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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)<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-

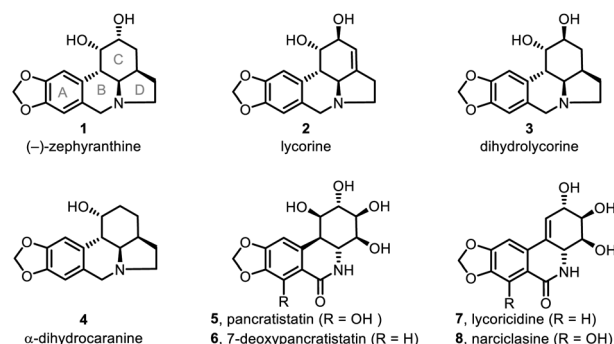
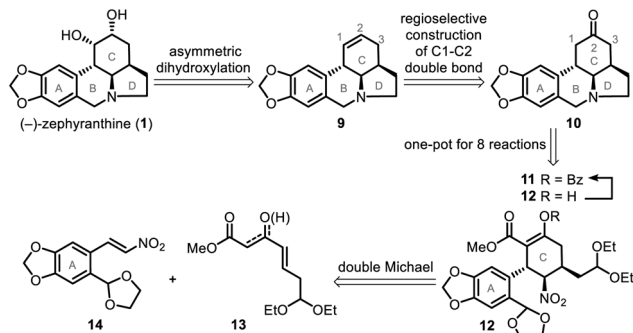


Fig. 1 Selected Amaryllidaceae alkaloids.

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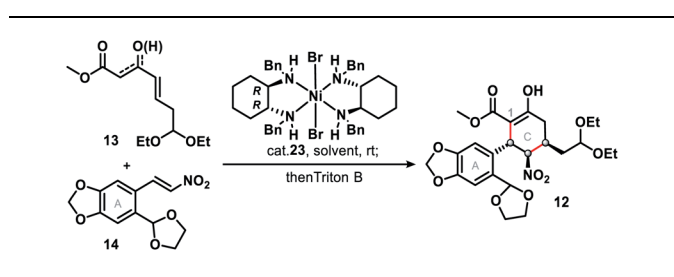


Scheme 1 Retrosynthetic analysis of (–)-zephyranthine (1).

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

$\gamma,\delta$ -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

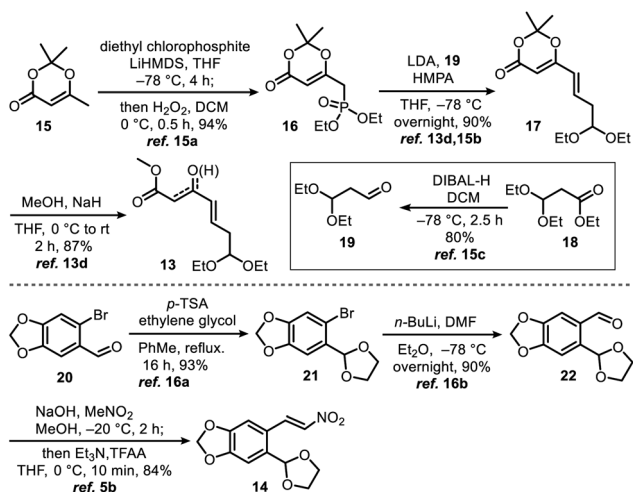
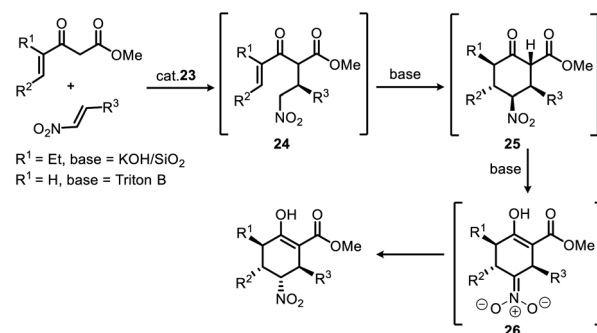
Table 1 Optimization of conditions for asymmetric double Michael addition<sup>a</sup>

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

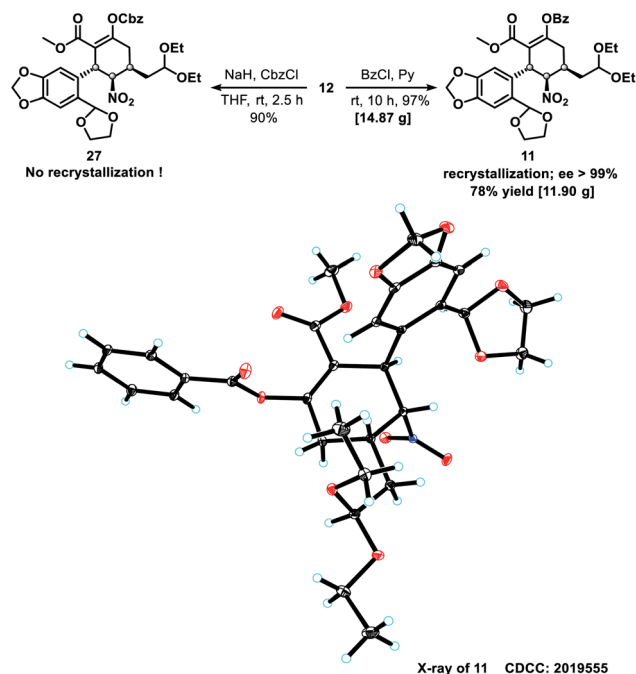
<sup>a</sup> The reaction was performed in the presence of Triton B as a base (1.0 equiv.) at room temperature. <sup>b</sup> Isolated yields after chromatographic purification. <sup>c</sup> Enantiomeric excess was determined by high performance liquid chromatography (HPLC), chiral columns. <sup>d</sup> 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 $\alpha$ -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.



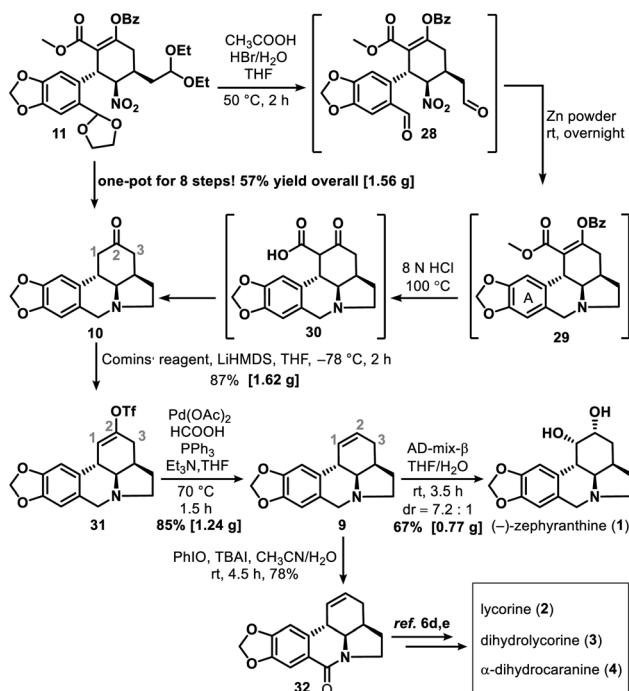
Scheme 4 Protection of the enol hydroxy group of **12** and the absolute configuration of compound **11**.

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 carbonochloride (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.

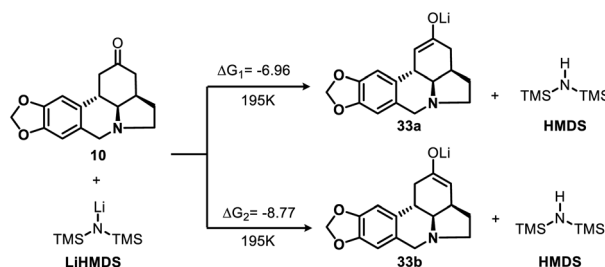
The reaction of ketone **10** with lithium bis(trimethylsilyl) amide and Comins' reagent<sup>17</sup> at –78 °C was a kinetically



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

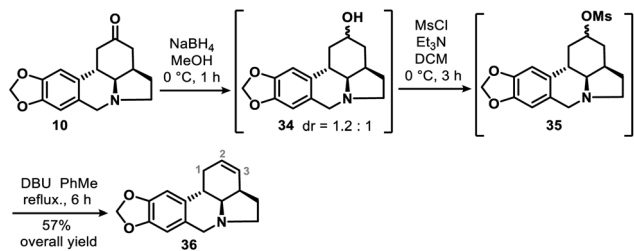
controlled regioselective enolization, which was followed by triflation to afford enol triflate **31** in 87% yield. This then underwent a palladium-promoted hydrogenolysis<sup>18</sup> to give **9** in 85% yield. In the last step, an attempt to avoid oxidative damage of the amino nitrogen atom was made by adding some acid to the reaction system; however, this failed owing to the deactivation of AD-mix-β under acidic conditions. Fortunately, the most conventional Sharpless asymmetric dihydroxylation<sup>19</sup> 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<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**.

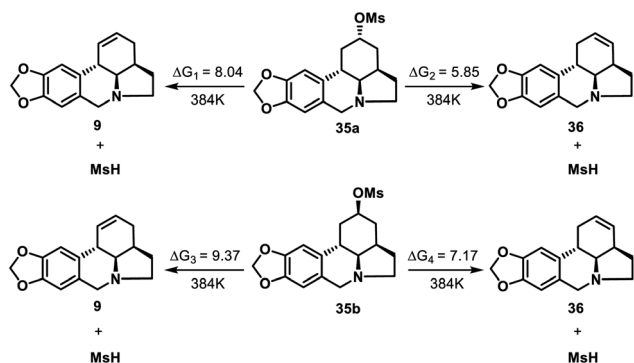


Scheme 6 DFT calculations for enolization reaction of **10** (kcal mol<sup>–1</sup>).





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

Scheme 8 DFT calculations for elimination reaction of 35 (kcal mol<sup>-1</sup>).

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.

## 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

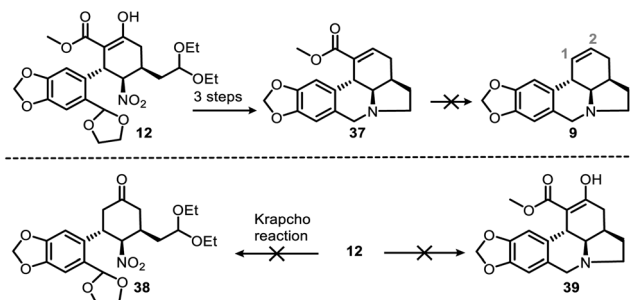
H. Z. and J. C. conceived the idea. Y. Z. conducted the most of experiments. Y. Z., G. M., Q. W., S. Y. and X. Z. co-synthesized part of substrates. H. Z. and J. C. co-wrote the paper. All the authors discussed the results and commented on the manuscript.

## Conflicts of interest

There are no conflicts to declare.

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



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## Notes and references

- (a) R. D. Harken, C. P. Christensen and W. C. Wildman, *J. Org. Chem.*, 1976, **41**, 2450; (b) S. F. Martin, in *The Alkaloids*, ed. A. Brossi, Academic Press, New York, 1987, vol. 30, pp. 25–376; (c) M. F. Grundon, *Nat. Prod. Rep.*, 1989, **6**, 79; (d) J. R. Lewis, *Nat. Prod. Rep.*, 1995, **11**, 339; (e) O. Hoshino, in *The Alkaloids*, ed. G. A. Cordell, Academic Press, San Diego, 1998, vol. 51, pp. 323–424.
- (a) J. W. Cook and J. D. Loudon, in *The Alkaloids*, ed. R. H. F. Manske and H. L. Holmes, Academic Press, New York, 1952, vol. 2, pp. 331–352; (b) D. R. Dalton, in *The Alkaloids: The Fundamental Chemistry – A Biogenetic Approach*, Marcel Dekker, New York, 1979.
- (a) D. B. Fitzgerald, J. L. Hartwell and J. J. Leiter, *Nat. Cancer Inst.*, 1958, **20**, 763; (b) T. Okamoto, Y. Torii and Y. Isogai, *Chem. Pharm. Bull.*, 1968, **16**, 1860; (c) S. Ghosal, K. S. Saini and S. Razdan, *Phytochemistry*, 1985, **24**, 2141; (d) J. Liu, Y. Li, L. J. Tang, G. P. Zhang and W. X. Hu, *Biomed. Pharmacother.*, 2007, **61**, 229.
- (a) G. R. Pettit, S. Freeman, M. J. Simpson, M. A. Thompson, M. R. Boyd, M. D. Williams, G. R. Pettit III and D. L. Doubek, *Anti-Cancer Drug Des.*, 1995, **10**, 243; (b) G. R. Pettit, S. Orr and S. Ducki, *Anti-Cancer Drug Des.*, 2000, **15**, 389; (c) V. Zarotsky, J. J. Sramek and N. R. Cutler, *Am. J. Health-Syst. Pharm.*, 2003, **60**, 446.
- For the synthesis of the tetracyclic skeleton of Amaryllidaceae alkaloids, see: (a) L. D. Miranda and S. Z. Zard, *Org. Lett.*, 2002, **4**, 1135; (b) T. Yasuhara, K. Nishimura, M. Yamashita, N. Fukuyama, K. Yamada, O. Muraoka and K. Tomioka, *Org. Lett.*, 2003, **5**, 1123; (c) B. C. Hong, R. Y. Nimje, M. F. Wu and A. A. Sadani, *Eur. J. Org. Chem.*, 2008, 1449; (d) Y. Wang, Y. C. Luo, H. B. Zhang and P. F. Xu, *Org. Biomol. Chem.*, 2012, **10**, 8211; (e) G. Li, J. H. Xie, J. Hou, S. F. Zhu and Q. L. Zhou, *Adv. Synth. Catal.*, 2013, **355**, 1597; (f) Y. G. Jung, S. C. Lee, H. K. Cho, N. B. Darvatkar, J. Y. Song and C. G. Cho, *Org. Lett.*, 2013, **15**, 132; (g) N. K. Rana, H. Huang and J. C.-G. Zhao, *Angew. Chem., Int. Ed.*, 2014, **53**, 7619; (h) X. L. Meng, T. Liu, Z. W. Sun, J. C. Wang, F. Z. Peng and Z. H. Shao, *Org. Lett.*, 2014, **16**, 3044; (i) Z. W. Sun, M. T. Zhou, X. Li, X. L. Meng, F. Z. Peng, H. B. Zhang and Z. H. Shao, *Chem.-Eur. J.*, 2014, **20**, 6112; (j) E. Ghirardi, R. Giera, M. Picciche, E. Molins, I. Fernandez, J. Bosch and M. Amat, *Org. Lett.*, 2016, **18**, 5836.
- For the syntheses of lycorine, dihydrolycorine, and  $\alpha$ -dihydrocaranine, see: (a) E. W. Warnhoff and W. C. Wildman, *J. Am. Chem. Soc.*, 1957, **79**, 2192; (b) K. Takeda, K. Kotera and S. Mizukami, *J. Am. Chem. Soc.*, 1958, **80**, 2562; (c) Y. Nakagawa and S. Uyeo, *J. Chem. Soc.*, 1959, 3736; (d) Y. Tsuda, T. Sano, J. Taga, K. Isobe, J. Toda, H. Irie, H. Tanaka, S. Takagi, M. Yamaki and M. Murata, *J. Chem. Soc., Chem. Commun.*, 1975, **23**, 933; (e) Y. Tsuda, T. Sano, J. Taga, K. Isobe, J. Toda, S. Takagi, M. Yamaki, M. Murata, H. Irie and H. Tanaka, *J. Chem. Soc., Perkin Trans. 1*, 1979, 1358; (f) T. Sano, N. Kashiwaba, J. Toda, Y. Tsuda and H. Irie, *Heterocycles*, 1980, **14**, 1097; (g) O. Hoshino, M. Ishizaki, K. Kamei, M. Taguchi, T. Nagao, K. Iwaoka, S. Sawaki, B. Ymezawa and Y. Iitaka, *Chem. Lett.*, 1991, **8**, 1365; (h) O. Hoshino, M. Ishizaki, K. Kamei, M. Taguchi, T. Nagao, K. Iwaoka, S. Sawaki, B. Umezawa and Y. Iitaka, *J. Chem. Soc., Perkin Trans. 1*, 1996, 571; (i) A. G. Schultz, M. A. Holoboski and M. S. Smyth, *J. Am. Chem. Soc.*, 1996, **118**, 6210; (j) K. Yamada, M. Yamashita, T. Sumiyoshi, K. Nishimura and K. Tomioka, *Org. Lett.*, 2009, **11**, 1631; (k) H. S. Shin, Y. G. Jung, H. K. Cho, Y. G. Park and C. G. Cho, *Org. Lett.*, 2014, **16**, 5718.
- For the syntheses of 7-deoxypancratistatin, see: (a) H. Paulsen and M. Stubbe, *Tetrahedron Lett.*, 1982, **23**, 3171; (b) G. E. Keck, S. F. McHardy and J. A. Murry, *J. Am. Chem. Soc.*, 1995, **117**, 7289; (c) X. Tian, R. Maurya, K. Königsberger and T. Hudlicky, *Synlett*, 1995, 1125; (d) T. Hudlicky, X. Tian, K. Königsberger, R. Maurya, J. Rouden and B. Fan, *J. Am. Chem. Soc.*, 1996, **118**, 10752; (e) N. Chida, M. Jitsuoka, Y. Yamamoto, M. Ohtsuka and S. Ogawa, *Heterocycles*, 1996, **43**, 1385; (f) G. E. Keck, T. T. Wager and S. F. McHardy, *J. Org. Chem.*, 1998, **63**, 9164; (g) H. Akgun and T. Hudlicky, *Tetrahedron Lett.*, 1999, **40**, 3081; (h) J. L. Acena, O. Arjona, M. A. León and J. Plumet, *Org. Lett.*, 2000, **2**, 3683; (i) A. E. Hakansson, A. Palmelund, H. Holm and R. Madsen, *Chem.-Eur. J.*, 2006, **12**, 3243; (j) H. Zhang and A. Padwa, *Tetrahedron Lett.*, 2006, **47**, 3905; (k) O. Nieto-García, H. Lago-Santome, F. Cagide-Fagín, J. C. Ortiz-Lara and R. Alonso, *Org. Biomol. Chem.*, 2012, **10**, 825; (l) S. L. Cai, B. H. Yuan, Y. X. Jiang, G. Q. Lin and X. W. Sun, *Chem. Commun.*, 2017, **53**, 3520.
- For the syntheses of pancratistatin, see: (a) S. Danishefsky and J. Y. Lee, *J. Am. Chem. Soc.*, 1989, **111**, 4829; (b) X. Tian, T. Hudlicky and K. Königsberger, *J. Am. Chem. Soc.*, 1995, **117**, 3643; (c) B. M. Trost and S. R. Pulley, *J. Am. Chem. Soc.*, 1995, **117**, 10143; (d) V. Van-Rheenen, R. C. Kelly and D. Y. Cha, *Tetrahedron Lett.*, 1976, **17**, 1973; (e) P. Magnus and I. K. Sebat, *J. Am. Chem. Soc.*, 1998, **120**, 5341; (f) J. H. Rigby, U. S. M. Maharoor and M. E. Mateo, *J. Am. Chem. Soc.*, 2000, **122**, 6624; (g) S. Kim, H. Ko, E. Kim and D. Kim, *Org. Lett.*, 2002, **4**, 1343; (h) M. Li, A. Wu and P. Zhou, *Tetrahedron Lett.*, 2006, **47**, 3707; (i) J. H. Dam and R. Madsen, *Eur. J. Org. Chem.*, 2009, 4666; (j) Y. G. Jung, H. U. Kang, H. K. Cho and C. G. Cho, *Org. Lett.*, 2011, **13**, 5890; (k) F. Cagide-Fagín, O. Nieto-García, H. Lago-Santomé and R. Alonso, *J. Org. Chem.*, 2012, **77**, 11377; (l) S. Akai, M. Kojima, S. Yamauchi, T. Kohji, Y. Nakamura and K.-i. Sato, *Asian J. Org. Chem.*, 2013, **2**, 299; (m) T. J. Potter and J. A. Ellman, *Org. Lett.*, 2017, **19**, 2985.
- For the syntheses of lycoricidine, see: (a) S. Ohta and S. Kimoto, *Tetrahedron Lett.*, 1975, **16**, 2279; (b) B. G. Ugarkar, J. Dare and E. M. Schubert, *Synthesis*, 1987,



- 715; (c) N. Chida, M. Ohtsuka and S. Ogawa, *Tetrahedron Lett.*, 1991, **32**, 4525; (d) N. Chida, M. Ohtsuka and S. J. Ogawa, *Org. Chem.*, 1993, **58**, 4441; (e) T. Hudlicky and H. F. Olivo, *J. Am. Chem. Soc.*, 1992, **114**, 9694; (f) T. Hudlicky, H. Olivo and B. McKibben, *J. Am. Chem. Soc.*, 1994, **116**, 5108; (g) S. F. Martin and H. H. Tso, *Heterocycles*, 1993, **35**, 85; (h) G. E. Keck and T. T. Wager, *J. Org. Chem.*, 1996, **61**, 8366; (i) G. E. Keck, T. T. Wager and J. F. D. Rodriguez, *J. Am. Chem. Soc.*, 1999, **121**, 5176; (j) S. Elango and T. H. Yan, *Tetrahedron*, 2002, **58**, 7335; (k) A. Padwa and H. Zhang, *J. Org. Chem.*, 2007, **72**, 2570; (l) M. Matveenko, O. J. Kokas, M. G. Banwell and A. C. Willis, *Org. Lett.*, 2007, **9**, 3683; (m) J. S. Yadav, G. Satheesh and C. V. S. R. Murthy, *Org. Lett.*, 2010, **12**, 2544; (n) E. H. Southgate, D. R. Holycross and D. Sarlah, *Angew. Chem., Int. Ed.*, 2017, **56**, 15049.
- 10 For the syntheses of narciclasine, see: (a) J. H. Rigby and M. E. Mateo, *J. Am. Chem. Soc.*, 1997, **119**, 12655; (b) D. Gonzalez, T. Martinot and T. Hudlicky, *Tetrahedron Lett.*, 1999, **40**, 3077; (c) T. Hudlicky, U. Rinner, D. Gonzalez, H. Akgun, S. Schilling, P. Siengalewicz, T. A. Martinot and G. R. Pettit, *J. Org. Chem.*, 2002, **67**, 8726; (d) S. Elango and T. Yan, *J. Org. Chem.*, 2002, **67**, 6954; (e) M. Matveenko, M. G. Banwell and A. C. Willis, *Tetrahedron*, 2008, **64**, 4817; (f) T. W. Bingham, L. W. Hernandez, D. G. Olson, R. L. Svec, P. J. Hergenrother and D. Sarlah, *J. Am. Chem. Soc.*, 2019, **141**, 657.
- 11 For the isolation of zephyranthine, see: (a) S. Ozeki, *Chem. Pharm. Bull.*, 1964, **12**, 253; (b) M. R. Herreraa, A. K. Machochoa, J. J. Nair, W. E. Campbell, R. Brun, F. Viladomat, C. Codina and J. Bastida, *Fitoterapia*, 2001, **72**, 444.
- 12 For the syntheses of zephyranthine see: (a) Y. J. Chen, S. L. Cai, C. C. Wang, J. D. Cheng, S. Kramer and X. W. Sun, *Chem.-Asian. J.*, 2017, **12**, 1309; (b) K. Ishii, Y. Seki-Yoritake, M. Ishibashi, M. W. Liaw, T. Oishi, T. Sato and N. Chida, *Heterocycles*, 2019, **99**, 111.
- 13 (a) This catalyst was selected from a primary screening from chiral thioureas, cinchona alkaloids and Evans' chiral nickel(II) catalyst;; (b) D. A. Evans and D. Seidel, *J. Am. Chem. Soc.*, 2005, **127**, 9958; (c) D. A. Evans, S. Mito and D. Seidel, *J. Am. Chem. Soc.*, 2007, **129**, 11583; (d) J. B. Chen, J. C. Chen, Y. Xie and H. B. Zhang, *Angew. Chem., Int. Ed.*, 2012, **51**, 1024; (e) X. Zhang and J. C. Anderson, *Angew. Chem., Int. Ed.*, 2019, **58**, 18040.
- 14 S. M. Weinreb, *Chem. Rev.*, 2006, **106**, 2531.
- 15 (a) J. H. Sahrner, H. Sucipto, S. C. Wenzel, M. Groh, R. W. Hartmann and R. Müller, *ChemBioChem*, 2015, **16**, 946; (b) D. Petrović and R. Brückner, *Org. Lett.*, 2011, **13**, 6524; (c) B. M. Trost, W. M. Segamish, C. K. Chung and D. Amans, *Chem.-Eur. J.*, 2012, **18**, 2948.
- 16 (a) A. E. Gatland, B. S. Pilgrim, P. A. Procopiou and T. J. Donohoe, *Angew. Chem., Int. Ed.*, 2014, **53**, 14555; (b) C. J. Moody and G. J. Warrellow, *Tetrahedron Lett.*, 1987, **28**, 6089.
- 17 D. L. Comins and A. Dehghani, *Tetrahedron Lett.*, 1992, **33**, 6299.
- 18 S. Cacchi, E. Morera and G. Ortari, *Tetrahedron Lett.*, 1984, **25**, 4821.
- 19 (a) S. G. Hentges and K. B. Sharpless, *J. Am. Chem. Soc.*, 1980, **102**, 4263; (b) E. N. Jacobsen, I. Marko, W. S. Mungall, G. Schroeder and K. B. Sharpless, *J. Am. Chem. Soc.*, 1988, **110**, 1968.
- 20 W. J. Huang, O. V. Singh, C. H. Chen, S. Y. Chiou and S. S. Lee, *Helv. Chim. Acta*, 2002, **85**, 1069.

