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Asymmetric synthesis of (+)-lentiginosine using a chiral aziridine based approach

Hojong Yoon [a], Kyung Seon Cho [a], Taebo Sim [a,b,*]

[a] *Chemical Kinomics Research Center, Korea Institute of Science and Technology, Hwarangro 14-gil 5, Seongbuk-gu, Seoul 136-791, Republic of Korea*
[b] *KU-KIST Graduate School of Converging Science and Technology, 145, Anam-ro, Seongbuk-gu, Seoul 136-713, Republic of Korea*

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ABSTRACT

The synthesis of the indolizidine alkaloid, (+)-lentiginosine, is described. A key feature of the preparative route is the efficient and stereoselective construction of a dihydroxylated pyrrolidine via Sharpless asymmetric dihydroxylation of an aziridine-enoate, which was prepared from commercially available 1-(*S*)-α-methylbenzylaziridine-2-methanol. In addition, a regioselective aziridine-to-pyrrolidinone ring expansion process followed by a Wittig olefination was employed to construct a late stage pyrrolidine intermediate that was transformed into (+)-lentiginosine.

1. Introduction

Glycosidases are enzymes that catalyze glycoside hydrolysis reactions that occur in numerous anabolic/catabolic processes in living systems.[1] Since blocking these enzymes can be used as a general strategy to treat various diseases, the development of potent and selective glycosidase inhibitors is in high demand. Since nojirimycin, a natural glycosidase inhibitor, was isolated and characterized from a *Streptomyces* strain in 1966,[2] a number of glycosidase inhibitors that possess carbosugar and iminosugar like structures have been developed. These inhibitors have received great attention because of their interesting anti-diabetic, anti-tumor metastasis, anti-HIV, anti-influenza, and pharmaceutical properties.[3] Especially interesting in this regard are the iminosugar type glycosidase inhibitors miglitol (Glyset®), a drug used for the treatment of type II diabetes mellitus,[4] and miglistat (*N*-butyl-deoxynojirimycin, Zavesca®), a drug employed for the treatment of Gaucher's disease.[5]

(+)-Lentiginosine **1**, an indolizidine alkaloid that was first isolated from *Astragalus lentiginosus* in 1990 by Elbein et al.[6] (Fig. 1), has been reported to be a selective and highly potent inhibitor (IC_{50} = 0.43 μg/L) on amyloglucosidase.[1] Furthermore, Piaz et al. in 2011 reported that (+)-lentiginosine has anti-Hsp90 activity.[7] These observations make this dihydroxylated indolizidine an interesting lead compound for drug discovery. In addition to its interesting biological activities, (+)-lentiginosine **1** has an attractive chemical structure because it contains three contiguous and functionalized stereogenic centers. As a consequence of these features, new strategies for the preparation of this iminosugar would have both synthetic and biomedical significance.

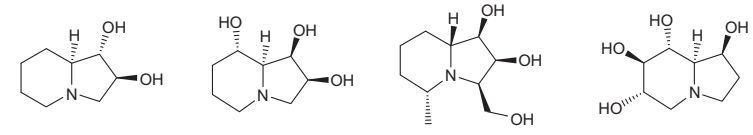

Figure 1. Naturally occurring polyhydroxylated indolizidines.

* Corresponding author. Tel.: +82 2 958 6437; fax: +82 2 958 5189.
E-mail address: tbsim@kist.re.kr (T. Sim).

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Several routes have been developed for the synthesis of (+)-lentiginosine, all of which employ modern synthetic methods to accomplish the key steps. Successful approaches to this target have relied on a variety of processes including (1) RCM to generate a piperidine backbone;[8] (2) dihydroxylation of an (*E*)-unsaturated ester;[8b,9] (3) an Aza-cope rearrangement[8b] and tandem Mitsunobu reaction/[3.3]-sigmatropic rearrangement of an azide;[10] (4) a sequential enantioselective diethylzinc addition and [3.3]-sigmatropic rearrangement of an allylcyanate;[11] (5) intramolecular radical cyclization of an acylsilane;[12] (6) a coupled catalytic asymmetric Heck-type cyclization and stereoselective epoxidation;[13] (7) stereospecific alkene bromohydration using a chiral β-hydroxy-γ,δ-unsaturated sulfoxides;[14] (8) asymmetric deoxygenation of a quaternary α-hydroxypyrrolidine derivative derived from D-xylose;[15] (9) thermal rearrangement of an isoxazolidine derived by using a 1,3-dipolar cycloaddition reaction of a nitrone;[16] and (10) organometallic addition to a nitrone followed by reduction and RCM.[17] Importantly, most of reported routes begin with non-racemic chiral starting materials that are derived from naturally occurring sugars or acids.[8a,c,11–13,16–18]

In continuing studies focused on the synthesis of biologically and structurally interesting alkaloids, we have developed a novel and efficient approach to the synthesis of (+)-lentiginosine **1**, which began with the use of the commercially available 1-(*S*)-α-methylbenzylaziridine-2-methanol **6**. The route uses a key Sharpless asymmetric dihydroxylation reaction of an (*E*)-aziridine-enoate, derived from **6**, and a regioselective aziridine-to-pyrrolidinone ring expansion process to generate a key dihydroxylated pyrrolidine intermediate, which contains the three contiguous stereogenic centers of the target with the correct absolute configurations.

2. Results and discussion

Our strategy to prepare (+)-lentiginosine **1** is based on the retrosynthetic analysis illustrated in Scheme 1. We envisioned that the indolizidine ring in the target compound could be formed from 2-butenylpyrrolidine derivative **2** via hydrogenolysis and subsequent cyclization. In addition, we believed that a regioselective aziridine ring opening/lactam ring formation sequence starting with diol **4** would serve as an efficient method to generate the functionalized pyrrolidine **3**, a precursor of **2**. Finally, we reasoned that the *anti*-diol array in **4** could be readily installed in a highly diastereoselective manner via Sharpless asymmetric dihydroxylation of the (*E*)-3-(aziridin-2-yl)acrylate **5**, a substance directly produced from chiral aziridine **6**.

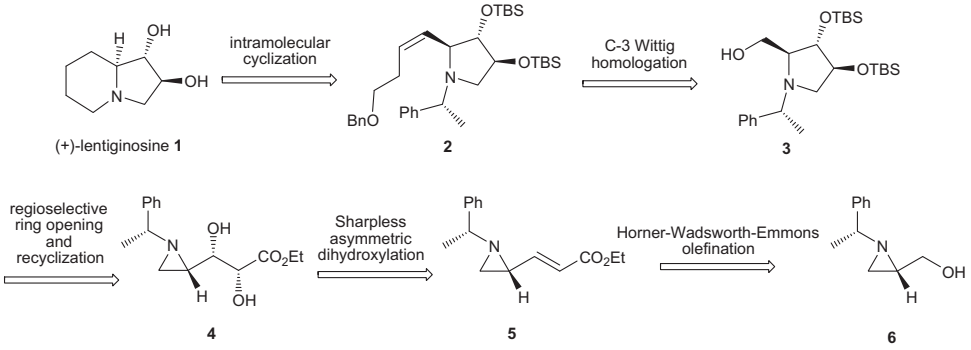
The preparation of (+)-lentiginosine **1** started with a two-step synthesis of (*E*)-3-(aziridin-2-yl)acrylate **5** in 72% yield by using previously described procedures (Scheme 2).[19] Although we developed various conditions for carrying out dihydroxylation reactions for aziridine-enoate type substrates in an earlier effort,[19] a brief exploratory study was conducted to uncover an ideal method for the conversion of (*E*)-3-(aziridin-2-yl)acrylate **5** into diol **4**.

Dihydroxylation of **5** employing conditions described by Donohoe et al. (OsO_4/TMEDA complex)[20] did not yield the desired product. In addition, catalytic dihydroxylation using OsO_4/NMO in the absence of a chiral ligand resulted in formation of a mixture of diols **4a** and **4b** with a low level (3:2) of diastereoselectivity. Both of these outcomes are consistent with previously reported observations.[21] Sharpless asymmetric dihydroxylation of **5** using AD-mix-α generated the desired diol **4a** with high diastereoselectivity (**4a**/**4b** = 11:1), and which was isolated in 63% yield using silica gel column chromatography (Table 1).

The C-3 bond of the aziridine ring in diol **4a** was cleaved regioselectively by using excess AcOH in CH_2Cl_2 (Scheme 3).[22] This process furnished a ring opened amine product that subsequently underwent efficient (72%) lactam forming cyclization[23] in toluene at 90 °C to produce pyrrolidinone **8**. It is important to note that this ring expansion strategy should be applicable to the synthesis of various polyhydroxylated pyrrolidine alkaloids.[24]

Protection of the alcohol groups in **8** using TBSOTf afforded the bis-TBS-ether **9** (91%). Since the simultaneous reduction of both the acetate and amide groups in **9** using BH_3SMe_2 resulted in a low yield of **3** (62%), an alternate route was employed. Accordingly, hydrolysis of the acetate group with KOH followed by in situ reduction of the amide group using BH_3SMe_2 furnished the corresponding hydroxypyrrolidine **3** in high yield (81% over two steps). Following the strategy proposed for the synthesis of (+)-lentiginosine that is outlined retrosynthetically in Scheme 1, the primary alcohol group in **3** was oxidized using Swern conditions to yield the corresponding aldehyde, which in a crude form was subjected to a Wittig 3-carbon homologation process using the benzyloxypropylphosphonium salt **12**. This reaction produced *cis*-olefin **2** as a single isomer in high yield (66% over two steps, 2 g scale).

Cleavage of the *N*-phenylethyl group and reduction of the olefin moiety in **2** were readily accomplished by utilizing catalytic hydrogenation with $Pd(OH)_2$ in methanol at room temperature containing a catalytic amount of TFA. This process produced amino alcohol **10** in 88% yield as a mixture of a free base and a TFA salt. Neutralization with triethylamine then gave the free base form of **10**. After purification by using silica gel column chromatography, compound **10** was treated sequentially with CBr_4/PPh_3 and triethylamine to promote piperidine ring formation, a process that generated indolizidine **11**[25] in 74% yield. Finally, removal of the TBS protecting groups under acidic conditions (3 M HCl) furnished (+)-lentiginosine **1** in 86% yield. The identity of synthetic (+)-lentiginosine **1** was confirmed by showing that its spectroscopic and optical properties {^{1}H and ^{13}C NMR, and specific rotation: $[\alpha]_D^{19.8} = +2.2$



Scheme 1. Retrosynthetic analysis of (+)-lentiginosine **1**.