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

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Abstract – The chiral β-amino alcohols are widely presented in the natural products, privileged ligands, and medicinal molecules. In the past decades, the construction of *anti*-β-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*-β-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

Chiral β-amino alcohols are important architectures that are commonly found in natural products, transition metal ligands or chiral auxiliaries, and synthetic biologically active compounds.[1–4] Interestingly, natural products containing chiral β-amino alcohol motif display various biological activities, such as antitumor,[5,6] antibacterial,[7] antiviral[8] and antiproliferative activities.[9] Owing to their privileged structure motif and potent biological properties, methods for the construction of chiral β-amino alcohols have attracted considerable attention from the synthetic chemists.[9–27] In 2000, List reported proline-catalyzed asymmetric three-component Mannich reaction to afford *syn*-β-amino alcohol in good yield with excellent diastereoselectivity.[16] Latter, Barbas III and Trost's group individually described direct addition of unmodified ketone with imine to yield enantiopure *syn*-β-amino alcohol.[13,15] Very recently, Frauhoffer and White demonstrated an elegant Pd(II)-catalyzed allylic C–H amination reaction to provide *syn*-β-amino alcohol in good diastereoselectivity.[11] So far, great achievements have been made by studies on the construction of *syn*-β-amino alcohols, but enantioselective synthesis of *anti*-β-amino alcohol is less explored. Furthermore synthetic methods for the construction *anti*-β-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 β-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*-β-amino alcohol[28] 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.[28] used $LiAlH(O^tBu)_3$ in EtOH at –78 °C for highly diastereoselective reduction of carbamate-protected amino ketone to afford *anti*-β-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*-β-diastereomer.[28]

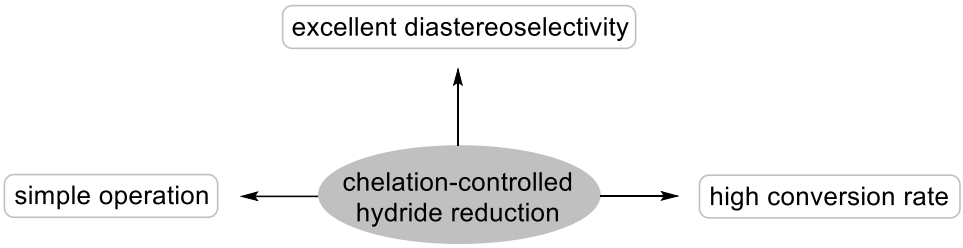
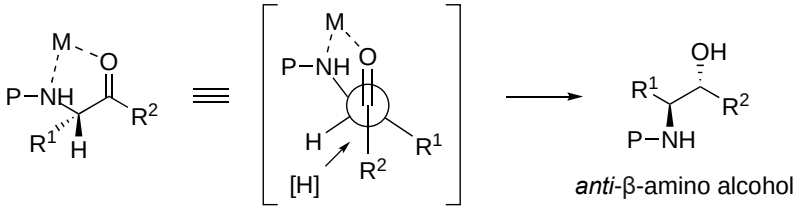


Figure 1. Advantage of chelation-controlled hydride reduction



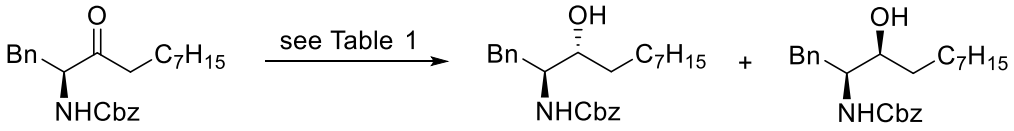
M = aluminum ion (from the reducing agent)
P = alkyl, H, protecting group
R^1 = aryl, alkyl, H
R^2 = aryl, alkyl, H

Figure 2. Chelation-controlled hydride reduction model

In the pioneering work of Hoffman,[28] as depicted in Table 1, at first, reduction of amino ketone **I** with $NaBH_4$ in THF at –78 °C yielded conversion rate (*anti*-**II$_a$**/*syn*-**II$_b$** = 7:1) and excellent isolated yield (Table 1, entry 1). Replacement of $NaBH_4$ by other reducing agents such as $LiBH_4$ or KBH_4 or $Me_4N^+BH_4^-$ in EtOH at –78 °C gave same conversion rate (*anti*-**II$_a$**/*syn*-**II$_b$** = 7:1) and up to 98% isolated yield (Table 1, entry 2–4). In addition, treatment of amino ketone **I** with $NaBH_4$ in the combination of $CeCl_3$ as the additive afforded same conversion rate (*anti*-**II$_a$**/*syn*-**II$_b$** = 7:1, Table 1, entry 5). The reaction

of amino ketone **I** with $Zn(BH_4)_2$ at –78 °C to 0 °C in THF gave low conversion rate (*anti*-**II$_a$**/*syn*-**II$_b$** = 2:1) and 95% yield (Table 1, entry 6). Interestingly, by treating with L-selectride in ether at –78 °C to 0 °C produced conversion rate of *anti*-**II$_a$**/*syn*-**II$_b$** = 1:2 and 94% yield (Table 1, entry 7). Treatment of amino ketone **I** with N-selectride in ether at –78 °C provided conversion rate (*anti*-**II$_a$**/*syn*-**II$_b$** = 1:9) and 91% yield (Table 1, entry 8).

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



amino ketone **I** *anti*-**II$_a$** *syn*-**II$_b$**

entry	reagents	conditions	yield (%)	*anti*-**II$_a$**/*syn*-**II$_b$**
1	$NaBH_4$	EtOH, –78 °C	98	7:1
2	$LiBH_4$	EtOH, –78 °C	97	7:1
3	KBH_4	EtOH, –78 °C	98	7:1
4	$Me_4N^+BH_4^-$	EtOH, –78 °C	97	7:1
5	$NaBH_4/CeCl_3$	EtOH, –78 °C	97	7:1
6	$Zn(BH_4)_2$	THF, –78 °C to 0 °C	95	2:1
7	L-selectride	Et_2O, –78 °C to 0 °C	94	1:2
8	N-selectride	THF, –78 °C	91	1:9
9	$LiAlH(O^tBu)_3$	THF, –78 °C	93	1:9
10	$LiAlH(O^tBu)_3$	THF, –78 °C to –20 °C	95	1:1
11	$LiAlH(O^tBu)_3$	EtOH, –78 °C	98	19:1[b]

[a] The *anti/syn* ratio was determined on the crude product.
[b] Only one diastereomer could be observed in the NMR spectrum of the crude product.

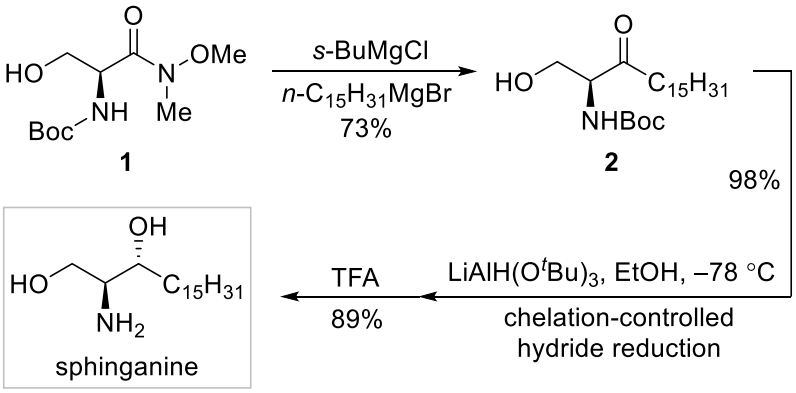
$LiAlH(O^tBu)_3$ as the reducing agent in THF at –78 °C gave conversion rate (*anti*-**II$_a$**/*syn*-**II$_b$** = 1:9) with excellent isolated yield (Table 1, entry 9). When the reduction of amino ketone **I** was carried out in THF at –78 °C to 20 °C by using $LiAlH(O^tBu)_3$, the isomers (*anti*-**II$_a$**/*syn*-**II$_b$**) were generated in only 1:1 dr (Table 1, entry 10). Surprisingly, reduction of amino ketone **I** with $LiAlH(O^tBu)_3$ as the reducing agent in EtOH as the solvent at –78 °C afforded high conversion rate (*anti*-**II$_a$**/*syn*-**II$_b$** = 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 $LiAlH(O^tBu)_3$ as reducing agent in EtOH at –78 °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*-β-amino alcohol in high isolated yield with excellent diastereoselectivity.[29]

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 from the skeletons of the sphingolipids, is an essential components of eukaryotic cells.[30] Recent studies revealed that some of sphingoid bases and their derivatives were evaluated in a Phase I clinical trial for the treatment of solid tumors. In 2004, Howell[31] 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 sacrificial base (*s*-BuMgCl) and Grignard reagent (*n*-$C_{15}H_{31}MgBr$) in 73% yield. Reaction of this compound with $LiAlH(O^tBu)_3$ 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.

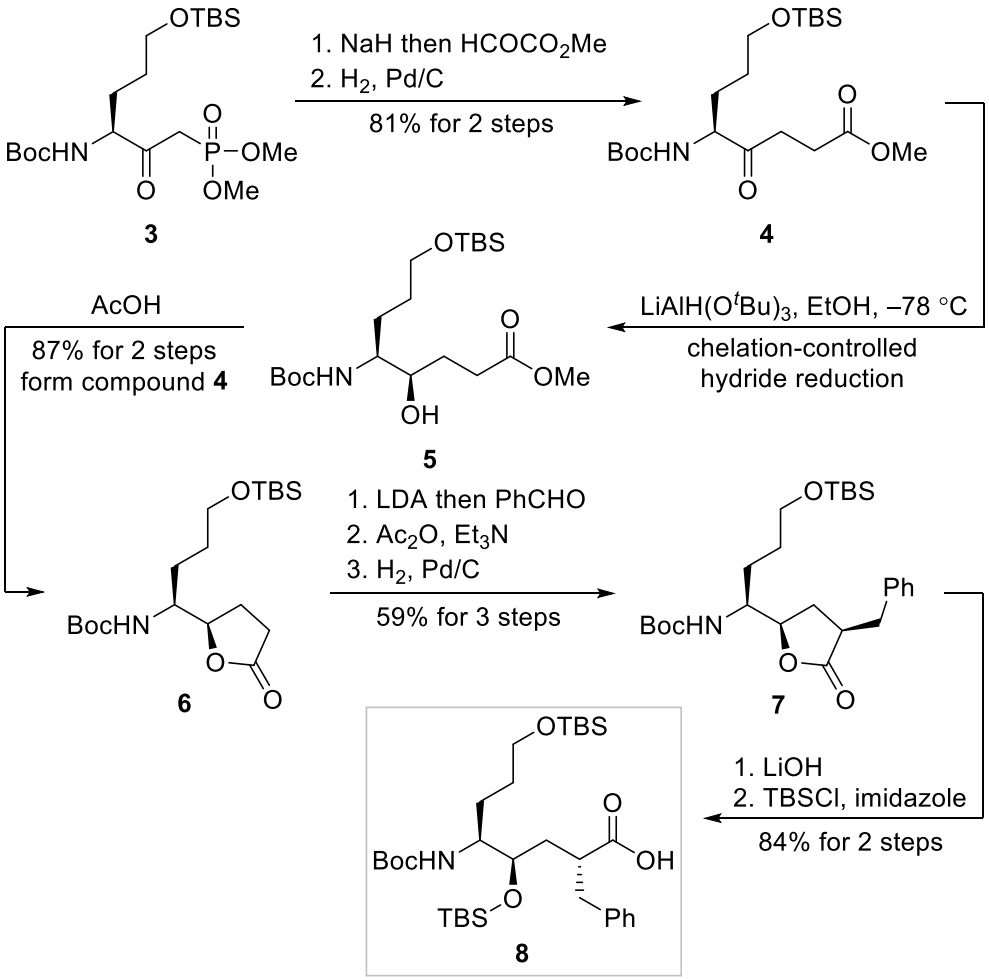


Scheme 1. Highlights of the total synthesis of sphinganine by Howell and co-workers

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.[32] In 2004, Rich and Huang described[32] the total synthesis of hydroxylethylene 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 H_2/Pd–C to furnish saturated keto ester **4**. Subsequent reduction of **4** on the basis of chelation-controlled hydride reduction strategy using $LiAlH(O^tBu)_3$ as the reducing agent in EtOH at –78 °C produced *anti*-β-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 $LiOH{\cdot}H_2O$ followed by protection of resulting alcohol as the *tert*-butyldimethylsilyl ether afforded intermediate **8** in two steps.

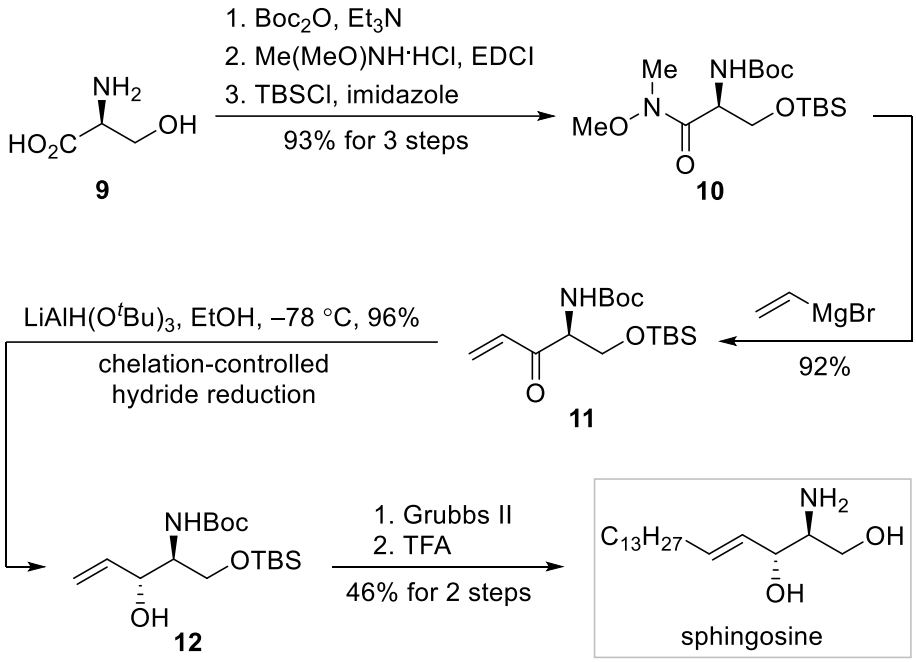


Scheme 2. Highlights of the total synthesis of hydroxyethylene dipeptide isostere dipeptide isostere by Rich and Huang

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[33] 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*-β-amino alcohol **12** as a one isomer in 96% yield via chelation-controlled hydride reduction process using $LiAlH(O^tBu)_3$ in EtOH at –78 °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.[33]

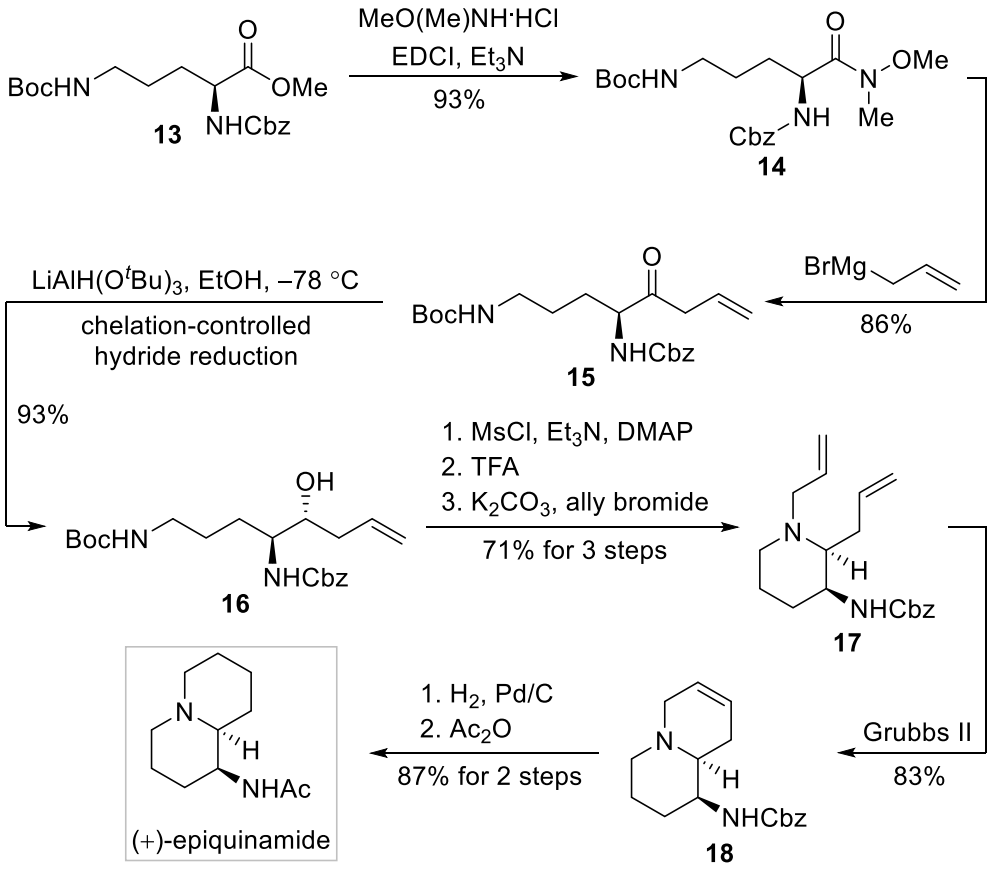


Scheme 3. Highlights of the total synthesis of sphingosine by Katsumura and co-workers

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 β2 nicotinic receptors.[34,35] In 2006, Gerwick and Suyama reported[34] 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 MeO(Me)NH·HCl in the presence of EDCI and Et_3N. Reaction of **14** with allylmagnesium bromide provided compound **15**, which underwent chelation-controlled hydride reduction process ($LiAlH(O^tBu)_3$/EtOH/–78 °C) to afford *anti*-β-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.



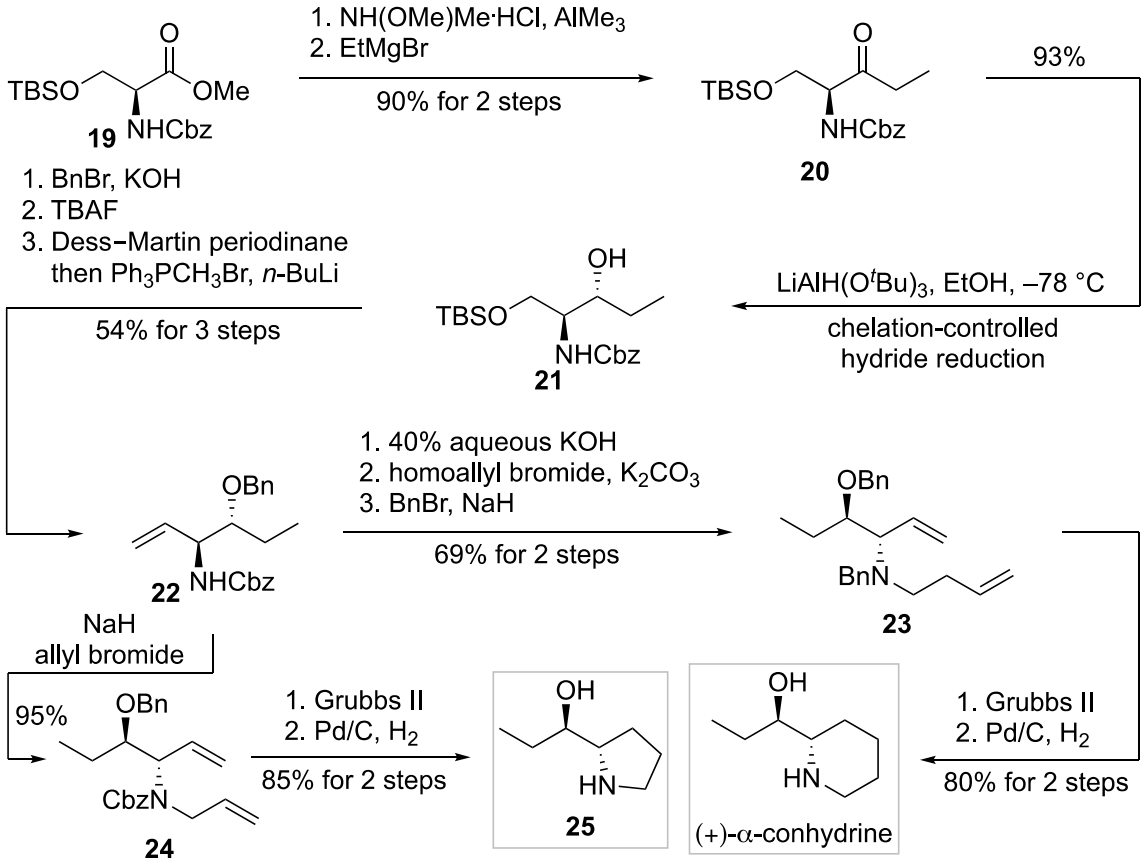
Scheme 4. Highlights of the total synthesis of (+)-epiquinamide by Gerwick and Suyama

3-5. Total synthesis of (+)-α-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.[8,36] In 2012, our group disclosed[8] the total syntheses of piperidine alkaloid (+)-α-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 $AlMe_3$ followed by Grignard reaction with EtMgBr in 90% for two steps. Chelation-controlled hydride reduction of **20** using $LiAlH(O^tBu)_3$ in EtOH at –78 °C conditions provided *anti*-β-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 (+)-α-conhydrine in 80% yield for two steps. In another direction, alkylation of **22** followed by RCM and catalytic hydrogenation gave pyrrolidine analog **25**.



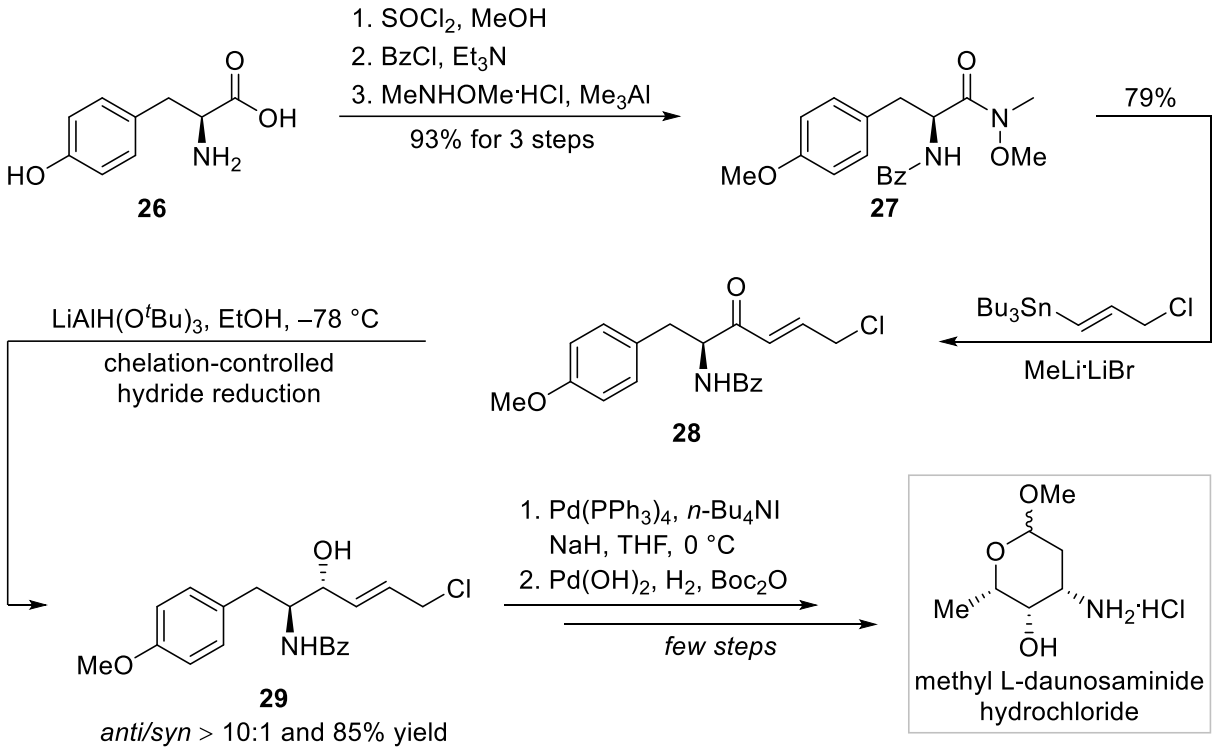
Scheme 5. Highlights of the total synthesis of (+)-α-conhydrine and its pyrrolidine analog by Ham and co-workers

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.[37] In 2012, our group reported[37] 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 $AlMe_3$ 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 $LiAlH(O^tBu)_3$ in EtOH at –78 °C for 3 h yielded *anti*-β-amino alcohol in two steps with excellent diasteroselectivity (*anti/syn*>10:1 determined by ^1H NMR spectroscopy). Further elaborations including palladium catalyzed intromolecular oxazine formation [$Pd(PPh_3)_4$/*n*-Bu_4NI/NaH/THF, 0 °C] and catalytic hydrogenation [$Pd(OH)_2/H_2/Boc_2O$] smoothly furnished methyl L-daunosaminide hydrochloride in few steps.

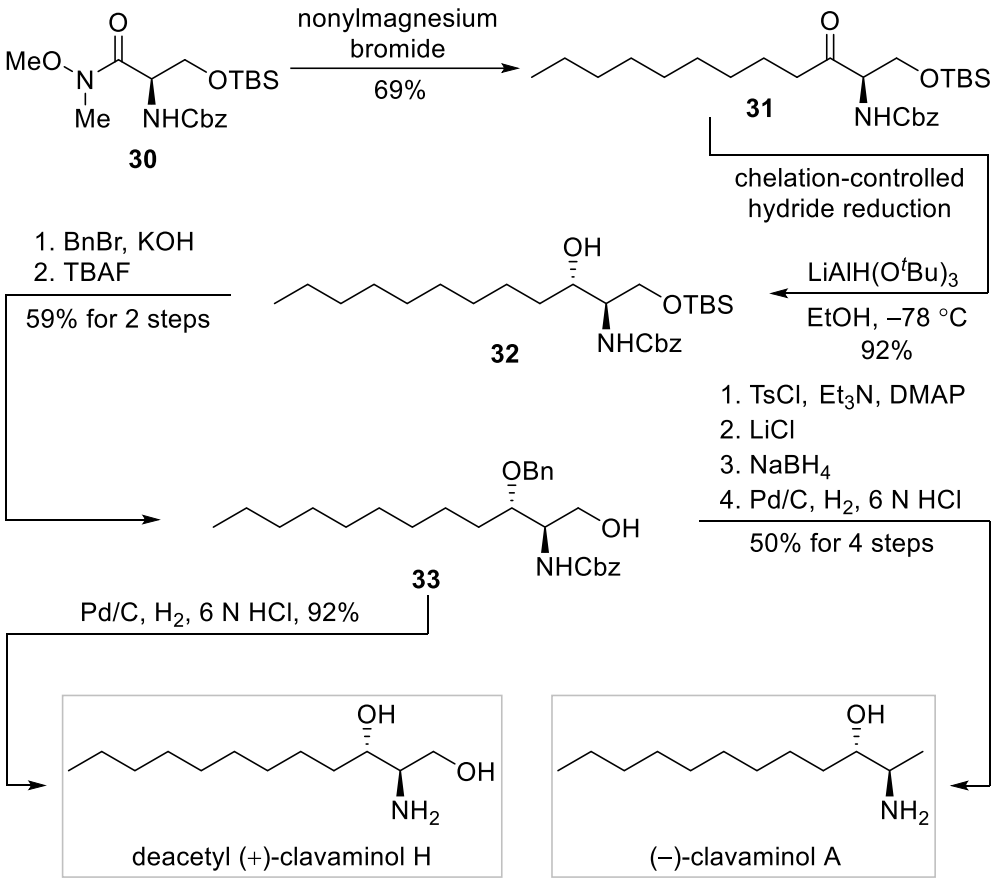


Scheme 6. Highlights of the total synthesis of methyl L-daunosaminide hydrochloride by Ham and co-workers

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.[38] Very recently, our group completed[39,40] 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 $LiAlH(O^tBu)_3$ 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_2 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,[25–27] 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*-β-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*-β-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 (ARRLKF18-01) for financial support.

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