Investigation of Bis(tributyltin)-Initiated Free Radical Cyclization Reactions of 4-Pentenyl Iodoacetates

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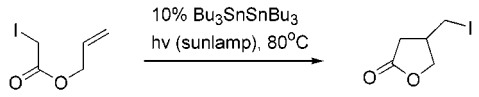
Bis(tributyltin)-initiated atom transfer cyclization reactions of 4-pentenyl iodoacetates (**1**) at 80 °C led to the formations of 5-(3-iodopropyl)-substituted dihydro-2(3*H*)-furanones (**3**) in high yield. With BF_3·Et_2O as the catalyst, the reactions were run at room temperature to afford the corresponding γ-iodoheptanolactones (**2**), which could be further transformed into 3-(tetrahydro-2-furyl)propanoic acids (**6**) upon treatment with aqueous $NaHCO_3$. The reaction mechanism was postulated to be the 8-endo free radical cyclization to generate γ-iodoheptanolactones which easily underwent intramolecular nucleophilic substitution to form bicyclic acylium species (**7**) as the key intermediate. Subsequent attack by iodide ion furnished γ-lactones while attack by hydroxide ion gave the tetrahydrofuran derivatives.

Introduction

The past two decades have witnessed a rapid growth in free radical reactions and their applications in organic synthesis.[1] Among them, cyclizations of α-carbonyl radicals leading to the formations of lactones, lactams, and cycloalkanones are of primary interests due to their great potential in natural product synthesis. Several methods have been developed to carry out the cyclization reactions, including the standard tributylstannane method, a halogen atom transfer method[2] with bis(tributyltin) or triethylborane, and the organomercurial method.[3] The halogen atom transfer annulation method developed by Curran et al., in particular, has been demonstrated to be a unique tool in the investigations of α-carbonyl radical cyclization reactions. For example, sunlamp irradiation of allyl iodoacetate with 10 mol % of bis(tributyltin) at 80 °C led to the formation of 4-iodomethyltetrahydrofuran-2-one in 41% yield (Scheme 1), while reaction of allyl bromoacetate with tributyltin hydride gave only the direct reduction product allyl acetate.[2] More recently, triethylborane-initiated iodine atom transfer annulation reactions in water have been reported by Oshima et al.[4]

Scheme 1



While the initial attempts in the cyclization of α-carbonyl radicals were concentrated mainly in the preparations of γ- and δ-lactones,[5] recent efforts[6] have been put into the formations of medium and large size lactones which are difficult to synthesize via traditional lactone-forming reactions starting from ω-halo- or ω-hydroxycarboxylic acids.[7] Among them, heptanolactones are the least accessible ones and only a few examples have been reported.[8] Investigations in the cyclization of (4-pentenoxycarbonyl)methyl radicals in an 8-endo mode have shown its potential in the preparations of heptanolactones.[3e,9,10] Russell and Li employed *tert*-butylmercury iodide and diphenyl disulfide to react with 4-pentenyl acrylates to afford the heptanolactones in moderate

(1) For review articles, see: (a) Curran, D. P. *Synthesis* **1988**, *417*, 489. (b) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237. (c) Melikyan, G. G. *Synthesis* **1993**, 833. (d) Iqbal, J.; Bhatia, B.; Nayyar, N. K. *Chem. Rev.* **1994**, *94*, 519. (e) Snider, B. B. *Chem. Rev.* **1996**, *96*, 339. (f) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1996. (g) Gansauer, A.; Bluhm, H. *Chem. Rev.* **2000**, *100*, 2771.

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(3) (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.

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(6) For a review on the synthesis of medium-sized rings via free radical processes, see: Yet, L. *Tetrahedron* **1999**, *55*, 9349.

(7) For reviews, see: (a) Back, T. G. *Tetrahedron* **1977**, *33*, 3041. (b) Rousseau, G. *Tetrahedron* **1995**, *51*, 2777.

(8) (a) Funk, R. L.; Abelman, M. M. *J. Org. Chem.* **1986**, *51*, 3247. (b) Buszek, K. R.; Sato, N.; Jeong, Y. *J. Am. Chem. Soc.* **1994**, *116*, 5511. (c) Andrus, M. B.; Argade, A. B. *Tetrahedron Lett.* **1996**, *37*, 5049. (d) Shiina, I.; Fujisawa, H.; Ishii, T.; Fukuda, Y. *Heterocycles* **2000**, *52*, 1105.

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(10) (a) Lee, E.; Yoon, C. H.; Lee, T. H. *J. Am. Chem. Soc.* **1992**, *114*, 10981. (b) Lee, E.; Yoon, C. H.; Lee, T. H.; Kim, S. Y.; Ha, T. J.; Sung, Y.; Park, S.-H.; Lee, S. *J. Am. Chem. Soc.* **1998**, *120*, 7469.

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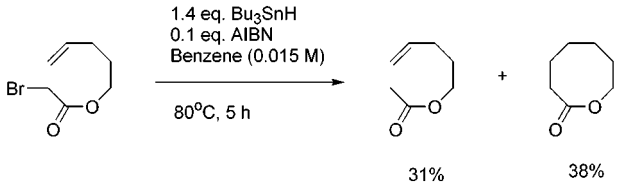
Scheme 2



yield.[3e] Speckamp and Verlhac treated 4-pentenyl di- or trichloroacetates with Cu(I) or Fe(II) complexes to give the corresponding 8-endo cyclization products which could be transferred to heptanolactones by Bu_3SnH/AIBN reduction.[9] Lee et al. used tributyltin hydride and AIBN to carry out the reaction of 4-pentenyl bromoacetates at 80 °C and obtained the 8-endo cyclization products. However, the yields were moderate because of the contamination of the direct reduction products (Scheme 2).[10]

Compared to the tin hydride method, halogen atom transfer annulation with bis(tributyltin) or triethylborane as initiator could be a more efficient way to conduct the 8-endo cyclization. However, to our surprise, the atom transfer annulation method using bis(tributyltin) or triethylborane has never been employed in the 8-endo radical cyclizations of α-carbonyl radicals and sometimes was omitted from published studies with no clear reasons.[4] We were lured to the field by our curiosity of the above situation.

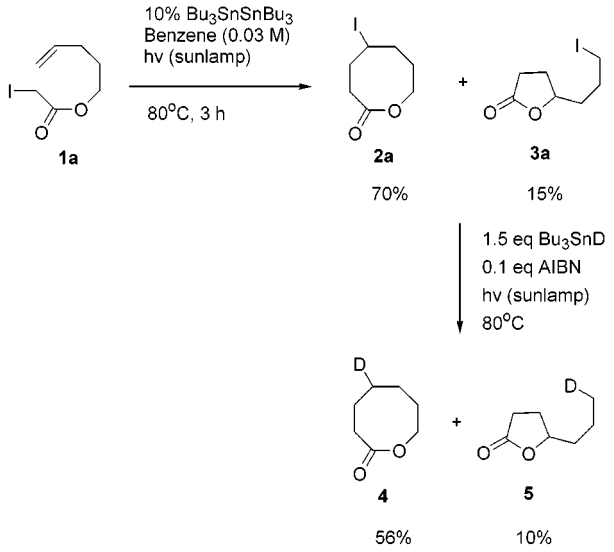
Results and Discussion

Tributyltin hydride/AIBN-initiated reaction of 4-pentenyl iodoacetate (**1a**) gave mainly the direct reduction product 4-pentenyl acetate (70%) while less than 15% of the cyclized product heptanolactone could be isolated. When **1a** was irradiated with the aid of a 300 W sunlamp in the presence of 10 mol % of bis(tributyltin) in benzene at 80 °C, it was consumed within 3 h and two products were formed as indicated by TLC monitoring. GC analysis showed the ratio of the two products to be 80:20. After usual workup and column chromatography on silica, the minor product was isolated in 15% yield and its structure was characterized to be 5-(3-iodopropyl)dihydro-2(3*H*)-furanone **3a**. However, the major product underwent decomposition in the column and could not be obtained in pure form. To get more information on the structure of the major product, we treated the two products, without isolation, with 1.5 equiv of tributyltin deuteride and 5 mol % of AIBN at 80 °C in benzene for 1 h and two deuterated compounds, **4** and **5**, were isolated and identified. The formation of **4** clearly indicated the major product to be the expected 8-endo cyclization product **2a** (Scheme 3).

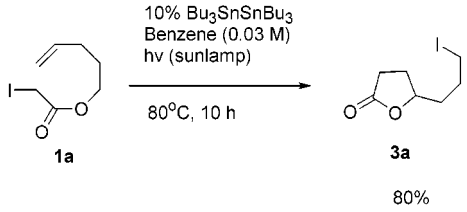
To understand the instability of **2a** as well as the mechanism for the formation of **3a**, we carried out the reaction of **1a** at 80 °C for a longer time and TLC and GC monitoring showed that **2a** was converted to **3a** smoothly. After 7 h, **2a** was completely consumed and **3a** was isolated in 80% yield (Scheme 4).

To gain more information on the isomerization reaction, we tested various substrates, **1b**−**i**. Compounds **1b**−**f** afforded the corresponding **3b**−**f** under the same reaction conditions (Table 1). In the cases of **1d**−**f**, no corresponding intermediates **2d**−**f** could be detected by GC or TLC throughout the reaction, implying their much

Scheme 3



Scheme 4



faster isomerization than **2a**. For compounds **1g**−**i**, however, no rearrangement products **3** could be detected while the corresponding γ-iodoheptanolactones **2g**−**i** were isolated in high yields (Table 2, method A).

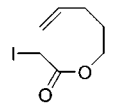
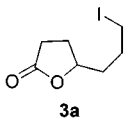
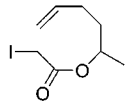
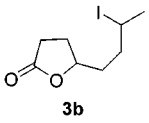
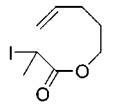
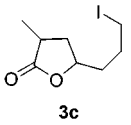
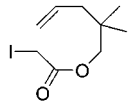
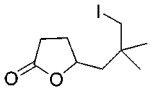
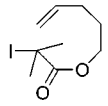
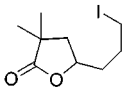
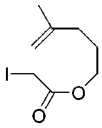
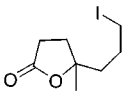
To obtain γ-iodoheptanolactones **2** without contamination of the rearrangement products **3**, we carried out the cyclization reaction of **1a** at lower temperature. The reaction was very slow at 20 °C and more than half of **1a** remained unchanged after 24 h. To accelerate the reaction, we turned to Lewis acids for help as they were used to enhance radical reactivity and to improve product selectivity in many examples.[11,12]

Among the Lewis acids screened ($Yb(OTf)_3$, $Zn(OTf)_2$, $Mg(OTf)_2$, $BF_3{\cdot}OEt_2$), $BF_3{\cdot}OEt_2$ gave the best result. When the reaction was carried out with the catalysis of 3 equiv of $BF_3{\cdot}OEt_2$ at room temperature, all starting **1a** was smoothly consumed within 6 h. TLC monitoring showed that only **2a** was formed while no **3a** could be detected. The usual workup followed by flash chromatography on silica, however, failed to give **2a** in pure form. Careful examination revealed that the cyclization product was very sensitive to moisture. Thus, when the purification was performed under strict anhydrous condi-

(11) For a review article, see: Renaud, P.; Gerster, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2562.

(12) For more recent examples, see: (a) Sibi, M. P.; Ji, J.; Sausker, J. B.; Jaspersse, C. P. *J. Am. Chem. Soc.* **1999**, *121*, 7517. (b) Iserloh, U.; Curran, D. P.; Kanemasa, S. *Tetrahedron: Asymmetry* **1999**, *10*, 2417. (c) Dakternieks, D.; Dunn, K.; Tamara Perchyonok, V.; Schiesser, C. H. *Chem. Commun.* **1999**, 1665. (d) Mero, C. L.; Porter, N. A. *J. Am. Chem. Soc.* **1999**, *121*, 5155. (e) Porter, N. A.; Feng, H.; Kavrakova, I. *Tetrahedron Lett.* **1999**, *40*, 6713. (f) Sibi, M. P.; Rheault, T. R. *J. Am. Chem. Soc.* **2000**, *122*, 8873. (g) Friestad, G. K.; Qin, J. *J. Am. Chem. Soc.* **2000**, *122*, 8329. (h) Munakata, R.; Totani, K.; Takao, K.-I.; Tadano, K.-I. *Synlett* **2000**, 979. (i) Hayen, A.; Koch, R.; Metzger, J. O. *Angew. Chem., Int. Ed.* **2000**, *39*, 2758. (j) Porter, N. A.; Zhang, G.; Redd, A. D. *Tetrahedron Lett.* **2000**, *41*, 5773. (k) Yang, D.; Ye, X.-Y.; Xu, M.; Pang, K.-W.; Cheung, K.-K. *J. Am. Chem. Soc.* **2000**, *122*, 1658.

Table 1. Compounds 3 Synthesized[a]

Substrate	Product	Yield (%)[b]
 **1a**	 **3a**	80
 **1b**	 **3b**	88 (1 : 1 mixture of isomers)[c]
 **1c**	 **3c**	89 (cis : trans = 1 : 1)[c]
 **1d**	 **3d**	74
 **1e**	 **3e**	71
 **1f**	 **3f**	75

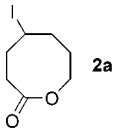
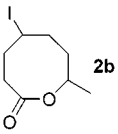
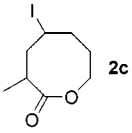
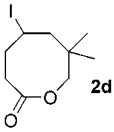
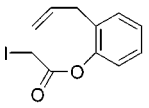
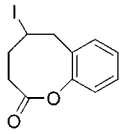
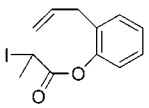
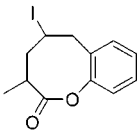
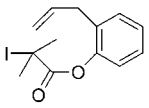
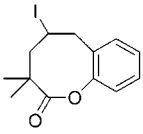
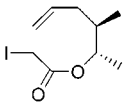
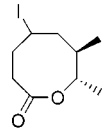
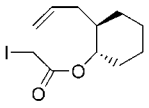
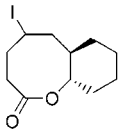
[a] Photostimulation of **1** with 10 mol % of bis(tributyltin) in benzene at 80 °C for 3−10 h until TLC monitoring showed that the reaction was complete. [b] Isolated yield based on the starting **1**. [c] Determined by ^{1}H NMR.

tions with care, the product **2a** was isolated in 80% yield (Scheme 5). Substrates **1b**−**d**,**g**,**h**,**j**,**k** showed similar behavior. For compound **1i**, the cyclization was slower probably because of steric hindrance. However, when the reaction was run at 30 °C for 14 h, an almost quantitative yield of product **2i** was obtained. In the case of **1e**,**f**, no corresponding product **2** could be isolated in pure form, which might be ascribed to the steric hindrance or the very low stability of the products. The results are summarized in Table 2 (method B). The reactions showed remarkable regioselectivity and no corresponding 7-exo cyclization products could be detected.

Although no detailed work was done to elucidate the function of $BF_3{\cdot}OEt_2$ in the cyclization reactions, we presume that the effect of $BF_3{\cdot}OEt_2$ might be attributed to its effective coordination with the carbonyl oxygen of **1**, which made the α-ester radicals more reactive toward electron-rich alkenes because of the polar effect. The ineffectiveness of other Lewis acids screened might be ascribed to their poor coordination to **1** owing to their very low solubility in benzene.

Among the products **2** prepared, **2g**−**i** were relatively stable and the structure of **2g** was further confirmed by its X-ray diffraction analysis. However, in all other cases, the products **2** were very sensitive to moisture and sometimes decomposed within hours at room temperature. Careful identification of the decomposition products

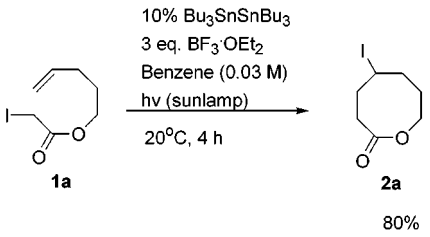
Table 2. Compounds 2 Synthesized

Substrate	Product	Method[a]	Yield (%)[b]
1a	 **2a**	B	80
1b	 **2b**	B	81 (1 : 1 mixture of stereoisomers)[c]
1c	 **2c**	B	79 (cis : trans = 1 : 1)[c]
1d	 **2d**	B	79
 **1g**	 **2g**	A B	83 87
 **1h**	 **2h**	A B	93 (cis : trans = 84:16)[c] 90 (cis : trans = 88:12)[c]
 **1i**	 **2i**	A B	78 95[d]
 **1j**	 **2j**	B	74 (1 : 1 mixture of stereoisomers)[c]
 **1k**	 **2k**	B	86 (1 : 1 mixture of stereoisomers)[c]

[a] Method A: photostimulation of **1** with 10 mol % of bis(tributyltin) in benzene at 80 °C for 3 h. Method B: photostimulation of **1** with 3 equiv of $BF_3{\cdot}OEt_2$ and 10 mol % of bis(tributyltin) in benzene at 20 °C for 3−10 h until TLC showed that the reaction was complete. [b] Isolated yield based on **1**. [c] Determined by ^{1}H NMR. [d] The reaction was run at 30 °C for 14 h.

of **2a** under neutral condition showed that one of the decomposition products was 3-(tetrahydro-2-furyl)propanoic acid (**6a**). In light of the above result, we treated **2a** with aqueous $NaHCO_3$ in acetone at room temperature and a high yield of **6a** was isolated. Thus, after the cyclization of **1a** was complete, an excess amount of aqueous $NaHCO_3$ was added and the solution was stirred at room temperature overnight. After the usual workup, **6a** was isolated in 72% yield in this one-pot, two-stage manner (Scheme 6). The results are summarized in Table 3.

Scheme 5



Scheme 6

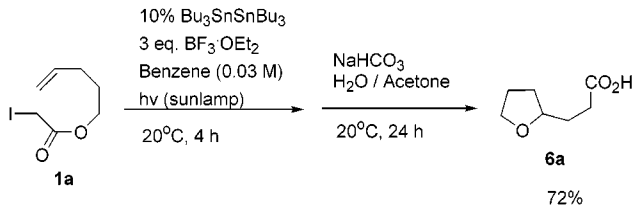
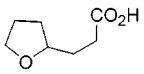
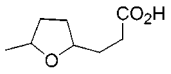
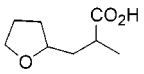
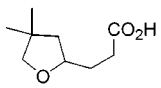
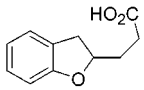
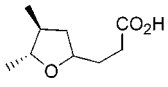


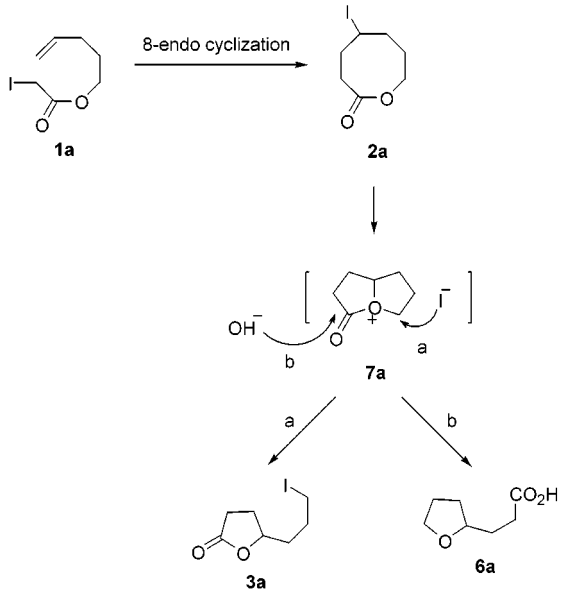
Table 3. Compounds 6 Synthesized

Substrate	Product	Yield (%)[a]
1a	 **6a**	72
1b	 **6b**	87[b]
1c	 **6c**	75[c]
1d	 **6d**	62
1g	 **6g**	64
1j	 **6j**	82[b]

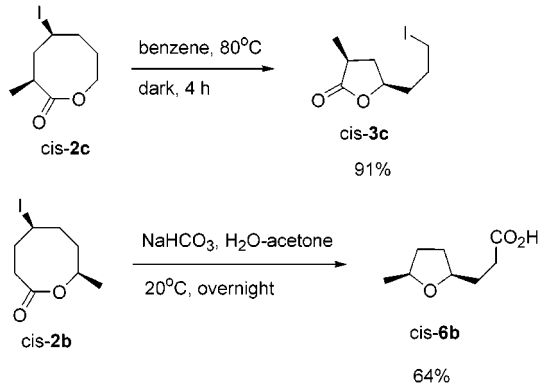
[a] Isolated yield based on the starting **1**. [b] Mixture of two stereoisomers in approximately 1:1 ratio determined by ^{1}H NMR. [c] Mixture of two stereoisomers in 25:75 ratio determined by ^{13}C NMR.

On the basis of the above results, a plausible mechanism could be drawn as depicted in Scheme 7. First, iodoacetate **1a** underwent free radical iodine atom transfer cyclization reaction to afford γ-iodoheptanolactone **2a**, which might be in equilibrium with the bicyclic acylium intermediate **7**[13] via intramolecular nucleophilic substitution of the γ-iodide by the "ether" oxygen atom. Upon heating, the iodide ion attacked the C-7 of **7** to generate **3a** (path a). Treatment with aqueous $NaHCO_3$ led to the hydrolysis of **7** to give **6a** (path b). Therefore, the one-pot formations of **3** resulted from radical atom transfer annulation followed by ionic reaction.[14] For compounds **2g**−**i**, iodide attack at the C-7 of **7** (C-10a of **2g**−**i**) was unfavorable because of the phenyl substitution and no corresponding rearrangement product **3** could be detected. However, hydroxide attack at the carbonyl to form **6** was not affected by the phenyl substitution and **6g** was thus obtained.

Scheme 7



Scheme 8

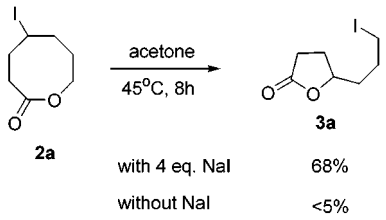


To provide further evidence for the mechanism, we designed the following experiments. Direct reflux of the cis isomer of **2c** in benzene in the dark for 4 h led to the exclusive formation of the cis isomer of **3c**. Treatment of the trans isomer of **2b** in acetone with aqueous $NaHCO_3$ afforded the trans isomer of **6b** as the only product (Scheme 8). Similarly, *trans*-**2c** gave *trans*-**3c** and *cis*-**2b** gave *cis*-**6b** only. The results indicated the reversion of configuration at the C-5 center of **2**, which was consistent with the proposed mechanism. When **2a** was treated with 4 equiv of NaI in dry acetone at 45 °C for 8 h, it was smoothly consumed to give the rearrangement

(13) The intermediate **7** was also postulated in the reaction of **6a** with trifluoroacetic anhydride: Grayson, D. H.; Roycroft, E. D. *J. Chem. Soc., Chem. Commun.* **1992**, 1296.

(14) For radical atom transfer reactions followed by irreversible ionic reactions, see: (a) Yorimitsu, H.; Wakabayashi, K.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **1999**, *40*, 519. (b) Curran, D. P.; Ko, S.-B. *Tetrahedron Lett.* **1998**, *39*, 6629. (c) Joung, M. J.; Ahn, J. H.; Lee, D. W.; Yoon, N. M. *J. Org. Chem.* **1998**, *63*, 2755. (d) Nagahara, K.; Ryu, I.; Komatsu, M.; Sonoda, N. *J. Am. Chem. Soc.* **1997**, *119*, 5465.

Scheme 9

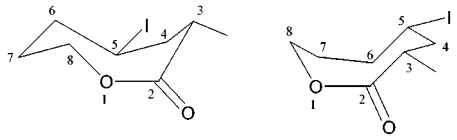


product **3a** in 68% yield, while less than 5% of **3a** could be achieved under similar experimental conditions without NaI (Scheme 9). This experiment clearly showed the faster isomerization of **2** catalyzed by iodide ion, indicating the nucleophilic nature in the rearrangement step.

The above results unambiguously demonstrated that 8-endo cyclization of α-ester radicals is a highly efficient process and atom transfer annulation is so far the best method to carry out the transformations. The cyclization reactions were significantly accelerated by the catalysis of BF_3·OEt_2. Although in the cases of **1e** and **1f** the corresponding heptanolactones were not obtained, the further rearrangement products **3e** and **3f** could be achieved in high yield, indicating not only the efficiency of 8-endo ester cyclization process but also the instability of heptanolactone products. Our results are in good agreement with Lee's calculation that 8-endo ester cyclization is the fundamentally preferred mode of reaction for (alkoxycarbonyl)methyl radicals which might be attributed to the low-energy s-trans conformations of the radicals in the transition states.[10]

The easy formation of acylium intermediate **7** should be associated with the conformations of γ-iodoheptanolactones **2**. The dipole moment for heptanolactone in the nonpolar solvent benzene indicates that the major conformation of heptanolactone is *E* (s-cis).[15] Noe et al.'s study[16] showed that heptanolactone has two stable conformations, both possessing the *Z* conformation and in boat-chair shape. On the other hand, s-trans conformation in a chair-chair shape was also reported for a substituted heptanolactone by Speckamp et al.[9a] To have a better picture of the conformations of substituted heptanolactones, we chose **2c** for 2D NOESY experiments.

The two stereoisomers of **2c** could be separated by careful column chromatography on silica. The NOESY spectrum of *trans*-**2c** showed strong NOE between C-3 proton (δ 2.47) and one of the C-8 protons (δ 3.78−3.85), indicating the boat conformation of the ester group. NOE was also observed between the C-3 proton (δ 2.47) and one of the C-6 protons (δ 1.61). The NOESY spectrum along with the coupling constants observed in proton NMR (600 MHz) could be best analyzed according to conformation **8**. For *cis*-**2c**, strong NOE between the C-3



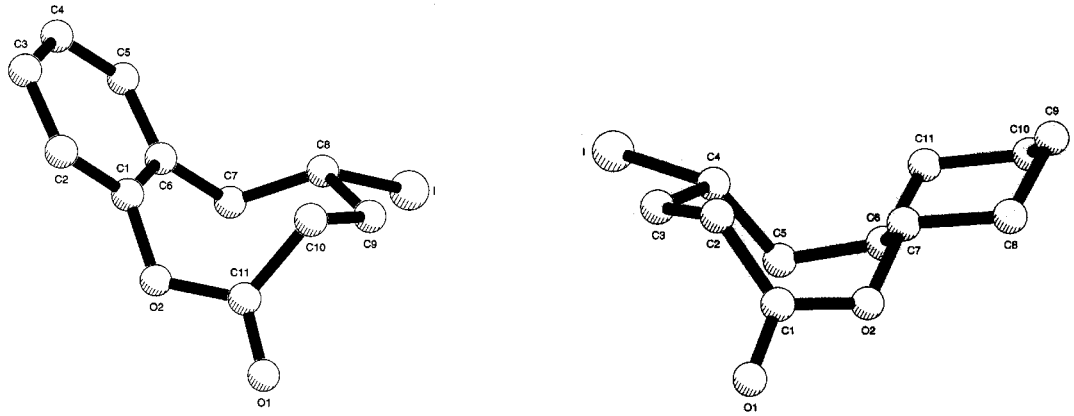
proton (δ 2.10−2.15) and one of the C-8 protons (δ 3.53) was observed in its NOESY spectrum, indicating the boat conformation of the ester group. Strong NOEs were also observed between the C-3 proton (δ 2.10−2.15) and the C-5 proton (δ 4.13) and between the C-5 proton (δ 4.13) and one of the C-8 protons (δ 3.53). These NOEs clearly showed that *cis*-**2** possessed the boat-chair conformation **9**. The conformations **8** and **9** are consistent with Noe's calculation in heptanolactone.[16] Thus, the "ether" oxygen (O-1) lying at the backside of the C(5)−I bond readily attacks C-5 based on the above conformations. Unfortunately, our attempts to grow single crystals of *cis*-**2c** and *trans*-**2c** were unsuccessful. Nevertheless, the X-ray crystal structure of the (5α,6aα,10a*β*) isomer of **2k** clearly showed that it possessed the boat-chair conformation as **9**. **2g** also existed in the boat-chair conformation in the solid state, which was only slightly distorted from **9** due to phenyl substitution (Scheme 10).

The above halogen atom transfer annulation reactions provided a convenient and efficient route to the synthesis of γ-iodoheptanolactones **2**, 3-iodopropyl-substituted γ-lactones **3**, and tetrahydrofuran derivatives **6**. A number of naturally occurring heptanolactones have been reported and the free radical pathway should be of potential application in their synthesis. Furthermore, the rearrangement products **3** can be utilized to prepare γ-hydroxycycloheptanones by treatment with SmI_2 as demonstrated by Molander and co-workers.[17]

Conclusion

8-Endo cyclization of α-ester radicals is an intrinsically favored process and halogen atom transfer annulation is a highly effective method to carry out the transformation. The cyclization reactions can be significantly ac-

Scheme 10. Crystal Structures of 2g and the (5α,6aα,10a*β*) Isomer of 2k



2g (5α,6aα,10aβ)-**2k**

celerated by boron trifluoride etherate. The products, γ-iodoheptanolactones **2**, can be rearranged in high yield to 3-iodopropyl-substituted γ-lactones **3** upon heating, while treatment of **2** with aqueous $NaHCO_3$ leads to the formation of tetrahydrofuran derivatives **6**. The mechanism is postulated to be the formation of bicyclic acylium intermediate **7** via intramolecular nucleophilic substitution.

Experimental Section

NMR spectra were recorded in $CDCl_3$ or C_6D_6 (^{1}H at 300 or 400 MHz and ^{13}C at 75.47 MHz) using TMS as the internal standard. All melting points were uncorrected. Most products were isolated by column chromatography on silica gel with hexane−ethyl acetate or acetone in the appropriate ratio as the eluent. Photostimulated reactions utilized a 300 W fluorescent sunlamp. Benzene was dried over CaH_2 and freshly distilled prior to use. Boron trifluoride etherate was distilled and stored under nitrogen. The preparation of substrates that were not commercially available is summarized in the Supporting Information.

5-Iodo-2-oxocanone (2a). Typical Procedure. Boron trifluoride etherate (0.37 mL, 3 mmol) was added to a benzene (33 mL) solution of 4-pentenyl iodoacetate (**1a**, 254 mg, 1.0 mmol) in a dry, 50 mL three-necked flask under nitrogen at room temperature. Bis(tributyltin) (0.050 mL, 0.1 mmol) was added and the mixture was irradiated at 20 °C with the aid of a 300 W sunlamp. The reaction was monitored by TLC. After the substrate **1a** disappeared (6 h), the resulting mixture was concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel with dry hexane−ethyl acetate (2:1, v:v) as the eluent to afford the product **2a** as a colorless oil. Yield: 203 mg (80%). ^{1}H NMR (300 MHz, C_6D_6) δ 1.12−1.20 (2H, m), 1.43−1.59 (2H, m), 1.78−1.86 (1H, m), 1.92−1.99 (2H, m), 2.02−2.10 (1H, m), 3.53 (1H, dt, J = 12.1, 5.4 Hz), 3.76−3.89 (2H, m). ^{13}C NMR (C_6D_6) δ 30.8, 31.4, 32.0, 35.2, 39.8, 66.5, 174.7. EIMS: *m*/*z* (relative intensity) 255 ($M^+ + 1$, 27), 237 (4), 209 (1), 127 (100), 109 (8), 85 (33), 81 (13). HRMS calcd for $C_7H_{11}IO_2$: 253.9804. Found: 253.9833.

5-(3-Iodopropyl)dihydro-2(3*H*)-furanone (3a). Typical Procedure. Bis(tributyltin) (0.050 mL, 0.1 mmol) was added to a benzene (33 mL) solution of 4-pentenyl iodoacetate (**1a**, 254 mg, 1.0 mmol) in a dry, 50 mL three-necked flask under nitrogen at room temperature. The reaction mixture was heated to reflux and irradiated with the aid of a 300 W sunlamp. The reaction was monitored by TLC. After the substrate **1a** disappeared (3 h), the sunlamp was turned off and the reaction mixture was kept at reflux for an additional 7 h. The resulting mixture was cooled and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel with hexane−ethyl acetate (1:1, v:v) as the eluent to obtain pure product **3a** as a colorless oil. Yield: 204 mg (80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.77−1.84 (2H, m), 1.86−1.97 (2H, m), 1.98−2.08 (1H, m), 2.32−2.41 (1H, m), 2.55 (2H, dd, J = 7.1, 9.5 Hz), 3.19−3.29 (2H, m), 4.48−4.55 (1H, m). ^{13}C NMR ($CDCl_3$) δ 5.9, 27.9, 28.6, 29.2, 36.3, 79.6, 176.7. EIMS: *m*/*z* (relative intensity) 255 ($M^+ + 1$, 59), 127 (100), 109 (10), 85 (32), 55 (8), 41 (11). Anal. Calcd for $C_7H_{11}IO_2$: C, 33.09; H, 4.36. Found: C, 33.30; H, 4.26. The structure was confirmed by its 2D COSY and HETCOR spectra.

3-(Tetrahydro-2-furyl)propanoic Acid (6a). Typical Procedure. Boron trifluoride etherate (0.37 mL, 3 mmol) was added to a benzene (33 mL) solution of 4-pentenyl iodoacetate (**1a**, 254 mg, 1.0 mmol) in a dry, 50 mL three-necked flask under nitrogen at room temperature. Bis(tributyltin) (0.050 mL, 0.1 mmol) was added and the mixture was irradiated at 20 °C for 6 h with the aid of a 300 W sunlamp. A saturated aqueous $NaHCO_3$ solution (12 mL) was added and the resulting mixture was stirred vigorously for 10 min. The mixture was evaporated under reduced pressure to allow most of the solvent benzene to be removed. Acetone (30 mL) was added to the residue and the mixture was stirred in dark at room temperature overnight. The resulting solution was concentrated in vacuo, washed with CH_2Cl_2 (2 × 10 mL), and then acidified with aqueous HCl (1 N). The solution was extracted with ether (6 × 30 mL) and the combined organic phase was dried over anhydrous $MgSO_4$. After removal of the solvent, the crude product was purified by flash chromatography on silica gel with hexane−acetone (2:1, v:v) as the eluent to give pure **6a**[13,14a] as a colorless oil. Yield: 104 mg (72%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41−1.53 (1H, m), 1.77−2.04 (5H, m), 2.35−2.53 (2H, m), 3.68−3.76 (1H, m), 3.80−3.92 (2H, m), 9.89 (1H, br). ^{13}C NMR ($CDCl_3$) δ 25.7, 30.4, 31.0, 31.2, 67.8, 78.3, 178.9. EIMS: *m*/*z* (relative intensity) 145 (M^++1, 0.9), 144 (M^+, 0.4), 127 (4), 116 (10), 98 (7), 85 (16), 71 (100), 55 (11), 43 (53). HRMS calcd for $C_7H_{10}O_2$ ($M - H_2O$): 126.0681. Found: 126.0634.

Acknowledgment. This project is supported by the Hundreds of Talent program of the Chinese Academy of Sciences, by the National Natural Science Foundation of China (No. 20002006 and No. 29832050), and by the QiMingXing Program of the Shanghai Municipal Scientific Committee. We also thank Dr. Xicheng Dong and Ms. Weiqi Zhang for their help in theoretical calculations.

Supporting Information Available: General procedure for the preparations of **1a**−**k**. Characterization data for compounds **1a**−**k**, **2b**−**k**, **3b**−**f**, **4**, and **6b**,**c**,**d**,**g**,**j**. X-ray crystal structural data for **2g** and the (5α,6aα,10aβ) isomer of **2k**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0109568

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