Pergamon

Tetrahedron, Vol. 52, No. 3, pp. 869-876, 1996

0040-4020/96 $15.00 + 0.00

0040-4020(95)00928-0

First Total Synthesis of Pyrrolam A

Yutaka Aoyagi, Tomofumi Manabe, Akihiro Ohta*
Teruo Kurihara†, Gui-Lin Pang†, and Takeo Yuhara†

School of Pharmacy, Tokyo University of Pharmacy and Life Science,
1432-1 Horinouchi, Hachioji, Tokyo 192-03, Japan

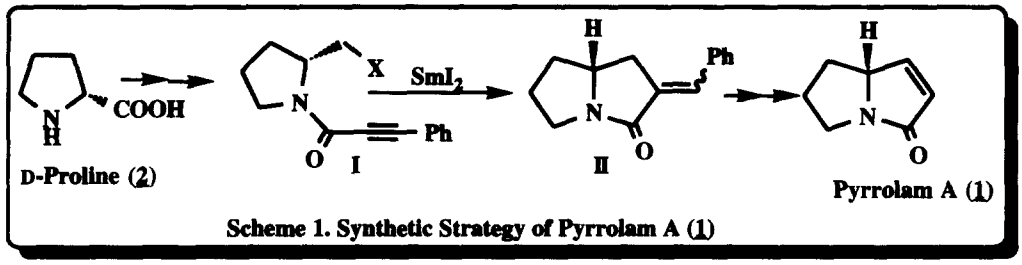
†Faculty of Science, Josai University,
1-1 Keyakidai, Sakado, Saitama, 350-02, Japan

Abstract: First synthesis of pyrrolam A (**1**), a pyrrolizidine alkaloid from *Streptomyces olivaceus*, was accomplished. The SmI_2-mediated intramolecular coupling reaction between a bromoalkyl and ynamide group gave solely a cyclized product, which was converted to pyrrolam A (**1**) efficiently.

Many pyrrolizidine alkaloids have been obtained from plants and insects.[1] Much interest has been focused on their broad range of biological activity. Pyrrolam A (**1**), (*5R*)-1-azabicyclo[3.3.0]oct-3-en-2-one, isolated from *Streptomyces olivaceus* (strain Tü 3082) by R. Grote *et al.*, contains an enamide structure in the molecule and is reported to cause damage to fertilized eggs at a low concentration of 5 μg/ml.[2] We planned the synthesis of pyrrolam A (**1**) based on a samarium diiodide (SmI_2)-mediated cyclization.

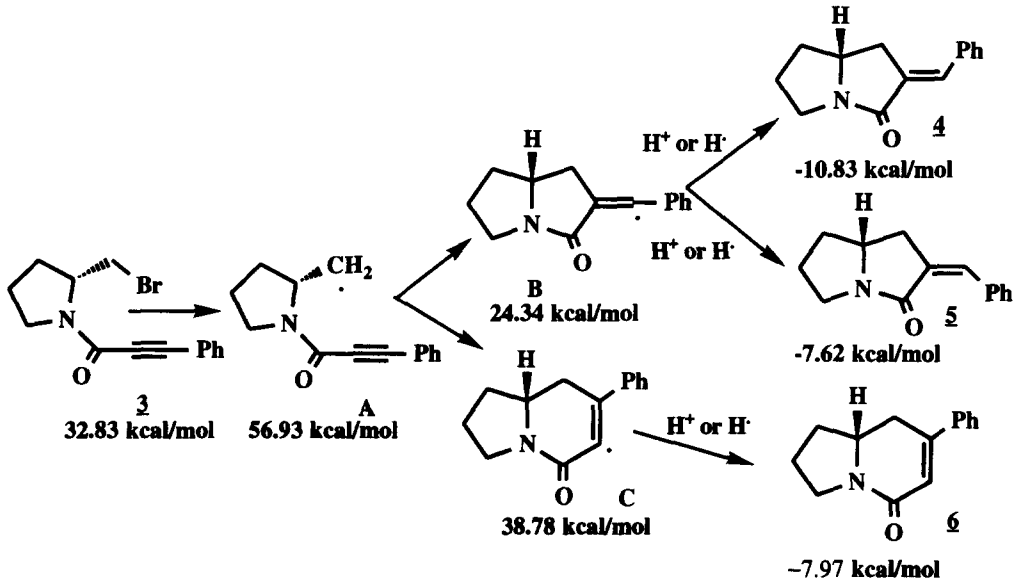
SmI_2 is a useful reagent in organic synthesis.[3] There exist several examples of construction of heterocyclic compounds using this reagent. For example, Fukuzawa *et al.* reported the syntheses of γ-lactones using SmI_2-mediated intramolecular cyclization of haloacetals and intermolecular coupling reaction of ethyl 2-(bromo- or alkoxy-methyl)acrylates with carbonyl compounds.[4] Preparation of dihydrofuran derivatives *via* 1,5-C-H insertion of alkylidenecarbenes by the reaction of 2,2-dialkyl-1,1-dihalogenoalkans with SmI_2 in benzene was reported by Kunishima *et al.*[5] The construction of pyrrolidino[1,2-*a*]indoles and furo[3,4-*b*]indoles using SmI_2-promoted hydroalkylations of indol-3-carbonyls was described by Fang *et al.*[6] Baldwin's group prepared substituted pyrrolidines using the SmI_2-promoted intramolecular coupling reactions of ketyl radicals with alkenyl and alkynyl groups.[7] The SmI_2-mediated cyclization of alkynyl and alkenyl halides giving carbocycles were also reported,[8,9] but there are only a few reports concerning with the heterocycle syntheses using these reactions.[10,11] Previously, we described the first total synthesis of (±)-oxerine by using the SmI_2-mediated cyclization of γ–ethynyl halide, which was the key step of the synthesis.[12] In this paper, we report an efficient total synthesis of pyrrolam A (**1**) by using the SmI_2-mediated intramolecular coupling reaction between the haloalkyl and the ynamide group of **I**.

Our synthetic strategy is shown in the scheme 1. (*R*)-Proline (**2**), having *R*-configuration at the 2-position carbon was chosen as the starting material. By treating with SmI_2, compound **I**, containing a haloalkyl and an ynamide group in the molecule, prepared from **2** *via* a several steps, may give compound **II** having a 5-5 ring system, which could be converted to the aimed compound, pyrrolam A (**1**).



Scheme 1. Synthetic Strategy of Pyrrolam A (1)

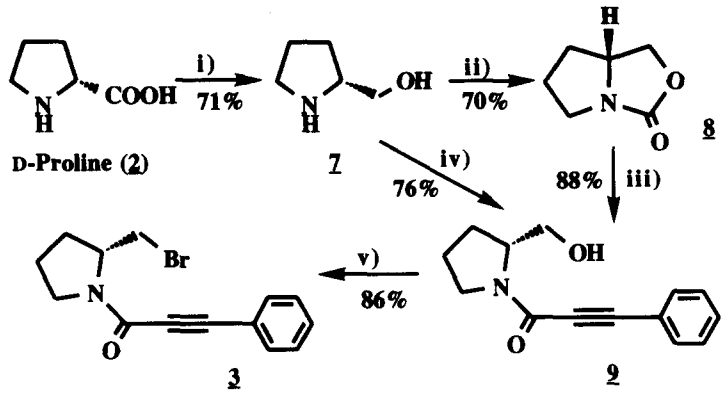
Treatment of **I** (or **3**, X = Br) with SmI_2 may produce bicyclic compounds **4**, **5**, and **6** having either a 5-5 or 5-6 ring system (scheme 2). The heat of formation (ΔHf) obtained from the molecular orbital calculations,[13] indicated that the formation of the 5-5 ring system (pyrrolizidine skeleton) was more favored, and thus the radical intermediate B was the major intermediate to produce **4** and **5** as the major products, with **6** as the minor product. Of the cyclized compounds **4** and **5**, the heat of formation **4** was smaller than that of **5** to predict that **4** would be the major product of the scheme. Finally, pyrrolam A (**1**) will be synthesized by transformation of **4**.



Scheme 2. Heat of Formation (ΔHf) of 3-6 and A-C Calculated by Means of PM3 and UHF/PM3 Methods

D-Proline (**2**) was reduced with lithium aluminium hydride (LAH) according to the previously described method[14] to give an aminoalcohol **7** in 71% yield. The compound **7** was cyclized to give a bicyclic oxazolidinone **8**,[15] which was treated with phenylacetylide, prepared from phenylacetylene and butyllithium *in situ*, to give an alcohol **9** in 62% overall yield (2 steps). Compound **9** was also prepared in 76% yield by the condensation of **7** with 3-phenylpropiolic acid in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (water soluble

carbodiimide: WSC). Bromination of **9** with *N*-bromosuccinimide (NBS)-triphenylphosphine system[16] gave the corresponding bromide **3** in 86% yield (Scheme 3).

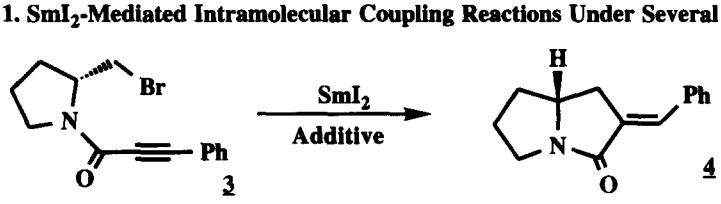


i) LHA ii) $(EtO)_2CO$ / K_2CO_3 iii) Lithium phenylacetylide iv) Phenylpropiolic acid / WSC/ Et_3N v) NBS / PPh_3

Scheme 3. Preparation of Halide (3)

The SmI_2-mediated intramolecular ring closure was studied under several conditions (Table 1). The best result was obtained in entry 2, in which, **4** was the only cyclized compound. The structure of the product **4** obtained, (*R*)-*E*-phenylmethylene-1-azabicyclo[3.3.0]octan-2-one, was identified by ^1H-^1H-NOESY (NOE) experiment. The experimental data agreed with the prediction that the production of **4** is more favored than those of **5** and **6**.

Table 1. SmI_2-Mediated Intramolecular Coupling Reactions Under Several Conditions



Entry	Additives	Reaction Temp. (°C)	Yield (%) of 4 after isolation
1	HMPA*1	-78	66
2	HMPA*1	0	90
3	HMPA*1	r.t.	68
4	HMPA-^{t}BuOH*2	-78	30(52)*4
5	DMPU*3	-78	---(63)*4
6	none	r.t.	---(75)*4

***1 HMPA : 0.1 M SmI_2 in THF= 1 : 10. *2 ^{t}BuOH: HMPA:0.1 M SmI_2 in THF= 1 : 10 : 100. *3 DMPU : 0.1 M SmI_2 in THF= 1 : 10. *4 Figures in parenthesis are % of recovered starting compound 3.**

Treatment of **4** with O_3 gave a keto amide **10** in 94% yield. The trifluoromethan sulfonylation of **10** using proton sponge®[17] or 2,6-di-^{t}butyl-4-methylpyridine[18] as a base did not produce a triflate **11**. When $^i Pr_2NEt$ was used as a base,[17] **11** was synthesized in 50% yield. Finally, reduction of **11** with tributyltin hydride (Bu_3SnH) [19] in the presence of tetrakis(triphenylphosphine)palladium $Pd(PPh_3)_4$ produced pyrrolam A (**1**), the physical data of which were identical with those of an authentic natural product.[2]

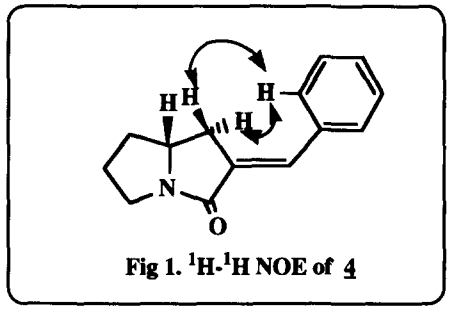
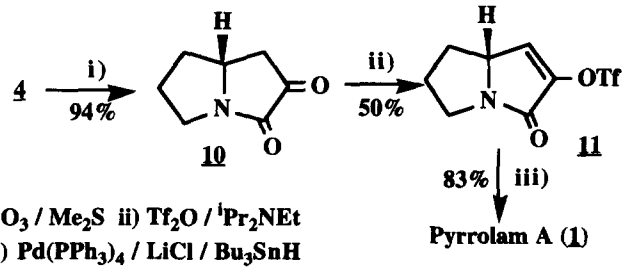


Fig 1. ^{1}H-^{1}H NOE of 4



i) O_3 / Me_2S ii) Tf_2O / $^iPr_2NEt$
iii) $Pd(PPh_3)_4$ / LiCl / Bu_3SnH

Scheme 4. Synthesis of Pyrrolam A (1)

In this way, the total synthesis of pyrrolam A (**1**) was accomplished. It was shown that this short step synthesis is efficient.

Experimental

Infrared spectra were measured by using a JASCO A-100 spectrophotometer. ^{1}H-NMR spectra were recorded in $CDCl_3$ with tetramethylsilane (TMS) as an internal standard on a Varian Gemini 300 or a Brucker AM-400 instrument. Medium-pressure liquid chromatography (MPLC) was conducted by using a UVILOG ALPC-100 as the pump, UVILOG-5IIIa as the UV detector (Oyo Bunko Kiki Co. Ltd., Tokyo) and Kiesel gel

60 (Merck AG, Darmstadt) as the packing material. Preparative thin layer chromatography (PTLC) was carried out with Kiesel gel Art. 5744 (Merck Co. Ltd.). Mass spectral data were obtained with a Hitachi M-80 (Hitachi Co. Ltd.) or a VG Auto Spec (Faisons Co. Ltd.). High-Resolution MS (HRMS) was measured with a VG Auto Spec (Faisons Co. Ltd.). 0.1 M SmI_2 in THF was purchased from Aldrich Chemical Co. Ltd.

(*R*)-1-Aza-3-oxobicyclo[3.3.0]octan-2-one (8): A mixture of **7** (3.00 g, 29.7 mmol), $(EtO)_2CO$ (4.20 g, 35.6 mmol), and Na_2CO_3 (0.30 g, 2.97 mmol) was heated in an oil bath maintained at 120-130 °C until no more EtOH distillated (*ca.* 2h). Then the reaction mixture was cooled to room temperature and was poured into $CHCl_3$ (50 ml). The mixture was washed with sat. NaCl (30 ml x 2) and dried over Na_2SO_4. The organic solvent was evaporated under reduced pressure to give a brown oil, which was distillated to give **8** (2.59 g, 70 %) as a colorless oil. Bp. 130-140 °C / 3 torr (oil bath temp.); $[\alpha]_D$ +37.1 ° (*c* 1.61, $CHCl_3$); IR (film): 1740 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 4.51 (1H, dd, J = 8.9 and 7.9 Hz), 4.16 (1H, dd, J = 8.9 and 3.5 Hz), 3.94-3.85 (1H, m), 3.69-3.60 (1H, m), 3.23-3.14 (1H, m), 2.14-1.84 (3H, m), 1.54-1.40 (1H, m); CIMS: M/Z 128 (M^++1); *Anal.* Calcd for C_6H_9NO: C, 56.68; H, 7.14; N, 11.02. Found: C, 56.38; H, 7.39; N, 10.72.

(*R*)-2-Hydroxymethyl-*N*-(3-phenyl-2-propynoyl)pyrrolidine (9):

Method A: Reaction of **8** with phenylacetylide: To a THF solution (10 ml) of phenylacetylene (0.67 g, 6.6 mmol), 1.6 M BuLi in hexane (3.75 ml, 6 mmol) was added at -78°C under Ar atmosphere. After stirring the reaction mixture for 0.5 h, a dry THF solution (10 ml) of **8** (0.508 g, 4 mmol) was added dropwise. The resulting mixture was stirred at -78 °C for 2 h and then at 0°C for 1h. To the reaction mixture, sat. NH_4Cl (20 ml) was carefully added. The resulting solution was diluted with Et_2O (25 ml), and the organic layer was separated. The aqueous layer was extracted with Et_2O (20 ml x 2). The combined organic layer was washed with sat. NaCl (30 ml x 3) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give a residue, which was purified with MPLC (AcOEt) to give 0.81 g (88 %) of **9** as viscous colorless oil. $[\alpha]_D$ +33.0 ° (*c* 0.80, $CHCl_3$); IR (film): 3400 (OH), 2205 (triple bond), 1610 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.56-7.53 (2H, m), 7.43-7.35 (3H, m), 4.24 (1H, ddd, J = 14.6, 7.3 and 2.6 Hz), 3.99 (1H, m), 3.76-3.65 (3H, m), 2.20-2.12 (1H, m), 2.09-1.84 (3H, m), 1.74-1.65 (1H, m); MS : M/Z 229 (M^+), 211 (M^+-H_2O), 198 (M^+-CO); HRMS Calcd for $C_{14}H_{15}NO_2$: 229.110279. Found: 229.110687.

Method B: Reaction of **7** with phenylpropiolic acid in the presence of WSC: A mixture of **7** (1.00 g, 9.9 mmol), propiolic acid (1.44 g, 9.81 mmol), WSC (2.1 g, 11.0 mmol), Et_3N (1.02 ml, 14.9 mmol), and dry $CH_2Cl_2$was stirred at r.t. overnight. Then the mixture was poured into ice-water (50 ml) , and the organic layer was separated. The aqueous layer was extracted with $CHCl_3$ (20 ml x 2). The combined organic layer was washed with 5% HCl (30 ml x 3), 5% $NaHCO_3$ (30 ml x 3), and sat. NaCl (30 ml x 3), successively, and then dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give a residue, which was purified by MPLC (AcOEt) to give 1.72 g (76 %) of **9** as viscous colorless oil.

(*R*)-2-Bromomethyl-*N*-(3-phenyl-2-propynoyl)pyrrolidine (3): To a suspension of NBS (1.42 g, 7.98 mmol) in dry CH_2Cl_2 (10 ml), a dry CH_2Cl_2 solution (10 ml) of PPh_3 (2.30 g, 8.78 mmol) was added at 0 °C under Ar atmosphere. After stirring the resulting solution at r.t. for 5 min, **5** (0.610 g, 2.66 mmol) in dry CH_2Cl_2 (10 ml) was slowly added at 0 °C. The mixture was further stirred at r.t. for 3 h. To the mixture, was added sat. $NaHCO_3$ (30 ml) and the resulting deposit was filtered off on ®Celite . The filtrate was washed with sat. NaCl (30 ml x 3) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give a brownish residue, which was purified by MPLC (Hexane-AcOEt = 1:1) to give compound **3** (0.669 g, 86 %) as colorless oil, which solidified gradually when left in a refrigerator. Mp. 54-55 °C. $[\alpha]_D$ +14.6 ° (*c* 0.55, $CHCl_3$); IR (film): 2210 (triple bond), 1630 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.61-7.53 (2H, m), 7.47-7.34 (3H, m), 4.51 (0.5H, m), 4.37 (0.5H, m), 3.93-3.87 (0.5H, m), 3.83 -3.79 (0.5H, m), 3.76-3.55 (2.5H, m), 3.34 (0.5H, dd, J = each 10 Hz), 2.21-1.83 (4H, m); MS: M/Z 293 (M^+), 291 (M^+); HRMS Calcd for $C_{14}H_{14}BrNO$: 291.025875. Found: 291.024385.

(*R*)-*E*-3-Phenylmethylene-1-azabicyclo[3.3.0]octan-2-one (4): A dry THF solution (5 ml) of **3** (0.154 g, 0.52 mmol) was added dropwise to a mixture of 0.1 M SmI_2 in THF (16 ml, 1.6 mmol) and HMPA (1.6 ml), at 0 °C under Ar atmosphere. The reaction mixture was stirred at 0°C for 1 h. Then, sat. NH_4Cl (10 ml) was added to the solution and the resulting deposit was filtered off on ®Celite. The deposit was washed with Et_2O (30 ml). The filtrate was washed with sat. NaCl (30 ml), 8% $Na_2S_2O_3$ (20 ml) and sat. NaCl (20 ml), successively. The organic layer was dried over Na_2SO_4 and the solvent was evaporated to give a residue, which was purified by MPLC (Hexane-AcOEt = 1 : 2) to give **4** as colorless crystalline mass (0.10 g, 90 %). Mp. 93-94 °C ($^iPr_2O$). $[\alpha]_D$ +140 ° (*c* 0.52, $CHCl_3$); IR (KBr): 1690 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.47 (2H, d, J = 7.5 Hz), 7.39 (2H, m), 7.33-7.30 (1H, m), 7.32 (1H, d, J = 1.4 Hz), 3.90-3.84 (1H, m), 3.79-3.72 (1H, m), 3.33-3.23 (2H, m), 2.81 (1H, dt, J = 17.8 and 3.3 Hz), 2.20-2.00 (3H, m), 1.32-1.22 (1H, m); MS: M/Z 213 (M^+), 185 (M^+-CO); *Anal.* Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.53; H, 7.14; N, 6.63.

(*R*)-1-Azabicyclo[3.3.0]octane-2,3-dione (10): A dry MeOH (2 ml) - dry CH_2Cl_2 (5 ml) solution of **4** (0.217 g, 1.01 mmol) was ozonized at -78 °C until the starting material could no longer be detected on TLC (*ca.* 0.5 h). After Ar gas bubbled at -78 °C for 0.5 h to remove excess O_3, Me_2S (0.3 ml) was added and the reaction mixture was allowed to warmed to r.t. The solvent was evaporated under reduced pressure to give a residue, to which, $CHCl_3$ (30 ml) was added. The solution was washed with sat. NaCl (15 ml x 3) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give an oil, which was purified with PTLC ($CHCl_3$-MeOH = 9:1) to give a ketoamide (**10**) (0.132 g, 94 %) as colorless solid. Mp. 102-103 °C (benzene-$^iPr_2O$). $[\alpha]_D$ +143 ° (*c* 0.34, $CHCl_3$); IR (KBr): 1760, 1700 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 3.93-3.77 (2H, m), 3.50 (1H, ddd, J = 13, 9.6, and 3.0 Hz), 3.04 (1H, dd, J = 19.2 and 4.1 Hz), 2.40 (1H, dd, J = 19.2 and 4.1 Hz), 2.39-2.10 (3H, m), 1.47-1.33 (1H, m); MS: M/Z 139 (M^+), 111 (M^+-CO); *Anal.* Calcd for $C_7H_9NO_2$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.38; H, 6.41; N, 10.07.

(*R*)-1-Aza-2-oxabicyclo[3.3.0]oct-3-enyl trifloromethanesulfonate (11): To a dry CH_2Cl_2 (5 ml) solution of the keto amide **10** (0.045 g, 0.32 mmol), $^iPr_2NEt$ (0.055 ml, 0.32 ml) and then Tf_2O (0.054 ml, 0.32 mmol) were added at -78°C. The reaction mixture was stirred at -78°C for 0.5 h. CH_2Cl_2 (30 ml) was added to the reaction mixture and the reaction mixture was allowed to warm to r.t. The solution was washed with H_2O (20 ml x 3) and dried over Na_2SO_4. The solvent was evaporated *in vacuo* to give a brown oily residue, which was purified by silica gel column chromatography (Hexane-AcOEt = 2 :1) to give **11** (0.043 g, 50 %) as colorless solid. Mp. 69-71 °C. $[\alpha]_D$ -9.7 ° (*c* 0.31, $CHCl_3$); IR (film): 1708 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.02 (1H, d, J = 2.1 Hz), 4.27-4.21 (1H, m), 3.57-3.48 (1H, m), 3.40-3.33 (1H, m), 2.42-2.19 (3H, m), 1.39-1.18 (1H, m); MS: M/Z 271 (M^+) ; HRMS Calcd for $C_8H_8F_3NO_4S$: 271.012614. Found: 271.011383.

Pyrrolam A (1): Compound **11** (0.023 g, 0.085 mmol) in dry THF (1.5 ml) was added to a dry THF (1.0 ml) solution of $Pd(PPh_3)_4$ (0.010 g, 0.009mmol) and LiCl (0.011 g, 0.25 mmol). Then, Bu_3SnH (0.025 ml, 0.093 mmol) was added slowly by using a micro syringe. After refluxing for 2h under Ar atmosphere, the reaction mixture was treated with CH_2Cl_2 (20 ml). The organic layer was washed with cold 5% NaOH (20 ml x 2) and sat. NaCl (20 ml x 2), successively, and then dried over Na_2SO_4. The solvent was removed under reduced pressure to give an oily residue, which was purified by a combination of silica gel column chromatography (AcOEt) and PTLC (AcOEt) to give pyrrolam A (**1**) (0.009 g, 83 %) as colorless solid. Mp. 60-62°C. $[\alpha]_D$ -26.3° (*c* 0.31, $CHCl_3$) (natural: Mp. 62 °C; $[\alpha]_D$ -29.3° (*c* 1.00, $CHCl_3$)).[2] The physical data of thus obtained **1** were identical with those reported of the authentic natural product.[2]

REFERENCES AND NOTES

1. Wrobel, J. T. *The Alkaloids*, Brossi, A. Ed.; Academic Press, New York, 1985.
2. Grote, R.; Zeeck, A.; Stümpfel, J.; Zähner, H. *Liebigs Ann. Chem.* **1990**, 525-530.
3a. Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am Chem. Soc.* **1980**, 103, 2693-2698.
3b. Kagan, H. B.; Namy, J. L.; Girard, P. *Tetrahedron* **1981**, 37, 175-180.
3c. Molander, G. A. *Chem Rev.* **1992**, 92, 29-68.
4a. Fukuzawa, S.; Sakai, S. *Nippon Kagak Kaishi* **1993**, 513-515.
4b. Fukuzawa, S.; Tsuchimoto, T. *Synlett* **1993**, 803-804.
5. Kunishima, M.; Hioki, K.; Tani, S.; Kato, A. *Tetrahedron Lett.* **1994**, 35, 7253-7254.
6. Shiue, J. -S.; Fang, J. -M. *J. Chem. Soc. Chem. Commun.* **1993**, 1277-1278.
7a. Baldwin, J. E.; Turner, S. C. M.; Moloney, M. G. *Tetrahedron* **1994**, 50, 9411-9424.
7b. *Idem*, *Tetrahedron* **1994**, 50, 9425-9438.
8. Bennett, S. M.; Larouche, D. *Synlett* **1991**, 805-807.
9. Curran, D. P.; Wolin, R. L. *Synlett* **1991**, 317-318.
10. Curran, D. P.; Fevig, T. L.; Totleben, M. J. *Synlett* **1990**, 773-774.
11. Capella, L.; Montevecchi, P. C. *Tetrahedron Lett.* **1994**, 35, 8445-8448.

12. Aoyagi, Y.; Inariyama, T.; Arai, Y.; Tsuchida, S.; Matuda, Y.; Kobayashi, H.; Ohta, A.; Kurihara, T.; Fujihira, S. *Tetrahedron* **1994**, 50, 13575-13582.
13. Stewart, J. J. P. MOPAC Ver. 6.0, QCPE No. 455, Chemistry Deparment, Indiana University, Bloomington, IN, **1987**. Hirano, T. MOPAC Ver. 6.01, JCPE Newslett. **1991**, 2, 26.
14. Dickman, D. A.; Meyers, A. I.; Smith, G. A.; Gawley, R. E. *Org. Synth. Coll. Vol 7* ; Freeman, J. P. Ed.; John Wiley & Sons, Inc.: New York, 1990; pp.530-533.
15. Scholz, K. -H.; Heine, H. -G.; Hartmann, W. *Org. Synth. Coll. Vol 7* ; Freeman, J. P. Ed.; John Wiley & Sons, Inc.: New York, 1990; pp.4-8.
16. Bates, H. A.; Farina, J.; Tong, J. *J. Org. Chem.* **1986**, 51, 2637-2641.
17. Farina, V.; Stephen, R. B.; Sheila, I. H. *J. Org. Chem.* **1989**, 54, 4962-4966.
18. Stang, P. J.; Treptow, W. *Synthesis* **1980**, 283-284.
19. Dupre, B.; Meyers, A. I. *J. Org. Chem.* **1991**, 56, 3197-3198.

(*Received in Japan* 2 *August* 1995; *accepted* 16 *October* 1995)