Electrophilic Olefin Heterocyclization in Organic Synthesis.[1] Highly Stereoselective Synthesis of Trans 3,5-Disubstituted Pyrrolidin-2-ones by Iodolactamization via Homoallylic Asymmetric Induction

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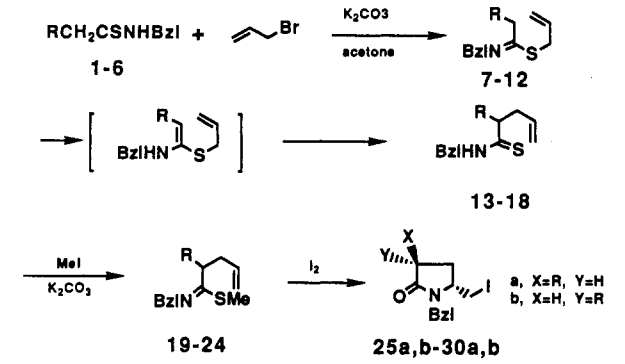
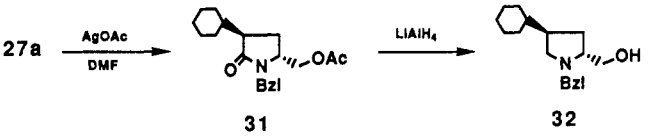
α-Substituted γ,δ-unsaturated thioimidates **19–24**, prepared by methylation of the corresponding thioamides **13–18**, undergo iodine-induced lactamization to provide the 3,5-disubstituted pyrrolidin-2-ones **25a,b–30a,b**. High 1,3-asymmetric induction by the homoallylic substituents is observed in this iodolactamization. The origin of the trans diastereoselectivity of the reaction is explained by nonbonded interactions in transition states. The γ-lactams served as precursors for pharmacologically active compounds.

Diastereoselective eletrophilic heterocyclization reactions which proceed with asymmetric induction are commonly employed to control relative stereochemistry in cyclic compounds.[2] A reaction particularly well-suited for this kind of asymmetry transfer is the formation of five-membered rings by using various allylic inducer groups.[3] However, homoallylic chiral induction (1,3-asymmetric induction) is rare due to the remoteness of the homoallylic center together with the conformational flexibility of five-membered transition states.[4] Indeed, electrophile-mediated intramolecular amination accompanied by homoallylic induction has been only rarely studied.[5] We became interested in homoallylic asymmetric induction in the formation of γ-lactams after we had developed a method which allows, via allylic asymmetric induction, the stereoselective preparation of 4,5-disubstituted pyrrolidin-2-ones leading to biologically active compounds.[1d] We now describe the details of our investigation of homoallylic asymmetric induction in the iodine-driven lactamization of α-substituted γ,δ-unsaturated thioimidates, strategy with considerable potential in the synthesis of stereochemically defined nitrogen heterocycles.[6]

Scheme I



Scheme II



Results and Discussion

The preparation of α-substituted γ,δ-unsaturated secondary thioamides **13–18**, iodolactamization precursors to substrates **19–24**, is depicted in Scheme I. Treatment of α-substituted *N*-benzylthioamides **1–6** with allyl bromide in the presence of potassium carbonate in acetone at room temperature for 15 h gave *N*-benzyl-*S*-allylthioimidates **7–12**, respectively. Without further purification, **7–12** underwent thio-Claisen rearrangement at 175 °C for **7–9** and at 90 °C for **10–12** to provide the desired thioamides **13–18** in good yields as shown in Table I.

The iodolactamization reactions of **19–24**, prepared by methylation of **13–18** with methyl iodide, were performed by using 1.5 equiv of iodine in tetrahydrofuran (THF) at 5 °C providing diastereomeric mixtures of γ-lactams **25a,b–30a,b**, respectively, with high 1,3-asymmetric induction as shown in Table II. Diastereomeric ratios for **25a,b–27a,b** were determined by examining ^{1}H NMR spectra of these crude reaction mixtures. Since diastereomers of **28a,b–30a,b** can be separated easily by column chromatography, their isolated ratios are described.

Table I. Preparation of *N*-Benzyl-2-substituted-thiopent-4-enamides 13–18

entry	substrate	R	reaction temp, °C	product	yield, %
1	1	CH_3	175	13	79
2	2	Ph	175	14	86
3	3	cyclohexyl	175	15	84
4	4	CbzNH	90	16	85
5	5	BocNH	90	17	90
6	6	BzlO	90	18	93

Table II. Formation of γ-Lactams 25–30

entry	substrate	product	yield,[a] %	ratio (a:b)
1	**19**	**25a,b**	48	12:1
2	**20**	**26a,b**	71	13:1
3	**21**	**27a,b**	48	14:1
4	**22**	**28a,b**	58	5.2:1
5	**23**	**29a,b**	53	4.5:1
6	**24**	**30a,b**	57	2.4:1

[a] Yields from thioamides **13–18** are shown.

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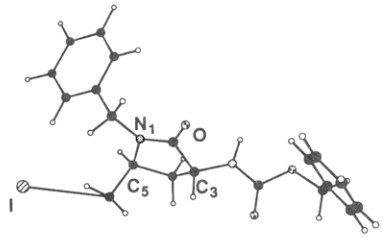


Figure 1. X-ray crystal structure of **28a** drawn by Chem 3D.

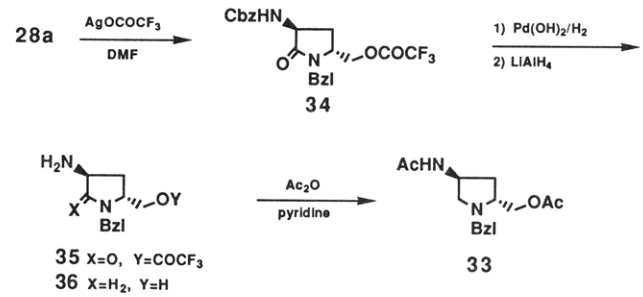
Table III. ^{1}H NMR Data for Methylene Protons at C-4 in 3,5-Disubstituted Pyrrolidin-2-ones

compd	δ, ppm
25a	1.76–2.12 (m, 2 H)
26a	2.19–2.43 (m, 2 H)
27a	1.91–2.02 (m, 2 H)
28a	2.08–2.17 (m, 1 H), 2.43 (m, 1 H)
28b	2.06–2.26 (m, 1 H), 2.71–2.82 (m, 1 H)
29a	2.01–2.17 (m, 1 H), 2.42–2.50 (m, 1 H)
29b	1.50–1.70 (m, 1 H), 2.73 (m, 1 H)
30a	2.09 (m, 2 H)
30b	1.87–1.95 (m, 1 H), 2.35–2.45 (m, 1 H)

The trans relationship between the cyclohexyl and the iodomethyl group of the major isomer **27a** was determined by its transformation into the known compound **32** as follows (Scheme II). Treatment of **27a** with silver acetate in DMF gave the acetate **31**, which was reduced with lithium aluminum hydride ($LiAlH_4$) to afford the racemate of *trans*-4-cyclohexyl-L-prolinol (**32**), a constituent of fosenopril (angiotensin converting enzyme inhibitor).[7] The ^{13}C NMR spectrum of **32** was identical with that of the reported sample. The trans stereochemical assignment for **28a** was confirmed by X-ray crystallographic analysis (Figure 1).

With these results in hand, the trans or cis relationship between the C-3 substituent and the iodomethyl group was assigned by inspection of the ^{1}H NMR spectrum involving the characteristic behavior by using chemical shift data for the methylene protons at C-4 (Table III). In the case of the cis isomers (**28b–30b**), the signals for 4α-H and 4β-H were split into two sets, usually separated by 0.5–1.1 ppm, presumably due to a stable conformation in which the 3- and 5-substituents are in quasi-equatrial positions. On the other hand, the chemical shift of C-4 methylene in the trans isomers (**25a–30a**) and usually overlapped appeared between 4α-H and 4β-H of the cis isomers, presumably owing to conformational mobility. Similar arguments have been discussed for the γ-lactone ring by Altaman et al.[8]

Scheme III



As shown in Table II, 1,3-trans asymmetric induction was observed for this homoallylic system. In contrast to allylic chiral induction, homoallylic chiral induction has only recently been investigated, and the control elements operative in these cyclizations are less understood. The literature contains few examples of homoallylic induction. Among them, Labelle et al.[4c] recently reported the etherification with homoallylic chiral induction under kinetic condition, results cleanly rationalized by estimating transition-state energies for the various conformers on the basis of AM1 calculations. While their rationalization can not explain our all-trans selectivities, they may be rationalized as follows (Figure 2). It is assumed that transition states arising from conformations with minimum nonbonded interaction are more favored.[9] Among four possible conformers for transition states, the conformers **31B** and **31D** may be diminished due to $A^{1,2}$ strain[10] arising from eclipsed relationship between the homoallylic substituent (R) and the bulky methylthio group[11] (Newman projection B). The conformer **31C** presents pseudo-1,3-diaxial interaction between R and the alkene–I_2 π-complex,[12] accounting for a modest preference for the product (trans) from the conformer **31A**. On the other hand, in a halolactonization goverened by a homoallylic nitrogen substituent, Ohfune found that the major isomer formed with a cis product owing to chelation control between an amino group and halonium.[4b] Their results are in sharp contrast with our observed trans selectivity (entries 4 and 5). It seems likely that their reaction would proceed under thermodynamic conditions. However, in our systems controlled by a homoallylic nitrogen or an oxygen substituent (entries 4–6), trans selectivity is not as high as in systems with a homoallylic alkyl substituent (entries 1–3). When R is a substituent containing an unpaired electron such as nitrogen or oxygen, the chelation effect rather than nonbonded interaction between R and the olefin–iodine π-complex[13]

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Table IV. Final Atomic Coordinates and Equivalent Isotropic or Isotropic Thermal Parameters with esd in Parentheses

no.	atom	position	x	y	z	B_{eq}[a]
1	I	1	0.83253 (5)	0.08528 (9)	0.02541 (5)	7.5 (0.4)
2	N	2	0.6230 (5)	−0.1634 (7)	0.0236 (4)	3.7 (3)
3	C	3	0.5413 (6)	−0.1516 (8)	−0.0430 (5)	3.6 (3)
4	C	4	0.5637 (5)	−0.0931 (8)	−0.1262 (5)	3.4 (3)
5	C	5	0.6779 (6)	−0.1205 (9)	−0.1055 (5)	3.9 (4)
6	C	6	0.7129 (5)	−0.1170 (8)	−0.0012 (5)	3.4 (3)
7	O	7	0.4582 (4)	−0.1790 (7)	−0.0401 (4)	5.2 (3)
8	C	8	0.6250 (6)	−0.2003 (9)	0.1150 (5)	4.5 (4)
9	C	9	0.6895 (6)	−0.3240 (9)	0.1520 (5)	3.9 (4)
10	C	10	0.6546 (7)	−0.4609 (10)	0.1326 (5)	4.8 (4)
11	C	11	0.7122 (8)	−0.5733 (10)	0.1644 (6)	6.2 (5)
12	C	12	0.8075 (8)	−0.5531 (12)	0.2135 (7)	7.0 (6)
13	C	13	0.8426 (7)	−0.4199 (12)	0.2339 (7)	6.8 (5)
14	C	14	0.7835 (6)	−0.3070 (10)	0.2011 (6)	5.0 (4)
15	C	15	0.7415 (6)	0.0301 (10)	0.0375 (6)	5.3 (4)
16	N	16	0.5099 (5)	−0.1561 (6)	−0.2098 (4)	3.8 (3)
17	C	17	0.4538 (6)	−0.0784 (8)	−0.2756 (5)	3.7 (3)
18	O	18	0.4490 (4)	0.0489 (5)	−0.2792 (3)	4.1 (2)
19	O	19	0.4012 (4)	−0.1632 (5)	−0.3429 (3)	4.3 (2)
20	C	20	0.3342 (7)	−0.0908 (9)	−0.4173 (5)	4.8 (4)
21	C	21	0.2429 (6)	−0.0448 (8)	−0.3970 (5)	4.3 (4)
22	C	22	0.2144 (7)	−0.0940 (11)	−0.3231 (6)	5.7 (5)
23	C	23	0.1268 (8)	−0.0484 (13)	−0.3098 (7)	7.0 (6)
24	C	24	0.0690 (7)	0.0462 (12)	−0.3772 (8)	7.0 (6)
25	C	25	0.0948 (7)	0.0929 (12)	−0.4425 (7)	6.7 (5)
26	C	26	0.1826 (7)	0.0479 (9)	−0.4558 (6)	5.4 (4)
27	H	1	0.554 (5)	0.003 (8)	−0.131 (5)	1.4
28	H	2	0.711 (5)	−0.048 (8)	−0.138 (5)	1.6
29	H	3	0.691 (5)	−0.226 (9)	−0.131 (5)	3.3
30	H	4	0.759 (5)	−0.183 (9)	0.024 (5)	2.8
31	H	5	0.559 (5)	−0.218 (9)	0.109 (5)	2.6
32	H	6	0.650 (6)	−0.118 (9)	0.153 (5)	3.0
33	H	7	0.587 (5)	−0.464 (8)	0.095 (5)	1.4
34	H	8	0.687 (7)	0.342 (11)	0.152 (6)	5.7
35	H	9	0.849 (6)	−0.637 (9)	0.239 (6)	3.6
36	H	10	0.909 (7)	−0.406 (10)	0.267 (6)	5.3
37	H	11	0.804 (6)	−0.214 (11)	0.219 (6)	5.7
38	H	12	0.701 (6)	0.085 (9)	0.999 (6)	3.9
39	H	13	0.744 (6)	0.040 (9)	0.104 (5)	3.5
40	H	14	0.503 (5)	0.754 (9)	0.784 (5)	2.8
41	H	15	0.315 (7)	−0.151 (11)	−0.470 (6)	6.1
42	H	16	0.366 (6)	−0.013 (10)	−0.436 (5)	3.5
43	H	17	0.259 (6)	−0.173 (9)	−0.282 (5)	3.7
44	H	18	0.109 (7)	−0.097 (10)	−0.260 (6)	5.6
45	H	19	0.015 (6)	0.072 (10)	0.646 (6)	4.8
46	H	20	0.049 (5)	0.162 (9)	−0.487 (5)	2.8
47	H	21	0.209 (6)	0.074 (9)	−0.507 (6)	4.0

[a] $B_{eq} = {}^4/_3\Sigma_i\Sigma_j A_i A_j \beta_{ij}$.

Table V. Bond Lengths

I1–C15	2.12 (1)	C11–C12	1.37 (1)
N2–C3	1.32 (1)	C12–C13	1.37 (1)
N2–C6	1.48 (1)	C13–C14	1.38 (1)
N2–C8	1.43 (1)	N16–C17	1.33 (1)
C3–C4	1.53 (1)	C17–O18	1.22 (1)
C3–C7	1.22 (1)	C17–O19	1.36 (1)
C4–C5	1.52 (1)	O19–C20	1.45 (1)
C4–N16	1.45 (1)	C20–C21	1.47 (1)
C5–C6	1.54 (1)	C21–C22	1.37 (1)
C6–C15	1.54 (1)	C21–C26	1.38 (1)
C8–C9	1.51 (1)	C22–C23	1.38 (1)
C9–C10	1.40 (1)	C23–C24	1.37 (1)
C9–C14	1.35 (1)	C24–C25	1.37 (1)
C10–C11	1.36 (1)	C25–C26	1.38 (1)

in the conformer **31C** may be expected. Accordingly, **31C** may contribute to this cyclization, leading to a cis product, though this directing effect is weak owing to the remoteness of the chiral and prochiral centers.

The resulting iodo lactams constitute a promising class of bifunctional compounds which are amenable to manipulation. Indeed, 4-substituted pyrrolidin-2-ones have been converted to related biologically active compounds such as alkaloids and unusual γ-amino acids.[1c] Since the 3-substituted pyrrolidin-2-ones obtained have high potential as educts for the synthesis of stereochemically defined 5-membered nitrogen heterocycles such as 4-substituted prolines,[14] γ-lactam antibiotics,[15] and 4-aminopyrrolidines[16] with pharmacological interest, we directed our attention to the transformation of **28a** into racemate **33**, and a constituent of the potent DNA gyrase inhibitor (Scheme III). Treatment of **28a** with silver trifluoroacetate in DMF provided trifluoroacetate **34**, which was converted by subsequent hydrogenolysis [$Pd(OH)_2/H_2$], reduction ($LiAlH_4$), and acetylation (acetic anhydride/pyridine) without purification into the diacetate **33** in 15% yield from **28a**. The spectral data of **33** were identical with those reported.

(13) An iodonium character may exist, see ref 12.

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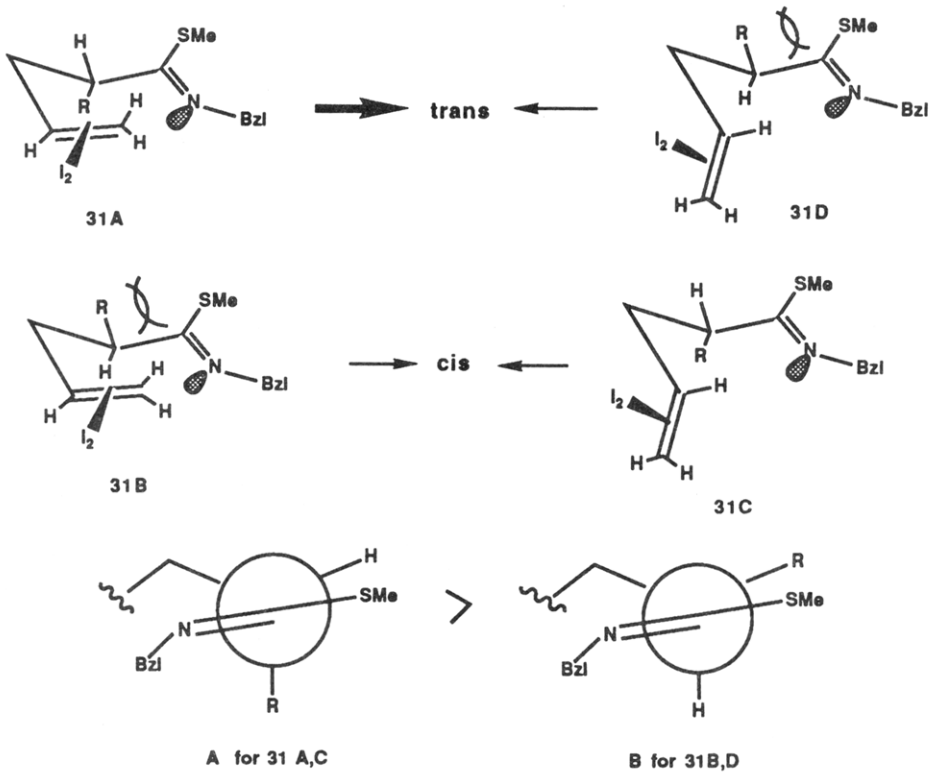

Figure 2.

Table VI. Bond Angles (deg)

atom 2	atom 1	atom 3	
C3	N2	C6	114.4 (6)
C3	N2	C8	123.7 (7)
C6	N2	C8	121.5 (5)
N2	C3	C4	107.8 (6)
N2	C3	O7	127.6 (7)
C4	C3	O7	124.6 (6)
C3	C4	C5	103.4 (5)
C3	C4	N16	111.3 (6)
C5	C4	N16	115.4 (6)
C4	C5	C6	104.2 (6)
N2	C6	C5	101.0 (5)
N2	C6	C15	109.4 (6)
C5	C6	C15	113.4 (6)
N2	C8	C9	114.5 (7)
C8	C9	C10	120.3 (6)
C8	C9	C14	121.7 (7)
C10	C9	C14	118.0 (7)
C9	C10	C11	121.1 (7)
C10	C11	C12	119.7 (9)
C11	C12	C13	120.0 (9)
C12	C13	C14	119.6 (8)
C9	C14	C13	121.5 (8)
I1	C15	C6	110.8 (6)
C4	N16	C17	121.3 (6)
N16	C17	O18	127.2 (6)
N16	C17	O19	109.6 (6)
O18	C17	O19	123.1 (6)
C17	O19	C20	114.8 (5)
O19	C20	C21	114.2 (7)
C20	C21	C22	122.2 (7)
C20	C21	C26	118.8 (8)
C22	C21	C26	119.0 (9)
C21	C22	C23	118.8 (8)
C22	C23	C24	121.6 (9)
C23	C24	C25	120.3 (9)
C24	C25	C26	118.1 (9)
C21	C26	C25	122.1 (9)

In summary, these iodine-driven α-substituted γ,δ-unsaturated thioimidates undergo high homoallylic asymmetric induction to provide γ-lactams, with a preferential trans arrangement of the two substituents on the newly formed heterocycle. The stereochemical control depends upon the choice of homoallylic substituents, and the trans selectivity diminishes somewhat by changing from alkyl to heteroatom (nitrogen or oxygen) substituent. The present method provides an interesting entry to functionalized γ-lactams, which should be convertible into related pharmacologically active compounds.

Experimental Section

Melting points were determined with a Yanaco micro melting point apparatus and are not corrected. Unless otherwise specified, short-path (bulb-to-bulb) distillations were carried out in a Kugelrohr apparatus. Microanalyses were performed by Microanalysis Center of Toyama Medical & Pharmaceutical University. Infrared spectra (IR) were measured with a JASCO A 102 spectrophotometer. Proton magnetic resonance (^{1}H NMR) were recorded either at 60 MHz on a JEOL PMX-60 instrument or at 270 MHz on a JEOL-FX270 instrument with tetramethylsilane as an internal standard. Carbon-13 NMR spectra were determined on a Varian XL-200 instrument with tetramethylsilane as an internal standard unless otherwise specified. Mass spectra (MS) and high-resolution mass spectra (HRMS) were measured on a JEOL JMS D-200. Column chromatography was performed on silica gel (Fuji-Davision BW-200, Merck 60 (No 9385), or Nakarai 60) with a medium-pressure apparatus. Separation of diastereomers was performed on a Kusano (Micro Pump KP-6H) apparatus with a silica gel column (Kusano CIG-10 mm and 5 mm). A solution of ethyl acetate/hexane as eluant was used unless otherwise specified. The extracts were dried with Na_2SO_4 unless otherwise specified.

***N*-Benzyl-2-methylpent-4-enethioamide (13).** To a suspension of *N*-benzylpropionthioamide (**1**) (195.6 mg, 1.10 mmol) and potassium carbonate (151.6 mg, 1.10 mmol) in acetone (5 mL) was added allyl bromide (0.14 mL, 1.65 mmol), and the reaction mixture was stirred for 48 h at room temperature. The insoluble materials were filtered off through Celite, and the filtrate was evaporated. To the residue was added water, and the mixture was extracted with ether three times. The extracts were washed with brine, dried with potassium carbonate, and evaporated to produce *S*-allylthioimidate **7**. Without further purification, **7** was heated for 1 h at 175 °C. The product was purified by column chromatography to yield **13** (190.1 mg, 79%) as a pale yellow oil:

IR (neat) 3250, 1520 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (d, J = 6.4 Hz, 3 H), 2.09–2.86 (m, 3 H), 4.79 (d, J = 5.0 Hz, 2 H), 4.78–5.23 (m, 2 H), 5.40–6.06 (m, 1 H), 7.30 (s, 5 H); HRMS calcd for $C_{13}H_{17}NS$ 219.1080, found 219.1072.

***N*-Benzyl-2-phenylpent-4-enethioamide (14)** was obtained in the same manner from *N*-benzylphenylacetothioamide (**2**) in 86% yield: mp 80–82.5 °C; IR (Nujol) 3175, 1535 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.74 (d, J = 5 Hz, 2 H), 4.85–5.16 (m, 2 H), 5.43–6.05 (m, 1 H), 7.23–7.33 (m, 10 H). Anal. Calcd for $C_{18}H_{19}NS$: C, 76.82; H, 6.81; N, 4.98. Found: C, 76.57; H, 6.80; N, 5.02.

***N*-Benzyl-2-cyclohexylpent-4-enethioamide (15)** was prepared in the same manner from *N*-benzylcyclohexylthioacetamide (**3**) in 84% yield as an oil: bp 127–135 °C (0.25 mmHg); IR (neat) 3175, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07–2.08 (m, 2 H), 2.15–2.66 (m, 2 H), 4.85 (d, J = 6.0 Hz, 2 H), 5.05–5.27 (m, 2 H), 5.47–6.12 (m, 1 H), 7.36 (s, 5 H); HRMS calcd for $C_{18}H_{25}NS$ 287.1706, found 287.1694.

***N*-Benzyl-2-[(benzyloxycarbonyl)amino]pent-4-enethioamide (16)** was obtained in a similar manner except for reaction temperature (at 90 °C) from [*N*-(benzyloxycarbonyl)amino]-thioacetamide (**4**) in 85% yield: mp 100–100.5 °C; IR (Nujol) 3230, 1680, 1530 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.54–2.78 (m, 2 H), 4.85 (d, J = 5.4 Hz, 2 H), 5.00 (s, 2 H), 4.98–4.29 (m, 2 H), 5.47–6.03 (m, 1 H), 7.32 (s, 10 H). Anal. Calcd for $C_{20}H_{22}N_2O_2S$: C, 67.77; H, 6.26; N, 7.90. Found: C, 67.77; H, 6.24; N, 7.67.

***N*-Benzyl-2-[(*tert*-butoxycarbonyl)amino]pent-4-enethioamide (17)** was prepared in a similar manner for **16** from *N*-benzyl[(*tert*-butoxycarbonyl)amino]thioacetamide (**5**) in 90% yield: mp 83–84.5 °C; IR (Nujol) 3320, 1670, 1510 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (s, 9 H), 2.66 (t, J = 7.2 Hz, 2 H), 4.52 (q, J = 7.2 Hz, 1 H), 4.88 (d, J = 5.4 Hz, 2 H), 5.18–5.37 (m, 2 H), 5.50–6.13 (m, 1 H), 7.40 (s, 5 H). Anal. Calcd for $C_{17}H_{24}N_2O_2S$: C, 63.72; H, 7.55; N, 8.74. Found: C, 63.46; H, 7.64; N, 8.61.

***N*-Benzyl-2-(benzyloxy)pent-4-enethioamide (18)** was obtained in the same manner from *N*,2-bis(benzyloxy)thioacetamide (**6**) in 93% yield as an oil: IR (neat) 3200, 1520 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.43–2.92 (m, 2 H), 4.52 (s, 2 H), 4.86 (d, J = 4.8 Hz, 2 H), 4.97–5.33 (m, 2 H), 5.56–6.12 (m, 1 H), 7.32 (s, 5 H), 7.37 (s, 5 H); HRMS $C_{19}H_{21}NOS$ 311.1335, found 311.1294.

General Procedure for Iodolactamization of α-Substituted γ,δ-Unsaturated Thioimidates. To a suspension of γ,δ-unsaturated secondary thioamides **13–18** (1 mmol) and K_2CO_3 (1 mmol) in acetone (5 mL) was added methyl iodide (1.5 mmol), and the reaction mixture was stirred for 15 h at room temperature. The insoluble material was removed by filtration through Celite, and the filtrate was evaporated. To the residue was added water. The mixture was extracted with ether three times. The extracts were washed with brine, dried with K_2CO_3, and evaporated to yield γ,δ-unsaturated thioimidates **19–24**, respectively. A solution of iodine (1.5 mmol) in THF (10 mL) was added dropwise to a solution of the thioimidates in THF (50 mL) with ice cooling. The reaction mixture was allowed to stand for 48 h at 5 °C. To the mixture was added saturated Na_2SO_3 until the color of iodine disappeared. The precipitate was filtered off. The filtrate was evaporated. The residue was extracted with ethyl acetate three times. The extracts were washed with brine, dried, and evaporated. Column chromatography of the residue yielded γ-lactams **25a,b–30a,b**, respectively.

***trans*-*N*-Benzyl-5-(iodomethyl)-3-methylpyrrolidin-2-one (25a)**: an oil; IR (neat) 1685 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (d, J = 7.0 Hz, 3 H), 1.70–1.81 (m, 1 H), 2.07–2.16 (m, 1 H), 2.71–2.79 (m, 1 H), 3.15 (dd, AB type J = 10.6, 7.0 Hz, 1 H), 3.24 (dd, AB type, J = 10.6, 2.9 Hz, 1 H), 3.39–3.47 (m, 1 H), 3.96, 4.99 (AB q, J = 15.0 Hz, each 1 H), 7.20–7.37 (m, 5 H); HRMS $C_{13}H_{16}INO$ 329.0278, found 329.0281.

***trans*-*N*-Benzyl-5-(iodomethyl)-3-phenylpyrrolidin-2-one (26a)**: mp 145–146 °C; IR (Nujol) 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.11–2.19 (m, 1 H), 2.46–2.534 (m, 1 H), 3.11–3.18 (m, 1 H), 3.22–3.27 (m, 1 H), 3.34 (br s, 1 H), 3.44–3.49 (m, 1 H), 4.08, 5.16 (AB q, J = 15.4 Hz, each 1 H), 7.26–7.53 (m, 10 H); HRMS calcd for $C_{18}H_{18}INO$ 391.0434, found 391.0395.

***trans*-*N*-Benzyl-5-(iodomethyl)-3-cyclohexylpyrrolidin-2-one (27a)**: mp 92.5–93.5 °C; IR (Nujol) 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00–1.86 (m, 11 H), 1.91–2.02 (m, 2 H), 2.61–2.69 (m, 1 H), 3.15–3.27 (m, 2 H), 3.32–3.36 (m, 1 H), 3.87, 5.08 (AB q, J = 16.2 Hz, each 1 H), 7.20–7.36 (m, 5 H). Anal. Calcd for $C_{18}H_{24}INO$: C, 54.42; H, 6.09; N, 3.53. Found: C, 54.12; H, 5.97; N, 3.24.

***trans*- or *cis*-*N*-Benzyl-5-(iodomethyl)-3-[(benzyloxycarbonyl)amino]pyrrolidin-2-one (28a,b). 28a**: mp 105.5–107.5 °C; IR (Nujol) 3340, 1710, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.08–2.17 (m, 1 H), 2.43 (t, J = 10.8 Hz, 1 H), 3.18 (t, J = 5.4 Hz, 2 H), 3.57 (br s, 1 H), 4.43–4.52 (m, 1 H), 3.99, 4.99 (AB q, J = 16.2 Hz, each 1 H), 5.11 (s, 2 H), 5.65 (m, 1 H), 7.30–7.35 (m, 10 H). Anal. Calcd for $C_{20}H_{21}IN_2O_3$: C, 51.74; H, 4.56; N, 6.03. Found: C, 51.75; H, 4.75; N, 5.89.

28b: mp 99–103 °C; IR (Nujol) 3250, 1710, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.06–2.26 (m, 1 H), 2.71–2.82 (m, 1 H), 3.26 (q, J = 5.4 Hz, 2 H), 4.33–4.42 (m, 1 H), 3.98, 5.09 (AB q, J = 15.4 Hz, each 1 H), 5.14 (s, 2 H), 5.47 (m, 1 H), 7.29–7.38 (m, 10 H). Anal. Calcd for $C_{20}H_{21}IN_2O_3$: C, 51.74; H, 4.56; N, 6.03. Found: C, 52.35; H, 4.56; N, 6.05.

***trans*- or *cis*-*N*-Benzyl-5-(iodomethyl)-3-[(*tert*-butoxycarbonyl)amino]pyrrolidin-2-one (29a,b). 29a**: mp 137–139 °C; IR (Nujol) 3370, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (s, 9 H), 2.01–2.17 (m, 1 H), 2.42–2.50 (m, 1 H), 3.16–3.26 (m, 2 H), 3.57 (t, J = 5.4 Hz, 1 H), 4.41–4.50 (m, 1 H), 4.01, 4.98 (AB q, J = 16.2 Hz, each 1 H), 5.40 (br s, 1 H), 7.23–7.36 (m, 5 H). Anal. Calcd for $C_{17}H_{23}IN_2O_3$: C, 47.76; H, 5.39; N, 6.51. Found: C, 47.46; H, 5.55; N, 6.42.

29b: mp 113–115 °C; IR (Nujol) 3360, 1695, 1675 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.47 (s, 9 H), 1.50–1.70 (m, 1 H), 2.73 (m, 1 H), 3.19–3.33 (m, 2 H), 4.32 (m, 1 H), 3.98, 5.08 (AB q, J = 16.2 Hz, each 1 H), 5.26 (br s, 1 H), 7.18–7.34 (m, 5 H). Anal. Calcd for $C_{17}H_{23}IN_2O_3$: C, 47.46; H, 5.39; N, 6.51. Found: C, 47.86; H, 5.71; N, 6.39.

***trans*- or *cis*-*N*-Benzyl-5-(iodomethyl)-3-(benzyloxy)-pyrrolidin-2-one (30a,b). 30a**: an oil; IR (neat) 1685 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.09 (q, J = 5.4 Hz, 2 H), 3.20 (t, J = 2.7 Hz, 2 H), 3.42–3.50 4.36 (m, 1 H), (m, 1 H), 3.90, 5.06 (AB q, J = 16.2 Hz, each 1 H), 4.77, 5.05 (AB q, J = 10.8 Hz, each 1 H), 7.22–7.42 (m, 10 H); HRMS $C_{19}H_{20}INO_2$ – $C_6H_5CH_2$ 329.9992, found 329.9957.

30b: mp 107–108.5 °C; IR (Nujol) 1685 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.87–1.95 (m, 1 H), 2.354–2.45 (m, 1 H), 3.11–3.18 (m, 1 H), 3.30–3.32 (m, 1 H), 3.34–3.40 (m, 1 H), 4.15 (q, J = 4.0 Hz, 1 H), 4.81, 4.95 (AB q, J = 10.8 Hz, each 1 H), 4.10, 5.00 (AB q, J = 16.2 Hz, each 1 H), 7.19–7.43 (m, 10 H). Anal. Calcd for $C_{19}H_{20}INO_2$: C, 54.17; H, 4.79; N, 3.32. Found: C, 54.13; H, 4.80; N, 3.15.

***trans*-*N*-Benzyl-2-(acetoxymethyl)-4-cyclohexylpyrrolidin-2-one (31).** A mixture of **27a** (0.3414 g, 0.86 mmol) and silver acetate (190 mg, 1.14 mmol) in DMF (5 mL) was stirred for 15 h at 70 °C. The insoluble material was removed by filtration through Celite and washed with ethyl acetate, and the combined solvents were evaporated. Column chromatography of the residue yielded **31** (153.5 mg, 54.2%) as an oil together with the recovery of **27a** (17 mg): IR (neat) 1755, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.09–1.72 (m, 11 H), 1.93 (m, 2 H), 2.04 (s, 3 H), 3.50–3.60 (m, 1 H), 3.95 (q, J = 5.4 Hz, 2 H), 4.18 (d, J = 5.4 Hz, 1 H), 4.00, 5.03 (AB q, J = 16.2 Hz, each 1 H), 7.26 (s, 5 H); HRMS calcd for $C_{20}H_{27}NO_3$ 329.1989, found 329.1972.

***trans*-*N*-Benzyl-2-(hydroxymethyl)-4-cyclohexylpyrrolidine (32).** To a solution of **31** (0.169 g, 0.513 mmol) in THF (8 mL) was added $LiAlH_4$ (97.3 mg, 2.56 mmol) with ice cooling. The reaction mixture was refluxed for 15 h. To the mixture was successively added water (0.1 mL), 15% NaOH solution (0.1 mL), and water (0.2 mL), and then it was dried. The mixture was filtered through Celite, and the filtrate was evaporated to yield **32** (0.14 g, 100%) as an oil: IR (neat) 3300 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89–1.71 (m, 11 H), 1.78–1.88 (m, 1 H), 1.92–2.07 (m, 2 H), 2.85 (m, 1 H), 3.07–3.13 (m, 1 H), 3.40–3.45 (m, 1 H), 3.66 (q, J = 5.4 Hz, 2 H), 3.43, 3.99 (AB q, J = 13.5 Hz, each 1 H), 7.32 (s, 5 H); ^{13}C NMR ($CDCl_3$) δ 26.203, 26.435, 31.759, 31.913, 33.307, 42.719, 43.638, 58.719, 59.296, 62.232, 64.198, 127.123, 128.336, 128.792, 138.864; HRMS calcd for $C_{18}H_{27}NO$ 273.2092, found 273.2092.

***trans*-*N*-Benzyl-5-[(trifluoroacetoxy)methyl]-3-[(benzyloxycarbonyl)amino]pyrrolidin-2-one (34).** A mixture of **28a** (0.304 g, 0.65 mmol) and silver trifluoroacetate (0.29 g, 1.31 mmol) in DMF (5 mL) was stirred at room temperature for 20 h. The insoluble material was removed by filtration through Celite and washed with ethyl acetate, and the combined solvents were

evaported. Column chromatography of the residue yielded **34** (0.18 g, 61%) as an oil: IR (neat) 3300, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.02-2.17 (m, 1 H), 2.39-2.42 (m, 1 H), 3.64-3.67 (m, 1 H), 3.94-3.95 (m, 1 H), 4.10, 4.92 (AB q, J = 15.2 Hz, each 1 H), 4.27-4.32 (m, 1 H), 4.42-4.51 (m, 1 H), 5.01 (s, 2 H), 6.02-6.04 (br s, 1 H), 7.32 (s, 10 H); HRMS calcd for $C_{22}H_{21}F_3N_2O_5$ 450.1403, found 450.1411.

***trans*-*N*-Benzyl-2-(acetoxymethyl)-4-(acetylamino)-pyrrolidine (33).** A suspension of **33** (0.18 g, 0.40 mmol) and $Pd(OH)_2$ (15 mg) in methanol (4 mL) was stirred under hydrogen at atmosphere for 3 h. The mixture was filtered through Celite and washed with methanol. The combined solvents were evaported and dried in vacuo to give crude *trans*-*N*-benzyl-5-[(trifluoroacetoxy)methyl]-3-aminopyrrolidin-2-one (**35**) (0.14 g). Without further purification, to a solution of **35** (0.14 g) in THF (5 mL) was added $LiAlH_4$ (31 mg, 0.8 mmol) with ice cooling. The reaction mixutre was refluxed for 7 h. To the mixture was successively added water (0.02 mL), 10% NaOH solution (0.02 mL), water (0.04 mL), and THF (10 mL), and then the mixture was dried with potassium carbonate. The mixture was filtered through Celite, and the filtrate was evaporated to afford the crude *trans*-*N*-benzyl-5-(hydroxymethyl)-3-aminopyrrolidine (**36**) (0.1 g). To a solution of **36** (0.06 g) in pyridine (0.39 ml) was added triethylamine (0.11 mL, 0.8 mmol) and acetic anhydride (0.19 mL, 2 mmol) with ice cooling. The reaction mixture was stirred at room temperature for 15 h, diluted with ethyl acetate, and washed with water and brine. The combined aqueous washings were extracted with methylene chloride. The combined organic solvents were dried and evaporated. Column chromatography of the residue yielded **33** (0.06 g) in 52% yield from **34**: mp 69-70 °C (lit.[16] 72-73 °C); IR (Nujol) 3300, 1720, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.77-1.78 (m, 1 H), 1.91 (s, 3 H), 2.07 (s, 3 H), 2.13-2.14 (m, 2 H), 3.00-3.05 (m, 1 H), 3.25 (dd, J = 6.3, 6.8 Hz, 1 H), 3.47 (d, J = 13.2 Hz, 1 H), 4.05-4.10 (m, 3 H), 4.32-4.40 (m, 1 H), 5.41 (br s, 1 H), 7.28-7.29 (m, 5 H).

X-ray Analysis of 28a. Crystals were obtained from the ethyl acetate solution which was kept in the desiccator filled with *n*-hexane vapor. The diffraction experiments were carried out using a crystal, the size of which was 0.3 × 0.2 × 0.1 mm. The diffractometer AFC/5(RIGAC) was used with a gfaphite-monochromated Cu Kα (r = 1.5418 Å) radiation. The unit cell dimensions were refined using the precisely measured 2θ values in the range of 30-60°. The crystal data are as follows: a = 14.166 (3) Å, b = 9.550 (2) Å, c = 15.226 (3) Å, β = 105.23 (9)°, U = 1987.4 $Å^3$, space group $P2_1/c$, Z = 4, D_x = 1.552 kg/m^3, μ(Cu Kα) = 130.95 cm^{-1}, 3376 unique reflections (2θ ≤ 130°) were measured, of which 2803 with $|F_{obs}| \geq 2.667\sigma(F)$ were used in the analysis. The structure was solved by the direct method using the program SIR85[17] and the difference Fourier method. The refinement of atomic parameters was carried out using the block-diagonal matrix least-squares method. After all the non-hydrogen atoms were refined with isotropic temperature factors, the empirical absorption corrections were applied following the DIFABS method.[18] The corrected structure factors were used throughout the successive refinement cycles. The anisotropic temperature factors were used for all the non-hydrogen atoms and the isotropic ones for the hydrogen atoms. The final R and R_w values were 0.076 and 0.081, where the minimized function was $\sum w = (|F_o| - |F_c|)^2$ and $\sqrt{w} = 1/\sigma(F)$. The maximum residual electron density is 0.4 $e/Å^3$. The atomic scattering factors were taken from the *International Tables for X-ray Crystallography*.[19]

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Synthesis and Crystal and Molecular Structure of the Conformationally Restricted Methionine Analogue (±)-2-*exo*-Amino-6-*endo*-(methylthio)bicyclo[2.2.1]heptane-2-*endo*-carboxylic Acid and Neighboring Group Participation in Its Anodic Oxidation

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(±)-2-*exo*-Amino-6-*endo*-(methylthio)bicyclo[2.2.1]heptane-2-*endo*-carboxylic acid (**1c**) was synthesized by amination of the lithium enolate of methyl 6-*endo*-(methylthio)bicyclo[2.2.1]heptane-2-*endo*-carboxylate with *O*-(mesitylenesulfonyl)hydroxylamine followed by hydrolysis. Its crystal and molecular structure was determined by single-crystal X-ray analysis. It crystallizes in the monoclinic space group $P2_{1/c}$ with a = 9.681 (6) Å, b = 10.276 (5) Å, c = 9.773 (4) Å, β = 91.23 (4)°, and Z = 4. The structure was solved by direct methods. Full-matrix least-squares refinement led to a conventional R factor of 0.048 after several cycles of anisotropic refinement. The structure is compared both with 6-*exo*-(methylthio)bicyclo[2.2.1]heptane-2-*endo*-carboxylic acid (**3**) and the HBr salt of 2-*exo*-aminobicyclo[2.2.1]heptane-2-*endo*-carboxylic acid (**2**). Electrochemical oxidation of **1c** in acetonitrile, using the technique of cyclic voltammetry, revealed two oxidation waves with peak potentials of 0.90 and 1.35 V. Controlled potential electrolysis of **1c** provided the corresponding sulfoxides as a mixture of diastereomers (in 60 and 25-30% yield, respectively), which were also prepared by chemical oxidation, derivatized, separated, and characterized. The remarkable cathodic shift of 450 mV for **1c** is ascribed to neighboring carboxylate participation in oxidation of the thioether moiety.

Electrochemical oxidation of the salt obtained from *endo*-acid **1a** and 2,6-di-*tert*-butylpyridine occurs with bromide catalysis of oxidation of the thioether moiety with neighboring carboxylate participation.[1] The bromide ion is oxidized to bromine at a peak potential of 0.65 V vs Ag/0.1 M $AgNO_3$ in acetonitrile reference electrode. The bromine then reacts with the thioether, and bromide ion is rapidly displaced by the neighboring carboxylate group

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