrahedron* **1977**, *33*, 1561. (b) Philip, T.; Cook, R. L.; Malloy, T. B., Jr.; Allinger, N. L.; Chang, S.; Yuh, Y. *J. Am. Chem. Soc.* **1981**, *103*, 2151. (c) Wiberg, K. B.; Waldron, R. F. *J. Am. Chem. Soc.* **1991**, *113*, 7697. (d) Saunders, M.; Jimenez-Vazquez, H. A. *J. Comput. Chem.* **1993**, *14*, 330. (e) Allinger, N. L.; Zhu, Z. S.; Chen, K. *J. Am. Chem. Soc.* **1992**, *114*, 6120. (f) Abraham, R. J.; Ghersi, A.; Petrillo, G.; Sancassan, F. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1279.

was dried over anhydrous $MgSO_4$. After removal of the solvent, the crude product was purified by column chromatography on silica gel with ethyl acetate−hexane in an appropriate ratio as the eluent to give the corresponding products **6** and **7**, respectively.

***cis*-4-Iodomethyl-3-methyltetrahydro-2*H*-pyran-2-one (6a).** Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (3H, d, J = 7.3 Hz), 1.84−1.97 (1H, m), 2.07−2.16 (1H, m), 2.42−2.50 (1H, m), 2.88 (1H, dq, J = 7.2, 7.3 Hz), 2.99 (1H, t, J = 9.8 Hz), 3.29 (1H, dd, J = 9.9, 5.5 Hz), 4.28 (1H, ddd, J = 11.5, 10.8, 4.3 Hz), 4.40 (1H, ddd, J = 11.6, 5.8, 3.7 Hz). ^{13}C NMR ($CDCl_3$) δ 174.0, 66.8, 38.7, 37.7, 28.2, 12.1, 7.6. EIMS: m/z (rel intensity) 254 (M^+, 2), 127 (7), 99 (5), 83 (64), 69 (16), 55 (100), 41 (48). Anal. Calcd for $C_7H_{11}IO_2$: C, 33.09; H, 4.36. Found: C, 33.34; H, 4.42. The coupling constant between 3- and 4-protons is 7.2 Hz.

***trans*-4-Iodomethyl-3-methyltetrahydro-2*H*-pyran-2-one (7a).** Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (3H, d, J = 6.8 Hz), 1.52−1.62 (1H, m), 1.71−1.82 (1H, m), 2.01−2.13 (1H, m), 2.46 (1H, dq, J = 10.6, 6.8 Hz), 3.28 (1H, dd, J = 10.3, 5.6 Hz), 3.44 (1H, dd, J = 10.3, 3.4 Hz), 4.24−4.40 (2H, m). ^{13}C NMR ($CDCl_3$) δ 174.0, 66.2, 40.4, 38.2, 29.3, 14.00, 13.7. EIMS: m/z (rel intensity) 254 (M^+, 4), 205 (2), 127 (32), 99 (10), 83 (44), 69 (15), 55 (100), 41 (48). Anal. Calcd for $C_7H_{11}IO_2$: C, 33.09; H, 4.36. Found: C, 33.42; H, 4.51. The coupling constant between 3- and 4-protons is 10.6 Hz.

(3α,4α,6α)-4-Iodomethyl-3,6-dimethyltetrahydro-2*H*-pyran-2-one (6b). White Solid. Mp 88−90 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (3H, d, J = 7.2 Hz), 1.40 (3H, d, J = 6.2 Hz), 1.49 (1H, ddd, J = 14.3, 11.7, 9.2 Hz), 2.15 (1H, ddd, J = 14.3, 6.7, 3.2 Hz), 2.41−2.51 (1H, m), 2.85 (1H, dq, J = 7.1, 7.1 Hz), 2.97 (1H, t, J = 9.7 Hz), 3.24 (1H, dd, J = 9.9, 5.6 Hz), 4.41−4.49 (1H, m). ^{13}C NMR ($CDCl_3$) δ 174.5, 74.6, 37.8, 37.4, 35.8, 21.3, 11.8, 8.7. EIMS: m/z (rel intensity) 268 (M^+, 0.5), 141 (4), 97 (49), 69 (27), 67 (8), 55 (100), 41 (28). Anal. Calcd for $C_8H_{13}IO_2$: C, 35.84; H, 4.89. Found: C, 35.99; H, 4.80. The structure was confirmed by its NOESY spectrum which showed strong NOE between 3-H (δ 2.85) and 6-H (δ 4.41−4.49) but no NOE between 3-H and iodomethyl protons. The structure was further confirmed by its X-ray diffraction analysis.

(3α,4*β*,6α)-4-Iodomethyl-3,6-dimethyltetrahydro-2*H*-pyran-2-one (7b). Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (3H, d, J = 6.6 Hz), 1.38 (3H, d, J = 6.3 Hz), 1.55−1.64 (1H, m), 1.72−1.89 (2H, m), 2.49 (1H, dq, J = 10.0, 6.6 Hz), 3.34 (1H, dd, J = 10.3, 5.3 Hz), 3.43 (1H, dd, J = 10.3, 3.0 Hz), 4.45−4.56 (1H, m). ^{13}C NMR ($CDCl_3$) δ 175.1, 72.1, 39.2, 36.8, 36.2, 20.8, 15.2, 13.4. EIMS: m/z (rel intensity) 269 (M^+ + 1, 5), 253 (1), 141 (9), 97 (34), 69 (23), 55 (100), 53 (13), 41 (27). HRMS calcd for $C_8H_{13}IO_2$: 267.9960. Found: 267.9976. Anal. Calcd for $C_8H_{13}IO_2$: C, 35.84; H, 4.89. Found: C, 36.69; H, 5.12. The coupling constant between 3- and 4-protons is 10.0 Hz. The structure was further confirmed by its 2D NOESY spectrum which showed strong NOE between 3-H (δ 2.49) and 6-H (δ 4.45−4.56) and strong NOE between 4-H (δ 1.547−1.639) and 3-methyl protons.

(3α,4α,5*β*)-4-Iodomethyl-3,5-dimethyltetrahydro-2*H*-pyran-2-one (6c). White Solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (3H, d, J = 6.8 Hz), 1.24 (3H, d, J = 7.0 Hz), 1.97−2.04 (1H, m), 2.10−2.18 (1H, m), 2.85 (1H, dq, J = 6.9, 6.9 Hz), 3.01 (1H, t, J = 9.7 Hz), 3.31 (1H, dd, J = 10.1, 4.7 Hz), 3.89 (1H, t, J = 11.5 Hz), 4.27 (1H, dd, J = 11.5, 6.0 Hz). ^{13}C NMR ($CDCl_3$) δ 174.6, 71.3, 44.6, 36.7, 34.1, 16.9, 12.1, 8.3. EIMS: m/z (rel intensity) 269 (M^+ + 1, 34), 141 (20), 113 (14), 97 (30), 69 (20), 55 (100), 43 (22), 41 (26). HRMS calcd for $C_8H_{13}IO_2$: 267.9960. Found: 267.9944. Anal. Calcd for $C_8H_{13}IO_2$: C, 35.84; H, 4.89. Found: C, 36.34; H, 4.95. The NOESY spectrum showed strong NOE between 3-H (δ 2.85) and the 6-axial proton (δ 3.89) and between 6-axial and 5-methyl protons but no NOE between 3-H and iodomethyl protons.

(3α,4*β*,5*β*)-4-Iodomethyl-3,5-dimethyltetrahydro-2*H*-pyran-2-one (7c). Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85−0.93 (1H, m), 1.03 (3H, d, J = 6.7 Hz), 1.23 (3H, d, J = 6.8 Hz), 1.90−2.01 (1H, m), 2.47 (1H, dq, J = 10.8, 6.8 Hz), 3.35 (1H, dd, J = 10.7, 3.8 Hz), 3.46 (1H, dd, J = 10.7, 3.1 Hz), 3.97 (1H, dd, J = 11.3, 6.6 Hz), 4.30 (1H, dd, J = 11.3, 4.4 Hz). ^{13}C NMR ($CDCl_3$) δ 173.3, 70.5, 43.8, 38.7, 32.5, 15.4, 12.9, 12.1. EIMS: m/z (rel intensity) 269 (M^+ + 1, 52), 141 (24), 113 (13), 97 (30), 69 (25), 55 (100), 53 (17), 41 (36). HRMS calcd for $C_8H_{13}IO_2$: 267.9960. Found: 267.9986. Anal. Calcd for $C_8H_{13}IO_2$: C, 35.84; H, 4.89. Found: C, 36.37; H, 5.05. The coupling constant between 3- and 4-protons is 10.8 Hz.

(3α,4α,5*β*,6α)-4-Iodomethyl-3,5,6-trimethyltetrahydro-2*H*-pyran-2-one (6d). White solid. Mp 129−130 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12 (3H, d, J = 6.9 Hz), 1.26 (3H, d, J = 7.0 Hz), 1.41 (3H, d, J = 6.2 Hz), 1.65−1.77 (1H, m), 1.94−2.02 (1H, m), 2.81 (1H, dq, J = 4.0 Hz), 2.91 (1H, t, J = 10.0 Hz), 3.35 (1H, dd, J = 10.0, 2.8 Hz), 4.06 (1H, dq, J = 10.2, 6.1 Hz). ^{13}C NMR (CDCl3) δ 174.8, 78.5, 45.9, 41.8, 36.8, 19.6, 18.1, 12.2, 8.8. EIMS: m/z (rel intensity) 283 (M^+ + 1, 5), 182 (3), 155 (10), 127 (27), 111 (19), 83 (34), 69 (36), 55 (100), 43 (28). Anal. Calcd for $C_9H_{15}IO_2$: C, 38.32; H, 5.36. Found: C, 38.64; H, 5.32. The structure was confirmed by its 2D NOESY spectrum, which showed strong NOE between 3-H (δ 2.81) and 6-H (δ 4.06) and between 3-H and 4-H (δ 1.94−2.02) but no NOE between 3-H and iodomethyl protons. The structure was further confirmed by its X-ray diffraction analysis.

(3α,4*β*,5*β*,6α)-4-Iodomethyl-3,5,6-trimethyltetrahydro-2*H*-pyran-2-one (7d). Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01 (3H, d, J = 7.2 Hz), 1.19 (3H, d, J = 6.6 Hz), 1.18−1.26 (1H, m), 1.32 (3H, d, J = 6.5 Hz), 1.81−1.93 (1H, m), 2.51 (1H, dq, J = 10.9, 6.6 Hz), 3.35 (1H, dd, J = 10.4, 5.0 Hz), 3.47 (1H, dd, J = 10.4, 2.8 Hz), 4.51 (1H, dq, J = 3.6, 6.5 Hz). ^{13}C NMR ($CDCl_3$) δ 175.1, 74.3, 45.7, 38.7, 38.3, 17.0, 14.4, 14.2, 13.5. EIMS: m/z (rel intensity) 283 (M^+ + 1, 8), 182 (4), 155 (15), 127 (17), 111 (20), 83 (34), 55 (100), 43 (26). HRMS calcd for $C_9H_{15}IO_2$: 282.0117. Found: 282.0120. Anal. Calcd for $C_9H_{15}IO_2$: C, 38.32; H, 5.36. Found: C, 38.70; H, 5.21. The coupling constant between 3- and 4-protons is 10.9 Hz.

***cis*-3-Ethyl-4-iodomethyltetrahydro-2*H*-pyran-2-one (6e).** White solid. Mp 50−52 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01 (3H, t, J = 7.4 Hz), 1.44−1.55 (1H, m), 1.79−1.94 (2H, m), 2.11−2.21 (1H, m), 2.49−2.62 (2H, m), 2.86 (1H, t, J = 10.1 Hz), 3.31 (1H, dd, J = 10.0, 3.7 Hz), 4.25 (1H, ddd, J = 11.8, 10.4, 4.4 Hz), 4.35 (1H, ddd, J = 11.8, 6.1, 3.8 Hz). ^{13}C NMR ($CDCl_3$) δ 173.2, 65.7, 45.5, 36.2, 29.4, 19.8, 12.1, 7.9. EIMS: m/z (rel intensity) 269 (M^+ + 1, 2), 240 (20), 113 (52), 69 (24), 55 (100), 53 (13), 43 (12), 41 (44). Anal. Calcd for $C_8H_{13}IO_2$: C, 35.84; H, 4.89. Found: C, 36.13; H, 4.97. The structure was confirmed by its 2D NOESY spectrum, which showed NOE between 3-H and 6-axial protons (δ 4.252) while no NOE between 5-equitorial (δ 2.11−2.21) and iodomethyl protons.

***trans*-3-Ethyl-4-iodomethyltetrahydro-2*H*-pyran-2-one (7e).** Yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (3H, t, J = 7.4 Hz), 1.46−1.97 (4H, m), 2.01−2.14 (1H, m), 2.35−2.46 (1H, m), 3.23 (1H, dd, J = 6.1, 10.4 Hz), 3.40 (1H, dd, J = 3.1, 10.4 Hz), 4.24−4.39 (2H, m). ^{13}C NMR ($CDCl_3$) δ 173.2, 66.3, 46.9, 35.6, 29.5, 21.8, 10.8, 7.9. EIMS: m/z (rel intensity) 269 (M^+ + 1, 2), 240 (18), 113 (50), 69 (27), 55 (100), 53 (15), 41 (35). HRMS calcd for $C_8H_{13}IO_2$: 267.9960. Found: 267.9968. Anal. Calcd for $C_8H_{13}IO_2$: C, 35.84; H, 4.89. Found: C, 36.23; H, 4.66.

***cis*-4-Iodomethyl-3-(1-methylethyl)tetrahydro-2*H*-pyran-2-one (6f).** White solid. Mp 87−88 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (3H, d, J = 6.7 Hz), 1.09 (3H, d, J = 6.3 Hz), 1.78−1.90 (1H, m), 2.02−2.12 (1H, m), 2.14−2.27 (2H, m), 2.69−2.82 (2H, m), 3.35 (1H, dd, J = 8.7, 1.7 Hz), 4.25 (1H, dt, J = 4.5, 11.7 Hz), 4.35 (1H, ddd, J = 11.7, 6.9, 2.2 Hz). ^{13}C NMR ($CDCl_3$) δ 173.4, 65.3, 50.7, 35.7, 29.9, 25.2, 22.6, 19.9, 8.9. EIMS: m/z (rel intensity) 283 (M^+ + 1, 27), 240 (30), 113 (100), 95 (17), 69 (32), 55 (36), 43 (17), 41 (34). Anal. Calcd for $C_9H_{15}IO_2$: C, 38.32; H, 5.36. Found: C, 38.54; H, 5.51. The structure was confirmed by its HETCOR and NOESY spectra.

The NOESY spectrum showed strong NOE between the 3-proton (δ 2.25) and the 6-axial proton (δ 4.25) while no NOE between the 3-proton and iodomethyl protons was observed. The structure was further confirmed by its X-ray diffraction analysis.

***trans*-4-Iodomethyl-3-(1-methylethyl)tetrahydro-2*H*-pyran-2-one (7f).** Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (3H, d, J = 6.8 Hz), 1.13 (3H, d, J = 6.7 Hz), 1.64−1.77 (1H, m), 1.92−2.00 (1H, m), 2.06−2.17 (2H, m), 2.32 (1H, dd, J = 7.0, 4.4 Hz), 3.15 (1H, dd, J = 10.2, 7.7 Hz), 3.33 (1H, dd, J = 10.1, 3.8 Hz), 4.24 (1H, ddd, J = 11.3, 10.2, 3.1 Hz), 4.37 (1H, dt, J = 11.4, 4.4 Hz). ^{13}C NMR ($CDCl_3$) δ 172.0, 66.6, 52.8, 36.6, 30.8, 29.9, 20.9, 19.1, 12.8. EIMS: *m*/*z* (rel intensity) 283 ($M^+ + 1$, 6), 240 (27), 113 (100), 83 (44), 71 (50), 69 (62), 57 (60), 55 (89), 43 (76), 41 (72). HRMS calcd for $C_9H_{15}IO_2$: 282.0117. Found: 282.0157.

***cis*-4-Iodomethyl-3-(2,2-dimethylpropyl)tetrahydro-2*H*-pyran-2-one (6g).** White solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (9H, s), 1.19 (1H, dd, J = 14.1, 3.1 Hz), 1.84−1.96 (1H, m), 2.08 (1H, dd, J = 14.1, 7.1 Hz), 2.17−2.28 (1H, m), 2.46−2.58 (1H, m), 2.65 (1H, ddd, J = 13.1, 6.8, 3.1 Hz), 2.79 (1H, dd, J = 11.6, 10.0 Hz), 3.39 (1H, dd, J = 10.0, 3.4 Hz), 4.29−4.43 (2H, m). ^{13}C NMR ($CDCl_3$) δ 173.8, 65.5, 40.5, 39.6, 39.5, 30.8, 29.5, 29.3, 8.5. EIMS: *m*/*z* (rel intensity) 295 ($M^+ - CH_3$, 19), 253 (100), 211 (2), 183 (125), 165 (5), 127 (57), 113 (11), 55 (96). HRMS calcd for $C_9H_{15}IO_2$: 310.0430. Found: 310.0414.

***trans*-4-Iodomethyl-3-(2,2-dimethylpropyl)tetrahydro-2*H*-pyran-2-one (7g).** Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (9H, s), 1.17 (1H, dd, J = 14.2, 2.1 Hz), 1.76−1.88 (2H, m), 2.14 (1H, dd, J = 14.3, 7.2 Hz), 2.07−2.21 (1H, m), 2.33 (1H, ddd, J = 16.4, 6.9, 2.1 Hz), 3.23 (1H, dd, J = 10.3, 6.6 Hz), 3.44 (1H, dd, J = 10.3, 3.8 Hz), 4.26 (1H, dt, J = 11.5, 4.4 Hz), 4.40 (1H, dt, J = 3.3, 11.4 Hz). ^{13}C NMR ($CDCl_3$) δ 174.5, 65.1, 43.4, 41.6, 38.4, 31.1, 29.7, 29.4, 12.9. EIMS: *m*/*z* (rel intensity) 310 (M^+, 3), 295 (30), 253 (37), 183 (100), 127 (81), 113 (30), 71 (52), 57 (100), 55 (71). HRMS calcd for $C_9H_{15}IO_2$: 310.0430. Found: 310.0428.

***cis*-4-Iodomethyl-3-(1,1-dimethylethyl)tetrahydro-2*H*-pyran-2-one (6h).** White solid. Mp 96−98 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (9H, s), 2.00−2.24 (2H, m), 2.42 (1H, d, J = 4.9 Hz), 2.73−2.83 (1H, m), 2.89 (1H, dd, J = 12.6, 9.6 Hz), 3.68 (1H, dd, J = 9.3, 2.7 Hz), 4.19−4.37 (2H, m). ^{13}C NMR ($CDCl_3$) δ 171.2, 64.7, 53.8, 36.1, 32.6, 31.3, 29.3, 9.4. EIMS: *m*/*z* (rel intensity) 297 ($M^+ + 1$, 2), 240 (15), 169 (10), 113 (100), 99 (16), 83 (20), 69 (23), 57 (32), 41 (32). HRMS calcd for $C_{10}H_{17}IO_2$: 296.0273, Found: 296.0228. Anal. Calcd for $C_{10}H_{17}IO_2$: C, 40.52; H, 5.79. Found: C, 40.17; H, 6.09. The structure was confirmed by its 2D NOESY spectrum and further confirmed by its X-ray diffraction analysis.

***trans*-4-Iodomethyl-3-(1,1-dimethylethyl)tetrahydro-2*H*-pyran-2-one (7h).** White solid. Mp 111−112 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (9H, s), 1.53−1.67 (1H, m), 2.03−2.12 (1H, m), 2.19 (1H, d, J = 5.6 Hz), 2.20−2.28 (1H, m), 3.04 (1H, dd, J = 9.9, 9.0 Hz), 3.29 (1H, dd, J = 10.1, 3.1 Hz), 4.21 (1H, dt, J = 1.7, 11.4 Hz), 4.35 (1H, ddd, J = 11.2, 3.9, 2.8 Hz). ^{13}C NMR ($CDCl_3$) δ 171.3, 67.1, 58.2, 36.6, 35.3, 31.0, 28.2, 13.7. EIMS: *m*/*z* (rel intensity) 297 ($M^+ + 1$, 20), 240 (24), 169 (4), 113 (100), 99 (18), 95 (21), 57 (25), 41 (21). Anal. Calcd for $C_{10}H_{17}IO_2$: C, 40.52; H, 5.79. Found: C, 40.78; H, 5.76. The structure was confirmed by its X-ray diffraction analysis.

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Supporting Information Available: Synthesis and characterization of **5**; computational results for **6a**, **7a**, **6h**, **7h**, *cis*- and *trans*-3,4-dimethyltetrahydro-2*H*-pyran-2-ones, and the transition states **C-5** and **T-5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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