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SYNTHESIS OF (-)-5-EPIINDOLIZIDINE 167B AND FORMAL SYNTHESIS OF 5*E*, 9*Z*-INDOLIZIDINE 223AB

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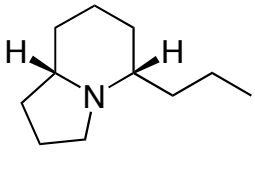
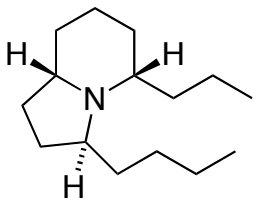
Abstract – Synthesis of (-)-5-epiindolizidine **167B** has been described using the highly stereoselective reduction of the enyne (**2**) as the key step.

INTRODUCTION

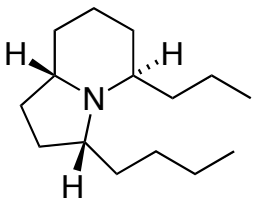
A number of indolizidine alkaloids have been found in amphibian skin,[1] and many of these alkaloids showed intriguing biological activities.[2] Among them, the indolizidine **167B** is one of minor alkaloid detected in unidentified dendrobatid frogs,[3] and numerous syntheses of this alkaloid have been reported to date.[4] On the other hand, 5-epi-167B is also the target molecule for the evaluation of new synthetic strategy.[5] All of possible stereoisomers of indolizidine **223AB** have been detected in the skin extracts of dendrobatid frog or bufonid toad.[1] Here we would like to report the synthesis of 5-epi-**167B** starting from the enol triflate (**1**).[6]



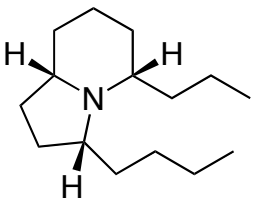
167B



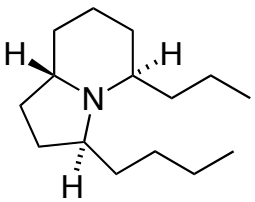
5*E*,9*E*-**223AB**



5*E*,9*Z*-**223AB**



5*E*,9*E*-**223AB**



5*Z*,9*E*-**223AB**

RESULTS AND DISCUSSION

The synthesis of 5-epi-**167B** (**7**) began with the enol triflate (**1**),[6] which was converted to enyne (**2**) using the Sonogashira-type coupling reaction[7] in good yield. Reduction of **2** with $NaBH_3CN$ in the presence of TFA provided the alcohol (**3**) in the single stereoisomer.[8] Elongation of the carbon-chain in **3** was

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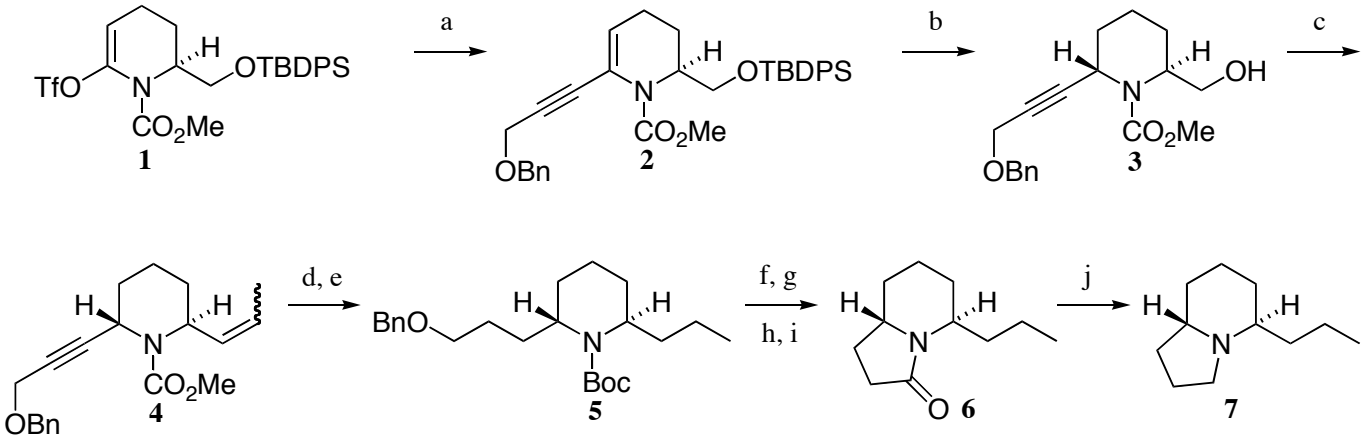
This paper is dedicated to the memory of the Emeritus Professor Kenji Koga of Tokyo University.

performed by the Wittig reaction after Swern oxidation of **3** to afford **4**. Hydrogenation of both double and triple bonds in **4** followed by conversion of the methyl carbamate to *t*-butyl carbamate gave ether (**5**). Hydrogenolysis of the benzyl protecting group in **5**, oxidation of the resulting alcohol to carboxylic acid in 2 steps, followed by deprotection of the Boc group with TFA and lactamization of the resulting amino acid using the Shioiri's reagent (DEPC)[9] gave rise to the lactam (**6**). Finally the reduction of **6** with $LiAlH_4$ furnished the 5-epi-**167B** (**7**), whose spectral data were completely identical with those for the reported values. Hart *et al.*[10] reported the racemic synthesis of 5*E*, 9*Z*-**223AB**, which is detected in skin extracts of the bufonid toad, from the racemic **6**. This synthesis means the formal synthesis of 5*E*, 9*Z*-**223AB**.



Scheme 1: a: $Pd(Ph_3P)_4$, $BnOCH_2CCH$, CuI, *i*-Pr_2NH, THF, rt (91%); b: $NaBH_3CN$, TFA, CH_2Cl_2, -78~-10 °C (65%); c: Swern ox. then $EtP^+Ph_3Br^-$, *n*-BuLi, THF, 0 °C~rt (73%); d: H_2, 10% Pd-C, EtOAc; e: *n*-PrSLi, HMPA, THF, 0 °C~rt then Boc_2O, NaOH, dioxane-H_2O , 0 °C~rt (88%); f: 20% $Pd(OH)_2$ on carbon, H_2, 4 atm, MeOH; g: Swern ox. then $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH-H_2O; h: TFA, CH_2Cl_2, rt; i: DEPC, DMF, rt (84%); j: $LiAlH_4$, THF, reflux (90%)

EXPERIMENTAL

General ^1H and ^{13}C NMR spectra were taken on a Varian Gemini 300 or Unity Plus 500 spectrometer. ^1H NMR spectra were recorded at the indicated field strength as solutions in $CDCl_3$ unless otherwise indicated. Chemical shifts are given in parts per million (ppm, δ) downfield from TMS and are referenced to $CHCl_3$ (7.26 ppm) as internal standard. ^{13}C NMR spectra were recorded at the indicated field strength as solutions in $CDCl_3$ unless otherwise indicated. Chemical shifts are given in parts per million (ppm, δ) downfield from TMS and are referenced to the center line of $CDCl_3$ (77.0 ppm) as internal standard. Carbon signals were assigned by a DEPT pulse sequence, q = methyl, t = methylene, d = methyne, and s = quaternary carbons. IR spectra were measured with a Perkin-Elmer 1600 series FT-IR spectrophotometer. MS spectra and HRMS spectra were measured on a JEOL JMS-AX505HAD mass spectrometer. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. Column chromatography was performed on Merck silica gel 60 (No 7734-5B) or (No

9385). Elemental analysis was performed by the micro analytical laboratory on this University.

Methyl (2*S*)-(-)-6-(3-Benzyloxyprop-1-ynyl)-2-*tert*-butyldiphenylsilyloxymethyl-3,4-dihydro-2*H*-pyridine-1-carboxylate (2)

To a stirred solution of CuI (100 mg, 0.53 mmol), $Pd(Ph_3P)_4$ (581 mg, 0.5 mmol) in *i*-Pr_2NH (30 mL) and THF (15 mL) was added a solution of **1** (2.8 g, 5.03 mmol) and $BnOCH_2CCH$ (2.2 g, 15.1 mmol) in THF (15 mL) *via* a double-tipped stainless steel needle at rt. The resulting solution was stirred at rt for 20 h. The reaction was quenched with satd. NH_4Cl (aq), and the aqueous mixture was extracted with Et_2O (50 mL x 3). The organic extracts were combined, dried over $MgSO_4$, and evaporated to give pale brown oil, which was chromatographed on SiO_2 (80 g, hexane : acetone= 50 : 1~20 : 1) to afford 2 (2.53 g, 91%) as pale yellow oil.

IR (neat) 1714, 1626 cm^{-1}; ^1H NMR (500 MHz) δ 1.10 (9H, s), 1.80-1.84 (1H, m), 1.97-2.03 (1H, m), 2.09-2.13 (2H, m), 3.61 (1H, t-like, *J* = 10.1 Hz), 3.75 (3H, s), 3.76-3.79 (1H, m), 4.34 (2H, s), 4.63 (1H, br), 4.65 (2H, s), 5.60 (1H, t-like, *J* = 4.0 Hz), 7.29-7.48 (11H, m), 7.69-7.72 (4H, m); ^{13}C NMR (75 MHz) δ 19.21 (s), 20.73 (t), 21.89 (t), 26.75 (q), 52.54 (q), 52.81 (d), 61.06 (t), 68.25 (t), 72.76 (t), 78.05 (s), 85.06 (s), 119.60 (s), 121.09 (d), 127.45 (d), 128.14 (d), 129.47 (d), 133.09 (s), 133.31 (s), 135.31 (d), 135.36 (d), 137.87 (s), 153.92 (s); MS: 553 (M^+); HRMS: Calcd for $C_{34}H_{39}NO_4Si$ 553.2646, Found 553.2632; $[\alpha]_D^{26}$ –87° (*c* 1.17, $CHCl_3$).

Methyl (2*S*, 6*S*)-(-)-2-(3-Benzyloxyprop-1-ynyl)-6-hydroxymethylpiperidine-1-carboxylate (3)

To a stirred suspension of **2** (1.16 g, 2.1 mmol) and $NaBH_3CN$ (693 mg, 10.49 mmol) in CH_2Cl_2 (30 mL) was added TFA (1.62 mL, 20.98 mmol) at –78 °C, and the resulting suspension was stirred at –78 ~ -10 °C for 1 h. The reaction was quenched with satd. $NaHCO_3$ (aq.), and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (15 mL x 4), and the organic layer and extracts were combined, dried over $MgSO_4$, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (20 g, hexane : acetone = 25 : 1-4 : 1) to afford **3** (432 mg, 65%) along with small amounts of desilylated product of **2**.

3: IR (neat) 3445, 1673 cm^{-1}; ^1H NMR (500 MHz) δ 1.59-1.82 (5H, br m), 1.88-1.92 (1H, m), 3.73 (3H, s), 3.79-3.89 (3H, br m), 4.21 (2H, s), 4.60 (2H, s), 5.23 (1H, br), 7.30-7.38 (5H, m); ^{13}C NMR (75 MHz) δ 19.42 (t), 27.35 (t), 29.95 (t), 46.65 (d), 52.91 (q), 57.26 (d), 57.41 (t), 64.69 (t), 71.61 (t), 80.66 (s), 84.38 (s), 127.76 (d), 127.87 (d), 128.29 (d), 137.12 (s), 155.50 (s); MS: 317 (M^+); HRMS: Calcd for $C_{18}H_{23}NO_4$ 317.1626, Found 317.1644; $[\alpha]_D^{26}$ –113.5° (*c* 1.15, $CHCl_3$).

Desilylated product of **2**: IR (neat) 3448, 1711 cm^{-1}; ^1H NMR (500 MHz) δ 1.82-1.92 (2H, m), 2.09-2.15 (2H, m), 2.21 (1H, br), 3.55 (1H, dd, *J* = 11.0, 6.0 Hz), 3.71 (1H, dd, *J* = 11.0, 8.2 Hz), 3.77 (3H, s), 4.31 (2H, s), 4.51-4.56 (1H, m), 4.62 (2H, s), 5.67 (1H, t-like, *J* = 4.1 Hz), 7.26-7.37 (5H, m); ^{13}C NMR (75 MHz) δ 20.16 (t), 22.78 (t), 53.10 (q), 53.88 (d), 57.76 (t), 61.32 (t), 71.48 (t), 82.94 (s), 83.91 (s), 118.89

(s), 122.93 (d), 127.69 (d), 127.93 (d), 128.26 (d), 137.30 (s), 154.95 (s); MS: 315 (M^+); HRMS: Calcd for $C_{18}H_{21}NO_4$ 315.1469, Found 315.1475.

Methyl (2*S*,6*S*)-2-(3-Benzyloxyprop-1-ynyl)-6-propenylpiperidine-1-carboxylate (4)

To a stirred solution of $(COCl)_2$ (0.24 mL, 2.77 mmol) in CH_2Cl_2 (6 mL) was added DMSO (0.39 mL, 5.51 mmol) at –78 °C, and the reaction mixture was stirred at –78 °C for 5 min. To the resulting mixture was added a solution of **3** (584 mg, 1.84 mmol) in CH_2Cl_2 (4 mL) *via* a double-tipped stainless steel needle. After the reaction mixture was stirred at –78 °C for 30 min, Et_3N (1.1 mL, 7.94 mmol) was added to the reaction mixture. The reaction mixture was warmed to 0 °C for 1 h, and quenched with H_2O. The aqueous mixture was diluted with Et_2O (50 mL), and the organic layer was separated, washed with brine, dried, and evaporated to give pale yellow oil, which was used directly in the next step.

To a stirred suspension of $EtP^+Ph_3Br^-$ (3.43 g, 9.22 mmol) in THF (10 mL) was added a solution of *n*-BuLi (1.6 M in hexane, 5.2 mL, 8.33 mmol) at 0 °C, and the resulting orange solution was stirred at 0 ° C for 5 min. To the mixture was added a solution of the above aldehyde in THF (6 mL) via a double-tipped stainless steel needle. The reaction mixture was stirred at room temperature for 4 h, and quenche wwith H_2O. The aqueous mixture was diluted with Et_2O (30 mL), and the organic layer was separated. The aqueous layer was extracted with Et_2O (15 mL x 3), and the organic layer and extracts were combined, dried over $MgSO_4$, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (25 g, hexane : acetone = 90 : 1-40 : 1) to afford **4** (439 mg, 73%) as pale yellow oil.

IR (neat) 1677 cm^{-1}; ^1H NMR (500 MHz) δ 1.54-1.60 (1H, m), 1.63-1.74 (1H, m), 1.70 (3H, d, J = 6.5 Hz), 1.85-1.93 (3H, m), 2.00-2.19 (1H, m), 3.71 (3H, s), 4.22 (2H, s), 4.59-4.63 (1H, m), 4.61 (2H, s), 5.04 (1H, br), 5.46-5.57 (2H, m), 7.30-7.39 (5H, m).

tert-Butyl (2*S*,6*R*)-(-)-2-(3-Benzyloxypropyl)-6-propylpiperidine-1-carboxylate (5)

To a stirred solution of **4** (194 mg, 0.59 mmol) in EtOAc (15 mL) was added 10% Pd-C (20 mg), and the resulting suspension was hydrogenated under hydrogen atmosphere at 1 atm for 3 days. The catalyst was removed by filtration and the filtrate was evaporated to give colorless oil, which was used directly in the next step.

To a stirred solution of *n*-PrSH (0.53 mL, 5.88 mmol) in HMPA (2 mL) was added a solution of *n*-BuLi (1.6 M, 3.52 mL, 5.85 mmol) at 0 °C, and the reaction mixture was stirred at 0 ° C for 30 min. To the mixture was added a solution of the hydrogenated product obtained above in THF (2 mL) *via* a double-tipped stainless steel needle at 0 °C, and then the reaction mixture was stirred at room temperature for 52 h. The reaction was quenched with 28% NH_3 (aq.), and the aqueous mixture was extracted with Et_2O (10 mL x 10). The extracts were combined, dried over K_2CO_3, and evaporated to give pale yellow oil, which was used directly in the next step.

To a stirred solution of the amine obtained above in dioxane (4 mL) and H_2O (2 mL) were added NaOH

(70 mg, 1.76 mmol) and Boc_2O (350 mg, 1.60 mmol) at 0 °C, and the resulting mixture was stirred at rt for 17 h. The reaction mixture was diluted with CH_2Cl_2 and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (10 mL x 4), and the organic layer and extracts were combined, dried over $MgSO_4$, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (20 g, hexane : acetone = 100 : 1-60 : 1) to afford **5** (195 mg, 88%) as pale yellow oil.

IR (neat) 1669 cm^{-1}; ^1H NMR (500 MHz) δ 0.93 (3H, t, *J* = 7.2 Hz), 1.28-1.36 (2H, m), 1.41-1.50 (1H, m), 1.46 (9H, s), 1.53-1.82 (11H, m), 3.46-3.54 (2H, m), 3.72 (2H, br), 4.52 (2H, s), 7.27-7.37 (5H, m); ^{13}C NMR (75 MHz) δ 14.21 (q), 15.32 (t), 20.39 (t), 24.68 (t), 24.87 (t), 27.44 (t), 28.66 (q), 30.73 (t), 36.29 (t), 52.00 (d), 52.05 (d), 70.40 (t), 72.81 (t), 127.35 (d), 127.50 (d), 128.21 (d), 138.52 (s), 155.44 (s); MS: 375 (M^+); HRMS: Calcd for $C_{23}H_{37}NO_3$ 375.2771, Found 375.2759; $[\alpha]_D^{26}$ –29.9° (*c* 1.30, $CHCl_3$).

(5*R*,9*S*)-(-)-5-Propylhexahydroindolizin-3-one (6)

To a solution of **5** (190 mg, 0.51 mmol) in MeOH (10 mL) was added 20% $Pd(OH)_2$ on carbon (50 mg), and the resulting suspension was hydrogenated at 4 atom. for 20 h. The catalyst was removed by filtration and the filtrate was evaporated to give colorless oil, which was used directly in the next step.

To a stirred solution of $(COCl)_2$ (0.1 mL, 1.15 mmol) in CH_2Cl_2 (2 mL) was added DMSO (0.17 mL, 2.4 mmol) at –78 °C, and the reaction mixture was stirred at –78 °C for 5 min. To the resulting mixture was added a solution of the alcohol obtained above in CH_2Cl_2 (2 mL) via a double-tipped stainless steel needle. After the reaction mixture was stirred at –78 °C for 30 min, Et_3N (0.6 mL, 4.34 mmol) was added to the reaction mixture. The reaction mixture was warmed to 0 °C for 1 h, and quenched with H_2O. The aqueous mixture was diluted with Et_2O (30 mL), and the organic layer was separated, washed with brine, dried over $MgSO_4$, and evaporated to give pale yellow oil, which was used directly in the next step.

To a stirred solution of the aldehyde obtained above in *t*-BuOH (6 mL) were added 2-methyl-2-butene (1 mL, 10.1 mmol), $NaH_2PO_4 \bullet 2H_2O$ (790 mg, 5.10 mmol), and then a solution of $NaClO_2$ (344 mg, 3.04 mmol) in H_2O (2 mL) at 0 °C, and the resalting mixture was stirred at room temperature for 1 h. The reaction was quenched with satd. $NaHSO_3$ (aq.), and the aqueous mixture was acidified with 10% HCl (aq.), saturated with NaCl, and extracted with EtOAc (15 mL x 5). The extracts were combined, dried over $MgSO_4$, and evaporated to give pale yellow oil, which was used directly in the next step.

To a stirred solution of the acid obtained above in CH_2Cl_2 (2 mL) was added TFA (0.23 mL, 3.03 mmol) at 0 °C, and the reaction mixture was stirred at room teperature for 5 h. The volatiles were removed, and the residue was dissolved in DMF (1 mL). To the solution were added DEPC (0.11 mL, 0.76 mmol) and Et_3N (0.21 mL, 1.51 mmol) at 0 °C, and the reaction mixture was stirred at rt for 1 h. The volatiles were removed, and the residue was chromatographed on SiO_2 (20 g, hexane : acetone = 20 : 1-15 : 1) to afford **6** (77 mg, 84%) as pale yellow oil.

IR (neat) 1684 cm^{-1}; ^1H NMR (500 MHz) δ 0.93 (3H, t, *J* = 7.3 Hz), 1.10-1.19 (1H, m), 1.20-1.44 (4H, br

m), 1.46-1.66 (6H, m), 1.86 (1H, d-like, *J* = 14.0 Hz), 2.15-2.22 (1H, m), 2.37 (1H, t-like, *J* = 6.8 Hz), 3.54-3.60 (1H, m), 4.21-4.25 (1H, m); ^{13}C NMR (75 MHz) δ 14.13 (q), 19.05 (t), 19.71 (t), 25.37 (t), 27.51 (t), 30.39 (t), 32.33 (t), 33.95 (t), 47.91 (d), 53.21 (d), 173.40 (s); MS: 181 (M^+); HRMS: Calcd for $C_{11}H_{19}NO$ 181.1466, Found 181.1459; Anal. Calcd. for $C_{11}H_{19}NO$ C, 72.88; H, 10.56; N, 7.73. Found C, 72.81; H, 10.53; N, 7.72; $[\alpha]_D^{26}$ –47.7° (*c* 2.06, $CHCl_3$).

(5*R*,9*S*)-(-)-5-Propyloctahydroindolizine (7)

To a stirred solution of **6** (77 mg, 0.42 mmol) in THF (10 mL) was added $LiAlH_4$ (32 mg, 0.85 mmol), and the resulting suspension was refluxed for 5 h. After cooling, the reaction was quenched with 10% NaOH (aq), and the mixture was extracted with $CHCl_3$ (10 mL x 5). The organic extracts were combined, dried over K_2CO_3, and evaporated to give **7** (63 mg, 90%) as colorless oil.

IR (neat) 2956, 2929, 2870, 2801, 1458, 1379, 1263, 1171, 1139, 1093, 899 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.88 (3H, t, *J* = 7.0 Hz), 1.03-1.81 (14H, br m), 2.49 (1H, br m), 2.60 (1H, q-like, *J* = 8.0 Hz), 2.77 (1H, td-like, *J* = 8.5, 3.0 Hz), 2.90 (1H, br m); ^{13}C NMR (75 MHz) δ 14.48 (q), 19.40 (t), 20.91 (t x 2), 25.63 (t), 27.67 (t), 30.69 (t), 31.36 (t), 48.72 (t), 55.03 (d), 55.17 (d); MS: 167 (M^+); HRMS: Calcd for $C_{11}H_{21}N$ 167.1673, Found 167.1678; $[\alpha]_D^{26}$ –9.3° (*c* 3.04, CH_2Cl_2), lit.,[5] $[\alpha]_D^{26}$ +9.59° (*c* 0.75, CH_2Cl_2).

ACKNOWLEDGEMENTS

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