ASYMMETRIC SYNTHESIS OF INDOLIZIDINES 167B AND 223AB

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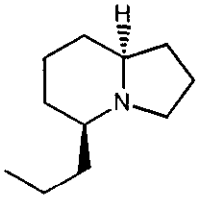
Abstract-The total synthesis of (+)-indolizidine 167B (**1**) and the formal synthesis of (-)-indolizidine 223AB (**2**) starting with L- and D-norvaline-derived *cis*-2-hydroxymethyl-6-propylpiperidines (**3** and *ent*-**3**), respectively, are described.

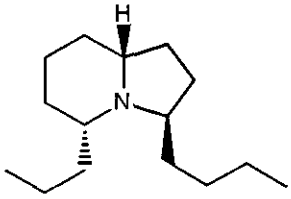
Indolizidines bearing alkyl appendages have been isolated from the skin secretions of neotropical frogs (family Dendrobatiae).[1] These alkaloids vary in its ring substitution from a type with a single substituent at C-5 to the one with substituents at C-3 and C-5 or at C-5 and C-8. Since many of these alkaloids are potent moderators of neuromuscular transmission, they have attracted much attention of synthetic chemists.[2] Indeed, many syntheses of these compounds have been reported.[3] On allowing for the simultaneous construction of carbon-hetero atom bonds of the ring system and installation of several stereogenic centers on the newly formed heterocycle,[4] our attention in this field has been focused on the application of an electrophile-mediated heterocyclization to the synthesis of this class of compounds.[5] Recently we described a stereoselective synthesis of *cis*-2,6-disubstituted piperidines based on intramolecular amidomercuration of α-amino acid-derived, homochiral alkenylurethanes and application of the sequence to the synthesis of (-)-pinidine[6] and (+)-monomorine I.[7] In this paper we disclose the total synthesis of (+)-indolizidine 167B (**1**) and the formal synthesis of (-)-indolizidine 223AB (**2**) starting from *cis*-2-hydroxymethyl-6-propylpiperidine (**3** or *ent*-**3**) derived from L- and D-norvaline.

Synthesis of (+)-Indolizidine 167B (**1**)

The synthesis of **1**, isolated in trace amounts in the skin of a Dendrobatid frog (Panamà),[8] has been reported four times[9] in its scalemic form. The construction of its indolizidine skeleton starts with the five-membered ring (pyrrolidine or pyrrole) to elaborate of the fused six-membered ring. Our protocol is the first example starting from a six-membered ring (the *cis*-2,6-disubstituted piperidine **3**).



(+)-indolizidine 167 B
1



(-)-indolizidine 223 AB
2

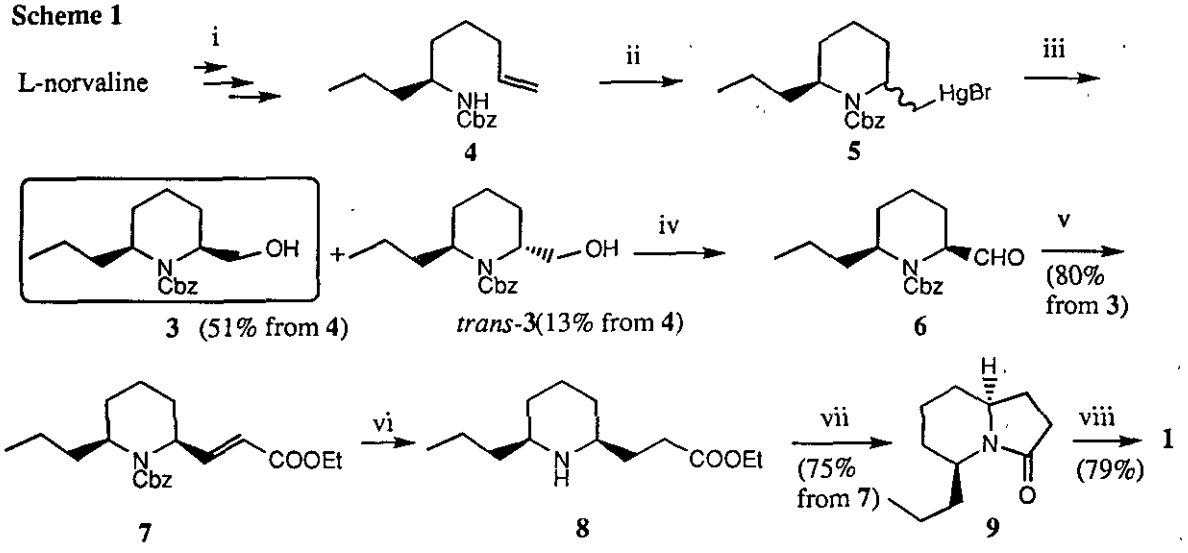
Our synthesis of **1** began with the intramolecular amidomercuration of (*S*)-*N*-(benzyloxycarbonyl)-1-propyl-5-hexenylamine (**4**), readily available from L-norvaline. The unsaturated carbamate (**4**) underwent the cyclization induced by mercuric trifluoroacetae in nitromethane followed by treatment with sodium bromide to afford the organomercurial bromide (**5**), which was oxidatively demercurated to provide a 4:1 (*cis*:*trans*) mixture of diastereomeric 2,6-disubstituted piperidines (**3**). The pure *cis*-diastereomer was isolated by chromatography in 51% yield from **4**. The Swern oxidation of **3** gave the aldehyde (**6**), which on subsequent Horner-Emmons reaction with triethyl phosphonoacetate provided the α,β-unsaturated ester (**7**) in 80% overall yield from **3**. Exposure of **7** to an atmosphere of hydrogen in the presence of palladium hydroxide as a catalyst in methanol caused reduction of its double bond and debenzyloxycarbonylation simultaneously to give the piperidino ester (**8**), which on subsequent annulation by action of triethylaluminum[10] afforded the indolizinone (**9**) in 75% yield. Finally, reduction of **9** with lithium aluminum hydride gave the desired (**1**) {$[\alpha]^{24}_D$ +118.2° (CH_2Cl_2) lit.,[9a] -113.2° (CH_2Cl_2) for *ent*-**1**} in 79% yield. Spectral data (^1H and ^{13}C nmr) for **1** were completely identical with those reported.[9a]

Formal Synthesis of (-)-Indolizidine 223AB (2)

With the *cis*-disubstituted piperidino ester (**7**) in hand, our attention was turned to the transformation of *ent*-**7** into (-)-indolizidine 223AB (**2**), extracted from *Dendrobates histrionicus*,[11] whose chiral syntheses have been reported several times since 1985.[12] We aimed at the synthesis of a synthetic intermediate (**10**) in the Husson's route[12a] to **2**. By means of a procedure similar to that described for the preparation of **7**, the

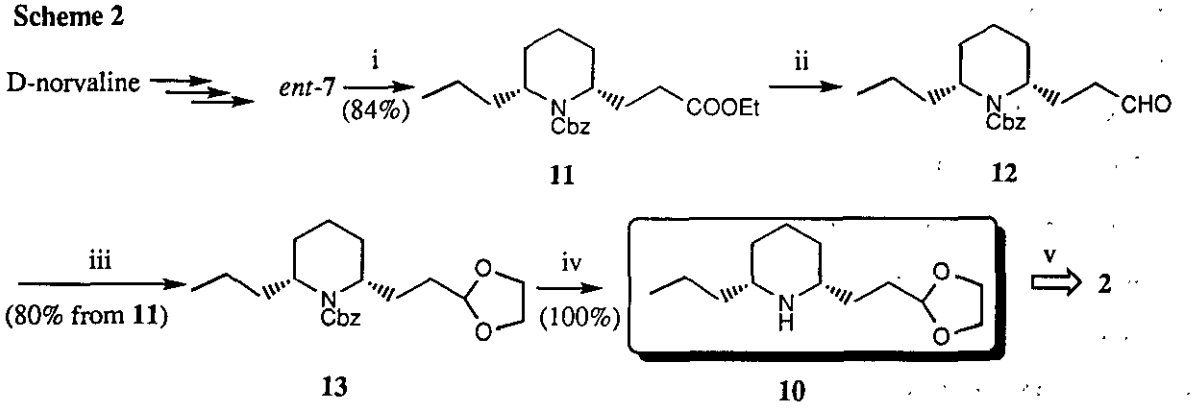
conversion of D-norvaline into *ent*-**7** has been achieved. Chemoselective reduction of *ent*-**7** with Red-Al® in the presence of cuprous bromide was carried out to provide the saturated ester (**11**) in 84% yield.[13] Treatment of the ester (**11**) with DIBAL afforded the aldehyde (**12**), which without purification was transformed into the acetal (**13**) in 80% overall yield from **11**. Finally, hydrogenolysis of **13** gave the synthetic intermediate (**10**) ($[\alpha]^{24}_D$ +2.7° ($CHCl_3$)) in quantitative yield. Spectral data for **10** were completely identical with those reported.[14]

Scheme 1



i,Experimental; ii, 1) $Hg(OCOCF_3)_2$; 2) NaBr; iii, $O_2/NaBH_4$/DMF; iv, $(COCl)_2$/DMSO/Et_3N; v, $(EtO)_2P(O)CH_2COOEt$/NaH; vi, $H_2/Pd(OH)_2$; vii, Me_3Al; viii $LiAlH_4$

Scheme 2



i, Red-Al®/CuBr; ii, DIBAL; iii, $(CH_2OH)_2$/*p*-TsOH; iv, $H_2/Pd(OH)_2$; v, ref. 12a

In summary, we demonstrated the enantioselective synthesis of (+)-indolizidine 167B (**1**) *via* the *cis*-2,6-disubstituted piperidine (**3**) starting from L-norvaline and the formal synthesis of (-)-indolizidine 223AB (**2**) *via ent*-**3** from D-norvaline. Further application of our procedure to the preparation of the related biologically acive indolizidines are under study.

EXPERIMENTAL

Chemical sifts are expressed in ppm to internal tetramethylsilane (0 ppm). Column chromatography was performed on silica gel with medium pressure apparatus and a mixture of ethyl acetate/hexane was used as eluant. The extracts were dried over Na_2SO_4 unless otherwise specified.

(*S*)-*N*-Benzyloxycarbonyl)-1-propyl-5-hexenylamine (4). To a suspension of copper(I) iodide (3.025 g, 15.9 mmol) in THF (67 ml) was added 1 M 3-butenylmagnesium bromide in THF (31.5 ml, 31.5 mmol) dropwise at -78 °C. The reaction mixture was allowed to warm to -30 °C and stirred for 10 min. After cooling at -78 °C, a solution of (*S*)-2-benzyloxycarbonylamino-1-iodopentane {(mp 66-7 °C, $[\alpha]^{26}_D$ -24.4° (c 1.02, $CHCl_3$)}[15] (3.678 g, 10.678 mmol) in THF (6.7 ml), prepared from L-norvaline by means of a procedure similar to that described for the preparation of (*S*)-2-benzyloxycarbonylamino-1-iodohexane,[16] was added to the mixture. The reaction mixture was stirred for 6 h at -30 °C and quenched with saturated NH_4Cl. After evaporation, ether was added to the residue. The mixture was filtered and the solid was washed with ether. The combined organic phase was washed with brine, 10% NH_4OH, and brine and dried. After removal of the solvent, the residue was chromatographed to yield **4** (2.396 g, 82%) as a solid; mp 79-79.5 °C (hexane); $[\alpha]^{26}_D$ -2.99° (c 1.045, CH_2Cl_2); ir (KBr) 3312, 3072, 3037, 2992, 2938, 2861, 2846, 1688, 1641, 1588, 1547, 1499, 1466, 1351, 1304, 1279, 1259, 1234, 1120, 1103, 1058, 1013, 916, 731, 696 cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.91 (3 H, t, *J* = 7 Hz), 1.33-1.61 (8 H, m), 2.04 (2 H, m), 3.64 (2 H, br s), 4.46 (1 H, m), 4.97 (2 H, m), 5.09 (2 H, m), 5.70-5.85 (1 H, m), 7.35 (5 H, m). Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 73.87; H, 9.16; N, 5.10.

(2*S*,6*S*)- and (2*R*,6*S*)-1-Benzyloxycarbonyl-2-hydroxymethyl-6-propylpiperidines (3 and *trans*-3). To a solution of **4** (2.824 g, 10.26 mmol) in nitromethane (150 ml) was added mercuric trifluoroacetate (6.565 g, 15.39 mmol), and the reaction mixture was stirred for 18 h at room temperature. Saturated $NaHCO_3$ (1.293 g, 5.735 mmol) was added to the mixture with ice-cooling. After 0.5 h of stirring, saturated KBr (7.325 g, 61.56 mmol) was added to the mixture. After 2 h of stirring, the organic layer was washed with saturated KBr and dried. After evaporation, the residue was chromatographed to yield the organomercurial bromide (**5**) (5.685 g, 10.26 mmol) as an oil. Oxygen (O_2) was bubbled into a

suspension of $NaBH_4$ (581 mg, 15.35 mmol) in DMF (115 ml) for 1 h, and to this was added dropwise a solution of **5** in DMF (430 ml) over 3 h with continuous introduction of O_2. The bubbling of O_2 into the mixture was continued for 1 h, and ether was added. The reaction mixture was filtered through Celite, and the filtrate was evaporated *in vacuo*. To the residue were added ether and water. The organic layer was separated, and the aqueous layer was extracted with ether three times. The combined organic phase was dried and evaporated. Fractionation of the residue was effected by chromatography to yield **3** (1.532 g, 51%) and *trans*-**3** (384 mg, 13%) as oils.

3: $[\alpha]^{26}_D$ +9.3° (c 1.285, MeOH); ir (neat) 3432, 1670, 1586, 1453, 1273; ^{1}H nmr ($CDCl_3$) δ 0.87 (3 H, t, J = 7.1 Hz), 1.22-1.33 (2 H, m), 1.44-1.49 (2 H, m), 1.53-1.58 (6 H, m), 1.79 (1 H, m), 3.04 (1 H, br s), 3.64 (2 H, m), 4.19 (1 H, m), 4.33 (1 H, m) 5.10, 5.15 (each 1 H, ABq, J = 12.4 Hz) 7.35 (5 H, m); HRms Calcd for $C_{17}H_{25}NO_3$: 291.1833. Found: 291.1880.

trans-**3**: $[\alpha]^{26}_D$ +30.6° (c 1.18, MeOH); ir (neat) 3443, 1678, 1586, 1453, 1273; ^{1}H nmr ($CDCl_3$) δ 0.87 (3 H, t, J = 7.2 Hz), 1.19-1.44 (4 H, m), 1.58-1.79 (6 H, m), 3.45 (1 H, br s), 3.72-3.88 (3 H, m), 4.30 (1 H, m) 5.10, 5.15 (each 1 H, ABq, J = 12.4 Hz) 7.35 (5 H, m); HRms Calcd for $C_{17}H_{25}NO_3$: 291.1833. Found: 291.1807.

(2*S*,6*S*)-1-Benzyloxycarbonyl-2-(3-ethoxycarbonyl-1-propenyl)-6-propylpiperidine (7). To a solution of oxalyl chloride (324 μl, 3.837 mmol) in CH_2Cl_2 (3 ml) was added dropwise a mixture of DMSO (408 μl, 5.754 mmol) in CH_2Cl_2 (3 ml) at -78 °C. After being stirred for 10 min at the same temperature, a solution of **3** (559 mg, 1.92 mmol) in CH_2Cl_2 (9 ml) was added to the mixture. After being stirred for 30 min, triethylamine (1.2 ml, 8.63 mmol) was added to the mixture. The resulting mixture was stirred for 2 h, and then quenched with 20% $KHSO_3$. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic phase was successively washed with saturated $NaHCO_3$ and brine, dried, and evaporated to leave a crude aldehyde (**6**). To a suspension of 60% sodium hydride (115 mg, 2.877 mmol) in THF (7.5 ml) was added triethyl phosphonoacetae (685 μl, 2.877 mmol) over 5 min at 0 °C. After being stirred for 10 min, a solution of **6** (550 mg, 1.90 mmol) in THF (2.5 ml) was added to the reaction mixture, and the whole mixture was stirred for 2 h at 0 °C. Saturated NH_4Cl was added to the reaction mixture. After separation of organic layer, the aqueous phase was extracted with ether three times. The combined organic phase was washed with brine, dried, and evaporated to give an oil, which was chromatographed to yield **7** (610 mg, 80%) as an oil; $[\alpha]^{26}_D$ -69.3° (c 2.075, $CHCl_3$); ir (neat) 1718, 1694; ^{1}H nmr ($CDCl_3$) δ 0.86 (3 H, t, J = 7.3 Hz), 1.29 (3 H, t, J = 7.0

Hz), 1.36-1.86 (10 H, m), 4.19 (2 H, q, J = 7.1 Hz), 4.28 (1 H, m), 4.97 (1 H, m), 3.64 (2 H, m), 5.14 (2 H, s), 5.90(1 H, dd, J = 16.2, 1.6 Hz) 6.98 (1 H, dd, J = 16.2, 5.4 Hz) 7.35 (5 H, s); HRms Calcd for $C_{21}H_{31}NO_4$: 359.2095. Found: 359.2059.

(5*S*,9*S*)-5-Propylindolizidin-3-one (9). A suspension of **7** (137 mg, 0.380 mmol) and palladium hydroxide (10 mg) in ethanol (7 ml) was stirred under a hydrogen atmosphere for 2 h. The insoluble materials were removed by filtration, and the filtrate was evaporated to give a crude **8**. Triethylaluminum in hexane (0.99 M, 0.461 ml, 0.46 mmol) was dropwise added to a solution of **8** (86 mg, 0.380 mmol) in CH_2Cl_2 (3.8 ml). The reaction mixture was stirred at room temperature for 1 h, refluxed for 14 h, and quenched with 1% hydrochloric acid. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic phase was dried and evaporated. The residue was fractionated by chromatography to yield **9** (52 mg, 75%) as an oil; $[\alpha]^{26}_D$ +28.1° (c 1.125, CH_2Cl_2); ir (neat) 1686, 1458, 1423, 1353 cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.94 (3 H, t, J = 7.3 Hz), 1.12-1.90 (14 H, m), 2.03-2.42 (4 H, m), 3.15-3.23 (1 H, m), 3.30-3.45 (1 H, m); HRms Calcd for $C_{11}H_{19}NO$: 181.1466. Found: 181.1476.

(5*S*,9*S*)-5-Propylindolizidine [(+)-indolizidine 165B] (1). To a solution of **9** (37 mg, 0.2041 mmol) in ether (4 ml) was added $LiAlH_4$ (15.5 mg, 0.408 mmol) at 0 °C. The suspension was stirred for 0.5 h at room temperature and then refluxed for 3 h. After cooling, water (15.6 µl), 20% NaOH (11 µl), and water (57 µl) were successively added to the reaction mixture. The mixture was dried and filtered through Celite. The Celite was washed with ether, and the combined organic phase was evaporated to yield **1** (27 mg, 79%) as an oil. $[\alpha]^{26}_D$ +118.2° (c 0.075, CH_2Cl_2); ir (neat) 2931, 2870, 2362, 2344, 1458, 1380 cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.91 (3 H, t, J = 7.1 Hz), 1.16-1.49 (6 H, m), 1.61-2.02 (10 H, m), 3.26-3.23 (1 H, td, J = 8.5, 2.2 Hz); ^{13}C nmr ($CDCl_3$) δ 14.55, 19.14, 20.42, 24.69, 30.52, 30.77, 30.92, 36.84, 51.50, 63.78, 65.13.

(2*R*,6*R*)-1-Benzyloxycarbonyl-2-(3-ethoxycarbonylpropyl)-6-propylpiperidine (11). To a suspension of cuprous bromide (246 mg, 1.714 mmol) in THF (4 ml) was added 3.4 M Red Al® in THF (504 ml, 1.714 mmol) at 0 °C. After being stirred for 0.5 h, a solution of *ent*-**7** (154 mg, 0.482 mmol) in THF (3 ml) was added to the mixture at -78 °C. After being stirred for 10 min at the same temperature, the reaction mixture was allowed to warm to -20 °C. After being stirred for 2 h at the same temperature, the reaction mixture was quenched with water. Saturated NH_4Cl and ether were added to the mixture. The organic layer was separated, washed with water, dried, and evaporated. The residue was fractionated

by chromatography to yield **11** (130 mg, 84%) as an oil; $[\alpha]^{26}_D$ +5.1° (c 3.51, $CHCl_3$); ir (neat) 1734, 1686 cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.89 (3 H, t, *J* = 7.1 Hz), 1.24 (3 H, t, *J* = 7.1 Hz), 1.20-1.36 (2 H, m), 1.36-2.03 (12 H, m), 2.30 (2 H, t, *J* = 7.5 Hz), 4.09 (2 H, q, *J* = 7.1 Hz), 4.23 (2 H, m), 5.12 (2 H, m), 7.35 (5 H, s); HRms Calcd for $C_{21}H_{31}NO_4$: 361.2251. found: 361.2248.

(2*R*,6*R*)-1-Benzyloxycarbonyl-2-[2-(1,3-dioxolan-2-yl)ethyl]-6-propylpiperidine (13). To a solution of **11** (165 mg, 0.457 mmol) in toluene (1.7 ml) was slowly added 0.93 M DIBAL in hexane (555 µl, 0.516 mmol) at -78 °C. After being stirred for 15 min at the same temperature, the reaction mixture was quenched with saturated NH_4Cl. Ether was added to the mixture. After being stirred for 1.5 h, anhydrous $MgSO_4$ was added to the mixture. The mixture was filtered through Celite, and the Celite was washed with ether. The combined organic phase was evaporated to yield a crude aldehyde (**12**, 124 mg). A mixture of **12** (124 mg), ethylene glycol (145 µl, 2.234 mmol), and *p*-toluenesulfonic acid monohydrate (8 mg, 0.045 mmol) in benzene (4.5 ml) was refluxed for 2 h with the Dean-Stark apparatus. After cooling, the reaction was quenched with saturated $NaHCO_3$. The organic layer was separated, washed with water, dried, and evaporated. The residue was chromatographed to yield **13** (132 mg, 80%) as an oil; $[\alpha]^{26}_D$ +9.7° (c 3.36, $CHCl_3$); ir (neat) 1684 cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.89 (3 H, t, *J* = 7.1 Hz), 1.15-1.78 (14 H, m), 3.74-4.00 (4 H, m), 4.21 (2 H, br s), 4.84 (1 H, br s), 5.12 (2 H, s), 7.34 (5 H, m); HRms Calcd for $C_{21}H_{31}NO_4$: 361.2261. Found: 361.2228.

(2*R*,6*R*)-2-[2-(1,3-Dioxolan-2-yl)ethyl]-6-propylpiperidine (10). A suspension of **13** (80 mg, 0.223 mmol) and palladium hydroxide (8 mg) in methanol (2.5 ml) was stirred under a hydrogen atmosphere for 7.5 h. The insoluble materials were removed by filteration through Celite, and the filtrate was evaporated to yield **10** (51mg, 100%) as an oil; $[\alpha]^{26}_D$ +2.7° (c 0.925, $CHCl_3$); ir (neat) 2928, 1125, 1037 cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.91 (3 H, t, *J* = 6.6 Hz), 1.01 (2 H, m), 1.18-1.83 (12 H, m), 2.48 (2 H, m), 3.77-4.04 (4 H, m), 4.86 (1 H, t, *J* = 4.7 Hz); ^{13}C nmr ($CDCl_3$) δ 14.25, 19.12, 24.85, 30.47, 31.62, 32.63, 32.68, 39.65, 56.85, 56.90, 64.88, 64.94, 104.65; HRms Calcd for $C_{13}H_{25}NO_2$: 227.1886. found: 227.1893; Anal. Calcd for $C_{13}H_{25}NO_2$: C, 68.68; H, 11.08; N, 6.16. Found: C, 68.63; H, 11.26; N, 6.10.

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14. We are grateful for Professor H. P. Husson for spectral data for **10**.

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