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CHIRAL SYNTHESIS OF POISON-FROG ALKALOIDS **251N** AND **221K**

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Abstract – The chiral synthesis of 8-butyl 5-substituted poison-frog alkaloids **251N** and **221K** has been achieved, and the relative stereochemistry of natural **251N** was determined by the present chiral synthesis.

INTRODUCTION

The 5,8-disubstituted indolizidines are found in amphibian skin as the largest subclass of poison-frog alkaloids.¹ We recently reported the structural elucidation of the 8-butyl 5-propyl indolizidine poison-frog alkaloid **223V**, and synthetic studies on **223I**.² Furthermore, we showed one of the diastereoisomers of 8-butyl-5-propylindolizidine (8*Z*-, 9*E*-**223V** designated as compound III in reference 2) selectively inhibited the $\alpha 7$ nicotinic receptor.³ As part of a program directed at studying the synthesis of biologically active alkaloids,⁴ we would like to report here the chiral syntheses of poison-frog alkaloids **251N** and **221K**, which again possess the butyl substituent at the 8-position, to further investigate the inhibitory effect of such indolizidines to nicotinic receptors.

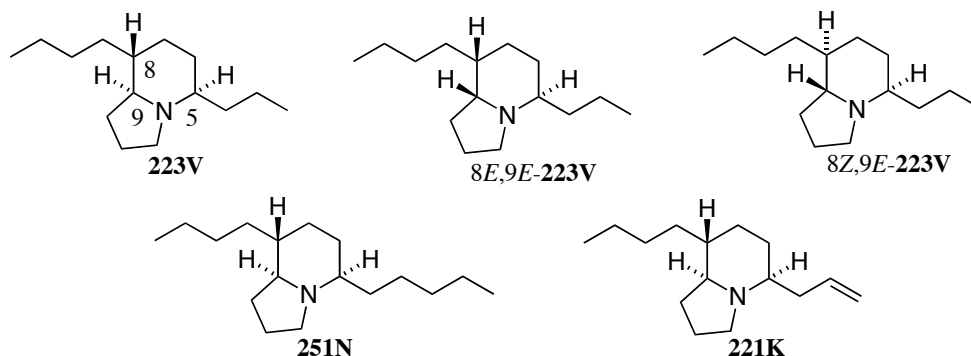
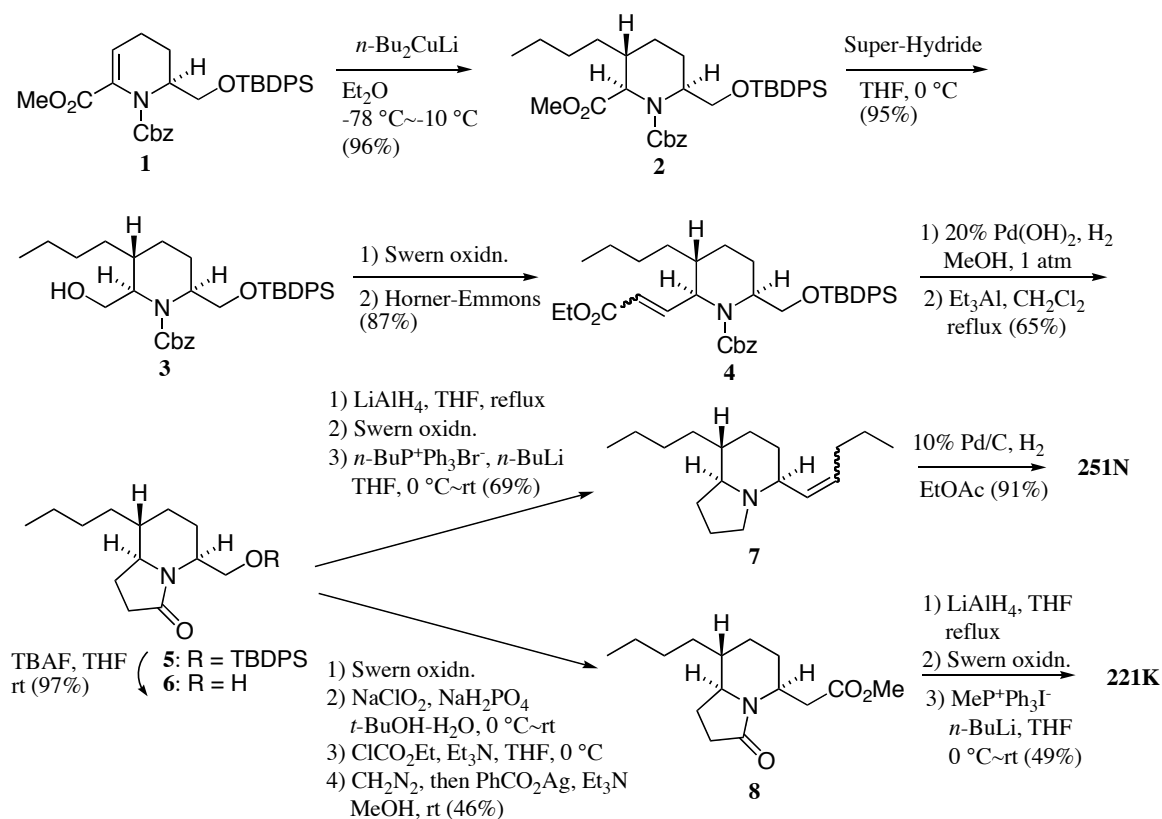


Figure 1

RESULTS AND DISCUSSION

Chiral enaminoester (**1**)⁴ was subjected to a conjugate-addition reaction to afford the adduct (**2**) as the single isomer in high yield.⁵ Reduction of the ester moiety in **2** followed by carbon-chain elongation of the resulting alcohol (**3**) by Swern oxidation and the Horner-Emmons reaction gave rise to the α,β -unsaturated ester (**4**) as a mixture of *E*- and *Z*-isomers. After hydrogenation of the double bond and removal of the Cbz-group, the resulting aminoester was converted to lactam (**5**) using Weinreb's procedure.⁶ Cleavage of the silylether with TBAF provided the alcohol (**6**), which was transformed into the olefin (**7**) by Swern oxidation and the Wittig olefination reaction. Hydrogenation of **7** over 10% Pd/C furnished the alkaloid **251N**, whose FT-IR spectrum was identical in all respects to that obtained from natural **251N** detected in the *Dendrobates granuliferous*. It was also co-chromatographed with natural **251N**.

On the other hand, the alcohol (**6**) was converted to homologated ester (**8**) using the Arndt-Eistert sequence. Finally, reduction of both lactam and ester moieties with LiAlH₄, and Swern oxidation of the resulting alcohol followed by Wittig reaction gave the proposed structure of alkaloid **221K**. This trace alkaloid could no longer be detected in 1981 extracts from a Panamanian *Dendrobates pumilio* and thus direct comparisons could not be made.



Scheme 1

In summary, we have achieved the synthesis of 8-butyl 5-substituted indolizidine poison-frog alkaloids **251N** and **221K**. The relative stereochemistry of natural **251N** was determined to be that of the proposed structure by the present work.

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 JASCO FT/IR-660 spectrophotometer. MS and HMMS spectra were measured on JEOL JMS-AX505HAD mass spectrometer. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. Column chromatography was performed using Silica Gel 60N (neutral, KANTO Chemical Co.).

(2*R*, 3*R*, 6*S*)-(-)-1-Benzyl 2-methyl 3-butyl-6-(*tert*-butyldiphenylsilyloxymethyl)piperidine-1,2-dicarboxylate (**2**)

To a stirred suspension of CuI (5.96 g, 31.3 mmol) in Et_2O (200 mL) was added a solution of *n*-BuLi (1.6 M in hexane, 39 mL, 62.6 mmol) at -78°C , and the temperature was gradually raised to -35°C . The resulting suspension was cooled to -78°C , and a solution of **1**⁴ (3.4 g, 6.26 mmol) in Et_2O (40 mL) was added to the reaction mixture via a double-tipped stainless steel needle. The resulting mixture was stirred at -78°C ~ -10°C for 1 h, and then quenched with saturated aqueous NH_4Cl solution. The aqueous mixture was diluted with CH_2Cl_2 , and the insoluble material was removed through a celite pad. The filtrate was separated and the aqueous layer was extracted with CH_2Cl_2 . The filtrate and organic layers were combined, dried, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (70 g, hexane : acetone = 30 : 1) to afford **2** (3.6 g, 96%) as a colorless oil.

IR (neat) 2953, 2858, 1737, 1703 cm^{-1} ; ^1H NMR (500 MHz) δ 0.88 (3H, t, J = 6.9 Hz), 1.04 (9H, s), 1.28-1.63 (8H, br m), 1.80 (2H, br), 2.22 (1H, br), 3.38 (3H, s), 3.47 (1H, m), 3.72 (1H, m), 4.35 (1H, br), 4.60 (1H, br), 5.12 (2H, s), 7.30-7.43 (11H, m), 7.64 (4H, d-like, J = 7.4 Hz); ^{13}C NMR (75 MHz) δ 14.00 (q), 18.32 (t), 19.19 (s), 19.95 (t), 22.54 (t), 26.78 (q), 29.43 (t), 31.13 (t), 33.23 (d), 51.63 (q), 52.34 (d), 56.78 (d), 62.34 (t), 67.09 (t), 127.27 (d), 127.37 (d), 127.56 (d), 128.13 (d), 128.27 (d), 128.94 (d), 129.34 (d), 133.26 & 133.35 (each s), 135.25 (d), 136.40 (s), 156.38 (s), 172.61 (s); MS: 544 (M^+ -57); HRMS: Calcd for $\text{C}_{32}\text{H}_{38}\text{NO}_5\text{Si}$ 544.2517; Found 544.2541; $[\alpha]_{\text{D}}^{26} -2.4^\circ$ (c 2.89, CHCl_3).

(2*R*, 3*R*, 6*S*)-(+)-Benzyl 3-butyl-6-(*tert*-butyldiphenylsilyloxymethyl)-2- hydroxymethylpiperidine-

1-carboxylate (3)

To a stirred solution of **2** (510 mg, 0.85 mmol) in THF (25 mL) was added a solution of lithium triethylborohydride (Super-Hydride[®], 1 M in THF, 1.7 mL, 1.7 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 2 h. The reaction was quenched with small pieces of ice, and the mixture was diluted with CH₂Cl₂. The organic layer was dried and evaporated to give a colorless oil, which was chromatographed on SiO₂ (20 g, hexane : acetone = 20 : 1~10 : 1) to afford **3** (460 mg, 95%) as a colorless oil.

IR (neat) 3445, 3060, 2930, 2853, 1695 cm⁻¹; ¹H NMR (500 MHz) δ 0.88 (3H, br), 1.03 (9H, s), 1.20-1.60 (10H, br m), 1.77 (1H, br), 3.57 (2H, br), 3.69 (1H, br), 4.22 (1H, br), 4.40 (1H, br), 5.16 (1H, d-like, *J* = 12.4 Hz), 7.30-7.44 (11H, br m), 7.64 (4H, br); ¹³C NMR (75 MHz) δ 13.92 (q), 18.95 (s), 19.64 (t), 22.56 (t), 26.60 (q), 29.37 (t), 32.40 (t), 32.77 (d), 51.49 (d), 57.12 (d), 64.69 (t), 67.11 (t), 126.69 (d), 127.57 (d), 127.59 (d), 127.67 (d), 128.21 (d), 128.27 (d), 128.82 (d), 129.61 (d), 132.90 (s), 135.34 (d), 136.71 (s), 157.70 (s); MS: 516 (M⁺-57); HRMS: Calcd for C₃₁H₃₈NO₄Si 516.2568; Found 516.2561; [α]_D²⁶ +5.6 ° (c 1.06, CHCl₃).

(2R, 3R, 6S)-Benzyl 3-butyl-6-(tert-butyldiphenylsilyloxymethyl)-2-(2-ethoxycarbonylvinyl)-piperidine-11-carboxylate (4)

To a stirred solution of (COCl)₂ (0.4 mL, 4.44 mmol) in CH₂Cl₂ (20 mL) was added DMSO (0.63 mL, 8.88 mmol) at -78 °C, and the resulting mixture was stirred at -78 °C for 5 min. To the reaction mixture was added a solution of **3** (1.27 g, 2.22 mmol) in CH₂Cl₂ (5 mL) via a double-tipped stainless steel needle at -78 °C. The resulting solution was stirred at -78 °C for 30 min. and then triethylamine (1.84 mL, 13.32 mmol) was added to the reaction mixture. The reaction mixture was warmed to 0 °C for 1 h., and quenched with H₂O. The aqueous mixture was extracted with Et₂O (30 mL x 3), and the organic extracts were combined, dried, and evaporated to give pale yellow oil, which was used directly in the next step.

To a stirred suspension of NaH (60%, 112 mg, 2.66 mmol) in THF (20 mL) was added (EtO)₂P(O)CH₂CO₂Et (0.52 mL, 2.66 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 30 min. To the resulting mixture was added dropwise a solution of the above aldehyde in THF (5 mL) via a double-tipped stainless steel needle at 0 °C. The reaction mixture was stirred at room temperature for 20 h. The reaction was quenched with H₂O, and the aqueous mixture was extracted with CH₂Cl₂ (30 mL x 4). The organic extracts were combined, dried, and evaporated to give pale yellow oil, which was chromatographed on SiO₂ (30 g, hexane : acetone = 20 : 1~10 : 1) to afford **4** (1.24 g, 87%) as a 2 : 1 mixture of the *E*- and *Z*-isomers in a pale yellow oil.

(5S, 8R, 9S)-(-)-8-Butyl-5-(tert-butyldiphenylsilyloxymethyl)hexahydroindolizin-3-one (5)

To a stirred solution of **4** (430 mg, 0.67 mmol) in MeOH (15 mL) was added 20% Pd(OH)₂/C (30 mg), and the resulting suspension was hydrogenated at 1 atm for 44 h. The catalyst was removed by filtration and the filtrate was evaporated to give a pale yellow oil. To the solution of this oil in CH₂Cl₂ (15 mL) was

added a solution of Et_3Al (0.92 M in toluene, 0.8 mL, 0.74 mmol) at 0 °C, and the resulting solution was refluxed for 15 h. After cooling, the reaction was quenched with 10% HCl (aq), and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (15 mL x 3), and the organic layer and extracts were combined, dried, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (20 g, hexane : acetone = 20 : 1~10 : 1) to afford **5** (200 mg, 65%) as colorless oil.

IR (neat) 3071, 2930, 2857, 1694 cm^{-1} ; ^1H NMR (500 MHz) δ 0.90 (3H, t, $J = 7.3$ Hz), 0.98-1.12 (1H, m), 1.06 (9H, s), 1.18-1.42 (7H, br m), 1.53 (2H, m), 1.87 (1H, m), 2.05 (1H, m), 2.12 (1H, m), 2.27 (2H, m), 3.06 (1H, m), 3.40 (1H, m), 4.01 (1H, t-like, $J = 9.8$ Hz), 4.48 (1H, dd, $J = 9.8, 3.9$ Hz), 7.45-7.41 (6H, m), 7.66-7.68 (4H, m); ^{13}C NMR (75 MHz) δ 14.01 (q), 16.90 (t), 19.27 (t), 22.87 (t), 24.66 (t), 26.53 (t), 26.89 (q), 27.49 (t), 28.37 (t), 31.25 (t), 31.62 (t), 41.95 (d), 56.78 (d), 62.67 (d), 63.55 (t), 127.57 (d), 129.51 (d), 133.74 (s), 135.56 & 135.61 (each d), 174.81 (s); MS: 406 (M^+ -57); HRMS: Calcd for $\text{C}_{25}\text{H}_{32}\text{NO}_2\text{Si}$ 406.2200; Found 406.2232; $[\alpha]_{\text{D}}^{26} -47.0^\circ$ (c 0.86, CHCl_3).

(5*S*, 8*R*, 9*S*)-(-)-8-Butyl-5-hydroxymethylhexahydroindolizin-3-one (**6**)

To a stirred solution of **5** (260 mg, 0.56 mmol) in THF (10 mL) was added a solution of TBAF (1M in THF, 1.12 mL, 1.12 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 13 h. The reaction mixture was evaporated, and the residue was chromatographed on SiO_2 (10 g, hexane : acetone = 20 : 1~2 : 1) to afford **6** (123 mg, 97%) as colorless oil.

IR (neat) 3343, 2930, 2859, 1667 cm^{-1} ; ^1H NMR (500 MHz) δ 0.90 (3H, t, $J = 7.3$ Hz), 1.03-1.47 (9H, br m), 1.61-1.69 (2H, m), 1.97-2.00 (1H, m), 2.26 (1H, m), 2.39-2.43 (2H, m), 3.05-3.13 (2H, m), 3.77 (1H, dd, $J = 12.4, 2.6$ Hz), 3.80 (1H, br), 3.90 (1H, dd, $J = 12.4, 7.7$ Hz); ^{13}C NMR (75 MHz) δ 13.90 (q), 22.75 (t), 24.13 (t), 27.98 (t), 28.24 (t), 29.01 (t), 30.99 (t), 31.41 (t), 42.86 (d), 60.47 (d), 63.70 (t), 64.59 (d), 175.39 (s); MS: 225 (M^+); HRMS: Calcd for $\text{C}_{13}\text{H}_{23}\text{NO}_2$ 225.1728; Found 225.1739; $[\alpha]_{\text{D}}^{26} -65.9^\circ$ (c 1.92, CHCl_3).

(5*S*, 8*R*, 9*S*)-8-Butyl-5-pent-1-enylindolizidine (**7**)

To a stirred solution of **6** (140 mg, 0.62 mmol) in THF (10 mL) was added LiAlH_4 (47 mg, 1.24 mmol) at 0 °C, and the resulting suspension was refluxed for 17 h. After cooling, the reaction was quenched with 10% NaOH (aq), and the aqueous mixture was extracted with hot CHCl_3 (15 mL x 10). The organic extracts were combined, dried over K_2CO_3 , and evaporated to give a colorless oil, which was used directly in the next step.

To a stirred solution of $(\text{COCl})_2$ (0.11 mL, 1.24 mmol) in CH_2Cl_2 (6 mL) was added DMSO (0.18 mL, 2.49 mmol) at -78 °C, and the reaction mixture was stirred at -78 °C for 5 min. To the resulting mixture was added dropwise a solution of the above alcohol in CH_2Cl_2 (4 mL) via a double-tipped stainless steel needle at -78 °C, and the reaction mixture was stirred at the same temperature for 30 min. Triethylamine (0.52 mL, 3.73 mmol) was added to the reaction mixture, and the reaction mixture was warmed to 0 °C for 1 h. The reaction was quenched with saturated aqueous NaHCO_3 , and the organic layer was separated.

The aqueous mixture was extracted with CH_2Cl_2 (15 mL x 2), and the organic layer and extracts were combined, dried over K_2CO_3 , and evaporated to give a pale yellow oil, which was used directly in the next step.

To a stirred suspension of $n\text{-BuP}^+\text{Ph}_3\text{Br}^-$ (1.25 g, 2.80 mmol) in THF (20 mL) was added a solution of $n\text{-BuLi}$ (1.6 M in hexane, 1.6 mL, 2.61 mmol) at 0 °C, and the resulting orange solution was stirred at 0 °C for 10 min. To the reaction mixture was added dropwise a solution of the above aldehyde in THF (6 mL) via a double-tipped stainless steel needle at 0 °C. After stirring the reaction mixture for 18 h, the reaction was quenched with H_2O . The aqueous mixture was extracted with Et_2O (20 mL x 3), and the organic extracts were combined, dried over K_2CO_3 , and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (50 g, hexane : acetone = 100 : 1~20 : 1) to afford **7** (107 mg, 69%) as a pale yellow oil.

^1H NMR (500 MHz) δ 0.90 (6H, m), 0.90-1.07 (2H, br m), 1.19-1.50 (10H, br m), 1.52-1.66 (3H, m), 1.73 (1H, m), 1.87 (1H, m), 1.95 (2H, m), 2.05 (2H, m), 2.80 (1H, br m), 3.16 (1H, br m), 5.40 (2H, br m).

(5*R*, 8*R*, 9*S*)-(-)-8-Butyl-5-pentylindolizidine (**251N**)

To a stirred solution of **7** (107 mg, 0.43 mmol) in EtOAc (20 mL) was added 10% Pd/C (100 mg), and the resulting suspension was hydrogenated at 1 atm for 20 h. The catalyst was removed by filtration, and the filtrate was evaporated to give indolizidine **251N** (98 mg, 91%) as pale yellow oil.

IR (neat) 2956, 2929, 2859, 2778, 1457, 1378 cm^{-1} ; ^1H NMR (300 MHz) δ 0.88 (3H x 2, each t, each J = 6.9 Hz), 1.02-2.05 (26H, br m), 3.34 (1H, br m); ^{13}C NMR (75 MHz) δ 14.14 (q), 20.40 (t), 22.69 (t), 23.04 (t), 25.57 (t), 28.75 (t), 29.13 (t), 30.44 (t), 31.05 (t), 32.31 (t), 33.01 (t), 34.48 (t), 41.28 (d), 51.81 (t), 63.59 (d), 70.21 (d); MS: 251 (M^+), 181 (100); HRMS: Calcd for $\text{C}_{17}\text{H}_{33}\text{N}$ 251.2611; Found 251.2636; $[\alpha]_{\text{D}}^{26}$ -91.1 ° (c 4.90, CHCl_3).

(5*S*, 8*R*, 9*S*)-(-)-Methyl (8-butyl-3-oxooctahydroindolizin-5-yl)acetate (**8**)

To a stirred solution of $(\text{COCl})_2$ (0.25 mL, 2.86 mmol) in CH_2Cl_2 (6 mL) was added DMSO (0.4 mL, 5.08 mmol) at -78 °C, and the resulting mixture was stirred at the same temperature for 5 min. To the reaction mixture was added dropwise a solution of **6** (200 mg, 0.89 mmol) in CH_2Cl_2 (3 mL) via a double-tipped stainless steel needle at -78 °C, and the reaction mixture was stirred at -78 °C for 30 min. Triethylamine (1.2 mL, 7.62 mmol) was added to the reaction mixture, and the reaction mixture was warmed to 0 °C for 1 h. The reaction was quenched with H_2O , and the aqueous mixture was extracted with Et_2O (15 mL x 3). The organic layers were combined, dried, and evaporated to give a pale yellow oil, which was used directly in the next step.

To a stirred solution of the above aldehyde in $t\text{-BuOH}$ (9 mL) were added 2-methyl-2-butene (6.3 mL, 59.4 mmol), $\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$ (2.3 g, 14.69 mmol), and then a solution of NaClO_2 (80%, 1 g, 8.81 mmol) in H_2O (3 mL) at 0 °C. The reaction mixture was stirred at rt for 1 h. and quenched with sat'd. NaHSO_3

(aq) at 0 °C. The aqueous mixture was acidified with 10% HCl (aq), saturated with solid NaCl, and extracted with EtOAc (10 mL x 10). The organic extracts were combined, dried, and evaporated to give pale yellow oil, which was used directly in the next step.

To a stirred solution of the above carboxylic acid in THF (15 mL) were added Et₃N (0.46 mL, 3.25 mmol) and ClCO₂Et (0.32 mL, 3.25 mmol) at 0 °C, and the resulting suspension was stirred at the same temperature for 1 h. The insoluble material was filtered off, and the filtrate was evaporated to give pale yellow oil, which was used directly in the next step.

To a stirred solution of the above oil in Et₂O (15 mL) was added a solution of CH₂N₂ in Et₂O at 0 °C, and yellow mixture was stirred at rt for 12 h. The solvent was removed in vacuo and the residue was dissolved in MeOH (12 mL). To the MeOH solution were added PhCO₂Ag (40 mg, 0.17 mmol) and Et₃N (0.4 mL, 2.89 mmol), and the resulting suspension was stirred at rt in the dark for 20 h. The insoluble material was filtered off, and the filtrate was evaporated to give pale brown oil, which was chromatographed on SiO₂ (20 g, hexane : acetone = 20 : 1~10 : 1) to afford **8** (108 mg, 46%) as pale yellow oil.

IR (neat) 2929, 1739, 1693 cm⁻¹; ¹H NMR (500 MHz) δ 0.89 (3H, t, *J* = 7.3 Hz), 1.00-1.48 (7H, br m), 1.58 (1H, m), 1.68 (2H, m), 1.92 (2H, m), 2.16 (1H, m), 2.30 (2H, m), 2.43 (1H, dd, *J* = 17.0, 4.3 Hz), 3.05 (1H, q-like, *J* = 8.6 Hz), 3.46 (1H, dd, *J* = 8.6, 8.5 Hz), 3.61 (1H, m), 3.70 (3H, s); ¹³C NMR (75 MHz) δ 14.03 (q), 22.90 (t), 24.11 (t), 28.41 (t), 29.06 (t), 31.18 (t), 31.49 (t), 31.94 (t), 37.94 (t), 42.78 (d), 51.45 (q), 52.62 (d), 63.90 (d), 172.04 (s), 175.08 (s); MS: 267 (M⁺); HRMS: Calcd for C₁₅H₂₅NO₃ 267.1833; Found 267.1808; [α]_D²⁶ -76.5 ° (*c* 3.92, CHCl₃).

(5*S*, 8*R*, 9*R*)-(-)-5-Allyl-8-buty lindolizidine (221K)

To a stirred solution of **8** (78 mg, 0.29 mmol) in THF (10 mL) was added LiAlH₄ (45 mg, 1.17 mmol) at 0 °C, and the resulting suspension was refluxed for 11 h. After cooling, the reaction was quenched with 10% NaOH (aq), and the aqueous mixture was extracted with hot CHCl₃ (10 mL x 10). The organic extracts were combined, dried over K₂CO₃, and evaporated to give a colorless oil, which was used directly in the next step.

To a stirred solution of (COCl)₂ (0.051 mL, 0.59 mmol) in CH₂Cl₂ (2 mL) was added DMSO (0.083 mL, 1.17 mmol) at -78 °C, and the reaction mixture was stirred at -78 °C for 5 min. To the reaction mixture was added dropwise a solution of the oil obtained above in CH₂Cl₂ (2 mL) via a double-tipped stainless steel needle at -78 °C, and the reaction mixture was stirred at -78 °C for 30 min. Triethylamine (0.24 mL, 1.76 mmol) was added to the reaction mixture, and the reaction mixture was warmed to 0 °C for 1 h. The reaction was quenched with saturated aqueous NaHCO₃, and the aqueous mixture was extracted with CH₂Cl₂ (15 mL x 3). The organic layers were combined, dried over K₂CO₃, and evaporated to give a pale yellow oil, which was used directly in the next step.

To a stirred suspension of CH₃P⁺Ph₃I⁻ (592 mg, 1.47 mmol) in THF (10 mL) was added a solution of *n*-BuLi (1.6 M in hexane, 0.88 mL, 1.41 mmol) at 0 °C, and the resulting solution was stirred at 0 °C for

5 min. To the reaction mixture was added a solution of the aldehyde obtained above in THF (2 mL) via a double-tipped stainless steel needle at 0 °C, and the reaction mixture was stirred at room temperature for 18 h. The reaction was quenched with H₂O, and the aqueous mixture was extracted with Et₂O (10 mL x 4). The organic extracts were combined, dried over K₂CO₃, and evaporated to give a pale yellow oil, which was chromatographed on SiO₂ (20 g, hexane : acetone = 20 : 1~10 : 1) to afford indolizidine **221K** (47 mg, 49%) as pale yellow oil.

IR (neat) 3066, 2928, 2858, 2779, 1457, 910 cm⁻¹; ¹H NMR (500 MHz) δ 0.88 (3H, t, *J* = 7.3 Hz), 0.80-0.99 (1H, br m), 1.03 (1H, m), 1.17-2.26 (19H, br m), 2.48 (1H, br m), 3.34 (1H, br m), 5.03 (1H, d-like, *J* = 10.7 Hz), 5.07 (1H, d-like, *J* = 17.9 Hz), 5.79 (1H, m); ¹³C NMR (75 MHz) δ 14.16 (q), 20.37 (t), 23.04 (t), 28.67 (t), 28.90 (t), 30.18 (t), 32.94 (t), 39.24 (t), 40.97 (d), 51.87 (t), 63.31 (d), 70.30 (d), 116.85 (t), 135.34 (d); MS: 221 (M⁺), 181 (100); HRMS: Calcd for C₁₅H₂₇N 221.2142; Found 221.2155; [α]_D²⁶ -75.2 ° (*c* 0.70, CHCl₃).

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REFERENCES

1. J. W. Daly, T. F. Spande, and H. M. Garraffo, *J. Nat. Prod.*, 2005, **68**, 1556; J. W. Daly, *J. Med. Chem.*, 2003, **46**, 445; J. W. Daly, H. M. Garraffo, and T. F. Spande, 'Alkaloids: Chemical and Biological Perspectives: Alkaloids from Amphibian Skins,' Vol. 13, ed. by S. W. Pelletier, Pergamon Press, Inc., New York, 1999, pp. 1-161.
2. T. Momose and N. Toyooka, *J. Org. Chem.*, 1994, **59**, 943; N. Toyooka, K. Tanaka, T. Momose, J. W. Daly, and H. M. Garraffo, *Tetrahedron*, 1997, **53**, 9553; N. Toyooka, H. Nemoto, M. Kawasaki, H. M. Garraffo, T. F. Spande, and J. W. Daly, *Tetrahedron*, 2005, **61**, 1187.
3. H. Tsuneki, Y. You, N. Toyooka, S. Kagawa, S. Kobayashi, T. Sasaoka, H. Nemoto, I. Kimura, and J. A. Dani, *Mol. Pharmacol.*, 2004, **66**, 1061; N. Toyooka, H. Nemoto, and H. Tsuneki, *J. Synth. Org. Chem. Jpn.*, 2006, **64**, 49.
4. N. Toyooka, Z. Dejun, H. Nemoto, H. M. Garraffo, T. F. Spande, and J. W. Daly, *Tetrahedron Lett.*, 2006, **47**, 577; *Idem*, *Tetrahedron Lett.*, **47**, 581, and references cited therein.
5. N. Toyooka and H. Nemoto, *Recent Res. Dev. Org. Chem.*, 2002, **6**, 611.
6. A. Basha, M. Lipton, and S. M. Weinreb, *Tetrahedron Lett.*, **1977**, 4171.