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A novel concise total synthesis of (+)-lentiginosine

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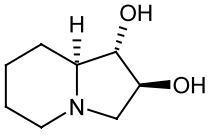
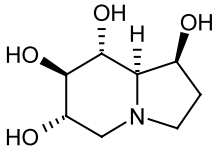
Abstract—A total synthesis of (+)-lentiginosine was achieved by using ethyl 3-(pyridin-2-yl)acrylate *N*-oxide as the starting material and an improved Sharpless asymmetric dihydroxylation as the key step.

Lentiginosine **1**, was isolated from the leaves of *Astragalus lentiginosus*, whose absolute configuration created an ambiguity.[1] It was reported to be a selective and powerful inhibitor of amyloglucosidases[1a,2] and to be twice as powerful as another natural polyhydroxyindolizidine, castanospermine **2**, which has potent glycosidase inhibitory and anti-HIV activity.[3] Consequently, much attention has been devoted to the synthesis of (+)-lentiginosine during the past decade. Most of the previous methodologies utilized tartaric acid as starting material.[4] Others used a furanose derivative,[5] 1,2,7-trihydroxyindolizidine derivatives,[6] enol ether[7] or pipecolinic acid[8] as the chiral precursors. However, to the best of our knowledge, only one approach to the target compound **1** has been reported,[9] starting from a nonchiral pyridine derivative instead of the above-mentioned chiral pool.



lentiginosine 1



castanospermine 2

Despite this plethora of methods, interest in the synthesis of (+)-lentiginosine and its analogues remains undiminished. Development of general methods which could have flexibility for the construction of these compounds continues to be important for investigating their structure–activity relationships. In continuation of our previous work[10] for asymmetric dihydroxylation of heteroaromatic acrylates, herein we describe an easy route to (+)-lentiginosine starting from ethyl 3-(pyridin-2-yl)acrylate *N*-oxide **3**, which was derived from picolinaldehyde by Wittig reaction followed by oxidation[11] (Scheme 1).

Asymmetric dihydroxylation (AD) of ethyl 3-(pyridyl-2-yl)acrylate was not successful, so the nitrogen atom on the pyridine ring was blocked with oxygen in order not to interfere with the catalytic cycle of AD. AD of **3** using 3 mol% $(DHQ)_2PHAL$ and 5 equiv. of K_2CO_3 gave the diol **4** in 62% yield with 20% recovery of the starting material and >99.9% ee.[12] This new reaction system has an advantage over the usual system (1 mol% $(DHQ)_2PHAL$ and 3 equiv. of K_2CO_3) in the AD reaction in that it reduces the reaction time and increases the yield and the enantioselectivity, most likely due to greater proportion of ligand[13] and higher pH[14] used. In the next step, reduction of **4** using ammonium formate[15] as hydrogen source failed to produce **5** or **6**. However, removal of oxygen atom from *N*-oxide, reduction of pyridine ring and intramolecular cyclization of the diol **4** were achieved in one step by hydrogenation under 10 atm with 10% Pd–C in MeOH/Et_3N, affording a 3.2:1 (determined by ^1H NMR) mixture of the lactam **5** and **6** in 95% yield. The minor isomer **6** could be readily removed by recrystallization from ethyl acetate and pure **5** {$[\alpha]_D$ +77.3 (*c* 1.4, MeOH)} was obtained in 43% yield from **4**. The stereochemistry of **5** was assigned by a 2D-NOESY spectrum recorded with 600 MHz ^1H NMR, in which no NOE correlation was found between 6-H and 7-H. Meanwhile, the characteristic doublet at δ 4.29 (H-8) and a triplet at δ 3.91 (H-7) with coupling constants $J_{6,7} = J_{7,8} = 6.9$ Hz established the *trans–trans* relationship. Reduction of **5** with BH_3:Me_2S in THF[8] furnished **1** in 75% yield {$[\alpha]_D$ +1.7 (*c* 0.37, MeOH) (lit. $[\alpha]_D$ +0.19 (*c*

Keywords: (+)-lentiginosine; total synthesis; asymmetric dihydroxylation.

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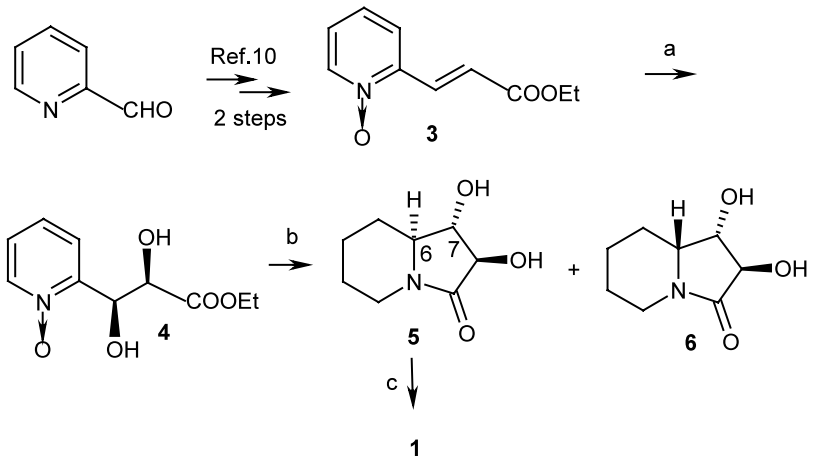

Scheme 1. *Reagents and conditions*: (a) 0.4 mol% $K_2[OsO_2(OH)_4]$, 3 mol% $(DHQ)_2PHAL$, 3 equiv. of $K_3[Fe(CN)_6]$, 5 equiv. of K_2CO_3 and 1 equiv. of $MeSO_2NH_2$ in $H_2O/^tBuOH$ (1:1), 24 h, 62% with 20% recovery of the starting material; (b) 10% Pd–C, 10 atm H_2, MeOH, 24 h, 43% of **5**; (c) BH_3:SMe_2, THF, 0°C–rt, 10 h, 75%.

6 MeOH),[4a] $[\alpha]_D$ +3.2 (*c* 0.27, MeOH);[4d] mp 104–106°C (lit. 106–107°C)[4d]) whose ^1H NMR spectrum was consistent with the previous report.[1b,4d]

In conclusion, a very concise total synthesis gave (+)-lentiginosine **1** in 20% overall yield in only three steps from a readily available material **3** based on an improved Sharpless asymmetric dihydroxylation and a highly efficient protocol of cyclization. So far as we know, this is the shortest route among those for using non-chiral starting materials. Extension of this methodology to the synthesis of other polyhydroxy indolizidine alkaloids is in progress.

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