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Short, enantioselective, gram-scale synthesis of (−)-zephyranthine†

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A reasonable synthesis design by strategically integrating functional group manipulation into the ring system construction resulted in a short, enantioselective, gram-scale total synthesis of (−)-zephyranthine. The concise route includes a catalytic Michael/Michael cascade for the asymmetric synthesis of a penta-substituted cyclohexane with three contiguous stereogenic centers, a remarkable 8-step one-pot operation to easily assemble the zephyranthine tetracyclic skeleton, the regioselective construction of a double bond in the C ring and an asymmetric dihydroxylation. This synthesis is also flexible and paves a potential path to a variety of cyclohexylamine-fused tricyclic or polycyclic alkaloids.

Introduction

Lycorine-type alkaloids (*e.g.*, **1–4**; Fig. 1)[1] are members of an Amaryllidaceae alkaloid sub-class[2] and display useful biological properties,[3] including anticholinergic, antiviral, insect antifeedant, and antineoplastic activities, as well as other pharmacological properties.[4] These alkaloids have attracted substantial synthetic attention because of their tetracyclic core structure, multiple chiral centers and bioactivities. As a result, significant effort has been devoted to assembling the tetracyclic skeleton of such alkaloids[5] and to the syntheses of the natural products themselves.[6–10]

Unlike other members of the lycorine family, (−)-zephyranthine (**1**)[11] has only a limited number of syntheses reported for its fabrication,[6e,12] none of which detail a catalytic asymmetric approach. Herein, we report an efficient, enantioselective, gram-scale protocol for **1** that takes advantage of two one-pot reactions. The first is a catalytic asymmetric double Michael addition to construct the C ring with three consecutive chiral centers. The second is a novel 8-step procedure involving double deacetalyzation, nitro group reduction to its corresponding amine, tandem double ring-closing reductive amination, and then double ester hydrolysis with subsequent tandem decarboxylation to give the tetracyclic skeleton of **1**. Although we have successfully developed a remarkably facile route to **1**, we encountered obstacles at a later stage. Unfortunately, the crucial regioselective construction of the C1–C2 double bond in the C ring was hindered by mutable substrates containing nitro groups or amine-type nitrogen atoms. However, this failure was counteracted with the successful, kinetically controlled regioselective enolization of the C ring ketone moiety.

Results and discussion

The catalytic double Michael addition of γ,δ-unsaturated-β-ketoester and nitroolefin was previously developed by our group[13d] for the asymmetric synthesis of multiple-substituted cyclohexanes bearing 3–5 stereogenic centers, which is expected to develop into the key step of a general method to stereoselectively synthesize a variety of cyclohexylamine-fused alkaloids, including (−)-zephyranthine and lepadiformine-type alkaloids.[14]

Our simple retrosynthetic analysis of the target natural product (Scheme 1) revealed that penta-substituted cyclohexane **12**, which arose from a catalytic asymmetric double Michael addition of **13** and **14**, was likely a key intermediate that would result in the direct formation of tetracyclic ketone **10** *via* a one-

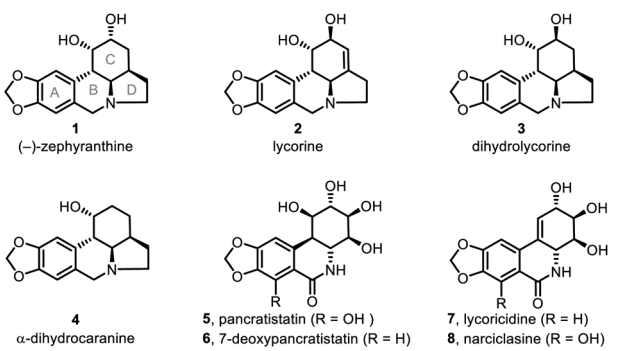

Fig. 1 Selected Amaryllidaceae alkaloids.

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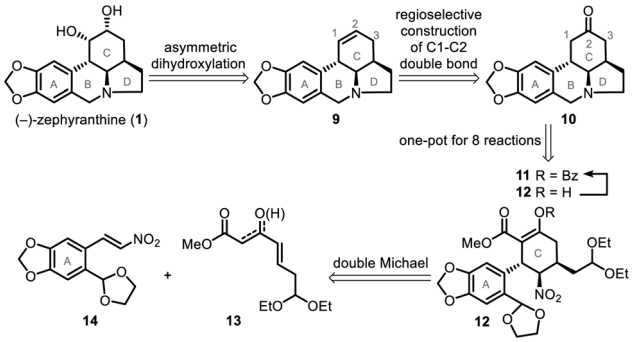
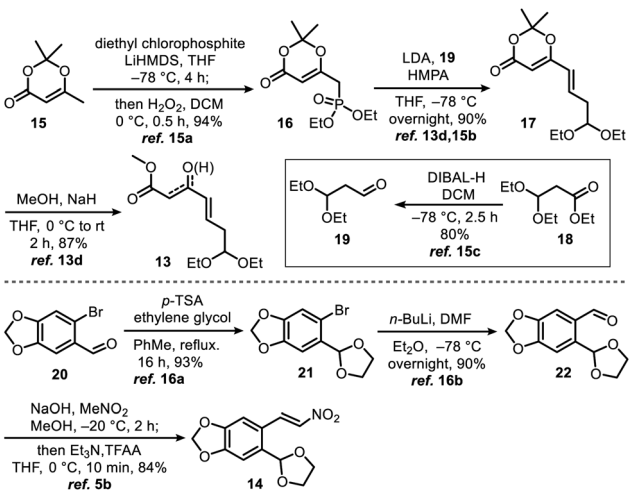


Scheme 1 Retrosynthetic analysis of (−)-zephyranthine (**1**).

pot operation. Subsequent regioselective construction of a double bond in the C ring, followed by dihydroxylation, would lead to **1**.

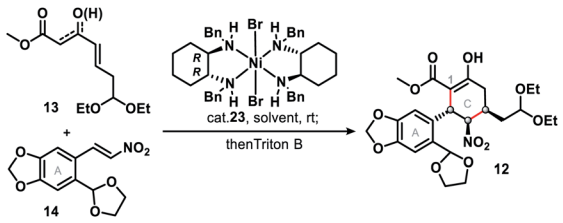
γ,δ-Unsaturated-β-ketoester **13** (ref. 13*d* and 15) and nitro-olefin **14** (ref. 5*b* and 16) were prepared on 10 gram scales using a literature method with minor modifications (Scheme 2, see ESI† for detailed preparation methods).

The synthetic journey commenced with a catalytic asymmetric double Michael addition cascade reaction of **13** and **14**, which was promoted by Evans' chiral nickel(II) catalyst (**23**).[13] Condition screening (Table 1) revealed that the 1st Michael addition, unlike that in the synthesis of (−)-stenine,[13d] was very sluggish with the low conversion (<10%) even after 10 days' reaction at room temperature with THF as solvent or in solvent-free conditions; DCM as solvent brought about the fastest reaction that afforded 84% yield of the product with inadequate ee (entry 3) in 48 hours. Finally we found that PhMe as the solvent and Triton B as the base gave both the highest enantioselectivity (90%) and diastereoselectivity (>20 : 1), as well as high yield (85%) of penta-substituted cyclohexane **12**, which was identified as the single isomer of an enol ester. Furthermore, NMR analysis showed that three consecutive chiral



Scheme 2 Synthesis of γ,δ-unsaturated-β-ketoester **13** and nitro-olefin **14**.

Table 1 Optimization of conditions for asymmetric double Michael addition[a]

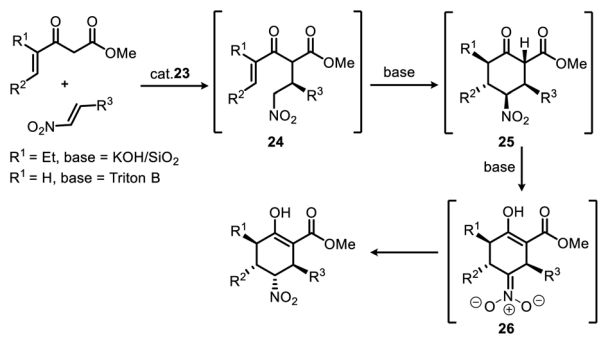


Entry	13 : 14	Solvent	Time (h)	Cat. 23 (mol%)	Yield[b] (%)	ee[c] (%)
1	1 : 1	—	240	2	Trace[d]	ND
2	1 : 1	THF	240	2	Trace[d]	ND
3	1 : 1	DCM	48	2	84	76
4	1 : 1	PhMe	96	2	76	90
5	1 : 1	PhMe	96	3	78	90
6	1.1 : 1	PhMe	96	2	81	90
7	**1.2 : 1**	**PhMe**	**96**	**2**	**85**	**90**
8	1.3 : 1	PhMe	96	2	85	90

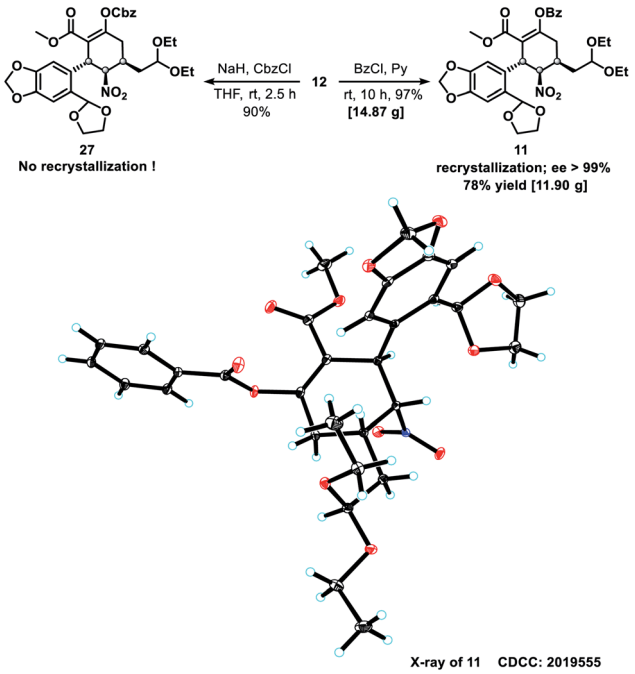
[a] The reaction was performed in the presence of Triton B as a base (1.0 equiv.) at room temperature. [b] Isolated yields after chromatographic purification. [c] Enantiomeric excess was determined by high performance liquid chromatography (HPLC), chiracel columns. [d] Reaction was very sluggish with the low conversion after 10 days.

centers (in the C ring) had been correctly constructed so that **1** would be produced in the subsequent steps.

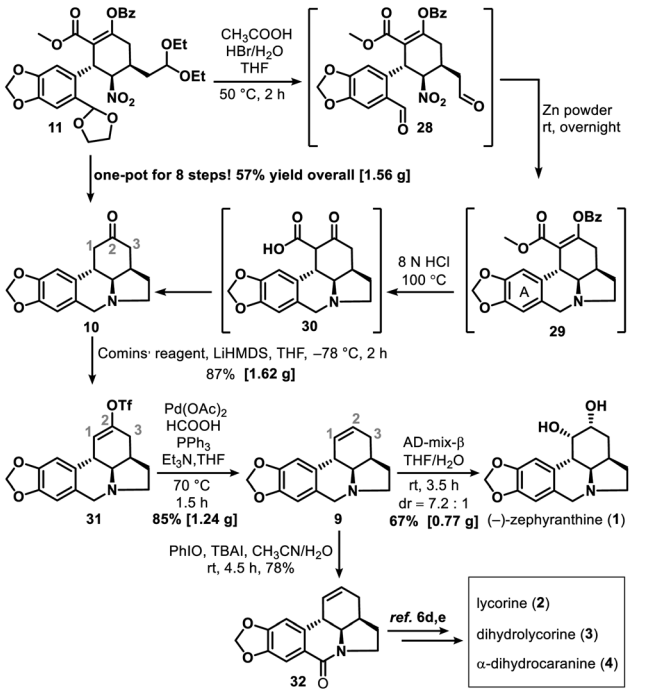
It can be speculated, as shown in Scheme 3, the steric and electronic effects caused by the γ-ethyl group of the product (R^1 = Et, for enantioselective synthesis of stenine)[13d] of 1st Michael addition make the intermediate **24** (R^1 = Et) a less active Michael acceptor in the 2nd Michael addition, therefore, a heterogeneous strong base (KOH/SiO_2) condition was required to promote this reaction while avoiding damage to the nitro group. Moreover, an isomerisation phenomenon was observed after the 2nd Michael addition that the keto ester intermediate **25** gradually transformed into its enol ester isomer accompanied by inversion of configuration at the N_α-carbon. Evidently, γ,δ-unsaturated-β-ketoester (R^1 = H) in this work is more active, and the 2nd Michael addition as well as the subsequent isomerisation progressed rapidly and completed in



Scheme 3 Stereoselective synthesis of multiple-substituted cyclohexanes *via* a Michael/Michael/isomerization cascade reaction.



Scheme 4 Protection of the enol hydroxy group of **12** and the absolute configuration of compound **11**.



Scheme 5 Total synthesis of (–)-zephyranthine (**1**) and synthesis of **32**.

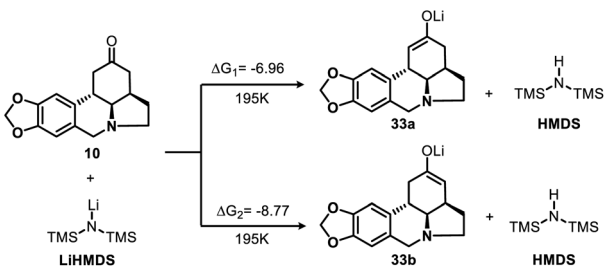
20 minutes after addition of Triton B to the reaction mixture upon completion of 1st Michael addition.

To confirm the absolute configuration of compound **12**, its enol moiety was either benzyloxycarbonyl (Cbz)- or benzoyl (Bz)-protected to prevent unwanted aldol reactions between the α-carbon (C1) of the β-keto ester and the aldehydes that would form from the acetal moieties upon their subsequent deprotection. Cbz-protection was achieved by treating **12** with benzyl carbonochloridate (CbzCl) in the presence of NaH to give ester **27** in 90% yield. However, **27** was difficult to purify by recrystallization. By replacing CbzCl with benzoyl chloride (BzCl), similar esterification of **12** afforded benzoate **11** in quantitative yield. After recrystallization, the isomeric purity of **11** was greater than 99% ee, as determined by high performance liquid chromatography (HPLC). The absolute configuration of benzoate **11** was confirmed by X-ray crystallography (Scheme 4) with Cu-K_α radiation.

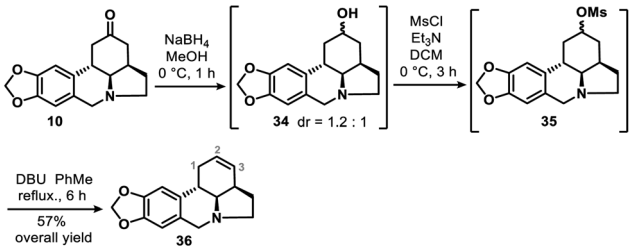
Successful construction of the three contiguous stereogenic centers in the newly formed cyclohexane ring allowed us to begin synthesizing **1**. Cyclization of **11** to form tetracyclic ketone **10** was accomplished through a multistep one-pot operation (Scheme 5), which began by treating **11** with HBr (1.0 equiv., 33% in HOAc) in HOAc–THF–H_2O (5 : 1 : 1) at 50 °C for 2 h to give dialdehyde **28**. Subsequent reaction of **28** with zinc powder at room temperature overnight gave **29**. After a simple filtration to remove the excess zinc and other solid substances, HCl (8.0 N, 100 equiv.) was added to the reaction mixture to hydrolyze **29** into **30**. Tandem decarboxylation of **30** then delivered key intermediate **10** in a total yield of 57% *via* an eight-step one-pot synthesis.

The reaction of ketone **10** with lithium bis(trimethylsilyl) amide and Comins' reagent[17] at −78 °C was a kinetically controlled regioselective enolization, which was followed by triflation to afford enol triflate **31** in 87% yield. This then underwent a palladium-promoted hydrogenolysis[18] to give **9** in 85% yield. In the last step, an attempt to avoid oxidative damage of the amino nitrogen atom was made by adding some acid to the reaction system; however, this failed owing to the deactivation of AD-mix-β under acidic conditions. Fortunately, the most conventional sharpless asymmetric dihydroxylation[19] of **9** with AD-mix-β under acid-free conditions proceeded smoothly and gave **1** in 67% isolated yield (76% yield of **1** and its diastereoisomer in a ratio of 7.2 : 1). After that, amide **32** was synthesized in 78% yield *via* a PhIO promoted oxidation[20] of **9**. Our approach thus provided a formal synthesis of a number of other lycorine-type alkaloids[12a] (Scheme 5), such as lycorine (**2**),[6d,e] dihydrolycorine (**3**)[6d,e] and α-dihydrocaranine (**4**).[6d,e]

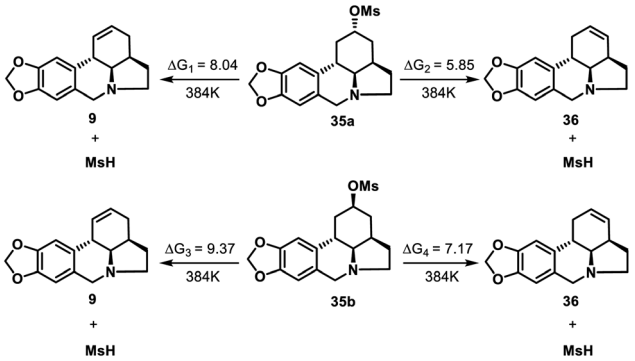
To gain additional insight into the nature of the regioselective enolization of ketone **10**, we conducted a theoretical study and the DFT quantum-chemical calculations (Scheme 6, see ESI† for details) revealed that the formation of intermediate **33a** is kinetically favored over that of **33b**.



Scheme 6 DFT calculations for enolization reaction of **10** (kcal mol^{-1}).



Scheme 7 Synthesis of the double bond positional isomer (**36**) of **9**.

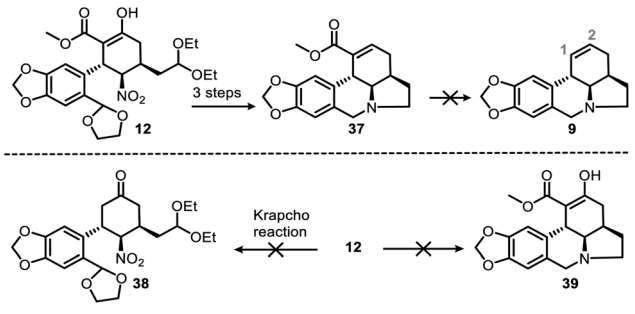


Scheme 8 DFT calculations for elimination reaction of **35** (kcal mol^{-1}).

We also obtained **36**, the double bond positional isomer of **9**, from the same intermediate **10** that gave **9**. This was accomplished through a 3-step chemical manipulation of the ketone moiety of the C ring (Scheme 7). Intermediate **10** was reduced with sodium borohydride in methanol to give secondary alcohol **34** (dr = 1.2 : 1), which underwent mesylation and then DBU-promoted, thermodynamically controlled methanesulfonic acid elimination to afford **36** as a single regioisomer in 57% overall yield.

To confirm the proposed thermodynamically controlled process, we conducted DFT calculations (see ESI† for details) of elimination reactions of mesylate **35** as indicated in Scheme 8. For both **35a** and **35b**, the formation of olefin **36** is more favorable than formation of **9** according to the free energy changes. **35a** is more likely to undergo elimination than **35b** to form compound **36** as less energy required. The calculation results supported our conclusion that the formation of **36** by elimination reaction of **35** (both **35a** and **35b**) is a thermodynamically controlled process.

We had also attempted other routes to regioselectively construct the double bond in the C ring, but these did not proceed as we expected (see ESI† for detailed informations). Ideally, deesterification of **37** could efficiently provide **9** (Scheme 9, top) and ensure that the double bond remained in the correct position (C1–C2); however, this reaction was unsuccessful. We did manage to convert the ester group of **37** into a carboxyl or aldehyde group, but the subsequent decarboxylation or deformylation failed. In addition, transformation of **12** to **38** (Scheme 9, bottom) could not be achieved through direct deesterification, and attempts to obtain **39** from **12** with the same one-pot protocol that gave **10** from **11** (Scheme 5) were also unsuccessful due to unwanted aldol reactions.



Scheme 9 Failed alternative routes to produce (top) the C-ring double bond and (bottom) compounds **38** and **39** from **12**.

Conclusions

The natural product (−)-zephyranthine (**1**) was synthesized using a highly efficient and practical approach. Strategically integrating functional group manipulation into the ring system construction resulted in two, multi-step, one-pot reactions that greatly simplified the overall operation and improved its efficiency. From readily available **13** and **14**, only six steps (18.7% overall isolated yield) were necessary to acquire 1 g of (−)-**1**. In addition, regioselective construction of the C ring double bond from **10** delivered **9** or **36** through kinetically or thermodynamically controlled pathways, respectively. This, together with the concise synthesis of amide **32**, provided a flexible and practical synthetic pathway for lycorine-type alkaloids and their analogs. The development of multistep one-pot reactions with greater efficiency and further applications in lepadiformine-type alkaloid syntheses are currently underway.

Data availability

All computational data associated with this article have been inserted in ESI.

Author contributions

H. Z. and J. C. conceived the idea. Y. Z. conducted the most of experiments. Y. Z., G. M., Q. W., S. Y. and X. Z co-synthesized part of substrates. H. Z. and J. C. co-wrote the paper. All the authors discussed the results and commented on the manuscript.

Conflicts of interest

There are no conflicts to declare.

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