

Cite this: *Chem. Sci.*, 2021, 12, 9452

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 10th June 2021

Accepted 11th June 2021

DOI: 10.1039/d1sc03147c

rsc.li/chemical-science

## 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)<sup>1</sup> are members of an Amaryllidaceae alkaloid sub-class<sup>2</sup> and display useful biological properties,<sup>3</sup> including anticholinergic, antiviral, insect anti-feedant, and antineoplastic activities, as well as other pharmacological properties.<sup>4</sup> 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<sup>5</sup> and to the syntheses of the natural products themselves.<sup>6–10</sup>

Unlike other members of the lycorine family, (–)-zephyranthine (1)<sup>11</sup> has only a limited number of syntheses reported for its fabrication,<sup>6e,12</sup> 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 deacetalization, 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  $\gamma,\delta$ -unsaturated- $\beta$ -ketoester and nitroolefin was previously developed by our group<sup>13d</sup> 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.<sup>14</sup>

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-

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† Electronic supplementary information (ESI) available. CCDC 2019555. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1sc03147c

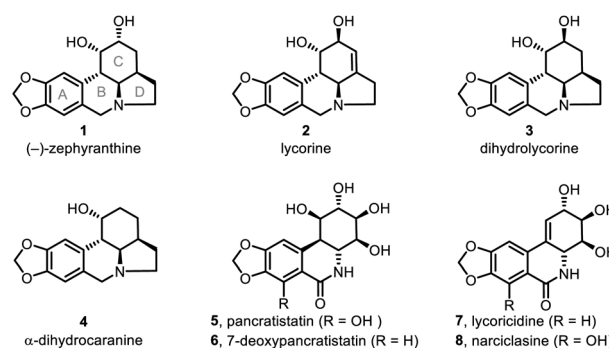
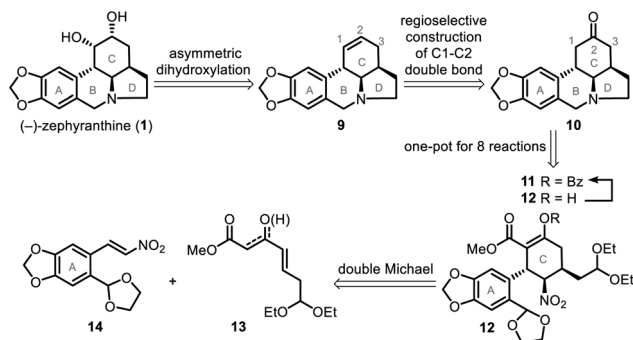


Fig. 1 Selected Amaryllidaceae alkaloids.

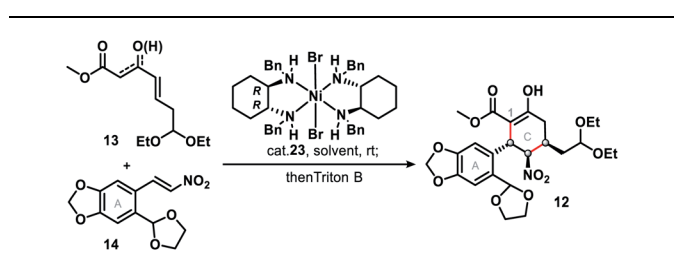


Scheme 1 Retrosynthetic analysis of (-)-zephyranthine (1).

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

$\gamma,\delta$ -Unsaturated- $\beta$ -ketoester **13** (ref. 13d and 15) and nitroolefin **14** (ref. 5b 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**).<sup>13</sup> Condition screening (Table 1) revealed that the 1st Michael addition, unlike that in the synthesis of (-)-stenine,<sup>13d</sup> 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

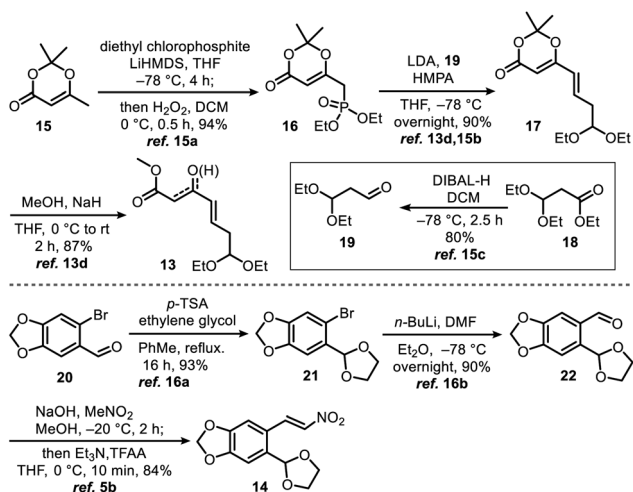
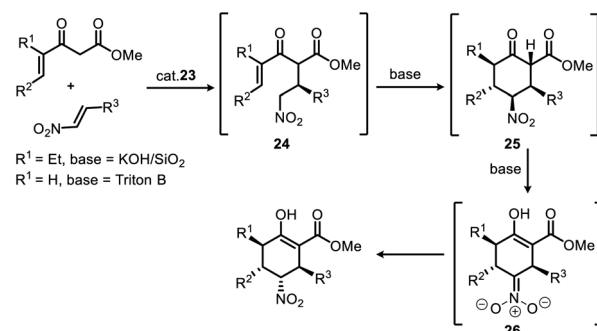
Table 1 Optimization of conditions for asymmetric double Michael addition<sup>a</sup>

Entry	13 : 14	Solvent	Time (h)	Cat. 23 (mol%)	Yield <sup>b</sup> (%)	ee <sup>c</sup> (%)
1	1 : 1	—	240	2	Trace <sup>d</sup>	ND
2	1 : 1	THF	240	2	Trace <sup>d</sup>	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

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

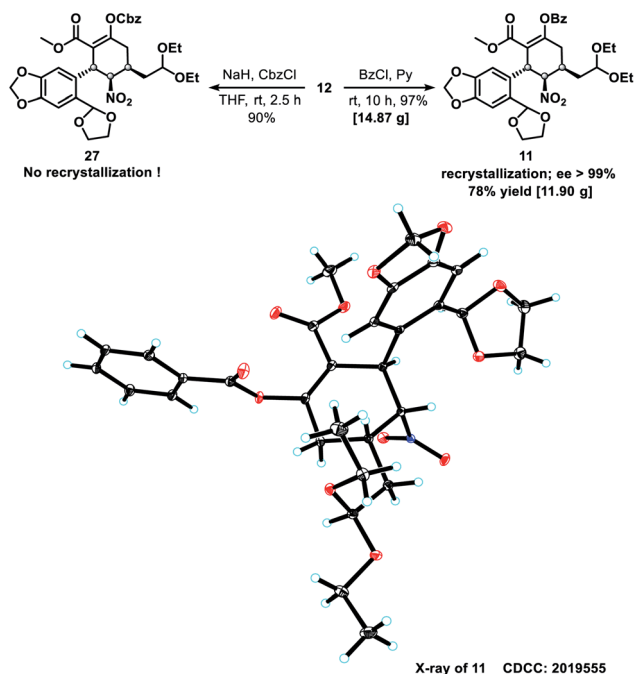
centers (in the C ring) had been correctly constructed so that **1** would be produced in the subsequent steps.

It can be speculated, as shown in Scheme 3, the steric and electronic effects caused by the  $\gamma$ -ethyl group of the product ( $R^1 = Et$ , for enantioselective synthesis of stenine)<sup>13d</sup> 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<sub>2</sub>) 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<sub>z</sub>-carbon. Evidently,  $\gamma,\delta$ -unsaturated- $\beta$ -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 2 Synthesis of  $\gamma,\delta$ -unsaturated- $\beta$ -ketoester **13** and nitroolefin **14**.

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





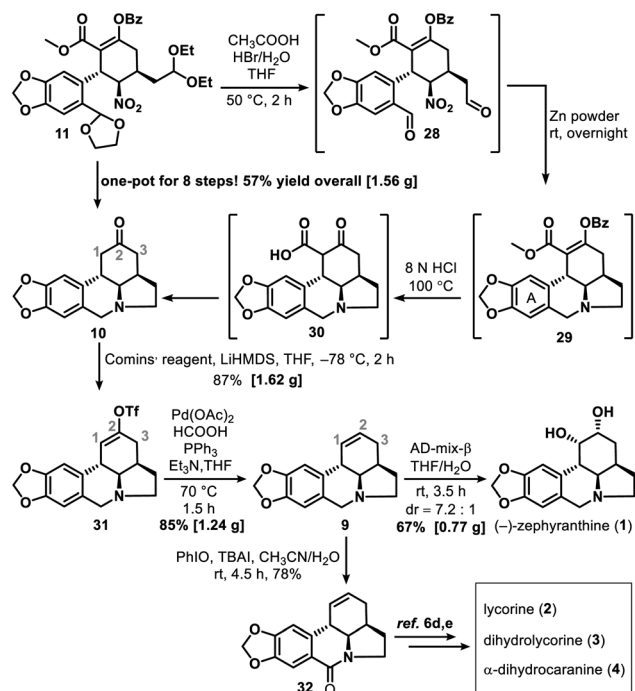
Scheme 4 Protection of the enol hydroxy group of **12** and the absolute configuration of compound **11**.

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  $\alpha$ -carbon (C1) of the  $\beta$ -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 $\alpha$  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<sub>2</sub>O (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.

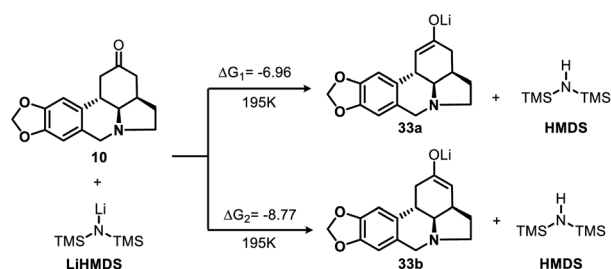
The reaction of ketone **10** with lithium bis(trimethylsilyl) amide and Comins' reagent<sup>17</sup> at -78 °C was a kinetically



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

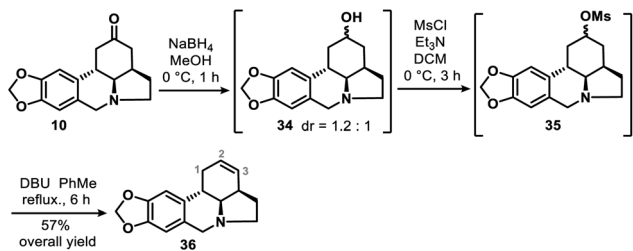
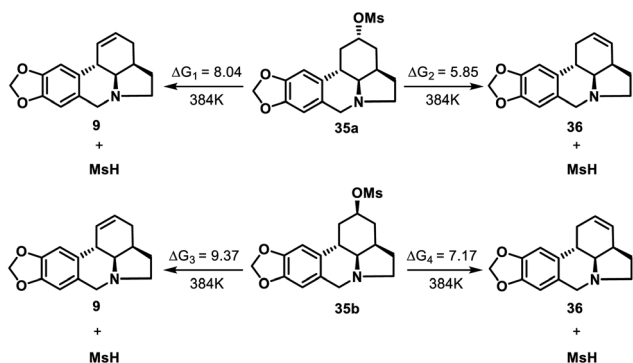
controlled regioselective enolization, which was followed by triflation to afford enol triflate **31** in 87% yield. This then underwent a palladium-promoted hydrogenolysis<sup>18</sup> to give **9** in 85% yield. In the last step, an attempt to avoid oxidative damage of the amino nitrogen atom was made by adding some acid to the reaction system; however, this failed owing to the deactivation of AD-mix- $\beta$  under acidic conditions. Fortunately, the most conventional sharpless asymmetric dihydroxylation<sup>19</sup> of **9** with AD-mix- $\beta$  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<sup>20</sup> of **9**. Our approach thus provided a formal synthesis of a number of other lycorine-type alkaloids<sup>12a</sup> (Scheme 5), such as lycorine (**2**),<sup>6d,e</sup> dihydrolycorine (**3**)<sup>6d,e</sup> and  $\alpha$ -dihydrocaranine (**4**).<sup>6d,e</sup>

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**.



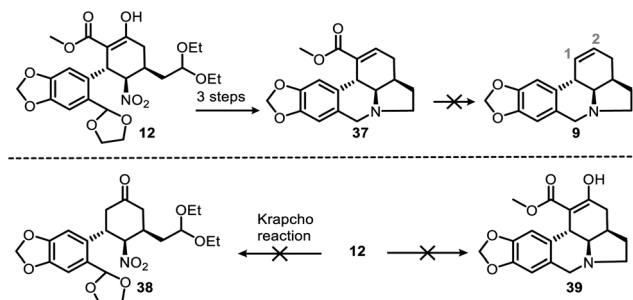
Scheme 6 DFT calculations for enolization reaction of **10** (kcal mol<sup>-1</sup>).



Scheme 7 Synthesis of the double bond positional isomer (**36**) of **9**.Scheme 8 DFT calculations for elimination reaction of **35** ( $\text{kcal mol}^{-1}$ ).

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** ( $\text{dr} = 1.2 : 1$ ), 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

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

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.

## 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.

## Acknowledgements

This work was financially supported by the National Natural Science Foundation of China (21662041, U1702286), the Yunnan Provincial Science & Technology department



(2018FA045), the Program for Changjiang Scholars and Innovative Research Teams in Universities (IRT17R94), and the Project of Innovative Research Team of Yunnan Province (202005AE160005). We thank A/Prof. Ruihan Zhang and Dr Chang Xu for their help with the DFT calculations.

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