120.8, 109.7, 68.5. Anal. Calcd for $C_{21}H_{16}N_4$: C, 77.76; H, 4.97; N, 17.27. Found: C, 77.81; H, 4.96; N, 17.22.

Bis(benzotriazolo)(4-methylphenyl)methane (9c): mp 182.5-184.0 °C (lit.[12] mp 183-185 °C); ^{13}C NMR ($CDCl_3$) δ 146.2, 140.0, 132.4, 129.9, 129.7, 128.4, 126.9, 124.7, 120.1, 110.8, 72.4, 21.1.

Bis(benzotriazolo)-*n*-propylmethane (9d): mp 109-111 °C (lit.[12] mp 107-108 °C); ^{13}C NMR ($CDCl_3$) δ 131.2, 128.1, 124.7, 110.5, 72.2, 40.9, 20.7, 14.3 (one carbon is not observed).

Bis(phenylthio)(4-methylphenyl)methane (10). To a solution of **1a** or **1h** (1 mmol) in dry acetonitrile (5 mL) was added sodium thiophenolate (2 mmol) at -30 °C under nitrogen. The reaction was completed within 15 min, and the solid was filtered off as soon as possible. The solution was evaported, and product was recrystallized from petroleum ether to yield **10** (50%): mp 72-73 °C (lit.[19] oil was obtained); ^1H NMR ($CDCl_3$) δ 7.54-6.80 (m, 14 H), 5.40 (s, 1 H, CH), 2.32 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 137.7, 136.6, 134.7, 132.2, 129.1, 128.7, 127.7, 127.6, 60.1, 21.1. Anal. Calcd for $C_{20}H_{18}S_2$: C, 74.49; H, 5.63. Found: C, 74.14; H, 5.58.

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Electrophilic Olefin Heterocyclization in Organic Synthesis.[1] Stereoselective Synthesis of 4,5-Disubstituted γ-Lactams by Iodine-Induced Lactam Formation of γ,δ-Unsaturated Thioimidates

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Iodine-induced lactamization of γ,δ-unsaturated thioimidates proceeds regioselectively to provide γ-lactams. The iodolactamization with allylic substituents brings about 1,2-asymmetric induction, which depends on the allyl groups. Transformation of the *cis*-4-hydroxy-5-(iodomethyl)pyrrolidin-2-one (**24a**) among these highly functionalized γ-lactams into several biologically active compounds is described. In addition, the conversion of an optically active form of **24a** is discussed.

Electrophile-mediated additions to olefins are among the most fundamental and versatile tools in organic synthesis.[2] Recent experimental and theoretical studies have contributed significantly to the understanding of the origin of the stereoselectivity observed during the electrophilic addition to chiral alkenes.[3] The stereoselective synthesis of functionalized 4-6-membered heterocyclic ring systems by such oxidative additions (electrophilic olefin heterocyclization) has been especially notable. Most of these examples, however, are confined to the cyclization with oxygen nucleophiles as exemplified by halogenolactonization and -etherification. We found that γ,δ-unsaturated thioimidates underwent regioselective iodine-induced cyclization based on diastereoselective intramolecular addition of an amino nucleophile to afford γ-lactams, and we developed approaches to the stereoselective formation of 4,5-disubstituted pyrrolidin-2-ones from β-substituted γ,δ-unsaturated thioimidates via 1,2-asymmetric induction (allylic chiral induction).[4,5] In this paper we describe the experimental details for the iodine-induced lactamization method and the synthesis of biologically active compounds with further manipulation of the resulting iodolactams containing functional groups.

Results and Discussion

Iodine-Induced Lactamization of γ,δ-Unsaturated Thioimidates. The iodolactamization of *N*-benzyl γ,δ-unsaturated thioimidate **2a**, prepared from the corresponding secondary thioamide **1a** by methylation with methyl iodide in the presence of potassium carbonate, can be performed by using iodine in tetrahydrofuran (THF) at 5 °C to give γ-lactam **3a** in 72% overall yield from **1a**. The use of other solvents (CH_2Cl_2 and acetonitrile) resulted in low yields (20-35%). Thioimidates **2b-d** and **4** bearing substituents at the olefin underwent regio- and diastereoselective iodine-induced cyclization to provide γ-lactams **3b-d** and **5** as single isomers, respectively (see Table I).[6]

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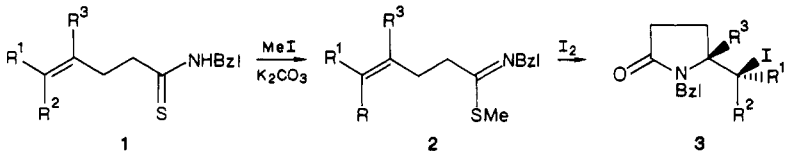
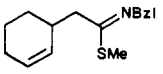
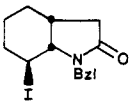
Table I. Iodolactamization of γ,β-Unsaturated Thioimidates 2a–e and 4



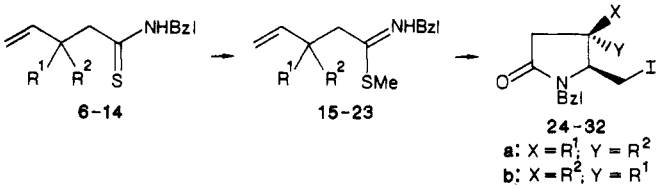
1 2 3

entry	thioimidates	R^1	R^2	R^3	γ-lactams	yields,[a] %
1	**2a**	H	H	H	**3a**	72
2	**2b**	Ph	H	H	**3b**	32
3	**2c**	Me	H	H	**3c**	51
4	**2d**	H	H	Me	**3d**	56
5	**2e**	Me	Me	H	**3e**	–
6						63

4 5

[a] Yields from secondary thioamides **1a–e** and **77** are shown.

Table II. Iodolactamization of β-Substituted γ,δ-Unsaturated Thioimidates 15–23



6–14 15–23 24–32

a: X = R^1; Y = R^2

b: X = R^2; Y = R^1

entry	thioimidates	R^1	R^2	γ-lactams	yields,[a] %	ratio[b] (a:b)
1	**15**	OH	H	**24a,b**	66	(12:1)
2	**16**	OTBS	H	**25a,b**	56	(7:1)
3	**17**	OH	Me	**26a,b**	40	(10:1)
4	**18**	OMOM	H	**27a,b**	66	(4.5:1)
5	**19**	NHBoc	H	**28a,b**	78	(3.8:1)
6	**20**	Me	H	**29a,b**	60	(3:1)
7	**21**	Ph	H	**30a,b**	74	(2.6:1)
8	**22**	*n*-Pr	H	**31a,b**	78	(1.2:1)
9	**23**	*i*-Pr	H	**32a,b**	79	(1:2.7)

[a] Yields are shown from the γ,δ-unsaturated secondary thioamides **6–14**. [b] The ratios of **24a,b 25a,b**, **31a,b**, and **32a,b** were determined by ^{1}H NMR (270 MHz) and those of **2a,b–30a,b** by isolated yields.

However, iodolactamization of the 5,5-disubstituted thioimidate **2e** did not proceed. In the IR spectra carbonyl absorptions of **3a–d** and **5** appeared at 1680 cm^{-1}, which indicated the five-membered ring lactam structure.[7]

With these results in hand, we next turned our attention to examining the effect of allylic substituents. Allylic-substituted unsaturated thioamides **6–14** were mainly obtained by employing aldol condensation of dianions of secondary amide or thioamide with acrolein derivatives for **6–10** and ortho- or thio-Claisen rearrangement for **11–14** as key steps (see the Experimental Section). Thioimidates **15–23** prepared by the methylation of **6–14** underwent iodolactamization under the same conditions described above, affording γ-lactams **24a,b–32a,b**, respectively. The results are summarized in Table II. High 1,2-cis asymmetric induction was observed in the case of polar substituents such as hydroxy and amino groups (entries 1–5). In particular, hydroxy-bearing thioimidate **15** underwent remarkably selective lactamization, giving a 12:1 mixture of **24a** and **24b**, respectively. On the other hand, when the alkyl substituents were located at the allylic position, the stereoselectivities depended on the bulkiness of the alkyl groups (entries 6–9). It is interesting to note that the reactions (entries 6–8) favored the cis compounds though with moderate selectivities, while the reaction of **23** (bearing a bulky isopropyl substituent, entry 9) favored the trans product.[8]

The relative cis and trans stereochemistry was established on the basis of transformations to the known compounds or NMR spectroscopy. Treatment of the major compound **24a** with silver acetate followed by reduction with lithium aluminum hydride ($LiAlH_4$) gave *cis*-2-(hydroxymethyl)-3-hydroxypyrrolidine **34**, of which the spectral data (IR, ^{1}H and ^{13}C NMR) were identical with those of an authentic sample[9] (eq 1). Spectral data of **25a** and **27a** were identical with those of synthetic compounds prepared by *tert*-butyldimethylsilylation and methoxy-

(6) In the system of the presence of the substituent at the 5-position (entries 2 and 3), γ,δ-unsaturated amides prepared by the hydrolysis of the starting materials (**2** and **3**) through column chromatography were more or less (20–35%) recovered due to slow progress of the reaction.

(7) A wealth of examples in cyclic systems have demonstrated that the addition of electrophile and nucleophile to the double bond anti. Based on these examples, the stereochemistries of **3b–d** and **5** were determined: ref 2.

(8) Very recently similar trans selectivity has been observed in the iodolactamization of γ,δ-unsaturated oxazolines bearing bulky *tert*-butyl substituent at allylic position. ref. 5i.

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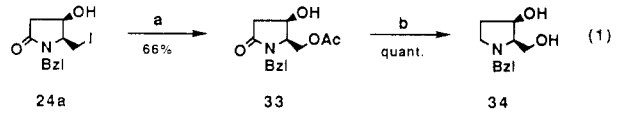
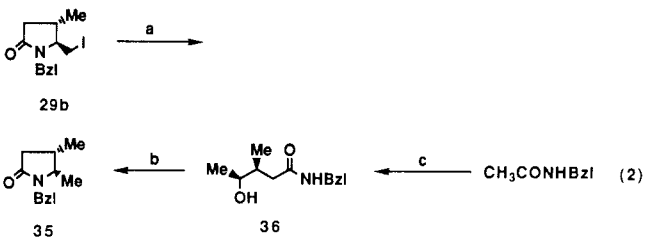


(a) AgOAc; (b) $LiAlH_4$

methylation of **24a**, respectively. The NOE NMR (9.6%) between H^4 and H^5 in **28a** was observed, showing the cis relationship between the iodomethyl and the *tert*-butoxycarbonylamino group.[10] The trans isomer **29b** was transformed with *n*-Bu_3SnH in the presence of AIBN into *trans*-4,5-dimethylpyrrolidin-2-one **35**, of which the spectral data (IR and ^1H NMR) were identical with those of a synthetic product obtained by the treatment of *trans*-2,3-epoxybutane with dianion of *N*-benzylacetamide followed by O-tosylation and ring closure[11] (eq 2). In the



(a) n-Bu_3SnH/AIBN; (b) (1) ^tBuOK; (2) TsCl;
(c) (1) n-BuLi; (2) trans-2,3-epoxybutane/BF_3-OEt_2

270-MHz ^1H NMR spectrum of the cis isomer **30a** relative to that of the trans **30b**, the signal of the iodomethyl group is strongly shielded by the nearby phenyl ring (δ 2.91 for **30a** and δ 3.30 for **30b**). In the ^{13}C NMR spectru, the signals [C-5 (57.97 ppm) and iodomethyl (3.66 ppm)] of cis isomer **31a** due to a steric compression were upfield from the corresponding signals [C-5 (61.91 ppm) and iodomethyl (10.08 ppm)] of the trans isomer.[12] The NOE (6.0%) between H^4 and H^5 in the cis isomer **32a** was observed, while in the trans isomer **32b** the NOE was weak (1.5%). The signals of methyne protons at C-5 in the trans isomers appeared at a higher field than those of the cis without exception (Table III), though the reason remains unclear, so the stereochemistry of **26a,b** was estimated by chemical shifts of the corresponding methyne protons.

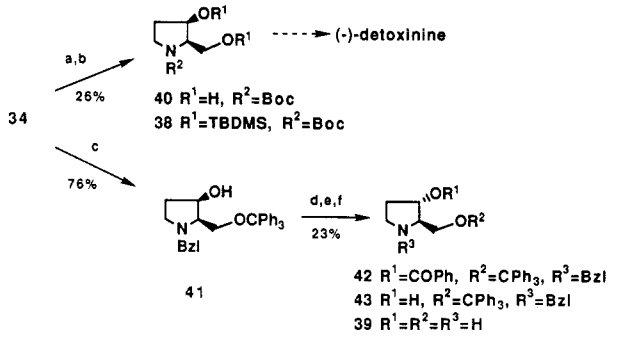
This interesting stereochemistry may be rationalized as follows. The polar substituents (OH, OTBS, OMOM, NHBoc) may favor a *quasi*-axial position due to 1,2-cis directing ability of iodonium ion in the transition state **37a** of this cyclization, assuming that methylthio and iodonium groups of (the bulkiest substituents) are located *quasi*-equatorial. In these cases, the electrophile (I_2) adds to the face of the double bond which is syn to the electron-rich allylic substituents.[13] This can afford some electrostatic stabilization as expected from ab initio calculation proposed by Houk.[14] In addition, the methyl, phenyl,[17] or

Table III. Chemical Shifts (^1H NMR) of Methyne Protons at C-5[a]

γ-lactams (cis)	H^5 (ppm)	γ-lactams (trans)	H^5 (ppm)
24a	3.70	**24b**	3.64
25a	3.68	**25b**	3.51
26a	3.32	**26b**	3.20
27a	3.76	**27b**	3.44
28a	3.75	**28b**	3.53
29a	3.57	**29b**	2.87
30a	3.87	**30b**	3.15
31a	3.53	**31b**	2.93
32a	3.51	**32b**	3.02

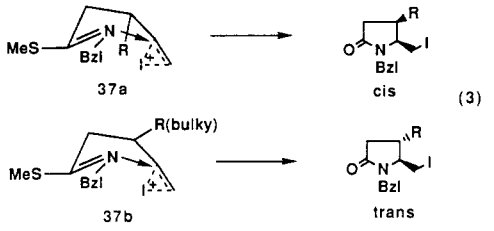
[a] The signals of H^5 exhibited multiplets. The central values are shown.

Scheme I



[a] (a) (1) $Pd(OH)_2/H_2$; (2) $(Boc)_2O/NEt_3$; (b) TBDMSCl/Imidazole/DMF; (c) Ph_3CCl/NEt_3/cat. DMAP; (d) PhCOOH/DEAD/Ph_3P; (e) 1% NaOH; (f) $Pd(OH)_2/H_2$.

n-propyl substituent-bearing transition state somewhat favors **37a**, giving preferentially the 4,5-cis isomer.[18] Very recently, in allylic methyl-bearing iodoetherification a similar preference for the cis product with selectivity of 2.3:1 has been observed by Labelle.[20] This rationale is explained on the basis of AM1 calculation[21] that the methyl substituent favors an axial orientation rather than an equatorial in transition models, which may be applied to our results. On the other hand, a bulky substituent such as an isopropyl group may be discounted due to steric repulsion between the bulky substituent and iodonium. This strain forces the allylic substituent to take a *quasi*-equatorial orientation as in transition state **37b**, affording preferentially the 4,5-trans isomer (eq 3).



(10) That ^1H NOE's for cis vicinal hydrogens in five-membered rings are larger than those for trans vicinal hydrogens forms the basis for these assignments; Nakanishi, K.; Schooley, D. A.; Koreeda, M.; Miura, I. *J. Am. Chem. Soc.* **1972**, *94*, 2865.

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(13) Similar cis selectivities were observed in the iodolactonization of Chamberlin[14] and the iodoetherification of Reitz and Liotta.[15].

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(17) Although the pheny substituent is bulky, it may favor *quasi*-axial due to a π-stacking interaction between the pheny and the iodonium; cf. Trost, B. M.; O'Krongly, D.; Belletire, J. L. *J. Am. Chem. Soc.* **1980**, *102*, 7595.

(18) Similar cis selectivities were observed in the iodolactamization of Knapp[5g] and the iodolactonization of Bartlett[19] under kinetic control, so our reaction is most likely under kinetic conditions.

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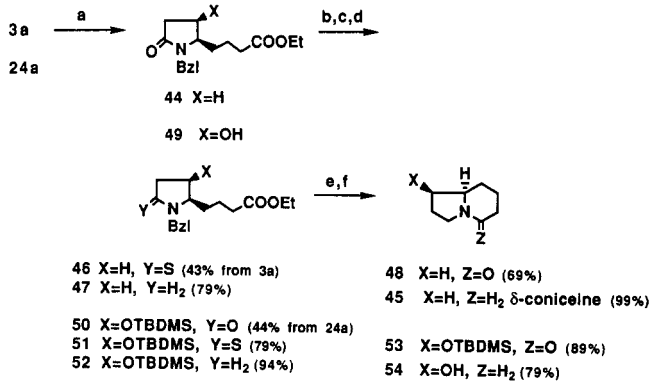
Scheme II[a]



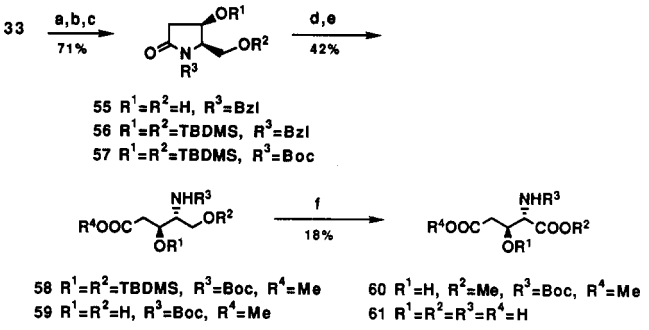
[a] (a) ethyl acrylate/n-$Bu_3SnCl/NaBH_4/h\nu$; (b) TBDMSCl/Imidazole (only for **49**); (c) Lawesson's reagent; (d) (1) $(EtO)_3^+BF_4^-$; (2) $NaBH_4$; (e) $Pd(OH)_2/H_2$; (f) $LiAlH_4$.

Transformation of Iodolactams into Some Biologically Active Compounds. Since the cis configuration of the C-5 substituent with respect to the C-4 hydroxyl group in the γ-lactams such as **24a** among highly functionalized lactams thus prepared is abundantly observed in many interesting alkaloids containing the pyrrolidine ring (detoxinine,[22] slaframine,[23] retronecin,[24] anisomycin,[25] etc.[26]) and unusual γ-amino acids having 1,2-amino alcohol functions (statine,[27] 3-hydroxyglutamic acid,[28] etc.[29]), we turned our attention to the transformation of **24a** into several biologically active compounds. We first examined the conversion of **34** derived from **24a** into the key intermediate **38** in the synthesis of (−)-detoxinine and (±)-*trans*-2-(hydroxymethyl)-3-hydroxypyrrolidine (**39**)[30] as described in Scheme I. Debenzylation (hydrogenolysis) of **34** using palladium hydroxide $[Pd(OH)_2]$[31] as a catalyst followed by *tert*-butoxycarbonylation and *tert*-butyldimethylsilylation provided **38** in moderate yields. Selective tritylation of **34** gave the primary hydroxy-protected **41**; the inversion of the secondary hydroxy group of **41** was carried out by Mitsunobu reaction[32] (Ph_3P, DEAD, PhCOOH) to afford the benzoate **42**. After the hydrolysis of the benzoate, **43** underwent deprotection of both *O*-trityl and *N*-benzyl groups with $Pd(OH)_2$ under hydrogen to give **39**.

Carbon–carbon bond formation reaction employing radical addition to alkenes is one of the most important methodologies in organic synthesis.[33] Since alkyl iodides were frequently used as a radical precursors, radical propagation employing **3a** as an educt to form radical with ethyl acrylate by Giese's procedure[34] (Bu_3SnCl, $NaBH_4$, $h\nu$) was carried out to give ester **44**, which was transformed into δ-coniceine (**45**),[35] indolizidine alkaloid. The reduction of the amide by Raucher's method[36] (1, thiocarbonylation with Lawesson's reagent;[37] 2, methylation with Meerwein's reagent; 3, reduction with $NaBH_4$) gave the pyrrolidine **47**, which was converted to indolizidinone **48** by the debenzylation with $Pd(OH)_2$ accompanied by the simultaneous ring closure (Scheme II). The lactam **48** was reduced with $LiAlH_4$ to afford **45**. Likewise, the reaction of **24a** with ethyl acrylate gave the ester **49**. After *tert*-butyldimethylsilylation of **49**, according to the same manner described above, the protected compound **50** was transformed into *cis*-1-hydroxyindolizidine (**54**) as the racemate of a key precursor in the biosynthesis[38] of the toxic indolizidine alkaloid, slaframine.

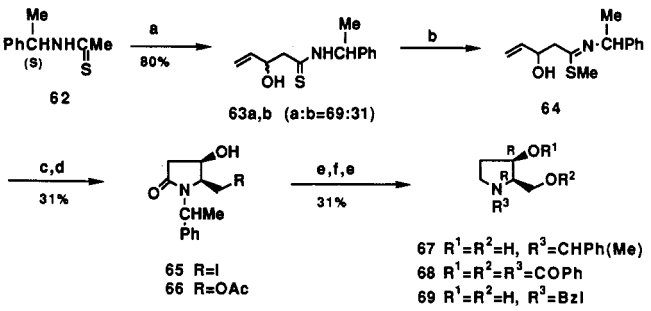
It was expected that ring-opening of γ-lactams would lead to γ-amino acids of biological interest. Indeed, (2*S**,3*R**)-3-hydroxyglutamic acid (**61**)[39] was obtained by a stereocontrolled transformation of **33** as shown in Scheme III. Saponification of **33** followed by di-*tert*-butyldimethylsilylation gave the protected lactam **56**. Next, the exchange of N-protected group from benzyl to *tert*-butoxycarbonyl (**56** → **57** was performed in order to facilitate the ring opening. Therefore, **57** underwent easily the ring cleavage with a base to provide **58** as a methyl ester after methylation with diazomethane. Di-*tert*-butyldimethyl-

Scheme III[a]



[a] (a) 0.5 M K_2CO_3; (b) TBDMSCl/Imidazole; (c) (1) Na/NH_3; (2) $(Boc)_2O/NaH$; (d) (1) KOH; (2) CH_2N_2; (e) Bu_4NF; (f) (1) O_2/Pt; (2) CH_2N_2.

Scheme IV



[a] (a) (1) *n*-BuLi; (2) acrolein; (b) MeI/K_2CO_3; (c) I_2; (d) AgOAc; (e) $LiAlH_4$; (f) (1) $Pd(OH)_2/H_2$; (2) $PhCOCl/NEt_3$.

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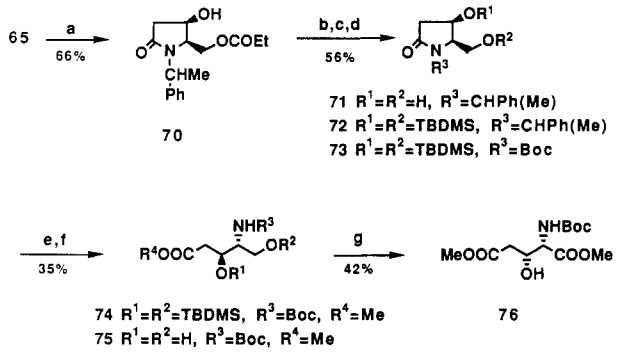
Scheme V



[a] (a) CsOCOEt; (b) 0.5 M K_2CO_3; (c) TBDMSCl/Imidazole; (d) (1) Na/NH_3; (2) $(Boc)_2O/NaH$; (e) (1) KOH; (2) CH_2N_2; (f) Bu_4NF; (g) (1) O_2/Pt; (2)CH_2N_2.

silylation of **58** with *n*-Bu_4NF gave the dihydroxy **59**, the selective oxidation of the primary hydroxyl group of which with O_2 in the presence of catalytic platinum[40] followed by methylation was accomplished, furnishing dimethyl ester **60** as the protected form of **61**.

Our attention was focused on the synthesis of its optically pure enantiomer. In order to obtain the optically pure thioamides of type **6**, we examined the aldol condensation of dianions, generated from secondary thioamide **62** derived from (*S*)-α-phenylethylamine, with acrolein, giving a 61:39 ratio of diastereomers **63a** and **63b**, respectively, of hydroxy unsaturated thioamides in 80% yield. They could be readily separated by column chromatography despite the low diastereomeric selectivity. The absolute configuration of the major isomer **63a** was determined by the transformation of **63a** into the known (2*R*,3*R*)-1-benzyl-2-(hydroxymethyl)-3-hydroxypyrrolidine (**69**) [$[\alpha]^{25.5}_D$ −54.9° (*c* 0.685, $CHCl_3$) {lit.[9] $[\alpha]^{20}_D$ −56.5° (*c* 0.5, $CHCl_3$)}] as shown in Scheme IV. Therefore, the synthesis of the protected form **76**[28] of (2*S*,3*R*)-3-hydroxyglutamic acid was achieved from **65** by the procedure similar to that described for the synthesis of the racemate **60** except for the displacement of the iodide of **65** by an oxygen nucleophile[41] as shown in Scheme V.

In summary, this study exhibits that the iodolactamization of γ,δ-unsaturated thioimidates results in the regioselective formation of γ-lactams and the stereochemistry in teh allylic chiral induction strongly depends on the allylic substituents. Most of these substrates give a good selectivity for the product in which the stereogenic allylic substituents and iodomethyl side chain are cis. One notable exception is the case where the substrate has a bulky allylic substituent such as an isopropyl group. The present method provides a new and promising access to highly functionalized γ-lactams (including optically active forms), which should be convertible into related biologically active compounds such as alkaloids and amino acids, and some examples are actually demonstrated.

Experimental Section

Melting points were determined with a Yanaco micro melting point apparatus and were not corrected. Unless otherwise specified, short-path (bulb-to-bulb) distillation was 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 (^1H NMR) was performed 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. Optical rotations were measured on a JASCO DIP-140 instrument. 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 μm and 5 μm). A solution of ethyl acetate/hexane as eluant was used unless otherwise specified. The extracts were dried with Na_2SO_4 unless otherwise specified.

Preparation of γ,δ-Unsaturated Secondary Thioamides. Preparations of **1a–c** and **1e** have been already reported by us.[1b] According to a similar procedure, *N*-benzyl-4-methylpent-4-enethioamide (**1d**) and *N*-benzyl-2-(2′-cyclohexenyl)thioacetamide (**77**)[42] were prepared in 55% and 62% yields, respectively. *N*-Benzyl-3-hydroxypent-4-enethioamide (**6**) and *N*-benzyl-3-hydroxy-3-methylpent-4-enethioamide (**8**) were obtained as follows. A 15% solution of *n*-BuLi in hexane (7.1 mL, 11 mmol) was added to a stirred solution of *N*-benzylthioacetamide (5 mmol) in THF (10 mL) at 0 °C. After the mixture was stirred for 1 h at the same temperature, acrolein or methyl vinyl ketone (7.5 mmol) was added to the reaction mixture −78 °C. The reaction mixture was stirred for 10 s for acrolein or for 30 min for methyl vinyl ketone, quenched with ammonium chloride solution, and extracted with ethyl acetate. The extracts were washed with brine, dried, and evaporated. Column chromatography of the residue yielded **6** (72%) and **8** (72%), respectively. *N*-Benzyl-3-[(*tert*-butyldimethylsilyl)oxy]pent-4-enethioamide (**7**) was obtained by *tert*-butyldimethylsilylation of **6**. A mixture of **6** (345.5 mg, 1.56 mmol), *tert*-butyldimethylsilyl chloride (TBDMSCl) (293.9 mg, 1.95 mmol), and imidazole (265.5 mg, 3.90 mmol) in DMF (0.78 mL) was stirred for 15 h at room temperature. Water (1.2 mL) was added to the reaction mixture. The mixture was extracted with ethyl acetate three times. The extracts were washed with brine, dried, and evaporated. Column chromatography of the residue yielded **7** (445.5 mg, 85%). *N*-Benzyl-3-(methoxymethoxy)pent-4-enethioamide (**9**) was prepared by the methoxymethylation of *N*-benzyl-3-hydroxypent-4-enamide (**78**)[42] followed by thionation. A 15% solution of *n*-BuLi in hexane (13.4 mL, 22 mmol) was added to a stirred solution of *N*-benzylacetamide (1.50 g, 10 mmol) in THF (40 mL) at 0 °C. After stirring for 1 h at the same temperature, acrolein (22 mmol) was added to the reaction mixture at −78 °C. After 30 s, the mixture was quenched with ammonium chloride solution and extracted with ethyl acetate three times. The extracts were washed with brine, dried, and evaporated. Column chromatography of the residue yielded **78** (65%). *N*,*N*-Diisopropylethylamine (1.57 mL, 9 mmol) and chloromethyl methyl ether (0.34 mL, 4.5 mmol) were successively added to a solution of **78** (615 mg, 3 mmol) in CH_2Cl_2 (5 mL) with ice cooling. The reaction mixture was stirred for 15 h at room temperature. After addition of water to the reaction mixture, the mixture was extracted with CH_2Cl_2 three times. The extracts were washed with brine, dried, and evaporated. Column chromatography of the residue yielded *N*-benzyl-3-(methoxymethoxy)-pent-4-enamide (**79**)[42] (69%). A mixture of **79** (414.3 mg, 1.66 mmol) and 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide (Lawesson's reagent) (252.1 mg, 0.623 mmol) in THF (8 mL) was stirred for 15 h at room temperature. After evaporation of the mixture, column chromatography of the residue yielded **9** (71%). *N*-Benzyl-3-[(*tert*-butoxycarbonyl)amino]-pent-4-enethioamide (**10**) was prepared as shown in Scheme VI. According to the similar procedure described for **78**, the reaction

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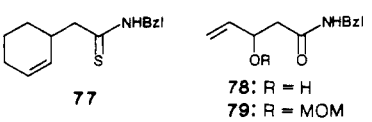
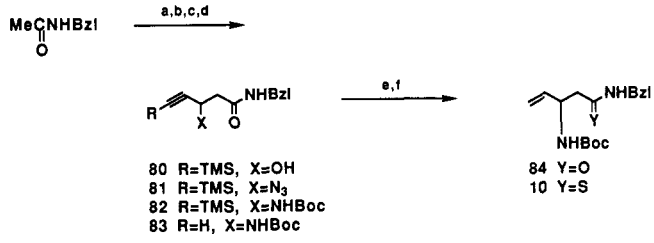
(41) Although reaction of **65** with AgOAc gave an analogue of **70** in 37% yield, the yield (66%) of **70** was improved by using cesium propionate in place of AgOAc: DiJkstra, G.; Kruizinga, W. H.; Kelogg, R. M. *J. Org. Chem.* **1987**, *52*, 4230.

(42) The structures of **77–79**:



Scheme VI



[a] (1) *n*-BuLi; (2) 3-trimethylsilyl-2-propynal; (b) HN_3/Ph_3P/diethyl azodiacarboxylate; (c) (1) H_2S/NEt_3; (2) $(Boc)_2O/NEt_3$; (d) *n*-Bu_4NF; (e) $H_2/Pd/BaSO_4$/quinoline; (f) Lawesson's reagent.

of *N*-benzylacetamide (523 mg, 3.5 mmol) and 3-(trimethylsilyl)-2-propynal (531 mg, 4.2 mmol) with *n*-BuLi (7.7 mmol) gave *N*-benzyl-3-hydroxy-5-(trimethylsilyl)pent-4-enethioamide (**80**) (47%) together with *N*-benzylacetamide (33%). To a solution of **80** (180 mg, 0.654 mmol) in THF (3 mL) was added a mixture of triphenylphosphine (514.2 mg, 1.96 mmol) and 2.5 N HN_3 in toluene (0.8 mL, 1.96 mmol) at 0 °C. A solution of diethyl azodicarboxylate (DEAD) (0.3 mL, 1.96 mmol) in THF (1 mL) was added dropwise to the reaction mixture, and the mixture was stirred for 24 h at −20 °C. After evaporation of the solvent, a mixture of hexane and diethyl ether (1%1) was added to the residue. The insoluble materials were filtered off, and the filtrate was evaporated. Column chromatography of the residue yielded *N*-benzyl-3-azido-5-(trimethylsilyl)pent-4-enamide (**81**) (97%). Hydrogen sulfide was bubbled into a mixture of **81** (568.6 mg, 1.893 mmol) and triethylamine (1.06 mL, 7.57 mmol) in CH_2Cl_2 (10 mL) for 100 min with ice cooling.[43] After evaporation of the mixture, the residue was dried under vacuum. To a solution of the dried residue in CH_2Cl_2 (5 mL) were added successively triethylamine (0.4 mL, 2.84 mmol) and di-*tert*-butyl dicarbonate $(Boc)_2O$ (0.65 mL, 2.84 mmol) with ice cooling. The mixture was stirred for 12 h at room temperature and quenched with saturated citric acid. The mixture was extracted with CH_2Cl_2 three times. The extracts were washed with brine, dried, and evaporated. Column chromatography of the residue yielded *N*-benzyl-3-[(*tert*-butoxycarbonyl)amino]-5-(trimethylsilyl)pent-4-enamide (**82**) (85%). To a solution of **82** (499.3 mg, 1.33 mmol) in THF (4 mL) was added 1 M *n*-Bu_4NF in THF (2.0 mL, 2.0 mmol), and the reaction mixture was stirred for 1 h. Ethyl acetate was added to the reaction mixture. The mixture was washed with water and brine, dried, and evaporated. Column chromatography of the residue yielded *N*-benzyl-3-[(*tert*-butoxycarbonyl)amino]pent-4-enamide (**83**) (99%). A suspension of **83** (195.4 mg, 0.646 mmol)8 5% palladium/$BaSO_4$, and quinoline (0.12 mL) in acetone (10 mL) was shaken under a hydrogen atmosphere for 36 h. After the removal of the catalyst, the filtrate was evaporated. Column chromatography of the residue yielded *N*-benzyl-3-[(*tert*-butoxycarbonyl)amino]pent-4-enamide (**84**) (99%). A mixture of **84** (180.2 mg, 0.592 mmol) and Lawesson's reagent (89.8 mg, 0.222 mmol) in benzene was refluxed for 1.5 h. After the solvent was evaporated, column chromatography of the residue yielded **10** (86%). *N*-Benzyl-3-methylpent-4-enethioamide (**11**) was prepared by thio-Claisen rearrangement. *trans*-Crotyl bromide (0.77 mL, 7.5 mmol) was added to a suspension of *N*-benzylthioacetamide (826.3 mg, 5 mmol) and K_2CO_3 (691.1 mg, 5 mmol) in acetone (10 mL). The reaction mixture was stirred for 48 h at room temperature. The insoluble materials were removed off, 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. The residue was heated for 1 h at 180 °C and chromatographed to yield **11** (54%). *N*-Benzyl-3-phenylpent-4-enethioamide (**12**), *N*-benzyl-3-propylpent-4-enethioamide (**13**), and *N*-benzyl-3-isopropylpent-4-enethioamide (**14**) were prepared by *o*-Claisen rearrangement[44] of the corresponding allyl alcohols with orthoformic ester followed by condensation with benzylamine and then thionation with Lawesson's reagent. A mixture of allyl alcohol (cinnamyl alcohol, 2-hexen-1-ol, or 4-methyl-2-penten-1-ol[45]) (2 mmol), ethyl orthoformation (2.59 mL, 14.1 mmol), and propionic acid (0.01 mL, 0.121 mmol) was heated for 2 h at 138 °C. The mixture was evaporated. Column chromatography of the residue yielded γ,δ-unsaturated ester. A mixture of the ester and benzylamine (1.2 equiv) in a sealed tube was heated for 22 h at 165–170 °C. Column chromatography of the mixture yielded the corresponding amide. A mixture of the amide and Lawesson's reagent (0.5 equiv) in benzene was refluxed for 1 h. Column chromatography of the mixture yielded **12**, **13**, or **14**, respectively.

1d: mp 39–40 °C (isopropyl ether/petroleum ether); IR (Nujol) 3230, 1645, 1530 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.72 (s, 3 H), 2.21–2.93 (m, 4 H), 4.71 (d, *J* = 5.4 Hz, 2 H), 4.71 (m, 2 H), 7.32 (br, s, 5 H). Anal. Calcd for $C_{13}H_{17}NS$: C, 71.18; H, 7.81; N, 6.39. Found: C, 71.26; H, 8.02; N, 6.17.

77: mp 59–60 °C (isopropyl ether/petroleum ether); IR (Nujol) 3175, 1530 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90–2.27 (m, 6 H), 2.70 (m, 3 H), 4.87 (d, *J* = 5.4 Hz, 2 H), 5.68 (m, 2 H), 7.44 (br s, 5 H). Anal. Calcd for $C_{15}H_{19}NS$: C, 73.42; H, 7.80; N, 5.71. Found: C, 73.45; H, 7.91; N, 5.72.

6: an oil; IR (neat) 3220, 1640, 1530 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.78–3.04 (m, 2 H), 3.68 (m, 1 H), 4.30–4.80 (m, 1 H), 4.80 (d, *J* = 5.4 Hz, 2 H), 5.00–5.45 (m, 2 H), 5.60–6.20 (m, 1 H), 7.35 (s, 5 H), 8.50 (br s, 1 H); HRMS calcd for $C_{12}H_{15}NOS$ 221.0874, found 221.0829.

7: mp 37–41 °C (isopropyl ether/petroleum ether); IR (Nujol) 3220, 1550 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.00 (s, 6 H), 0.79 (s, 9 H), 3.00 (d, *J* = 4.8 Hz, 2 H), 4.36–4.88 (m, 3 H), 5.03–5.40 (m, 2 H), 5.65–6.40 (m, 1 H), 7.36 (s, 5 H). Anal. Calcd for $C_{18}H_{29}NOSSi$: C, 64.42; H, 8.71; N, 4.17. Found: C, 64.52; H, 8.52; N, 4.34.

8: mp 53–56 °C (isopropyl ether/petroleum ether); IR (Nujol) 3230, 1565 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (s, 3 H), 2.92 (s, 2 H), 4.81 (d, *J* = 5.4 Hz, 2 H), 4.96–5.39 (m, 2 H), 5.69–6.16 (m, 1 H), 7.39 (s, 5 H), 9.09 (br s, 1 H). Anal. Calcd for $C_{13}H_{17}NOS$: C, 66.35; H, 7.28; N, 5.95. Found: C, 66.59; H, 7.35; N, 5.88.

78: mp 77–78 °C (isopropyl ether); IR (Nujol) 3300, 1615, 1570 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.40–2.49 (m, 2 H), 4.46 d, *J* = 5.9 Hz, 2 H), 4.56 (m, 1 H), 5.15–5.31 (m, 2 H), 5.82–5.94 (m, 1 H), 6.20 (br s, 1 H), 7.3 (br s, 5 H). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.02; H, 7.38; N, 6.91.

9: mp 64–65 °C (isopropyl ether/petroleum ether); IR (Nujol) 3200, 1530 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.92–3.06 (m, 2 H), 3.24 (s, 3 H), 4.42–4.70 (m, 1 H), 4.56, 4.62 (s, each 1 H), 4.85 (d, *J* = 4.8 Hz, 2 H), 5.11–6.07 (m, 3 H), 7.37 (s, 5 H). Anal. Calcd for $C_{14}H_{19}NO_2S$: C, 63.36; H, 7.22; N, 5.28. Found: C, 62.87; H, 7.20; N, 5.27.

80: mp 123–124 °C (CH_2Cl_2/hexane); IR (Nujol) 3300, 2170, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.15 (s, . H), 2.58 (d, *J* = 5.8 Hz, 2 H), 4.10 (br s, 1 H), 4.39 (d, *J* = 5.6 Hz, 2 H), 4.70 (br s, 1 H), 6.62 (br s, 1 H), 7.27 (s, 5 H). Anal. Calcd for $C_{15}H_{21}NO_2Si$: C, 65.41; H, 7.69; N, 5.09. Found: C, 65.29; H, 7.60; N, 4.91.

81: a yellow oil; IR (neat) 2190, 2120, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.18 (s, 9 H), 2.53 (d, *J* = 7.2 Hz, 2 H), 6.23 (br s, 1 H), 7.28 (s, 5 H); HRMS calcd for $C_{15}H_{20}N_4OSi$ 300.1405, found 300.1371.

82: mp 125–126 °C (isopropyl ether); IR (Nujol) 3350, 3300, 2170, 1685, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.13 (s, 9 H), 1.45 (s, 9 H), 2.59 (d, *J* = 5.6 Hz, 2 H), 4.42 (d, *J* = 5.6 Hz, 2 H), 4.55–4.88 (m, 1 H), 5.54 (d, *J* = 8.6 Hz, 1 H), 6.40 (br s, 1 H), 7.30 (s, 5). Anal. Calcd for $C_{20}H_{30}N_2O_3Si$: C, 64.13; H, 8.07; N, 7.48. Found: C, 64.17; H, 8.05; N, 7.62.

83: mp 150–151 °C ($CHCl_3$/hexane); IR (Nujol) 3350, 3300, 1680, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (s, 9 H), 2.26–2.30 (m, 1 H), 2.61 (d, *J* = 5.6 Hz, 2 H), 4.44 (d, *J* = 6.0 Hz, 2 H), 4.53–4.90 (m, 1 H), 5.67 (br s, 1 H), 6.10 (br s, 1 H), 7.28 (s, 5 H). Anal. Calcd for $C_{17}H_{22}N_2O_3$: C, 67.53; H, 7.33; N, 9.26. Found: C, 67.34; H, 7.28; N, 9.13.

84: mp 148–149 °C (CH_2Cl_2/hexane); IR (Nujol) 3300, 1685, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43 (s, 9 H), 2.49 d, *J* = 6.2 Hz, 2 H), 4.38 (d, *J* = 5.8 Hz, 2 H), 4.30–4.52 (m, 1 H), 4.97–5.91 (m,

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(45) Ikota, N.; Takamura, N.; Young, S. D.; Ganem, B. *Tetrahedron Lett.* **1981**, *22*, 4163.

3 H), 6.07 (br s, 1 H), 7.28 (s, 5 H). Anal. Calcd for $C_{17}H_{24}N_2O_3$: C, 67.08; H, 7.95; N, 9.20. Found: C, 66.94; H, 7.87; N, 9.10.

10: mp 126–128 °C (isopropyl ether); IR (Nujol) 3400, 3320, 1670, 1540 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (s, 9 H), 3.01 (d, J = 6.6 Hz, 2 H), 4.29–4.59 (m, 1 H), 4.79 (d, J = 5.0 Hz, 2 H), 4.99–5.33 (m, 2 H), 5.58–6.15 (m, 1 H), 7.33 (s, 5 H), 8.08 (br s, 1 H). Anal. Calcd for $C_{17}H_{24}N_2O_2S$: C, 63.72; H, 7.55; N, 8.74. Found: C, 63.54; H, 7.30; N, 8.42.

11: a yellow oil; IR (neat) 3230, 1530 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 (d, J = 6.4 Hz, 3 H), 2.56–3.05 (m, 3 H), 4.83 (d, J = 5.4 Hz, 2 H), 4.82–5.21 (m, 2 H), 5.48–6.09 (m, 1 H), 7.36 (s, 5 H); HRMS calcd for $C_{13}H_{17}NS$ 219.1072, found 219.1092.

12: mp 71–72 °C (isopropyl ether); IR (Nujol) 3200, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.88–3.09 (m, 2 H), 3.79–4.09 (m, 1 H), 4.55 (d, J = 5.6 Hz, 2 H), 4.86–5.20 (m, 2 H), 5.60–6.28 (m, 1 H), 6.79–7.38 (m, 10 H). Anal. Calcd for $C_{18}H_{19}NS$: C, 76.82; H, 6.81; N, 4.98. Found: C, 76.71; H, 6.76; N, 5.18.

13: an oil; IR (neat) 3250, 1530 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.67–1.49 (m, 7 H), 2.50–2.77 (m, 3 H), 4.74 (d, J = 5.2 Hz, 2 H), 4.73–5.87 (m, 3 H), 7.27 (s, 5 H), 7.64 (br s, 1 H); HRMS calcd for $C_{15}H_{21}NS$ 247.1394, found 247.1364.

14: an oil; IR (neat) 3230, 1530 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82 (d, J = 3.4 Hz, 3 H), 0.94 (d, J = 3.4 Hz, 3 H), 1.41–2.03 (m, 1 H), 2.41–2.97 (m, 3 H), 4.75 (d, J = 5.2 Hz, 2 H), 4.80–4.95 (m, 1 H), 5.10–5.12 (m, 1 H), 5.33–5.96 (m, 1 H), 7.26 (br s, 1 H), 7.31 (s, 5 H); HRMS calcd for $C_{15}H_{21}NS$ 247.1394, found 247.1374.

General Procedure for Iodolactamization of γ,δ-Unsaturated Thioimidates. To a suspension of γ,δ-unsaturated secondary thioamides **1a–e**, **77**, and **6–14** (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 **2a–e**, **4**, and **15–23**, respectively. A solution of iodine (1.5 mmol) in THF (10 mL) was dropwise added 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 **3a–d**, **5**, and **24a,b–32a,b**, respectively.

***N*-Benzyl-5-(iodomethyl)pyrrolidin-2-one (3a)**: mp 66–70 °C (CH_2Cl_2/petroleum ether); IR (Nujol) 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.78 (m, 2 H), 2.25–2.74 (m, 2 H), 3.24 (m, 2 H), 3.42 (m, 2 H), 3.92, 5.02 (AB q, J = 15.2 Hz, each 1 H), 7.28 (m, 5 H). Anal. Calcd for $C_{12}H_{14}INO$: C, 45.73; H, 4.48; N, 4.44. Found: C, 45.65; H, 4.48; N, 4.39.

(5*R,6*R**)-*N*-Benzyl-5-(1-iodobenzyl)pyrrolidin-2-one (3b)**: viscous oil; IR (neat) 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.84–3.00 (m, 4 H), 3.25 (m, 1 H), 3.68, 5.17 (AB q, J = 15.2 Hz, each 1 H), 5.40 (d, J = 4.6 Hz, 1 H), 7.30 (m, 10 H); HRMS calcd for $C_{18}H_{18}INO$ 391.0435, found 391.0420.

(5*R,6*R**)-*N*-Benzyl-5-(1-iodoethyl)pyrrolidin-2-one (3c)**: bp 95–98 °C (0.6 mmHg); IR (neat) 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.75 (d, J = 7.33 Hz, 3 H), 2.70 (m, 1 H), 3.78, 5.17 (AB q, J = 15.4 Hz, each 1 H), 4.48 (m, 1 H), 7.27 (m, 5 H); HRMS calcd for $C_{13}H_{16}INO$ 329.0278, found 329.0323.

***N*-Benzyl-5-methyl-5-(iodomethyl)pyrrolidin-2-one (3d)**: bp 113–117 °C (0.7 mmHg); IR (neat) 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (s, 3 H), 1.92 (m, 1 H), 2.20 (m, 1 H), 2.44–2.78 (m, 2 H), 3.17 (s, 2 H), 4.34, 4.57 (AB q, J = 15.2 Hz, each 1 H), 7.30 (s, 5 H); HRMS calcd for $C_{13}H_{16}INO$ 329.0278, found 329.0255.

(3a*R,7*S**,7a*S**)-*N*-Benzyl-2-oxo-7-iodo-2,3,3a,4,5,6,7,7a-octahydroindole (5)**: bp 110–115 °C (0.6 mmHg); IR (neat) 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32–2.64 (m, 9 H), 3.74 (m, 1 H), 4.50 (m, 1 H), 4.44, 4.92 (AB q, J = 15.0 Hz, each 1 H), 7.30 (m, 5 H); HRMS calcd for $C_{15}H_{18}INO$ 355.0436, found 355.0457.

***cis*-*N*-Benzyl-4-hydroxy-5-(iodomethyl)pyrrolidin-2-one (24a)**: mp 109–112 °C (CH_2Cl_2/petroleum ether); IR (Nujol) 3250, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.62 (dd, J = 17.2, 3.7 Hz, 1 H), 2.72 (dd, J = 17.2, 6.2 Hz, 1 H), 3.23 (dd, J = 9.9, 9.5 Hz, 1 H), 3.33 (dd, J = 9.5, 3.7 Hz, 1 H), 3.66–3.73 (m, 1 H), 4.13, 4.85 (AB q, J = 15.4 Hz, each 1 H), 4.52–4.66 (br s, 1 H), 7.18–7.36 (m, 5 H). Anal. Calcd for $C_{12}H_{14}INO_2$: C, 43.52; H, 4.26; N, 4.23. Found: C, 43.66; H, 4.31; N, 4.09.

***cis*-*N*-Benzyl-4-[(*tert*-butyldimethylsilyl)oxy]-5-(iodomethyl)pyrrolidin-2-one (25a)**: viscous oil; IR (neat) 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.06 (s, 6 H), 0.89 (s, 9 H), 2.56–2.67 (m, 2 H), 3.16–3.34 (m, 2 H), 3.62–3.73 (m, 1 H), 4.19, 4.85 (AB q, J = 15.6 Hz, each 1 H), 4.43–4.52 (m, 1 H); HRMS calcd for $C_{18}H_{28}INO_2Si$ 445.1015, found 445.0975.

***cis*-*N*-Benzyl-4-hydroxy-5-(iodomethyl)-4-methylpyrrolidin-2-one (26a)**: mp 139–142 °C (CH_2Cl_2/petroleum ether); IR ($CHCl_3$) 1685 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.34 (s, 3 H), 2.46, 2.90 (AB q, J = 17.0 Hz, each 1 H), 3.28–3.41 (m, 3 H), 3.93, 5.12 (AB q, J = 14.9 Hz, each 1 H), 7.22–7.38 (m, 5 H). Anal. Calcd for $C_{13}H_{16}INO_2$: C, 45.24; H, 4.67; N, 4.06. Found: C, 44.99; H, 4.73; N, 3.82.

***trans*-*N*-Benzyl-4-hydroxy-5-(iodomethyl)-4-methylpyrrolidin-2-one (26b)**: mp 152–155 °C (CH_2Cl_2/petroleum ether); IR ($CHCl_3$) 1685 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.47 (s, 3 H), 2.43–2.49 (m, 1 H), 2.87–2.94 (m, 1 H), 3.15–3.35 (m, 3 H), 3.87, 5.17 (AB q, J = 15.4 Hz, each 1 H), 7.26–7.37 (m, 5 H). Anal. Calcd for $C_{13}H_{16}INO_2$: C, 45.24; H, 4.67; N, 4.06. Found: C, 44.94; H, 4.62; N, 3.79.

***cis*-*N*-Benzyl-5-(iodomethyl)-4-(methoxymethoxy)pyrrolidin-2-one (27a)**: viscous oil; IR (neat) 1685 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.65 (dd, J = 17.1, 6.8 Hz, 1 H), 2.78 (dd, J = 17.1, 4.6 Hz, 1 H), 3.25–3.41 (m, 2 H), 3.41 (s, 3 H), 3.72–3.79 (m, 1 H), 4.10, 4.96 (AB q, J = 15.4 Hz, each 1 H), 7.20–7.37 (m, 5 H); HRMS calcd for $C_{14}H_{18}INO_3$ 375.0332, found 375.0358.

***trans*-*N*-Benzyl-5-(iodomethyl)-4-(methoxymethoxy)pyrrolidin-2-one (27b)**: viscous oil; IR (neat) 1685 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.48 (dd, J = 17.7, 2.7 Hz, 1 H), 2.90 (ddd, J = 17.7, 7.3, 1.2 Hz, 1 H), 3.08–3.15 (m, 1 H), 3.28 (s, 3 H), 3.29–3.34 (m, 1 H), 3.42–3.46 (m, 1 H), 3.93, 5.08 (AB q, J = 15.4 Hz, each 1 H), 4.11–4.15 (m, 1 H), 4.63 (s, 2 H), 7.24–7.38 (m, 5 H); HRMS calcd for $C_{14}H_{18}INO_3$ 375.0332, found 375.0290.

***cis*- or *trans*-*N*-Benzyl-4-[(*tert*-butylcarbonyl)amino]-5-(iodomethyl)pyrrolidin-2-one (28a,b). 28a**: mp 136–138 °C (ethyl acetate/hexane); IR (Nujol) 3330, 1680, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43 (s, 9 H), 2.71 (d, J = 10.0 Hz, 2 H), 3.18 (dd, J = 11.5, 2.0 Hz, 1 H), 3.31 (dd, J = 11.5, 4.4 Hz, 1 H), 3.72–3.78 (m, 1 H), 3.81, 5.17 (AB q, J = 15.1 Hz, each 1 H), 4.40–4.56 (m, 1 H), 5.05 (br s, 1 H), 7.22–7.37 (m, 5 H); HRMS calcd for $C_{17}H_{23}IN_2O_3$ 430.0754, found 430.0714. Differential NOE: increase of intensity (9.6%) of H^5 by irradiation at H^4 was observed.

28b: mp 142–143 °C (CH_2Cl_2/petroleum ether); IR (Nujol) 3250, 1690, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (s, 9 H), 2.26 (dd, J = 17.8, 4.2 Hz, 1 H), 3.06 (dd, J = 17.8, 8.8 Hz, 1 H), 3.21 (br s, 1 H), 3.31 (dd, J = 11.2, 4.4 Hz, 1 H), 3.48–3.57 (m, 1 H), 3.86, 511 (AB q, J = 15.1 Hz, each 1 H), 3.95–4.02 (m, 1 H), 4.75 (d, J = 5.9 Hz, 1 H), 7.23–7.37 (m, 5 H). Anal. Calcd for $C_{17}H_{23}IN_2O_3$: C, 47.45; H, 5.39; N, 6.51. Found: C, 47.43; H, 5.45; N, 6.22.

***cis*- or *trans*-*N*-Benzyl-5-(iodomethyl)-4-methylpyrrolidin-2-one (29a,b). 29a**: viscous oil; IR (neat) 1685 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16 (d, J = 6.6 Hz, 3 H), 2.44–2.66 (m, 3 H), 3.12–3.28 (m, 2 H), 3.57 (dt, J = 7.1, 2.7 Hz, 1 H), 3.97, 5.03 (AB q, J = 15.4 Hz, each 1 H), 7.18–7.37 (m, 5 H); HRMS calcd for $C_{13}H_{16}INO$ 329.0278, found 329.0229.

29b: viscous oil; IR (neat) 1685 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 (d, J = 7.1 Hz, 3 H), 2.02–2.30 (m, 2 H), 2.75–2.89 (m, 2 H), 3.17–3.30 (m, 2 H), 3.87, 5.09 (AB q, J = 15.4 Hz, each 1 H), 7.21–7.37 (m, 5 H); HRMS calcd for $C_{13}H_{16}INO$ 329.0278, found 329.0248.

***cis*- or *trans*-*N*-Benzyl-5-(iodomethyl)-4-phenylpyrrolidin-2-one (30a,b). 30a**: viscous oil; IR (neat) 1685 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.71 (dd, J = 16.6, 8.4 Hz, 1 H), 2.91 (d, J = 4.4 Hz, 2 H), 3.17 (dd, J = 16.6, 9.4 Hz, 1 H), 3.73–3.89 (m, 2 H), 4.04, 5.17 (AB q, J = 15.4 Hz, each 1 H), 7.26–7.40 (m, 10 H); HRMS calcd for $C_{18}H_{18}INO$ 391.0434, found 391.009.

30b: viscous oil; IR (neat) 1685 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.62 (dd, J = 17.3, 6.8 Hz, 1 H), 3.04 (ddd, J = 17.3, 9.5, 1.0 Hz, 1 H), 3.12–3.17 (m, 1 H), 3.22–3.35 (m, 3 H), 3.88, 5.21 (AB q, J = 15.1 Hz, each 1 H), 7.06–7.36 (m, 10 H); HRMS calcd for $C_{18}H_{18}INO$ 391.0434, found 391.0417.

***cis* or *trans*-*N*-Benzyl-5-(iodomethyl)-4-*n*-propylpyrrolidin-2-one (31a,b). 31a**: viscous oil; IR (neat) 1690 cm^{-1};

^{1}H NMR ($CDCl_3$) δ 0.93 (t, J = 7.1 Hz, 3 H), 1.21–1.59 (m, 4 H), 2.41–2.57 (m, 3 H), 3.20–3.32 (m, 2 H), 3.51–3.55 (m, 1 H), 3.87, 5.15 (AB q, J = 15.1 Hz, each 1 H), 7.23–7.37 (m, 5 H); ^{13}C NMR ($CDCl_3$): δ 3.66, 14.09, 21.28, 30.41, 44.44, 57.97, 127.73, 128.10, 128.80, 136.80, 174.56; HRMS calcd for $C_{15}H_{20}INO$ 357.0592, found 357.0558.

31b: viscous oil; IR (neat) 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7.3 Hz, 3 H), 1.19–1.59 (m, 4 H), 2.07–2.16 (m, 2 H), 2.71–2.81 (m, 1 H), 2.91–2.95 (m, 1 H), 3.24–3.27 (m, 2 H), 3.86, 5.09 (AB q, J = 15.1 Hz, each 1 H), 7.21–7.37 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 10.08, 13.97, 20.13, 36.97, 37.14, 44.16, 61.91, 127.80, 128.14, 128.83, 135.87, 174.40; HRMS calcd for $C_{15}H_{20}INO$ 357.0592, found 357.0612.

***cis*- or *trans*-*N*-Benzyl-5-(iodomethyl)-4-isopropylpyrrolidin-2-one (32a,b).** **32a**: a viscous oil; IR (neat) 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.79 (d, J = 6.4 Hz, 3 H), 0.81 (d, J = 6.4 Hz, 3 H), 1.57–1.69 (m, 1 H), 1.88–1.96 (m, 1 H), 2.21 (dd, J = 17.6, 4.4 Hz, 1 H), 2.64–2.74 (m, 1 H), 3.00–3.04 (m, 1 H), 3.21 (dd, J = 10.7, 2.2 Hz, 1 H), 3.33 (dd, J = 10.7, 5.1 Hz, 1 H), 3.80, 5.10 (AB q, J = 15.9 Hz, each 1 H), 7.22–7.37 (m, 5 H); HRMS calcd for $C_{15}H_{20}INO$ 357.0592, found 357.0556. Differential NOE: increase of intensity (6.0%) of H^4 by irradiation at H^5 was observed.

32b: mp 118–120 °C (isopropyl ether); IR (Nujol) 1665 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.93 (d, J = 6.1 Hz, 3 H), 0.95 (d, J = 6.4 Hz, 3 H), 1.87–2.17 (m, 2 H), 2.37 (dd, J = 16.6, 8.5 Hz, 1 H), 2.63–2.74 (m, 1 H), 3.30 (dd, J = 11.7, 2.8 Hz, 1 H), 3.38 (dd, J = 11.7, 3.9 Hz, 1 H), 3.48–3.53 (m, 1 H), 3.86, 5.23 (AB q, J = 15.1 Hz, each 1 H), 7.25–7.38 (m, 5 H). Anal. Calcd for $C_{15}H_{20}INO$: C, 50.43; H, 5.64; N, 3.92. Found: C, 50.58; H, 5.55; N, 3.93. Differential NOE: increase of intensity (1.5%) of H^4 by irradiation at H^5 was observed.

***cis*-*N*-Benzyl-5-(acetoxymethyl)-4-hydroxypyrrolidin-2-one (33).** A mixture of **24a** (662.3 mg, 2 mmol) and silver acetate (367.2 mg, 2.2 mmol) in DMF (5 mL) was stirred for 30 h at 65 °C. The insoluble material was removed by filtration through Celite and washed with ethyl acetate. The filtrate was evaporated. Column chromatography of the residue yielded **33** (348 mg, 66%) as a pale yellow oil: IR (neat) 1735, 1665 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.04 (s, 3 H), 2.52 (dd, J = 16.9, 5.9 Hz, 1 H), 2.74 (dd, J = 16.9, 7.7 Hz, 1 H), 3.63–3.68 (m, 1 H), 4.11, 4.94 (AB q, J = 15.4 Hz, each 1 H), 4.20 (dd, J = 12.1, 4.0 Hz, 1 H), 4.43–4.52 (m, 1 H), 4.46 (dd, J = 12.1, 4.4 Hz, 1 H), 7.20–7.34 (m, 5 H); HRMS calcd for $C_{14}H_{17}NO4$ 263.1156, found 263.1119.

***cis*-*N*-Benzyl-2-(hydroxymethyl)-3-hydroxypyrrolidine (34).** To a solution of **33** (91.6 mg, 0.348 mmol) in dry THF (11 mL) was added $LiAlH_4$ (26.6 mg, 0.70 mmol) with ice cooling. The reaction mixture was refluxed for 15 h. Water (0.1 mL), 15% NaOH (0.1 mL), and water (0.1 mL) were successively added to the mixture with ice cooling. The mixture was dried and filtered through Celite. The filtrate was evaporated. Column chromatography of the residue yielded **34** (74.2 mg, quan) as white crystals: mp 45–46 °C (isopropyl ether); IR (Nujol) 3350 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.57–1.72 (m, 1 H), 2.06–2.21 (m, 2 H), 2.55–2.61 (m, 1 H), 2.93–2.98 (m, 1 H), 3.34, 3.91 (AB q, J = 12.9 Hz, each 1 H), 3.71–3.94 (m, 2 H), 4.32–4.40 (m, 1 H), 7.22–7.29 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 35.37, 50.74, 58.71, 59.33, 66.57, 73.67, 127.28, 128.43, 128.77, 138.38. Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.27; H, 8.39; N, 6.84. Spectral data (IR, ^{1}H NMR, and ^{13}C NMR) were identical with those of the optically active authentic sample.[9]

***trans*-*N*-Benzyl-4,5-dimethylpyrrolidin-2-one (35). Procedure A.** A mixture of **34** (125 mg, 0.38 mmol), n-Bu_3SnH (0.16 mL, 0.57 mmol), and 2,2′-azobisisobutyronitrile (AIBN) (12 mg, 0.076 mmol) in toluene (5 mL) was refluxed for 17 h. The mixture was evaporated. Column chromatography of the residue yielded **35** (71.9 mg, 93%) as an oil: bp 111–113 °C (0.22 mmHg); IR (neat) 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.03 (d, J = 7.0 Hz, 3 H), 1.14 (d, J = 6.4 Hz, 3 H), 1.65–2.21 (m, 2 H), 2.41–2.71 (m, 1 H), 2.81–3.21 (m, 1 H), 3.93, 4.94 (AB q, J = 15.2 Hz, each 1 H), 7.28 (s, 5 H); HRMS calcd for $C_{13}H_{17}NO$ 203.1308, found 203.1308.

Procedure B. To a solution of N-benzylacetamide (0.597 g, 4 mmol) in THF (16 mL) was added 15% n-BuLi in hexane (2.5 mL, 8 mmol) at −40 °C. The reaction mixture was warmed to 0 °C and stirred for 1 h at the same temperature. After cooling at −78 °C, to the mixture were successively added *trans*-2,3-epoxybutane (0.18 mL, 2 mmol) and boron trifluoride ether complex (0.25 mL, 2 mmol). The reaction mixture was gradually warmed to 0 °C, stirred for 2 h at the same temperature, and quenched with ammonium chloride solution. The mixture was extracted with ethyl acetate three times. The extracts were washed with brine, dried, and evaporated. Column chromatography of the residue yielded (3*R**,4*S**)-*N*-benzyl-4-hydroxy-3-methylpentanamide (**36**) (294 mg, 66%) as a viscous oil: IR (neat) 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.89 (d, J = 6.0 Hz, 3 H), 1.09 (d, J = 6.0 Hz, 3 H), 1.80–2.60 (m, 3 H), 3.60–4.17 (m, 1 H), 4.42 (d, J = 6.0 Hz, 2 H), 6.30–6.87 (br s, 1 H), 7.38 (s, 5 H). A solution of **36** (250 mg, 1.13 mmol) in THF (1.7 mL) was added to a suspension of *t*-BuOK (308 mg, 2.74 mmol) and 18-crown-6-ether (5 mg) in THF (7.5 mL) at 0 °C. After 1 h, a solution of *p*-toluenesulfonyl chloride (228 mg, 1.2 mmol) in THF (4.2 mL) was dropwise added to the reaction mixture at −10 °C. The mixture was heated for 5 h at 50 °C. After cooling, the reaction mixture was quenched with ammonium chloride solution. The mixture was extracted with ethyl acetate three times. The extracts were washed with brine, dried, and evaporated. Column chromatography of the residue yielded **35** (91 mg, 40%), the spectral data of which were identical with those of **35** prepared by procedure A.

***cis*-*N*-(*tert*-Butoxycarbonyl)-2-(hydroxymethyl)-3-hydroxypyrrolidine (40).** A suspension of **34** (25.5 mg, 0.123 mmol) and $Pd(OH)_2$ (5 mg) in methanol (1 mL) was stirred under hydrogen atmosphere for 20 h. The mixture was filtered through Celite and washed with methanol. The combined solvents were evaporated to leave an oil. Without further purification, triethylamine (0.04 mL, 0.271 mmol) and di-*tert*-butyl dicarbonate (0.03 mL, 0.135 mmol) were successively added to a solution of the oil in CH_2Cl_2 (1 mL) with ice cooling. The reaction mixture was stirred for 15 h at room temperature. The mixture was acidified with saturated aqueous citric acid and extracted with CH_2Cl_2 three times. The extracts were washed with brine, dried, and evaporated. Column chromatography of the residue yielded **40** (8.3 mg, 31%) as an oil: IR (neat) 3400, 1700, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9 H), 1.80–2.20 (m, 2 H), 3.32–3.60 (m, 2 H), 3.72–4.02 (m, 3 H), 4.30–4.65 (m, 1 H); HRMS calcd for $C_{10}H_{19}NO_4$ 217.1314, found 217.1311.

***cis*-*N*-(*tert*-Butoxycarbonyl)-2-[[(*tert*-butyldimethylsilyl)oxy]methyl]-3-[(*tert*-butyldimethylsilyl)oxy]pyrrolidine (38).** According to the similar method described for **7**, treatment of **40** (57.9 mg, 0.27 mmol) with imidazole (90.7 mg, 1.33 mmol), TBDMSCI (100.4 mg, 0.67 mmol), and 4-(dimethylamino)pyridine (DMAP) (6.5 mg, 0.05 mmol) in DMF (1 mL) gave **38** (100 mg, 84%) as white crystals: mp 39.5–42.0 °C (petroleum ether/isopropyl ether); IR (Nujol) 1695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.05 (s, 12 H), 0.85 (s, 9 H), 0.87 (s, 9 H), 1.45 (s, 9 H), 1.75–2.18 (m, 2 H), 3.13–3.75 (m, 3 H), 3.81–4.00 (m, 2 H), 4.15–4.58 (m, 1 H). Anal. Calcd for $C_{22}H_{47}NO_4Si_2$: C, 59.27; H, 10.63; N, 3.14. Found: C, 59.13; H, 10.74; N, 3.34.

***cis*-*N*-Benzyl-3-hydroxy-2-[(triphenylmethoxy)methyl]pyrrolidine (41).** A mixture of **34** (231.0 mg, 1.114 mmol), triethylamine (0.23 ml, 1.672 mmol), chlorotriphenylmethane (342.0 mg, 1.226 mmol), and DMAP (5.4 mg, 0.0496 mmol) in CH_2Cl_2 (4 mL) was stirred for 20 h at room temperature. Ice water was added to the reaction mixture. The mixture was extracted with CH_2Cl_2 three times. The extracts were washed with ammonium chloride solution and water, dried, and evaporated. Column chromatography of the residue yielded **41** (382.0 mg, 76%) as an oil: IR (neat) 3370, 1490, 1450 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.61–2.24 (m, 3 H), 2.42–3.17 (m, 3 H), 3.24, 3.86 (AB q, J = 13.4 Hz, each 1 H), 3.29–3.39 (m, 2 H), 4.28–4.56 (m, 1 H), 7.17–7.56 (m, 20 H); HRMS calcd for $C_{31}H_{31}NO_2$ 449.2354, found 449.2306.

***trans*-*N*-Benzyl-3-(benzoyloxy)-2-[(triphenylmethoxy)methyl]pyrrolidine (42).** To a solution of **41** (378.4 mg, 0.842 mmol), triphenylphosphine (662.3 mg, 2.525 mmol), and benzoic acid (308.3 mg, 2.525 mmol) in THF (30 mL) was dropwise added a solution of diethyl azodicarboxylate (DEAD) (0.39 mL, 2.525 mmol) in THF (10 mL) over 1 h at −40 °C. The reaction mixture was stirred for 5 h at the same temperature and for additional 14 h at −20 °C. After evaporation of the solvent, the residue was chromatographed to yield **42** (264.3 mg, 57%) as an oil: IR (neat) 1715 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.84–1.92 (m, 1 H), 2.12–2.21 (m, 1 H), 2.50–2.59 (m, 1 H), 2.94–3.06 (m, 2 H), 3.19–3.28 (m, 2 H), 3.50, 4.08 (AB q, J = 13.2 Hz, each 1 H), 5.34–5.37 (m, 1 H),

7.16–8.03 (m, 25 H); HRMS calcd for $C_{38}H_{35}NO_3$ 553.2615, found 553.2600.

***trans*-*N*-Benzyl-3-hydroxy-2-[(triphenylmethoxy)methyl]pyrrolidine (43).** A solution of NaOH (116.5 mg, 2.913 mmol) in MeOH (16.5 mL) was added to **42** (234.1 mg, 0.423 mmol). The reaction mixture was stirred for 4 h at room temperature and evaporated. Water was added to the residue. The mixture was extracted with CH_2Cl_2 three times. The extracts were washed with brine, dried, and evaporated. Column chromatography of the residue yielded **43** (166.5 mg, 88%) as an oil: IR (neat) 3440, 1490, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60–1.73 (m, 1 H), 1.91–2.07 (m, 1 H), 2.17 (br s, 1 H), 2.45–2.60 (m, 1 H), 2.62–2.71 (m, 1 H), 2.82–2.89 (m, 1 H), 3.02–3.09 (m, 1 H), 3.32–3.38 (m, 1 H), 3.40, 3.86 (AB q, J = 13.2 Hz, each 1 H), 4.19–4.21 (m, 1 H), 7.20–7.44 (m, 20 H); HRMS calcd for $C_{31}H_{31}NO_2$: 449.2354, found 449.2354.

(±)-*trans*-2-(Hydroxymethyl)-3-hydroxypyrrolidine (39). A suspension of **43** (163.3 mg, 0.363 mmol) and $Pd(OH)_2$ (40 mg) in EtOH (4 mL) was shaken under hydrogen at 4 atm for 42 h. The mixture was filtered through Celite and washed with EtOH. The solvent was evaporated. A solution of the residue in CH_2Cl_2 was extracted with 2 N HCl three times. The extracts were basified with NaOH with ice cooling. The mixture was extracted with CH_2Cl_2 three times. The aqueous solution was chromatographed with an ion-exchange resin (Dowex 50W-X8, 200–400 mesh) using 0.5 N NH_4OH as eluant to yield **39** (19.5 mg, 46%): ^{13}C NMR of hydrochloride salt of **39** (D_2O) δ 71.60, 67.88, 59.14, 44.56, 32.66, 1,4-dioxane was used as internal standard (lit.[9] 71.69, 67.93, 59.21, 44.14, 32.75); identical with that of an optically active authentic sample.

***N*-Benzyl-5-(3-carbethoxypropyl)pyrrolidine-2-thione (46).** A mixture of **3a** (630.3 mg, 2 mmol), ethyl acrylate (6.5 mL, 6 mmol), and $NaBH_4$ (113.5 mg, 3 mmol) in EtOH (25 mL) was irradiated (Pyrex reaction vessel) with a high-pressure Hg lamp (350 W, USHIO UM-453-A) at 38 °C, and a solution of *n*-Bu_3SnCl (0.06 mL), 0.2 mmole in EtOH (1 mL) was added over 20 min. After 1 h of irradiation, the mixture was filtered through Celite. The filtrate was evaporated to leave an oil, which was chromatographed to give **44** (449.6 mg) with an impurity. A mixture of the crude **44** and Lawesson's reagent (206.5 mg, 0.511 mmol) in benzene (7 mL) was refluxed for 2 h. After evaporation, column chromatography of the residue yielded **46** (248.7 mg, 43% from **3a**) as a pale yellow oil: IR (neat) 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (t, J = 7.8 Hz, 3 H), 1.37–2.45 (m, 8 H), 3.07 (t, J = 7.8 Hz, 2 H), 3.53–3.98 (m, 1 H), 4.13 (q, J = 7.8 Hz, 2 H), 4.28, 5.80 (AB q, J = 14.8 Hz, each 1 H), 7.31 (s, 5 H); HRMS calcd for $C_{17}H_{23}NO_2S$ 305.1447, found 305.1442.

***N*-Benzyl-2-(3-carbethoxypropyl)pyrrolidine (47).** To a solution of **46** (199.2 mg, 0.652 mmol) in CH_2Cl_2 (0.5 mL) was added 1.0 M triethyloxonium boron tetrafluoride–CH_2Cl_2 solution (0.8 mL) with ice cooling. After 5 min of stirring, the mixture was warmed at room temperature and stirred for an additional hour. After evaporation of the mixture, dry MeOH (1.1 mL) was added the residue. To the mixture was added $NaBH_4$ (74.0 mg, 1.957 mmol) over 3 min with ice cooling. After 5 min of stirring, the mixture was warmed at room temperature and stirred for an additional hour; 10% HCl (1.1 mL) was added to the reaction mixture with ice cooling. After 5 min of stirring, 10% NaOH was added to the mixture until the pH of the solution became 10. The mixture was extracted with CH_2Cl_2 three times. The extracts were washed with brine, dried, and evaporated. Column chromatography of the residue yielded **47** (142.3 mg, 79%) as an oil: IR (neat) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (t, J = 7.2 Hz, 3 H), 1.37–2.67 (m, 12 H), 2.71–3.04 (m, 1 H), 3.15, 4.02 (AB q, J = 13.0 Hz, each 1 H), 4.13 (q, J = 7.2 Hz, 2 H), 7.24 (s, 5 H); HRMS calcd for $C_{17}H_{25}NO_2$ 275.1884, found 275.1877.

5-Oxoindolizidine (48). A suspension of **47** (129.0 mg, 0.468 mmol) and $Pd(OH)_2$ (20 mg) in MeOH (1 mL) was stirred under a hydrogen atmosphere for 4 h. After addition of $Pd(OH)_2$ (30 mg), the reaction mixture was stirred for 21 h. After filtration of the catalyst, the filtrate was evaporated. Column chromatography of the residue yielded **48** (45.1 mg, 69%) as an oil: IR (neat) 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08–2.43 (m, 10 H), 3.20–3.70 (m, 3 H); HRMS calcd for $C_8H_{13}NO$ 139.0995, found 139.0953.

δ-Coniceine (45). A mixture of **48** (50.4 mg, 0.362 mmol) and $LiAlH_4$ (34.4 mg, 0.905 mmol) in THF (5 mL) was refluxed for 15 h. After ice cooling, water (0.07 mL), 15% NaOH (0.07 mL), and water (0.14 mL) were successively added to the reaction mixture. The mixture was dried and filtered through Celite. The filtrate was evaporated to give **45** (47 mg, 99%) as an oil; mp 228–231 °C (MeOH) as picrate [lit.[35] mp 225–228 °C (MeOH)].

***cis*-*N*-Benzyl-4-hydroxy-5-(3-carbethoxypropyl)-pyrrolidin-2-one (49).** According to the similar method described for **46**, treatment of **24a** (662.3 mg, 2 mmol) with ethyl acrylate (6.5 mL, 60 mmol), $NaBH_4$ (113.5 mg, 3 mmol), and *n*-Bu_3SnCl (0.06 mL, 0.2 mmol) yielded **49** (452.5 mg) an oil: IR (neat) 1730, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (t, J = 7.0 Hz, 3 H), 1.63–2.62 (m, 8 H), 3.33–3.57 (m, 2 H), 3.97, 4.98 (AB q, J = 15.6 Hz, each 1 H), 4.13 (q, J = 7.0 Hz, 2 H), 7.31 (s, 5 H); HRMS calcd for $C_{17}H_{23}NO_4$ 305.1625, found 305.1588.

***cis*-*N*-Benzyl-4-[(*tert*-butyldimethylsilyl)oxy]-5-(3-carbethoxypropyl)pyrrolidinethione (51).** According to the similar procedure described for **7**, the treatment of **49** (452.5 mg), imidazole (253.8 mg, 3.728 mmol), and TBDMSCl (280.9 mg, 1.864 mmol) in DMF (4mL) for 36 h gave **50** (251.0 mg, 44% from **24a**) as an oil: IR (neat) 1720, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03–0.08 (m, 6 H), 0.93 (s, 9 H), 1.23 (t, J = 7.4 Hz, 3 H), 1.46–1.8 (m, 4 H), 1.99–2.56 (m, 4 H), 3.18–3.90 (m, 1 H), 3.93–4.46 (m, 4 H), 4.94 (q, J = 14.6 Hz, 1 H), 7.23 (s, 5 H); MZ m/e 419 (M^+), 362. A mixture of **50** (195.2 mg, 0.465 mmol) and Lawesson's reagent (56.4 mg, 0.140 mmol) was refluxed for 2 h. After evaporation, column chromatography of the residue yielded **51** (159.9, mg, 79%) an oil: IR (neat) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.06 (s, 3 H), 0.10 (s, 3 H), 0.89 (s, 9 H), 1.23 (t, J = 6.8 Hz, 3 H), 1.53–1.83 (m, 4 H), 2.13–2.33 (m, 2 H), 3.08 (d, J = 5.2 Hz, 2 H), 3.53–3.81 (m, 1 H), 4.11 (q, J = 6.8 Hz, 2 H), 4.29–4.48 (m, 1 H), 4.48, 5.63 (AB q, J = 15.2 Hz, each 1 H), 7.30 (s, 5 H); HRMS calcd for $C_{23}H_{37}NO_3SSi$ 435.2261, found 435.2243.

***cis*-*N*-Benzyl-3-[(*tert*-butyldimethylsilyl)oxy]-2-(3-carbethoxypropyl)pyrrolidine (52).** According to the similar method described for **47**, treatment of **51** (313.4 mg, 0.747 mmol) with 1 M $Et_3O^+ \cdot BF_4^-$–CH_2Cl_2 (0.7 mL) followed by reduction with $NaBH_4$ (84.8 mg, 2.24 mmol) gave **52** (272.1 mg, 94%) as an oil: IR (neat) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ, 0.07 (s, 6 H), 0.92 (s, 9 H), 1.24 (t, J = 7.0 Hz, 3 H), 1.43–2.50 (m, 11 H), 3.25, 3.98 (AB q, J = 13.4 Hz, each 1 H), 4.13 (q, J = 7.0 Hz, 2 H), 4.19–4.3l (m, 1 H), 7.31 (s, 5 H); HRMS calcd for $C_{23}H_{39}NO_3Si$ 405.2699, found 405.2659.

***cis*-1-[(*tert*-Butyldimethylsilyl)oxy]-5-oxoindolizidine (53).** According to the similar procedure described for **48**, treatment of **52** (220.6 mg, 0.544 mmol) with $Pd(OH)_2$ (23 mg) gave **53** (130.2 mg, 89%) as an oil: IR (neat); 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.06 (s, 3 H), 0.07 (s, 3 H), 0.86 (s, 9 H), 1.58–2.00 (m, 6 H), 2.20–2.47 (m, 2 H), 3.40–3.54 (m, 2 H), 3.63–3.74 (m, 1 H), 4.21–4.24 (m, 1 H); HRMS calcd for $C_{14}H_{27}NO_2Si$ 269.1809, found 269.1797.

***cis*-1-Hydroxyindolizidine (54).** According to the similar method described for **45**, treatment of **53** (89.4 mg, 0.332 mmol) and $LiAlH_4$ (31.5 mg, 0.829 mmol) in THF (4 mL) gave **54** (37.0 mg, 79%) as an oil: bp 53–58 °C (0.45 mmHg) [lit.[46] bp 72 °C (1.8 mmHg)]; mp 178–181 °C as picrate (EtOH/petroleum ether) (lit.[36] mp 178–180 °C).

***cis*-*N*-Benzyl-4-hydroxy-5-(hydroxymethyl)pyrrolidin-2-one (55).** A mixture of **33** (420.4 mg, 1.597 mmol) and aqueous 0.5 M K_2CO_3 solution (4.8 mL) in EtOH (7.5 mL) was stirred for 19 h at room temperature. After evaporation of the mixture, the residue was extracted with CH_2Cl_2 three times. The extracts were washed with brine, dried, and evaporated to give **55** (315.5 mg, 89%) as white crystals: mp 118–121 °C ($CHCl_3$/hexane); IR (Nujol) 3200, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.69 (br s, 1 H), 2.51–2.59 (m, 1 H), 2.73–2.82 (m, 1 H), 3.51–3.56 (m, 1 H), 3.85–3.95 (m, 2 H), 4.11, 4.99 (AB q, J = 15.1 Hz, each 1 H), 4.57–4.64 (m, 1 H), 7.22–7.37 (m, 5 H). Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.13; H, 6.89; N, 6.30.

***cis*-*N*-Benzyl-4-[(*tert*-butyldimethylsilyl)oxy]-5-[[(*tert*-butyldimethylsilyl)oxy]methyl]pyrrolidin-2-one (56).** According to the similar procedure described for **7**, treatment of **55** (199.0 mg, 0.899 mmol) with imidazole (269.4 mg, 3.957 mmol), TBDMSCl (298.2 mg, 1.979 mmol), and DMAP (5 mg) in DMF

(46) Aaron, H. S.; Rader, C. P.; Wicks, G. E., Jr. *J. Org. Chem.* **1966**, *31*, 3502.

(2 mL) for 18 h gave **56** (415.6 mg, 100%) as an oil: IR (neat) 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.09 (s, 6 H), 0.94 (s, 18 H), 2.59 (d, J = 8.0 Hz, 2 H), 3.32–3.61 (m, 1 H), 3.77–3.95 (m, 2 H), 4.10, 5.11 (AB q, J = 14.8 Hz, each 1 H), 4.40 (q, J = 7.6 Hz, 1 H), 7.32 (s, 5 H); HRMS calcd for $C_{24}H_{43}NO_2Si_2$ 449.2779, found 449.2776.

***cis*-*N*-(*tert*-Butoxycarbonyl)-4-[(*tert*-butyldimethylsilyl)oxy]-5-[[(*tert*-butyldimethylsilyl)oxy]methyl]pyrrolidin-2-one (57).** Sodium (45 mg, 1.96 mmol) was added to a solution of **56** (234.8 mg, 0.522 mmol) in liquid ammonia (10 mL). The reaction mixture was stirred for 1 h. After evaporation of ammonia, unsaturated ammonium chloride was added to the mixture. The mixture was extracted with ethyl acetate three times. The extracts were dried and evaporated. Column chromatography of the residue yielded *cis*-4-[(*tert*-butyldimethylsilyl)oxy]-5-[[(*tert*-butyldimethylsilyl)oxy]methyl]pyrrolidin-2-one (**85**) (84.7 mg, 45%) as white crystals: mp 98–99 °C (isopropyl ether); IR (Nujol) 3220, 1700, 1665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.00 (s, 12 H), 0.83 (s, 18 H), 2.20–2.45 (m, 2 H), 3.52–3.77 (m, 3 H), 4.28–4.62 (m, 1 H), 6.03 (br s, 1 H). Anal. Calcd for $C_{17}H_{37}NO_3Si_2$: C, 56.77; H, 10.37; N, 3.89. Found: C, 56.68; H, 10.23; N, 3.89. To a solution of **85** (85.1 mg, 0.237 mmol) in THF (2 mL) was added NaH (10.4 mg, 0.260 mmol) with ice cooling. After addition di-*tert*-butyl dicarbonate (0.06 mL, 0.237 mmol) to the mixture, the reaction mixture was stirred for 9 h at room temperature. After addition of water (0.1 mL) to the reaction mixture, the mixture was dried and evaporated. Column chromatography of the residue yielded **57** (86.7 mg, 80%) as white crystals: mp 64–65 °C (isopropyl ether/petroleum ether); IR (Nujol) 1785, 1765, 1750, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (s, 6 H), 0.07 (s, 6 H), 0.86 (s, 9 H), 0.90 (s, 9 H), 1.52 (s, 9 H), 2.22–3.06 (m, 2 H), 3.87–4.10 (m, 3 H), 4.15–4.72 (m, 1 H). Anal. Calcd for $C_{22}H_{45}NO_5Si_2$: C, 57.47; H, 9.87; N, 3.05. Found: C, 57.53; H, 9.71; N, 3.01.

(3*R,4*R**)-Methyl 4-[(*tert*-Butoxycarbonyl)amino]-3,5-bis[(*tert*-butyldimethylsilyl)oxy]pentanoate (58).** A solution of **57** (879.7 mg, 1.913 mmol) and KOH (322.1 mg, 5.740 mmol) in 95% MeOH (20 mL) was heated for 1.5 h at 85 °C. After evaporation, the residue was dissolved in $CHCl_3$. The mixture was acidified with 20% HCl at pH 2 and extracted with $CHCl_3$ three times. The extracts were dried and evaporated. Without further purification, the residue was treated with excess CH_2N_2 in ether. The mixture was evaporated to give an oil, which was chromatographed to yield **58** (706.0 mg, 75%) as an oil: IR (neat) 1740, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ, 0.06–0.10 (m, 12 H), 0.87 (s, 9 H), 0.90 (s, 9 H), 1.45 (s, 9 H), 2.43–2.62 (m, 2 H), 3.42–3.52 (m, 1 H), 3.56–3.70 (m, 2 H), 3.67 (s, 3 H), 4.43–4.52 (br s, 1 H), 4.74 (br d, J = 8.1 Hz, 1 H).

(3*R,4*R**)-Methyl 4-[(*tert*-Butoxycarbonyl)amino]-3,5-dihydroxypentanoate (59).** *n*-BuNF–THF (1 M, 2.0 mL, 2.0 mmol) was added to a solution of **58** (470.2 mg, 0.956 mmol) in THF (8 mL) with ice cooling. After stirring for 1 h, brine was added to the reaction mixture. The mixture was extracted with ethyl acetate three times. The extracts were dried and evaporated to give a residue, which was chromatographed to yield **59** (140.5 mg, 56%) as an oil: IR (neat) 1710, 1695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.46 (s, 9 H), 3.93 (d, J = 6.2 Hz, 2 H), 3.29–3.93 (m, 3 H), 3.72 (s, 3 H), 4.03–4.63 (m, 1 H), 5.32 (br, d, J = 8.0 Hz, 1 H).

(2*S,3*R**)-Dimethyl 2-[(*tert*-Butoxycarbonyl)amino]-3-hydroxyglutarate (60).** To PtO_2 (60 mg), reduced by shaking under H_2 (5 kg/cm^2) for 30 min in H_2O (3 mL), was added to a solution of **59** (52.8 mg, 0.201 mmol) and $NaHCO_3$ (25.3 mg, 0.301 mmol) in H_2O (6 mL), and oxygen was passed through the mixture at 55 °C for 32 h. The mixture was filtered and washed with acetone. After evaporation of the mixture, the aqueous solution was washed with ethyl acetate three times and then acidified with 1 N HCl at pH 2. The acidic solution was extracted with ethyl acetate three times, and the extracts were dried and evaporated to give an oil, which was treated with excess CH_2N_2 in ether for 3 h with ice cooling. After evaporation of the mixture, the residue was chromatographed to yield **60** (10.8 mg, 18%) as a pale yellow oil; IR (neat) 1740, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.46 (s, 9 H), 2.54–2.68 (m, 2 H), 3.30 (d, J = 3.4 Hz, 1 H), 3.73 (s, 3 H), 3.79 (s, 3 H), 4.43 (br d, J = 9.5 Hz, 1 H), 4.59 (br s, 1 H), 5.35 (br d, J = 9.5 Hz, 1 H); HRMS calcd for $C_{10}H_{18}NO_5$ ($M^+ - CO_2CH_3$) 232.1184, found 232.1179.

(3*R*)- and (3*S*)-3-Hydroxy-*N*-[(*S*)-1-phenylethyl]pent-4-enethioamide (63a,b). According to the similar method described for **6**, treatment of **62** (1.0757 g, 6 mmol) with acrolein (0.6 mL, 9 mmol) gave an oil, which was separated by column chromatography to yield **63a** (685.9 mg, 49%) and **63b** (440.4 mg, 31%), respectively. **63a**: $[\alpha]^{25.5}_D$ −176.9° (c 1.035, MeOH); IR (neat) 3250, 1640, 1535 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.56 (d, J = 7.1 Hz, 3 H), 2.74 (dd, J = 14.5, 8.5 Hz, 1 H), 2.90 (dd, J = 14.5, 2.9 Hz, 1 H), 3.87 (br s, 1 H), 4.51 (br s, 1 H), 5.10–5.14 (m, 1 H), 5.23–5.31 (m, 1 H), 5.63–5.88 (m, 2 H), 7.23–7.36 (m, 5 H), 8.56 (br s, 1 H); HRMS calcd for $C_{13}H_{17}NOS$ 235.1030, found 235.1016. **63b**: $[\alpha]^{25}_D$ −228.8° (c 1.005, MeOH); IR (neat) 3250, 1640, 1535 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.57 (d, J = 7.1 Hz, 1H), 2.73 (dd, J = 14.9, 8.5 Hz, 1 H), 2.89 (dd, J = 14.9, 2.9 Hz, 1 H), 3.92 (br s, 1 H), 4.54 (br s, 1 H), 5.09–5.14 (m, 1 H), 5.22–5.29 (m, 1 H), 5.65–5.88 (m, 2 H), 7.21–7.37 (m, 5 H), 8.50 (br s, 1 H); HRMS calcd for $C_{13}H_{17}NOS$ 235.1030, found 235.1079.

(4*R*,5*S*)-*N*-[(*S*)-1-Phenylethyl]-4-hydroxy-5-(iodomethyl)pyrrolidin-2-one (65). According to the similar method described for **3a**, methylation of **63a** (931.4 mg, 3.958 mmol) with methyl iodide followed by iodolactamization gave **65** (999.0 mg, 73%): mp 139–142 °C (CH_2Cl_2/petroleum ether); $[\alpha]^{25}_D$ −122.3° (c 0.965, $CHCl_3$); IR (Nujol) 1665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.62 (d, J = 7.2 Hz, 3 H), 2.19. (d, J = 5.1 Hz, 1 H), 2.67–2.72 (m, 3 H), 2.89 (dd, J = 10.0, 3.2 Hz, 1 H), 3.95–4.02 (m, 1 H), 4.54–4.61 (m, 1 H), 5.55 (q, J = 7.2 Hz, 1 H), 7.26–7.35 (m, 5 H). Anal. Calcd for $C_{13}H_{16}INO_2$: C, 45.24; H, 4.67; N, 4.06. Found: C, 45.19; H, 4.72; N, 3.84.

(4*R*,5*R*)-*N*-[(*S*)-1-Phenylethyl]-5-(acetoxymethyl)-4-hydroxypyrrolidin-2-one (66). According to the similar procedure described for **33**, treatment of **65** (138.3 mg, 0.401 mmol) with AgOAc (73.6 mg, 0.441 mmol) in DMF (2 mL) gave **66** (47.5 mg, 43%): mp 127–130 °C (CH_2Cl_2/petroleum ether); $[\alpha]^{25}_D$ −118.1° (c 1.08, $CHCl_3$); IR (Nujol) 1740, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.62 (d, J = 7.2 Hz, 3 H), 1.91 (s, 3 H), 2.56 (d, J = 7.4 Hz, 2 H), 3.27 (br s, 1 H), 3.53–4.0o (m, 3 H), 4.19–4.64 (m, 1 H), 5.45 (q, J = 7.2 Hz, 1 H), 7.27 (s, 5 H). Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 65.14, H, 6.91; N, 5.03.

(2*R*,3*R*)-*N*-Benzoyl-2-[(benzoyloxy)methyl]-3-(benzoyloxy)pyrrolidine (68). According to the similar method described for **34**, treatment of **66** (145.0 mg, 0.523 mmol) with $LiAlH_4$ (59.5 mg, 1.569 mmol) gave **67** (113.6 mg). According to the similar procedure described for **34**, treatment of **67** (113.6 mg) with $Pd(OH)_2$ (34 mg) gave the crude (2*R*,3*R*)-2-(hydroxymethyl)-3-hydroxypyrrolidine (**87**). To a solution of **87** and pyridine (0.22 mL, 2.615 mmol) in CH_2Cl_2 (3 mL) was added benzoyl chloride (0.3 mL, 2.615 mmol) with ice cooling, and the reaction mixture was stirred for 22 h at room temperature. After addition of H_2O, the mixture was extracted with CH_2Cl_2 three times. The extracts were washed with brine, dried, and evaporated. Column chromatography of the residue yielded **68** (134.3 mg, 60%) as an oil: $[\alpha]^{25}_D$ −114.7° (c 0.87, $CHCl_3$); IR (neat) 1720, 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.00–2.40 (m, 2 H), 3.41–3.88 (m, 2 H), 4.36–5.06 (m, 3 H), 5.66–5.94 (m, 1 H), 7.14–8.12 (m, 15 H); HRMS calcd for $C_{26}H_{23}NO_5$ 429.1576, found 429.1614.

(2*R*,3*R*)-*N*-Benzyl-2-(hydroxymethyl)-3-hydroxypyrrolidine (69). According to the similar procedure described for **34**, treatment of **68** (121.0 mg, 0.282 mmol) of $LiAlH_4$ (53.5 mg, 1.409 mmol) gave **69** (30.1 mg, 52%) as an oil: $[\alpha]^{25.5}_D$ −54.9° (c 0.685, $CHCl_3$) (lit.[8] $[\alpha]^{20}_D$ −56.5° (c 0.5, $CHCl_3$); IR was identical with that of **34**; HRMS calcd for $C_{12}H_{17}NO_2$ 207.1260, found 207.1296.

(4*R*,5*R*)-*N*-[(*S*)-1-Phenylethyl]-4-hydroxy-5-[(propionyloxy)methyl]pyrrolidin-2-one (70). A mixture of **65** (103.6 mg, 0. 3 mmol) and cesium propionate (68.0 mg, 0.33 mmol) in DMF (3.3 mL) was stirred for 24 h at 60 °C. After evaporation of the solvent, the residue was chromatographed to yield **70** (57.5 mg, 66%) as a pale yellow oil: $[\alpha]^{25}_D$ −97.4° (c 2.77, $CHCl_3$); IR (neat) 1735, 1665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (t, J = 7.4 Hz, 3 H), 1.63 (d, J = 7.2 Hz, 3 H), 2.20 (q, J = 7.4 Hz, 2 H), 2.58 (d, J = 7.8 Hz, 2 H), 3.30–4.19 (m, 4 H), 4.45 (br s, 1 H), 5.50 (q, J = 7.2 Hz, 1 H), 7.32 (s, 5 H); HRMS calcd for $C_{16}H_{21}NO_4$ 291.1471, found 291.1479.

Preparation of 76 from 70. According to the similar procedure described for the racemate **60**, **76** was obtained from **70** as shown in Scheme V.

(4*R*,5*R*)-*N*-[(*S*)-1-Phenylethyl]-4-hydroxy-5-(hydroxymethyl)pyrrolidin-2-one (71): 95%; mp 132–134 °C

($CHCl_3$/hexane); $[\alpha]^{25}_D$ -189.1° (c 1.02, $CHCl_3$); IR (Nujol) 3350, 1675 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60 (d, J = 7.2 Hz, 3 H), 2.57 (d, J = 6.8 Hz, 2 H), 2.80–3.50 (m, 2 H), 3.55–3.90 (m, 1 H), 4.30–4.78 (m, 1 H), 5.40 (q, J = 7.2 Hz, 1 H), 7.38 (s, 5 H). Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.09; H, 7.43; N, 5.78.

(4*R*,5*R*)-*N*-[(*S*)-1-Phenylethyl]-4-[(*tert*-butyldimethylsilyl)oxy]-5-[[(*tert*-butyldimethylsilyl)oxy]methyl]pyrrolidin-2-one (72): 98%; mp 62–65 °C (isopropyl ether); $[\alpha]^{25.5}_D$ -64.0° (c 1.05, $CHCl_3$); IR (Nujol) 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ -0.12 (s, 3 H), -0.08 (s, 3 H), 0.04 (s, 6 H), 0.85 (s, 9 H), 0.92 (s, 9 H), 2.64 (d, J = 7.0 Hz, 3 H), 1.64 (d, J = 7.0 Hz, 3 H), 2.40–2.70 (m, 2 H), 2.98–3.33 (m, 1 H), 3.40–3.77 (m, 2 H), 4.20–4.66 (m, 1 H), 5.40 (q, J = 7.0 Hz, 1 H), 7.18–7.60 (m, 5 H). Anal. Calcd for $C_{25}H_{45}NO_3Si_2$: C, 64.74; H, 9.78; N, 3.02. Found: C, 65.00; H, 9.74; N, 3.16.

(4*R*,5*R*)-*N*-(*tert*-Butoxycarbonyl)-4-[(*tert*-butyldimethylsilyl)oxy]-5-[[(*tert*-butyldimethylsilyl)oxy]-methyl]pyrrolidin-2-one (73): 60% from **72**; mp 89–90 °C (petroleum ether) (lit.[22c] mp 78–79 °C); $[\alpha]^{26}_D$ -49.8° (c 1.60, $CHCl_3$) [lit.[22c] $[\alpha]_D$ -43° (c 1.60, $CHCl_3$)]; spectral data (IR and ^1H NMR) were identical with those of **57**. Anal. Calcd for $C_{22}H_{45}NO_5Si_2$: C, 57.47; H, 9.87; N, 3.05. Found: C, 57.65; H, 9.95; N, 3.03.

(3*R*,4*R*)-Methyl 4-[(*tert*-butoxycarbonyl)amino]-3,5-bis-[(*tert*-butyldimethylsilyl)oxy]pentanoate (74): 75%; $[\alpha]^{25.5}_D$ 2.9° (c 2.77, $CHCl_3$); spectral data (IR and ^1H NMR) were identical with those of **58**.

(3*R*,4*R*)-Methyl 4-[(*tert*-butoxycarbonyl)amino]-3,5-dihydroxypentanoate (75): 47%; $[\alpha]^{25}_D$ 13.7° (c 2.17, $CHCl_3$); spectral data (IR and ^1H NMR) were identical with those of **59**.

(2*S*,3*R*)-Dimethyl 2-[(*tert*-butoxycarbonyl)amino]-3-hydroxyglutarate (76): 42%; $[\alpha]^{25.5}_D$ 30.5° (c 0.573, $CHCl_3$) [lit.[28] $[\alpha]^{20}_D$ 28.9° ($CHCl_3$)]; IR (neat) 1740, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.46 (s, 9 H), 2.53–2.69 (m, 2 H), 3.30 (d, J = 3.4 Hz, 1 H), 3.73 (s, 3 H), 3.79 (s, 3 H), 4.34 (br d, J = 9.5 Hz, 1 H), 4.60 (br s, 1 H), 5.34 (br d, J = 9.5 Hz, 1 H); HRMS calcd for $C_{10}H_{18}NO_5$ ($M^+ - CO_2CH_3$) 232.1184, found 232.1155.

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Synthesis of Halothiophene *S,C*-Ylides and the Corresponding 1,4-Oxathiocines†,[1]

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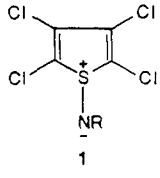
Crystalline halothiophenium *S,C*-ylides **2**, stabilized by α,α-biscarbonyl (or sulfonyl) substituents have been synthesized from the halo-substituted thiophenes and the corresponding diazoalkanes in the presence of rhodium(II) catalyst. Ylides **2** undergo smooth thermal rearrangement to 1,4-oxathiocines **3**, representing new hetero analogues (O,S) of an eight-membered 10π annulene system. NMR (^1H, ^{13}C) spectroscopy data are given for products **2** and **3**; for the latter no evidence of the aromatic character of the system was obtained.

The known isolable S-substituted derivatives of thiophene comprise alkylthiophenium salts,[2] the mono-[3] and dioxides,[4] and the recently prepared *S,N*-ylides of tetrachlorothiophene **1**.[5] Porter et al. reported[6] that thiophenes react with diazoalkanes under rhodium acetate catalysis to give, depending on the diazo compound used, the ring substituted products or the remarkably stable *S,C*-ylides (e.g. **2a**).



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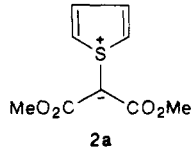

2a

We have recently demonstrated[1] that *S,C*-ylides **2**, prepared according to the procedure reported by Porter,[6] undergo a smooth thermal rearrangement to the hitherto unknown 1,4-oxathiocines **3**. In view of the interest in the heteroanalogues of the eight-membered 10π annulenes,[7] and in view of the interesting fragmentation of some these compounds to give polysubstituted benzenes,[8] we report here the full synthesis of ylides **2** and their rearrangement products, 1,4-oxathiocines **3**.

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