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doi.org/10.1002/ajoc.202500103

ASIAN JOURNAL OF ORGANIC CHEMISTRY
Research Article

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Synthesis of (−)-8a-*epi*-Lentiginosine via Tsuji–Trost Reaction of D-Glucose-Derived Allylic Alcohols and Crystal Structure Analysis

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An indolizidine alkaloid, (−)-8a-*epi*-lentiginosine was synthesized from D-glucose using the Pd-BiPhePhos catalyzed intramolecular Tsuji–Trost reaction of non−derivatized allylic alcohol as a key construction of the hydroxylated pyrrolidine ring to give the desired product in good yield and high stereospecificity (*dr* = 97:3). The absolute configuration and structure of (−)-8a-*epi*-lentiginosine were confirmed by NMR and X-ray crystal structure analysis. The crystal structure of (−)-8a-*epi*-lentiginosne showed the envelope conformation of the five-membered ring, which is an N-atom in the endo-position, and the fused six-membered ring adopts a chair conformation similar to the DFT optimized structure. The solid-state packing is dominated by a 1D-hydrogen-bonded network along the a-axis involving both hydroxyl groups and the amine. The large HOMO–LUMO energy gap indicated the high stability of the compound.

1. Introduction

D-Glucose, a monomer from cellulose and hemicellulose, is the most abundant building block in nature, which has been used as a substrate for synthesizing various natural products and biologically active compounds since it is an inexpensive chiral pool substrate.[1] The stereospecific nucleophilic substitution reaction, such as the direct substitution of the —OH by the Mitsunobu method[2] and the substitution of derivatized alcohol such as triflate and mesylate, has been manipulated to use the advantage of the chiral —OH group present in the structure of D-glucose and other monosaccharides. However, these methods generate a stoichiometric amount of chemical waste, and a greener alternative would be beneficial.[3] Our group has developed the direct stereospecific substitution reactions of the —OH group without prior derivatization delivering the chiral product using several catalysts such as the iron (III) trifluoromethane sulfonate ($Fe(OTf)_3$),[4] phosphinic acid (H_3PO_2)[5] and palladium with a bidentate phosphite ligand (Pd-BiPhePhos).[6] Both inversions of the configuration of the products and retention of the configuration of the products were obtained depending on the catalyst used.

(+)-Lentiginosine, an indolizidine alkaloid natural product from *Astragalus lentiginosus*, inhibited amyloglucosidase activity[7] as well as inhibited ATPase activity of Heat shock protein 90 (Hsp90),[8] making this class of compound an interesting lead for the design of a new class of multifunctional inhibitors. In contrast, (−)-lentiginosine was found to induce apoptosis in tumor cells, suggesting its potential as an anticancer agent.[9] The absolute stereochemistry of natural lentiginosine was initially uncertain due to the absence of any reported X-ray crystal structures. This ambiguity was resolved through the total synthesis of both enantiomers and by comparing their amyloglycosidase inhibitory activity.[10] Many synthetic applications of this compound and its non-natural isomer, as well as lentiginosine-related structures such as (−)-swainsonine (**3**) and (+)-castanospermine (**4**) (Figure 1) have been carried out by several research groups due to its interesting biological activities.[11] We reported the synthesis of (+)-lentiginosine from D-glucose using our developed intramolecular stereospecific substitution of non−derivatized allylic alcohol as a key construction of the hydroxylated pyrrolizidine ring using $Fe(OTf)_3$ as a catalyst to afford the ring C8a—N bond of (+)-lentiginosine with inversion of the stereochemistry at the C4 of the D-glucose.[4] In this study, we reported the synthesis of a non-natural isomer of (+)-letiginosine, (−)-8a-*epi*-lentiginosine from D-glucose using the Pd-BiPhePhos catalyzed intramolecular Tsuji–Trost reaction

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Supporting information for this article is available on the WWW under https://doi.org/10.1002/ajoc.202500103

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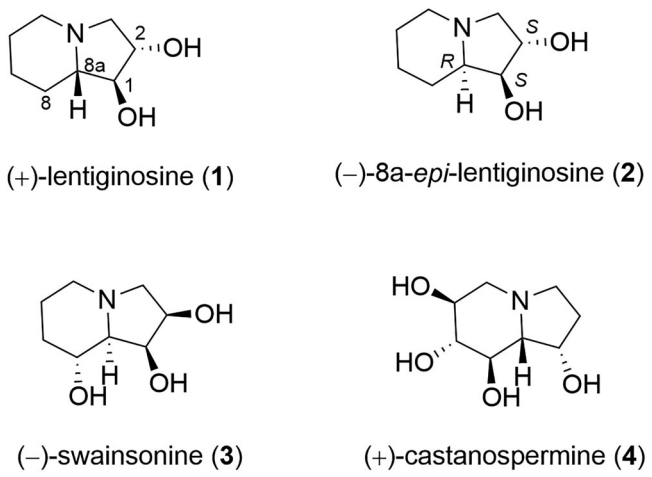
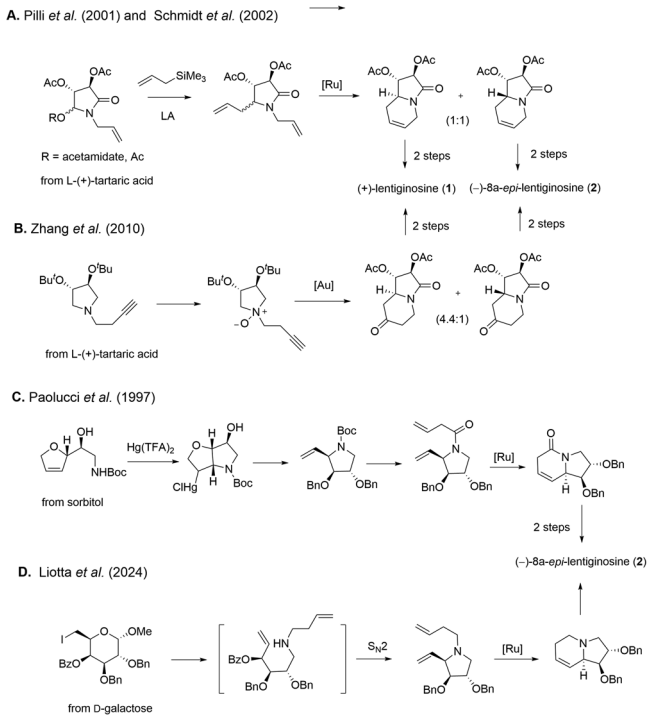


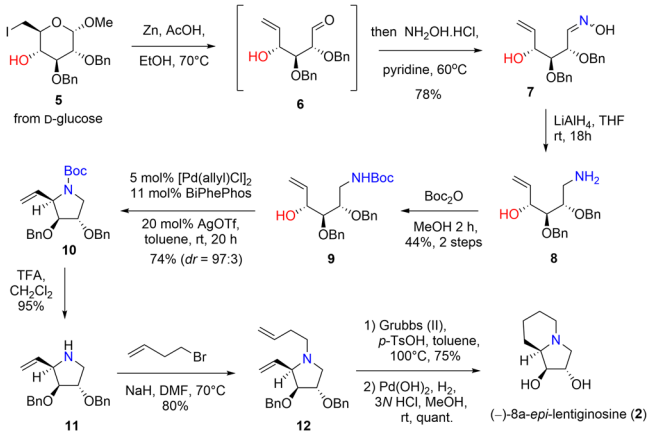
Figure 1. (+)-Lentiginosine and related indolizidine alkaloids.



Scheme 1. Previous synthesis of (−)-8a-*epi*-lentiginosine (**2**) from chiral substrates.

of non−derivatized allylic alcohol with X-ray crystal structure determination of (−)-8a-*epi*-lentiginosine.

The synthetic methods for (−)-8a-*epi*-lentiginosine were reported by employing both chiral and nonchiral substrates. Previous synthesis of (−)-8a-*epi*-lentiginosine from natural chiral pool material is illustrated in Scheme 1. Pilli[12] and Schmidt[13] used L-tartaric acid as the starting material which contained the *1S, 2S* configuration of the lentiginosine. However, formation of the C8—C8a bond via α-amido alkylation method with allyl silane nucleophile gave a mixture of the C8a stereoisomers and led to 1:1 mixture of (−)-8a-*epi*-lentiginosine (**2**) and (+)-lentiginosine (**1**) (Scheme 1A). Zhang and coworkers installed the C8a configuration via gold-catalyzed oxidative cyclization



Scheme 2. Synthesis of (−)-8a-*epi*-lentiginosine (**2**) from D-glucose.

method providing mixtures of (−)-8a-*epi*-lentiginosine (**2**) and (+)-lentiginosine (**1**) in 1:4.4 ratio (Scheme 1B).[14] Synthesis of (−)-8a-*epi*-lentiginosine from sorbitol was reported by Paolucci and coworkers (Scheme 1C).[15] The C8a—N bond of the *epi*-lentiginosine (**2**) was formed by Hg (II)-promoted cyclization of *N*-Boc amino dihydrofuran, affording the oxa-aza bicyclic intermediate with fully stereoselective installation of the 8a*R*-configuration. Recently, Liotta and coworkers disclosed the synthesis of lentiginosine and their non-natural isomers from monosaccharides.[16] The (−)-8a-*epi*-lentiginosine (**2**) was synthesized from D-galactose using intramolecular S_N2 substitution of alcohol derivative (OBz group) by amine to form C8a—N bond (Scheme 1D). In our synthetic route, we started from inexpensive D-glucose and employed an intramolecular Tsuji–Trost reaction of non−derivatized allylic alcohol as a key connection of C8a—N bond with retention of the configuration (Scheme 2). The hydroxyl groups at C1 and C2 of the (−)-8a-*epi*-lentiginosine (**2**) were derived from the monosaccharides. The piperidine ring was constructed via ring-closing metathesis and then hydrogenation. (−)-8a-*epi*-lentiginosine (**2**) was obtained as a single product after deprotection.

2. Results and Discussion

2.1. Synthesis of (−)-8a-*epi*-Lentiginosine (2)

The hydroxygenated pyrrolidine ring of the *epi*-lentiginosine was constructed by employing Pd-BiPhePhos that catalyzed an intramolecular allylic amination of non−derivatized allylic alcohol **9** derived from D-glucose. Previous studies of the Pd-BiPhePhos catalyzed substitution of allylic alcohols with weak amino-based nucleophiles such as aniline and carbamate that proceed smoothly and provide the product in high yield and stereospecificity.[6] 4-Methoxyaniline and other stronger nucleophilic amines, such as 4-butenylamine, did not produce the substituted product. This could be due to the formation of palladium hydride intermediate, which favors slightly acidic conditions.[17] *N*-Boc amino alcohol **9** was chosen as a substrate for the allylic amination since the Boc group is easy to install

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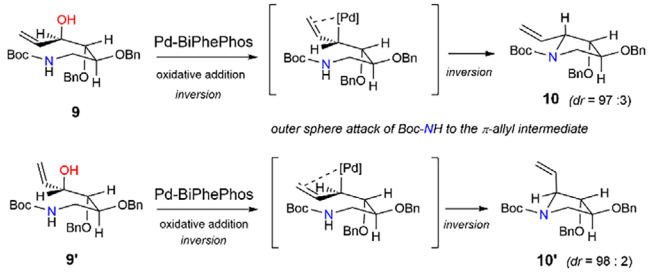

Scheme 3. Pd-BiPhePhos catalyzed intramolecular cyclization of amino alcohols **9** and **9′**.

by treating amine **8** with di-*tert*-butyl dicarbonate, and the Boc group is easily removed by treatment with acid such as TFA or HCl. Amine **8** was obtained from the domino Bernet–Vasella reductive elimination of the 5-iodoglucopyronoside **5** to transform the cyclic monosaccharide to an open chain aldehyde **6**, followed by oxime formation and reduction of the oxime by using $LiAlH_4$. The one-pot transformation of 5-iodoglucopyronoside **5** to amine **8** was performed using Timmer's method (Zn, NH_3/NH_4OAc, and $NaCNBH_3$).[18] Unfortunately, it resulted in a low yield of amine **8**. The intramolecular allylic substitution of **9** using Pd(allyl)BiPhePhos (OTf) complex afforded the pyrrolidine **10** with retention of the stereochemistry to the starting alcohol **9** (*dr* = 97:3, determined by ^{1}H-NMR, see SI) without observing any side products from S_N2' reaction. The net retention of the stereochemistry of the pyrrolidine **10** involved stereoinvertive oxidative addition of the Pd-BiPhePhos to form the π-allylpalladium intermediate, which was then attacked by NH-Boc nucleophile from the outer sphere to produce the product with inversion of the configuration to the π-allylpalladium intermediate.[17] The neighboring-benzyloxy group at C-2 and C-3 in the structure of D-glucose and D-galactose did not interfere with the catalyst reactivity and gave highly diastereomeric ratio of the product (Scheme 3). We observed a broad signal of ^{1}H-NMR and split signals in ^{13}C-NMR of *N*-Boc pyrrolidine **10** (see Supporting Information) due to carbamate bond rotation.[19] A sharp NMR signal was observed when the Boc group was removed. The Boc group was then replaced by a butenyl group to generate diene intermediate **12**, which forms a six-membered ring using Grubbs (2nd generation) catalyst. Reduction of the alkene and deprotection of the benzyloxy group by $Pd(OH)_2/H_2$ afforded (−)-8a-*epi*-lentiginosine (**2**) in an overall yield of 14% from **5**. This is an efficient synthetic method for (−)-8a-*epi*-lentiginosine (**2**) from abundant and renewable D-glucose without using highly toxic catalysts and reagents. Nevertheless, for broader application and scalability, certain synthetic steps still require further optimization to achieve a truly green and sustainable process.

2.2. X-ray Crystal Structure Analysis

Information from crystal structure analysis is not only essential for structural determination but also plays a crucial role in various research fields, including drug development[20] and other applications. To the best of our knowledge, this study represents the first X-ray crystal structure determination of lentiginosine and its stereoisomers. (−)-8a-*epi*-Lentiginosine crystallizes in the chiral orthorhombic space group $P2_12_12_1$ as colorless blocks with one independent molecule in the unit cell. The absolute structure is established based on the stereochemistry of the starting D-glucose. Atoms C1–C4 and N1 of the crystal structure build a five-membered ring with N1-atom in the endo-position of the envelope. The fused six-membered ring adopts a chair conformation. The trans-annular N1—C4 bond is significantly longer (1.4775(18) Å) than the other C—N distances (1.4681(19) Å) (Figure 2). All other bonding distances and angles are unexceptional.[21]

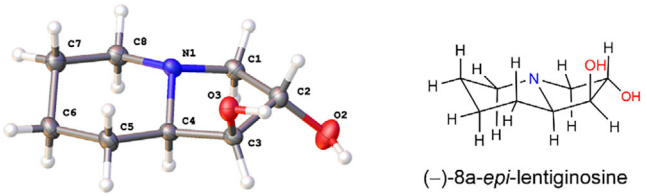

Figure 2. Solid-state structure ORTEP style with displacement ellipsoids set at 50% probability level.

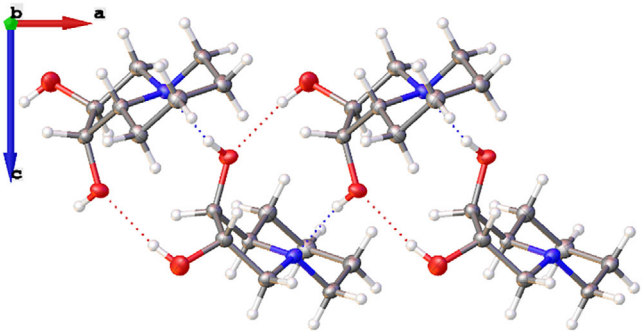

Figure 3. Hydrogen-bonded network.

The solid-state packing is dominated by a 1D-hydrogen bonded network along the a-axis involving both hydroxyl groups and the amine with O···HO and N···HO donor acceptor distances (angles) of 2.8352(16) Å (167.4°) and 2.7786(16) Å (168.0°), respectively (Figure 3).

2.3. Computational Studies

The structure of (−)-8a-*epi*-lentiginosine (**2**) was constructed using Discovery Studio Visualizer 2021[22] and geometrically optimized at the M062X/6-31++g(d,p) level of the method using the Gaussian 16 program.[23] The frequency calculations with the same level of method were also determined to confirm the local minima, as shown in the Supporting Information. By using the alignment by a combination of steric and electrostatic fields in Discovery Studio Visualizer 2021, the optimized structure, as compared with the crystal structure, is shown in Figure 4A

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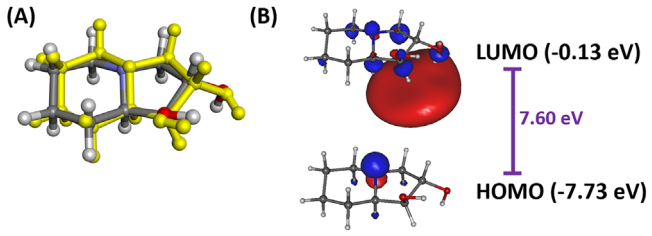

Figure 4. (A) Superimposition between crystal structure (yellow) and optimized structure (atom type color). (B) The HOMO, LUMO, and energy gap of (−)-8a-*epi*-lentiginosine.

with the root-mean-square deviation of non-hydrogen atoms of 0.40 Å. The structural parameters of the crystal structure and optimized structure are shown in Table S1 (Supporting Information). The results indicate that the optimization method can be utilized to predict the molecular structure of (−)-8a-*epi*-lentiginosine (**2**) and its potential stereoisomers. Subsequently, the stability and reactivity of (−)-8a-*epi*-lentiginosine (**2**) were assessed through analysis of highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) (Figure 4B). At the HOMO, the electron density was localized at the nitrogen atom. Whereas, the LUMO was found to localize at the hydroxyl group at the O2 atom. The large HOMO–LUMO energy gap, approximately 7.60 eV, further supports the stability of (−)-8a-*epi*-lentiginosine (**2**).

3. Conclusion

In this study, we report a facile synthetic route to (−)-8a-*epi*-lentiginosine from D-glucose using the intramolecular amination of non−derivatized allylic alcohols as a key construction of the hydroxylated pyrrolidine ring of the lentiginosine. The structure and absolute configuration of the synthesized (−)-8a-*epi*-lentiginosine were confirmed by X-ray crystallography. This report demonstrates the potential of using sugar-based starting materials as feedstock to produce natural products and their non-natural analogs. X-ray crystal structure analysis and computational calculations may reveal important information about molecular orientation, conformation, stability, and reactivity, which could be valuable for future drug development.

Acknowledgements

The authors thank the Swedish Research Council VR for financial support.

Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Allylic alcohol · Crystal structure · Green chemistry · Lentiginosine · Palladium

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Manuscript received: January 26, 2025
Revised manuscript received: April 24, 2025
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