Radical Cyclization in Heterocycle Synthesis. II.[1,2] Total Synthesis of (±)-Anantine and (±)-Isoanantine

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Received June 13, 1997; accepted July 20, 1997

(±)-Anantine, (±)-isoanantine and related compounds were synthesized *via* two key reactions, sulfanyl radical addition–cyclization and stereoselective construction of the *E*-benzylidene moiety.

Key words anantine; imidazole alkaloid; radical cyclization; sulfur; selenium; total synthesis

In the course of our studies on the sulfanyl radical addition–cyclization of dienyl amides,[2] we applied this radical cyclization to the synthesis of the imidazole alkaloid anantine and related alkaloids.[3] These alkaloids had been isolated from *Cynometra* species, which has been used in Africa as a traditional folk medicine with antitussive and analgesic activities.[3] In addition, structural similarity of the alkaloids to pilocarpine, which is used as a muscarine agonist for the symptomatic treatment of Alzheimer's disease, prompted us to explore a general and practical synthetic route for anantine and related compounds. Khuong-Huu and co-workers[3c] have reported the isolation, structure determination and synthesis of the alkaloids. However, the reported synthesis involved many steps with low selectivity and low yields.[3a,c] Recently, a related alkaloid, cynometrine, has been synthesized *via* a route involving the 1,3-dipolar cycloaddition reaction of azomethine ylide.[4]

Results and Discussion

Synthetic Strategy Our synthetic strategy for anantine and related alkaloids consists of three key steps. The first step is the construction of 3,4-disubstituted pyrrolidinone, which is the basic skeleton of the alkaloids, by sulfanyl radical addition–cyclization of dienylamide.[2] The second is conversion of the resulting phenylsulfanylmethyl group into the imidazole ring. The last step is the introduction of the benzylidene group at α-position of the lactam carbonyl group *via* the addition–elimination reaction of the phenylselenenyl group. This synthetic strategy should permit the divergent synthesis of a whole family of alkaloids, including anantine, *via* the 3,4-disubstituted pyrrolidinone as a common intermediate.

Total Synthesis of Dihydroanantine, (±)-Anantine and (±)-Isoanantine The *N*-allylcinnamamide **1** required for radical cyclization, as a first key step of our synthetic strategy, was readily prepared by acylation of *N*-allylbenzylamine with cinnamoyl chloride. Sulfanyl radical addition–cyclization[2] of the amide **1** in the presence of diphenyl disulfide and benzenethiol under photochemical conditions proceeded smoothly to give a 1 : 1 mixture of the cyclized lactams **2** and **3** (71% yield), which was readily separated by medium-pressure liquid chromatography (MPLC). The two lactams **2** and **3** showed a molecular ion peak at *m/z* 387 and IR absorptions at *ν* 1676—1678 cm^{-1} (five-membered NCO) and ^{1}H-NMR peaks at *δ* 3.15—2.50 due to two types of methylene hydrogens adjacent to the phenylsulfanyl group. The ^{1}H-NMR spectra of **2** and **3** did not disclose their stereostructures, but chemical isomerization[5] between the two lactams established their relative configurations. Upon treatment[5] with sodium ethoxide in refluxing ethanol for 1.5 h, the less polar lactam **3** was readily and quantitatively

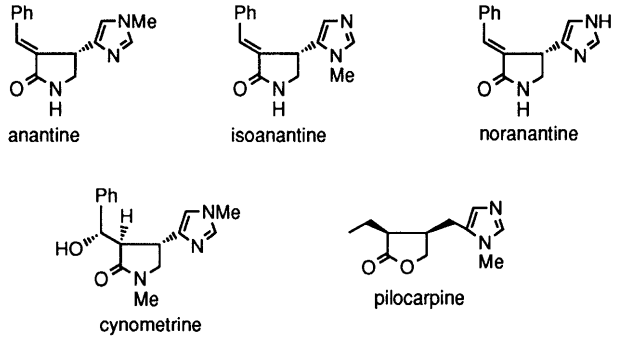

Fig. 1

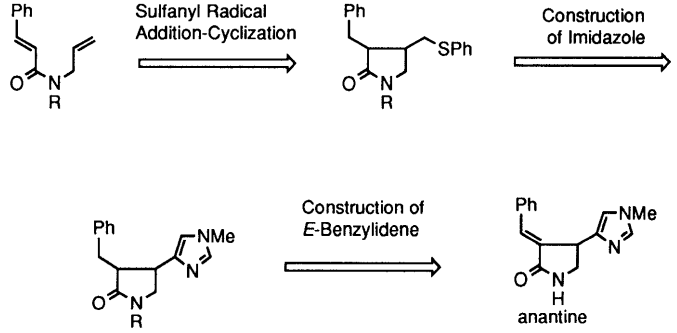

Chart 1

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isomerized into the polar isomer **2**, while **2** was recovered completely even after the same reaction for 4 h. The result clearly established that the less polar lactam **3** is the *cis*-isomer and the polar one **2** is the *trans*-isomer.

Construction of the imidazole ring was accomplished by the method developed by van Leusen *et al.*,[6] who established a potential synthetic method for the imidazole ring from an aldehyde. Oxidation of the sulfides **2** and **3** with potassium peroxymonosulfate (OXONE) followed by Pummerer rearrangement of the resulting sulfoxides in the presence of trifluoroacetic anhydride (TFAA) and 2,6-lutidine gave the desired aldehydes **4** and **5** in 92 and 82% yields, respectively. Both aldehydes **4** and **5** exhibited molecular ion peaks at *m/z* 293, IR absorptions at *v* 1726—1724 cm^{-1} (CHO), and ^{1}H-NMR peaks at δ 9.31 (1H, d, $J=2$ Hz) in **4** and 9.59 (1H, d, $J=2$ Hz) in **5**, both due to an aldehyde hydrogen. The fact that the aldehyde **5** was readily isomerized into the isomeric aldehyde **4** just by treatment with silica gel at room temperature clearly established that the aldehyde **5** is the *cis*-isomer while the aldehyde **4** is the *trans*-isomer.

In order to construct the imidazole ring,[6] the *trans*-aldehyde **4** was treated with *p*-(tolylsulfonyl)methyl isocyanide (TosMIC) in the presence of *tert*-BuOK to give the unstable formamide **6** in 77% yield. It showed the following characteristic signals [*v* 3390 cm^{-1} (NH), 1680 cm^{-1} (NCO), δ 7.90 (br d, $J=1$ Hz, CHO), 6.61 (d, $J=10$ Hz, olefinic H), 2.37 (s, ArMe)]. The geometrical structure around the newly formed olefin in **6** could not be deduced from the spectral data. Dehydration of the formamide **6** with phosphorus oxychloride in the presence of triethylamine gave the unstable isonitrile **7** [*v* 2108 cm^{-1} (NC)], which (without purification) was treated with methylamine to afford the 1-methylimidazole **8** in 41% yield from the aldehyde **4**. The spectral data of **8** [*m/z* 345 (M^+), δ 6.78 (s, 4′-H), 3.17 (s, NMe)] and the proposed[6] mechanism of formation of the imidazole ring support the 1,5-disubstituted imidazole structure. Removal of the *N*-benzyl group in **8** under Birch conditions[7] gave the *N*-norlactam **9a**, which was identical with (±)-dihydroisoanantine upon comparison of their spectral data with those of an authentic sample.[3a] Thus, we have succeeded in the synthesis of (±)-dihydroisoanantine (**9a**) by applying the sulfanyl radical addition–cyclization of dienylamide.

The alkaloid anantine[3a,b] and its regioisomer isoanantine possess a benzylidene group as a substituent on the pyrrolidinone ring. For the synthesis of both anantine and isoanantine from the corresponding dihydro derivatives, we sought to introduce the benzylidene group *via* a route involving substitution reaction with a selenenyl group followed by elimination of the selenoxide group at the α-position of the lactam carbonyl group. Stereoselective construction of an *E*-benzylidene group *via* the well-known oxidative *syn*-elimination of the selenoxide could be achieved by the stereoselective introduction of the *cis*-selenenyl group at the 3-position of dihydroisoanantine (**9a**).

As a preliminary experiment, we investigated the substitution–elimination reaction of the selenenyl group using a model compound, 3-benzyl-4-phenyllactam **11**.[8] The lactam **11** was readily prepared from methyl cinnamate *via* Michael addition of nitromethane, reductive lactamization to give **10a**, and finally benzylation to afford **10b**.[9] The stereostructure of **11** was confirmed to be *trans* by the failure of the isomerization reaction to generate the corresponding isomer under the conventional reaction conditions[5] using sodium ethoxide in ethanol.

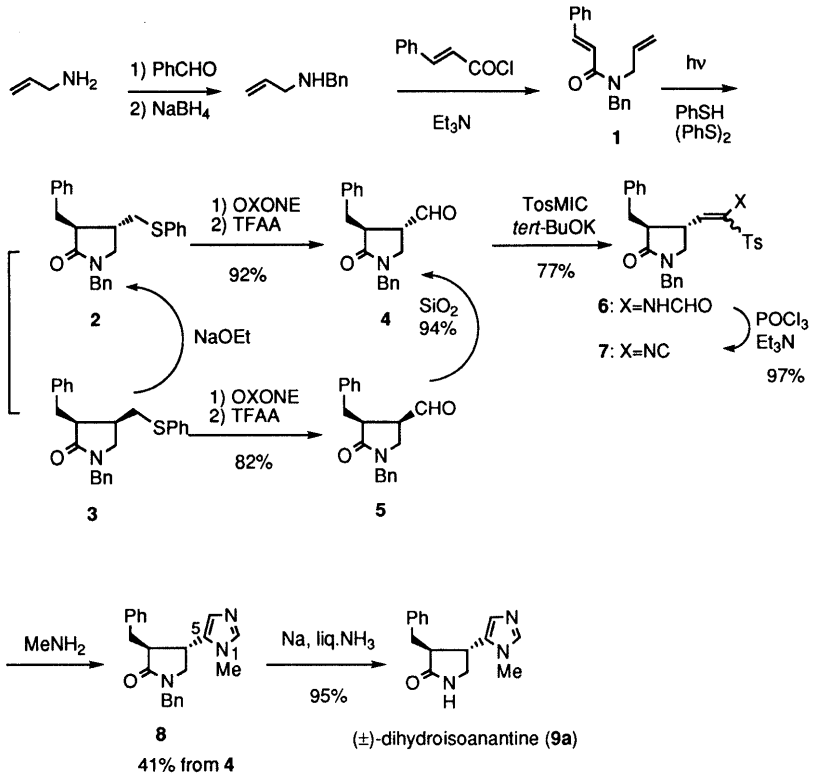
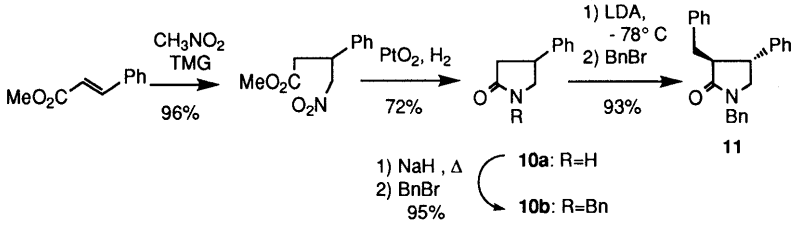
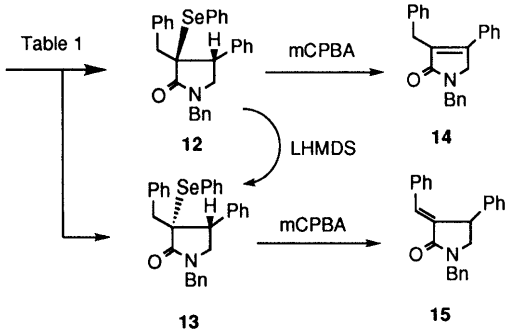


Chart 2





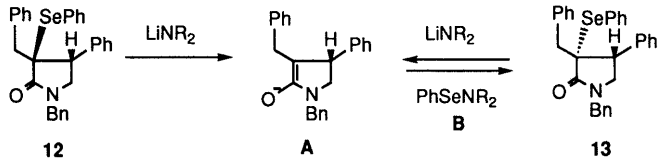
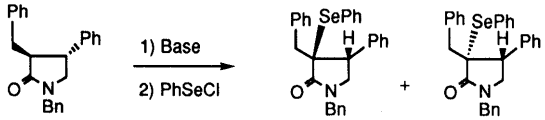


Chart 3

We first investigated the selenenylation of **11** under several reaction conditions as shown in Table 1. Treatment of **11** with lithium diisopropylamide (LDA) at −78 °C followed by the addition of phenylselenenyl chloride gave a mixture of two stereoisomers **12** and **13**, which were separated by MPLC. The stereostructures of two products **12** and **13** were indirectly deduced from the structures of **14** and **15** obtained by oxidative elimination of the selenoxide group. Oxidation of **12** with *m*-chloroperbenzoic acid (*m*CPBA) gave exclusively the *endo*-olefin **14**, while oxidation of **13** under the same reaction conditions gave the *exo*-olefin **15** in quantitative yield. Both olefins, **14** and **15**, exhibited a molecular ion peak at *m/z* 339. The olefin **15** showed ^{1}H-NMR peaks at δ 7.72 (d, $J=2$ Hz, olefinic H) suggesting *exo*-olefin structure, while the ^{1}H-NMR spectrum of **14** showed the absence of the olefinic proton signal. The fact that the *exo*- and *endo*-olefins were stereoselectively obtained from the respective selenides **13** and **12** suggested that **13** is the *cis*- and **12** is the *trans*-selenide, because the oxidative elimination of selenoxide is well known to proceed in a *syn*-fashion.

In order to establish a general and stereoselective method for the preparation of the *cis*-selenide **13**, which would be a precursor for the preparation of the *exo*-olefin **15**, we then investigated other reaction conditions for the introduction of the α-selenenyl group and found that the reaction at 0 °C is optimum, irrespective of the nature of the base used (Table 1).

Table 1. Phenylselenenylation Reaction of **11**



Entry	Base	Temp (°C)	Yield (%)	Ratio **12**:**13**
1	LDA	−78	49	3:2
2	*tert*-BuLi	−78	62	6:5
3	LHMDS	0	66	1:10
4	LDA	0	62	1:13

A possible reaction pathway of the stereoselective formation of the α-selenide **13** at 0 °C is as follows: In a preliminary experiment, we investigated the isomerization reaction between two selenides **12** and **13** and found that, upon treatment with lithium hexamethyldisilazide (LHMDS) at 0 °C, the *trans*-selenide **12** gave a mixture of two selenides **12** and **13**, while the *cis*-selenide **13** was recovered unchanged under the same reaction conditions. These results show that *cis*-**13** is thermodynamically more stable than *trans*-**12**. Thus, both *cis*-**13** and the *trans*-**12** were treated with base to give an identical enolate A and the selenamide B. The former enolate A was then re-selenenylated with the latter selenamide B to afford preferentially the stable *cis*-**13**.[10]

Total Synthesis of (±)-Isoanantine and (±)-Anantine

According to the procedure established with the model compound **11**, we then attempted the total synthesis of the alkaloid and related compounds. (±)-Dihydroisoanantine (**9a**) prepared in this study was protected with a *tert*-butoxycarbonyl (Boc) group and then selenenylated in the presence of 2 eq. of phenylselenyl bromide at 0 °C to give a 2.6:1 mixture of two selenides, **16** and **17**. Oxidative elimination of **16** and **17** gave the *exo*-**18** and *endo*-olefin **19**, respectively, both quantitatively, suggesting that **16** is the *cis*- and **17** is the *trans*-selenide.

The *exo*-olefin **18** was finally deprotected by treatment with trifluoroacetic acid (TFA) in methylene dichloride to give a lactam, which was found to be identical with (±)-isoanantine[3a] based on a comparison of their spectral data.

Khuong-Huu *et al.*[3a] have reported that methylation of noranantine gave a 4:3 mixture of two alkaloids, anantine and isoanantine. Based on that report, we prepared the *N*-unsubstituted imidazole **20** by the method established for the synthesis of (±)-isoanantine. The formamide **6** was converted into the imidazole **20** by

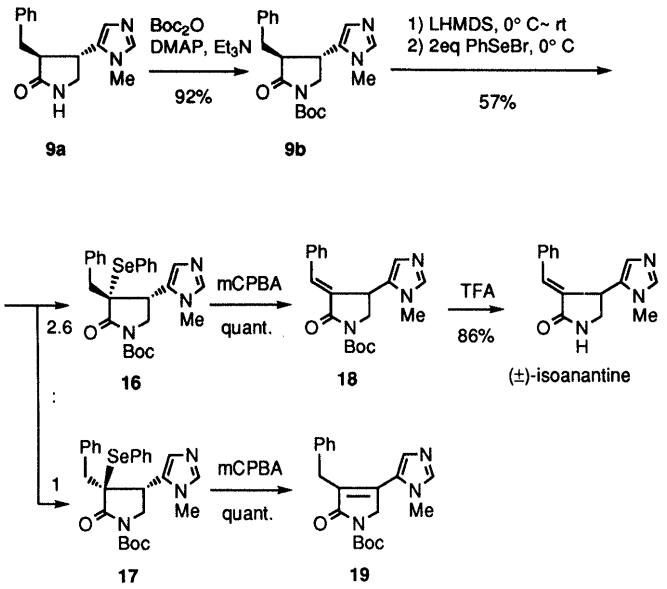
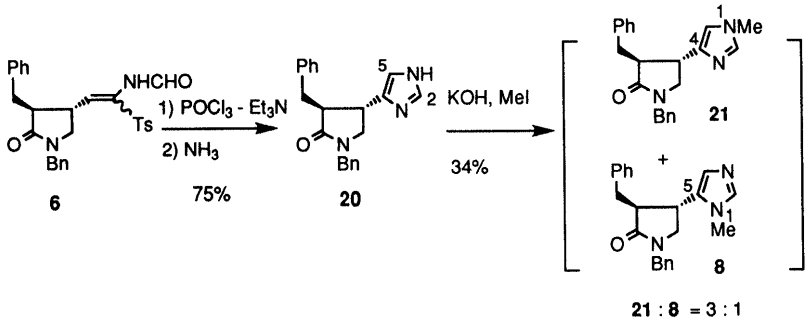
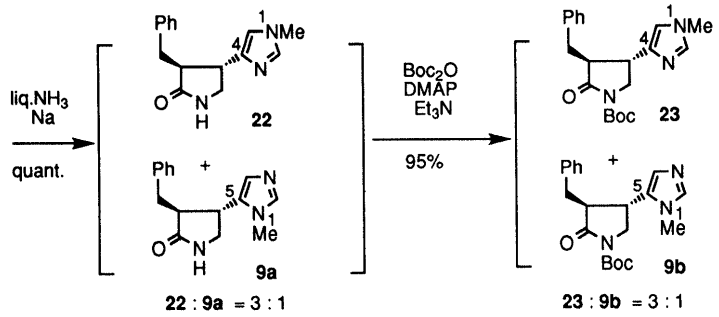


Chart 4





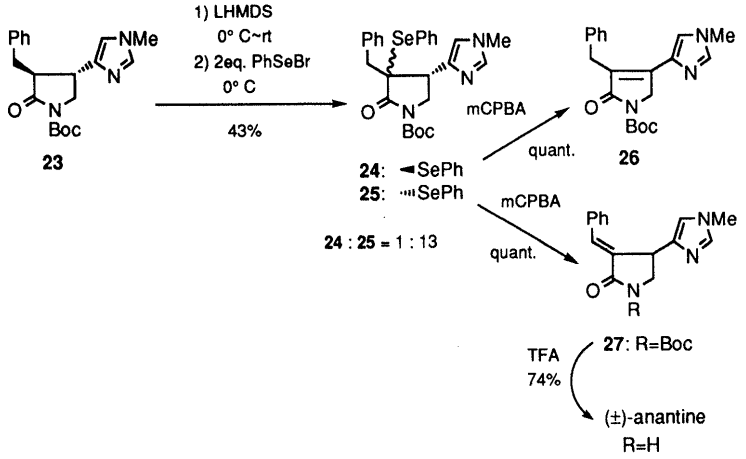


Chart 5

dehydration with $POCl_3$ in the presence of Et_3N, followed by treatment with ammonia. Methylation of the imidazole **20** with methyl iodide in the presence of KOH gave a 3 : 1 mixture of two lactams **21** and **8**, which (without separation) were hydrogenated with sodium in liquid ammonia and protected with $(Boc)_2O$ to give a mixture of two *N*-methylimidazoles **23** and **9b**. The imidazole **9b** thus prepared was identical with a sample which was prepared in the previously mentioned synthesis of (±)-isoanantine. Selenenylation of the lactam **23** with 2 eq. of phenylselenyl bromide at 0 °C gave two selenides **24** and **25** in a ratio of *ca.* 1 : 13, which were subjected to oxidative elimination to afford the olefins **26** and **27**, respectively. The *exo*-olefin **27** was finally deprotected to afford the *N*-norlactam, which was identical with (±)-anantine based on a comparison of their spectral data.[3a,b] Biological evaluation of the products prepared in this study is in progress.

In conclusion, we have established a practical synthetic method for anantine and related alkaloids to obtain sufficient quantities for pharmacological evaluation.

Experimental

The ^{1}H-NMR spectra were measured with JEOL PMX-60 (60 MHz), Varian XL-200 (200 MHz) and VXR-500 (500 MHz) instruments for solutions in deuteriochloroform (with tetramethylsilane as an internal reference), and the IR spectra were measured with a Hitachi 270-30 machine for solutions in chloroform. MS were taken with Hitachi M-80 and M-4100 spectrometers. All melting points were determined with a Kofler-type hot-stage apparatus. Extracts from the reaction mixture were washed with water and dried over anhydrous sodium sulfate. All reactions were carried out under an N_2 atmosphere unless otherwise stated. Thin layer chromatography (TLC) was performed on precoated Silica gel 60F-254 plates (0.25 mm thick, Merck) and preparative TLC (*p*-TLC) on pre-coated Silica gel 60F-254 plates (0.5 mm thick, Merck), and spots were detected by ultraviolet (UV) irradiation of the plates at 254 and 300 nm or exposure to iodine vapor. MPLC was undertaken on a Yamazen 530-4-10V using a Lobar grosse B column (310-25, Lichroprep Si60, Merck). Flash column chromatography (FCC) was undertaken using Silica gel 60 (230—400 mesh, Merck). Short column chromatography (SCC) was undertaken on a short glass filter using Silica gel 60F-254 (Merck) under reduced pressure.

***E*-3-Phenyl-*N*-(phenylmethyl)-*N*-(2-propenyl)-2-propenamide (1)** A solution of allylamine (7.8 g, 0.14 mol) and benzaldehyde (14.4 g, 0.14 mol) in benzene (200 ml) was refluxed for 2 h with a Dean–Stark apparatus. Evaporation of the solvent gave the crude imine, which was dissolved in MeOH (200 ml). A small portion of $NaBH_4$ (3.0 g, 0.08 mol) was added to the resulting ice-cooled solution. The mixture was stirred at room temperature for 30 min, then evaporated, and water and benzene were added to the residue. The water layer was extracted with benzene and the combined organic layer was washed, dried, and concentrated to give a yellow oil, which was distilled to give the secondary amine (15.6 g, 78%). A solution of the amine (4.4 g, 30 mmol) and Et_3N (4.5 ml, 32 mmol) in benzene (200 ml) was ice-cooled, then a solution of cinnamoyl chloride (5.5 g, 33 mmol) in benzene (200 ml) was added. The mixture was stirred for 2.5 h, then filtered to remove triethylamine hydrochloride. The filtrate was concentrated to give a residue, which was purified by FCC (AcOEt : hexane = 1 : 3) to afford **1** (6.5 g) as a pale-yellow oil. The ^{1}H-NMR spectrum showed that **1** exists as a mixture of two rotational isomers in chloroform. IR ν_{max} cm^{-1}: 1648 (NCO), 1604 (C=C, Ph). ^{1}H-NMR (200 MHz) δ: 7.84 (1H, d, J = 16 Hz, 3-H), 7.60—7.24 (10H, m, Ph × 2), 6.88 (1H, d, J = 16 Hz, 2-H), 5.96—5.76 (1H, m, C<u>H</u>=CH$_2$), 5.53—5.23 (2H, m, CH=C<u>H</u>$_2$), 4.76 (6/5H, s, NC<u>H</u>$_2$Ph), 4.71 (4/5H, s, NC<u>H</u>$_2$Ph), 4.17—3.99 (2H, m, NC<u>H</u>$_2$CH=CH$_2$). HR-MS *m/z*: Calcd $C_{19}H_{19}NO$ (M^+) 277.1465. Found: 277.1455.

Sulfanyl Radical Addition–Cyclization of the Amide 1 A solution of the amide **1** (830 mg, 3 mmol), diphenyl disulfide (654 mg, 3 mmol), and benzenethiol (0.31 ml, 3 mmol) in benzene (300 ml) was irradiated with a high-pressure (100 W) mercury lamp through a Pyrex filter (Eikosha, Osaka, Japan, PIH-100) at 5—10 °C for 10 h. The solvent was then evaporated to give a residue, which was purified by MPLC (AcOEt : hexane = 1 : 2) to give *trans*-1,3-bis(phenylmethyl)-4-[(phenylsulfanyl)-methyl]-2-pyrrolidinone (**2**) (390 mg, 34%) as colorless crystals, mp 88—91 °C (Et_2O) and the *cis*-isomer **3** (420 mg, 37%) as colorless crystals, mp 82—85 °C (Et_2O).

2: IR ν_{max} cm^{-1}: 1678 (NCO). ^{1}H-NMR (200 MHz) δ: 7.34—7.08 (15H, m, Ph × 3), 4.50, 4.38 (2H, ABq, J = 14 Hz, NC<u>H</u>$_2$Ph), 3.22 (1H, dd, J = 13, 4 Hz, 3-CH), 3.20 (1H, dd, J = 10, 8.5 Hz, 5-H), 2.93 (1H, dd, J = 10, 7 Hz, 5-H), 2.80 (1H, dd, J = 13, 9 Hz, 3-CH), 2.78 (1H, dd, J = 13, 5 Hz, 4-CH), 2.64 (1H, br td, J = 10, 4 Hz, 3-H), 2.55 (1H, dd, J = 13, 10 Hz, 4-CH), 2.23 (1H, m, 4-H). HR-MS *m/z*: Calcd $C_{25}H_{25}NOS$ (M^+) 387.1654. Found: 387.1644. *Anal.* Calcd for $C_{25}H_{25}NOS$: C, 77.49; H, 6.50; N, 3.61. Found: C, 77.47; H, 6.62; N, 3.60.

3: IR ν_{max} cm^{-1}: 1676 (NCO). ^{1}H-NMR (200 MHz) δ: 7.35—6.85 (15H, m, Ph × 3), 4.53 and 4.42 (2H, ABq, J = 15 Hz, NC<u>H</u>$_2$Ph), 3.41 (1H, dd, J = 15, 4 Hz, 3-CH), 3.25 (2H, d, J = 4 Hz, 5-H$_2$), 3.15 (1H, dd, J = 13, 3 Hz, 4-CH), 3.08 (1H, ddd, J = 12, 8, 4 Hz, 3-H), 2.75 (1H, dd, J = 15, 12 Hz, 3-CH), 2.50 (1H, dd, J = 13, 12 Hz, 4-CH), 2.41 (1H, m, 4-H). HR-MS *m/z*: Calcd $C_{25}H_{25}NOS$ (M^+) 387.1654. Found: 387.1648. *Anal.* Calcd for $C_{25}H_{25}NOS$: C, 77.49; H, 6.50; N, 3.61. Found: C, 77.23; H, 6.29; N, 3.67.

Isomerization Reaction of the *cis*-Lactam 3 According to the literature,[5] sodium (25 mg, 1.09 mmol) was dissolved in anhydrous ethanol (30 ml) and an aliquot of the resulting solution (1 ml) was diluted to 2 ml by the addition of further ethanol (1 ml). To this solution, the *cis*-lactam **3** (12 mg, 0.03 mmol) was added. The resulting solution was refluxed for 1.5 h and then diluted with aqueous ammonium chloride and finally extracted with methylene dichloride. The extract was washed, dried and concentrated to give the lactam, which was identical with the *trans*-lactam **1** based on comparison of their ^{1}H-NMR spectra. Under the same reaction conditions, the *trans*-lactam **2** was recovered quantitatively.

***trans*-1,3-Bis(phenylmethyl)-4-formyl-2-pyrrolidinone (4)** A solution of *m*CPBA (358 mg, 70% assay, 1.45 mmol) in methylene dichloride (10 ml) was added to a solution of the *trans*-sulfide **2** (564 mg, 1.45 mmol) in methylene dichloride (20 ml) with stirring under ice-cooling during 15 min. The mixture was stirred for 30 min, then aqueous $NaHCO_3$ was added and the whole was extracted with methylene dichloride. The extract was washed, dried and concentrated to give the crude sulfoxide, which (without purification) was dissolved in anhydrous acetonitrile (50 ml). A solution of TFAA (1.23 ml, 8.7 mmol) in acetonitrile (10 ml) was added to the resulting acetonitrile solution of the sulfoxide and 2,6-lutidine (1.01 ml, 8.7 mmol) at 0 °C. The mixture was stirred for 30 min, then an aqueous solution (20 ml) containing $NaHCO_3$ (2.2 g, 26.1 mmol) was added and the whole was stirred at room temperature for 2 h, then extracted with methylene dichloride. The extract was washed, dried and concentrated to give a residue, which was purified by MPLC (hexane and then methylene dichloride) to give **4** (391 mg, 92% from the sulfide **2**) as a pale-yellow oil. IR ν_{max} cm^{-1}: 1726 (CHO), 1678 (NCO). ^{1}H-NMR (200 MHz) δ: 9.31 (1H, d, J = 2 Hz, CHO), 7.38—7.16 (10H, m, Ph × 2), 4.56, 4.38 (2H, ABq, J = 15 Hz, NC<u>H</u>$_2$Ph), 3.44 (1H, dd, J = 10, 5 Hz, 5-H), 3.31 (1H, d, J = 10 Hz, 5-H), 3.14—2.92 (4H, m, 3-H, 4-H, 3-CH$_2$). HR-MS *m/z*: Calcd $C_{19}H_{19}NO_2$ (M^+) 293.1414. Found: 293.1416.

***cis*-1,3-Bis(phenylmethyl)-4-formyl-2-pyrrolidinone (5)** According to the procedure described for the preparation of the aldehyde **4**, the *cis*-sulfide **3** (564 mg, 1.45 mmol) was converted into the *cis*-aldehyde **5** (347 mg, 82% from the sulfide **3**) as a pale-yellow oil. IR ν_{max} cm^{-1}: 1724 (CHO), 1688 (NCO). ^{1}H-NMR (200 MHz) δ: 9.59 (1H, d, J = 2 Hz, CHO), 7.30—7.23 (10H, m, Ph × 2), 4.58, 4.46 (2H, ABq, J = 15 Hz, NC<u>H</u>$_2$Ph), 3.48—3.14 (5H, m, 3-CH, 3-H, 4-H, 5-H$_2$), 2.79 (1H, dd, J = 14, 10 Hz, 3-CH). HR-MS *m/z*: Calcd $C_{19}H_{19}NO_2$ (M^+) 293.1414. Found: 293.1411.

Isomerization of the *cis*-Aldehyde 5 to the *trans*-Isomer 4 A suspension of the *cis*-aldehyde **5** (894 mg, 3.05 mmol) and SiO_2 (4 g) in methylene dichloride (50 ml) was stirred at room temperature for 2 h. SiO_2 was filtered off and the filtrate was concentrated to give the *trans*-aldehyde **4** (835 mg, 93%) whose spectral data were identical with those of an authentic sample obtained from the sulfide **2**.

***trans*-*N*-[2-[1,3-Bis(phenylmethyl)-2-oxopyrrolidin-4-yl]-1-[(4-methylphenyl)sulfonyl]ethenyl]formamide (6)** According to the literature,[6] a solution of TosMIC (202 mg, 1.03 mmol) in tetrahydrofuran (THF) (5 ml) was added to a solution of *tert*-BuOK (154 mg, 1.38 mmol) in THF (10 ml) at −30 °C with stirring. The mixture was stirred for 10 min, then a solution of the *trans*-aldehyde **4** (303 mg, 1.03 mmol) in THF (5 ml)

was added at −40 °C and the resulting solution was stirred at −40 °C for 30 min, then poured into ice-cooled water (20 ml). After having been neutralized by the addition of AcOH, the solution was extracted with methylene dichloride and the extract was washed, dried and then concentrated to give a residue, which was purified by MPLC (AcOEt : Et_2O = 1 : 6) to give **6** (387 mg, 77%) as a colorless oil. The unstable amide **6** (without further purification) was used for the following transformation: IR ν_{max} cm^{-1}: 3390 (NH), 1680 (NCO). ^{1}H-NMR (200 MHz) δ: 7.90 (1H, br d, J = 1 Hz, CHO), 7.60 (2H, br d, J = 8 Hz, aromatic H), 7.40—7.14 (12H, m, aromatic H), 6.61 (1H, d, J = 10 Hz, olefinic H), 4.59, 4.32 (2H, ABq, J = 15 Hz, NC$\underline{H}_2$Ph), 2.37 (3H, s, Me).

***trans*-1,3-Bis(phenylmethyl)-4-[2-isocyano-2-[(4-methylphenyl)sulfonyl]ethenyl]-2-pyrrolidinone (7)** According to the literature,[6] triethylamine (0.56 ml, 4.0 mmol) was added to a solution of the crude formamide **6** (390 mg, 0.80 mmol) in THF (10 ml) at −5 °C with stirring. The mixture was cooled to −10 °C, a solution of $POCl_3$ (0.1 ml, 1.1 mmol) in THF (5 ml) was added and the whole was stirred at the same temperature for 30 min. The resulting solution was poured into ice-cooled water (20 ml) and then extracted with methylene dichloride. The extract was washed, dried and concentrated to give the unstable isonitrile **7** (355 mg, 97%), which (without purification) was used for the next step. IR ν_{max} cm^{-1}: 2108 (NC), 1690 (NCO).

***trans*-1,3-Bis(phenylmethyl)-4-(1-methyl-1*H*-imidazol-5-yl)-2-pyrrolidinone (8)** A saturated solution of methylamine in MeOH (10 ml) was added dropwise to a solution of the crude isonitrile **7** in MeOH (10 ml). The mixture was stirred for 1 h, then evaporated to give a residue which was extracted with methylene dichloride. The extract was washed, dried and concentrated to give a residue, which was purified by MPLC (EtOH : methylene dichloride = 5 : 95) to give the imidazole **8** (153 mg, 55%) as a pale-yellow oil. IR ν_{max} cm^{-1}: 1684 (NCO). ^{1}H-NMR (200 MHz) δ: 7.36—7.16 (11H, m, Ph, 2′-H), 6.78 (1H, s, 4′-H), 4.52, 4.50 (2H, ABq, J = 14 Hz, NC$\underline{H}_2$Ph), 3.37 (1H), 3.16—3.00 (5H) (each m, 3-H, 4-H, 5-H_2, 3-CH_2), 3.17 (3H, s, NMe). HR-MS m/z: Calcd $C_{22}H_{23}N_3O$ (M^+) 345.1840. Found: 345.1844.

4-(1-Methyl-1*H*-imidazol-5-yl)-3-(phenylmethyl)-2-pyrrolidinone, (±)-Dihydroisoanantine (9a) Metallic sodium (40 mg) was added to liquid ammonia (10 ml) at −30 °C with stirring. A solution of **8** (190 mg, 0.55 mg) in THF (5 ml) was added to the above solution and the resulting blue-colored solution was stirred for 10 min. Ammonium chloride was added until the blue color disappeared, then the liquid ammonia was evaporated to give a residue, to which water was added. The resulting mixture was extracted with methylene dichloride. The extract was washed, dried and concentrated to give (±)-dihydroisoanantine **9a** (134 mg, 95%) as a colorless oil. The spectral data were identical with the reported data.[3a] IR ν_{max} cm^{-1}: 3444 (NH), 1702 (NCO). ^{1}H-NMR (200 MHz) δ: 7.41 (1H, s, 2′-H), 7.30—7.16 (5H, m, Ph), 6.96 (1H, s, 4′-H), 6.62 (1H, br s, NH), 3.60 (1H), 3.27—2.90 (5H) (each m, 5-H_2, 4-H, 3-H, and 3-CH_2), 3.27 (3H, s, NMe). HR-MS m/z: Calcd $C_{15}H_{17}N_3O$ (M^+) 255.1370. Found: 255.1374.

4-Phenyl-2-pyrrolidinone (10a) According to the literature,[8] 1,1,3,3-tetramethylguanidine (0.5 ml, 4 mmol) was added to a mixture of methyl cinnamate (3.6 g, 22 mmol) and nitromethane (10 ml, 175 mmol) at room temperature with stirring. The mixture was refluxed for 3 h, then extracted with methylene dichloride. The extract was successively washed with dilute HCl, water, aqueous $NaHCO_3$, and finally water, then dried and concentrated to give a residue, which was distilled to give the nitroester (4.7 g, 96%) (bp 166 °C (3 mmHg)) (lit.[11] bp 140 °C (2 mmHg)). A solution of the nitroester (190 mg, 0.81 mmol) in methanol (10 ml) was subjected to catalytic hydrogenation in the presence of platinum dioxide (30 mg) under a hydrogen atmosphere for 20 h. The catalyst was filtered off, and the filtrate was concentrated to give a residue, which was purified by SCC (AcOEt and then MeOH : methylene dichloride = 5 : 95) to afford the pyrrolidinone **10a** (519 mg, 72%) as a colorless oil. IR ν_{max} cm^{-1}: 3444 (NH), 1690 (NCO). ^{1}H-NMR (200 MHz) δ: 7.24—7.43 (5H, m, Ph), 6.92 (1H, br s, NH), 3.82 (1H, t, J = 9 Hz, 5-H), 3.71 (1H, br quint, J = 8.5 Hz, 4-H), 3.45 (1H, dd, J = 9, 7 Hz, 5-H), 2.76 (1H, dd, J = 17, 9 Hz, 3-H), 2.52 (1H, dd, J = 17, 9 Hz, 3-H). HR-MS m/z: Calcd $C_{10}H_{11}NO$ (M^+) 161.0839. Found: 161.0830.

4-Phenyl-1-phenylmethyl-2-pyrrolidinone (10b) A solution of the pyrrolidinone **10a** (805 mg, 5 mmol) in xylene (10 ml) was added to a suspension of sodium hydride (218 mg, 55% assay; 5 mmol) in xylene (40 ml) and the solution was refluxed for 5 h. It was cooled to room temperature, then benzyl bromide (1.2 ml, 10 mmol) was added dropwise. The reaction mixture was refluxed for 4 h, and extracted with benzene. The separated organic layer was washed, dried and then concentrated to give a residue, which was purified by MPLC (AcOEt : hexane = 1 : 2) to afford **10b**[9] (1.19 g, 95%) as colorless crystals, mp 142—145 °C (Et_2O). IR ν_{max} cm^{-1}: 1674 (NCO). ^{1}H-NMR (200 MHz) δ: 7.40—7.16 (10H, m, Ph × 2), 4.61, 4.49 (2H, ABq, J = 15 Hz, NC$\underline{H}_2$Ph), 3.66 (1H, t, J = 8 Hz, 5-H), 3.56 (1H, m, 4-H), 3.20 (1H, dd, J = 8, 6 Hz, 5-H), 2.90 (1H, dd, J = 17, 9 Hz, 3-H), 2.63 (1H, dd, J = 17, 9 Hz, 3-H). HR-MS m/z: Calcd $C_{17}H_{17}NO$ (M^+) 251.1308. Found: 251.1305.

***trans*-1,3-Bis(phenylmethyl)-4-phenyl-2-pyrrolidinone (11)** An LDA solution was prepared from diisopropylamine (0.3 ml, 2.11 mmol) and *n*-butyllithium (1.60 M in hexane) (1.3 ml, 2.11 mmol) at −78 °C. A solution of the pyrrolidinone **10b** (530 mg, 2.11 mmol) in THF (10 ml) was added to the above LDA solution at −78 °C. The mixture was stirred at −78 °C for 1 h, then benzyl bromide (0.5 ml, 4.22 mmol) was added and the whole was stirred for 1 h. Aqueous ammonium chloride was added and the resulting solution was extracted with methylene dichloride. The extract was washed, dried and concentrated to give a residue, which was purified by MPLC (AcOEt : hexane = 1 : 2) to give the lactam **11** (672 mg, 93%) as colorless crystals, mp 79—82 °C (Et_2O–MeOH). IR ν_{max} cm^{-1}: 1676 (NCO). ^{1}H-NMR (200 MHz) δ: 7.40—7.06 (15H, m, Ph × 3), 4.64, 4.42 (2H, ABq, J = 15 Hz, NC$\underline{H}_2$Ph), 3.40—2.94 (6H, m, 3-H, 4-H, 5-H_2, 3-CH_2). HR-MS m/z: Calcd $C_{24}H_{23}NO$ (M^+) 341.1778. Found: 341.1781. *Anal.* Calcd for $C_{24}H_{23}NO$: C, 84.42; H, 6.79; N, 4.10 Found: C, 84.42; H, 6.76; N, 4.02.

Phenylselenenylation of the Lactam 11 a) Using LDA as a Base and at −78 °C: An LDA solution was prepared from diisopropylamine (0.14 ml, 1 mmol) and *n*-butyllithium (1.62 M in hexane) (0.62 ml, 1 mmol) at −78 °C. A solution of the pyrrolidinone **11** (340 mg, 1 mmol) in THF (10 ml) was added dropwise to the above LDA solution and then the solution was stirred at −78 °C for 30 min. A solution of phenylselenenyl chloride (199 mg, 1.04 mmol) in THF (10 ml) was added to the above solution, and the mixture was stirred at the same temperature for 30 min, quenched by addition of aqueous ammonium chloride and extracted with methylene dichloride. The extract was washed, dried and concentrated to give a residue, which was purified by MPLC (AcOEt : hexane = 1 : 5) to give the selenenylated products **12** and **13**, as shown in Table 1.

b) Using *tert*-BuLi as a Base and at −78 °C: A solution of the pyrrolidinone **11** (170 mg, 0.5 mmol) in THF (5 ml) was added dropwise at −78 °C to a solution of *tert*-BuLi (1.5 M in hexane; 0.75 mmol) in THF (5 ml) and the solution was stirred for 30 min. A solution of phenylselenenyl chloride (96 mg, 0.5 mmol) in THF (5 ml) was added at −78 °C, then the whole was stirred for 30 min, quenched by addition of aqueous ammonium chloride and treated in the same manner as described in a).

c) Using LHMDS as a Base and at 0 °C: An LHMDS solution was prepared from 1,1,1,3,3,3-hexamethyldisilazane (HMDS) (0.16 ml, 0.76 mmol) and *n*-butyllithium (1.68 M solution in hexane) (0.45 ml, 0.76 mmol) at 0 °C. A solution of the pyrrolidinone **11** (260 mg, 0.76 mmol) in THF (5 ml) was added dropwise to the above LHMDS solution and the whole was stirred for 30 min. A solution of phenylselenenyl chloride (146 mg, 0.76 mmol) in THF (8 ml) was further added at 0 °C. The reaction mixture was stirred for 1 h, quenched by addition of aqueous ammonium chloride and then treated in the same manner as described in a).

d) Using LDA as a Base and at 0 °C: An LDA solution was prepared according to method a), and the pyrrolidinone **11** (494 mg, 1.45 mmol) was allowed to react with phenylselenenyl chloride (278 mg, 1.45 mmol) at 0 °C. *trans*-1,3-Bis(phenylmethyl)-4-phenyl-3-(phenylseleno)-2-pyrrolidinone (**12**): Colorless crystals, mp 144—147 °C (MeOH). IR ν_{max} cm^{-1}: 1684 (NCO). ^{1}H-NMR (200 MHz) δ: 7.81—6.80 (20H, m, Ph × 4), 4.51, 4.15 (2H, ABq, J = 15 Hz, NC$\underline{H}_2$Ph), 3.73 (1H, br dd, J = 7.5, 6 Hz, 4-H), 3.22 (2H, s, 3-CH_2), 3.15 (1H, dd, J = 9.5, 7.5 Hz, 5-H), 2.71 (1H, dd, J = 9.5, 6 Hz, 5-H). HR-MS m/z: Calcd $C_{30}H_{27}NO^{80}Se$ (M^+) 497.1257. Found: 497.1268. *Anal.* Calcd for $C_{30}H_{27}NOSe$: C, 72.58; H, 5.48; N, 2.82. Found: C, 72.51; H, 5.64; N, 2.83. *cis*-1,3-Bis(phenylmethyl)-4-phenyl-3-(phenylseleno)-2-pyrrolidinone (**13**): Colorless crystals, mp 103—107 °C (MeOH) IR ν_{max} cm^{-1}: 1686 (NCO). ^{1}H-NMR (200 MHz) δ: 7.64—7.20 (20H, m, Ph × 4), 4.71, 4.28 (2H, ABq, J = 15 Hz, NC$\underline{H}_2$Ph), 3.78, 3.14 (2H, ABq, J = 14 Hz, 3-CH_2), 3.44 (2H, m, 5-H_2), 3.20—3.07 (1H, m, 4-H). HR-MS m/z: Calcd $C_{30}H_{27}NO^{80}Se$ (M^+) 497.1257. Found: 497.1258. *Anal.* Calcd for $C_{30}H_{27}NOSe$:C, 72.58; H, 5.48; N, 2.82. Found: C, 72.38; H, 5.63; N, 2.79.

Oxidative Elimination of the Selenenylated Lactam 13 A solution of *m*CPBA (70% assay: 90 mg, 0.36 mmol) in methylene dichloride (5 ml)

was added dropwise to a solution of the lactam **13** (181 mg, 0.36 mmol) in methylene dichloride (20 ml) at 0 °C during 10 min. Aqueous $NaHCO_3$ was added and the mixture was extracted with methylene dichloride. The combined extract was washed, dried and concentrated to give a residue, which was purified by MPLC (EtOH : methylene dichloride = 5 : 95) to give *E*-4-phenyl-1-phenylmethyl-3-phenylmethylene-2-pyrrolidinone (**15**) (114 mg, 92%) as colorless crystals, mp 140—142 °C (MeOH). IR ν_{max} cm^{-1}: 1676 (NCO), 1644 (C=C). ^{1}H-NMR (200 MHz) δ: 7.72 (1H, d, J=2 Hz, 1′-H), 7.38—7.20 (15H, m, Ph×3), 4.76, 4.55 (2H, ABq, J=15 Hz, NC$\underline{H}_2$Ph), 4.46 (1H, br dt, J=8, 2 Hz, 4-H), 3.80 (1H, dd, J=10, 8 Hz, 5-H), 3.19 (1H, dd, J=10, 2 Hz, 5-H). HR-MS *m/z*: Calcd $C_{24}H_{21}NO$ (M^+) 339.1621. Found: 339.1622. *Anal.* Calcd for $C_{24}H_{21}NO$: C, 84.92; H, 6.24; N, 4.13. Found: C, 84.66; H, 6.41; N, 4.15.

Oxidative Elimination of the Selenenylated Lactam 12 According to the method described for **13**, the lactam **12** (77 mg, 0.15 mmol) was subjected to oxidative elimination and purified by MPLC (EtOH : methylene dichloride = 5 : 95) to give 1,3-bis(phenylmethyl)-1,5-dihydro-4-phenyl-2*H*-pyrrol-2-one (**14**) (49 mg, 92%) as a colorless oil. IR ν_{max} cm^{-1}: 1676 (NCO), 1644 (C=CCO). ^{1}H-NMR (200 MHz) δ: 7.38—7.20 (15H, m, Ph×3), 4.76 (2H, s, NC$\underline{H}_2$Ph), 4.15 (2H, s, 5-H_2), 3.95 (2H, s, 3-CH_2). HR-MS *m/z*: Calcd $C_{24}H_{21}NO$ (M^+) 339.1621. Found: 339.1619.

Isomerization of the Selenenylated Lactams 12 and 13 A solution of LHMDS (0.04 mmol) was prepared according to the method described for phenylselenenylation of the lactam **11**. A solution of the lactam **12** (22 mg, 0.04 mmol) in THF (2 ml) was added to the above LHMDS solution and the mixture was stirred at 0 °C for 1 h. It was quenched by addition of aqueous ammonium chloride, and the solution was worked up in the usual manner. Purification of the crude product gave **12** (10 mg, 47%) and **13** (11 mg, 48%). These products were identical with those obtained by selenenylation of the lactam **11**, based on comparison of their ^{1}H-NMR spectra. Similarly, attempted isomerization of the lactam **13** in the presence of LHMDS was unsuccessful and **13** was recovered in 94% yield.

***trans*-1-*tert*-Butoxycarbonyl-4-(1-methyl-1*H*-imidazol-5-yl)-3-(phenylmethyl)-2-pyrrolidinone (9b)** Triethylamine (0.03 ml, 0.22 mmol) and a solution of $(Boc)_2O$ (96 mg, 0.44 mmol) in methylene dichloride (5 ml) were successively added to a solution of (±)-dihydroisoanantine (**9a**) (57 mg, 0.22 mmol) and 4-(dimethylamino)-pyridine (DMAP) (27 mg, 0.22 mmol) in methylene dichloride (15 ml) at room temperature. The mixture was stirred for 4 h, then evaporated to give a residue, which was purified by SCC (methylene dichloride) to afford the carbamate **9b** (73 mg, 94%) as a colorless oil. IR ν_{max} cm^{-1}: 1782, 1746, 1712 (CONCOOR). ^{1}H-NMR (200 MHz) δ: 7.41 (1H, s, 2′-H), 7.34—7.10 (5H, m, Ph), 6.95 (1H, s, 4′-H), 3.98 (1H, dd, J=11, 8 Hz, 5-H), 3.47 (1H, dd, J=11, 8 Hz, 5-H), 3.31 (3H, s, NMe), 3.20—3.04 (4H, m, 3-H, 4-H, and 3-CH_2), 1.53 (9H, s, Me×3). HR-MS *m/z*: Calcd $C_{20}H_{25}N_3O_3$ (M^+) 355.1894. Found: 355.1882.

Selenenylation of the Lactam 9b An LHMDS solution was prepared from HMDS (0.04 ml, 0.19 mmol) and *n*-butyllithium (1.60 M solution in hexane) (0.12 ml, 0.19 mmol) at 0 °C. A solution of the lactam **9b** (68 mg, 0.19 mmol) in THF (2 ml) was added to the above LHMDS solution and the mixture was stirred for 30 min. It was cooled to 0 °C, then a solution of phenylselenenyl bromide (90 mg, 0.38 mmol) was added and stirring was continued for 30 min. The mixture was quenched by the addition of aqueous ammonium chloride, then extracted with methylene dichloride. The extract was washed, dried and concentrated to give a residue, which was purified by MPLC (EtOH : methylene dichloride = 5 : 95) to afford *cis*-1-*tert*-butoxycarbonyl-4-(1-methyl-1*H*-imidazol-5-yl)-3-(phenylmethyl)-3-(phenylseleno)-2-pyrrolidinone (**16**) (40 mg, 41%) as a colorless oil and *trans*-1-*tert*-butoxycarbonyl-4-(1-methyl-1*H*-imidazol-5-yl)-3-(phenylmethyl)-3-(phenylseleno)-2-pyrrolidinone (**17**) (16 mg, 16%) as colorless crystals, mp 162—165 °C (Et_2O–MeOH).

16: IR ν_{max} cm^{-1}: 1778, 1744, 1712 (CONCOOR). ^{1}H-NMR (200 MHz) δ: 7.80 (1H, br s, 2′-H), 7.72 (2H, br dd, J=8, 1.5 Hz, aromatic H), 7.50 (1H, br s, 4′-H), 7.48—7.00 (8H, m, aromatic H), 3.76 (1H, dd, J=10, 7.5 Hz, 5-H), 3.68, 3.16 (2H, ABq, J=14.5 Hz, 3-CH_2), 3.58 (1H, t, J=10 Hz, 5-H), 3.24 (3H, s, NMe), 3.24 (1H, m, 4-H), 1.50 (9H, s, Me×3). HR-MS *m/z*: Calcd $C_{26}H_{29}N_3O_3{}^{80}Se$ (M^+) 511.1372. Found: 511.1362.

17: IR ν_{max} cm^{-1}: 1778, 1740, 1714 (CONCOOR). ^{1}H-NMR (200 MHz) δ: 7.68 (2H, br dd, J=8, 1.5 Hz, aromatic H), 7.50—6.98 (8H, m, aromatic H), 7.32 (1H, s, 2′-H), 6.96 (1H, br s, 4′-H), 3.99 (1H, dd, J=11, 7 Hz, 5-H), 3.54 (1H, dd, J=11, 1 Hz, 5-H), 3.36, 3.10 (2H, ABq, J=15 Hz, 3-CH_2), 3.26 (1H, br d, J=7 Hz, 4-H), 2.89 (3H, s, NMe), 1.50 (9H, s, Me×3). HR-MS *m/z*: Calcd $C_{26}H_{29}N_3O_3{}^{80}Se$ (M^+) 511.1372. Found: 511.1369. *Anal.* Calcd for $C_{26}H_{29}N_3O_3Se$: C, 61.18; H, 5.73; N, 8.23. Found: C, 61.10; H, 5.59; N, 8.01.

Oxidative Elimination of the *cis*-Selenenylated Lactam 16 A solution of *m*CPBA (70% assay: 8 mg, 0.03 mmol) in methylene dichloride (1 ml) was added dropwise to a solution of the *cis*-lactam **16** (15 mg, 0.03 mmol) in methylene dichloride (2 ml) under ice-cooling. The mixture was stirred for 30 min, then aqueous $NaHCO_3$ was added and the whole was extracted with methylene dichloride. The extract was washed, dried and concentrated to give a residue, which was purified by MPLC (EtOH : methylene dichloride = 5 : 95) to afford *E*-1-*tert*-butoxycarbonyl-4-(1-methyl-1*H*-imidazol-5-yl)-3-(phenylmethylene)-2-pyrrolidinone (**18**) (11 mg, 99%) as a colorless amorphous solid. IR ν_{max} cm^{-1}: 1774, 1728, 1712 (CONCOOR), 1644 (C=C). ^{1}H-NMR (200 MHz) δ: 7.79 (1H, d, J=2 Hz, olefinic H), 7.49 (1H, br s, 2′-H), 7.37—7.28 (5H, m, aromatic H), 6.83 (1H, br s, 4′-H), 4.46 (1H, br dt, J=8, 2 Hz, 4-H), 4.07 (1H, dd, J=11, 8 Hz, 5-H), 3.72 (1H, dd, J=11, 2 Hz, 5-H), 3.67 (3H, s, NMe), 1.55 (9H, s, Me×3) HR-MS *m/z*: Calcd $C_{20}H_{23}N_3O_3$ (M^+) 353.1738. Found: 353.1725.

Oxidative Elimination of the *trans*-Selenenylated Lactam 17 According to the method described for the *cis*-lactam **16**, oxidative elimination of the *trans*-lactam **17** (6 mg, 0.01 mmol) gave 1-*tert*-butoxycarbonyl-1,5-dihydro-4-(1-methyl-1*H*-imidazol-5-yl)-3-(phenylmethyl)-2*H*-pyrrol-2-one (**19**) (3.5 mg, 99%) as a colorless oil. IR ν_{max} cm^{-1}: 1774, 1728 (C=C–CONCOOR). ^{1}H-NMR (200 MHz) δ: 7.58 (1H, s, 2′-H), 7.30—7.16 (6H, m, aromatic H and 4′-H), 4.57 (2H, s, 5-H_2), 3.79 (2H, s, 3-CH_2), 3.62 (3H, s, NMe), 1.38 (9H, s, Me×3). HR-MS *m/z*: Calcd $C_{20}H_{23}N_3O_3$ (M^+) 353.1738. Found: 353.1728.

(±)-Isoanantine A solution of TFA (0.12 ml, 1.5 mmol) in methylene dichloride (2 ml) was added dropwise to a solution of the pyrrolidinone **18** (11 mg, 0.03 mmol) in methylene dichloride (1 ml) at room temperature. The mixture was stirred for 30 min, then aqueous $NaHCO_3$ was added and the whole was extracted with methylene dichloride. The extract was washed, dried and concentrated to give a solid, which was recrystallized from acetone to give (±)-isoanantine (7 mg, 86%) as colorless crystals, mp 168—170 °C (acetone) (lit.[3a,b] 201 °C). The product was identical with an authentic sample based on comparison of their spectral data. IR ν_{max} cm^{-1} (Nujol): 3401 (NH), 1678 (NCO), 1642, 1502 (C=C). ^{1}H-NMR (200 MHz) δ: 7.61 (1H, d, J=2.5 Hz, olefinic H), 7.42 (1H, br s, 2′-H), 7.27 (5H, br s, Ph), 6.84 (1H, br s, 4′-H), 6.08 (1H, br s, NH), 4.63 (1H, br dt, J=8, 2 Hz, 4-H), 3.90 (1H, br t, J=9 Hz, 5-H), 3.61 (3H, s, NMe), 3.35 (1H, dd, J=9, 2.5 Hz, 5-H). HR-MS *m/z*: Calcd $C_{15}H_{15}N_3O$ (M^+) 253.1215. Found: 253.1223.

***trans*-1,3-Bis(phenylmethyl)-4-(1*H*-imidazol-4-yl)-2-pyrrolidinone (20)** According to the procedure described for the preparation of **8**, the amide **6** (761 mg, 1.56 mmol) was dehydrated to afford the isonitrile **7**, which was dissolved in MeOH (20 ml). A saturated methanolic solution of ammonia (20 ml) was added to the above solution to afford the imidazole **20** (386 mg, 75% from **6**) as a colorless oil. IR ν_{max} cm^{-1}: 3464 (NH), 1674 (NCO). ^{1}H-NMR (200 MHz) δ: 7.48 (1H, br s, 2′-H), 7.28—7.06 (10H, m, aromatic H), 6.55 (1H, br s, 5′-H), 4.56, 4.29 (2H, ABq, J=15 Hz, NC$\underline{H}_2$Ph), 3.30—2.98 (6H, m, 3-H, 4-H, 5-H_2, 3-CH_2). HR-MS *m/z*: Calcd $C_{21}H_{21}N_3O$ (M^+) 331.1682. Found: 331.1666.

Methylation of the Imidazole 20 A solution of **20** (207 mg, 0.62 mmol), KOH (45 mg, 0.81 mmol), and MeI (88 mg, 0.62 mmol) in EtOH (3.5 ml) was stirred at room temperature for 19 h. The solvent was evaporated off and the residue was extracted with methylene dichloride. The extract was washed, dried and concentrated to afford a residue, which was purified by MPLC (EtOH : methylene dichloride = 5 : 95) to give a 3 : 1 mixture of 1,3-bis(phenylmethyl)-4-(1-methyl-1*H*-imidazol-4-yl)-2-pyrrolidinone (**21**) and **8** (73 mg, 34%) and the starting imidazole **20** (139 mg, 65%). The inseparable mixture of **21** and **8** was used directly for the next step.

***trans*-4-(1-Methyl-1*H*-imidazol-4-yl)-3-(phenylmethyl)-2-pyrrolidinone ((±)-Dihydroanantine) (22)** According to the procedure described for the preparation of dihydroisoanantine, treatment of a 3 : 1 mixture of **21** and **8** (207 mg, 0.60 mmol) with sodium (44 mg, 1.8 mmol) in liquid ammonia (20 ml) gave a 3 : 1 mixture of **22** and **9a** (162 mg, 98%) as a colorless oil. This mixture was used directly for the next step. **9a** was identical with the product **9a** formed from **8** based on a comparison of their spectra.

22: A colorless oil. IR ν_{max} cm^{-1}: 3448 (NH), 1692 (NCO). ^{1}H-NMR (200 MHz) δ: 7.35 (1H, br s, 2′-H), 7.30—7.20 (5H, m, Ph), 6.40 purified

by PTLC (EtOH : methylene dichloride = 1 : 9), the 3 : 1 mixture of (1H, br s, 5′-H), 6.28 (1H, br s, NH), 3.57 (3H, s, NMe), 3.46 (2H, d, J = 8 Hz, 5-H), 3.28 (1H, q, J = 8 Hz, 4-H), 3.10—2.95 (3H, m, 3-H, 3-CH_2). HR-MS m/z: Calcd $C_{15}H_{17}N_3O$ (M^+) 255.1370. Found: 255.1378.

***trans*-1-*tert*-Butoxycarbonyl-4-(1-methyl-1*H*-imidazol-4-yl)-3-(phenylmethyl)-2-pyrrolidinone (23)** According to the procedure described for the preparation of **9b**, treatment of the 3 : 1 mixture of **22** and **9a** (121 mg, 0.47 mmol) with $(Boc)_2O$ followed by purification by MPLC (EtOH : methylene dichloride = 5 : 95) gave **23** (119 mg, 71%) and **9b** (40 mg, 24%), each as a colorless oil. **9b** was identical with the product **9b** formed from **9a** based on a comparison of their spectra.

23: IR ν_{max} cm^{-1}: 1778, 1742, 1712 (CONCOOR). ^{1}H-NMR (200 MHz) δ: 7.38 (1H, br s, 2′-H), 7.26—7.16 (5H, m, Ph), 6.48 (1H, br d, J = 2 Hz, 5′-H), 3.88 (1H, dd, J = 10, 8 Hz, 5-H), 3.70 (1H, dd, J = 10, 9 Hz, 5-H), 3.59 (3H, s, NMe), 3.20—3.04 (4H, m, 3-H, 4-H, 3-CH_2), 1.50 (9H, s, Me × 3). HR-MS m/z: Calcd $C_{20}H_{25}N_3O_3$ (M^+) 355.1894. Found: 355.1894.

Phenylselenenylation of the Lactam 23 According to the procedure described for the selenenylation of **9b**, the product obtained from the pyrrolidinone **23** (103 mg, 0.29 mmol) was purified by MPLC (EtOH : methylene dichloride = 5 : 95) to afford *trans*-1-*tert*-butoxycarbonyl-4-(1-methyl-1*H*-imidazol-4-yl)-3-(phenylmethyl)-3-(phenylseleno)-2-pyrrolidinone (**24**) (5 mg, 3%) as a pale yellow oil and *cis*-1-*tert*-butoxycarbonyl-4-(1-methyl-1*H*-imidazol-4-yl)-3-(phenylmethyl)-3-(phenylseleno)-2-pyrrolidinone (**25**) (59 mg, 40%) as a colorless oil, as well as the starting lactam **23** (37 mg, 36%).

24: IR ν_{max} cm^{-1}: 1774, 1712 (CONCOOR). ^{1}H-NMR (200 MHz) δ: 7.60 (2H, br dd, J = 8, 1.5 Hz, aromatic H), 7.41 (1H, br s, 2′-H), 7.28 (8H, m, aromatic H), 6.74 (1H, br s, 5′-H), 3.84—3.44 (3H, m, 5-H_2, 4-H), 3.67 (3H, s, NMe), 3.26, 3.12 (2H, ABq, J = 15 Hz, 3-CH_2), 1.46 (9H, s, Me × 3). HR-MS m/z: Calcd $C_{26}H_{29}N_3O_3{}^{80}Se$ (M^+) 511.1372. Found: 511.1382.

25: IR ν_{max} cm^{-1}: 1774, 1742, 1710 (CONCOOR). ^{1}H-NMR (200 MHz) δ: 7.64 (2H, br dd, J = 8, 1,5 Hz, aromatic H), 7.55 (1H, br s, 2′-H), 6.90 (1H, br s, 5′-H), 3.96 (1H, t, J = 10 Hz, 5-H), 3.80 (1H, dd, J = 10, 7.5 Hz, 5-H), 3.78 (3H, s, NMe), 3.55, 3.39 (2H, ABq, J = 14 Hz, 3-CH_2), 3.43 (1H, m, 4-H), 1.50 (9H, s, Me × 3). HR-MS m/z: Calcd $C_{26}H_{29}N_3O_3{}^{80}Se$ (M^+) 511.1372. Found: 511.1374.

***E*-1-*tert*-Butoxycarbonyl-4-(1-methyl-1*H*-imidazol-4-yl)-3-(phenylmethylene)-2-pyrrolidinone (27)** According to the procedure described for the oxidative elimination of **16**, the product obtained from the *cis*-selenenylated compound **25** (55 mg, 0.11 mmol) was purified by MPLC (EtOH : methylene dichloride = 5 : 95) to give **27** (37 mg, 98%) as a colorless oil. IR ν_{max} cm^{-1}: 1766, 1724, 1648 (C=C–CONCOOR). ^{1}H-NMR (200 MHz) δ: 7.71 (1H, d, J = 2 Hz, olefinic H), 7.48 (1H, br s, 2′-H), 7.58—7.33 (5H, m, aromatic H), 6.61 (1H, br s, 5′-H), 4.50 (1H, br d, J = 7 Hz, 4-H), 4.09 (1H, dd, J = 11, 2 Hz, 5-H), 4.02 (1H, dd, J = 11, 7 Hz, 5-H), 3.60 (3H, s, NMe), 1.57 (9H, s, Me × 3). HR-MS m/z: Calcd $C_{20}H_{23}N_3O_3$ (M^+) 353.1738. Found: 353.1735.

1-*tert*-Butoxycarbonyl-1,5-dihydro-4-(1-methyl-1*H*-imidazol-4-yl)-3-(phenylmethylene)-2*H*-pyrrol-2-one (26) According to the procedure described for the oxidative elimination of **16**, the product obtained from the *trans*-selenenylated compound **24** (11 mg, 0.02 mmol) was purified by MPLC (EtOH : methylene dichloride = 5 : 95) to give **26** (7 mg, 98%) as a colorless oil. IR ν_{max} cm^{-1}: 1766, 1720, 1650 (C=C–CONCOOR). ^{1}H-NMR (200 MHz) δ: 7.56 (1H, br s, 2′-H), 7.37—7.20 (5H, m, Ph), 7.18 (1H, br s, 5′-H), 4.70 (2H, s, 5-H_2), 3.99 (2H, s, 3-CH_2), 3.72 (3H, s, NMe), 1.57 (9H, s, Me × 3). HR-MS m/z: Calcd $C_{20}H_{23}N_3O_3$ (M^+) 353.1738. Found: 353.1741.

(±)-Anantine According to the procedure described for the deprotection of the Boc group in **18**, the product obtained from the pyrrolidinone **27** (31 mg, 0.09 mmol) was recrystallized from acetone to afford colorless crystals (25 mg, 98%), mp 204—206 °C (lit.[3a,b] 179 °C). Spectral data of the crystals were identical with those of authentic anantine. IR ν_{max} cm^{-1}: 3448 (NH), 1694 (NCO), 1640. (C=C) ^{1}H-NMR (200 MHz) δ: 7.55 (1H, d, J = 2 Hz, olefinic H), 7.45 (1H, br s, 2′-H), 7.52—7.28 (5H, m, Ph), 6.61 (1H, br s, 5′-H), 6.36 (1H, br s, NH), 4.63 (1H, br d, J = 7 Hz, 4-H), 3.87 (1H, dd, J = 10, 7 Hz, 5-H), 3.67 (1H, br d, J = 10 Hz, 5-H), 3.55 (3H, s, NMe). HR-MS m/z: Calcd $C_{15}H_{15}N_3O$ (M^+) 253.1215. Found: 253.1223.

Acknowledgments We are grateful to Dr. F. Khuong-Huu for providing an authentic sample of isocynometrine. This work was supported in part by a Grant-in-Aid for Scientific Research (No. 09672293) from the Ministry of Education, Science, Sports, and Culture, Japan and by a grant from the Science Research Promotion Fund of the Japan Private School Promotion Foundation.

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