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A concise synthesis of (−)-lentiginosine via an *anti*,*syn*-oxazine

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ABSTRACT

A concise and stereocontrolled total synthesis of (−)-lentiginosine, a potent glycosidase inhibitor, has been achieved. Starting from *anti*,*syn*-oxazine as a chiral building block, the key features in these strategies are the Wittig reaction and cyclization.

1. Introduction

Polyhydroxylated indolizidine alkaloids such as swainsonine, castanospermine, and lentiginosine are known to be potential glycosidase inhibitors.[1,2] Among them, the least hydroxylated lentiginosine was isolated from the leaves of *Astragalus lentiginous* in 1990;[3] (−)-lentiginosine **1** was found to be a selective inhibitor (IC_{50} 5 mg/mL) of amyloglucosidase, an enzyme that hydrolyzes 1,4- and 1,6-α-glucosidic linkages, and also exhibits anti-HIV activity.[4] Several synthetic approaches to this structure have been reported[5] (Fig. 1). In recent representative publications, Liu et al.

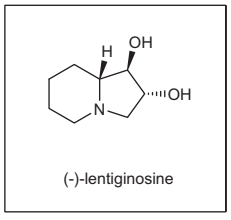
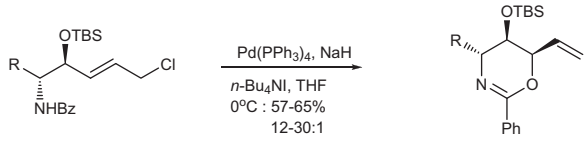


Figure 1. Structure of (−)-lentiginosine.

demonstrated an asymmetric synthesis of (−)-lentiginosine by a double aza-Michael reaction.[5a] Kim et al. reported a facile synthesis of lentiginosine analogues based on a highly regio- and diastereoselective allylic amination using chlorosulfonyl isocyanate.[5b] Azzouz et al. also described a concise synthesis of lentiginosine derivatives using pyridinium formation via a Mitsunobu reaction.[5e] These routes give products with good enantiopurity but are limited in terms of access to structural analogues.

In a previous report, we found that the palladium(0)-catalyzed oxazine formation of γ-allyl benzamide, with a benzoyl substituent as an *N*-protecting group in the presence of $Pd(PPh_3)_4$, NaH, and *n*-Bu_4NI might proceed with high stereoselectivity. The bulk of the protecting group on the secondary alcohol is responsible for controlling the diastereoselectivity of oxazine ring formation[6] (Scheme 1). This process efficiently adjusted the stereochemistry



R = (a) C_6H_5, (b) $C_6H_5CH_2$, (c) $(CH_3)_2CH$, (d) $(CH_3)_2CHCH_2$, (e) $TBSOCH_2$

Scheme 1. Oxazine formation catalyzed by Pd(0).

and provided simultaneous protection for the newly generated hydroxyl group. The synthetic utility of *anti*,*syn*-oxazines as chiral building blocks has been demonstrated by their successful application to the synthesis of biologically active natural products such as DAB-1, D-fagomine, D-*lyxo*-phytosphingosine, and pachastrissamine.[7a,b]

As part of the expansion of the synthetic utility of chiral *anti*,*syn*-oxazines, we have also been exploring the development of a novel strategy for the concise total synthesis of a bicyclic natural product. Herein we report a straightforward procedure for the highly stereocontrolled total synthesis of (−)-lentiginosine **1**. We envisioned that our intramolecular palladium(0)-catalyzed oxazine formation reaction could be utilized to set the three contiguous stereocenters of (−)-lentiginosine **1**.

As shown in Scheme 2, our retrosynthetic analysis suggested that (−)-lentiginosine **1** could be easily obtained from a common

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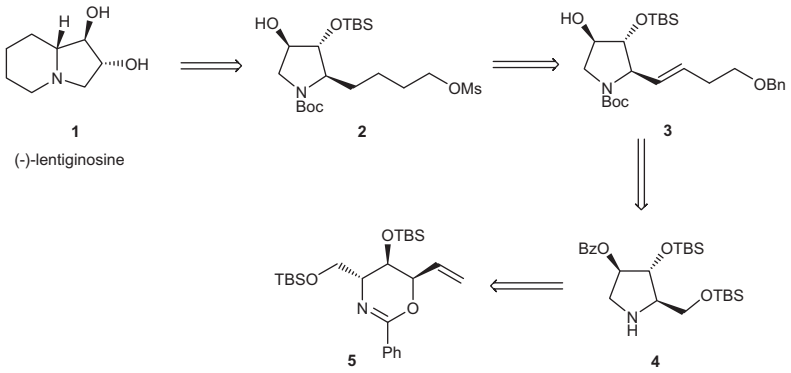


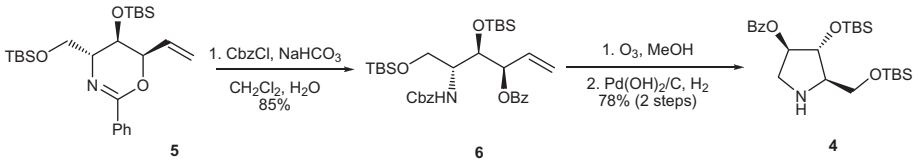
Scheme 2. Retrosynthesis of (−)-lentiginosine **1**.

intermediate, *anti*,*syn*-oxazine **5**. (−)-Lentigonosine **1** could be prepared from compound **2** by cyclization. Compound **2** could be synthesized by hydrogenation of **3** and subsequent mesylation of the primary hydroxyl group. Compound **3** could be converted from compound **4** by Wittig reaction and DMP oxidation. The vinyl group of *anti*,*syn*-oxazine **5** could be converted into the corresponding aldehyde, which could be employed in the formation of the pyrrolidine ring via catalytic hydrogenation of *anti*,*syn*-oxazine **5**. Therefore, *anti*,*syn*-oxazine **5** was prepared from *N*-benzoyled-D-serine methyl ester according to a known procedure by palladium(0) catalyzed oxazine formation reaction.[7b,10]

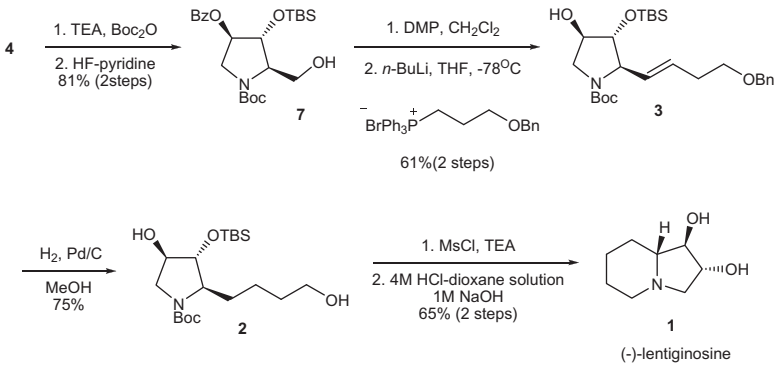
2. Results and discussion

Under the reported conditions,[7b] *anti*,*syn*-oxazine **5** was treated with benzyl chloroformate in the presence of aqueous $NaHCO_3$ (Schotten–Baumann conditions), to afford the carbamate product **6** in 85% yield. Ozonolysis of the terminal olefin gave the corresponding aldehyde. Hydrogenolysis of the aldehyde in MeOH was performed under 70 psi of H_2 catalyzed by $Pd(OH)_2$ at ambient temperature. Under these conditions, a single isomer **4** was formed by cleavage of the carbamate moiety followed by cyclization of the intermediate aminoaldehyde with 78% yield (two steps), as shown in Scheme 3.

As shown in Scheme 4, the pyrrolidine ring **4** was protected with Boc_2O. The *N*-Boc compound **4** was reacted with HF–pyridine to afford the selectively deprotected free primary alcohol in good yield. Oxidation of the primary hydroxyl group **7** with Dess–Martin periodinane produced the corresponding aldehyde, which was subsequently reacted with (3-benzyloxypropyl)triphenylphosphonium bromide in the presence of 3.0 equiv of *n*-BuLi in THF at 0 °C to give the debenzoylated olefin **3** in moderate yield.[8] Catalytic hydrogenation of **3** with Pd/C produced **2** by simultaneous deprotection of the benzyl group and reduction of the internal olefin. Mesylation of the primary alcohol gave the mesylate compound in excellent yield. After removal of the Boc and TBS groups with 4 M HCl–dioxane solution, subsequent cyclization (effected by treatment of NaOH) afforded (−)-lentiginosine **1** in 65% yield (two steps).[9] The specific rotation of **1**, $[\alpha]_D^{25} = -3.2$ (*c* 1.0, MeOH), compared to the reported values, $[\alpha]_D^{25} = -3.0$ (*c* 0.3, MeOH),[5a] $[\alpha]_D^{25} = -3.05$ (*c* 1.0, MeOH),[5g] confirmed the absolute configuration of **1**.



Scheme 3. Synthesis of the pyrrolidine ring.



Scheme 4. Synthesis of (−)-lentiginosine **1**.

The spectroscopic (^{1}H and ^{13}C NMR) data for synthetic **1** were fully identical with those of synthetic compounds and the properties of **1** showed good agreement with those reported.[5a,g,f]

3. Conclusion

In conclusion, we have shown that the indolizidine alkaloid (−)-lentiginosine can be readily obtained through a convergent sequence starting from a chiral 1,3-oxazine. The key features in these strategies are the Wittig reaction and cyclization. The net results were the synthesis via a linear sequence of 10 steps from *anti*,*syn*-oxazine **5** in 15.7% overall yield for (−)-lentiginosine **1**.[5]

4. Experimental section

4.1. General

Optical rotations were measured on a polarimeter in the solvent specified. ^{1}H NMR and ^{13}C NMR spectra were obtained from Cooperative Center for Research Facilities in Sungkyunkwan University on FT-NMR 125, 175, 500, or 700 MHz spectrometers. Chemical shift values are reported in parts per million relative to TMS or $CDCl_3$ as an internal standard and coupling constants in Hertz. IR spectra were measured on a FT-IR spectrometer. Mass spectroscopic data were obtained from the Korea Basic Science Institute (Daegu) on Jeol JMS 700 high resolution mass spectrometer. Flash chromatography was executed using mixtures of ethyl acetate and hexane as eluents. Unless otherwise noted, all non-aqueous reactions were carried out under an argon atmosphere with commercial grade reagents and solvents. Tetrahydrofuran (THF) was distilled over sodium and benzophenone (indicator). Methylene chloride (CH_2Cl_2) was distilled from calcium hydride.

4.2. Experimental procedures

4.2.1. (4*R*,5*R*,6*R*)-5-(*tert*-Butyldimethylsilyloxy)-4-((*tert*-butyldimethylsilyloxy)methyl)-2-phenyl-6-vinyl-5,6-di-hydro-4*H*-1,3-oxazine 5

Colorless oil; R_f = 0.5 (ethyl acetate/hexane = 1/30); $[\alpha]_D^{25} = +3.8$ (*c* 1.0, $CHCl_3$); IR (neat) ν_{max}: 2929, 2360, 1661, 1471, 1254, 1115, 836, 777 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.08–0.20 (m, 12H), 0.88–0.96 (m, 18H), 3.47 (dd, *J* = 3.0, 5.0, 8.0 Hz, 1H), 3.83 (dd, *J* = 5.0, 10.0 Hz, 1H), 4.02 (dd, *J* = 3.0, 10.0 1H), 4.21 (dd, *J* = 4.0, 7.0 Hz, 1H), 4.80 (ddd, *J* = 2.0, 4.0, 7.0 Hz, 1H), 5.35 (ddd, *J* = 1.0, 2.0, 7.0 Hz, 1H), 5.40 (ddd, *J* = 1.0, 2.0, 13.0 Hz, 1H), 6.10 (ddd, *J* = 5.0, 10.5, 17.0 Hz, 1H), 7.38–7.47 (m, 3H), 8.01–8.04 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.04, −4.99, −4.51, −4.35, 18.27, 18.55, 26.00, 26.13, 26.27, 59.62, 64.13, 65.35, 75.93, 117.54, 127.62, 128.21, 130.59, 133.72, 133.79, 154.43; HRMS (FAB$^+$) (M$^+$+H) *m*/*z* calcd for $C_{25}H_{44}NO_3Si_2$ 462.2860 found 462.2860.

4.2.2. (3*R*,4*R*,5*R*)-5-(Benzyloxycarbonylamino)-4,6-bis (*tert*-butyldimethylsilyloxy)hex-1-en-3-yl benzoate 6

To a solution of oxazine **5** (1.1 g, 2.38 mmol) in CH_2Cl_2 (15.9 mL) was added a solution of $NaHCO_3$ (800 mg, 9.53 mmol) in water (15.9 mL), and the mixture was cooled in an ice bath. To this solution was added dropwise a solution of benzyl chloroformate (0.68 mL, 4.76 mmol). The mixture was stirred at room temperature for 24 h. Next, benzyl chloroformate (0.68 mL, 4.76 mmol) was added. The mixture was continued stirring (24 h) until TLC indicated that the reaction was complete. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layer was washed with water, dried ($MgSO_4$), and concentrated in vacuo. Purification by silica gel chromatography (ethyl acetate/hexane = 1/15) gave alkene **6** (1.24 g, 85%) as a colorless oil; R_f = 0.67 (ethyl acetate/hexane = 1/6); $[\alpha]_D^{25} = +39.6$ (*c* 1.0, $CHCl_3$); IR (neat) ν_{max}: 3455, 2952, 2857, 1724, 1260, 1103, 930 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.03–0.10 (m, 12H), 0.86 (s, 9H), 0.88 (s, 9H), 3.75 (dd, *J* = 4.7, 10.0 Hz, 2H), 3.92 (dd, *J* = 5.4, 10.0 Hz, 1H), 4.16 (t, *J* = 5.1 Hz, 1H), 5.04–5.14 (m, 2H), 5.29–5.43 (m, 2H), 5.64 (t, *J* = 5.6 Hz, 1H), 6.04 (ddd, *J* = 6.2, 10.7, 17.2 Hz, 1H), 7.32–7.41 (m, 7H), 7.52–7.57 (m, 1H), 8.05 (d, *J* = 7.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −5.26, −5.16, −4.46, −4.13, 0.21, 18.39, 26.09, 54.92, 61.42, 66.81, 72.67, 76.57, 118.82, 128.17, 128.21, 128.67, 129.89, 130.47, 133.89, 133.27, 136.94, 156.64, 165.61; HRMS (FAB$^+$) (M$^+$+H) *m*/*z* calcd for $C_{33}H_{51}NO_6Si_2$ 614.3333 found 614.3331.

4.2.3. (3*R*,4*R*,5*R*)-4-(*tert*-Butyldimethylsilyloxy)-5-((*tert*-butyldimethylsilyloxy)methyl)pyrrolidin-3-yl-benzo-ate 4

Alkene **6** (1.24 g, 2.02 mmol) was dissolved in dry methanol (50 mL) and cooled to −78 °C. Ozone was then passed through the solution until the reaction was complete. The reaction mixture was quenched with $(CH_3)_2S$ (1.5 mL) and allowed to warm to room temperature. The solvents were evaporated under reduced pressure. The crude aldehyde was immediately employed in the next step without further purification. A solution of the aldehyde in MeOH (30 mL), to which was added 620 mg of 20% $Pd(OH)_2$/C, was vigorously shaken under 75 psi H_2 for 24 h at ambient temperature. The mixture was then filtered through a pad of silica and concentrated in vacuo. Purification by column chromatography over silica gel (ethyl acetate/hexane = 1/10) gave the pyrrolidine **4** (734 mg, 78% for two steps) as a colorless oil; R_f = 0.38 (ethyl acetate/hexanes = 1/2); $[\alpha]_D^{25} = -39.2$ (*c* 1.0, $CHCl_3$); IR (neat) ν_{max}: 2941, 2859, 1722, 1462, 1388, 1263, 1107, 841 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.04–0.14 (m, 12H), 0.93–0.96 (m, 18H), 2.14 (s, br, 1H, NH), 3.02–3.14 (m, 2H), 3.45 (dd, *J* = 5.7, 13.2 Hz, 1H), 3.78 (dd, *J* = 4.5, 10.0 Hz, 1H), 3.86 (dd, *J* = 4.5, 10.2 Hz, 1H), 4.34–4.37 (m, 1H), 5.19–5.23 (m, 1H), 7.30–7.49 (m, 2H), 7.57–7.63 (m, 1H), 8.05–8.08 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −5.27, −5.22, −4.73, −4.33, 18.17, 18.53, 25.97, 26.12, 51.92, 62.14, 68.13, 78.21, 83.67, 128.58, 129.86, 130.32, 133.26, 166.27; HRMS (FAB$^+$) (M$^+$+H) *m*/*z* calcd for $C_{24}H_{44}NO_4Si_2$ 466.2809 found 466.2802.

4.2.4. (2*R*,3*R*,4*R*)-*tert*-Butyl 4-(benzoyloxy)-3-(*tert*-butyl-dimethylsilyloxy)-2-(hydroxymethyl)pyrrolidine-1-carb-oxylate 7

To a solution of **4** (734 mg, 1.58 mmol) in methanol (15.8 mL) was added triethylamine (0.26 mL, 1.89 mmol) via syringe followed by di(*tert*-butyl)dicarbonate (413 mg, 1.89 mmol) in one portion. The reaction mixture was then stirred for 4 h after which the resulting yellow solution was poured into NH_4Cl. The layer was separated, and the organic layer was washed with water. The organic layer was dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. The crude compound was purified by flash column chromatography (ethyl acetate/hexane = 1/15) to afford Boc protected pyrrolidine **7** (855 mg, 96%) as a colorless oil; R_f = 0.73 (ethyl acetate/hexane = 1/6); $[\alpha]_D^{25} = -10.1$ (*c* 1.0, $CHCl_3$); IR (neat) ν_{max}: 2995, 2931, 2886, 2858, 1727, 1703, 1106, 1073, 837, 778 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.03–0.15 (m, 12H), 0.83 (s, 9H), 0.89 (s, 9H), 1.47 (d, *J* = 11 Hz, 9H), 3.40–3.96 (m, 5H), 4.53 (d, *J* = 16.5 Hz, 1H), 5.17 (d, *J* = 12.5 Hz, 1H), 7.44 (t, *J* = 7.0 Hz, 2H), 7.57 (t, *J* = 7.0 Hz, 1H), 8.01 (t, *J* = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 175 MHz) δ −5.42, −5.18, −4.64, −4.48, 18.11, 25.92, 26.02, 28.70, 50.91, 61.44, 67.23, 75.53, 78.94, 128.67, 129.87, 130.00, 133.45, 154.91, 165.58; HRMS (FAB$^+$) (M$^+$+H) *m*/*z* calcd for $C_{29}H_{51}NO_6Si_2$ 566.3333 found 566.3330.

To a solution of Boc protected pyrrolidine (855 mg, 1.511 mmol) in THF (15 mL) were added pyridine (5.04 mL) and a buffered HF–pyridine solution (1.51 mL, 1.511 mmol) at 0 °C. The reaction mixture was then stirred at room temperature for 4 h before being quenched with saturated aqueous $NaHCO_3$. The

mixture was extracted with EtOAc (50 mL × 3) and the organic layer was washed with distilled water and saturated $CuSO_4$ solution, brine, dried with Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography (ethyl acetate/hexane = 1/6) afforded primary alcohol **7** (564 mg, 83%) as crude oil; R_f = 0.53 (ethyl acetate/hexane = 1/2); $[\alpha]_D^{25} = -15.3$ (*c* 1.0, $CHCl_3$); IR (neat) ν_{max}: 3435, 2954, 2931, 2887, 2858, 1725, 1701, 1407, 1368, 1268, 1109, 838, 779, 712 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.15 (m, 6H), 0.89 (s, 9H), 1.49 (s, 9H), 3.53 (dd, *J* = 1.0, 12.5 Hz, 1H), 3.80–3.90 (m, 4H), 4.15 (s, 1H), 4.40 (s, 1H), 5.15 (br, 1H, OH), 7.46 (t, *J* = 8.0 Hz, 2H), 7.59 (m, 1H), 8.01 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 175 MHz) δ −4.67, −4.44, 18.13, 25.87, 28.61, 51.11, 65.24, 68.65, 77.79, 81.15, 128.77, 129.63, 129.91, 133.66, 154.79, 165.77; HRMS (FAB^+) (M^++H) *m*/*z* calcd for $C_{23}H_{38}NO_6Si$ 452.2468 found 452.2466.

4.2.5. (2*S*,3*R*,4*R*)-*tert*-Butyl 2-((*E*)-4-(benzyloxy)but-1-enyl)-3-(*tert*-butyldimethylsilyloxy)-4-hydroxypyrrolid-ine-1-carboxylate 3

To a solution of Dess–Martin periodinane (2.52 g, 6.25 mmol) in anhydrous CH_2Cl_2 (3 mL) was added a solution of primary alcohol **7** (564 mg, 1.25 mmol) in CH_2Cl_2 (1 mL) at room temperature. The reaction mixture was then stirred at ambient temperature for 2 h. The mixture was diluted with Et_2O after which saturated aqueous $NaHCO_3$ (5 mL) and $Na_2S_2O_3$ (2.39 g) were added and the heterogeneous mixture was stirred at room temperature until the organic layer was clear. The ether layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give the crude aldehyde. Next, *n*-BuLi (2.5 M in hexane, 1.51 mL, 3.76 mmol) was added dropwise to a mixture of (3-benzyloxypropyl)-triphenylphosphonium bromide (1.85 g, 3.76 mmol) in THF (4 mL) at 0 °C. After 30 min of stirring at 0 °C, the crude aldehyde (564 mg, 1.25 mmol) dissolved in anhydrous THF (2.3 mL) was added dropwise. After 6 h, the reaction was partitioned between Et_2O and H_2O. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by chromatography on a silica gel column (ethyl acetate/hexane = 1/6) to afford **3** (358 mg, 61% for two steps) as a colorless oil; R_f = 0.37 (ethyl acetate/hexane = 1/4); $[\alpha]_D^{25} = -18.8$ (*c* 1.0, $CHCl_3$); IR (neat) ν_{max}: 3423, 3064, 3030, 2886, 2857, 1695, 1672, 1473, 1412, 1365, 1307, 1170, 1094, 1000, 838, 778, 737, 698, 671, 609 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.07 (m, 6H), 0.87 (m, 9H), 1.49 (s, 9H), 1.62 (s, 2H), 2.36 (dd, *J* = 4.0, 6.5 Hz, 4H), 2.47 (dd, *J* = 7.5, 13.5 Hz, 1H), 3.35–3.53 (m, 3H), 3.74–4.04 (m, 2H), 4.31 (s, 1H), 4.49 (d, *J* = 1.5 Hz, 1H), 4.52 (s, 1H), 5.50–5.60 (m, 2H), 7.27–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 175 MHz) δ −4.46, −4.47, 18.13, 25.90, 28.59, 28.66, 32.85, 52.90, 63.32, 69.68, 69.99, 73.17, 79.64, 82.72, 126.07, 127.86, 128.55, 128.70, 128.75, 130.83, 132.29, 138.70, 155.10; HRMS (FAB^+) (M^++H) *m*/*z* calcd for $C_{26}H_{43}NO_5Si$ 478.2989 found 478.2985.

4.2.6. (2*S*,3*R*,4*R*)-*tert*-Butyl 3-(*tert*-butyldimethylsilylox-y)-4-hydroxy-2-(4-hydroxybutyl)pyrrolidine-1-carboxy-late 2

A suspension of the above olefin compound (358 mg, 0.75 mmol) in MeOH (8 mL) in the presence of 20% $Pd(OH)_2/C$ (210 mg) at room temperature was hydrogenated at atmospheric pressure overnight. The catalyst was removed by filtration through a Celite pad. The filtrate was evaporated to dryness. The residue was purified by a flash column chromatography (silica gel, chloroform/methanol = 9/1) to give compound **2** (220 mg, 75%) as a colorless oil; R_f = 0.23 (chloroform/methanol = 10/1); $[\alpha]_D^{25} = -18.0$ (*c* 1.0, MeOH); IR (neat) ν_{max}: 3424, 2954, 2930, 1723, 1469, 1407, 1361, 1270, 1070, 837, 778, 712, 371 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.09 (d, *J* = 2.3 Hz, 6H), 0.87 (d *J* = 2.1 Hz, 9H), 0.98 (m, 1H), 1.25–1.35(m, 5H) 1.46 (s, 9H), 1.62–1.68 (m, 1H), 3.25–3.68 (m, 5H), 3.98 (m, 2H), 4.07 (s, 1H, OH), 4.14 (s, 1H, OH); ^{13}C NMR ($CDCl_3$, 175 MHz) δ −4.68, −4.56, 15.07, 17.91, 22.68, 26.43, 28.51, 29.70, 62.99, 66.74, 75.52, 76.18, 80.07, 80.67, 155.21; HRMS (FAB^+) (M^++H) *m*/*z* calcd for $C_{19}H_{39}NO_5Si$ 390.2676 found 390.2678.

4.2.7. (1*R*,2*R*,8a*R*)-Octahydroindolizine-1,2-diol 1 [(−)-lentiginosine]

To a solution of **2** (220 mg, 0.567 mmol) in CH_2Cl_2 (1.13 mL) at 0 °C were successively added triethylamine (0.08 mL), and MsCl (0.05 mL). The reaction mixture was then stirred at 0 °C for 2 h, after which water was added. The aqueous layer was extracted with CH_2Cl_2. The organic layer was washed with saturated NH_4Cl, $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by short flash chromatography on a silica gel column (chloroform/methanol = 10/1) to afford a mesylate compound. To the mesylate compound (198 mg, 0.423 mmol) was added a 4 M HCl–dioxane solution (1.1 mL). The mixture was stirred for 12 h. The mixture was evaporated to dryness and the residue was taken up in water (1.1 mL) and washed three times with CH_2Cl_2 (1.1 mL). The organic layer was back-extracted with water (1.1 mL), and the combined aqueous fractions were adjusted to pH 13 with 1 M NaOH, allowed to stir for 1 h, and extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, and concentrated in vacuo to give lentiginosine **1** (56 mg, 65% for two steps) as a white solid; R_f = 0.32 (chloroform/methanol = 6/1); Mp 102–105 °C; $[\alpha]_D^{25} = -3.2$ (*c* 1.0, MeOH); IR (neat) ν_{max}: 3758, 3694, 2987, 1445, 1210, 1130 cm^{-1}; ^1H NMR (D_2O, 500 MHz) δ 1.05–1.11 (m, 2H), 1.24–1.31 (m, 1H), 1.46 (d, *J* = 13.5 Hz, 1H), 1.63 (dd, *J* = 1.5, 10.0 Hz, 1H), 1.75–1.80 (m, 2H), 1.86–1.91 (m, 1H), 2.46 (dd, *J* = 7.5, 11.5, 1H), 2.66 (dd, *J* = 2.0, 11.5 Hz, 1H), 2.77 (d, *J* = 11.5 Hz, 1H), 3.47 (dd, *J* = 4.0, 9.0 Hz, 1H), 3.91 (m, 1H); ^{13}C NMR ($CDCl_3$, 175 MHz) δ 23.02, 23.95, 27.54, 52.64, 50.21, 68.57, 75.65, 82.89; HRMS (FAB^+) (M^++H) *m*/*z* calcd for $C_8H_{16}NO_2$ 158.1181 found 158.1184.

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10. The requisite *anti,syn*-oxazine precursor was prepared in high yield from the commercially available *N*-benzoyl-D-serine by the five steps sequence shown in following scheme.