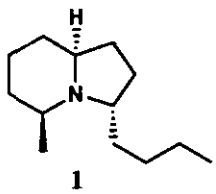
AN ASYMMETRIC SYNTHESIS OF (+)-INDOLIZIDINE 195B[1]

Hiroki Takahata,* Hiroshi Bandoh, and Takefumi Momose*

Faculty of Pharmaceutical Sciences, Toyama Medical & Pharmaceutical University, Sugitani 2630, Toyama 930-01, Japan

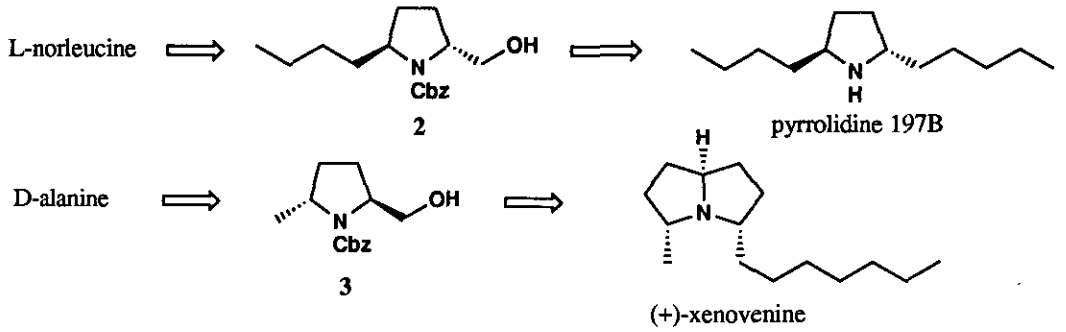
Abstract - An asymmetric synthesis of (+)-indolizidine 195B (**1**) starting from the known pyrrolidino alcohol (**2**) available from L-norleucine has been achieved.

The widespread occurrence and diverse biological activity of indolizidine alkaloids and the short supply of many of them from natural sources have made them attractive research objectives.[2] In continuation of a study in our laboratory on developing synthetic entries into optically active alkaloids,[3] we have been interested in a new approach to homochiral (+)-indolizidine 195B (**1**),[4] extracted from the skin of the Colombian poison-frog *Dendrobates histrionicus* as a new alkaloidal component.[5] So far, only two procedures have been reported, both by the Kibayashi group.[6] The first enantiospecific synthesis[6a] of **1** was achieved from diethyl L-tartrate, which permitted the absolute stereochemistry to be assigned as 3*S*,5*S*,8a*S*. Additionally, his group has very recently succeeded in an excellent enantiodivergent synthesis of **1** from C_2-symmetric, chiral diepoxides available from D-mannitol.[6b] However, the approach has required relatively lengthy sequences from chiral educts, and this prompted us to disclose our short synthesis of (+)-indolizidine 195B (**1**) from the known (2*S*,5*R*)-1-benzyloxycarbonyl-2-butyl-5-hydroxymethylpyrrolidine (**2**) available from L-norleucine.[3d]



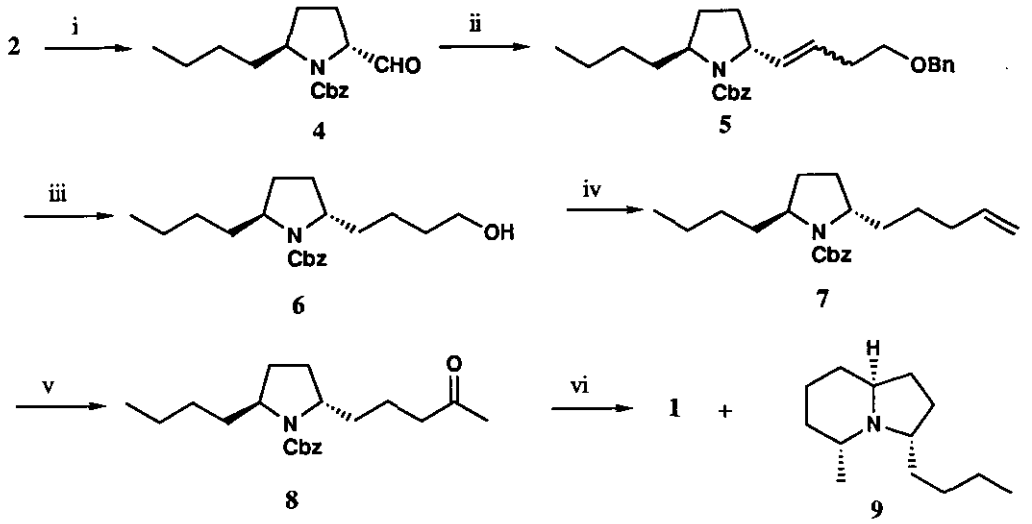
1

Recent investigations in this laboratory have revealed that the homochiral *trans*-2-alkyl-5-hydroxymethylpyrrolidines (**2**[3d] and **3**[3a]) prepared by a stereoselective intramolecular amidomercuration of *N*-alkenylurethanes available from α-amino acids serve as a versatile chiral building blocks in the preparation of several biologically active nitrogen-containing compounds such as (+)-pyrrolidine 197B[7] and (+)-xenovenine.[8]



The Swern oxidation (DMSO/$COCl_2$/Et_3N) of **2** gave the aldehyde (**4**), and the Wittig reaction of **4** with 3-benzyloxypropylidenetriphenylphosphorane, generated *in situ* from the appropriate phosphonium bromide and n-butyllithium (n-BuLi), afforded the olefin (**5**) in 70% yield from **2**. Catalytic hydrogenation (H_2/10%Pd-C/HCl-MeOH) of **5** followed by benzyloxycarbonylation of the resulting pyrrolidine alcohol provided the *N*-protected alcohol (**6**) {$[\alpha]^{26}_D$ + 59.9° (*c* 0.970, $CHCl_3$), lit.[6b] $[\alpha]^{23}_D$ + 60.4° (*c* 5.90, $CHCl_3$)} in 57% yield. The Swern oxidation of **6** and subsequent reaction of the resulting aldehyde with methyltriphenylphosphorane gave the olefin (**7**) in 71%. The Wacker oxidation of **7** afforded the methyl ketone (**8**) in 77% yield. Finally, hydrogenation (H_2/$Pd(OH)_2$) of **8** resulted in cyclization to produce (+)-indolizidine 195B {**1**,$[\alpha]^{26}_D$ + 99.6° (*c* 0.23, MeOH), lit.,[6b] $[\alpha]^{24}_D$ + 98.0° (*c* 0.30, MeOH)} and its C-5 epimer (**9**) in a ratio of 5:1 in 89% yield. The spectral data for the synthesized compound (**1**) were identical with the values reported.[6b]

In summary, we have demonstrated a useful, short synthesis of (+)-indolizidine 195B (**1**) starting from the readily available, substituted pyrrolidine (**2**). This procedure could be applied to the synthesis of the 3,5-disubstituted indolizidine subclass. In practice, starting from the pyrrolidine alcohol (**6**) as the common chiral building block, both (-)-indolizidine 223AB and (-)-indolizidine 239AB or other 3,5-disubstituted indolizidines have been prepared by Kibayashi.[6b] The extension of this methodology to the synthesis of naturally scarce alkaloids is the subjects of active investigations in our laboratory, the results of which will be reported in due course.



i DMSO/$(COCl)_2$/Et_3N; ii $Ph_3P^+(CH_2)_3OBnBr^-$/n-BuLi; iii 1) H_2/10%Pd-C/HCl-MeOH; 2) CbzCl/K_2CO_3; *iv 1) DMSO/$(COCl)_2$/Et_3N; 2) $Ph_3P^+CH_3I^-$/n-BuLi; v* O_2/cat. $PdCl_2$/CuCl; vi H_2/$Pd(OH)_2$

EXPERIMENTAL

Microanalyses were performed by Microanalysis Center of Toyama Medical & Pharmaceutical University. Infrared spectra (ir) were measured with a Perkin-Elmer 1600 series FTIR spectrophotometer. Proton magnetic resonance (^1H nmr) spectra were recorded at 270 MHz on a JEOL-FX270 instrument with tetramethylsilane as an internal standard. Carbon-13 nmr spectra were determined on a JEOL-FX270 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 spectrometer. Optical rotations were measured on a JASCO DIP-140 instrument. Chromatography was performed on a silica gel column [Fuji-Davision BW-200 or Merck 60 (No. 9385)] with a medium pressure apparatus and a mixture of ethyl acetate and hexane was used as eluant unless otherwise specified. The extracts were dried over Na_2SO_4 unless otherwise specified.

(2*R*,5*S*)-2-(4-Benzyloxy-1-butenyl)-1-Benzyloxycarbonyl-5-butylpyrrolidine (A mixture of *E* and *Z*) (5). To a solution of oxalyl chloride (160 µl, 1.64 mmol) in CH_2Cl_2 (1.6 ml) was added dropwise DMSO (306 µl, 2.15 mmol) at -78 °C. After being stirred for 10 min, a solution of (2*S*,5*R*)-1-benzyloxycarbonyl-2-butyl-5-hydroxymethyl)pyrrolidine (**2**) (318 mg, 1.09 mmol) in CH_2Cl_2 (7 mL) was added to the mixture. After being stirred at -60 °C for 30 min, triethylamine (684 ml, 4.91 mmol) was added to the mixture. The reaction mixture was warmed to 0 °C and then quenched with 20% $KHSO_3$. The mixture was extracted with CH_2Cl_2. The extract was washed with sat. $NaHCO_3$ and then brine, dried, and evaporated.

The residue was chromatographed to yield the aldehyde (**4**) (297 mg, 94%). To a solution of benzyloxypropyltriphenylphosphonium bromide (1.6 g, 3.25 mmol) in THF (3.5 ml) was added n-BuLi (1.6 M in hexane) (1.68 ml, 2.70 mmol) at -78 °C. The reaction mixture was gradually warmed to room temperature and then stirred for 30 min. A solution of **4** in THF (1 ml) was added dropwise to the mixture at 0 °C and the resulting mixture was stirred at 0 °C for 3 h. The mixture was quenched with sat. NH_4Cl and extracted with ether. The organic phase was washed with brine, dried, and evaporated. The residue was chromatographed to yield **5** (315 mg, 69%) as an oil. Ir (neat) 3356, 1718, 1700 cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.89 (3 H, m), 1.29 (4 H, m), 1.50-2.11 (8 H, m), 2.12-2.61 (2 H, m), 3.38 (2 H, m), 3.88 (1 H, m), 4.46 (2 H, m), 4.57 (1 H, m), 5.06 (2 H, m), 5.39 (2 H, m), 7.39 (10 H, m). Anal. Calcd for $C_{27}H_{35}NO_3$: C, 76.92; H, 8.37; N, 3.32. Found: C, 77.07; H, 8.40; N, 3.21.

(2*S*,5*S*)-1-Benzyloxycarbonyl-2-butyl-5-(4-hydroxybutyl)pyrrolidine (6). A suspension of **5** (260 mg, 0.619 mmol) and 10% palladium carbon (30 mg) in 2% HCl in MeOH (5 ml) was stirred under a hydrogen atmosphere at 3 atm for 20 h. The insoluble materials were removed by filtration and washed with CH_2Cl_2. The combined organic phases were evaporated and 2N NaOH was added to the residue. The mixture was extracted with CH_2Cl_2. The extract was dried and evaporated to yield the crude product. Benzyloxycarbonyl chloride (88 μl, 0.619 mmol) was added to a solution of a crude amino alcohol and 2N NaOH (619 μl, 1.24 mmol) in THF (3 ml) at 0 °C. After being stirred for 2 h, ethyl acetate and anhyd. Na_2SO_4 was added to the mixture. After filtration, the filtrate was evaporated to yield a residue, which was chromatographed to give **6** (118 mg, 57%) as an oil; $[\alpha]_D^{26}$ +59.9° (*c* 0.97, $CHCl_3$); ir (neat) 3448, 1697 cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.82, 0.89 (3 H, 1:1 ratio, t, *J*=6.9 Hz), 1.10-2.03 (17 H, m), 3.52, 3.64 (3 H, 1:1 ratio, t, *J*= 6.9 Hz), 3.83 (2 H, m), 5.05, 5.06 (1 H, 1:1 ratio, ABq, *J*= 12.4 Hz), 5.18, 5.20 (1 H, 1:1 ratio, ABq, *J*= 12.4 Hz), 7.35 (5 H, m). Anal. Calcd for $C_{20}H_{31}NO_3$: C, 72.05; H, 9.37; N, 4.20. Found: C, 71.83; H, 9.23; N, 4.17.

(2*S*,5*S*)-1-Benzyloxycarbonyl-2-butyl-5-(4-pentenyl)pyrrolidine (7). According to the procedure described for **5**, treatment of **6** (131 mg, 0.393 mmol) with oxalyl chloride (68.3 μl, 0.786 mmol), DMSO (96 μl, 1.178 mmol), and triethylamine (246 μl, 1.768 mmol) in CH_2Cl_2 (2.6 ml) gave crude aldehyde. To a solution of methyltriphenylphosphonium bromide (281 mg, 0.786 mmol)) in THF (600 μl) was added n-BuLi (1.6 M in hexane) (442 μl, 0.707 mmol) at 0 °C. After being stirred for 1 h, a solution of the crude aldehyde in THF (400 μl) was added dropwise to the mixture at 0 °C and the resulting mixture was stirred at 0 °C for 2 h. The mixture was quenched with sat. NH_4Cl and extracted with ether. The organic phase was washed with

brine, dried, and evaporated. The residue was chromatographed to yield **7** (92 mg, 71%) as an oil. $[\alpha]_D^{26}$ +62.8° (*c* 3.045, $CHCl_3$); ir (neat) 1700, 1638 cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.83, 0.89 (3 H, 1:1 ratio, t, *J*= 6.6 Hz), 1.14-1.47 (7 H, m), 1.47-1.74 (4 H, m), 1.82-2.18 (5 H, m), 3.76 (2 H, m), 3.77 (2 H, m), 4.91 (2 H, m), 5.03, 5.08 (1 H, 1:1 ratio, ABq, *J*= 12.4 Hz), 5.17, 5.22 (1 H, 1:1 ratio, ABq, *J*= 12.4 Hz), 5.78 (1 H, m), 7.35 (5 H, m). Anal. Calcd for $C_{21}H_{31}NO_2$: C, 76.55; H, 9.48; N, 4.25. Found: C, 76.83; H, 9.67; N, 4.10.

(2*S*,5*S*)-1-Benzyloxycarbonyl-2-butyl-5-(4-oxopentyl)pyrrolidine (8). A suspension of $PdCl_2$ (4.9 mg, 0.028 mmol) and CuCl (27.6 mg, 0.279 mmol) in 223 µl of dimethylformamide-water (7:1) was bubbled with oxygen for 1 h. To the mixture was added a solution of **7** (92 mg, 0.28 mmol) in 75 µl of dimethylformamide-water (7:1). The reaction mixture was stirred under oxygen for 24 h, and then to this was added 3N HCl (1 ml). The aqueous layer was extracted with ether. The extract was washed with sat. $NaHCO_3$, dried, and evaporated. The residue was chromatographed to yield **8** (74 mg, 77%) as an oil; $[\alpha]_D^{26}$ +62.6° (*c* 3.225, $CHCl_3$); ir (neat) 1696 cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.82, 0.89 (3 H, 1:1 ratio, t, *J*= 6.9 Hz), 1.14-2.63 (11 H, m), 2.04, 2.13 (3 H, 1:1 ratio, s), 3.68-3.92 (2 H, m), 5.03, 5.08 (1 H, 1:1 ratio, ABq, *J*= 12.4 Hz), 5.16, 5.20 (1 H, 1:1 ratio, ABq, *J*= 12.4 Hz), 7.35 (5 H, m). HRms calcd for $C_{21}H_{31}NO_3$: 345.2284. Found: 345.2302.

(3*S*,5*S*,8a*S*)-3-Butyl-5-methylindolizidine [(+)-indolizidine *195B*), *1*] and (3*S*,5*R*,8a*S*)-3-Butyl-5-methylindolizidine (9). A suspension of **8** (127 mg, 0.368 mmol) and palladium hydroxide (13 mg, 0.093 mmol) in MeOH (5 ml) was stirred under a hydrogen atmosphere for 7 h. The insoluble materials were removed by filtration and the filtrate was evaporated to give a residue, which was chromatographed on basic alumina using hexane-$CHCl_3$ (1:3) as eluant to yield **1** (54 mg, 75%) and **9** (10 mg, 14%) as oils.

1: $[\alpha]_D^{26}$ +99.6° (*c* 0.23, MeOH); ir (neat) 2959, 2926, 2869, 2856, 2787, 1654, 1458, 1375, 1132, 1052 cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.89 (3 H, t, *J*= 7.0 Hz), 0.98-2.15 (13 H, m), 1.08 (3 H, d, *J*= 6.1 Hz), 2.37 (1 H, m), 2.52 (1 H, m), 3.26 (1 H, m); ^{13}C nmr ($CDCl_3$) δ 59.00, 58.92, 52.09, 34.44, 32.28, 29.98, 29.14, 26.32, 24.97, 24.71, 23.01, 20.39, 14.20. HRms calcd for $C_{13}H_{25}N$: 195.1987. Found: 195.2008.

9: $[\alpha]_D^{26}$ +68.5° (*c* 0.145, MeOH); ir (neat) 2926, 2857, 1701, 1654, 1637, 1560, 1458, 1376 cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.89 (3 H, t, *J*= 7.1 Hz), 1.01-2.09 (13 H, m), 1.16 (3 H, d, *J*= 6.7 Hz), 2.91 (2 H, m), 3.29 (1 H, m); ^{13}C nmr ($CDCl_3$) δ 59.25, 55.51, 48.98, 35.81, 29.05, 28.81, 28.39, 26.92, 26.77, 22.93, 20.23, 18.84, 14.11. HRms calcd for $C_{13}H_{25}N$: 195.1987. Found: 195.2008.

ACKNOWLEDGMENT:

We are grateful for Daiichi Pure Chemicals Co. Ltd. for a gift of L-norleucine.

RERERENCES AND NOTES

1. A preliminary account of this work has been presented at the 34th Symposium on the Chemistry of Natural Products, Tokyo, October, 1992; Abstract, p. 663.
2. A. S. Howard and J. P. Michael, in "The Alkaloids", A. Brossi, Ed., Vol. 28, p. 183, Academic Press, New York, 1986.
3. a) H. Takahata,.H. Bandoh, and T. Momose, *J. Org. Chem.,* 1992, **57**, 4401; b) H. Takahata, H. Bandoh, M. Hanayama, and T. Momose, *Tetrahedron: Asymmetry* ,1992, **3**, 607; c) H. Takahata, Y. Banba, M. Tajima, and T. Momose, *J. Org. Chem.,* 1991, **56**, 240; d) H. Takahata, H. Takehara, N. Ohkubo, and T. Momose, *Tetrahedron: Asymmetry*, 1990, **1**, 561.
4. T. Tokuyama, N. Nishimori,I. Karle, M. W. Edwards, and J. W. Daly, *Tetrahedron*, 1986, **42**, 3453.
5. A large number of alkaloids have been isolated in minute quantity from the skin extracts of neotropical poison-dart frogs (*Dendrobatidae*); J. W. Daly, H. M. Garraffo, and T. F. Spande, in "The Alkaloids", G. A. Cordell, X.. Ed., Vol. 43, p. 185, Academic Press, San Diego, 1993.
6. a) N. Yamazaki and C. Kibayashi, *J. Am. Chem. Soc.*, 1989, **111**, 1396; b) N. Machinaga and C.; Kibayashi, *J. Org. Chem.*, 1992, **57**, 5178.
7. J. W. Daly, T. F. Spande, N. Whittaker, R. J. Highet, D. Feigl, N. Nishimori, T. Tokuyama, and C. W. Meyers, *J. Nat. Prod.*, 1986, **49**, 265.
8. T. H. Jones, M. Blum, H. M. Fales, and C. R. Thompson, *J. Org. Chem.*, 1980, **45**, 4778.

Received, 12th July, 1993