JOC*Note*

O-Attack versus N-Attack: Electrophilic Halocyclization of Unsaturated Amides with Vinylic Halogen Substitution

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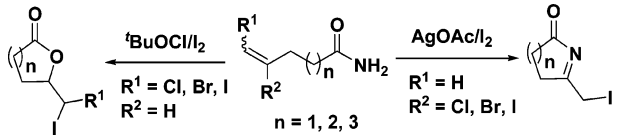
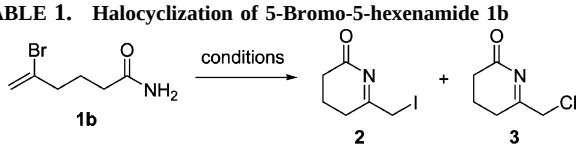


Electrophilic iodocyclization of unsaturated amides with an internal vinylic halogen (Cl, Br, or I) substitution afforded exclusively the corresponding cyclic iminoketones via iodolactamization. On the other hand, amides having a terminal vinylic halogen substituent underwent iodolactonization only. Theoretical calculations revealed that the iodocyclization proceeds via the intramolecular iodonium ion transfer from the amide nitrogen to the C═C double bond.

Electrophilic halocyclizations of unsaturated compounds have been well-established to be an indispensable tool in the synthesis of heterocyclic compounds and continue to be actively pursued.[1,2] Among them, the most widely studied type of reaction is iodolactonization, which has found extensive application in natural product synthesis.[3] Unsaturated amides are among the typical substrates for iodolactonization. This is because the halocyclization of amides usually produces lactones rather than lactams, a well-known fact that can be well interpreted based on HSAB theory.[1,4] To achieve lactamization, methods such as *N*,*O*-bissilylation,[5] *N*-tosyl or *N*-alkyloxycarbonyl substitution,[6] and use of a strong base[7] have been developed.

TABLE 1. Halocyclization of 5-Bromo-5-hexenamide 1b



entry	conditions	yield (%)[c] 2	3
1[a]	$NaHCO_3$ (3 equiv), I_2 (3 equiv), rt, 16 h	trace	
2[b]	^{t}BuOCl (4 equiv), I_2 (2 equiv), rt, 16 h	8	62
3[b]	^{t}BuOCl (3 equiv), I_2 (2 equiv), rt, 16 h	37	34
4[b]	^{t}BuOCl (2 equiv), I_2 (4 equiv), rt, 16 h	61	9
5[b]	AgOAc (2 equiv), I_2 (3 equiv), rt, 4 h	94	0

[a] Solvent: H_2O/ether (1:2, v:v). [b] Solvent: CH_2Cl_2. [c] Isolated yield based on **1b**.

During our investigation on the cyclization of unsaturated amidyl radicals,[8] we found that efficient and regiospecific amidyl radical cyclizations could be accomplished by the photostimulated reactions of unsaturated amides with $Pb(OAc)_4/I_2$ if they bear a vinylic halogen substituent.[8d] To confirm the above reactions to be radical processes, we also carried out the ionic iodocyclization of the same substrates. In most cases, no reaction was observed under typical iodocyclization conditions (with $NaHCO_3/I_2$ at ambient temperature), indicating the retardation of iodocyclization by vinylic halogen substitution, a phenomenon also observed in our later study on the cyclization of unsaturated sulfonamides.[9] However, during the optimization of reaction conditions for amidyl radical cyclization, we found the photostimulated reaction of 5-chloro-5-hexenamide (**1a**) with ^{t}BuOCl/I_2 at rt afforded 6-chloro-6-iodoazepan-2-one (52%) as the 7-endo amidyl radical cyclization product along with the formation of 6-iodomethyl-2,3,4,5-tetrahydropyridine-2-one (**2**) in 37% yield, the latter being the ionic iodocyclization product.[8d] This observation was surprising in that iodolactamization (via N-attack) rather than iodolactonization (via O-attack) occurred in the ionic cyclization. As a comparison, amides without vinylic halogen substitution such as 5-hexenamide and 5-methyl-5-

(1) For reviews, see: (a) Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321. (b) Harding, K. E.; Tiner, T. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 4, p 363. (c) Robin, S.; Rousseau, G. *Tetrahedron* **1998**, *54*, 13681. (d) Robin, S.; Rousseau, G. *Eur. J. Org. Chem.* **2002**, 3099.

(2) For recent selected examples, see: (a) Minakata, S.; Morino, Y.; Oderatoshi, Y.; Komatsu, M. *Org. Lett.* **2006**, *8*, 3335. (b) Blot, V.; Reboul, V.; Metzner, P. *J. Org. Chem.* **2004**, *69*, 1196. (c) Wang, M.; Gao, L. X.; Mai, W. P.; Xia, A. X.; Wang, F.; Zhang, S. B. *J. Org. Chem.* **2004**, *69*, 2874. (d) Mellegaard, S. R.; Tunge, J. A. *J. Org. Chem.* **2004**, *69*, 8979. (e) Peng, A. Y.; Ding, Y. X. *Org. Lett.* **2004**, *6*, 1119. (f) Galeazzi, R.; Martelli, G.; Mobblili, G.; Orena, M.; Rinaldi, S. *Org. Lett.* **2004**, *6*, 2571. (g) Kang, S. H.; Lee, S. B.; Park, C. M. *J. Am. Chem. Soc.* **2003**, *125*, 15748. (h) Hessian, K. O.; Flynn, B. L. *Org. Lett.* **2003**, *5*, 4377.

(3) For recent selected examples, see: (a) Murata, Y.; Kamino, T.; Aoki, T.; Hosokawa, S.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3175. (b) Bodkin, J. A.; Humphries, E. J.; McLeod, M. D. *Tetrahedron Lett.* **2003**, *44*, 2869. (c) Jung, M.; Ham, J.; Song, J. *Org. Lett.* **2002**, *4*, 2763.

(4) For examples, see: (a) Fleet, G. W. J.; Spensley, C. R. C. *Tetrahedron Lett.* **1982**, *23*, 109. (b) Takano, S.; Sato, S.; Goto, E.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1986**, 156. (c) Cairns, P. M.; Howes, C.; Jenkins, P. R. *J. Chem. Soc., Perkin Trans. 1* **1990**, 627. (d) Lee, C.-W.; Gil, J. M.; Oh, D. Y. *Heterocycles* **1997**, *45*, 943. (e) Kündig, E. P.; Cannas, R.; Laxmisha, M.; Liu, R.; Tchertchian, S. *J. Am. Chem. Soc.* **2003**, *125*, 5642. (f) Kündig, E. P.; Laxmisha, M. S.; Cannas, R.; Tchertchian, S.; Liu, R. *Helv. Chim. Acta* **2005**, *88*, 1063.

(5) (a) Knapp, S.; Rodriques, K. E.; Levorse, A. T.; Ornaf, R. M. *Tetrahedron Lett.* **1985**, *26*, 1803. (b) Knapp, S.; Levorse, A. T. *J. Org. Chem.* **1988**, *53*, 4006. (c) Knapp, S.; Gibson, F. S. *Org. Synth.* **1992**, *70*, 101. (d) Knapp, S. In *Advances in heterocyclic Natural Product Synthesis*; JAI Press: Greenwich, CT, 1996; Vol. 3, p 57.

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(7) (a) Boeckman, R. K., Jr.; Connell, B. T. *J. Am. Chem. Soc.* **1995**, *117*, 12368. (b) Kitagawa, O.; Fujita, M.; Li, H.; Taguchi, T. *Tetrahedron Lett.* **1997**, *38*, 615. (c) Fujita, M.; Kitagawa, O.; Suzuki, T.; Taguchi, T. *J. Org. Chem.* **1997**, *62*, 7330.

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(9) Lu, H.; Chen, Q.; Li, C. *J. Org. Chem.* **2007**, *72*, 2564.

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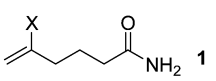
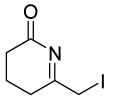
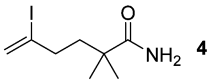
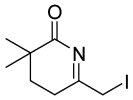
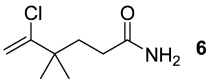
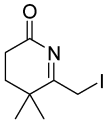
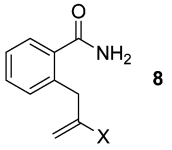
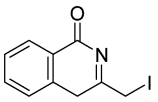
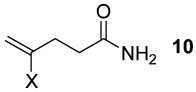
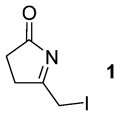
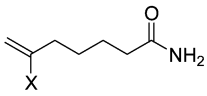
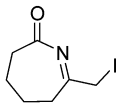
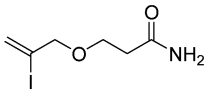
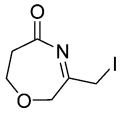
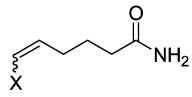
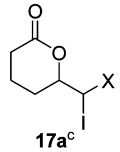
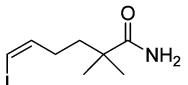
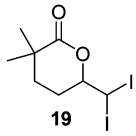
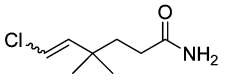
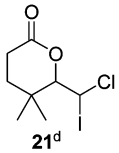
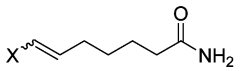
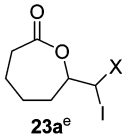
TABLE 2. Iodocyclization of Unsaturated Amides with AgOAc/I_2

entry	substrate	product	yield (%)[a]
	 **1**	 **2**	
1	X = Cl (**a**)		98
2	Br (**b**)		94
3	I (**c**)		98
4	 **4**	 **5**	68
5	 **6**	 **7**	56
	 **8**	 **9**	
6	X = Cl (**a**)		99
7	I (**b**)		99
	 **10**	 **11**	
8	X = Cl (**a**)		99
9	I (**b**)		99
	 **12**	 **13**	
10[b]	X = Cl (**a**)		64
11[b]	Br (**b**)		79
12[b]	I (**c**)		75
13[b]	 **14**	 **15**	52

[a] Isolated yields based on the starting amides. [b] $^tBuOCl/I_2$ was used instead of AgOAc/I_2.

TABLE 3. Iodolactonization of Unsaturated Amides with $^tBuOCl/I_2$

entry	substrate	product	yield (%)[a]
			
1	**16a**[b] (X = Cl)	**17a**[c]	60
2	(*Z*)-**16b** (X = I)	**17b**	61
3	 **18**	 **19**	68
4	 **20**[b]	 **21**[d]	84
			
5	**22a**[b] (X = Cl)	**23a**[e]	80
6	**22b**[b] (X = Br)	**23b**[c]	63
7	**22c**[f] (X = I)	**23c**	80

[a] Isolated yields based on the starting amides. [b] *Z*:*E* = 1:3. [c] Two stereoisomers in ~2.3:1 ratio. [d] Two stereoisomers in ~5:1 ratio. [e] Two stereoisomers in ~13:1 ratio. [f] *Z*:*E* = 9:1.

hexenamide underwent iodolactonization to produce δ-lactones exclusively.[8d] Our interest in electrophilic halocyclization[10] pushed us to examine the ionic reactions in detail. We report here that, with internal vinylic halogen substitution, the unsaturated amides underwent exclusive iodolactamization leading to the efficient synthesis of cyclic iminoketones. On the other hand, with terminal halogen substitution, only iodolactonization was observed. Theoretical calculations in combination with the experimental results offer a detailed understanding of the mechanism of these halocyclizations.

We first used 5-bromo-5-hexenamide (**1b**) as the model substrate to optimize the experimental conditions for iodocyclization (Table 1). To avoid the competing amidyl radical cyclization, the reactions were always kept in the dark. As can be seen in Table 1, the combination of *tert*-butyl hypochlorite and iodine allowed the halocyclization to proceed smoothly. However, the iodocyclization (product **2**) was always accompanied by the chlorocyclization (product **3**) and the latter even predominated when excess *tert*-butyl hypochlorite was employed (entries 2−4, Table 1). To our delight, with the use of AgOAc/I_2, a clean reaction was observed in the dark at rt leading to the formation of **2** in almost quantitative yield (entry 5, Table 1).

We then prepared a number of substrates having an internal vinylic halogen substituent and subjected them to the treatment with AgOAc/I_2 under the optimized conditions (entry 5, Table 1). The results are summarized in Table 2. The Cl, Br, and I substitution (**1a**−**c**) all gave excellent yields of the cyclic iminoketone **2** via a 6-exo cyclization mode. With *gem*-dimethyl substitution, amides **4** and **6** afforded the cyclic iminoketones in good yields while no products derived from O-attack could be detected.[11] The benzo-fused amides **8a** and **8b** led to the quantitative generation of iminoketone **9**. The N-attack was also observed in the reactions of 4-halo-4-pentenamides **10a** and **10b** in which five-membered iminoketone **11** was achieved quantitatively. Furthermore, the reactions of 6-halo-6-heptenamides **12** and **14** also furnished the N-attack products in good yields via a 7-exo ring closure along with the rest of the starting materials recovered. These results demonstrated the generality of N-attack in halocyclization of amides bearing an internal vinylic halogen substituent.

As a comparison, the electrophilic iodocyclization of the corresponding amides with terminal vinylic halogen substitution

(10) (a) Shen, M.; Li, C. *J. Org. Chem.* **2004**, *69*, 7906. (b) Tang, Y.; Li, C. *Tetrahedron Lett.* **2006**, *47*, 3823.

(11) The byproducts (~25% yield) isolated from the reactions of **4** and **6** were the 7-membered lactams via radical processes probably because the dimethyl-substitution significantly accelerates the competing radical cyclization in a 7-endo mode, allowing it to proceed even in the dark. See ref 7d.

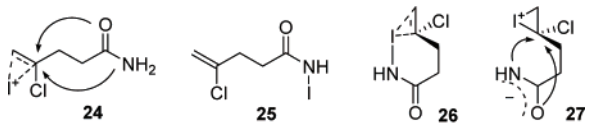
was also studied. The above optimized conditions with use of $AgOAc/I_2$ turned out to be less satisfactory than the use of ^{t}-$BuOCl/I_2$ (entry 4, Table 1). We then carried out the reactions with ^{t}$BuOCl/I_2$ and the results are summarized in Table 3. In all cases, only the corresponding iodolactonization products were obtained while no products derived from N-attack could be detected.

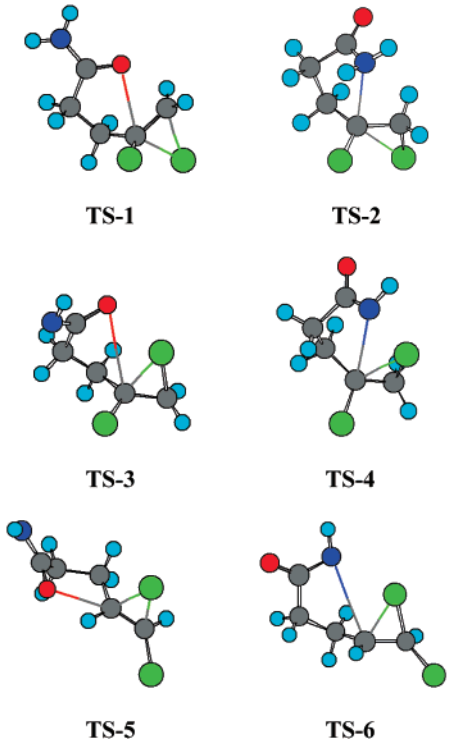
The above results provided a convenient and efficient method for the iodocyclization of unsaturated amides under acidic conditions rather the usual basic conditions. More importantly, the results clearly revealed the unique effect of halogen atom substitution in directing the iodocyclization to proceed via exclusive N-attack or O-attack.

The above different behaviors of halocyclization of amides (N-attack versus O-attack) are not easily understood based on HSAB theory. To gain more insight into the halogen effect on the reactivity of unsaturated amides, we turned to density functional calculations for help, which have become an increasingly important tool in modeling organic reactions and mechanisms.[12,13] The transition state structures and energies were fully optimized at the B3LYP/6-31G* level. Once convergence is reached, the harmonic vibration frequencies were calculated at this point to confirm the geometry obtained to be a true first-order saddle point. 4-Chloro-4-pentenamide (**10a**) was chosen as the model substrate. Cl^+ was used as the substitute for I^+ in calculation; this should be reasonable because chlorocyclization showed similar behavior as indicated in Table 1.

One possible mechanism is, of course, the iodination of the C═C double bond followed by nucleophilic attack of the amide moiety, as depicted in model **24**. The transition states (TS) for O-attack and N-attack are computed as **TS-1** and **TS-2**, respectively. However, **TS-1** is 5.9 kcal/mol lower in energy than **TS-2**, indicating the preference of O-attack that is inconsistent with the experimental results. The halocyclization of the unsubstituted 4-pentenamide was also computed based on this model, and the TS for O-attack is 13.7 kcal/mol lower than the TS for N-attack (see the Supporting Information for details).

Another plausible mechanism is the oxidative generation of the N−I bond followed by its heterocleavage. The subsequent intramolecular iodonium ion transfer to the C═C double bond generates the amide anion, which in turn adds to the iodinated double bond. Such a process is exemplified by structures **25**, **26**, and **27**. On the basis of this mechanism, the TS's for O-attack and N-attack are computed to be **TS-3** and **TS-4**, respectively. These two structures are different from the previous ones (**TS-1** and **TS-2**) in that the amide moiety and the iodonium ion are at the same side of the olefin plane in **TS-3** and **TS-4** but at the opposite sides in **TS-1** and **TS-2**. We were delighted to find that the calculated energy of **TS-3** is 2.8 kcal/mol higher than that of **TS-4**, indicating the predominance of N-attack, consistent with the experimental observations in Table 2.





The reaction of 5-bromo-4-pentenamide was then also computed based on the iodonium ion transfer mechanism and the transition state structures are shown as **TS-5** and **TS-6**. In this case the computed TS for O-attack (**TS-5**) is 4.2 kcal/mol lower in energy than the TS for N-attack (**TS-6**), clearly indicating the predominance of O-attack, also consistent with the experimental results in Table 3. As a comparison, the cyclization of the parent 4-pentenamide was also computed based on this model and the TS for O-attack is only 1.8 kcal/mol lower in energy that the TS for N-attack (also see the Supporting Information).

By comparison of the calculated results with the experimental data, we conclude that the above halocyclization of amides is more likely to proceed via the iodonium ion transfer mechanism. The unlikelihood of the mechanism via the intermediacy of **24** can also be inferred from the fact that vinylic halogen substituted amides are reluctant to cyclize under typical iodocyclization conditions (e.g., $NaHCO_3/I_2$). On the other hand, the oxidative generation of the N−I bond by reaction of amides with ^{t}$BuOCl/I_2$ or $AgOAc/I_2$[14] is well documented as it serves as an important method for the generation of amidyl radicals (via homocleavage of the N−I bond upon UV photolysis). Furthermore, the iodonium ion transfer process was also observed in the iodocyclization of unsaturated sulfonamides as reported by Minakata et al.[2a] The question is why N-attack is preferred in the halocyclization of amides with an internal vinylic halogen substituent. One possible explanation is the lone pair−lone pair electron repulsion effect. Once the nucleophile (N or O)

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(13) For examples of DFT calculations on the reactions involving reactive halogen species, see: (a) Bakalbassis, E. G.; Spyroudis, S.; Tsiotra, E. *J. Org. Chem.* **2006**, *71*, 7060. (b) Abbasoglu, R. *J. Mol. Model.* **2006**, *12*, 991. (c) Abbasoglu, R.; Yilmaz, S. S. *J. Mol. Model.* **2006**, *12*, 290. (d) Lenoir, D.; Chiappe, C. *Chem.−Eur. J.* **2003**, *9*, 1036. (e) Chiappe, C.; Rubertis, A. D.; Detert, H.; Lenoir, D.; Wannere, C. S.; Schleyer, P. R. *Chem.−Eur. J.* **2002**, *8*, 967.

(14) Beebe, T. R.; Barnes, B. A.; Bender, K. A.; Halbert, A. D.; Miller, R. D.; Ramsay, M. L.; Ridenour, M. W. *J. Org. Chem.* **1975**, *40*, 1992.

approaches the internal carbon atom of the iodinated C=C double bond with internal halogen substitution, it will face the lone pair repulsion with the halogen atom. Because the lone pair repulsion with an oxygen atom is much stronger than the repulsion with a nitrogen atom, the O-attack becomes less favorable in *both* reaction pathways (**24** and **27**). As a result, **TS-1** is only 5.9 kcal/mol lower in energy than **TS-2** compared to the 13.7 kcal/mol energy difference in the case of 4-pentenamide based on the model **24**, while **TS-4** becomes more stable by 2.8 kcal/mol in energy than **TS-3** compared to the opposite (−1.8 kcal/mol) in the case of 4-pentenamide based on the model **27**. On the other hand, for iodocyclization of amides with terminal vinylic halogen substitution, the halogen atom is relatively far away from the reaction center (i.e., the internal vinylic carbon). Its interaction with the amide nitrogen or oxygen is negligible and thus O-attack is preferred as usual. The similar discussion based on lone pair electron repulsion was found to successfully explain the regioselectivities of amidyl radical cyclization with the same amides as the substrates.[8d] In the meantime, it should be noted that the retardation of iodination of vinylic halides might also be interpreted in terms of the lone pair electron repulsion between the vinylic halogen atom and the iodine species.

In summary, the chemistry detailed above has clearly demonstrated the unique effect of internal vinylic halogen substitution in directing the iodocyclization of unsaturated amides to proceed via lactamization rather than the usual lactonization, leading to the exclusive and efficient synthesis of 5-, 6-, and even 7-membered cyclic iminoketones. Theoretical analyses have uncovered the intramolecular iodonium ion transfer mechanism in the above halocyclization. The lone pair electron repulsion as the possible origin in controlling the selectivity of halocyclization should encourage further study on the chemistry of vinyl halides.

Experimental Section

Typical Procedure for Iodocyclization with AgOAc/I_2. Silver acetate (67 mg, 0.40 mmol) was added into the CH_2Cl_2 (7 mL) solution of I_2 (203 mg, 0.80 mmol) and the mixture was stirred at rt for 10 min. *tert*-Butanol (0.10 mL, 1.0 mmol) was added and the mixture was stirred at rt for 5 min. 5-Bromo-5-hexenamide (**1b**, 39 mg, 0.20 mmol) was added and the mixture was stirred in the dark at rt for 4 h. Saturated $Na_2S_2O_3$ solution (5 mL) was then added to quench the reaction. The two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was dried over anhydrous Na_2SO_4. After removal of the solvent in vacuo, the crude product was purified by column chromatography on silica gel with hexane−acetone (2:1, v:v) as the eluent to give the pure product **2** as a yellowish oil. Yield 45 mg (94%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.94−2.04 (2H, m), 2.45 (2H, t, J = 6.9 Hz), 2.95 (2H, t, J = 6.8 Hz), 3.84 (2H, d, J = 0.9 Hz). ^{13}C NMR ($CDCl_3$) δ 5.6, 16.1, 19.6, 36.8, 119.0, 201.4. EIMS m/z (rel intensity) 237 (M^+, 12), 209 (4), 195 (3), 169 (17), 141 (11), 110 (16), 96 (100), 68 (48). Anal. Calcd for C_6H_8INO: C, 30.40; H, 3.40; N, 5.91. Found: C, 30.42; H, 3.52; N, 5.83.

Typical Procedure for Iodolactonization with ^{t}BuOCl/I_2. Iodine (0.30 g, 1.2 mmol) was added into the CH_2Cl_2 (10 mL) solution of *tert*-butyl hypochlorite (68 μL, 0.60 mmol) and the mixture was stirred at rt for 30 min. (*Z*)-6-Iodo-5-hexenamide (**16b**, 72 mg, 0.30 mmol) was added and the solution was stirred in the dark at rt for 16 h. Saturated $Na_2S_2O_3$ solution (5 mL) was then added to quench the reaction. The same workup procedure outlined in the synthesis of **2** was followed to give the pure lactone **17b** as a yellowish oil. Yield 67 mg (61%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.62−1.71 (1H, m), 1.83−1.96 (2H, m), 2.36−2.48 (2H, m), 2.53−2.62 (1H, m), 3.85(1H, dt, J = 10.5, 3.6 Hz), 5.21(1H, d, J = 3.6 Hz). ^{13}C NMR ($CDCl_3$) δ −23.4, 17.8, 27.5, 29.3, 82.7, 176.8. EIMS m/z (rel intensity) 366 (M^+, 21), 239 (32), 211 (100), 169 (37), 141 (12), 127 (9), 99 (16), 55 (31). HRMS calcd for $C_6H_8I_2O_2$ 365.8614, found 365.8617.

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Supporting Information Available: Characterizations of **1**−**23** and the computational results on halocyclization. This material is available free of charge via the Internet at http://pubs.acs.org.

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