

CHEMOENZYMATIC ENANTIOSELECTIVE SYNTHESIS OF (-)-INDOLIZIDINE 167 B

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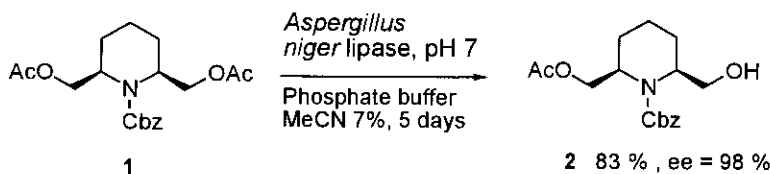
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Abstract - (5*R*, 9*R*)-(-)-Indolizidine 167 B was synthesized in 8 steps from *N*-benzyloxycarbonyl-*cis*-2(*R*)-acetoxymethyl-6(*S*)-hydroxymethylpiperidine (**2**) in an overall yield of 60%. This starting material was obtained from enzymatic desymmetrization of the corresponding *meso* diacetate (**1**).

The piperidine ring is a very common structural subunit in natural products and synthetic bioactive compounds. The interest in these compounds is well displayed by the wealth of published material detailing their sources, biological activities, and syntheses.¹ Indolizidines (also called gephyrotoxins) are piperidine alkaloids isolated from the skin secretions of neotropical frogs of the family Dendrobatidae.² These natural products appear to serve as defensive agents. Some of these compounds are non-competitive blockers of neuromuscular transmission by binding to the acetylcholine receptor complex.³

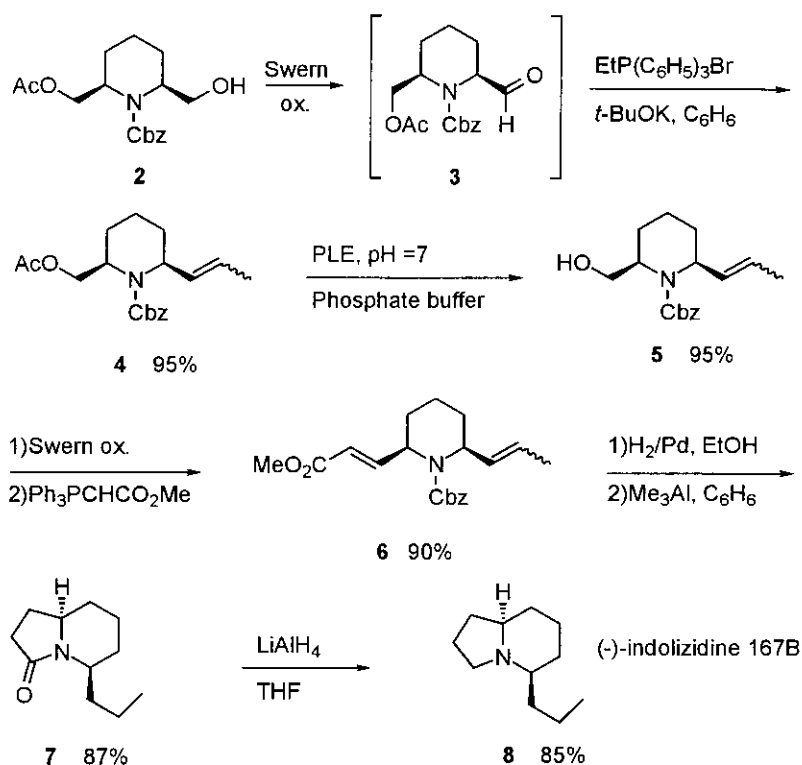
(-)-Indolizidine 167 B was isolated in minute quantities by Daly *et al.*⁴ from the skin secretions of neotropical frogs found in Panama. Several syntheses of racemic and enantiopure indolizidine 167 B have been reported.⁵ In this paper, we disclose the chemoenzymatic enantioselective synthesis of (-)-indolizidine 167 B starting with (2*R*, 6*S*)-monoacetate (**2**).

Recently, we described the enantioselective hydrolysis of *N*-benzyloxycarbonyl-*cis*-2,6-diacetoxymethylpiperidine (**1**) in the presence of *Aspergillus niger* lipase⁶ (**Scheme 1**). This desymmetrization provided the corresponding 2*R*,6*S* monoacetate (**2**) with high enantiomeric excess (ee ≥ 98%) and good chemical yield (83%).



Scheme 1

Swern oxidation of **2** gave the highly unstable aldehyde (**3**), which, after work up, was immediately added to the already prepared ethyl Wittig ylide to afford the olefin (**4**) in a mixture of *cis:trans* isomers (9/1) (**Scheme 2**). This ratio was measured by ^1H NMR. No special effort was made to completely isolate the two isomers, since one of the latter steps was the hydrogenation of the double bond. The acetate group was hydrolyzed in phosphate buffer in the presence of pig liver esterase to give alcohol (**5**).



Scheme 2

Swern oxidation of **5** gave the corresponding unstable aldehyde which was added to methyl (triphenylphosphoranylidene)acetate immediately after workup, and olefin (**6**) was obtained as the sole *trans* isomer on the newly formed double bond. Catalytic hydrogenation of **6** in the presence of palladium as a catalyst caused the reduction of the two double bonds and removal of the *N*-Cbz protecting group; the intermediate amino ester was treated with trimethylaluminum to give lactam (**7**). Finally, reduction of **7** with lithium aluminum hydride gave (5*R*,9*R*)-(-)-indolizidine 167 B (**8**).

In summary, the natural enantiomer of indolizidine 167 B was synthesized in 8 steps and 60% overall yield starting with enantiopure piperidine (**2**) obtained by enzymatic desymmetrization of the corresponding *meso* diacetate (**1**).

EXPERIMENTAL

IR spectra were recorded using a Bomem MB-100 spectrophotometer. NMR spectra were recorded in CDCl_3 solutions at 300 MHz (^1H), 282 MHz (^{19}F), 75 MHz (^{13}C) on a Bruker AC-300 instrument. Optical rotation values were obtained from a JASCO DIP-300 polarimeter (c as g of compound per 100 mL). Elemental analyses were performed on a Carlo Erba 1106 instrument. Column purifications were conducted by flash chromatography on silica gel 60 (230-400 mesh). Pig liver esterase was from Sigma or Amano.

(2*S*,6*R*)-1-Benzoyloxycarbonyl-2-(1-propenyl)-6-acetoxymethylpiperidine (**4**).

To a stirred solution of 2 equiv. of oxalyl chloride (0.13 mL, 1.57 mmol) in anhydrous CH_2Cl_2 (2.5 mL) at -78°C under N_2 was added 3 equiv. of anhydrous DMSO (0.167 mL, 2.36 mmol) in anhydrous CH_2Cl_2 (0.8 mL) dropwise and the mixture allowed to react for 5 min at -78°C . The alcohol (**2**) (253.5 mg, 0.79 mmol) in anhydrous CH_2Cl_2 (0.8 mL) was added, and the reaction mixture was stirred for 1 h at -78°C . On addition of 4 equiv. (320 mg) of anhydrous Et_3N , the dry ice/acetone bath was removed, and the reaction temperature was left to go to rt. The reaction was diluted with CH_2Cl_2 (4 mL) and then poured into 10 mL of CH_2Cl_2 / 5 mL of 10% NH_4OH solution. The aqueous phase was extracted twice with CH_2Cl_2 and the combined CH_2Cl_2 fractions were washed with brine, dried (MgSO_4) and evaporated. The residue was dissolved in ether and filtered through a MgSO_4 pad and the ether evaporated. The crude aldehyde (**3**) was used immediately in the next step of the synthesis (Wittig reaction). All attempts to purify or analyze the aldehyde resulted in its degradation.

Anhydrous benzene (6 mL) and potassium *tert*-butoxide (265 mg, 2.36 mmol) were mixed at rt under N_2 , and $\text{Ph}_3\text{P}(\text{Et})\text{Br}$ (877.5 mg, 2.35 mmol) was added to the mixture. After the mixture was stirred for 1.5 h, the crude aldehyde (**3**) (0.79 mmol, assuming 100% yield from the Swern oxidation of **2**) was added with 3 mL of anhydrous benzene to the reaction mixture, and it was refluxed for 3 h. The reaction mixture was then partitioned between 20 mL of ethyl acetate / 10 mL of 10% $\text{Na}_2\text{S}_2\text{O}_3$ solution, and the aqueous phase was extracted three times with ethyl acetate. The organic fractions were dried (MgSO_4) and evaporated. The crude product was purified by flash chromatography beginning with pure CH_2Cl_2 and progressing to 5% EtOAc / 95% CH_2Cl_2 to give **4** (248 mg, 95%, *cis:trans* 9:1) as a colorless oil. Data for *cis*-**4** obtained pure in fractions of the chromatography: $[\alpha]_D^{25} +63.2^\circ$ (c 0.73, CHCl_3); IR (neat) 2943, 1742, 1692 cm^{-1} ; ^1H NMR (CDCl_3) 1.55 (d, 3H, $J=5.0$ Hz), 1.36-1.89 (m, 6H), 1.91 (s, 3H), 3.89-3.94 (dd, 1H, $J_1=6.1$ Hz, $J_2=10.5$ Hz), 4.16-4.22 (dd, 1H, $J_1=8.9$ Hz, $J_2=10.5$ Hz), 4.43 (m, 1H), 4.48 (m, 1H), 5.02-5.11 (m, 2H), 5.37-5.50 (m, 2H), 7.19-7.28 (m, 5H); ^{13}C NMR (CDCl_3) 170.69, 155.70, 136.64, 130.49, 128.27, 127.76, 126.32, 67.07, 64.23, 48.72, 47.13, 29.87, 24.90, 20.69, 14.57, 12.85; HRMS (CI, isobutane) calcd for $\text{C}_{19}\text{H}_{25}\text{NO}_4$ (MH^+) 332.1862, found 332.1867 $\pm$ 0.0010. Anal. Calcd for $\text{C}_{19}\text{H}_{25}\text{NO}_4$: C, 68.86; H, 7.60; N, 4.23. Found: C,

68.56; H, 7.73; N, 4.37.

(2*S*,6*R*)-1-Benzylloxycarbonyl-2-(1-propenyl)-6-hydroxymethylpiperidine (5).

The ester (**4**) (40 mg, 0.12 mmol) was suspended in a phosphate buffer at pH 7.0 and pig liver esterase (40 mg) was added to the mixture. The mixture was stirred at rt and the pH of the solution was maintained at its initial value by addition of 0.1 M aqueous NaOH. After the addition of 1 equivalent of NaOH (24 h), the aqueous layer was extracted 3 times with EtOAc. The combined organic fractions were dried (MgSO₄) and evaporated. The crude product was purified by flash chromatography (100% CH₂Cl₂ to 20% EtOAc / 80% CH₂Cl₂) to give **5** (33 mg, 95%) as a colorless oil. Data for *cis*-**5** obtained pure in fractions of the chromatography: $[\alpha]_D^{25} +52.2^\circ$ (c 1.1, CHCl₃); IR (neat) 3400, 2910, 1680 cm⁻¹; ¹H NMR (CDCl₃) 1.60 (d, 3H, J = 6.2 Hz), 1.48-1.71 (m, 6H), 3.62-3.74 (m, 2H), 4.39 (m, 1H), 5.08-5.13 (m, 3H), 5.46-5.62 (m, 2H), 7.28-7.34 (m, 5H); ¹³C NMR (CDCl₃) 156.81, 136.54, 130.82, 128.30, 127.78, 126.08, 67.24, 64.55, 52.09, 47.33, 29.89, 24.69, 14.87, 12.78; HRMS (CI, NH₃) calcd for C₁₇H₂₃NO₃ (MH⁺) 290.1756, found 290.1761 ± 0.0008. Anal. Calcd for C₁₇H₂₃NO₃: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.67; H, 8.21; N, 4.97.

(2*R*,6*S*)-1-Benzylloxycarbonyl-2-(3-methoxycarbonyl-1-propenyl)-6-(1-propenyl)piperidine (6).

The Swern oxidation of alcohol (**5**) (228 mg, 0.79 mmol) was performed in the same manner as described for **2** (see above). To a solution of the crude aldehyde (0.79 mmol, assuming 100% yield from the Swern oxidation of **5**) in anhydrous benzene (8 mL), 3.0 equiv. of methyl (triphenylphosphoranylidene)acetate (792 mg, 2.37 mmol) was added, and the mixture was refluxed for 3 h. The reaction mixture was then partitioned between 20 mL of CH₂Cl₂ / 10 mL of 10% Na₂S₂O₃, and the aqueous phase was extracted three times with CH₂Cl₂. The organic fractions were dried (MgSO₄) and evaporated. The crude product was purified by flash chromatography beginning with pure CH₂Cl₂ and progressing to 5% ethyl acetate / 95% CH₂Cl₂ to give **6** (244 mg, 90%) as a colorless oil. $[\alpha]_D^{25} +111.2^\circ$ (c 1.09, CHCl₃); IR (neat) 2944, 1717, 1693, 1655 cm⁻¹; ¹H NMR (CDCl₃) 1.61 (d, 3H, J = 6.5 Hz), 1.55-1.91 (m, 6H), 3.73 (s, 3H), 4.96 (m, 1H), 5.13 (m, 3H), 5.47-5.58 (m, 2H), 5.89 (d, 1H, J = 17 Hz), 6.97-7.05 (dd, 1H, J₁ = 5.1 Hz, J₂ = 17 Hz), 7.33-7.25 (m, 5H); ¹³C NMR (CDCl₃) 166.69, 155.48, 146.36, 136.44, 130.13, 128.31, 127.92, 127.87, 125.73, 121.04, 67.29, 51.44, 50.78, 47.58, 30.01, 27.59, 14.96, 12.70; HRMS (EI, 70 eV) calcd for C₂₀H₂₅NO₄ (M⁺) 343.1783, found 343.1789 ± 0.0010. Anal. Calcd for C₂₀H₂₅NO₄: C, 69.95; H, 7.34; N, 4.08. Found: C, 70.18; H, 7.52; N, 4.19.

(5*R*,9*R*)-5-Propylindolizidin-3-one (7).

Compound (**6**) (140 mg, 0.407 mmol) was dissolved in 10 mL of freshly, degassed absolute ethanol.

Pearlman's catalyst ($\text{Pd}(\text{OH})_2$ 20% on carbon, 20 mg) was suspended in the solution, and the mixture was hydrogenated at 40 psi for 15 h. After filtration of the mixture through a pad of Celite, the solvent was evaporated to give the crude intermediate amino ester. To a solution of this crude amino ester in benzene (10 mL) was added dropwise 1.2 equiv. of trimethylaluminum in toluene (2.0 M, 0.245 mL, 0.49 mmol). The pale yellow solution was stirred for 2 h at rt and then refluxed overnight. The mixture was cooled to rt and then quenched with 1% HCl. After separation of the phases, the aqueous layer was extracted 3 times with CH_2Cl_2 . The combined organic fractions were dried (MgSO_4) and evaporated. Flash chromatography (40% EtOAc / 60% hexane to pure EtOAc) gave lactam (7) as an oil (64 mg, 87%). $[\alpha]_D^{25} - 27.3^\circ$ (c 1.165, CH_2Cl_2), lit.,^{5b} $[\alpha]_D^{25} - 27.6^\circ$ (c 0.021, CH_2Cl_2), lit.,^{5d} $[\alpha]_D^{25} + 28.1^\circ$ (c 1.125, CH_2Cl_2); IR (neat) 2932, 2870, 1688, 1423, 1310 cm^{-1} ; ^1H NMR (CDCl_3) 0.92 (t, 3H, $J = 7.3$ Hz), 1.20-1.52 (m, 6H), 1.53-1.85 (m, 4H), 2.02-2.14 (m, 1H), 2.28-2.42 (m, 3H), 3.13-3.18 (m, 1H), 3.33-3.42 (m, 1H); ^{13}C NMR (CDCl_3) 174.19, 59.54, 57.23, 34.41, 31.80, 31.70, 29.40, 24.94, 22.58, 19.93, 13.95.

(5*R*,9*R*)-5-Propylindolizidine ((-)-Indolizidine 167 B, 8).

To a solution of lactam (7) (64.4 mg, 0.355 mmol) in ether (4 mL) was added 2 equiv. of LiAlH_4 (27 mg, 0.71 mmol) at 0 $^\circ\text{C}$. The suspension was stirred for 0.5 h at rt and then refluxed for 3 h. After cooling to rt, water (27 μL), 20% NaOH (19 μL), and water (100 μL) were added, and the mixture was dried (Na_2SO_4) and filtered through a bed of Celite. The combined organic phases were evaporated and the crude product was purified by chromatography (Al_2O_3 , neutral, 100% hexane to 10% ether / 90% hexane) to give (-)-indolizidine 167 B 8 as a volatile oil (50 mg, 85%). $[\alpha]_D^{25} - 114.21^\circ$ (c 0.465, CH_2Cl_2); lit.,⁵ⁱ $- 111.3^\circ$ (c 1.3, CH_2Cl_2), lit.,^{5b} $[\alpha]_D^{25} - 116.6^\circ$ (c 0.0042, CH_2Cl_2); IR (neat) 2922, 2464, 2366, 2344, 1458, 1380 cm^{-1} ; ^1H NMR (CDCl_3) 0.89 (t, 3H, $J = 7.1$ Hz), 1.06-1.48 (m, 8H), 1.56-1.87 (m, 8H), 1.91-2.00 (q, 1H, $J = 8.8$ Hz), 3.24-3.42 (td, 1H, $J_1 = 2.1$ Hz, $J_2 = 8.8$ Hz); ^{13}C NMR (CDCl_3) 65.08, 63.66, 51.26, 36.55, 30.58, 30.28, 24.46, 20.21, 18.95, 14.31.

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