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Asymmetric Synthesis of (–)-Lentiginosine by Double Aza-Michael Reaction

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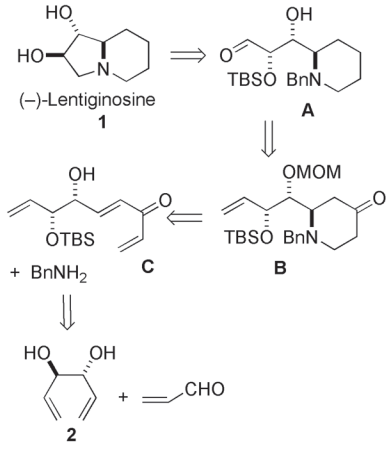
Total synthesis of (–)-lentiginosine (**1**) was achieved in nine steps from (3*R*,4*R*)-3,4-dihydroxy-1,5-hexadiene (**2**). Cross metathesis, vinyl addition and DDQ oxidation were applied to generate the key 3-oxonona-1,4,8-triene **6**, which was cyclised to 4-oxopiperidine **7** by diastereoselective double aza-Michael reaction. Both theoretical and empirical studies support that the stereochemical assignment of the major Michael adduct is the desired (2*R*)-4-oxopiperidine **7**.

Introduction

A variety of polyhydroxylated indolizidines, such as lentiginosine, castanospermine, swainsonine and slaframine, are naturally occurring alkaloids[1] and effective glycosidase inhibitors.[2] Due to the potential use of glycosidase inhibitors as antifungal agents, insecticides, antidiabetics and anti-obesities, antivirals, and therapeutic agents for some genetic disorders, syntheses of these polyhydroxylated indolizidines have attracted the attention of chemists.[3,4] For example, lentiginosine, isolated from the plant *Astragalus lentiginosus* in 1990 and later found as the most powerful, competitive inhibitor of amyloglucosidases known so far,[5,6] has been the subject of a considerable number of synthetic studies.[7,8] Most of the reported syntheses utilized or constructed the five-membered pyrrolidines as the precursors to indolizidines.[7] Recently, Bischoff and Fruit's group efficiently prepared lentiginosine by hydrogenating the corresponding pyridinium cation to the piperidine/lentiginosine in spite of the low stereoselectivity.[8a] However, several examples have shown that a stereocontrolled formation of piperidines could be achieved by double aza-Michael reaction between dienones and amines.[9] As part of our current interest in aza-Michael reactions[10] and the use of (3*R*,4*R*)-3,4-dihydroxy-1,5-hexadiene (**2**) as a versatile synthetic block,[11] we envisioned the double aza-Michael reaction as a new entry into lentiginosine (Scheme 1). We planned to prepared the core structure of the indolizidine by reductive amination of the intermediate **A**. The 4-oxopiperidine (intermediate **B**) could be prepared by diastereoselective double aza-Michael reaction of benzylamine and the dienone **C**, which was generated by cross metathesis between acrolein and **2**.



Scheme 1. Proposed retrosynthesis of (–)-lentiginose.

Results and Discussion

Dienediol **2** was first protected as silyl ether **3**.[12] Cross metathesis (CM) between **3** and acrolein provided the *trans*-α,β-unsaturated aldehyde **4**, which was converted into the dienone **6** after a sequence of protection with chloromethyl methyl ether, addition of vinyl Grignard reagent and oxidation (Scheme 2). We noticed that the use of Hoveyda–Grubbs catalyst[13] gave a better yield than the Grubbs catalyst in this CM reaction (75 and 37%, respectively).

Double aza-Michael reaction of **6** and benzylamine generated the 4-oxopiperidines **7** and **8** (Scheme 3). Solvent and temperature have modest effects on the diastereomeric ratio (Table 1), and acetonitrile is the solvent of choice, which is in agreement with related examples.[9a] Although this Michael reaction is sluggish in nonpolar solvents (Entries 4–7), we found that adding 10 mol-% of trifluoroacetic acid accelerated the reaction in dichloromethane and gave the most clean product under the reaction conditions screened (Entry 8). The two diastereomers were separated by column chromatography, and the major isomer was tempo-

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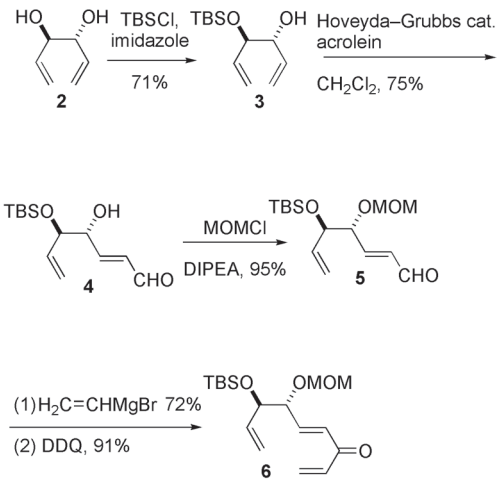
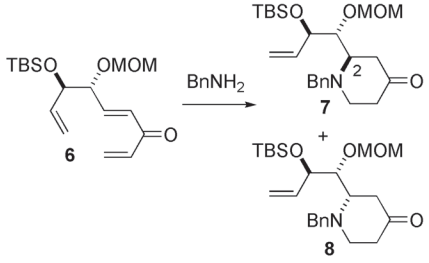


Scheme 2. Synthesis of dienone **6**.

rarily assigned as (2*R*)-**7**, since theoretical calculations suggested that compound **7** is thermodynamically more stable than the (2*S*) counterpart **8**.[14] We observed that the ^{1}H NMR spectrum of isolated **7** was unchanged after 72 h in [D_3]acetonitrile at room temperature; however, epimerization occurred after adding a trace of benzylamine–trifluoroacetic acid (0.1 equiv.) to the solution, and the final ratio of **7**/**8** was 2.4:1. This result supports that the formation of **7** is both kinetically and thermodynamically favored.



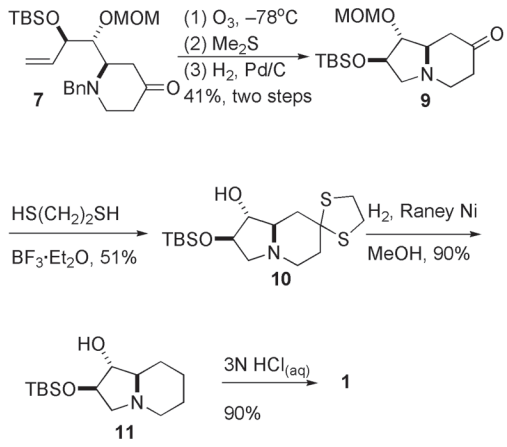
Scheme 3. Double aza-Michael reaction of **6**.

Table 1. Double aza-Michael reaction of **6** and benzylamine.

Entry	Solvent	*T* [°C]	Time [h]	**7**/**8**[a]	Yield [%][b]
1	CH_3CN	25	16	3.0:1	54
2	CH_3CN	0	96	5.2:1	41
3	CH_3CN[c]	0	16	2.0:1	56
4	THF	25	96	–	0
5	benzene	25	96	4.4:1	37
6	CH_2Cl_2	25	48	2.3:1	37
7	CH_2Cl_2	10	48	4.8:1	26
8	CH_2Cl_2[c]	25	16	2.1:1	75

[a] Determined by ^{1}H NMR spectroscopy of the crude product. [b] Isolated yield. [c] Addition of 10 mol-% trifluoroacetic acid.

The major isomer **7** was subjected to ozonolysis and reductive amination to generate the indolizidine **9** (Scheme 4). We screened several methods to achieve the reduction of the carbonyl group to a methylene group, and found that the sequence of the dithiolane formation and Raney nickel reduction gave the most satisfactory result in terms of efficiency. Deprotection of the remaining *tert*-butyldimethylsilyl group provided the title compound **1**. The spectroscopic data (^{1}H, ^{13}C NMR and optical rotation) of the synthetic (–)-lentiginosine are consistent with those in the literature;[8] therefore, the stereochemical assignment of the Michael adduct **7** was confirmed.



Scheme 4. Synthesis of (–)-lentiginosine from **7**.

Conclusions

We have accomplished the total synthesis of (–)-lentiginosine in nine steps from (*R*,*R*)-3,4-dihydroxy-1,5-hexadiene, readily available from inexpensive mannitol. This synthesis utilizes a cross metathesis to prepare the key trienone and a diastereoselective double aza-Michael reaction to form the corresponding 4-oxopiperidine, which was converted to the indolizidine after ozonolysis and reductive amination. This new approach could be applied to other polyhydroxylated indolizidines.

Experimental Section

(–)-Lentiginosine [(1*R*,2*R*,8a*R*)-1,2-Dihydroxyindolizidine, 1]: Hydrochloric acid (3 N, 2.5 mL) was added to the solution of **11** (31 mg, 0.12 mmol) and methanol (7.5 mL). The solution was stirred at 55 °C for 5 h, cooled to room temp. and concentrated to give the salt of lentiginosine (20 mg, 0.10 mmol, 90%). The salt was redissolved in satd. $KOH_{(aq)}$ (2 mL), extracted with THF (3 × 10 mL), dried with $Na_2SO_{4(s)}$, filtered and concentrated to give **1** as a colorless solid. M.p. 106–108 °C. $[a]_D^{20}$ = –3.00 (*c* = 0.3, MeOH). ^{1}H NMR (D_2O, 500 MHz): δ = 1.23–1.28 (t, *J* = 9.5 Hz, 2 H), 1.42–1.51 (m, 1 H), 1.64–1.66 (d, *J* = 12 Hz, 1 H), 1.79–1.85 (m, 1 H), 1.92–1.97 (m, 2 H), 2.03–2.08 (dt, *J* = 3, 12.5 Hz, 1 H), 2.61–2.65 (dd, *J* = 7.5, 11 Hz, 1 H, 3a-H), 2.82–2.85 (dd, *J* = 1.5, 11 Hz, 1 H, 3b-H), 2.94–2.96 (d, *J* = 11 Hz, 1 H, 8a-H), 3.65–3.67 (dd, *J* = 4, 8.5 Hz, 1 H, 1-H), 4.07–4.10 (m, 1 H, 2-H) ppm. ^{13}C NMR (D_2O, 125 MHz): δ = 22.8, 23.8, 27.4, 52.4, 60.0, 68.3, 75.5, 82.8 ppm.[7v]

Supporting Information (see footnote on the first page of this article): Experimental details for the synthesis of compounds **4**–**11**, copies of the ^{1}H and ^{13}C NMR spectra of compounds **4**–**11**, **1**, and the calculated stationary structures of **7** and **8** (Figure S1).

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[14] The stationary structures of **7** and **8**, where the *tert*-butyldimethylsilyl group was modelled as SiH_3, were calculated by using the gradient-corrected hybrid density functional theory (DFT) at the B3LYP/6-31G(d,p) level within the Gaussian 03 suite of programs[15] on an IBM cluster 1350 at the National Center for High-Performance Computing, Taiwan (Figure S1, Supporting Information). The calculated stable structures were examined in terms of vibrational frequency calculations with all positive values. The thermal energy at 25 °C and 1 atm was corrected for energy calculations. The calculated energies indicate that **7** is more stable than **8** by 2.20 kcal/mol in the gaseous Gibbs free energy. Both structures have similar conformations: the piperidine rings are in the stable, quasi-chair conformation; the carbon side chains are located in axial position, and the benzyl groups are in equatorial position.

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