A Mild and Highly Chemoselective α-Iodination of *N*-Allylic Carboxamides and Lactams

Osamu Kitagawa, Norihiko Kikuchi, Tokushi Hanano, Katsuyuki Aoki, Tomomi Yamazaki, Midori Okada, and Takeo Taguchi*

Tokyo College of Pharmacy, 1432-1 Horinouchi, Hachioji, Tokyo 192-03, Japan

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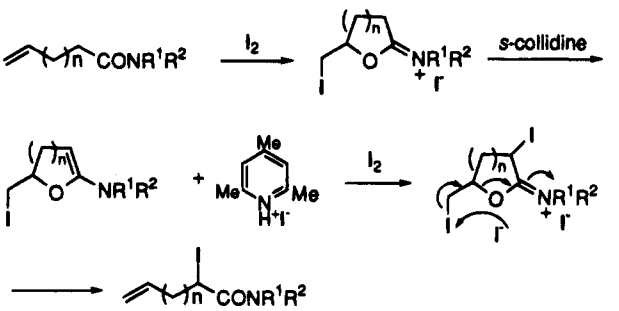
Mild and highly chemoselective α-iodination reactions of *N*-allylic carboxamides and lactams are reported. *N*-Allylic amides and lactams reacted with I_2 and 2,6-lutidine at room temperature to give α-iodo amides and lactams in moderate to good yields. The exclusive α-iodination of *N*-allylic amides having another acidic hydrogen in the molecule proceeded under these conditions. The iodides obtained were converted to the bicyclic lactam or the β-lactam derivatives with high stereoselectivity by a radical iodine atom-transfer reaction or a nucleophilic substitution reaction.

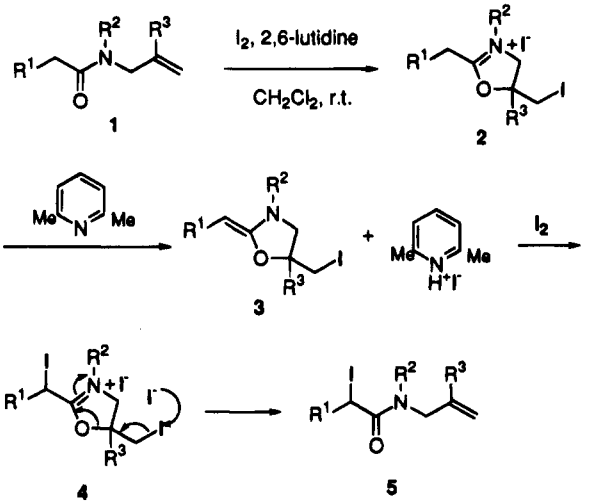
α-Halo amides and esters are important functionalities[1] which have been employed many times in the development of efficient synthetic methods.[2] The α-halogenation of *N,N*-disubstituted amides or esters is generally accomplished by their conversion to either enolate anions by treatment with a strong base or to enol derivatives, followed by reaction with an electrophilic halogenating reagent.[2] There are some limitations with respect to chemoselectivity in cases of substrates having ester, nitrile, or other carbanion stabilizing groups. Although methods for the α-halogenation of NH amides and lactams which involve the formation of imino ether intermediates are known,[3] these are not applicable to tertiary amides and lactams.

Recently, we reported a facile α-iodination of unsaturated carboxamides by reaction with I_2 and *s*-collidine.[4a] A reversible activating process via an iodolactonization intermediate was postulated for this reaction pathway (Scheme 1). The highly diastereoselective iodination of a 4-alkenoyl amide having a chiral center at C-3[4a] and asymmetric iodination of an alkenoyl amide of homochiral 2,5-disubstituted pyrrolidine[4b] were also demonstrated. These reactions are applicable to amides possessing an olefinic moiety at a suitable position to form an imidate intermediate, but not to amides of saturated carboxylic acids.

Scheme 1



Scheme 2



According to the reaction mechanism proposed,[4a,b] a similar activating process involving the formation of a reactive ketene *N,O*-acetal intermediate (**3**) might occur through reaction of *N*-allylic amide **1** with I_2 and a weak base to give α-iodo amide **5** (Scheme 2). In this paper, we report a mild and highly chemoselective α-iodination of *N*-allylic amides and lactams.[5] As applications of the present reaction, the stereoselective construction of bicyclic lactams and a β-lactam derivative by use of a radical iodine atom-transfer reaction and a nucleophilic substitution reaction are also reported.

[⊗] Abstract published in *Advance ACS Abstracts,* October 15, 1995.

(1) (a) House, H. O. *Modern Synthetic Reactions*, W. A. Benjamin, Inc.: Menlo Park, 1972; Chap. 8. (b) Hudlicky, M.; Hudlicky, T. Formation of carbon–halogen bonds. In *The Chemistry of Halides, Pseudohalides and Azides*; Patai, S., Rappoport, Z., Eds.; John Wiley: New York, 1983; p 1021.

(2) (a) Rathke, M. W.; Lindert, A. *Tetrahedron Lett.* **1971**, 3995–3998. (b) Arnold, R. T.; Kulenovic, S. T. *J. Org. Chem.* **1978**, *43*, 3687–3689. Asymmetric α-halogenations using ester enolate and boron enolates of active amides: (c) Oppolzer, W.; Dudfield, P. *Tetrahedron Lett.* **1985**, *26*, 5037. (d) Oppolzer, W.; Pedrosa, R.; Moretti, R. *Tetrahedron Lett.* **1986**, *27*, 831. (e) Evans, D. A.; Ellman, J. A.; Dorow, R. L. *Tetrahedron Lett.* **1987**, *28*, 1123. (f) Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011.

(3) (a) Winemen, R. J.; Hsu, E. T.; Anagnostopolos, C. E. *J. Am. Chem. Soc.* **1958**, *80*, 6233. (b) Francis, W. G.; Thorton, J. R.; Werner, J. C.; Hopkins, T. R. *J. Am. Chem. Soc.* **1958**, *80*, 6238. (c) Philips, W. G.; Ratts, K. W. *J. Org. Chem.* **1972**, *37*, 1526. (d) Merour, J. Y.; Coadou, J. Y.; *Tetrahedron Lett.* **1991**, *32*, 2469. (e) King, A. O.; Anderson, R. K.; Shuman, R. F.; Karady, S.; Abramson, N. L.; Douglas, A. W. *J. Org. Chem.* **1993**, *58*, 3384. (f) Armstrong, J. D., III; Eng, K. K.; Keller, J. L.; Purric, R. M.; Hartner, F. W., Jr.; Choi, W.-B.; Askin, D.; Volante, R. P. *Tetrahedron Lett.* **1994**, *35*, 3239.

(4) (a) Kitagawa, O.; Hanano, T.; Hirata, T.; Inoue, T.; Taguchi, T. *Tetrahedron Lett.* **1992**, *33*, 1299–1302. (b) Kitagawa, O.; Hanano, T.; Kikuchi, N.; Taguchi, T. *Tetrahedron Lett.* **1993**, *34*, 2165–2168.

(5) Recently, we also reported Diels–Alder reaction of *N*-allyl enamides and lactam derivatives through the similar activating process by I_2. Kitagawa, O.; Aoki, K.; Inoue, T.; Taguchi, T. *Tetrahedron Lett.* **1995**, *36*, 593.

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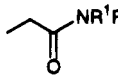
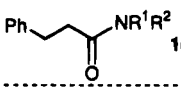
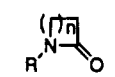
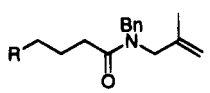
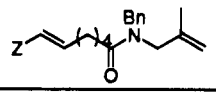
Table 1. α-Iodination of *N*-Allylic Amides and Lactams[a]

Entry	Substrate 1		Time (h)	5	Yield (%)[b]
1		1a R^1 = H, R^2 = allyl	20	5a	trace
2		1b R^1 = R^2 = allyl	23	5b	63
3		1c R^1 = Bn, R^2 = allyl	20	5c	61
4		1d R^1 = Bn, R^2 = methallyl	22	5d	73
5		1e R^1 = Bn, R^2 = methallyl	20	5e	73
6		1f R = allyl n = 3	20	5f	49
7		1g R = methallyl n = 3	20	5g	76
8		1h R = methallyl n = 4	16	5h	64
9		1i R = methallyl n = 2	20	5i	–[c]
10		1j R = methallyl n = 1	20	5j	–[c]
11		1k R = MOMO	16	5k	64
12		1l R = AcO	21	5l	62
13		1m Z = COOMe	20	5m	60

a) Iodination Reaction: Amide or lactam (1 mmol), I_2 (1.3 mmol), 2,6-lutidine (3 mmol), CH_2Cl_2 (8 mL), rt. b) Isolated yield. c) No reaction.

Results and Discussion

As expected, the α-iodination of various *N*-allylic amides and lactams **1** occurred in the presence of I_2 and 2,6-lutidine in CH_2Cl_2. Similar to the previous report, while the yield of iodination was not affected by the solvent used (THF, CH_3CN, DMF, or EtOH), it was dependent on the additive employed. Pyridine derivatives having 2,6-substituents such as 2,6-lutidine and *s*-collidine were the most effective. The use of a tertiary amine such as triethylamine instead of 2,6-lutidine gave a lower yield of the iodide **5**.[6]

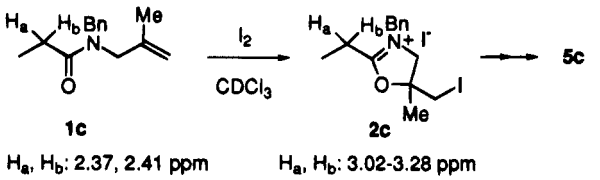
The results of the α-iodination of various *N*-allylic amides and lactams are summarized in Table 1. From the results shown, the following should be noted. Regarding the effect of amide nitrogen substituents, (1) *N*-monosubstituted amide **1a** did not give the α-iodo amide (entry 1),[7] (2) the present reaction can be carried out with an *N*,*N*-disubstituted amide having at least one allylic group, and (3) the methallyl derivative afforded a slightly higher yield of the iodide than allyl derivatives, as shown in entries 3, 4, 6, 7.

The α-iodination of δ-valerolactam and ε-caprolactam derivatives **1g,h** also proceeded smoothly to give α-iodo lactams **5g**, **5h** in good yields (entries 7, 8). Under the same conditions, the iodination reactions of *N*-methallyl-γ-butyrolactam and β-lactam failed (entries 9, 10). These results can be explained by considering the strain energy of the intermediary bicyclo[3.3.0]octene and bicyclo[3.2.0]-heptene system **2**, **3** [R^1, R^2 = $(CH_2)_2$ or R^1, R^2 = CH_2] formed from **1i** and **1j**, respectively.

(6) It is known that tertiary amines such as triethylamine form a strong charge transfer complex with iodine to bring about the decrease in the basicity of amine and the electrophilicity of iodine.

(7) In this case, the reaction gave a complex mixture.

Scheme 3



H_a, H_b: 2.37, 2.41 ppm H_a, H_b: 3.02-3.28 ppm

The functional selectivity of the present reaction is evident from the successful α-iodination of the amides **1k–m** which have methoxymethyl (MOM) and ester groups (entries 11–13). Furthermore, the high chemoselectivity of the present iodination method is demonstrated by substrates possessing additional strong electron-withdrawing groups such as **1l** and **1m** (entries 12, 13). Thus, the exclusive α-iodination of an *N*-allyl amide group, without the α-iodination of an ester or γ-iodination of an enoate group, proceeds under these reaction conditions. The characteristic features and synthetic value of the present method are clearly demonstrated by these results.

The reaction pathway is clarified by considering the conversion of cyclic imidate **2**, an intermediate of halolactonization, to the ketene *N*,*O*-acetal form **3** which, in turn, reacts with I_2 to form α-iodo cyclic imidate **4**. Subsequent ring cleavage occurs by nucleophilic attack of iodide on the iodine atom to give **5** and I_2 (Scheme 2). The ^{1}H-NMR spectrum of cyclic imidate **2c** (R^1 = Me, R^2 = Bn, R^3 = H), obtained by reaction of **1c** with I_2 in $CDCl_3$, indicated a considerable increase in the acidity of the α-hydrogens (downfield shifts of the α-hydrogens resonances of **2c** by 0.6–0.7 ppm compared with those of **1c**), resulting in abstraction of an α-hydrogen by a weak base such as 2,6-lutidine to form **3** and a subsequent iodination leading to **5c** (Scheme 3).

The synthetic applications of the α-iodo *N*-allylic amides are numerous. The radical iodine atom-transfer annulation of *N*-allylic α-iodoacetamides has been found to be quite useful as a synthetic approach to lactams and alkaloids.[8] However, few examples of stereoselectivity in lactam formation by the radical atom-transfer annulation of α-halo propionyl or higher alkanoyl derivatives have been reported.[9] Under the same conditions as above, α-iodination of (*S*)-2-vinylpyrrolidide **1n** and **1o**[10] proceeded to give **5n** and **5o** as mixtures of diastereomers in good yield.[11] We found that subsequent iodine atom-transfer annulation of the iodoamides **5n** and **5o** mediated by photoirradiation in the presence of hexabutylditin gives bicyclic lactams **6n** and **6o** having three consecutive chiral centers as single isomers. The stereochemistry of lactams **6n** and **60** was elucidated by an NOE experiment

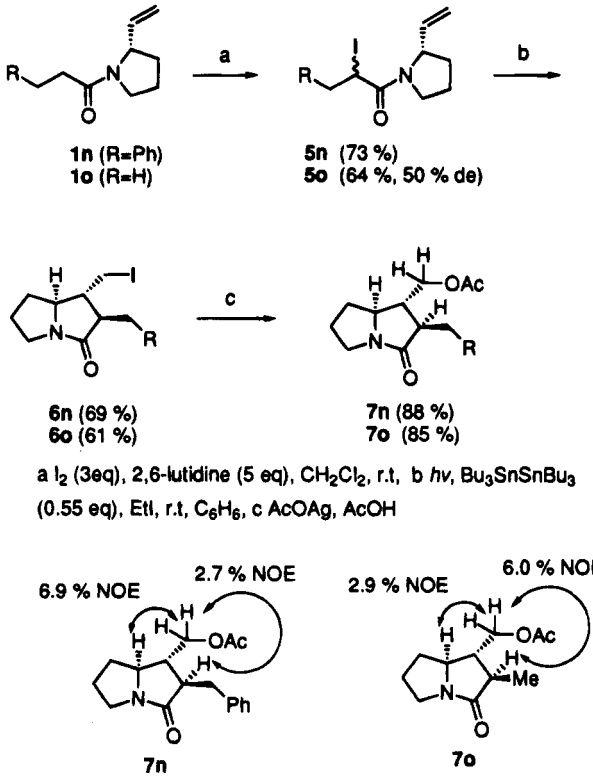
(8) Examples of the radical atom-transfer annulation of *N*-allylic α-iodoacetamides: (a) Mori, M.; Kanda, N.; Oda, I.; Ban, Y. *Tetrahedron* **1985**, *41*, 5465. (b) Jolly, R. S.; Livinghouse, T. *J. Am. Chem. Soc.* **1988**, *110*, 7536. (c) Curran, D. P.; Tamine, J. *J. Org. Chem.* **1991**, *56*, 2746.

(9) High stereoselectivity in the radical cyclization of *N*-(2-iodopropionyl)-2-vinyl-1,3-oxazine derivative was reported by Gennari et al. (a) Gennari, C.; Scolatico, C.; Vassalo, M. *Tetrahedron*: Asym. **1991**, *2*, 793. On the other hand, it is reported that the ruthenium-catalyzed chlorine atom-transfer reaction of *N*-(α-chloro-α-thioacetyl)-2-vinylpyrrolidine gives a mixture of the four possible diastereoisomers in a ratio of 84:11:3:2. (b) Ishibashi, H.; Uemura, N.; Nakatani, H.; Okazaki, M.; Sato, T.; Nakamura, N.; Ikeda, M. *J. Org. Chem.* **1993**, *58*, 2360.

(10) Synthesis of (*S*)-2-vinylpyrrolidine: Moriwake, T.; Hamano, S.; Saito, S.; Torii, S. *Chem. Lett.* **1987**, 2085.

(11) The iodide **5o** was isolated as a mixture of diastereomers in a ratio of 3:1 which was found to be in thermodynamic equilibrium, since each diastereomer obtained by MPLC separation gradually converted to a mixture in a same ratio on standing over night at rt.

Scheme 4



of its acetates **7n** and **7o**. Thus, the relative stereochemistries between the iodomethyl and benzyl substituents of **6n** and **6o** were confirmed to be *trans* (Scheme 4).

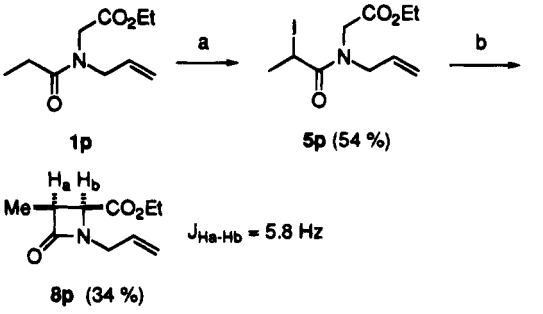
In an another application, we examined β-lactam synthesis by the sequential α-iodination of *N*-alkanoyl-*N*-allyl glycinate **1p** and an intramolecular substitution reaction.[12,13] Chemoselective iodination of **1p**, which has an active methylene moiety, was achieved by employing our present method, producing **5p** in moderate yield. Treatment of the iodide **5p** with *t*-BuOK exclusively gave *cis*-β-lactam derivative **8p** (Scheme 5).[13,14] The *cis* configuration of **8p** was deduced from the coupling constant between H_a and H_b.[14]

In conclusion, we have developed mild and chemoselective α-iodination reactions of *N*-allylic carboxamides and lactams. The iodides thus obtained can be converted to lactam derivatives through radical iodine atom-transfer reactions or nucleophilic substitution reactions.

Experimental Section

Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a 400- and 300-MHz spectrometer. In ^1H and ^{13}C NMR spectra, chemical shifts were expressed in δ (ppm) downfield from $CHCl_3$ (7.26 ppm) and $CDCl_3$ (77.0 ppm), respectively. Mass spectra were recorded by electron impact. Preparative TLC was performed on precoated plates (1 mm thickness, 20 × 20 cm, Merck silica gel 60F-254). Column chromatography was performed on silica gel, Wakogel C-200 (75–150 μm). Medium-pressure liquid chromatography (MPLC) was performed on a 30 × 4 cm i.d. prepacked column (silica gel, 50 μm) with a UV detector.

Scheme 5



General Procedure for α-Iodination Reactions. To a solution of the amide **1** (1.0 mmol) in dry CH_2Cl_2 (8 mL) were added 2,6-lutidine (0.4 mL, 3 mmol) and I_2 (380 mg, 1.5 mmol), and then the reaction mixture was stirred at rt for the indicated period (see Table 1). The mixture was poured into 2% HCl and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were washed with aqueous $Na_2S_2O_3$ solution, dried over $MgSO_4$, and evaporated to dryness. The residue was purified by column chromatography.

***N,N*-Diallyl-2-iodopropionamide (5b).** Compound **5b** was prepared from **1b** (163 mg, 1.1 mmol). Purification by column chromatography (hexane/AcOEt = 10:1) gave **5b** (187 mg, 63%). **5b**: colorless oil; IR (neat) 2950, 2890, 1650 cm^{-1}: ^1H-NMR ($CDCl_3$) δ 1.95 (d, J = 6.7 Hz, 3H), 3.61 (tdd, J = 1.3, 6.3, 15.4 Hz, 1H), 3.77 (tdd, J = 1.9, 4.5, 8.0 Hz, 1H), 4.04 (m, 1H), 4.38 (m, 1H), 4.50 (q, J = 6.7 Hz, 1H), 5.09–5.25 (m, 4H), 5.74–5.91 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ 13.7, 23.8, 48.6, 49.9, 116.3, 117.2, 132.2, 132.9, 171.1; MS (*m*/*z*) 279 (M^+), 264, 183, 153, 96. Anal. Calcd for $C_9H_{14}INO$: C, 38.72; H, 5.06; N, 5.02. Found: C, 38.59; H, 5.10; N, 5.00.

***N*-Allyl-*N*-benzyl-2-iodopropionamide (5c).** Compound **5c** was prepared from **1c** (106 mg, 0.5 mmol). Purification by column chromatography (hexane/AcOEt = 8:1) gave **5c** (106 mg, 61%). **5c**: colorless oil; IR (neat) 2920, 1650 cm^{-1}: ^1H-NMR ($CDCl_3$) δ 1.94 (d, J = 6.7 Hz, 1.05H), 2.01 (d, J = 6.7 Hz, 1.95H), 3.48–5.25 (m, 7H), 5.82 (m, 1H), 7.10–7.42 (m, 5H); MS (*m*/*z*) 329 (M^+), 202 (M^+ − I), 106, 91. Anal. Calcd for $C_{13}H_{16}INO$: C, 47.43; H, 4.90; N, 4.26. Found: C, 47.41; H, 4.92; N, 4.26.

***N*-Benzyl-*N*-methallyl-2-iodopropionamide (5d).** Compound **5d** was prepared from **1d** (117 mg, 0.5 mmol). Purification by column chromatography (hexane/AcOEt = 8:1) gave **5d** (135 mg, 73%). **5d**: colorless oil; IR (neat) 3029, 2972, 1651 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 1.71 (s, 1.8H, Me), 1.74 (s, 1.2H), 1.94 (d, J = 6.6 Hz, 1.2H), 1.99 (d, J = 6.6 Hz, 1.8H), 3.23–5.43 (m, 6H), 4.48 (q, J = 6.6 Hz, 0.4H), 4.50 (q, J = 6.6 Hz, 0.6H), 7.08–7.42 (m, 5H); MS (*m*/*z*) 343 (M^+), 216 (M^+ − I), 160, 120, 91. Anal. Calcd for $C_{14}H_{18}INO$: C, 48.99; H, 5.29; N, 4.08. Found: C, 49.32; H, 5.47; N, 4.23.

***N*-Benzyl-*N*-methallyl-2-iodo-3-phenylpropionamide (5e).** Compound **5e** was prepared from **1e** (295 mg, 1.0 mmol). Purification by column chromatography (hexane/AcOEt = 8:1) gave **5e** (305 mg, 73%). **5e**: colorless oil; IR (neat) 2933, 2835, 1651 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 1.55 (s, 1.7H), 1.71 (s, 1.3H), 3.15–5.20 (m, 9H), 6.71–7.38 (m, 10H); MS (*m*/*z*) 419 (M^+), 292 (M^+ − I), 202, 128. Anal. Calcd for $C_{20}H_{22}INO$: C, 57.29; H, 5.29; N, 3.34. Found: C, 57.27; H, 5.18; N, 3.38.

***N*-Allyl-3-iodopiperidin-2-one (5f).** Compound **5f** was prepared from **1f** (73 mg, 0.5 mmol). Purification by column chromatography (hexane/AcOEt = 4:1) gave **5f** (68 mg, 49%). **5f**: colorless oil; IR (neat) 2947, 1620 cm^{-1}: ^1H-NMR ($CDCl_3$)

(12) Examples of β-lactam synthesis by ring closure of *N*-α-haloacylated aminomalonate derivatives: (a) Sheehan, J. C.; Bose, A. K. *J. Am. Chem. Soc.* **1950**, *72*, 5158. (b) *Idem. Ibid.* **1951**, *78*, 1761. (c) Chatterjee, B. G.; Sahu, D. P. *Tetrahedron Lett.* **1977**, 1129. (d) Martin, T. A.; Comer, W. T.; Combs, C. M.; Corrigan, J. R. *J. Org. Chem.* **1970**, *35*, 3841. (e) Shiozaki, M.; Ishida, N.; Maruyama, H.; Hirooka, T. *Tetrahedron* **1983**, *39*, 2399.

(13) Examples of β-lactam synthesis using ring closure of *N*-(2,3-epoxybutyroyl)glycinate: (a) Shiozaki, M.; Ishida, N.; Hiraoka, T.; Yanagisawa, H. *Tetrahedron Lett.* **1981**, *22*, 5205. (b) Shiozaki, M.; Ishida, N.; Hiraoka, T.; Maruyama, H. *Tetrahedron* **1984**, *40*, 1795. (c) Maruyama, H.; Shiozaki, M.; Oida, S.; Hiraoka, T. *Tetrahedron Lett.* **1985**, *26*, 4521. (d) Hanessian, S.; Bedeshi, A.; Battistini, C.; Mongelli, N. *J. Am. Chem. Soc.* **1985**, *107*, 1438. (e) Chackalamannil, S.; Fett, N.; Kirkup, M.; Afonso, A. *J. Org. Chem.* **1988**, *53*, 450.

(14) An example of *cis* β-lactam synthesis: Kawabata, T.; Sumi, K.; Hiyama, T. *J. Chem. Soc.* **1989**, *111*, 6843.

δ 1.80−1.90 (m, 1H), 1.98−2.12 (m, 1H), 2.18−2.35 (m, 2H), 3.39−3.44 (m, 2H), 3.85 (dd, J = 6.0, 15.1 Hz, 1H), 4.09 (dd, J = 5.7, 15.1 Hz, 1H), 4.85 (m, 1H), 5.16−5.26 (m, 2H), 5.70−5.85 (m, 1H); ^{13}C-NMR ($CDCl_3$) δ 20.5, 23.0, 32.6, 46.9, 49.7, 117.4, 131.8, 167.3; MS (m/z) 265 (M^+), 138 (M^+ − I). Anal. Calcd for $C_8H_{12}INO$: C, 36.34; H, 4.56; N, 5.28. Found: C, 36.42; H, 4.65; N, 5.13.

***N*-Methallyl-3-iodopiperidin-2-one (5g).** Compound **5g** was prepared from **1g** (77 mg, 0.5 mmol). Purification by column chromatography (hexane/AcOEt = 5:1) gave **5g** (106 mg, 76%). **5g**: colorless oil; IR (neat) 2936, 1647 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.70 (s, 3H), 1.78−1.90 (m, 1H), 2.00−2.18 (m, 1H), 2.20−2.35 (m, 2H), 3.30−3.42 (m, 2H), 3.57 (d, J = 15.0 Hz, 1H), 4.27 (d, J = 15.0 Hz, 1H), 4.82 (brs, 1H), 4.86 (m, 1H), 4.90 (brs, 1H); ^{13}C-NMR ($CDCl_3$) δ 20.0, 20.6, 23.1, 32.6, 46.7, 52.5, 112.5, 140.2, 167.6; MS (m/z) 279 (M^+), 153, 124, 111. Anal. Calcd for $C_9H_{14}INO$: C, 38.72; H, 5.06; N, 5.02. Found: C, 38.64; H, 4.86; N, 5.07.

***N*-Methallylhexahydro-3-iodoazepin-2-one (5h).** Compound **5h** was prepared from **1h** (168 mg, 1.0 mmol). Purification by column chromatography (hexane/AcOEt = 5:1) gave **5h** (190 mg, 64%). **5h**: colorless oil; IR (neat) 2932, 1635 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.40−2.10 (m, 6H), 1.68 (s, 3H), 3.26 (m, 1H), 3.68 (d, J = 14.9 Hz, 1H), 3.76 (dd, J = 10.7, 15.1 Hz, 1H), 4.18 (d, J = 14.9 Hz, 1H), 4.81 (bs, 1H), 4.87 (bs, 1H), 5.02 (dd, J = 2.5, 6.3 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 20.0, 27.2, 28.1, 30.3, 32.4, 48.1, 55.2, 112.7, 140.9, 170.7; MS (m/z) 293 (M^+), 166 (M^+ − I), 153, 138, 111. Anal. Calcd for $C_{10}H_{16}INO$: C, 40.97; H, 5.50; N, 4.78. Found: C, 40.68; H, 5.46; N, 4.66.

***N*-Benzyl-*N*-methallyl-2-iodo-4-(methoxymethoxy)butanamide (5k).** Compound **5k** was prepared from **1k** (266 mg, 0.9 mmol). Purification by column chromatography (hexane/AcOEt = 5:1) gave **5k** (242 mg, 64%). **5k**: colorless oil; IR (neat) 2932, 1651 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.71 (s, 1.7H), 1.74 (s, 1.3H), 2.20−2.40 (m, 2H), 3.25 (s, 1.3H), 3.34 (s, 1.7H), 3.30−5.20 (m, 11H), 7.12−7.40 (m, 5H); MS (m/z) 402 (M^+ − Me), 386 (M^+ − OMe), 356, 290, 259, 258, 230, 160, 131. Anal. Calcd for $C_{17}H_{24}INO$: C, 48.93; H, 5.80; N, 3.36. Found: C, 48.76; H, 5.77; N, 3.33.

***N*-Benzyl-*N*-methallyl-2-iodo-4-acetoxybutanamide (5l).** Compound **5l** was prepared from **1l** (245 mg, 0.8 mmol). Purification by column chromatography (hexane/AcOEt = 5:1) gave **5l** (216 mg, 62%). **5l**: colorless oil; IR (neat) 3030, 2937, 1742, 1651 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.58, 1.72, 1.75, 2.01, 2.04 (s × 5, 6H), 2.28−2.50 (m, 2H), 3.28−5.40 (m, 9H), 7.10−7.40 (m, 5H); MS (m/z) 342 (M^+ − $AcOCH_2$), 288 (M^+ − I), 246, 228, 160, 131. Anal. Calcd for $C_{17}H_{22}INO_3$: C, 49.17; H, 5.34; N, 3.37. Found: C, 49.41; H, 5.33; N, 3.45.

***N*-Benzyl-*N*-methallyl-2-iodo-7-(methoxycarbonyl)-6-heptenamide (5m).** Compound **5m** was prepared from **1m** (168 mg, 0.5 mmol). Purification by column chromatography (hexane/AcOEt = 5:1) gave **5m** (139 mg, 60%). **5m**: colorless oil; IR (neat) 2947, 1723, 1651 cm^{-1}: ^{1}H-NMR ($CDCl_3$) δ 1.23−1.70 (m, 2H), 1.71, 1.75 (s × 2, 3H), 1.96−2.40 (m, 4H), 3.33 (d, J = 15.3 Hz, 0.4H), 3.53 (d, J = 15.6 Hz, 0.6H), 3.72, 3.78 (s × 2, 3H), 3.82−5.40 (m, 6H), 5.74 (d, J = 15.8 Hz, 0.6H), 5.82 (d, J = 15.6 Hz, 0.4H), 6.83 (td, J = 7.1, 15.6 Hz, 0.4H), 6.92 (td, J = 7.1, 15.7 Hz, 0.6H), 7.11−7.41 (m, 5H); MS (m/z) 455 (M^+), 424, 396, 328, 296, 268, 160, 137. Anal. Calcd for $C_{20}H_{26}INO_3$: C, 52.75; H, 5.76; N, 3.08. Found: C, 52.98; H, 5.83; N, 2.97.

Cyclic Imidate Intermediate (2d). To a solution of the amide **1d** (55 mg, 0.25 mmol) in $CDCl_3$ (10 mL) was added I_2 (190 mg, 0.75 mmol). After stirring for 2 h at rt, the ^{1}H- and ^{13}C-NMR spectra of the reaction mixture were measured. **2d**: ^{1}H-NMR ($CDCl_3$) δ 1.52 (t, J = 7.5 Hz, 3H), 2.08 (s, 3H), 3.15 (m, 2H), 3.54 (d, J = 11.9 Hz, 1H), 3.68 (d, J = 11.9 Hz, 1H), 4.02 (d, J = 12.2 Hz), 4.27 (d, J = 12.2 Hz, 1H), 5.05 (d, J = 14.7 Hz, 1H), 5.12 (d, J = 14.7 Hz, 1H), 7.26−7.53 (m, 5H); ^{13}C-NMR ($CDCl_3$) δ 9.4, 11.7, 22.4, 26.0, 53.4, 60.2, 91.4, 129.3, 129.5, 130.0, 130.3, 177.7.

(2*S*)-*N*-(2-Iodo-3-phenylpropionyl)-2-vinylpyrrolidine (5n). Compound **5n** was prepared from **1n** (607 mg, 2.7 mmol) in accordance with general procedure. Purification by column chromatography (hexane/AcOEt = 6:1) gave **5n** (690 mg, 73%). **5n**: colorless oil; IR (neat) 2972, 1651 cm^{-1}: ^{1}H-NMR ($CDCl_3$) δ 1.45−2.10 (m, 4H), 3.10−3.70 (m, 4H), 4.25−5.25 (m, 4H), 5.55−5.86 (m, 1H), 7.15−7.35 (m, 5H); MS (m/z) 355 (M^+), 228. 131, 91. Anal. Calcd for $C_{15}H_{18}INO$: C, 50.71; H, 5.11; N, 3.94. Found: C, 50.49; H, 5.15; N, 3.89.

(2*S*)-*N*-(2-Iodopropionyl)-2-vinylpyrrolidine (5o). Compound **5o** was prepared from **1o** (500 mg, 3.3 mmol) in accordance with general procedure. Purification by column chromatography (hexane/AcOEt = 10:1) gave **5o** (584 mg, 64%). **5o**: colorless oil; IR (neat) 2970, 2876, 1651 cm^{-1}: ^{1}H-NMR ($CDCl_3$) δ 1.80−2.15 (m, 7H), 3.30−3.70 (m, 2H), 4.41−4.52 (m, 2H), 5.01−5.25 (m, 2H), 5.81 (m, 1H); MS (m/z) 279 (M^+), 152 (M^+ − I), 124. Anal. Calcd for $C_9H_{14}INO$: C, 38.72; H, 5.06; N, 5.02. Found: C, 38.52; H, 5.07; N, 4.94.

(1*R*,2*R*,7a*S*)-Hexahydro-1-(iodomethyl)-2-(phenylmethyl)-3*H*-pyrrolizin-3-one (6n). To a solution of iodoamide **5n** (357 mg, 1 mmol) in dry benzene (5 mL) was added EtI (0.3 mmL, 3.5 mmol) and $(n\text{-}Bu_3Sn)_2$ (0.3 mL, 0.6 mmol), and then the reaction mixture was irradiated with high pressure mercury lamp (Ushio 100W) at rt for 1 h. Et_2O and 10% aqueous KF solution was added, and the mixture was stirred for 30 min. After filtration of the mixture with Celite, the filtrate was extracted with Et_2O. The Et_2O extracts were washed with brine, dried over $MgSO_4$, and evaporated to dryness. Purification of the residue by column chromatography (hexane/AcOEt = 2:1) and then MPLC (hexane/AcOEt = 1:1) gave **6n** (246 mg, 69%). **6n**: white crystals; mp 64−66 °C; $[\alpha]^{24}_D$ −40.58 (c = 1.02, $CHCl_3$); IR (KBr) 2889, 1679 cm^{-1}: ^{1}H-NMR ($CDCl_3$) δ 1.22 (quint, J = 11.5 Hz, 1H), 1.90−2.10 (m, 3H), 2.22 (m, 1H), 2.69 (dd, J = 8.8, 13.9 Hz, 1H), 2.76 (dd, J = 8.7, 10.1 Hz, 1H), 2.80 (m, 1H), 2.85 (dd, J = 3.7, 10.1 Hz, 1H), 3.07 (m, 1H), 3.28 (dd, J = 4.5, 13.9 Hz, 1H), 3.40−3.60 (m, 2H), 7.18−7.40 (m, 5H); ^{13}C-NMR ($CDCl_3$) δ 8.4, 26.4, 31.9, 36.1, 41.2, 49.5, 54.2, 66.3, 126.6, 128.7, 129.0, 138.9, 173.4; MS (m/z) 355 (M^+), 228 (M^+ − I), 131, 91. Anal. Calcd for $C_{15}H_{18}INO$: C, 50.71; H, 5.11; N, 3.94. Found: C, 50.89; H, 5.13; N, 4.07.

(1*R*,2*R*,7a*S*)-Hexahydro-1-(iodomethyl)-2-methyl-3*H*-pyrrolizin-3-one (6o). **6o** was prepared from **5o** (142 mg, 0.5 mmol) in accordance with the procedure for **6n** (irradiation for 20 h at rt). Purification by column chromatography (hexane/AcOEt = 1:1) gave **6o** (87 mg, 61%). **6o**: white crystals; mp 78−79 °C; $[\alpha]^{28}_D$ +43.01 (c = 1.00, $CHCl_3$); IR (KBr) 2964, 2871, 1678 cm^{-1}: ^{1}H-NMR ($CDCl_3$) δ 1.17 (d, J = 7.1 Hz, 3H), 1.42 (m, 1H), 1.84 (m, 1H), 2.04−2.11 (m, 2H), 2.32 (m, 1H), 2.53 (qd, J = 7.1, 10.7 Hz, 1H), 3.08 (m, 1H), 3.19 (dd, J = 9.0, 10.2 Hz, 1H), 3.42 (dd, J = 3.4, 10.2 Hz, 1H), 3.51−3.58 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ 6.5, 13.9, 26.6, 31.8, 41.1, 47.6, 53.2, 66.0, 174.4; MS (m/z) 279 (M^+), 152 (M^+ − I). Anal. Calcd for $C_9H_{14}INO$: C, 38.72; H, 5.06; N, 5.02. Found: C, 39.12; H, 5.06; N, 5.19.

(1*R*,2*R*,7a*S*)-Hexahydro-1-(acetoxymethyl)-2-(phenylmethyl)-3*H*-pyrrolizin-3-one (7n). To a solution of lactam **6n** (246 mg, 0.7 mmol) in AcOH (6 mL) was added AcOAg (380 mg, 2.2 mmol), and then the reaction mixture was stirred at 60 °C for 30 min. The mixture was poured into 5% aqueous $NaHCO_3$ solution and extracted with AcOEt. The AcOEt extracts were washed with brine, dried over $MgSO_4$, and evaporated to dryness. Purification by column chromatography (hexane/AcOEt = 2:1) gave **7n** (169 mg, 88%). **7n**: colorless oil; $[\alpha]^{26}_D$ −48.80 (c = 1.00, $CHCl_3$); IR (neat) 2948, 2888, 1740, 1693 cm^{-1}: ^{1}H-NMR ($CDCl_3$) δ 1.15 (m, 1H), 1.92−2.10 (m, 4H), 2.00 (s, 3H), 2.79 (dd, J = 8.0, 13.5 Hz, 1H), 2.90 (m, 1H), 3.07 (m, 1H), 3.21 (dd, J = 4.5, 13.5 Hz, 1H), 3.47−3.59 (m, 2H), 3.76 (dd, J = 7.5, 11.0 Hz, 1H), 3.79 (dd, J = 5.1, 11.0 Hz, 1H), 7.15−7.22 (m, 5H); ^{13}C-NMR ($CDCl_3$) δ 20.8, 26.5, 31.6, 36.0, 41.2, 46.5, 50.1, 63.1, 64.9, 126.5, 128.6, 129.2, 139.0, 170.5, 173.8; MS (m/z) 287 (M^+), 244 (M^+ − OAc), 228, 214, 136, 91; high-resolution MS calcd for $C_{17}H_{21}NO_3$ (M^+) 287.1521, found 287.1525.

(1*R*,2*R*,7a*S*)-Hexahydro-1-(acetoxymethyl)-2-methyl-3*H*-pyrrolizin-3-one (7o). **7o** was prepared from **6o** (80 mg, 0.3 mmol) in accordance with the procedure for **7n**. Purification by column chromatography (hexane/AcOEt = 1:1) gave **7o** (51 mg, 85%). **7o**: colorless oil; $[\alpha]^{24}_D$ +22.54 (c = 1.10, $CHCl_3$); IR (neat) 2968, 2885, 1742, 1696 cm^{-1}: ^{1}H-NMR

($CDCl_3$) δ 1.19 (d, J = 7.0 Hz, 3H), 1.39 (m, 1H), 1.93–2.11 (m, 4H), 2.08 (s, 3H), 2.61 (qd, J = 7.0, 11.2 Hz, 1H), 3.07 (m, 1H), 3.58 (m, 2H), 4.15 (dd, J = 7.6, 11.3 Hz, 1H), 4.26 (dd, J = 4.9, 11.3 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 14.3, 20.8, 26.7, 31.4, 41.2, 43.5, 50.5, 62.8, 64.5, 170.7, 174.9; MS (m/z) 211 (M^+), 183, 168, 152, 136, 124; high-resolution MS calcd for $C_{11}H_{17}NO_3$ (M^+) 211.1208, found 211.1216.

Ethyl *N*-Allyl-*N*-(2-iodopropionyl)glycinate (5p). Compound **5p** was prepared from **1p** (1.64 g, 8.2 mmol) in accordance with the general procedure. Purification by column chromatography (hexane/AcOEt = 4:1) gave **5p** (1.43 g, 54%). **5p**: colorless oil; IR (neat) 2982, 1746, 1656 cm^{-1}: ^{1}H-NMR ($CDCl_3$) δ 1.28 (t, J = 7.0 Hz, 2.1H), 1.30 (t, J = 7.0 Hz, 0.9H), 1.97 (d, J = 6.7 Hz, 2.1H), 1.98 (d, J = 6.7 Hz, 0.9H), 3.78–3.94 (m, 2H), 4.15–4.30 (m, 4H), 4.38 (q, J = 7.0 Hz, 0.4H), 4.58 (q, J = 7.0 Hz, 0.6H), 5.17–5.27 (m, 2H), 5.76 (tdd, J = 6.0, 10.3, 17.0 Hz, 0.4H), 5.89 (tdd, J = 5.2, 10.3, 17.0 Hz, 0.6 H); MS (m/z) 325 (M^+), 280 (M^+ − OEt), 252, 198, 183, 142. Anal. Calcd for $C_{10}H_{16}INO_3$: C, 36.94; H, 4.96; N, 4.31. Found: C, 36.83; H, 4.93; N, 4.37.

(3S*,4S*)-*N*-Allyl-4-(methoxycarbonyl)-3-methylazetidin-2-one (8p). To a solution of α-iodo amide **5p** (206 mg, 0.6 mmol) in THF (5 mL) was added slowly *t*-BuOK (100 mg, 0.9 mmol), and then the reaction mixture was stirred at rt for 1 h. After addition of 10% HCl solution to the mixture at 0 °C, the mixture was extracted with CH_2Cl_2. The CH_2Cl_2 extracts was washed with 5% aqueous $NaHCO_3$ solution and brine, dried over $MgSO_4$, and evaporated to dryness. Purification of the residue by column chromatography (hexane/AcOEt = 4:1) gave β-lactam **8p** (43 mg, 34%). **8p**: colorless oil; IR (neat) 2981, 1740–1760 cm^{-1}: ^{1}H-NMR ($CDCl_3$) δ 1.19 (d, J = 7.5 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H), 3.51 (dq, J = 5.8, 7.5 Hz, 1H), 3.67 (dd, J = 7.5, 15.3 Hz, 1H), 4.15–4.30 (m, 4H), 5.15–5.25 (m, 2H), 5.77 (m, 1H); ^{13}C-NMR ($CDCl_3$) δ 9.8, 14.3, 43.9, 48.4, 55.5, 67.3, 119.0, 131.4, 169.2, 169.6; MS (m/z) 198 (M^+ − H), 182 (M^+ − Me), 169 (M^+ − CO), 142, 124, 114, 99, 86. Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.89; H, 7.67; N, 7.10. Found: C, 60.57; H, 7.66; N, 7.00.

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