

HETEROCYCLES, Vol. 104, No. 2, 2022, pp. 215 - 228. © 2022 The Japan Institute of Heterocyclic Chemistry  
Received, 16th July, 2021, Accepted, 25th August, 2021, Published online, 15th September, 2021  
DOI: 10.3987/REV-21-969

## TOTAL SYNTHESIS OF NATURAL PRODUCTS AND MEDICINAL MOLECULES VIA CHELATION-CONTROLLED DIASTEREOSELECTIVE HYDRIDE REDUCTION OF AMINO KETONES

Tian Jin,<sup>a,1\*</sup> Lu Zhao,<sup>c,1</sup> Chichong Lu,<sup>b\*</sup> Zhe-Bin Zheng,<sup>a</sup> and Won-Hun Ham<sup>d\*</sup>

<sup>a</sup> Antibiotics Research and Re-evaluation Key Laboratory of Sichuan Province, Sichuan Industrial Institute of Antibiotics, School of Pharmacy, Chengdu University, Chengdu 610106, People's Republic of China; <sup>b</sup> Key Laboratory of Cosmetic, China National Light Industry, Beijing Technology and Business University, Beijing 100048, People's Republic of China; <sup>c</sup> Sichuan Institute for Drug Control (Sichuan Testing Center of Medical Devices), Chengdu 611731, People's Republic of China; <sup>d</sup> School of Pharmacy, Sungkyunkwan University, Seobu-ro 2066, Suwon-si, Gyeonggi-do 16419, Republic of Korea  
E-mail: jintian@cdu.edu.cn (T. Jin); luchichong@btbu.edu.cn (C. Lu); whham@skku.edu

<sup>1</sup> These authors contributed equally to this work.

**Abstract** – The chiral  $\beta$ -amino alcohols are widely presented in the natural products, privileged ligands, and medicinal molecules. In the past decades, the construction of *anti*- $\beta$ -amino alcohols have attracted in the interest of synthetic chemists. A number of studies indicated that the chelation-controlled hydride reduction approach is straightforward for the preparation of *anti*- $\beta$ -amino alcohol motifs in high yield with excellent diastereoselectivity and they can be used as chiral building block in the total synthesis of natural products and medicinal molecules. The aim of this review is to highlight application of chelation-controlled hydride reduction in total synthesis of natural products and medicinal molecules on the basis of a collection of recent literature studies.

## CONTENTS

1. Introduction
2. Historical background for chelation-controlled hydride reduction
3. Total synthesis of natural products and medicinal molecules via chelation-controlled hydride reduction as the key step
  - 3-1. Total synthesis of sphinganine by Howell and co-workers – 2004
  - 3-2. Total synthesis of hydroxyethylene dipeptide isostere by Rich and Huang – 2004
  - 3-3. Total synthesis of sphingosine by Katsumura and co-workers – 2006
  - 3-4. Total synthesis of (+)-epiquinamide enantiomers by Gerwick and Suyama – 2006
  - 3-5. Total synthesis of (+)- $\alpha$ -conhydrine and its pyrrolidine analogue by Ham and colleagues – 2012
  - 3-6. Total synthesis of methyl L-daunosaminide hydrochloride by Ham and colleagues – 2014
  - 3-7. Total synthesis of (–)-clavaminol A and deacetyl (+)-clavaminol H by Ham, Zheng, Jin and co-workers – 2017
4. Conclusion

## 1. INTRODUCTION

Chiral  $\beta$ -amino alcohols are important architectures that are commonly found in natural products, transition metal ligands or chiral auxiliaries, and synthetic biologically active compounds.<sup>1-4</sup> Interestingly, natural products containing chiral  $\beta$ -amino alcohol motif display various biological activities, such as antitumor,<sup>5,6</sup> antibacterial,<sup>7</sup> antiviral<sup>8</sup> and antiproliferative activities.<sup>9</sup> Owing to their privileged structure motif and potent biological properties, methods for the construction of chiral  $\beta$ -amino alcohols have attracted considerable attention from the synthetic chemists.<sup>9-27</sup> In 2000, List reported proline-catalyzed asymmetric three-component Mannich reaction to afford *syn*- $\beta$ -amino alcohol in good yield with excellent diastereoselectivity.<sup>16</sup> Latter, Barbas III and Trost's group individually described direct addition of unmodified ketone with imine to yield enantiopure *syn*- $\beta$ -amino alcohol.<sup>13,15</sup> Very recently, Frauhofer and White demonstrated an elegant Pd(II)-catalyzed allylic C–H amination reaction to provide *syn*- $\beta$ -amino alcohol in good diastereoselectivity.<sup>11</sup> So far, great achievements have been made by studies on the construction of *syn*- $\beta$ -amino alcohols, but enantioselective synthesis of *anti*- $\beta$ -amino alcohol is less explored. Furthermore synthetic methods for the construction *anti*- $\beta$ -amino alcohol protocols present intrinsic drawback including the use of expensive reagents and catalysts, the deficiency of stereoselectivity and difficult preparation of starting materials. Thus, novel synthetic strategy for the construction of *anti*-selective  $\beta$ -amino alcohols is still highly demanded.

## 2. Historical background for chelation-controlled hydride reduction

Recently, chelation-controlled hydride reduction of *N*-protected amino ketone has emerged as powerful synthetic method to access *anti*- $\beta$ -amino alcohol<sup>28</sup> in organic synthesis due to its high conversion rate and excellent diastereoselectivity in simple operation (Figure 1) and they can be used as chiral synthons in total synthesis of natural products and medically relevant molecules. The first example of this strategy can be dated back to 2002 when Hoffman et al.<sup>28</sup> used  $\text{LiAlH}(\text{O}^t\text{Bu})_3$  in EtOH at  $-78\text{ }^\circ\text{C}$  for highly diastereoselective reduction of carbamate-protected amino ketone to afford *anti*- $\beta$ -amino alcohol in high yield with excellent diastereoselectivity. As depicted in Figure 2, the stereoselectivity of this reaction mechanism can be explained by the chelation of the aluminum ion to both the carbonyl oxygen and the amine nitrogen, enforcing a *syn*-periplanar relationship between the amine and ketone groups and lead to the *anti*- $\beta$ -diastereomer.<sup>28</sup>

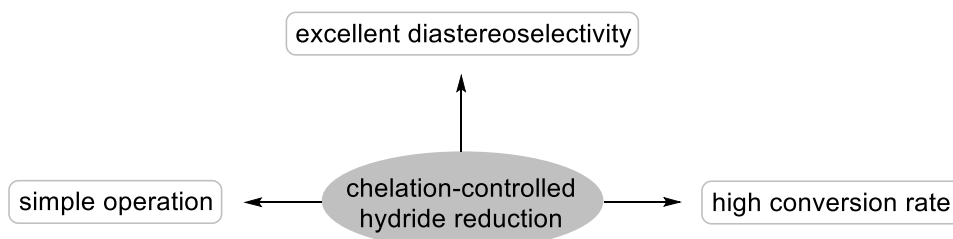


Figure 1. Advantage of chelation-controlled hydride reduction

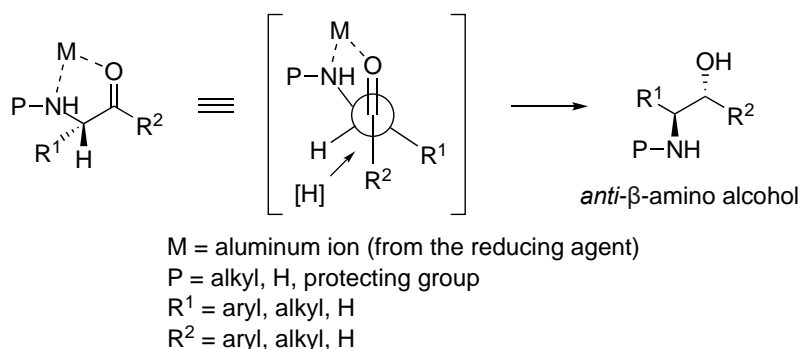


Figure 2. Chelation-controlled hydride reduction model

In the pioneering work of Hoffman,<sup>28</sup> as depicted in Table 1, at first, reduction of amino ketone **I** with  $\text{NaBH}_4$  in THF at  $-78\text{ }^\circ\text{C}$  yielded conversion rate (*anti*-**II<sub>a</sub>**/*syn*-**II<sub>b</sub>** = 7:1) and excellent isolated yield (Table 1, entry 1). Replacement of  $\text{NaBH}_4$  by other reducing agents such as  $\text{LiBH}_4$  or  $\text{KBH}_4$  or  $\text{Me}_4\text{N}^+\text{BH}_4^-$  in EtOH at  $-78\text{ }^\circ\text{C}$  gave same conversion rate (*anti*-**II<sub>a</sub>**/*syn*-**II<sub>b</sub>** = 7:1) and up to 98% isolated yield (Table 1, entry 2–4). In addition, treatment of amino ketone **I** with  $\text{NaBH}_4$  in the combination of  $\text{CeCl}_3$  as the additive afforded same conversion rate (*anti*-**II<sub>a</sub>**/*syn*-**II<sub>b</sub>** = 7:1, Table 1, entry 5). The reaction

of amino ketone **I** with  $\text{Zn}(\text{BH}_4)_2$  at  $-78\text{ }^\circ\text{C}$  to  $0\text{ }^\circ\text{C}$  in THF gave low conversion rate (*anti-II<sub>a</sub>*/*syn-II<sub>b</sub>* = 2:1) and 95% yield (Table 1, entry 6). Interestingly, by treating with L-selectride in ether at  $-78\text{ }^\circ\text{C}$  to  $0\text{ }^\circ\text{C}$  produced conversion rate of *anti-II<sub>a</sub>*/*syn-II<sub>b</sub>* = 1:2 and 94% yield (Table 1, entry 7). Treatment of amino ketone **I** with N-selectride in ether at  $-78\text{ }^\circ\text{C}$  provided conversion rate (*anti-II<sub>a</sub>*/*syn-II<sub>b</sub>* = 1:9) and 91% yield (Table 1, entry 8).

Table 1. The reduction of amino ketone **I** with various reducing agents/conditions

entry	reagents	conditions	yield (%)	<i>anti-II<sub>a</sub></i> / <i>syn-II<sub>b</sub></i>
1	$\text{NaBH}_4$	$\text{EtOH}, -78\text{ }^\circ\text{C}$	98	7:1
2	$\text{LiBH}_4$	$\text{EtOH}, -78\text{ }^\circ\text{C}$	97	7:1
3	$\text{KBH}_4$	$\text{EtOH}, -78\text{ }^\circ\text{C}$	98	7:1
4	$\text{Me}_4\text{N}^+\text{BH}_4^-$	$\text{EtOH}, -78\text{ }^\circ\text{C}$	97	7:1
5	$\text{NaBH}_4/\text{CeCl}_3$	$\text{EtOH}, -78\text{ }^\circ\text{C}$	97	7:1
6	$\text{Zn}(\text{BH}_4)_2$	$\text{THF}, -78\text{ }^\circ\text{C}$ to $0\text{ }^\circ\text{C}$	95	2:1
7	L-selectride	$\text{Et}_2\text{O}, -78\text{ }^\circ\text{C}$ to $0\text{ }^\circ\text{C}$	94	1:2
8	N-selectride	$\text{THF}, -78\text{ }^\circ\text{C}$	91	1:9
9	$\text{LiAlH}(\text{O}^t\text{Bu})_3$	$\text{THF}, -78\text{ }^\circ\text{C}$	93	1:9
10	$\text{LiAlH}(\text{O}^t\text{Bu})_3$	$\text{THF}, -78\text{ }^\circ\text{C}$ to $-20\text{ }^\circ\text{C}$	95	1:1
11	$\text{LiAlH}(\text{O}^t\text{Bu})_3$	$\text{EtOH}, -78\text{ }^\circ\text{C}$	98	19:1 <sup>b</sup>

<sup>a</sup> The *anti*/*syn* ratio was determined on the crude product.

<sup>b</sup> Only one diastereomer could be observed in the NMR spectrum of the crude product.

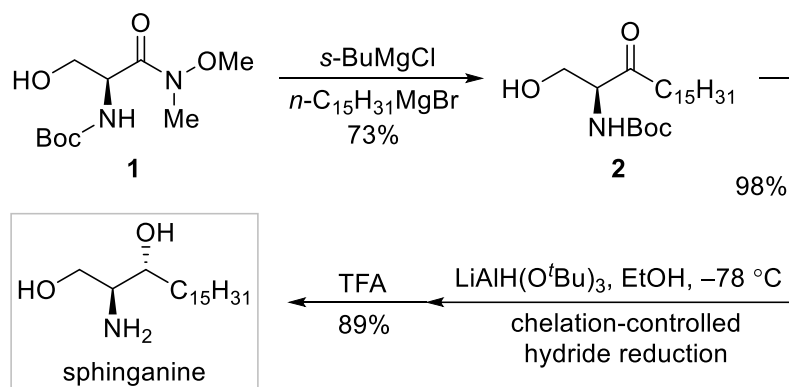
$\text{LiAlH}(\text{O}^t\text{Bu})_3$  as the reducing agent in THF at  $-78\text{ }^\circ\text{C}$  gave conversion rate (*anti-II<sub>a</sub>*/*syn-II<sub>b</sub>* = 1:9) with excellent isolated yield (Table 1, entry 9). When the reduction of amino ketone **I** was carried out in THF at  $-78\text{ }^\circ\text{C}$  to  $20\text{ }^\circ\text{C}$  by using  $\text{LiAlH}(\text{O}^t\text{Bu})_3$ , the isomers (*anti-II<sub>a</sub>*/*syn-II<sub>b</sub>*) were generated in only 1:1 dr (Table 1, entry 10). Surprisingly, reduction of amino ketone **I** with  $\text{LiAlH}(\text{O}^t\text{Bu})_3$  as the reducing agent in EtOH as the solvent at  $-78\text{ }^\circ\text{C}$  afforded high conversion rate (*anti-II<sub>a</sub>*/*syn-II<sub>b</sub>* = 19:1) with excellent isolated yield (Table 1, entry 11). The observations also show that the solvents and temperatures have a strong effect on the diastereoselectivity of this process. Therefore, the optimized conditions involved the use of  $\text{LiAlH}(\text{O}^t\text{Bu})_3$  as reducing agent in EtOH at  $-78\text{ }^\circ\text{C}$  for 2 h (entry 11). Nearly at the same time, Luthman and co-workers also reported their successful use of above-mentioned same conditions yielding *anti*- $\beta$ -amino alcohol in high isolated yield with excellent diastereoselectivity.<sup>29</sup>

So far, review with regard to the reactions and applications of chelation-controlled hydride reduction have not been published. Therefore, in this review, we will focus on the recent progress in chelation-controlled hydride reduction in organic synthesis and its applications to the total synthesis of natural products as well as bioactive compounds.

### 3. Total synthesis of natural products and medicinal molecules via chelation-controlled hydride reduction as the key step

#### 3-1. Total synthesis of sphinganine by Howell and co-workers – 2004

Sphinganine, one of the sphingoid bases that form the skeletons of the sphingolipids, is an essential component of eukaryotic cells.<sup>30</sup> Recent studies revealed that some of the sphingoid bases and their derivatives were evaluated in a Phase I clinical trial for the treatment of solid tumors. In 2004, Howell<sup>31</sup> and co-workers reported the concise total synthesis of sphinganine using chelation-controlled hydride reduction as the key step (Scheme 1). Their approach started from the known compound **1**, which was converted into amino ketone **2** by using a sacrificial base (*s*-BuMgCl) and Grignard reagent (*n*-C<sub>15</sub>H<sub>31</sub>MgBr) in 73% yield. Reaction of this compound with LiAlH(O<sup>*t*</sup>Bu)<sub>3</sub> in EtOH at –78 °C afforded *anti*-β-amino alcohol as a single isomer via the chelation-controlled hydride reduction strategy, which was further advanced to sphinganine via TFA mediated deprotection.

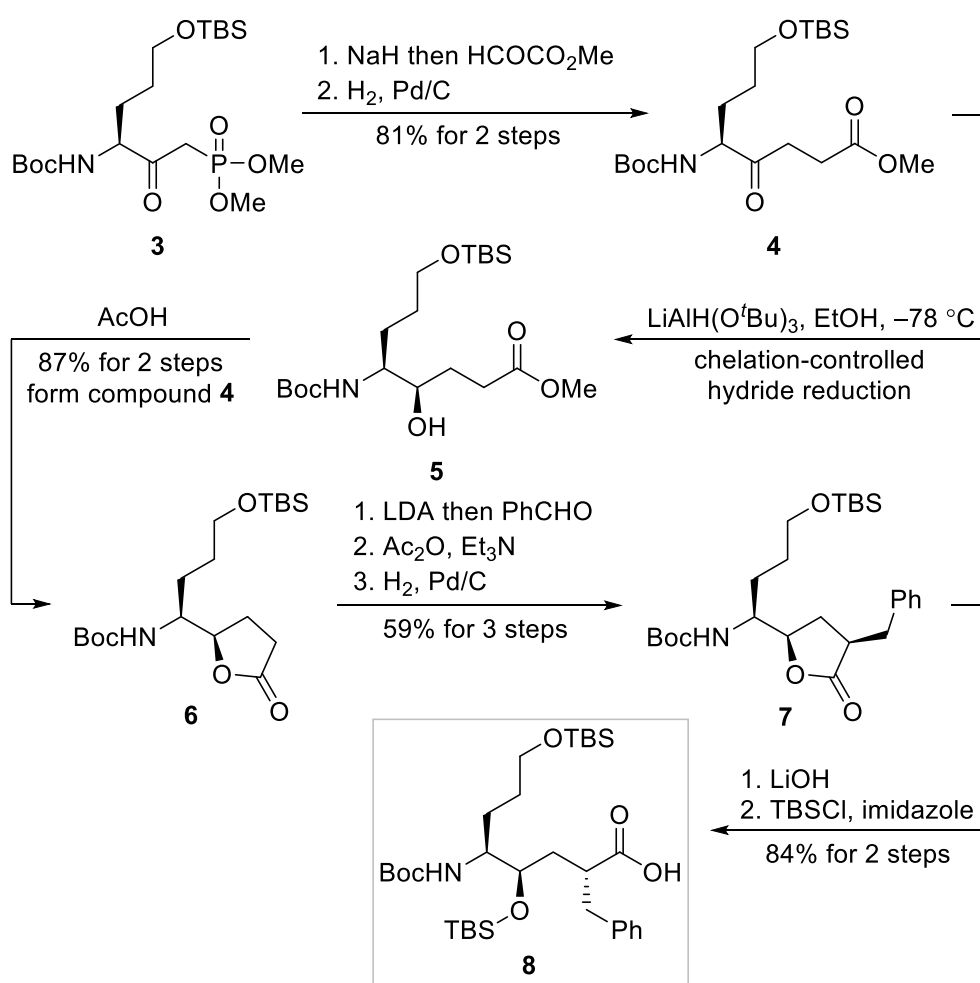


Scheme 1. Highlights of the total synthesis of sphinganine by Howell and co-workers

#### 3-2. Total synthesis of hydroxyethylene dipeptide isostere by Rich and Huang – 2004

Hydroxyethylene dipeptide isostere **8** is a precursor for the synthesis of powerful inhibitor of the butulinium neurotoxin B metalloprotease and has therefore attracted considerable attention from the organic chemists for a very long time.<sup>32</sup> In 2004, Rich and Huang described<sup>32</sup> the total synthesis of hydroxyethylene dipeptide isostere **8** using a highly diastereoselective chelation-controlled hydride reduction protocol as the key step. In Scheme 2, the ketone phosphonate **3** underwent

Horner–Wadsworth–Emmons (HWE) reaction with freshly synthesized methyl glyoxylate followed by hydrogenation with  $\text{H}_2/\text{Pd-C}$  to furnish saturated keto ester **4**. Subsequent reduction of **4** on the basis of chelation-controlled hydride reduction strategy using  $\text{LiAlH}(\text{O}^t\text{Bu})_3$  as the reducing agent in EtOH at  $-78\text{ }^\circ\text{C}$  produced *anti*- $\beta$ -amino alcohol **5** as a single diastereomer. Treatment of **5** with acetic acid in toluene at reflux provided lactone **6**. Having key intermediate **6** in hand, a sequence of alkylation and an Aldol-elimination–hydrogenation was performed to deliver **7**. Next, hydrolysis of **7** with  $\text{LiOH}\cdot\text{H}_2\text{O}$  followed by protection of resulting alcohol as the *tert*-butyldimethylsilyl ether afforded intermediate **8** in two steps.

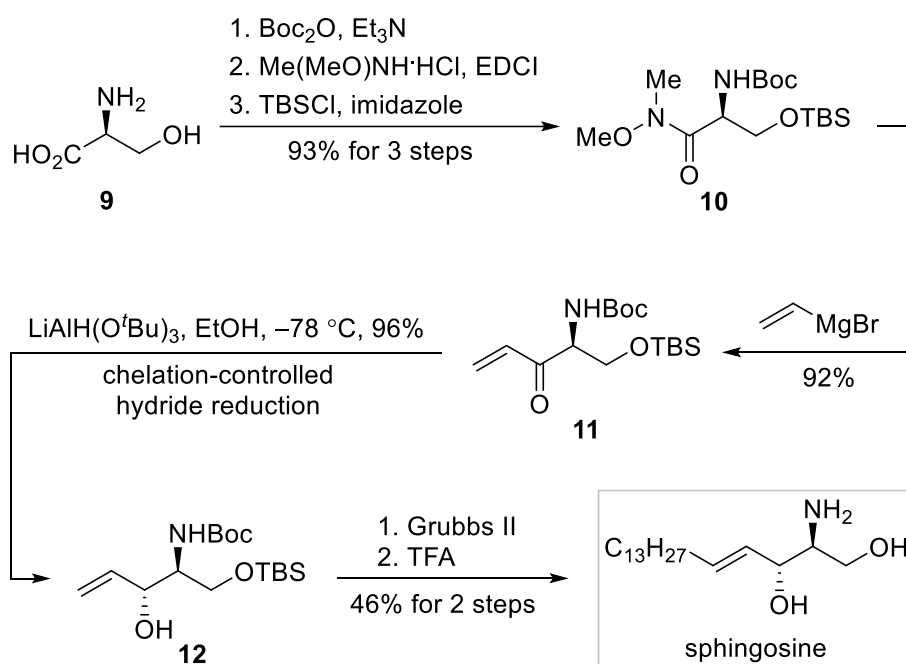


Scheme 2. Highlights of the total synthesis of hydroxyethylene dipeptide isostere by Rich and Huang

### 3-3. Total synthesis of sphingosine by Katsumura and co-workers – 2006

Sphingosine, a family of sphingolipids, has attracted considerable attention due to its signal transduction and molecular recognition processes in cell membranes. In 2006, Katsumura and co-workers completed<sup>33</sup> short and straightforward total synthesis of natural product sphingosine using chelation-controlled

hydride reduction and ring-closing metathesis (RCM) reaction as the key steps (Scheme 3). In this study, the common intermediate **10** was constructed using standard conditions from commercially available chiral source L-serine in three steps. Next, Grignard reaction of **10** with vinylmagnesium bromide afforded vinyl ketone **11**, which was converted to the *anti*- $\beta$ -amino alcohol **12** as a one isomer in 96% yield via chelation-controlled hydride reduction process using  $\text{LiAlH}(\text{O}^t\text{Bu})_3$  in EtOH at  $-78\text{ }^\circ\text{C}$ . Further elaborations including cross metathesis reaction with Grubbs II catalyst and deprotection of resulting vinyl alcohol with TFA smoothly afforded desired natural product sphingosine in two steps. In this study, sphingomyelin, ceramide and sphingosine 1-phosphate were synthesized under similar key reactions.<sup>33</sup>

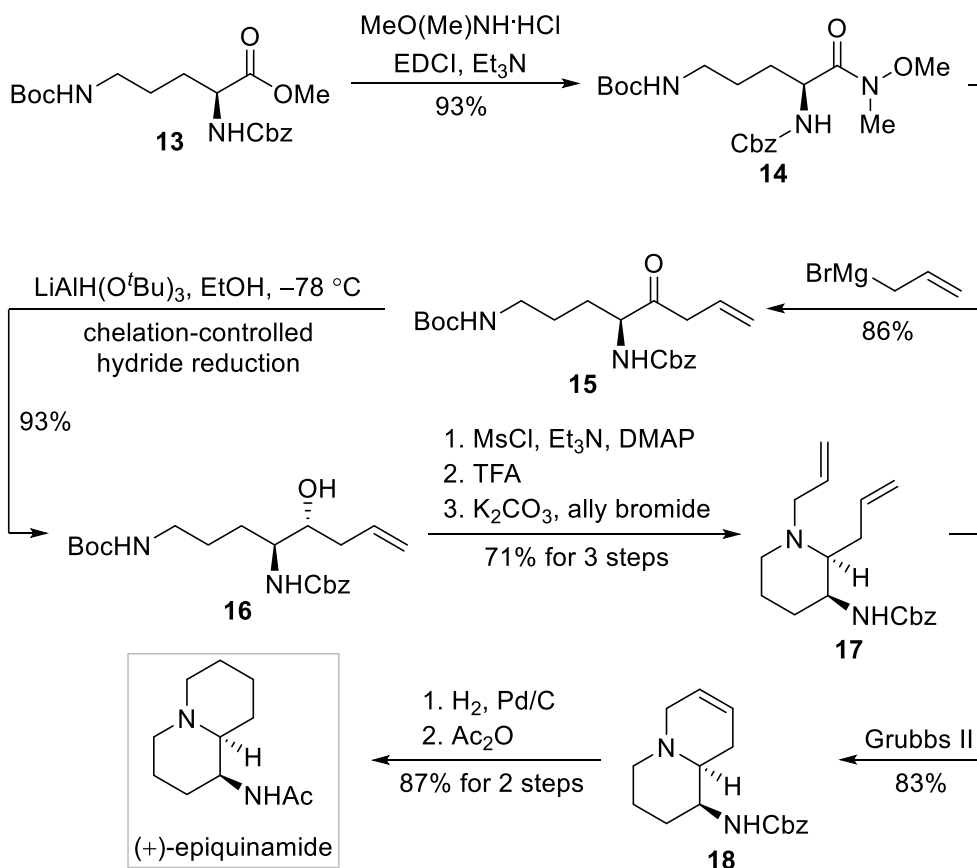


Scheme 3. Highlights of the total synthesis of sphingosine by Katsumura and co-workers

### 3-4. Total synthesis of (+)-epiquinamide enantiomers by Gerwick and Suyama – 2006

(+)-Epiquinamide, isolated from the Ecuadorian frog *Epipedobates tricolor* in 2003, is a potent and selective agonistic agent against  $\beta_2$  nicotinic receptors.<sup>34,35</sup> In 2006, Gerwick and Suyama reported<sup>34</sup> an elegant synthesis of (+)-epiquinamide using chelation-controlled hydride reduction and RCM reaction as the key steps (Scheme 4). Initially, the Weinreb amide **14** was constructed from **13** efficiently with  $\text{MeO}(\text{Me})\text{NH}\cdot\text{HCl}$  in the presence of EDCI and  $\text{Et}_3\text{N}$ . Reaction of **14** with allylmagnesium bromide provided compound **15**, which underwent chelation-controlled hydride reduction process ( $\text{LiAlH}(\text{O}^t\text{Bu})_3/\text{EtOH}/-78\text{ }^\circ\text{C}$ ) to afford *anti*- $\beta$ -amino alcohol **16** in excellent chemical yield. Further functionality manipulations afforded **17** in three steps with 71% overall yield, which then reacted with

Grubbs II catalyst to give **18**. Finally, Pd/C catalyzed hydrogenation followed by acetylation yielded (+)-epiquinamide.



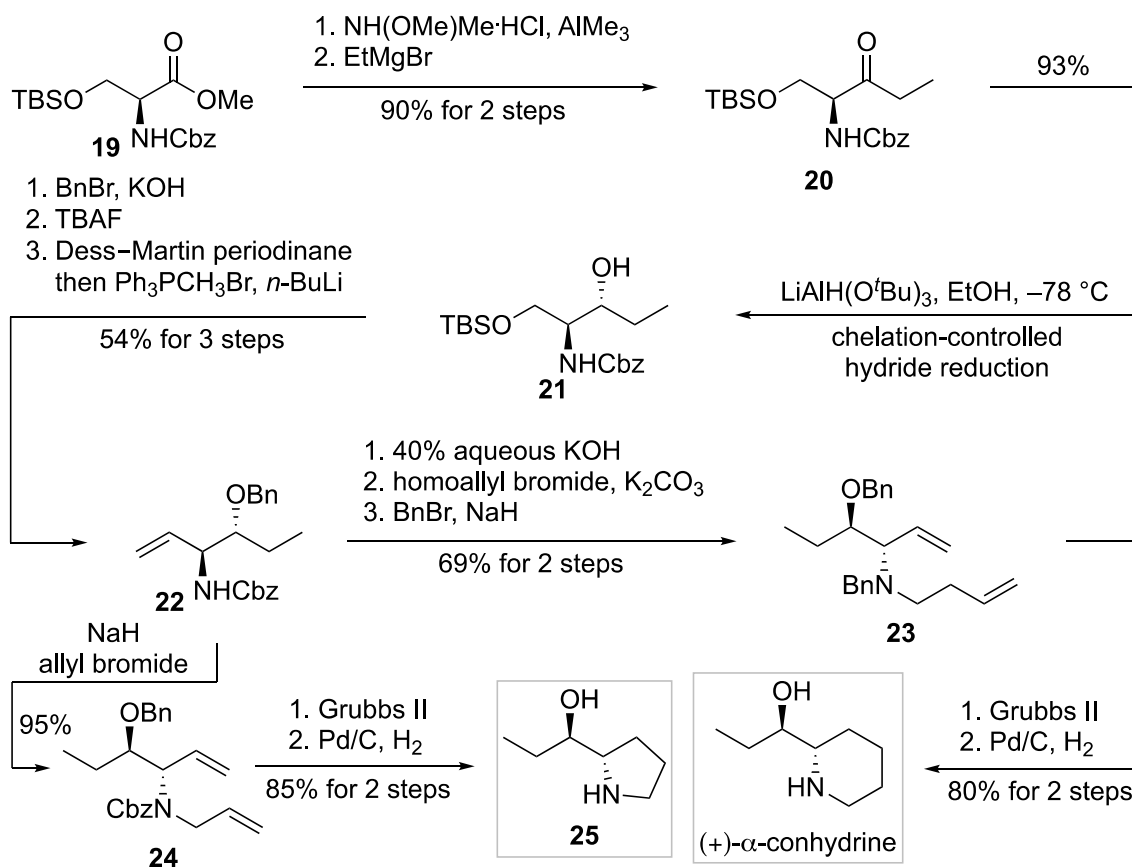
Scheme 4. Highlights of the total synthesis of (+)-epiquinamide by Gerwick and Suyama

### 3-5. Total synthesis of (+)- $\alpha$ -conhydrine and its pyrrolidine analogue by Ham and colleagues – 2012

Conhydrine, a natural product isolated from the seeds and leaves of the poisonous plant *Conium maculatum*, is a potent glycosidase inhibitor as well as it exhibits both antitumor and antiviral properties.<sup>8,36</sup> In 2012, our group disclosed<sup>8</sup> the total syntheses of piperidine alkaloid (+)- $\alpha$ -conhydrine and its pyrrolidine analog **25** using a highly diastereoselective chelation-controlled hydride reduction as the key step including RCM reaction.

As outlined in Scheme 5, the amino ketone **20** was obtained successfully from starting material methyl ester **19** via Weinreb amide formation with MeO(Me)NH·HCl in the presence of AlMe<sub>3</sub> followed by Grignard reaction with EtMgBr in 90% for two steps. Chelation-controlled hydride reduction of **20** using LiAlH(O<sup>t</sup>Bu)<sub>3</sub> in EtOH at -78 °C conditions provided *anti*- $\beta$ -amino alcohol **21** as a one isomer in 93% yield. Having the key intermediate **21** in hand, a sequence of benzylation, deprotection, Dess–Martin oxidation followed by Wittig reaction gave **22** in 54% for three steps. Treatment of **22** with 40% aqueous

KOH and homoallyl bromide followed by benzylaiton of resulting diene with benzyl bromide in the presence of NaH afforded **23** in a synthetically useful yield. Further elaborations including RCM reaction with Grubbs II catalyst and hydrogenation with Pd/C smoothly provided (+)- $\alpha$ -conhydrine in 80% yield for two steps. In another direction, alkylation of **22** followed by RCM and catalytic hydrogenation gave pyrrolidine analog **25**.



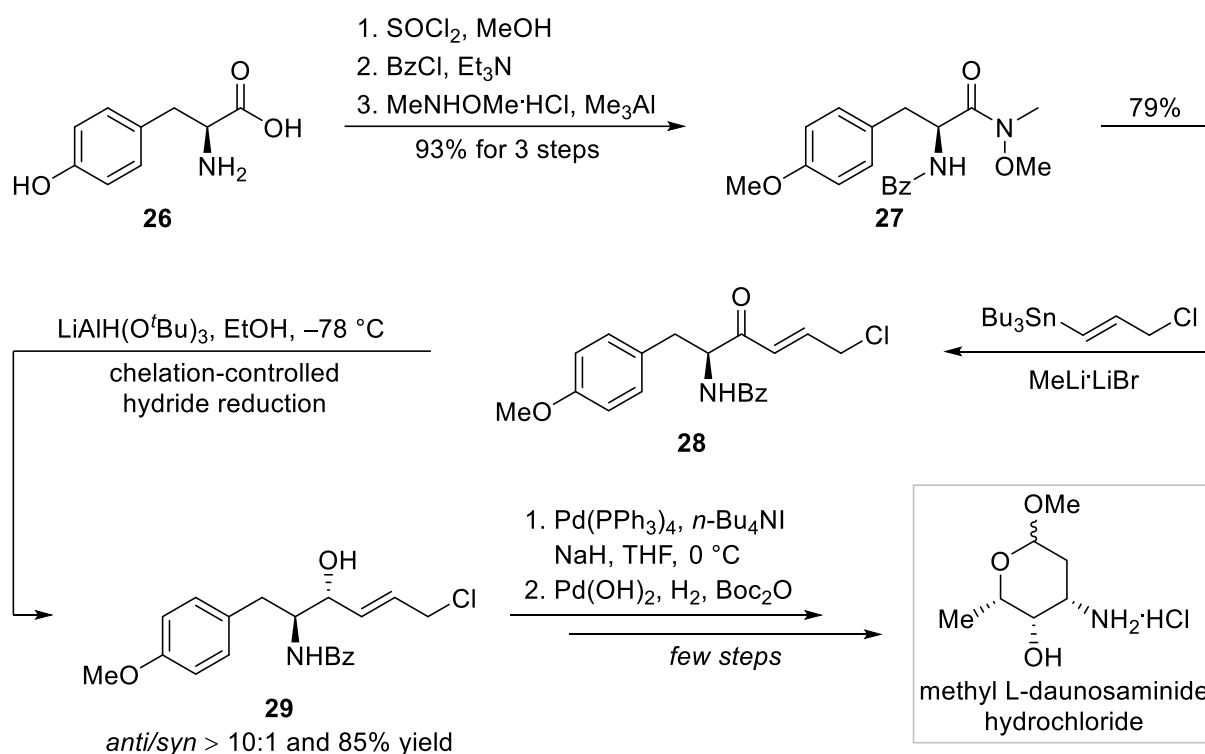
Scheme 5. Highlights of the total synthesis of (+)- $\alpha$ -conhydrine and its pyrrolidine analog by Ham and co-workers

### 3-6. Total synthesis of methyl L-daunosaminide hydrochloride by Ham and colleagues – 2014

L-Daunosaminide, an important segment of L-daunosamine (3-amino-2,3,6-trideoxy-L-*lyxo*-hexose), is a glycosidic component of anthracycline antibiotics such as daunomycin and adriamycin, and it displays impressive activity against various human tumor types.<sup>37</sup> In 2012, our group reported<sup>37</sup> efficient total synthesis of methyl L-daunosaminide hydrochloride using chelation-controlled hydride reduction as the key step.

In Scheme 6, the total synthesis started from commercially available L-tyrosine in three steps. Namely, reaction of L-tyrosine **26** with thionyl chloride in MeOH at reflux followed by protection of primary amine with BzCl resulted in ester, which underwent Weinreb amide formation process with

MeNHOMe·HCl in the presence of AlMe<sub>3</sub> to afford **27**. Treatment of Weinreb amide **27** with (*E*)-tributyl(3-chloroprop-1-en-1-yl)stannane and MeLi·LiBr followed by chelation-controlled hydride reduction using LiAlH(O<sup>t</sup>Bu)<sub>3</sub> in EtOH at –78 °C for 3 h yielded *anti*-β-amino alcohol in two steps with excellent diastereoselectivity (*anti*/*syn*>10:1 determined by <sup>1</sup>H NMR spectroscopy). Further elaborations including palladium catalyzed intramolecular oxazine formation [Pd(PPh<sub>3</sub>)<sub>4</sub>/*n*-Bu<sub>4</sub>NI/NaH/THF, 0 °C] and catalytic hydrogenation [Pd(OH)<sub>2</sub>/H<sub>2</sub>/Boc<sub>2</sub>O] smoothly furnished methyl L-daunosaminide hydrochloride in few steps.

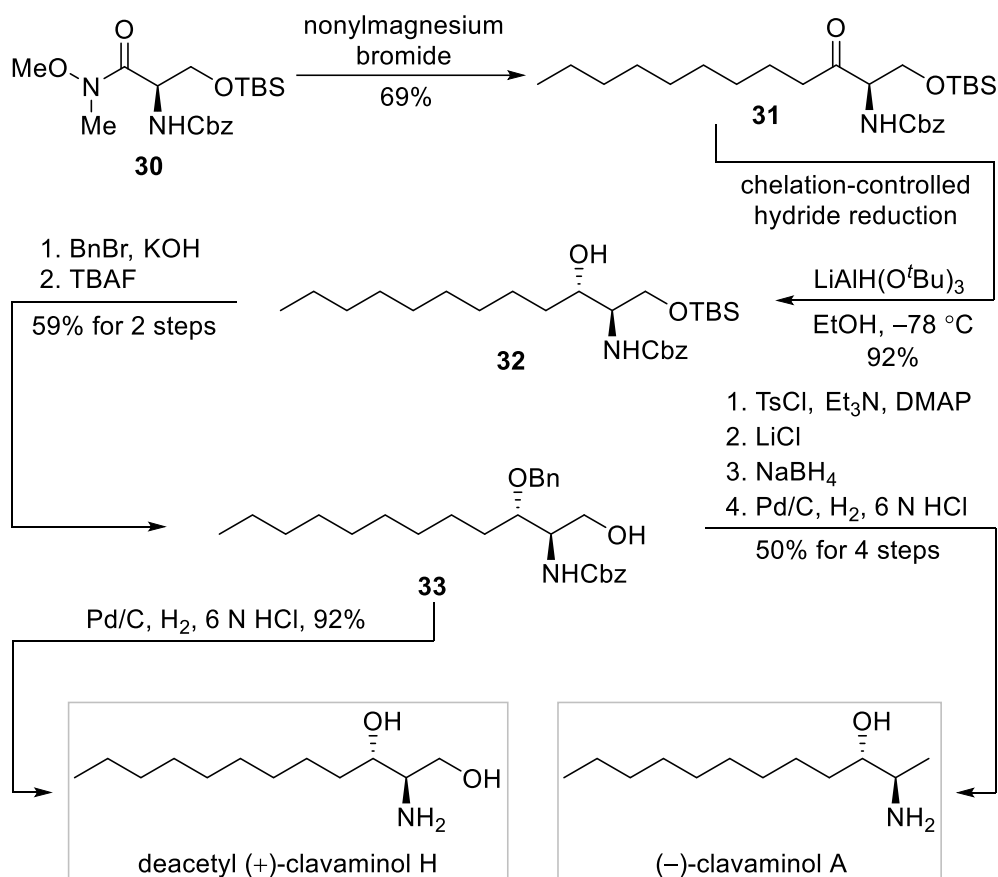


Scheme 6. Highlights of the total synthesis of methyl L-daunosaminide hydrochloride by Ham and co-workers

### 3-7. Total synthesis of (–)-clavaminol A and deacetyl (+)-clavaminol H by Ham, Zheng, Jin and co-workers – 2017

Clavaminol A, a long-chain 2-amino-3-alkanols, was isolated from the Mediterranean ascidian *Clavelina phlegraea*, and showed significant cytotoxic bioactivities.<sup>38</sup> Very recently, our group completed<sup>39,40</sup> the efficient asymmetric syntheses of (–)-clavaminol A and deacetyl (+)-clavaminol H using chelation-controlled hydride reduction strategy including palladium catalyzed hydrogenation as the key steps. As illustrated in Scheme 7, treatment of **30** with nonylmagnesium bromide led to corresponding amino ketone **31**, which was efficiently and high diastereoselectively converted based on the chelation-controlled hydride reduction process under LiAlH(O<sup>t</sup>Bu)<sub>3</sub> in EtOH at –78 °C conditions to give key intermediate *anti*-β-amino alcohol **32** as a single isomer in excellent yield. Subsequent benzylation of

secondary hydroxyl group with BnBr in compound **32** followed by deprotection of TBS ether in resulting carbamate with TBAF afforded primary alcohol **33**. Further functionality manipulations provided (–)-clavaminol A in four steps with a good overall yield of 50%. In addition, treatment of **33** with Pd/C and 6 N HCl under H<sub>2</sub> furnished deacetyl (+)-clavaminol H.



Scheme 7. Highlights of the total synthesis of (–)-clavaminol A and deacetyl (+)-clavaminol H by Ham, Zheng, Jin and co-workers

#### 4. CONCLUSION

*Anti*-β-amino alcohols mostly present in the natural products, privileged ligands, and synthetic bioactive molecules. Unfortunately, methods for the construction of *anti*-β-amino alcohols are by far less well developed. Chelation-controlled hydride reduction is one of the most important strategies for synthesis of optically active *anti*-β-amino alcohols, which can provide a number of important synthetic intermediates leading to natural products and bioactive compounds. Moreover, compared to other construction of *anti*-β-amino alcohols protocol such as transition metal-catalyzed strategy,<sup>25–27</sup> this procedure does display special properties providing in high conversion rate, excellent diastereoselectivity and without any expensive catalysts. In recent decades, the sphinganine has been efficiently prepared from the amino ketone using chelation-controlled hydride reduction as the key reaction (Scheme 1). In addition,

sphingosine was constructed based on cross metathesis reaction of *anti*- $\beta$ -amino alcohol with Grubbs' catalyst, which was prepared from amino ketone via chelation-controlled hydride reduction technology (Scheme 3). Very recently, we have reported a concise chemical syntheses of (–)-clavaminol A and deacetyl (+)-clavaminol H. Our route relies on a stereoselective reduction of amino ketone by using chelation-controlled reduction strategy to build the *anti*- $\beta$ -amino alcohol in simple operation (Scheme 7). We do hope that the content reported in this review may assist further developments in the field of natural products and pharmaceutically valuable compounds synthesis.

## ACKNOWLEDGEMENTS

We thank the Open Research Fund Program of Key Laboratory of Cosmetic, China National Light Industry, Beijing Technology and Business University (KLC-2020-YB12) and the Opening Project of the Antibiotics Research and Re-evaluation Key Laboratory of Sichuan Province (ARLKF18-01) for financial support.

## REFERENCES

1. D. J. Ager, I. Prakash, and D. R. Schaad, *Chem. Rev.*, 1996, **96**, 835.
2. S. C. Bergmeier, *Tetrahedron*, 2000, **56**, 2561.
3. C. A. de Parrodi and E. Juaristi, *Synlett*, 2006, 2699.
4. O. N. Burchak and S. Py, *Tetrahedron*, 2009, **65**, 7333.
5. A. G. Jamieson and A. Sutherland, *Org. Lett.*, 2007, **9**, 1609.
6. R. N. Patel, *Biomolecules*, 2013, **3**, 741.
7. W. Cunico, C. R. B. Gomes, M. L. G. Ferreira, T. G. Ferreira, D. Cardinot, M. V. N. de Souza, and M. C. S. Lourenço, *Eur. J. Med. Chem.*, 2011, **46**, 974.
8. T. Jin, Y. Mu, G.-W. Kim, S.-S. Kim, J.-S. Kim, S.-I. Huh, K.-Y. Lee, J.-E. Joo, and W.-H. Ham, *Asian J. Org. Chem.*, 2012, **1**, 232.
9. G. Silveira-Dorta, O. J. Donadel, V. S. Martín, and J. M. Padrón, *J. Org. Chem.*, 2014, **79**, 6775.
10. J. C. Chen, S. Gao, J. D. Gorden, and M. Chen, *Org. Lett.*, 2019, **21**, 4638.
11. K. J. Fraunhoffer and M. C. White, *J. Am. Chem. Soc.*, 2007, **129**, 7274.
12. Z. H. Zhou, Y. L. Tang, K. Y. Li, B. Liu, and C. C. Tang, *Chinese Chem. Lett.*, 2003, **14**, 1227.
13. B. M. Trost and L. R. Terrell, *J. Am. Chem. Soc.*, 2003, **125**, 338.
14. B. List, P. Pojarliev, W. T. Biller, and H. J. Martin, *J. Am. Chem. Soc.*, 2002, **124**, 827.
15. A. Córdova, W. Notz, G. F. Zhong, J. M. Betancort, and C. F. Barbas, *J. Am. Chem. Soc.*, 2002, **124**, 1842.
16. B. List, *J. Am. Chem. Soc.*, 2000, **122**, 9336.

17. C. Agami, F. Amiot, F. Couty, L. Dechoux, C. Kaminsky, and O. Venier, [Tetrahedron: Asymmetry](#), **1998**, **9**, 3955.
  18. E. Didier, B. Loubinoux, G. H. R. Tombo, and G. Rihs, [Tetrahedron](#), **1991**, **47**, 4941.
  19. E. D. D. Calder, A. M. Zaed, and A. Sutherland, [J. Org. Chem.](#), **2013**, **78**, 7223.
  20. G. Bartoli, M. Bosco, A. Carlone, M. Locatelli, M. Massaccesi, P. Melchiorre, and L. Sambri, [Org. Lett.](#), **2004**, **6**, 2173.
  21. S. Matsunaga, N. Kumagai, S. Harada, and M. Shibasaki, [J. Am. Chem. Soc.](#), **2003**, **125**, 4712.
  22. J. L. García Ruano and J. Alemán, [Org. Lett.](#), **2003**, **5**, 4513.
  23. N. A. Petasis and I. A. Zavialov, [J. Am. Chem. Soc.](#), **1998**, **120**, 11798.
  24. Y. Ichikawa, S.-I. Yamamoto, H. Kotsuki, and K. Nakano, [Synlett](#), **2009**, 2281.
  25. K. Spielmann, M. Xiang, L. A. Schwartz, and M. J. Krische, [J. Am. Chem. Soc.](#), **2019**, **141**, 14136.
  26. Y. Shi, Y. Wang, X. Lu, Y. Zhang, Y. Wu, and F. Zhong, [Green Chem.](#), **2019**, **21**, 780.
  27. W. Zhang, W. Chen, H. Xiao, and M. J. Krische, [Org. Lett.](#), **2017**, **19**, 4876.
  28. R. V. Hoffman, N. Maslouh, and F. Cervantes-Lee, [J. Org. Chem.](#), **2002**, **67**, 1045.
  29. J. Våbenø, M. Brisander, T. Lejon, and K. Luthman, [J. Org. Chem.](#), **2002**, **67**, 9186.
  30. S. Da Silva Pinto, S. G. Davies, A. M. Fletcher, S. K. Newton, P. M. Roberts, and J. E. Thomson, [Tetrahedron Lett.](#), **2021**, **66**, 152743.
  31. R. C. So, R. Ndonge, D. P. Izmirian, S. K. Richardson, R. L. Guerrero, and A. R. Howell, [J. Org. Chem.](#), **2004**, **69**, 3233.
  32. B. E. Haug and D. H. Rich, [Org. Lett.](#), **2004**, **6**, 4783.
  33. T. Yamamoto, H. Hasegawa, T. Hakogi, and S. Katsumura, [Org. Lett.](#), **2006**, **8**, 5569.
  34. T. L. Suyama and W. H. Gerwick, [Org. Lett.](#), **2006**, **8**, 4541.
  35. R. W. Fitch, H. M. Garraffo, T. F. Spande, H. J. C. Yeh, and J. W. Daly, [J. Nat. Prod.](#), **2003**, **66**, 1345.
  36. C. Bhat, S. T. Bugde, and S. G. Tilve, [Synthesis](#), **2014**, **46**, 2551.
  37. T. Jin, J.-S. Kim, Y. Mu, S.-H. Park, X. Jin, J.-C. Kang, C.-Y. Oh, and W.-H. Ham, [Tetrahedron](#), **2014**, **70**, 2570.
  38. A. M. Zaed and A. Sutherland, [Org. Biomol. Chem.](#), **2011**, **9**, 8030.
  39. T. Jin, L. Zhao, M. Huang, Y. Yue, Z.-B. Zheng, and W.-H. Ham, [Tetrahedron: Asymmetry](#), **2017**, **28**, 725.
  40. T. Jin, L. Zhao, X. Liu, L. Sun, J.-F. Lin, and Z.-B. Zheng, [Synthesis](#), **2018**, **50**, 4569.
-



**Tian Jin** was born in Jilin, China, and graduated from the College of Pharmacy, Yanbian University, in 2007. He received his Master's degrees from the Department of Pharmacy, Wonkwang University, Korea (February 2010) and the College of Pharmacy, Yanbian University (July 2010). In 2013, he obtained his doctoral degree in medicinal chemistry and biology (advisor: Prof. Won-Hun Ham) from the School of Pharmacy, Sungkyunkwan University, Korea. He then worked as a postdoctoral fellow at the West China School of Pharmacy, Sichuan University. In November 2015, he joined the Sichuan Industrial Institute of Antibiotics, School of Pharmacy, Chengdu University. His research interests are focused on the total synthesis of bioactive natural products, asymmetric organocatalysis and medicinal chemistry.



**Lu Zhao** received her Master's degree in pharmacology from the Chengdu University of Traditional Chinese Medicine in 2008. She is currently a deputy director at the Safety Evaluation Center of Sichuan Institute for Drug Control (Sichuan Testing Center of Medical Devices). Her research interests include the activity screening of effective constituents in traditional Chinese medicine and drug safety evaluation.



**Chichong Lu** completed his Bachelor's in materials chemistry in 2006 from Nanjing University of Technology, China. He received his Master's degree (2009) and PhD degree (2012) in chemistry from Wonkwang University, Korea. He is currently an associate professor in chemistry at Beijing Technology and Business University, China. His main research focuses on design and development of bioactive molecules and functional nanocrystals and their applications in imaging, sensing and diagnostics.



**Zhe-Bin Zheng** received his Master's degree in medicinal chemistry from the China Pharmaceutical University in 1993. He obtained his doctoral degree in medicinal chemistry from the Faculty of Pharmacy and Pharmaceutical Sciences, University of Toyama, Japan, in 1999. He then worked as a postdoctoral fellow at the University of Maryland Baltimore County, USA, from 2001 to 2005. In May 2010, he moved to the Sichuan Industrial Institute of Antibiotics, School of Pharmacy, Chengdu University. His research interests include medicinal chemistry and the synthesis of biologically important natural products.



**Won-Hun Ham** was received Bachelor's (1975) and Master's (1979) degrees from College of Pharmacy, Seoul National University, Korea. In 1986, he obtained his doctoral degree in organic chemistry from the Department of Chemistry, Ohio State University, USA. He then worked as a postdoctoral fellow at the Department of Chemistry, Harvard University, USA, from Jun 1986 to May 1987. He joined Department of Chemistry, Korea Advanced Institute of Science and Technology (KAIST) as an assistant professor in Jun 1987, and moved to School of Pharmacy, Sungkyunkwan University as an associate professor in March 1990. From 1999, he was promoted to professor at the same university. His research interests include asymmetric synthesis and the total synthesis of natural products.