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Total syntheses of (±)-lentiginosine and (±)-1-*epi*-lentiginosine from hexahydro-1*H*-indol-3-one

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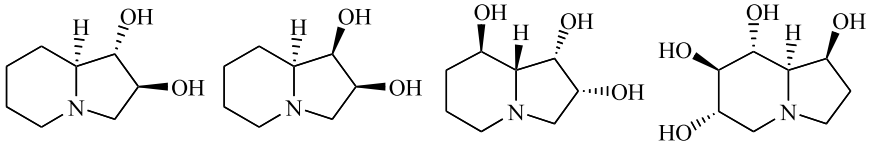
Abstract—Total syntheses of (±)-lentiginosine **1** and (±)-1-*epi*-lentiginosine **2** were achieved efficiently from hexahydro-1*H*-indol-3-one **7**.

A number of polyhydroxylated indolizidines, such as lentiginosine **1**, swainsonine **3**, and castanospermine **4**, isolated from natural sources are powerful and specific inhibitors of α- and β-glycosidases.[1]

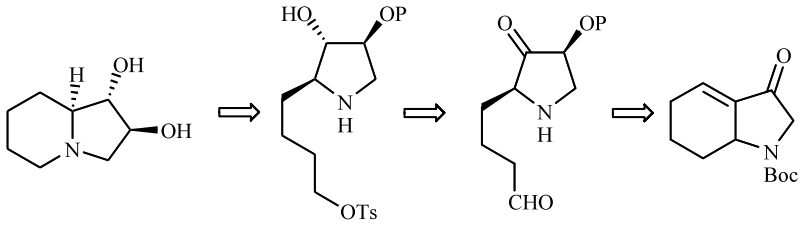


lentiginosine **1** *1-epi-lentiginosine* **2** *swainsonine* **3** *castanospermine* **4**

Lentiginosine **1**, containing only two hydroxyl groups, was isolated from the leaves of *Astragalus lentiginosus* in 1990.[2] Several successful total syntheses of **1** have been achieved.[3] In this communication, we report an efficient total synthesis of (±)-lentiginosine **1** and (±)-*epi*-lentiginosine **2** by an entirely different approach.

In our earlier work, we have developed a facile anionic cyclization approach towards hexahydro-1*H*-indol-3-one **7**, and also applied that method to the total synthesis of (−)-brunsvigine.[4] As a continuation, we were interested in the development of a general synthetic method for the construction of indolizidine alkaloids starting from compound **7**. We envisaged that reduction of the carbonyl group followed by cleavage of the double bond in **7** would provide the intermediate **6** having the necessary functional groups for elaboration of indolizidine alkaloids. The retro-synthetic analysis of (±)-lentiginosine **1** is depicted in Scheme 1. The target molecule **1** could be synthesized by cyclization of compound **5**. Functionalized intermediate **5** may be obtained from aldehyde **6**. Compound **6** should be readily prepared from hexahydro-1*H*-indol-3-one **7** by $NaBH_4$ reduction followed by ozonolysis.

Luche reduction[5] of compound **7** gave a single diastereomeric alcohol **8**, Scheme 2. Treatment of com-



1 **5** **6** **7**

Scheme 1. P = protecting group.

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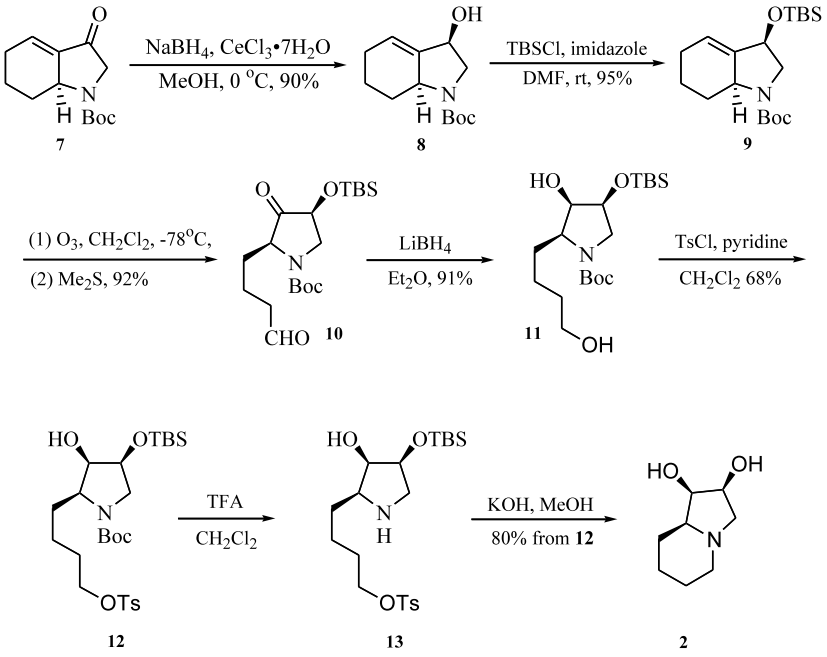
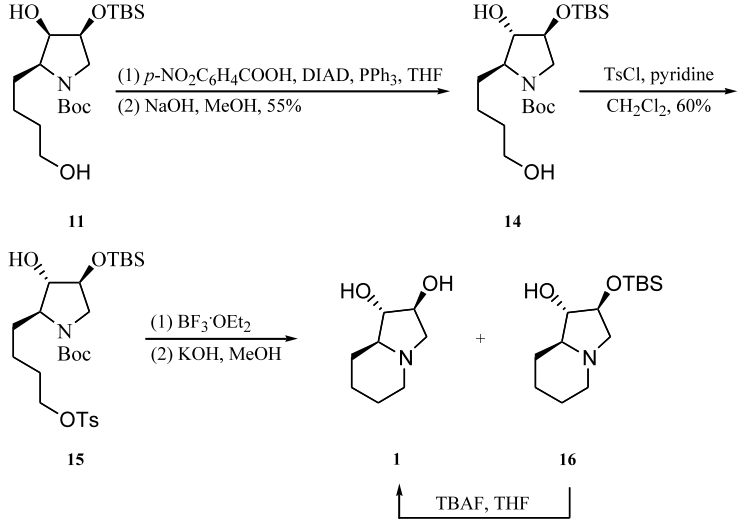


Scheme 2.



Scheme 3.

pound **8** with *tert*-butyldimethylchlorosilane (TBSCl) in the presence of imidazole in *N*,*N*-dimethylformamide (DMF) gave **9**. Ozonolysis of the double bond in **9** afforded compound **10**. Reduction of **10** with lithium borohydride ($LiBH_4$) furnished a single diastereomer **11**. The primary hydroxy group in **11** was tosylated with *p*-toluenesulfonyl chloride (TsCl) to afford **12**. Removal of Boc group in **12** by trifluoroacetic acid (TFA) in dichloromethane furnished **13**. Treatment of **13** with KOH in methanol afforded (±)-1-*epi*-lentiginosine **2**.

Furthermore, starting with intermediate **11**, the synthesis of (±)-lentiginosine **1** was achieved in three steps with good yield. Inversion of the configuration at C2 in **11** was achieved via a Mitsunobu reaction[6] to furnish **14** (Scheme 3). Reaction of **14** with TsCl gave compound **15** in 60% yield along with some recovered compound **14** (30%). Treatment of **15** with BF_3 etherate followed by reaction with KOH in methanol afforded target molecule (±)-lentiginosine **1** (36%) and some TBS group protected compound **16** (54%). Compound **16** was separated by flash column chromatography (SiO_2,

$CHCl_3$:MeOH:$NH_{3(aq.)}$; 80:20:1) and then treated with tetrabutylammonium fluoride (TBAF) in THF to give (±)-lentiginosine **1** in 88% yield. Overall, **1** was obtained in 84% from **15**. All spectral data[7] of **1** and **2** were in good agreement with those reported in the literature.[2]

In summary, we have achieved total syntheses of (±)-lentiginosine **1** and (±)-1-*epi*-lentiginosine **2** via a straightforward approach from a simple starting material, hexahydro-1*H*-indol-3-one **7**. This methodology might be applied to the total synthesis of other indolizidine or pyrrolizidine alkaloids. Further work along this line is in progress.

Acknowledgements

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7. Our data of (±)-lentiginosine **1**: ^{1}H NMR (600 MHz, D_2O), δ 4.07 (ddd, $J=7.6$, 4.0, 1.6 Hz, 1H), 3.65 (dd, $J=8.9$, 4.0 Hz, 1H), 2.97 (br, $J=11.2$ Hz, 1H), 2.85 (dd, $J=11.3$, 1.6 Hz, 1H), 2.68 (dd, $J=11.3$, 7.6 Hz, 1H), 2.11 (ddd, $J=11.3$, 11.3, 3.0 Hz, 1H), 2.01 (m, 1H), 1.94–1.91 (m, 1H), 1.82–1.78 (m, 1H), 1.66–1.63 (m, 1H), 1.50–1.41 (m, 1H), 1.30–1.21 (m, 2H); ^{13}C NMR (100 MHz, D_2O) δ 85.5 (CH), 78.3 (CH), 71.3 (CH), 62.9 (CH_2), 55.4 (CH_2), 30.2 (CH_2), 26.6 (CH_2), 25.7 (CH_2); IR (neat) 3625, 1094, 1090 cm^{-1}; MS (EI) m/z 157 (M^+, 4), 140 (36), 123 (100); HRMS (EI) m/z calcd for $C_8H_{15}NO_2$ 157.1103, found 157.1101.
Our data of (±)-1-*epi*-lentiginosine **2**: ^{1}H NMR (600 MHz, $CDCl_3$), δ 4.26–4.22 (m, 1H), 4.01 (dd, $J=6.0$, 4.1 Hz, 1H), 3.42 (br s, 2H), 3.12–3.09 (m, 1H), 3.02 (dd, $J=10.9$, 1.8 Hz, 1H), 2.40 (dd, $J=10.9$, 7.2 Hz, 1H), 2.01–1.95 (m, 2H), 1.87–1.83 (m, 1H), 1.77–1.73 (m, 1H), 1.67–1.52 (m, 3H), 1.28–1.18 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 75.5 (CH), 69.6 (CH), 67.9 (CH), 62.5 (CH_2), 53.2 (CH_2), 25.0 (CH_2), 24.9 (CH_2), 23.7 (CH_2); IR (neat) 3626, 1095, 1089 cm^{-1}; MS (EI) m/z 157 (M^+, 6), 140 (39), 123 (100); HRMS (EI) m/z calcd for $C_8H_{15}NO_2$ 157.1103, found 157.1100.