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A CONCISE SYNTHESIS OF (+)-INDOLIZIDINE 209D USING A C_2-SYMMETRIC 2,6-DIALLYLPIPERIDINE

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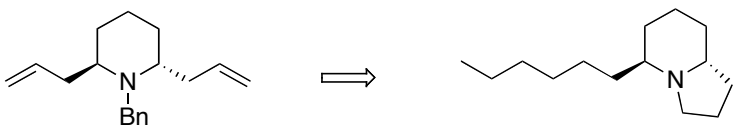
Abstract – An asymmetric synthesis of (+)-indolizidine 209D (**2**) using C_2-symmetric 2,6-diallylpiperidine (**1**) as a chiral building block is presented in a straightforward fashion.

The abundance of biologically active compounds containing the indolizidine ring has resulted in considerable synthetic efforts to reach these systems.[1] With respect to biologically active target molecules there is an increasing interest in the diastereo- and enantioselective synthesis of indolizidine. Our interest in this field has been focused on the synthetic application of the double or iterative asymmetric reaction to cause enantiomeric enhancement.[2] We have recently communicated an asymmetric synthesis of several piperidine-related alkaloids using an enantiomer of a novel C_2-symmetric 2,6-diallylpiperidine (**1**), which was prepared by a double asymmetric allylboration of glutaraldehyde followed by cyclic amination as key steps.[3] In this note, we describe an asymmetric synthesis of (+)-indolizidine 209D (**2**)[4] isolated from skin extracts of neotropical members of the Dendrobatidae family of frogs[5] starting from **1**.



1 **2**

Our synthesis of **2** began with the hydroboration of **1** prepared by our protocol (see EXPERIMENTAL).[3,6] The treatment of **1** with 9-BBN, followed by alkaline H_2O_2 oxidation gave diol (**3**) in 85% yield.[6] The

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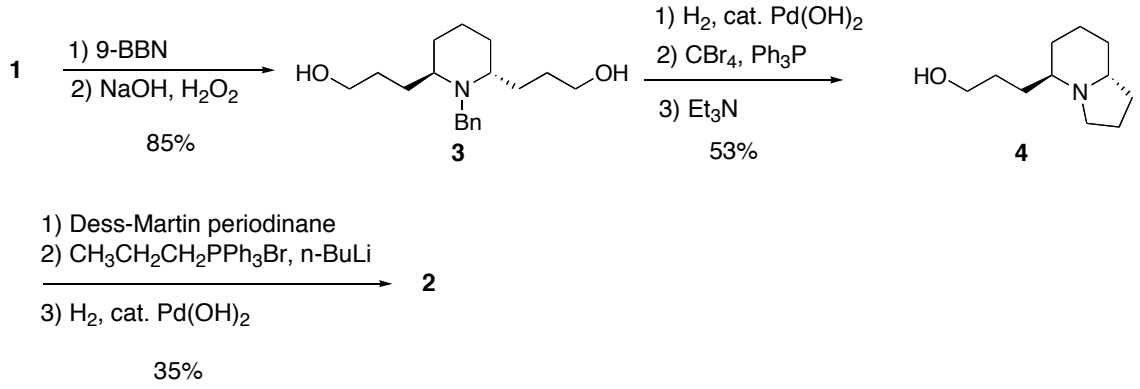
This paper is dedicated to Professor Barry M. Trost on his 65th birthday.

diol (**3**) was successively subjected to debenzylation with hydrogen in the presence of catalytic $Pd(OH)_2$ and indolizidine formation[7] under the bromination with carbon tetrabromide/triphenylphosphine to give the indolizidinol (**4**) in 53% yield. A three-step sequence (1. Dess-Martin oxidation; 2. Wittig olefination: 3. hydrogenation of olefin) of **4** afforded the desired (+)-indolizidine 209D (**2**) in 35% yield, whose physical and spectral data as well as the optical rotation were consistent with those previously reported {$[\alpha]^{25}_D$ +10.4° (c 0.59, CH_2Cl_2), lit.,[4c] $[\alpha]^{24}_D$ +10.1° (c 0.42, CH_2Cl_2)}.[4c]



In summary, the asymmetric synthesis of (+)-indolizidine 209D (**2**) was performed from C_2-symmetric 2,6-diallylpiperidine (**1**) in eight steps. The synthesis of several 5-substituted indolizidines would be expected starting from the indolizidinol (**4**).

EXPERIMENTAL

IR spectra were measured with a Perkin-Elmer 1600 series FTIR spectrophotometer. ^{1}H NMR spectra were recorded either at 300 MHz on a Varian Gemini-300, or 500 MHz on a Varian Unity-500 with $CHCl_3$ (7.26 ppm) as internal standards. ^{13}C NMR spectra were recorded at 75 or 125 MHz with $CHCl_3$ (77.2 ppm) as an internal standard unless otherwise specified. MS spectra and HRMS spectra were measured on a JEOL JMS D-200 spectrometer. Optical rotations were measured on a JASCO DIP-140 instrument. Column chromatography was performed on silica gel (Fuji-Division BW-200 or Merck 60 (No 9385). The extracts were dried over Na_2SO_4 unless otherwise specified.

(2*S*,6*S*)-1-Benzyl-2,6-bis(2-propenyl)piperidine (1). 1.0 M Allylmagnesium bromide (20 mL, 20 mmol) in ether was added to a solution of (+)-Ipc_2BOMe (6.32 g, 20.0 mmol) in ether (25 mL) at –78 °C. After being stirred for 15 min, the reaction was warmed to rt. To the mixture was added a solution of glutaraldehyde (1.0 g, 10mmol) in ether (5 mL) at –78 °C. After being stirred for 1 h, the reaction was warmed to rt. To the reaction mixture were successively added 3N NaOH (14.6 mL) and 30% H_2O_2 (6.0 mL) at 0 °C. The mixture was refluxed for 1 h and fractionated with separatory funnel. The aqueous layer was extracted with ether three times. The combined organic solvents were washed with brine, dried,

and evaporated. The residue was purified by flash column chromatography on silica gel (n-hexane : ethyl acetate = 2:1) to give the diastereomeric mixture of diol (1.15 g, 63%) as an oil. Et_3N (3.48 mL, 25.0 mmol) and 4-dimethylaminopyridine (305 mg, 2.50 mmol) were successively added to a mixture of the diol (1.15 g, 6.25 mmol) and *p*-toluenesulfonyl chloride (4.70 g, 25.0 mmol) at 0 °C and the mixture was stirred at rt for two days. A large amount of ether was added to the mixture. The mixture was filtered through Celite. The filtrate was washed with brine, dried, and evaporated. The residue was purified with chromatography using *n*-hexane:ethyl acetate (5:1) as eluent to yield the ditosylate as a yellow oil. A solution of the tosylate in benzylamine (5.3 mL, 0.4 mol) was heated at 75 °C for 2 days. The reaction was diluted with *n*-pentane (100 mL) at 0 ˚C and 2N NaOH (150 mL) was added to the dilute solution. The organic layer was separated and the aqueous layer was extracted with *n*-pentane (40 mL) four times. The combined organic layers were dried over K_2CO_3 and evaporated. The residue was separated with medium-pressure chromatography using *n*-hexane : ethyl acetate (80:1) as eluent to yield **1** (861 mg, 54%) and *meso*-**1** (240 mg, 15%) as oils. **1**: $[\alpha]_D^{26}$ +4.25° (*c* 1.07, $CHCl_3$); IR (neat) 2928, 1559, 1447 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.34-1.39 (m, 2 H), 1.57-1.60 (m, 4 H), 2.13-2.24 (m, 4 H), 2.79-2.83 (m, 2 H), 3.68, 3.82 (ABq, *J* = 14.3, 2 H), 4.95-5.02 (m, 4 H), 5.68-5.81 (m, 2 H), 7.20-7.38 (m, 5 H); ^{13}C NMR (75 Hz, $CDCl_3$) δ, 20.1, 26.1, 35.7, 51.1, 54.5, 115.7, 126.5, 128.1, 128.5, 137.0, 141.3; *Anal.* Calcd for $C_{18}H_{25}N$: C, 84.65; H, 9.87; N, 5.48. Found: C, 84.73; H, 9.74; N, 5.38.

(2*R*,6*R*)-1-Benzyl-2,6-bis(3-hydroxypropyl)piperidine (**3**). To a solution of 0.5 M 9-BBN (12.1 mL, 6.03 mmol) in THF was added **1** (385 mg, 1.51 mmol) at 0 °C and the reaction was stirred for 1 h at rt. 3N NaOH solution (16.5 mL) and 30% H_2O_2 solution (8.2 mL) were successively added at 0 °C. The mixture was stirred for 1 h and extracted with CH_2Cl_2 three times. The extracts were dried over K_2CO_3 and evaporated. The residue was acidified with 2N HCl and washed with CH_2Cl_2 three times. The aqueous layer was basified with 2N NaOH and extracted with CH_2Cl_2 three times. The extracts were dried over K_2CO_3 and evaporated. The residue was purified by flash column chromatography on silica gel (ethyl acetate : CH_3OH = 5:1) to give **3** (374 mg, 85%) as an oil. $[\alpha]^{26}_D$ +16.0 ° (*c* 1.65, $CHCl_3$): IR (neat) cm^{-1}: 3346, 2934, 1560, 1457, 1057; ^1H-NMR (300 MHz, $CDCl_3$) δ: 1.23-1.37 (m, 4 H), 1.40-1.48 (m, 2 H), 1.53-1.70 (m, 6 H), 1.75-1.85 (m, 2 H), 2.77 (br s, 2 H), 3.41-3.49 (m, 2 H), 3.56-3.64 (m, 2 H), 3.57, 3.86 (ABq, *J* = 13.2 Hz, 2 H), 5.60 (br s, 2 H), 7.17-7.33 (m, 5H); ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ: 20.7, 23.9, 30.2, 30.4, 49.4, 53.3, 62.3, 127.3, 128.4, 129.6, 138.6; HRMS calcd for $C_{18}H_{29}NO_2$ (M^+) 291.2198, found 291.2191.

(5*S*,9*R*)-5-(3-Hydroxypropyl)indolizidine (4). A mixture of **3** (185 mmg, 0.63 mmol) and $Pd(OH)_2$ (50 mg) in MeOH (8.8 mL) was stirred under hydrogen for 1 h at rt. The mixture was filtered on Celite and the filtrate was evaporated. To a solution of the residue in CH_2Cl_2 (4.9 mL) were added CBr_4 (418 mg, 1.58 mmol) and Ph_3P (330 mg, 1.58 mmol) at 0 °C and the reaction mixture was stirred overnight at rt. To

a mixture was added Et_3N (0.22 mL, 1.70 mmol) at 0 °C and the mixture was stirred for 30 min. After evaporation, the residue was acidified with 2N HCl and washed with ethyl acetate three times. The aqueous layer was basified with 2N NaOH and extracted with CH_2Cl_2 three times. The extracts were dried over K_2CO_3 and evaporated. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2 : MeOH = 10:1) to give **4** (54 mg, 53%) as an oil. $[\alpha]^{28}_D$ –1.08° (*c* 1.11, $CHCl_3$): IR (neat) cm^{-1}: 3383, 2932; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.20-1.62 (m, 8H), 1.69-1.97 (m, 6H), 2.76-2.94 (m, 3H), 3.03-3.12 (m, 1H), 3.44-3.65 (m, 2H); ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ: 19.7, 21.3, 25.4, 27.6, 30.3, 30.9, 32.2, 48.9, 52.8, 55.5, 63.5; HRMS calcd for $C_{11}H_{21}NO$ (M^+) 183.1623, found183.1617.

(5*S*,9*R*)-Indolizidine 209D (2). Dess-Martin periodinane (1.01 g, 2.39 mmol) was added to a solution of **4** (98 mg, 0.53 mmol) in CH_2Cl_2 (8 mL). After being stirred for 3 h at rt, the reaction mixture was clarified by addition of 2N NaOH with stirring and extracted with CH_2Cl_2 three times. The extracts were successively washed with H_2O and brine, dried over K_2CO_3, and evaporated. 1.6 M n-BuLi (0.83 mL, 1.33 mmol) in hexane was added to a suspension of $PrPPh_3Br$ (613 mg, 1.59 mmol) in THF (5 mL) at 0 °C and the reaction mixture was stirred for 15 min. A solution of the residue in THF (2 mL) was added to the mixture and stirred overnight at 0 °C. After addition of sat. NH_4Cl, the mixture was extracted with CH_2Cl_2 three times. The extracts were washed with brine, dried over K_2CO_3, and evaporated. After 2N HCl was added to the residue, the mixture was washed with ethyl acetate three times. The aqueous layer was basified with 2N NaOH and extracted with CH_2Cl_2 three times. The extracts were dried over K_2CO_3, and evaporated. A mixture of the residue and $Pd(OH)_2$ (45 mg) in MeOH (7.5 mL) was stirred under hydrogen for 9 h at rt. The mixture was filtered on Celite and the filtrate was evaporated. After 2N HCl was added to the residue, the mixture was washed with ethyl acetate three times. The aqueous layer was basified with 2N NaOH and extracted with CH_2Cl_2 three times. The extracts were dried over K_2CO_3, and evaporated. The residue was purified by flash column chromatography on silica gel (ethyl acetate : MeOH = 20:1) to give **2** (39 mg, 35%) as an oil. $[\alpha]^{25}_D$ +10.4° (*c* 0.59, CH_2Cl_2): IR (neat) cm^{-1}: 2928, 2858; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.88 (t, *J* = 7.14 Hz, 3H), 1.13-1.20 (m, 1H), 1.22-1.85 (m, 19H), 2.42-2.47 (m, 1H), 2.63 (q, *J* = 9.34 Hz, 1H), 2.81 (td, *J* = 8.79, 3.30 Hz, 1H), 2.88-2.93 (m, 1H); ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ: 14.5, 19.5, 21.2, 22.9, 23.7, 27.8, 27.9, 30.8, 31.4, 32.1, 48.9, 55.4, 55.7; HRMS calcd for $C_{14}H_{27}N$ (M^+) 209.2143, found 209.2125.

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REFERENCES AND NOTES

1. (a) J. P. Michael, *Nat. Prod. Rep.*, 2004, **21**, 625. (b) J. P. Michael, *Alkaloids*, ed. by G. A. Cordell, Academic Press, 2001, **55**, p. 91. (c) H. Takahata and T. Momose, *Alkaloids*, ed. by G. A. Cordell, Academic Press, 1993, **44**, p. 189.
2. (a) H. Takahata and N. Okamoto, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 1799. (b) H. Takahata, M. Kubota, and N, Ikota, *J. Org. Chem.*, 1999, **64**, 8594. (c) H. Takahata, M. Kubota, K. Ihara, N. Okamoto, T. Momose, N. Azer, A. T. Eldefrawi, and M. E. Eldefrawi, *Tetrahedron: Asymmetry.*, 1998, **9**, 3289. (d) H. Takahata, S, Takahashi, S. Kouno, and T. Momose, *J. Org. Chem.*, 1998, **63**, 2224.
3. H. Takahata, H. Ouchi, M. Ichinose, and H. Nemoto, *Org. Lett.*, 2002, **4**, 3459.
4. Synthesis of (+)-indolizidine 209D; (a) R. P. Polniaszek and S. E. Belmont, *J. Org. Chem.*, 1990, **55**, 4688. (b) D. L. Comins, S. P. Joseph, H. Hong, R. S. Al-awar, C. J. Foti, Y.-M. Zhang, X. Chen, D. H. LaMunyon, and M. Guerra-Weltzien, *Pure and Applied Chem.*, 1997, **69**, 477. (c) ref, 2c, Synthesis of (-)-indolizidine 209D; (d) N. T. Patil, N. K. Pahadi, and Y. Yamamoto, *Tetrahedron Lett.*, 2005, **46**, 2101. (e) P. G. Reddy and S. Baskaran, *J. Org. Chem.*, 2004, **69**, 3093. (f) G. Kim, S. D. Jung, and W. Kim, *Org. Lett.*, 2001, **3**, 2985.
5. J. W. Daly, H. M. Garraffo, and T. F. Spande, *Alkaloids*, ed. by G. A. Cordell, Academic Press, 1993, **43**, p. 185.
6. P. V. Ramachandran, G.-M. Chen, and H. C. Brown, *Tetrahedron Lett.*, 1997, **38**, 2417. Brown reported a double asymmetric allylboration of gultaldehyde to provide C_2-symmetric 1,5-diol in 90% de and >98% ee.
7. (a) N. Toyooka, A. Fukutome, H. Shinoda, and H. Nemoto, *Tetrahedron*, 2004, **60**, 6197. (b) Y. Shishido and C. Kibayashi, *J. Org. Chem.*, 1992, **57**, 2876.