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Stereoselective 6-*Exo* Cyclization of Amidyl Radicals. An Experimental and Theoretical Study

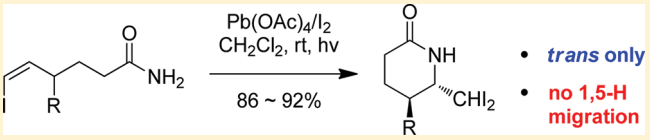
Shunjun Zhuang,[†] Kun Liu,*[,‡] and Chaozhong Li*[,†]

[†]Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, P. R. China

[‡]College of Chemistry, Tianjin Key Laboratory of Structure and Performance for Functional Molecule, Tianjin Normal University, Tianjin 300387, P. R. China

Supporting Information

ABSTRACT: Unsaturated primary amidyl radicals of *Z*-configurations underwent efficient chemo- and stereoselective 6-*exo* cyclization reactions via chair-conformational transition states, leading to the predominant formations of 3,6-*trans*, 4,6-*cis*, or 5,6-*trans* substituted δ-lactams.



Nitrogen-centered radicals are involved in a variety of useful organic transformations.[1] Amidyl radicals, in particular, have gained increasing popularity in the past decade.[1] The highly reactive and electrophilic nature[2] allows amidyl radicals to add to electron-rich C=C double bonds leading to the direct construction of C−N bonds.[3−10] More importantly, the intramolecular addition provides a unique entry to various substituted N-heterocycles,[4−10] thus offering a great potential in the synthesis of natural products such as alkaloids.[10] On the other hand, the high reactivity of amidyl radicals also imposes a significant challenge on the control of chemo-, regio-, and stereoselectivity of cyclization. While the efficiency and regioselectivity of cyclization of various modes have been well investigated, the stereoselectivity of cyclization is far less explored for this type of radicals. In fact, only 5-*exo* cyclization was studied by Clark et al., and poor to moderate stereoselectivities were observed.[11] It is certainly of interest to see if high stereoselectivity could be achieved in other modes of cyclization. However, the amidyl radical cyclization other than 5-membered ring closure suffers from the competing 1,5- or 1,6-hydrogen migration processes[12,13] (Hofmann−Löffler−Freytag reactions) and sometimes from the poor regioselectivity, which make the development of stereoselective reactions difficult. Herein, we report that efficient and highly stereoselective 6-*exo* cyclization reactions can be successfully implemented for amidyl radicals. Theoretical analysis in combination with experimental results provides a clear understanding on the control of stereoselectivity.

The cyclization of amidyl radicals in a 6-*exo* mode is rather uncommon. Kinetic studies by Newcomb et al. indicated that 6-*exo* amidyl radical cyclization is about 2 orders of magnitude slower than the corresponding 5-*exo* cyclization.[2c] Lessard and co-workers reported the Bu_3SnH-mediated 6-*exo* cyclization of *N*-(phenylthio)cyclohept-4-enecarboxamide.[7] During our recent investigation on the behaviors of amidyl radical reactions,[9] we found that the N-substituents play a crucial role in the reactivity of amidyl radicals.[9c] While *N*-*tert*-butyl-substituted hex-5-enamidyl radical underwent 1,5-hydrogen migration, primary hex-5-enamidyl radicals underwent cyclization exclusively.[9c] Furthermore, with vinylic halogen substitution, the regioselectivity of 5-hexenamidyl radical cyclization could be well controlled, leading to the regiospecific 6-*exo* and 7-*endo* cyclization.[9d] The halogen effect also allows the direct use of unsaturated amides as the substrates by inhibiting the competing ionic processes.[14] This remarkable halogen effect was then rationalized based on lone pair electron repulsion between the halogen atom and the radical center and was successfully extended to the control of regioselectivity in sulfonamidyl and primary aminyl radical cyclizations.[15] As an extension, we set out to explore the control of stereoselectivity of 6-*exo* cyclization.

Both (*E*)- and (*Z*)-6-iodo-2-methylhex-5-enamide (**1a**) were first used as the model substrates. The (*Z*)-isomer was readily prepared by the iodination of the 2-methylhex-5-ynamide with I_2 followed by reduction with $TsNHNH_2$.[16] The (*E*)-alkenyl iodide was synthesized via the hydroiodination of an alkyne with Cp_2ZrCl_2/DIBALH (diisobutylaluminum hydride)/I_2.[17] (*E*)-**1a** was then subjected to treatment with $Pb(OAc)_4$ and I_2 in CH_2Cl_2 (0.03 M) at room temperature (rt) under UV irradiation, a typical condition for the generation of amidyl radicals.[9d] The 6-*exo* cyclization product **2a** was thus obtained in 83% yield as the 50:50 mixture of two stereoisomers (eq 1). On the other hand, the reaction of the (*Z*)-isomer under the same conditions gave **2a** with the *trans*/*cis* ratio of 75:25. Switching $Pb(OAc)_4/I_2$ to other conditions such as diacetoxyiodobenzene (DIB)/I_2 resulted in lower yields of cyclized products. However, the *trans*/*cis* ratios remained unchanged. The C=C bond geometry

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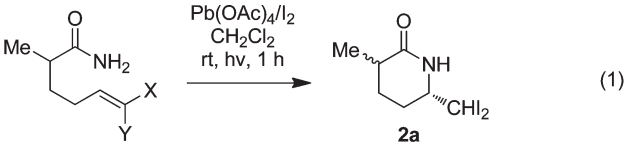
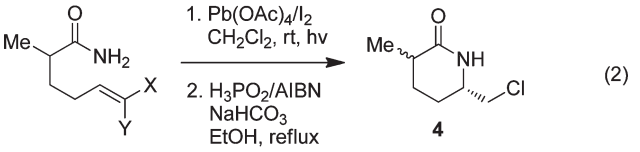
thus has a significant impact on the stereoselectivity but no effect on the efficiency and regioselectivity.[18]



(*E*)-**1a** (X = I, Y = H) 83% (*trans*/*cis* = 50/50)

(*Z*)-**1a** (X = H, Y = I) 83% (*trans*/*cis* = 75/25)



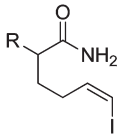
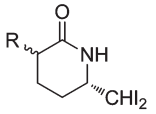
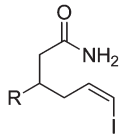
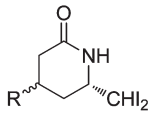
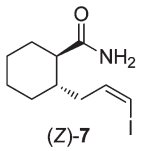
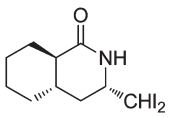
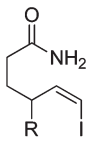
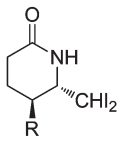
(*E*)-**3** (X = Cl, Y = H) 92% (*trans*/*cis* = 50/50)

To understand the effect of other halogen atoms, the vinylic chloro-substituted amides (*E*)-**3** and (*Z*)-**3** were also prepared, and their cyclization reactions were carried out under the above conditions. For ease of characterization, the cyclized products were then directly reduced with H_3PO_2/AIBN[19] to give the chlorides **4** (eq 2). Again, the *trans*/*cis* ratio of **4** was 50:50 in the reaction of (*E*)-**3** but 75:25 in the reaction of (*Z*)-**3**, indicating that the chlorine atom had the same effect as the iodine atom in controlling the stereoselectivity of cyclization.

On the basis of the above results, a number of (*Z*)-amides were then screened, and the results are summarized in Table 1. The reactions were clean in all cases, and the cyclized products were obtained in high yields. The relative configurations of δ-lactams were determined by the relevant proton coupling constants or by the 2D NOESY experiments of representative examples (see the Supporting Information). Interestingly, the α-carbonyl substituents R showed a remarkable influence on the product stereoselectivity. The ratio of *trans* to *cis* isomers increases when the size of R increases (entries 1−4, Table 1). A higher stereoselectivity but in favor of the *cis* isomers was observed when the R group was switched from the α-position to the β-position (entries 5−7, Table 1). The minor isomers could be observed from the crude ^{1}H NMR but could not be isolated in a pure form. When the *trans*-substituted cyclohexanecarboxamide (*Z*)-**7** was employed as the substrate, the bicyclic lactam **8** was secured in 81% yield as the only stereoisomer. Furthermore, with the amides (*Z*)-**9** bearing a substituent at the allylic position, the corresponding *trans*-isomers **10** were obtained exclusively in excellent yields (entries 9−12, Table 1). Surprisingly, although the substitution at the allylic position in (*Z*)-**9** significantly encourages the 1,5-H migration by lowering the allylic C−H bond dissociation energies (BDEs), no products derived from 1,5-H migration could be detected even in the case of (*Z*)-**9d** (R = Ph).

The above results have clearly shown that the 6-*exo* cyclization of amidyl radicals can be efficient and highly stereoselective. To gain further insight into the behaviors of amidyl radicals in 6-*exo* cyclization, we turned to theoretical calculations for help. Ab initio calculations were carried out with the Gaussian09 suite of program.[20] The density functional theory method was used, which has been demonstrated to be a fairly accurate tool for dealing with radical reactions.[21] All equilibrium geometry and

Table 1. Stereoselectivity of 6-*Exo* Cyclization

entry[a]	substrate		product	yield (%)[b]	*trans* : *cis*[c]
					
1	(*Z*)-**1a**	(R = Me)	**2a**	83	75 : 25
2	(*Z*)-**1b**	(R = Et)	**2b**	86	80 : 20
3	(*Z*)-**1c**	(R = *i*-Pr)	**2c**	82	~89 : 11
4	(*Z*)-**1d**	(R = Ph)	**2d**	86	~90 : 10
					
5	(*Z*)-**5a**	(R = Me)	**6a**	71	~11 : 89
6	(*Z*)-**5b**	(R = Et)	**6b**	72	~10 : 90
7	(*Z*)-**5c**	(R = *i*-Pr)	**6c**	71	~ 8 : 92
8	 (*Z*)-**7**		 **8**	81	–
					
9	(*Z*)-**9a**	(R = Me)	**10a**	92	> 95 : 5
10	(*Z*)-**9b**	(R = Et)	**10b**	93	> 95 : 5
11	(*Z*)-**9c**	(R = *i*-Pr)	**10c**	93	> 95 : 5
12	(*Z*)-**9d**	(R = Ph)	**10d**	86	> 95 : 5

[a] Reaction conditions: alkenyl iodide (0.2 mmol), $Pb(OAc)_4$ (0.7 mmol), I_2 (0.5 mmol), CH_2Cl_2 (6.6 mL), *rt*, *hν*, 1 h. [b] Isolated yield based on the starting alkenyl iodide. [c] Determined by ^{1}H NMR (400 MHz).

transition structures were fully optimized at the UB3LYP/6-31G** level and the IEFPCM (the Polarizable Continuum Model using the Integral Equation Formalism variant) model in dichloromethane. The default settings for IEFPCM in Gaussian09 were used. Once convergence was reached, the harmonic vibration frequencies were calculated at this point to confirm the geometry obtained to be a true minimum or first-order saddle point. The zero-point vibrational energy and thermal corrections were also obtained at the UB3LYP/6-31G** level and the IEFPCM model, from which the activation free energies can be calculated. Radicals **R-3E** and **R-3Z** derived from substrates (*E*)-**3** and (*Z*)-**3** were chosen as the models for the understanding of the effect of C=C bond configuration on the stereoselectivity of cyclization. Radical **R-9Z** derived from substrate **9d** (with the iodine atom replaced by chlorine atom) was also selected for computation in order to understand the chemoselectivity between 1,5-H migration and cyclization. The calculated activation free energies are summarized in Table 2, and the computed transition-state structures are listed in Figure 1 (also see the Supporting Information).

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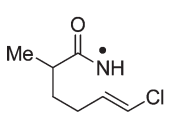
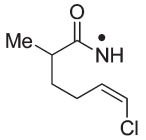
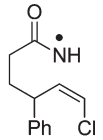
Table 2. Calculated (UB3LYP/6-31G) Activation Free Energies of 6-*Exo* Cyclization and 1,5-H Migration**



R-3E



R-3Z



R-9Z

		$\Delta G^{\ddagger}$ (kcal/mol)		
entry	radical	6-*exo* cyclization	1,5-H migration	calcd *trans*/*cis* ratio
1	**R-3E**	3.2 (3,6-*trans*), 3.3 (3,6-*cis*)	not calculated	54:46
2	**R-3Z**	3.2 (3,6-*trans*), 4.2 (3,6-*cis*)	not calculated	84:16
3	**R-9Z**	5.6 (5,6-*trans*), 8.4 (5,6-*cis*)	7.1	99:1

For the cyclization of radical **R-3E**, the two transition states, **TS-3E-trans** and **TS-3E-cis**, both in chairlike conformations, are of almost the same energy (entry 1, Table 2), in excellent agreement with the observed 50:50 ratio of stereoisomers in the cyclization of (*E*)-**3**. The distance between the internal vinylic carbon and the nitrogen is longer in **TS-3E-cis** (2.73 Å) than in **TS-3E-trans** (2.35 Å), which diminishes the steric unfavorableness of the pseudoaxial chloromethylene moiety in **TS-3E-cis**.

For the cyclization of radical **R-3Z**, the two computed transition states, **TS-3Z-trans** and **TS-3Z-cis**, are also in chairlike conformations (Figure 1). The *Z*-configuration of C=C bond now results in the steric hindrance between the chlorine atom and the axial β-carbonyl hydrogen in **TS-3Z-cis**, their distance being estimated to be 2.89 Å. As a result, **TS-3Z-cis** is 1.0 kcal/mol higher in energy than **TS-3Z-trans**, which corresponds to the *trans*/*cis* ratio of 84:16 in the cyclized products **4** if we assume that the cyclization is kinetically controlled, in good agreement with the experimental value (75:25).

The chairlike conformational transition state **TS-3Z-trans** well explains the preference of 3,6-*trans*, 4,6-*cis*, and 5,6-*trans* configurations in the cyclized products. It is also reasonable that, when the substituent on the alkyl chain of substrate gets closer to the vinyl group, the transition state similar to **TS-3Z-cis** will face more steric hindrance and the energy difference between the two transition states will become larger. This accounts for the higher stereoselectivity in the cyclization of (*Z*)-**5** and (*Z*)-**9**. Moreover, when the substituent gets bulkier, the transition-state conformations become more rigid. This may increase the steric instability of the disfavored transition state similar to **TS-3Z-cis**, which in turn enlarges the energy difference. These analyses are in excellent qualitative agreement with the experimental data.

In the case of radical **R-9Z**, the activation free energy is computed to be 5.6 kcal/mol for 6-*exo* cyclization with 5,6-*trans* stereochemistry and 7.1 kcal/mol for 1,5-H migration, indicating that cyclization predominates, consistent with the experimental observations. Similar to **TS-3Z-trans**, the transition state for 5,6-*trans* cyclization of **R-9Z** is in a chair conformation with both the phenyl and chloromethylene group at the equatorial positions. On the other hand, the transition state for 1,5-H migration, **TS-9Z-M**, is in a half-chair conformation with the vinyl group at the pseudoaxial position, resulting in an enhanced steric congestion in the transition state. Therefore, although the C−H BDE becomes much lower because of the phenyl substitution, the 6-*exo* cyclization still prevails. Note that the chlorine substitution does not have a significant steric influence on the 1,5-H migration based on the structure of **TS-9Z-M**.

The vinylic halogen substituted substrates serve as a good model for the study of stereoselectivity of amidyl radical cyclization. On the basis of the structural difference between **TS-3Z-trans** and **TS-3Z-cis**, it is conceivable that substituents other than a halogen atom should have a similar effect in controlling the stereoselectivity of cyclization.[22,23] The structure of **TS-9Z-M** also reveals that the 1,5-H migration from a tertiary C−H is sterically unfavorable because it requires one of the substituents to be at the axial position in the transition states. This finding should be of important implications in designing other modes of amidyl radical cyclization with the inhibition of the competing intramolecular hydrogen abstraction. These are currently under investigation in our laboratory.

In summary, the above experiments in combination with theoretical calculations have clearly demonstrated that, with *Z*-configurational vinylic halogen substitution, primary amidyl radicals undergo efficient chemo-, regio-, and stereoselective 6-*exo* cyclization via chairlike conformational transition states. The calculations offer a quantitative view on the mechanism of 6-*exo* cyclization of amidyl radicals, which will certainly allow more controlled and predictable applications of this important type of reactions.

EXPERIMENTAL SECTION

(*Z*)-6-Iodo-2-methylhex-5-enamide ((*Z*)-1a). Typical Procedure. The benzene (3.5 mL) solution of morpholine (2.9 mL) was added dropwise into the mixture of iodine (2.7 g, 10.8 mmol) and benzene (35 mL) at 45 °C. The solution was stirred for 20 min, and 2-methylhex-5-ynamide (0.9 g, 7.2 mmol) was added dropwise. The reaction mixture was stirred at 45 °C for 12 h. The resulting mixture was then filtered, and the precipitate was washed with ether (30 mL). The combined organic phase was washed with successively with saturated aqueous NaCl solution, $NaHSO_4$ solution (10%), and saturated $KHCO_3$ solution and then dried over anhydrous Na_2SO_4. After removal of solvent in vacuo, the crude product was purified by column chromatography on silica gel with hexane/acetone (3:1, v:1) as the eluent to give 6-iodo-2-methylhex-5-ynamide (1.8 g, 98% yield) as a white solid. The amide obtained was then added into the mixture of *p*-toluenesulfonyl hydrazine (2.6 g, 14 mmol) and NaOAc (1.7 g, 21 mmol) in THF/H_2O (1:1, v:v). The mixture was refluxed with stirring for 12 h. After being cooled to rt, the solution was extracted with ether (3 × 20 mL), and the combined organic phase was dried over anhydrous Na_2SO_4. The crude product was then purified by column chromatography on silica gel with hexane/acetone (3:1 v/v) as the eluent to give pure (*Z*)-**1a** as a white solid. Yield: 0.7 g (38%). Mp: 74−76 °C. IR (KBr): ν (cm^{-1}) 3348, 3168, 3053, 2967, 2931, 1662, 1630, 688, 657. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.19 (3H, d, J = 7.2 Hz), 1.45−1.59 (1H, m), 1.75−1.90 (1H, m), 2.13−2.23 (2H, m), 2.24−2.35 (1H, m), 5.56 (2H, br), 6.11−6.26 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.9, 32.2, 32.6, 40.1, 83.1, 140.5, 178.7. EIMS: m/z (rel intensity) 253 (M^+, 0.6), 167 (8), 127 (4), 126 (23), 73 (100), 72 (14), 55 (6), 44 (23), 41 (10). HRMS: calcd for $C_7H_{12}INO$ (M) 252.9964, found 252.9967.

(*E*)-6-Iodo-2-methylhex-5-enamide ((*E*)-1a). The hydroiodination of 2-(but-3-yn-1-yl)-2-methyl-1,3-dioxolane with Cp_2ZrCl_2/DIBALH/I_2 was performed according to the literature procedure.[17] The product was then deprotected with 6 N HCl solution (1 mL) and MeOH (10 mL) at rt for 12 h. After the usual workup, (*E*)-6-iodo-2-methylhex-5-en-2-one was obtained in 39% yield (for two steps). The ketone was cyanated with *p*-toluenesulfonylmethyl isocyanide/KOBu^t/DME to give the homologous nitrile, which was then converted to amide (*E*)-**1a** by hydrolysis with 30% H_2O_2 (30%)/NaOH (6 N) in EtOH according to the conventional procedures. White solid. Mp: 76−78 °C. IR (KBr):

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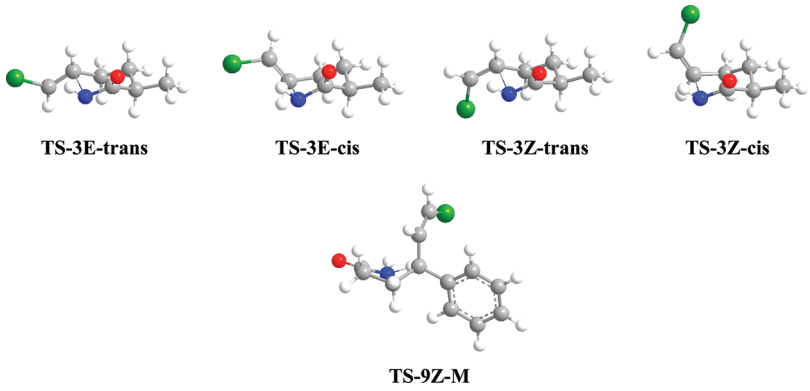

Figure 1. Computed (UB3LYP/6-31G**) transition-state structures.

ν (cm^{-1}) 3350, 3172, 2965, 2932, 1663, 1633, 1460, 942. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.16 (3H, d, J = 7.2 Hz), 1.41−1.56 (1H, m), 1.71−1.84 (1H, m), 2.04−2.16 (2H, m), 2.21−2.33 (1H, m), 5.50 (2H, br), 6.04 (1H, d, J = 14.4 Hz), 6.43−6.54 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.9, 32.5, 33.7, 39.8, 75.3, 145.6, 178.4. EIMS: m/z (rel intensity) 253 (M^+, 0.6), 167 (9), 126 (19), 73 (100), 72 (16), 57 (6), 55 (8), 44 (25), 41 (10). Anal. Calcd for $C_7H_{12}INO$: C, 33.22; H, 4.78; N, 5.53. Found: C, 33.57; H, 4.88; N, 5.46.

(*Z*)-2-Ethyl-6-iodohex-5-enamide ((*Z*)-1b). Yellowish solid. Mp: 58−60 °C. IR (KBr): ν (cm^{-1}) 3369, 3180, 3064, 2963, 2935, 1655, 1617, 1277, 643. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (3H, t, J = 7.2 Hz), 1.45−1.69 (3H, m), 1.71−1.86 (1H, m), 2.00−2.11 (1H, m), 2.17 (2H, q, J = 7.2 Hz), 5.55 (1H, br), 5.83 (1H, br), 6.10−6.25 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.9, 26.0, 30.7, 32.8, 48.1, 83.1, 140.6, 177.9. EIMS: m/z (rel intensity) 140 (M^+ − I, 33), 167 (11), 87 (100), 72 (89), 55 (20), 53 (6), 44 (25), 41 (15). Anal. Calcd for $C_8H_{14}INO$: C, 35.97; H, 5.28; N, 5.24. Found: C, 36.24; H, 5.45; N, 5.12.

(*Z*)-6-Iodo-2-isopropylhex-5-enamide ((*Z*)-1c). White solid. Mp: 52−54 °C. IR (KBr): ν (cm^{-1}) 3386, 3190, 2959, 2926, 1651, 1278, 652; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (6H, d, J = 5.6 Hz), 1.58−1.69 (1H, m), 1.71−1.91 (3H, m), 2.06−2.26 (2H, m), 5.49 (1H, br), 5.63 (1H, br), 6.12−6.26 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.4, 20.7, 28.2, 30.7, 33.1, 53.5, 83.0, 140.8, 177.6. EIMS: m/z (rel intensity) 281 (M^+, 2), 154 (27), 101 (58), 86 (100), 72 (14), 55 (15), 44 (23), 43 (12), 41 (21). HRMS: calcd for $C_9H_{16}INO$ (M) 281.0277, found 281.0273.

(*Z*)-6-Iodo-2-phenylhex-5-enamide ((*Z*)-1d). White solid. Mp: 61−63 °C. IR (KBr): ν (cm^{-1}) 3404, 3295, 3183, 3061, 2944, 2914, 1647, 1446, 1406, 701, 625. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.83−1.96 (1H, m), 2.05−2.19 (2H, m), 2.25−2.38 (1H, m), 3.40 (1H, t, J = 7.2 Hz), 5.41 (1H, br), 5.66 (1H, br), 6.10−6.26 (2H, m), 7.25−7.40 (5H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.1, 32.9, 52.0, 83.3, 127.6, 128.1, 129.1, 139.4, 140.3, 175.6. EIMS: m/z (rel intensity) 315 (M^+, 2), 188 (16), 167 (8), 136 (9), 135 (100), 118 (21), 115 (8), 91 (31), 44 (10). HRMS: calcd for $C_{12}H_{14}INO$ (M) 315.0120, found 315.0125.

(*E*)-6-Chloro-2-methylhex-5-enamide ((*E*)-3). White solid. Mp: 66−68 °C. IR (KBr): ν (cm^{-1}) 3358, 3176, 2967, 2928, 1663, 1636, 1463, 1420, 924. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (3H, d, J = 7.2 Hz), 1.40−1.53 (1H, m), 1.70−1.83 (1H, m), 2.01−2.17 (2H, m), 2.21−2.33 (1H, m), 5.55 (1H, br), 5.70−6.10 (3H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.8, 28.6, 33.1, 39.9, 117.6, 133.0, 178.7. EIMS: m/z (rel intensity) 161 (M^+, 0.3), 75 (11), 73 (100), 72 (20), 55 (6), 53 (6), 44 (40), 42 (7), 41 (14). HRMS: calcd for $C_7H_{12}ClNO$ (M) 161.0607, found 161.0610.

(*Z*)-6-Chloro-2-methylhex-5-enamide ((*Z*)-3). White solid. Mp: 78−80 °C. IR (KBr): ν (cm^{-1}) 3338, 3166, 2970, 2933, 1666, 1635, 1460, 1317, 737. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17 (3H, d, J = 6.8 Hz), 1.43−1.55 (1H, m), 1.73−1.86 (1H, m), 2.17−2.36 (3H, m), 5.58 (1H, br), 5.73 (1H, q, J = 7.2 Hz), 5.88 (1H, br), 6.03 (1H, d, J = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.8, 24.9, 32.6, 40.2, 118.7, 130.9, 178.8. EIMS: m/z (rel intensity) 161 (M^+, 0.5), 75 (12), 73 (100), 72 (17), 55 (10), 53 (6), 44 (38), 42 (9), 41 (13). Anal. Calcd for $C_7H_{12}ClNO$: C, 52.02; H, 7.48; N, 8.67. Found: C, 52.23; H, 7.52; N, 8.60.

(*Z*)-6-Iodo-3-methylhex-5-enamide ((*Z*)-5a). White solid. Mp: 65−67 °C. IR (KBr): ν (cm^{-1}) 3357, 3177, 3058, 2952, 2920, 1659, 1628, 1415, 1278, 666. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96−1.05 (3H, m), 1.95−2.32 (5H, m), 5.58 (2H, br), 6.13−6.32 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.7, 30.1, 41.5, 42.7, 84.2, 139.3, 174.9. EIMS: m/z (rel intensity) 126 (M^+ − I, 58), 67 (11), 59 (100), 55 (11), 44 (48), 43 (19), 42 (11), 41 (33). HRMS: calcd for $C_7H_{12}INO$ (M) 252.9964, found 252.9965.

(*Z*)-3-Ethyl-6-iodohex-5-enamide ((*Z*)-5b). White solid. Mp: 57−59 °C. IR (KBr): ν (cm^{-1}) 3353, 3177, 3059, 2961, 2931, 1666, 1626, 1411, 1269, 648. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (3H, t, J = 7.2 Hz), 1.30−1.50 (2H, m), 1.95−2.35 (5H, m), 5.59 (2H, br), 6.12−6.31 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.1, 26.5, 36.1, 38.5, 40.1, 84.1, 139.4, 175.1. EIMS: m/z (rel intensity) 140 (M^+ − I, 72), 167 (10), 141 (8), 81 (12), 59 (100), 55 (15), 44 (32), 41 (16). HRMS: calcd for $C_8H_{14}INO$ (M) 267.0120, found 267.0121.

(*Z*)-6-Iodo-3-isopropylhex-5-enamide ((*Z*)-5c). White solid. Mp: 84−86 °C. IR (KBr): ν (cm^{-1}) 3359, 3185, 3059, 2960, 2894, 1666, 1626, 1431, 1409, 1270, 652. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91 (6H, d, J = 6.8 Hz), 1.69−1.81 (1H, m), 2.00−2.30 (5H, m), 5.54 (1H, br), 5.77 (1H, br), 6.13−6.27 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1, 19.2, 30.0, 36.4, 37.2, 40.2, 83.9, 140.2, 175.3. EIMS: m/z (rel intensity) 154 (M^+ − I, 49), 95 (20), 69 (10), 59 (100), 55 (14), 44 (30), 43 (24), 41 (32). HRMS: calcd for $C_9H_{16}INO$ (M) 281.0277, found 281.0274.

(1*R,2*S**)-2-((*Z*)-3-Iodoallyl)cyclohexanecarboxamide ((*Z*)-7).** White solid. Mp: 114−116 °C. IR (KBr): ν (cm^{-1}) 3366, 3182, 3064, 2929, 2852, 1659, 1623, 1444, 1416, 1286, 669, 613. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93−1.10 (1H, m), 1.13−1.34 (2H, m), 1.44−1.57 (1H, m), 1.65−1.95 (6H, m), 1.98−2.10 (1H, m), 2.19−2.30 (1H, m), 5.58 (1H, br), 5.76 (1H, br), 6.11−6.28 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.5, 25.6, 30.8, 31.1, 38.4, 39.8, 51.1, 83.8, 139.4, 178.0. EIMS: m/z (rel intensity) 293 (M^+, 4), 167 (22), 166 (100), 107 (20), 81 (24), 79 (20), 72 (22), 67 (21), 55 (21). Anal. Calcd for $C_{10}H_{16}INO$: C, 40.97; H, 5.50; N, 4.78. Found: C, 41.07; H, 5.38; N, 4.73.

(*Z*)-6-Iodo-4-methylhex-5-enamide ((*Z*)-9a). White solid. Mp: 69−71 °C. IR (KBr): ν (cm^{-1}) 3341, 3163, 3059, 2954, 2920, 1664, 1633, 1455, 1414, 1164, 699. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.02 (3H, d, J = 6.8 Hz), 1.57−1.87 (2H, m), 2.21 (2H, t, J = 7.6 Hz),

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2.46−2.63 (1H, m), 5.53 (2H, br), 5.91 (1H, dd, J = 9.2 Hz, 7.2 Hz), 6.19 (1H, d, J = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.5, 31.5, 33.6, 39.2, 81.5, 145.9, 175.3. EIMS: m/z (rel intensity) 126 (M^+ − I, 74), 67 (15), 59 (100), 55 (22), 54 (17), 53 (27), 44 (54), 41 (23). HRMS: calcd for $C_7H_{12}INO$ (M) 252.9964, found 252.9967.

(*Z*)-4-Ethyl-6-iodohex-5-enamide ((*Z*)-9b). White solid. Mp: 54−56 °C. IR (KBr): ν (cm^{-1}) 3343, 3165, 3064, 2960, 2919, 1666, 1627, 1455, 1411, 1254, 697. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (3H, t, J = 7.2 Hz), 1.27−1.69 (3H, m) 1.78−1.93 (1H, m) 2.14−2.30 (2H, m) 2.32−2.48 (1H, m) 5.5 (2H, br) 5.86 (1H, dd, J = 9.2 Hz, 7.6 Hz) 6.30 (1H, d, J = 7.6 Hz). ^{13}C NMR (100 MHz, acetone-d_6) δ 11.0, 27.1, 29.7, 32.9, 46.0, 82.5, 145.3, 174.4. EIMS: m/z (rel intensity) 140 (M^+ − I, 88), 95 (21), 68 (24), 67 (32), 59 (100), 56 (40), 44 (63), 41 (39). Anal. Calcd for $C_8H_{14}INO$: C, 35.97; H, 5.28; N, 5.24. Found: C, 36.21; H, 5.28; N, 5.22.

(*Z*)-6-Iodo-4-isopropylhex-5-enamide ((*Z*)-9c). White solid. Mp: 34−36 °C. IR (KBr): ν (cm^{-1}) 3345, 3190, 3059, 2958, 2920, 1662, 1606, 1455, 1406, 1264, 710. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (3H, d, J = 6.8 Hz), 0.94 (3H, d, J = 6.8 Hz), 1.55−1.77 (2H, m), 1.85−1.95 (1H, m), 2.12−2.35 (3H, m), 5.60 (2H, br), 5.92 (1H, dd, J = 7.6 Hz, 10 Hz), 6.34 (1H, d, J = 7.6 Hz). ^{13}C NMR (100 MHz, acetone-d_6) δ 18.8, 19.9, 27.3, 31.6, 33.1, 50.4, 83.4, 143.7, 174.3. EIMS: m/z (rel intensity) 154 (M^+ − I, 92), 137 (34), 95 (29), 67 (45), 59 (100), 44 (65), 43 (37), 41 (69). HRMS: calcd for $C_9H_{16}INO$ (M) 281.0277, found 281.0287.

(*Z*)-6-Iodo-4-phenylhex-5-enamide ((*Z*)-9d). White solid. Mp: 62−64 °C. IR (KBr): ν (cm^{-1}) 3382, 3196, 3056, 3026, 2947, 2930, 1644, 1490, 1451, 1419, 1297, 710, 697. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.07−2.30 (4H, m), 3.69 (1H, q, J = 8.0 Hz), 5.44 (1H, br), 5.68 (1H, br), 6.24−6.35 (2H, m), 7.19−7.36 (5H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.5, 33.4, 50.1, 83.0, 126.9, 127.5, 128.9, 142.0, 143.7, 175.4. EIMS: m/z (rel intensity) 188 (M^+ − I, 16), 171 (100), 143 (64), 129 (61), 128 (39), 116 (53), 115 (87), 59 (56), 44 (34). HRMS: calcd for $C_{12}H_{14}NO$ (M − I) 188.1075, found 188.1079.

Typical Procedure for the 6-*Exo* Cyclization of Amidyl Radicals. (*Z*)-6-Iodo-2-methylhex-5-enamide ((*Z*)-**1a**, 51 mg, 0.20 mmol) was added into the mixture of $Pb(OAc)_4$ (0.31 g, 0.70 mmol) and iodine (0.13 g, 0.50 mmol) in dichloromethane (6.6 mL) at rt under nitrogen atmosphere. The mixture was irradiated with stirring at rt for 1 h with the aid of a 125 W high-pressure mercury lamp. The mercury lamp was then turned off, and saturated aqueous $Na_2S_2O_3$ (5.0 mL) was added into the reaction solution. The resulting mixture was then extracted with dichloromethane (3 × 10 mL). The combined organic phase was dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the crude products were purified by column chromatography on silica gel with petroleum ether/acetone (4:1 v/v) as the eluent to give separately the pure *trans*-**2a** (47 mg, 63% yield) and *cis*-**2a** (15 mg, 20% yield).

(3*R,6*S**)-6-(Diiodomethyl)-3-methylpiperidin-2-one (*trans*-2a).** White solid. Mp: 134−136 °C. IR (KBr): ν (cm^{-1}) 3192, 3090, 2957, 2927, 1662, 1617, 1490, 1406, 1315, 1278, 1101, 814. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (3H, d, J = 7.6 Hz), 1.40−1.65 (2H, m), 1.93−2.03 (1H, m), 2.17−2.25 (1H, m), 2.26−2.38 (1H, m), 3.10−3.18 (1H, m), 5.15 (1H, d, J = 3.2 Hz), 6.54 (1H, br). ^{13}C NMR (100 MHz, $CDCl_3$): δ −14.3, 16.4, 27.9, 29.4, 36.0, 61.0, 175.8. EIMS: m/z (rel intensity) 379 (M^+, 0.3), 127 (5), 113 (7), 112 (100), 82 (7), 69 (25), 56 (5), 42 (5), 41 (16). HRMS: calcd for $C_7H_{11}I_2NO$ (M) 378.8930, found 378.8929. The structure was further confirmed by its 2D NOESY experiments.

(3*S,6*S**)-6-(Diiodomethyl)-3-methylpiperidin-2-one (*cis*-2a).** White solid. Mp: 132−134 °C. IR (KBr): ν (cm^{-1}) 3221, 2962, 2929, 1676, 1612, 1401, 1299, 1199, 779. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 (3H, d, J = 7.2 Hz), 1.64−1.77 (2H, m), 1.90−2.07 (2H, m), 2.42−2.58 (1H, m), 3.14−3.27 (1H, m), 5.15 (1H, d, J = 4.0 Hz), 6.51 (1H, br). ^{13}C NMR (100 MHz, $CDCl_3$): δ −16.0, 17.9, 25.2, 25.6, 34.8, 60.8, 176. EIMS: m/z (rel intensity) 252 (M^+ − I, 0.7), 127 (4), 113 (7), 112 (100), 82 (7), 69 (19), 56 (4), 42 (4), 41 (12). HRMS: calcd for $C_7H_{11}I_2NO$ (M) 378.8930, found 378.8931. The structure was further confirmed by its 2D NOESY experiments.

(3*R,6*S**)-6-(Diiodomethyl)-3-ethylpiperidin-2-one (*trans*-2b).** White solid. Mp: 129−131 °C. IR (KBr): ν (cm^{-1}) 3189, 3075, 2959, 2934, 1646, 1402, 1316, 1090, 818. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (3H, t, J = 7.2 Hz), 1.38−1.62 (3H, m), 1.90−2.05 (2H, m), 2.11−2.29 (2H, m), 3.07−3.16 (1H, m), 5.15 (1H, d, J = 3.2 Hz), 6.61 (1H, br). ^{13}C NMR (100 MHz, $CDCl_3$): δ −14.3, 11.1, 23.5, 24.1, 29.3, 42.0, 60.7, 175.1. EIMS: m/z (rel intensity) 266 (M^+ − I, 6), 127 (14), 126 (100), 83 (41), 82 (11), 56 (10), 55 (34), 42 (9), 41 (30). HRMS: calcd for $C_8H_{13}I_2NO$ (M) 392.9087, found 392.9092.

(3*S,6*S**)-6-(Diiodomethyl)-3-ethylpiperidin-2-one (*cis*-2b).** White solid. Mp: 100−102 °C. IR (KBr): ν (cm^{-1}) 3186, 3065, 2959, 2868, 1660, 1409, 1299, 1093. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.01 (3H, t, J = 7.2 Hz), 1.53−1.74 (2H, m), 1.78−2.04 (4H, m), 2.22−2.32 (1H, m), 3.19−3.29 (1H, m), 5.13 (1H, d, J = 4.0 Hz), 6.27 (1H, br). ^{13}C NMR (100 MHz, $CDCl_3$): δ −16.2, 12.0, 22.1, 24.8, 25.4, 41.7, 60.8, 175.4. EIMS: m/z (rel intensity) 266 (M^+ − I, 1), 365 (8), 127 (14), 126 (100), 112 (13), 83 (30), 82 (9), 55 (19), 41 (18). HRMS: calcd for $C_8H_{13}I_2NO$ (M) 392.9087, found 392.9080.

(3*S,6*S**)-6-(Diiodomethyl)-3-isopropylpiperidin-2-one (*trans*-2c).** White solid. Mp: 120−122 °C. IR (KBr): ν (cm^{-1}) 3174, 3050, 2958, 2869, 1657, 1415, 1304, 1091, 838. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 (3H, d, J = 6.8 Hz), 0.98 (3H, d, J = 7.2 Hz), 1.33−1.47 (1H, m), 1.62 (1H, qd, J = 13.2 Hz, 2.8 Hz), 1.79−1.98 (1H, m), 2.18−2.30 (2H, m), 2.53−2.68 (1H, m), 3.10−3.22 (1H, m), 5.13 (1H, d, J = 3.2 Hz), 6.18 (1H, br). ^{13}C NMR (100 MHz, $CDCl_3$): δ −14.5, 17.5, 18.8, 20.3, 27.4, 29.3, 46.5, 60.6, 174.9. EIMS: m/z (rel intensity) 280 (M^+ − I, 25), 140 (100), 98 (27), 97 (56), 69 (50), 55 (35), 43 (28), 41 (84). HRMS: calcd for $C_9H_{15}I_2NO$ (M) 406.9243, found 406.9240.

(3*S,6*S**)-6-(Diiodomethyl)-3-phenylpiperidin-2-one (*trans*-2d).** White solid. Mp: 156−158 °C. IR (KBr): ν (cm^{-1}) 3200, 3078, 2981, 2959, 1656, 1491, 1405, 1306, 756, 700. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.57−1.71 (1H, m), 1.98−2.12 (1H, m), 2.14−2.24 (1H, m), 2.26−2.36 (1H, m), 3.25−3.35 (1H, m), 3.48−3.58 (1H, m), 5.17 (1H, d, J = 3.2 Hz), 6.67 (1H, br), 7.18−7.40 (5H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ −15.3, 28.8, 29.4, 48.4, 61.1, 127.2, 128.5, 128.7, 139.9, 173.5. EIMS: m/z (rel intensity) 441 (M^+, 0.4), 314 (11), 175 (13), 174 (100), 129 (11), 115 (12), 104 (16), 103 (21), 91 (20). HRMS: calcd for $C_{12}H_{13}I_2NO$ (M) 440.9087, found 440.9089.

(4*S,6*S**)-6-(Diiodomethyl)-4-methylpiperidin-2-one (*cis*-6a).** White solid. Mp: 156−158 °C. IR (KBr): ν (cm^{-1}) 3288, 2994, 2950, 2910, 1658, 1615, 1450, 1300, 745, 692. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.03−1.18 (4H, m), 1.88−2.22 (3H, m), 2.36−2.47 (1H, m), 3.09−3.19 (1H, m), 5.16 (1H, d, J = 3.2 Hz), 6.76 (1H, br). ^{13}C NMR (100 MHz, $CDCl_3$): δ −14.1, 21.1, 26.5, 37.1, 39.4, 60.1, 173.1. EIMS: m/z (rel intensity) 379 (M^+, 0.2), 113 (7), 112 (100), 82 (4), 69 (43), 56 (5), 42 (6), 41 (15), 40 (4). HRMS: calcd for $C_7H_{11}I_2NO$ (M) 378.8930, found 378.8934.

(4*S,6*S**)-6-(Diiodomethyl)-4-ethylpiperidin-2-one (*cis*-6b).** White solid. Mp: 121−123 °C. IR (KBr): ν (cm^{-1}) 3191, 3081, 2957, 2916, 1655, 1405, 1304, 816. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (3H, t, J = 7.6 Hz), 1.07 (1H, q, J = 12.0 Hz), 1.34−1.46 (2H, m), 1.78−2.00 (2H, m), 2.13−2.25 (1H, m), 2.43−2.53 (1H, m), 3.12−3.21 (1H, m), 5.16 (1H, d, J = 3.2 Hz), 6.49 (1H, br). ^{13}C NMR (100 MHz, $CDCl_3$): δ −15.1, 11.0, 28.5, 33.0, 35.4, 37.4, 60.4, 172.9. EIMS: m/z (rel intensity) 266 (M^+ − I, 0.5), 127 (11), 126 (100), 83 (47), 82 (5), 56 (7), 55 (13), 42 (4), 41 (17). HRMS: calcd for $C_8H_{13}I_2NO$ (M) 392.9087, found 392.9091.

(4*S,6*S**)-6-(Diiodomethyl)-4-isopropylpiperidin-2-one (*cis*-6c).** White solid. Mp: 138−140 °C. IR (KBr): ν (cm^{-1}) 3228,

2963, 2912, 1672, 1619, 1475, 1384, 1295, 765. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90−0.98 (6H, m), 1.11 (1H, q, J = 10.8 Hz), 1.51−1.64 (1H, m), 1.67−1.79 (1H, m), 1.96−2.04 (1H, m), 2.14−2.24 (1H, m), 2.39−2.49 (1H, m), 3.06−3.16 (1H, m), 5.19 (1H, d, J = 3.2 Hz), 6.76 (1H, br). ^{13}C NMR (100 MHz, $CDCl_3$): δ −15.1, 19.1, 19.6, 31.8, 33.2, 34.9, 37.4, 60.5, 173.2. EIMS: m/z (rel intensity) 280 (M^+ − I, 0.3), 141 (10), 140 (100), 97 (43), 69 (5), 67 (5), 55 (7), 43 (10), 41 (25). HRMS: calcd for $C_9H_{15}I_2NO$ (M) 406.9243, found 406.9245. The structure was further confirmed by its 2D NOESY experiments.

(3*S,4a*S**,8a*R**)-3-(Diiodomethyl)octahydroisoquinolin-1(2*H*)-one (8).** White solid. Mp: 172−174 °C. IR (KBr): ν (cm^{-1}) 3191, 3074, 2939, 2913, 2853, 1655, 1402, 1300. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.04−1.35 (5H, m), 1.55−1.68 (1H, m), 1.70−1.92 (4H, m), 2.05−2.15 (1H, m), 2.30−2.40 (1H, m), 3.17−3.27 (1H, m), 5.13 (1H, d, J = 2.8 Hz), 6.13 (1H, br). ^{13}C NMR (100 MHz, $CDCl_3$): δ −14.2, 25.5, 26.0, 26.6, 32.9, 36.4, 36.8, 45.8, 60.2, 174.4. ESI-MS m/z 419.5 (M^+ + H). HRMS: calcd for $C_{10}H_{16}I_2NO$ (M + H) 419.9316, found 419.9325. The structure was further confirmed by its 2D NOESY experiments.

(5*S,6*S**)-6-(Diiodomethyl)-5-methylpiperidin-2-one (*trans*-10a).** White solid. Mp: 114−116 °C. IR (KBr): ν (cm^{-1}) 3366, 2961, 2931, 1652, 1460, 1388, 1300, 632. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.03 (3H, d, J = 6.8 Hz), 1.48−1.83 (3H, m), 2.33−2.48 (2H, m), 2.77 (1H, d, J = 8.4 Hz), 5.46 (1H, d, J = 1.6 Hz), 6.09 (1H, br). ^{13}C NMR (100 MHz, $CDCl_3$): δ −17.0, 17.8, 27.7, 31.3, 35.1, 67.5, 172.5. EIMS: m/z (rel intensity) 379 (M^+, 0.05), 113 (7), 112 (100), 70 (7), 69 (7), 56 (6), 55 (30), 42 (9), 41 (17). HRMS: calcd for $C_7H_{11}I_2NO$ (M) 378.8930, found 378.8933. The structure was further confirmed by its 2D NOESY experiments.

(5*S,6*S**)-6-(Diiodomethyl)-5-ethylpiperidin-2-one (*trans*-10b).** White solid. Mp: 74−76 °C. IR (KBr): ν (cm^{-1}) 3440, 3184, 3063, 2963, 2929, 1682, 1409, 1099, 826. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (3H, t, J = 7.2 Hz), 1.22−1.36 (1H, m), 1.38−1.48 (1H, m), 1.50−1.64 (2H, m), 1.87−1.97 (1H, m), 2.28−2.48 (2H, m), 2.93 (1H, d, J = 7.6 Hz), 5.47 (1H, d, J = 2.4 Hz), 6.23 (1H, br). ^{13}C NMR (100 MHz, $CDCl_3$): δ −15.9, 11.0, 23.6, 24.8, 31.0, 40.6, 65.8, 172.5. EIMS: m/z (rel intensity) 266 (M^+ − I, 0.4), 127 (11), 126 (100), 84 (9), 83 (4), 69 (5), 55 (25), 42 (8), 41 (20). HRMS: calcd for $C_8H_{13}INO$ (M − I) 266.0042, found 266.0044.

(5*R,6*S**)-6-(Diiodomethyl)-5-isopropylpiperidin-2-one (*trans*-10c).** White solid. Mp: 86−88 °C. IR (KBr): ν (cm^{-1}) 3204, 3094, 2963, 2920, 1662, 1628, 1423, 1304, 1198, 805. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (3H, d, J = 6.8 Hz), 1.02 (3H, d, J = 6.8 Hz), 1.33−1.45 (1H, m), 1.54−1.68 (1H, m), 1.70−1.85 (2H, m), 2.27−2.51 (2H, m), 3.04 (1H, d, J = 8.0 Hz), 5.47 (1H, d, J = 2.4 Hz), 6.13 (1H, br). ^{13}C NMR (100 MHz, $CDCl_3$): δ −14.8, 16.9, 18.8, 21.4, 27.5, 31.2, 44.9, 63.8, 172.6. EIMS: m/z (rel intensity) 280 (M^+ − I, 0.2), 141 (10), 140 (100), 111 (10), 98 (10), 69 (10), 55 (22), 43 (12), 41 (27). HRMS: calcd for $C_9H_{15}INO$ (M − I) 280.0198, found 280.0203.

(5*R,6*S**)-6-(Diiodomethyl)-5-phenylpiperidin-2-one (*trans*-10d).** White solid. Mp: 146−148 °C. IR (KBr): ν (cm^{-1}) 3436, 3360, 3059, 3024, 2983, 2941, 1655, 1451, 759, 700, 638. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.91−2.01 (1H, m), 2.15−2.31 (1H, m), 2.50−2.68 (3H, m), 3.28 (1H, d, J = 9.6 Hz), 4.94 (1H, d, J = 1.2 Hz), 6.24 (1H, br), 7.22−7.28 (2H, m), 7.32−7.43 (3H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ −16.7, 27.5, 31.9, 47.0, 67.0, 127.4, 128.3, 129.5, 139.4, 172.1. EIMS: m/z (rel intensity) 314 (M^+ − I, 100), 174 (57), 127 (24), 117 (82), 115 (54), 104 (63), 103 (24), 91 (31). Anal. Calcd for $C_{12}H_{13}I_2NO$: C, 32.68; H, 2.97; N, 3.18. Found: C, 33.02; H, 3.10; N, 3.06.

Typical Procedure for the 6-*Exo* Cyclization Followed by Reduction with H_3PO_2/AIBN. (*E*)-6-Chloro-2-methylhex-5-enamide ((*E*)-**3**, 97 mg, 0.60 mmol) was added into the mixture of $Pb(OAc)_4$ (0.93 g, 2.1 mmol) and iodine (0.40 g, 1.5 mmol) in dichloromethane (20 mL) at rt under nitrogen atmosphere. The mixture was irradiated with stirring at rt for 1 h with the aid of a 125 W high-pressure mercury lamp. The mercury lamp was then turned off, and the resulting mixture was passed through a short silica gel column and washed with ethyl acetate. The combined organic phase was concentrated in vacuo, and the crude product was dissolved in ethanol (18 mL). Sodium bicarbonate (0.60 g, 7.2 mmol), H_3PO_2 (50% aqueous solution, 0.66 mL, 6.0 mmol), and AIBN (12 mg) were added successively. The mixture was refluxed for 5 h and then cooled down to rt. Brine (30 mL) was added, and the solution was extracted with ethyl acetate (30 mL × 2). The combined organic phase was dried over anhydrous Na_2SO_4. After the removal of solvent under reduced pressure, the crude product was purified by column chromatography on silica gel with petroleum/acetone (4:1 v/v) as the eluent to give separately the pure *trans*-**4** (45 mg, 46% yield) and *cis*-**4** (45 mg, 46% yield).

(3*R,6*S**)-6-(Chloromethyl)-3-methylpiperidin-2-one (*trans*-4).** White solid. Mp: 90−92 °C. IR (KBr): ν (cm^{-1}) 3250, 2971, 2933, 2869, 1668, 1625, 1471, 1400, 1302, 1267, 759, 737. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (3H, d, J = 7.2 Hz), 1.43−1.58 (2H, m), 1.94−2.10 (2H, m), 2.26−2.40 (1H, m), 3.39 (1H, dd, J = 11.2, 8.0 Hz), 3.57 (1H, dd, J = 11.2, 4.0 Hz), 3.61−3.71 (1H, m), 6.09 (1H, br). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.8, 26.4, 28.3, 36.1, 48.3, 54.5, 175.3. EIMS: m/z (rel intensity) 161 (M^+, 4), 113 (10), 112 (100), 84 (5), 69 (32), 56 (4), 42 (5), 41 (8). Anal. Calcd for $C_7H_{12}ClNO$: C, 52.02; H, 7.48; N, 8.67. Found: C, 52.10; H, 7.48; N, 8.76.

(3*S,6*S**)-6-(Chloromethyl)-3-methylpiperidin-2-one (*cis*-4).** White solid. Mp: 104−106 °C. IR (KBr): ν (cm^{-1}) 3199, 3085, 2957, 2935, 2868, 1661, 1617, 1486, 1437, 1325, 814. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (3H, d, J = 7.2 Hz), 1.56−1.67 (1H, m), 1.69−1.81 (1H, m), 1.84−1.97 (2H, m), 2.40−2.52 (1H, m), 3.44 (1H, dd, J = 11.2, 8.0 Hz), 3.55 (1H, dd, J = 11.2, 4.8 Hz), 3.61−3.71 (1H, m), 6.16 (1H, br). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.6, 23.1, 26.1, 35.4, 47.8, 53.7, 175.7. EIMS: m/z (rel intensity) 161 (M^+, 0.8), 113 (7), 112 (100), 84 (5), 69 (36), 56 (6), 55 (4), 42 (10), 41 (15). Anal. Calcd for $C_7H_{12}ClNO$: C, 52.02; H, 7.48; N, 8.67. Found: C, 52.33; H, 7.43; N, 8.75.

■ ASSOCIATED CONTENT

Supporting Information. Copies of ^{1}H, ^{13}C NMR and 2D NOESY spectra, DFT calculation data and complete reference.[20] This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: clig@mail.sioc.ac.cn; bnulk@yahoo.com.cn.

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