Tetrahedron: Asymmetry Vol. 4, No. 7, pp. 1455-1456, 1993
Printed in Great Britain

0957-4166/93 $6.00+.00
Pergamon Press Ltd

Synthesis of Natural Lentiginosine Employing a Cyclic Imide with C_2-Symmetry Derived from L-Tartaric Acid

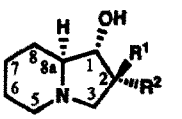
Hidemi Yoda,* Hidekazu Kitayama, Takao Katagiri, and Kunihiko Takabe*

Department of Applied Chemistry, Faculty of Engineering,
Shizuoka University, Hamamatsu 432, Japan

(*Received in Japan* 7 *April* 1993)

Abstract: *The first efficient and simple process is described for the synthesis of a new (1S, 2S, 8aS)-1,2-dihydroxyindolizidine alkaloid, lentiginosine. The synthetic strategy is based on asymmetric deoxygenation of the quarternary α-hydroxy lactam prepared from a C_2-symmetrical imide derived from L-tartaric acid.*

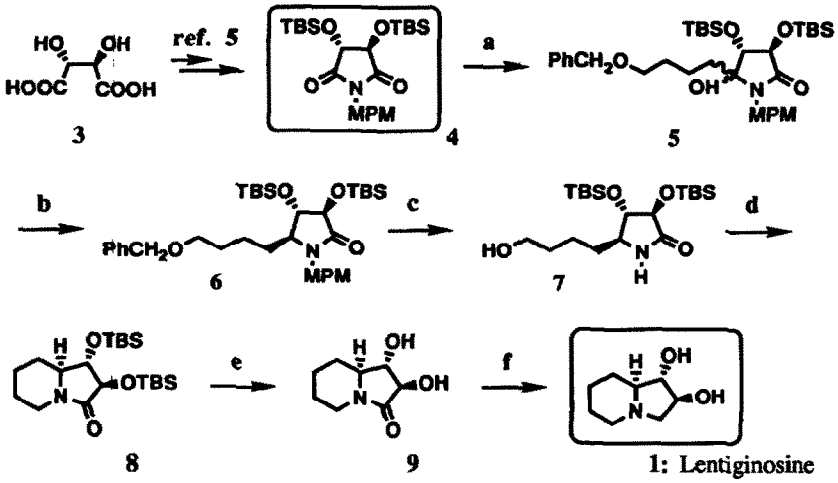
Lentiginosine (**1**), a *trans*-dihydroxyindolizidine alkaloid was first isolated from the spotted locoweed, *Astragalus lentiginosus var. diphysus* by Elbein et al. in 1990 and was indicated to be the first inhibitor of the fungal α-glucosidase, amyloglucosidase that has been found that has only two hydroxy groups.[1] Although the *cis*-diol (**2**) of the 2-epimer producing potent biologically active indolizidine alkaloids such as swainsonine and slaframine[2] has also been isolated[3] and racemic[3,4] and asymmetric enantiodivergent synthesis[2a] have been reported, the *cis*-compound as well as other dihydroxyindolizidines obtained from natural sources exhibit no significant glycosidase inhibitory activity.[1] In addition, no procedure for the synthesis of *trans*-**1** has so far appeared in spite of its simple structure.



1: $R^1 = OH$, $R^2 = H$
2: $R^1 = H$, $R^2 = OH$

Herein we wish to communicate the details of a synthetic strategy employing the method disclosed in the preceding report in which *trans*-selective asymmetric deoxygenation of quarternary α-hydroxy lactams is an essential step for introducing a stereogenic center bearing the alkyl side chain.

C_2-imide (**4**) with a *N*-*p*-methoxybenzyl group, obtained from L-tartaric acid (**3**) in 53% yield, was treated with Grignard reagent prepared from 1,4-butanediol to give the labile quarternary α-hydroxy lactam (**5**),[5] which readily underwent to reductive deoxygenation with Et_3SiH in the presence of $BF_3 \cdot OEt_2$.[6] The reaction proceeded smoothly at -78 °C to provide the homochiral lactam (**6**), $[\alpha]_D^{22}$+8.27(c 5.46, $CHCl_3$), with the desired stereochemistry (96.1 : 3.9 determined by HPLC using Daicel Chiralpak AS) *trans* with respect to the C-4 substituent.[7] After successive removal of the protecting groups from **6** with CAN and Pd(black), product **7**, $[\alpha]_D^{23}$+15.3(c 2.87, $CHCl_3$), thus obtained was mesylated and cyclized, leading to the bicyclic amide (**8**), $[\alpha]_D^{23}$+58.0(c 5.20, $CHCl_3$), in good yield. Treatment of **8** in acidic conditions resulted in the



Scheme 1. Reagents and Conditions: (a) $PhCH_2O(CH_2)_4MgBr$, THF, -78 - 0 °C; 85%; (b) Et_3SiH, $BF_3 \cdot OEt_2$, CH_2Cl_2, -78 °C; 95%; (c) 1, $Ce(NH_4)_2(NO_3)_6$,CH_3CN-H_2O, 0 °C; 2, Pd(black), HCOOH, *i*-PrOH; 27% (2 steps); (d) 1, MsCl, Et_3N, CH_2Cl_2; 2, NaH, THF; 90% (2 steps); (e) HCl, MeOH; 100%; (f) $LiAlH_4$, THF, reflux; 100%.

preparation of **9**, $[\alpha]_D^{22}$+58.0(c 1.36, MeOH), which was finally reduced effectively with $LiAlH_4$ in refuxing THF to complete the short and convenient total synthesis of lentiginosine (**1**), $[\alpha]_D^{23}$+0.19(c 6.10, MeOH).[8] The spectral data of the synthetic **1** were completely identical with those of reported natural compound[1] and homochiral **1** thus synthesized is determined with 92% de at the C-8a center based on the HPLC analysis (Daicel Chiralpak AS).

In summary, the first asymmetric synthesis of natural lentiginosine was established employing chiral C_2-imide (**4**) derived from L-tartaric acid as a key intermediate, which will furthermore serve for the synthesis of other natural products.

References and notes

1. Pastuszak, I.; Molyneux, R. J.; James, L. F.; Elbein, A. D. *Biochemistry* **1990**, *29*, 1886; Molyneux, R. J. *J. Nat. Prod.* **1990**, *53*, 609.
2. (a) Heitz, M.-P.; Overmann, L. E. *J. Org. Chem.* **1989**, *54*, 2591 and references cited therein; (b) Harris, C. M.; Schneider, M. J.; Ungemach, F. S.; Hill, J. E.; Harris, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 940.
3. Harris, T. M.; Harris, C. M.; Hill, J. E.; Ungemach, F. S. *J. Org. Chem.* **1987**, *52*, 3094.
4. Colegate, S. M.; Dorling, P. R.; Huxtable, C. R. *Aust. J. Chem.* **1984**, *37*, 1503.
5. Yoda, H.; Shirakawa, K.; Takabe, K. *Chem. Lett.* **1991**, 489; Yoda, H.; Shirakawa, K.; Takabe, K. *Tetrahedron Lett.* **1991**, *32*, 3401.
6. See our preceding report.
7. The absolute configuration of the newly formed chiral center of **5** was determined based on the observed chemical sift and vicinal coupling constants ($J_{4,5}$ and $J_{5,6}$) according to our preceding report; ^1H NMR data ($CDCl_3$, 90 MHz) for **5**: δ -0.015 (3H, s), 0.069 (3H, s), 0.18 (3H, s), 0.21 (3H, s), 0.83 (9H, s), 0.92 (9H, s), 1.19-1.85 (6H, m), 3.11 (1H, dt, $J_{4,5}$ = 1.8 Hz, $J_{5,6}$ = 5.3 Hz), 3.44 (2H, t, J = 5.93 Hz), 3.75 (3H, s), 3.83 (1H, t, J = 1.98 Hz), 3.83 (1H, d, J = 14.9 Hz), 4.00 (1H, d, J = 1.97 Hz), 4.48 (2H, s), 5.00 (1H, d, J = 14.9 Hz), 6.80 (2H, d, J = 8.79 Hz), 7.13 (2H, d, J = 8.79 Hz), 7.31 (5H, s).
8. Lentiginosine extracted from natural sources[1] showed $[\alpha]_D^{24}$-3.3(c 0.33, MeOH). The difference between natural and synthetic **1** in the specific rotation is due to the presence of its diastereomer in the product.