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A Chiral Synthesis of (*8R,8aS*)-Hexahydro-8-methyl-5(1H)-indolizinone

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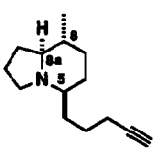
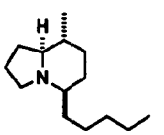
Abstract: The enantioselective synthesis of (*8R,8aS*)-hexahydro-8-methyl-5(1H)-indolizinone ((-)-**13**), which is a synthetic intermediate of 5,8-disubstituted indolizidine alkaloids has been carried out. Reaction of ethyl (*E*)-(*4R, 5R*)-8-benzyloxy-4, 5-epoxy-4-methyl-2-octenoate (**4**) with formic acid in the presence of $Pd_2(dba)_3CHCl_3$ and n-Bu_3P as a catalyst gave ethyl (*E*)-(*4R, 5R*)-8-benzyloxy-5-hydroxy-4-methyl-2-octenoate (**5**), which was converted to (-)-**13** in 8 steps.

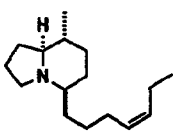
5,8-Disubstituted indolizidines, such as (-)-**205A** and (-)-**235B**, have been isolated from skin extracts of the neotropical poison-dart frog family.[1] Because of various biological activities of alkaloids from dendrobates, the synthesis of these compounds is of current interest.[2]



(-)-205A



(-)-209B

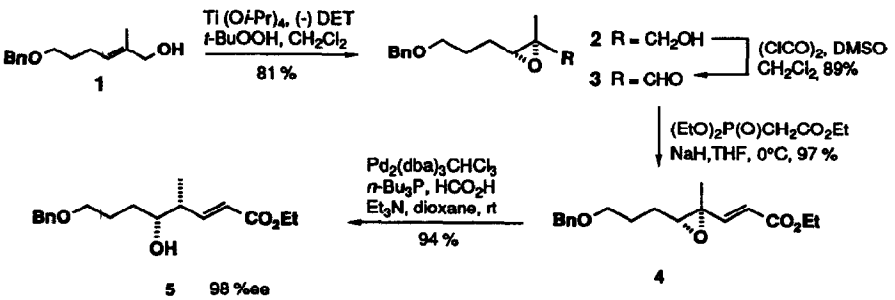


(-)-235B

A problem in the synthesis of 5,8-disubstituted indolizidines is the stereoselective construction of the stereogenic center at C-8 bearing the methyl group. Recently we have reported a stereoselective synthetic method for acyclic compounds having a methyl and a hydroxy group on vicinal stereogenic carbons by the palladium-catalyzed hydrogenolysis of alkenyl oxiranes with formic acid.[3] The method is applicable to a wide variety of optically active compounds.[4] In this paper we wish to demonstrate a novel synthetic method for (*8R,8aS*)-hexahydro-8-methyl-5(1H)-indolizinone ((-)-**13**), which is a synthetic intermediate of 5,8-disubstituted indolizidine alkaloids.

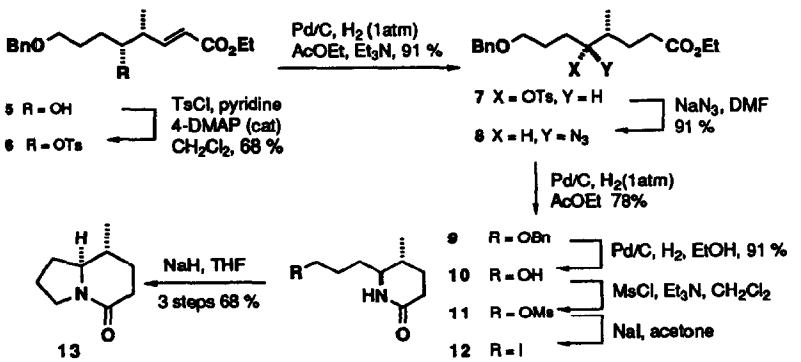
The alkenyloxirane **4** was prepared from the allylic alcohol **1** by Sharpless asymmetric epoxidation,

Swern oxidation, and Emmons-Horner reaction (70 % from **1**). Hydrogenolysis of the alkenyl oxirane **4** to the homoallylic alcohol **5** was carried out with formic acid using a palladium catalyst with high regio- and stereoselectivity in 94 % yield. The enantiomeric excess of **5** was found to be 98% ee by NMR analysis using the chiral shift reagent, Eu(TFC)$_3$ (Tris[3-(trifluoromethylhydroxymethylene)camphorato]-europium(III) derivative). There is no reference to any pevious data of **5** that would confirm the assignment. Therefore, the stereochemistry of **5** was proved by conversion to the known indolizidine alkaloids.



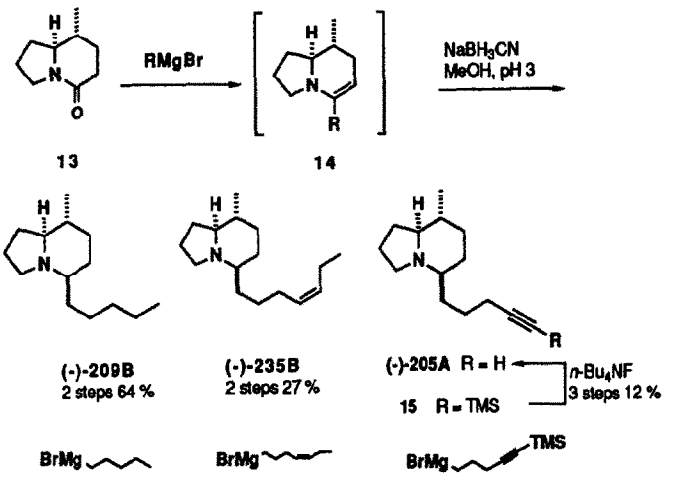
Scheme 1

Conversion of the ester **5** to the indolizidinone (-)-**13** was carried out as shown in Scheme 2. Reaction of the alcohol **5** with TsCl followed by hydrogenation of the olefin gave the sulfonyl ester **7** (62 % from **5**). Azidation of **7** was carried out with inversion to give **8** in 91 %, which was hydrogenated followed by subsequent cyclization to give the lactam **9** (78 %). The benzyl protecting group was removed by hydrogenolysis with Pd/C to give the alcohol **10**, which was methanesulfonylated followed by iodation to give **12**. Cyclization of **12** to the indolizidinone (-)-**13**[5] was carried out using NaH as a base (62 % from **9**).



Scheme 2

The indolizidinone (-)-**13** is an useful synthetic intermediate of 5,8-disubstituted indolizidine alkaloids[6] and converted to (-)-**209B**, (-)-**205A** and (-)-**235B**. Thus, reaction of (-)-**13** with pentylmagnesium bromide in THF followed by reduction with $NaBH_3CN$ in an acidic condition[7] gave (-)-**209B** ($[\alpha]^{24}_D$ -90.1 (c 1.38, MeOH))[8] in 64% yield. Similarly (-)-**205A** ($[\alpha]^{24}_D$ -81.7 (c 0.36, MeOH))[9] and (-)-**235B** ($[\alpha]^{24}_D$ -72.0 (c 0.80, MeOH))[10] were synthesized in 12% and 27% respectively by the reaction with the corresponding Grignard reagents.



Scheme 3

Acknowledgement. We thank Professor Takashi Tokuyama of Osaka City University for providing us NMR spectra of 205A and 235B. This research was financially supported by the Grant in Aid from Ministry of Education, Science and Culture (No 04217235).

References and Notes

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(5) (-)-**13**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.62-3.54 (m, 1 H), 3.50-3.45 (m, 1 H), 3.05-2.95 (m, 1 H), 2.54-2.43 (m, 1 H), 2.40-2.28 (m, 1 H), 2.20-2.13 (m, 1 H), 2.01-1.92 (m, 1 H), 1.86-1.80 (m, 1 H), 1.80-1.68 (m, 1 H), 1.52-1.34 (m, 3 H), 1.03 (d, 3 H, J = 5.8 Hz); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 168.2 (s), 64.5 (d), 44.7 (t), 34.9 (d), 31.8 (t), 31.0 (t), 29.6 (t), 21.6 (t), 17.7 (q); IR (KBr) 2958, 1618, 1474, 1289 cm^{-1}; MS m/z 153, 125, 111, 97, 83, 70, 56, 53, 50; HRMS calcd m/z 153.1154, found m/z 153.1126; $[\alpha]^{24}_D$ -21.5 (c 0.65, $CHCl_3$); Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.31; H, 10.09; N, 9.00.

(6) Synthesis of (*5α, 8β, 8aβ*)-(±)-5-(2-furanyl)-8-methyloctahydroindolizine (**16**) from (±)-**13** has described. LaLonde, R. T.; Muhammad, N.; Wong, C. F.; Sturiale, E. R. *J. Org. Chem.* **1980**, *45*, 3664-3671. By a similar procedure the optically active **16** ($[\alpha]_D$ -108 (c 1.04, $CHCl_3$)) was synthesized by the reaction of (-)-**13** and 3-lithiofuran followed by reduction with $NaBH_3CN$. Shimizu, I.; Shoji, K. unpublished results.

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(8) **(-)-209B**; [lit.2d $[\alpha]^{28}_D$ -91.3 (c 0.58, MeOH)], [lit.2b $[\alpha]^{20}_D$ -94.3 (c 1.85, MeOH)]

(9) **(-)-205A**; [lit.2a $[\alpha]^{28}_D$ -83.5 (c 0.30, MeOH)], [lit.1a $[\alpha]^{20}_D$ -35 (c 0.24, MeOH)]

(10) **(-)-235B**; [lit.2a $[\alpha]^{28}_D$ -73.4 (c 1, MeOH)], [lit.1a $[\alpha]^{20}_D$ +11.3 (c 1.0, MeOH)]