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Total synthesis of (+)-lentiginosine from D-glucose

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ABSTRACT

A total synthesis of (+)-lentiginosine, a potent and selective amyloglucosidase inhibitor, is reported from a D-glucose-derived epoxide in 38% overall yield. In this synthesis, ambient conditions and readily available starting materials and reagents are used.

The synthesis and biological evaluation of naturally occurring and rationally designed glycosidase inhibitors has gained importance[1] through the introduction of drugs for the treatment of various diseases such as diabetes type II,[2] Gaucher's disease[3] and influenza infections.[4] In addition, the design and synthesis of new glycosidase inhibitors against diseases such as AIDS[5] and cancer[6] are also being developed. The majority of glycosidase inhibitors are either derivatives of azasugars or carbasugars, and most of them are either mono or bicyclic. (+)-Lentiginosine **1** (Scheme 1), a bicylic azasugar and the least hydroxylated naturally occurring indolizidine derivative, was isolated in 1990 from the leaves of *Astragalus lentiginosus*.[7] It shows amyloglucosidase inhibition activity at submicromolar concentration (IC_{50} = 0.43 μg/L) and is the most potent and selective amyloglucosidase inhibitor known so far. Due to its interesting activity, many groups have reported its synthesis. Syntheses of optically active (+)-lentiginosine use starting materials such as ribonolactone,[8] tartaric acid,[9] D-xylose,[10] pipecolic acid,[11] D-homoproline,[12] chiral sulfoxide,[13] lactam derivatives[14] and pyridine *N*-oxide derivatives.[15] Some racemic syntheses are also reported in the literature.[16] Although the synthesis of (−)-lentiginosine is known from D-glucose,[17] to the best of our knowledge, no synthesis of (+)-lentiginosine from D-glucose has been reported.

In continuation of our efforts to synthesize glycosidase inhibitors,[18] we herein report a new synthesis of (+)-lentiginosine from D-glucose. Retrosynthetically (Fig. 1) the target molecule **1** can be obtained from the hydroxy pyrrolidine derivative **A** which, in turn, can be obtained from the dimesylate **B**. The dimesylate could readily be derived from the olefin **C** which can be obtained from the corresponding glucose-derived epoxide **D**, via epoxide opening and deoxygenation of the resulting alcohol.

Thus, epoxide **2**, obtained from D-glucose in four steps,[19] upon treatment with allylmagnesium chloride[20] gave the hydroxy derivative **3** in 95% yield, which was characterized by the presence of its internal olefinic proton at δ 5.74 as a multiplet in its ^{1}H NMR spectrum in addition to other spectral data.[21] The hydroxy group was removed using the Barton deoxygenation[22] to give the olefin **4**. Derivative **4** was treated with 10% HCl in methanol to give the acetonide-deprotected acetal[23] **5** in 98% yield, which typically showed the absence of the two geminal methyl groups at δ 1.0 and the appearance of one methoxy resonance at δ 3.39 in its ^{1}H NMR spectrum. The free hydroxy group of **5** was protected as its benzyl ether to give **6** in 97% yield. The acetal moiety of **6** was hydrolyzed[24] by treatment with 3 M HCl in refluxing dioxane, followed by reduction with $NaBH_4$ to give diol **7** in 88% yield. This diol was treated with $MsCl/Et_3N$ to give the corresponding dimesylate **8** in 96% yield, which showed the presence of two methyl singlets at δ 2.9 in its ^{1}H NMR spectrum. The double bond of **8** was cleaved using $OsO_4/NaIO_4$ followed by reduction with $NaBH_4$ to give the hydroxy derivative **9** in good yield.[25,26] Treatment of **9** with neat benzylamine[27] at 90 °C gave the pyrrolidine derivative **10**. The ^{1}H NMR spectrum showed the complete disappearance of the mesylate singlets and an increase in the number of phenyl protons, which confirmed the formation of the pyrrolidine system. Hydroxypyrrolidine **10** on treatment with $MsCl/Et_3N$ formed a very polar compound, most likely a quaternary ammonium salt,[28] which upon treatment with Pd/C in methanol under 5 atm H_2 gave (+)-lentiginosine **1** in 81% yield. All the spectral and analytical data for **1** were

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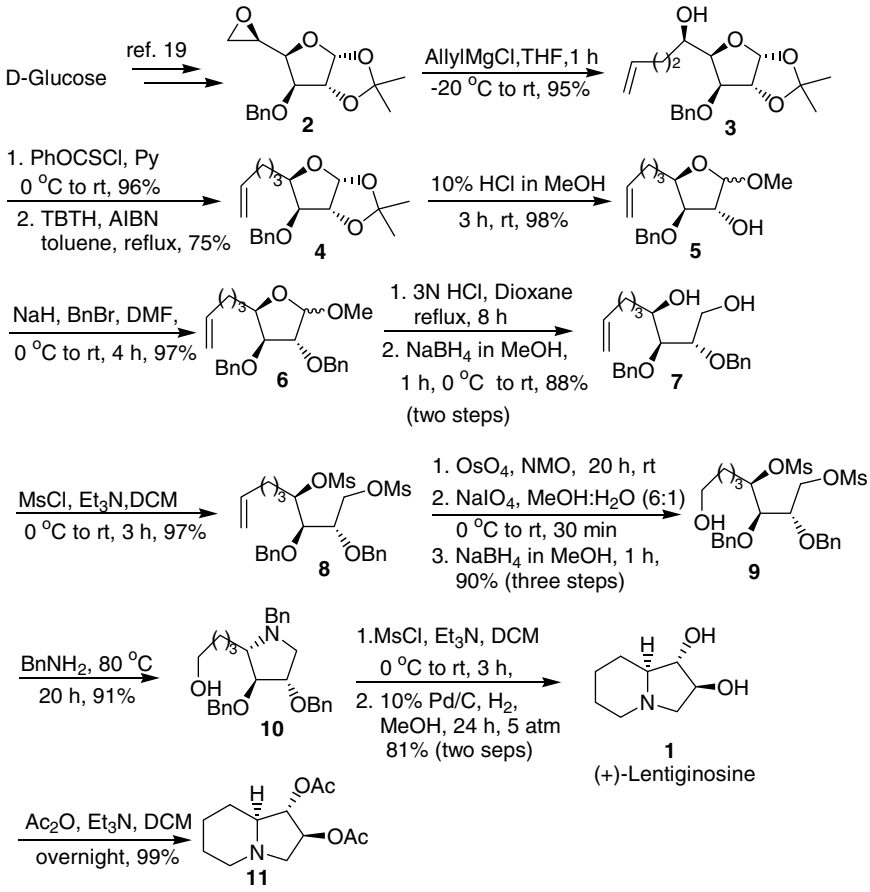

Scheme 1.

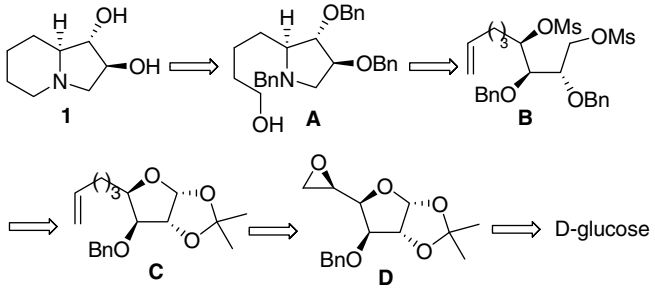

Figure 1. Retrosynthesis of (+)-lentiginosine.

in agreement with the data reported in the literature.[29] Moreover, **1** was further characterized as its acetate derivative **11**.[30]

In conclusion, we have synthesized (+)-lentiginosine from the D-glucose-derived epoxide **2** in an efficient manner in 38% overall yield. This synthetic scheme can be utilized for the preparation of analogues of lentiginosine, and work towards this direction is being pursued in our laboratory.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.07.057.

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26. *(2S,3R,4R)-2,3-Bis(benzyloxy)-8-hydroxyoctane-1,4-diyl dimethanesulfonate* (**9**): $[\alpha]_D^{25}$ +1.98 (*c* 0.50, CH_2Cl_2). IR (thin film, cm^{-1}): 3561, 3030, 2937, 2872, 1496, 1353, 1173, 1072. ^1H NMR (500 MHz, $CDCl_3$): δ 7.36–7.25 (10H, m), 4.81–44.78 (1H, m), 4.72 (1H, d, *J* = 9.2 Hz), 4.67 (1H, d, *J* = 9.2 Hz) 4.64 (1H, d, *J* = 9.2 Hz), 4.57 (1H, d *J* = 9.2 Hz), 4.38 (2H, d, *J* = 3.6 Hz), 3.88 (1H, q, *J* = 3.6, 7.6 Hz), 3.68 (1H, t, *J* = 4.0 Hz), 3.56 (2H, t, *J* = 5.2 Hz), 2.96 (3H, s), 2.96 (3H, s), 1.77–1.73 (1H, m), 1.60 (1H, m), 1.49–1.39 (3H, m), 1.37–1.27 (1H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.0, 128.6, 128.3, 128.2, 81.1, 75.9, 74.6, 73.4, 68.3, 62.2, 38.7, 37.4, 32.0, 30.6, 21.0. HRMS (ESI): calcd for $C_{24}H_{34}O_9S_2$ $[M+H]^+$ 531.1722, found 531.1720.
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30. *(+)-1,2-Diacetoxyindolizidine* (**11**): $[\alpha]_D^{25}$ +2.10 (*c* 1.00, CH_2Cl_2). IR (thin film, cm^{-1}): 2937, 2854, 2794, 1741, 1372, 1243, 1046. ^1H NMR (500 MHz, $CDCl_3$): δ 4.99–4.97 (1H, m), 4.92 (1H, dd, *J* = 2.0, 6.4 Hz), 3.01–2.96 (2H, m), 2.59 (1H, dd, *J* = 5.2, 8.8 Hz), 2.06 (3H, s), 2.05 (3H, s), 2.04–2.02 (1H, m), 1.99–1.85 (2H, m), 1.83–1.65 (2H, m), 1.40–1.33 (2H, m), 1.24–1.85 (1H, m). ^3C NMR (125 MHz, $CDCl_3$): δ 170.8, 170.2, 82.1, 67.6, 59.8, 53.0, 28.7, 24.5, 23.6, 21.0, 20.9; HRMS (ESI): calcd for $C_{12}H_{19}NO_4$ $[M+H]^+$ 242.1392, found 242.1392.