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Asymmetric synthesis of common aza-tricyclic core of various alkaloids

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ABSTRACT

The asymmetric synthesis of common aza-tricyclic core of different types of natural alkaloids had been accomplished from commercially available L-Cbz-tyrosine. This practical approach was capable of generating scale-up aza-tricyclic skeleton. Meanwhile, it will facilitate the manipulating functionalities on the aza-tricyclic framework further, for the purpose of target-oriented synthesis of a large number of different natural alkaloids containing this versatile aza-tricyclic structure.

Introduction

Multi-functionalized aza-[6,5,6]-tricyclic skeleton (**1**) (Fig. 1) is an important structural core that is found in many different types of natural products, such as daphnilongeranin B (**2**) (*Calyciphylline* A-type),[1] nominine (**3**) (*Hetisine*-type alkaloids),[2] strychnine (**4**),[3] minfiensine (**5**,[4] akuammicine (**6**),[5] dehydrotubifoline (**7**) (*Strychnos*-type), etc.[6] These natural products, which possess impressive structural complexities along with diverse biological activities, have stimulated many synthetic efforts by plenty of different research groups for decades.[7] The successes of these synthetic strategies, which generally and primarily circumvented the construction of the umbrella-like ABC tricyclic skeleton, brought about scientific milestones in the history of total synthesis. However, there are still considerable challenges, but also opportunities to establish this kind of umbrella-like polycyclic ring system in a more convenient and practical way. Herein, we reported a unique and scalable synthesis of this tricyclic framework, which held great potential for the total synthesis of many different types of natural alkaloids and their derivatives.

Results and discussion

To embark on the synthetic approach for aza-[6,5,6]-tricyclic skeleton (**1**), a general retrosynthetic scheme was designed and further experimentally explored as illustrated in Scheme 1. We envisioned that the enantioselective synthesis of aza-[6,5,6]-tricyclic ring could be directly achieved from the chiral functionalized tricyclic motif **8** with all the stereogenic carbon centers located densely. The transannular C ring, conjunction with two rings of compound **8**, could be constructed straight forward from [4,3,0]-bicyclic framework **9** by means of several different powerful methods which were well documented in literatures, such as Michael addition-type palladium-catalyzed reductive Heck reaction,[8] nickel(0)-mediated addition,[9] or radical cyclization.[10] The aliphatic amine **9** could be generated from the asymmetric enone intermediate **10**, which was facilely prepared from the commercially available L-tyrosine as the chiral pool to induce the global stereochemistry.

As shown in Scheme 2, our synthesis was commenced with the scalable synthesis of carbamate **11**. Carbamate **11** was readily and practically prepared on multiple grams from L-Cbz-tyrosine with known procedures developed by Peter Wipf et al.[11] The four-step preparation sequences involved an intramolecular oxidative coupling, ring-opening with spontaneously concomitant intramolecular aza-Michael addition, protecting the hydroxyl group generated in situ, and ring configuration inversion, in overall yield of 20%.

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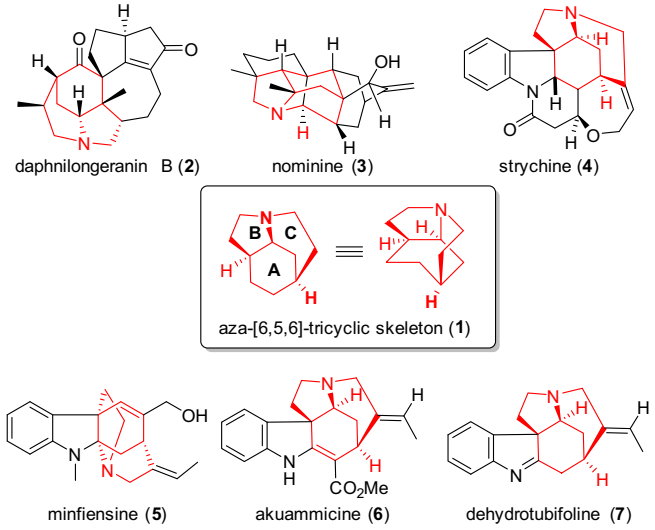
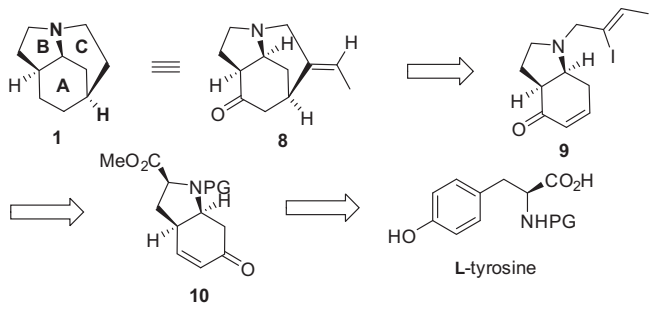


Figure 1. Selected natural alkaloids with tricyclic core.



Scheme 1. Retrosynthetic analysis of aza-[6,5,6]-tricyclic core.

Inspired by the synthetic protocol developed by Tokuyama and co-workers, we started to prepare alcohol **15**.[12] Carbamate **11** was treated with large excessive zinc dust to give β,γ-unsaturated ketone **12** in 93% yield. Then the ketone **12** was stereoselectively isomerized the unconjugated double-bond to the conjugated double-bond by treatment with catalytic amounts of DBU (0.15 equiv) to afford α,β-unsaturated ketone **13** in excellent yields on one-gram scale. When this reaction was conducted on multi-gram scale, the starting material ketone **12** was not consumed thoroughly no matter how long the reaction duration was. Then, an enantioselective epoxidation occurred with excess H_2O_2 in the presence of catalytic aqueous NaOH (4 N) to give the α,β-epoxy ketone **14** as a single diastereomer in almost quantitative yields without further purification. The resultant slurry was immediately subjected under Wharton transposition conditions to afford the desired alcohol **15** smoothly in 64% moderate yield over two-step operation on three-gram scale.[13] In order to enhance the reaction yield, further optimization was also performed, such as screening the solvents, but no improvement was achieved. After protection of the alcohol with TBSCl, the *N*-Cbz group was removed via Pd $(OAc)_2$-catalyzed hydrogenation to give the secondary basic amine **17** in 92% yield.[14] This hydrogenation was highly chemo-selective and none of olefin over-reducing byproduct was observed. After alkylation of secondary amine **17** with (*Z*)-1-bromo-2-iodo-2-butene,[15] we could linearly synthesize allylic tertiary amine **18** on multi-gram scale in one batch.

Having the key intermediate **18** in hand, we turned our attention to the studies of cyclization transformation. However, the cyclization transformation was problematic, after exploring a series of representative cyclization conditions (as depicted in Table 1),[8,9] such as $Pd(OAc)_2/K_2CO_3/HCO_2Na$,[8a] $PdCl_2(CH_3CN)_2/HCO_2H$/DIPEA,[8b] AIBN/Bu_3SnH, $Ni(cod)_2/Et_3SiH/Et_3N$, etc.[9a,d] Except the *N*-allylic side chain removal compound **17** or the de-iodide product **20**,[16] no desired cyclization product **19** was observed. We also tried to convert the allyl alcohol moiety of compound **18** to α,β-unsaturated ketone by removal of the TBS protecting group and oxidation of the alcohol. However, the related compound could not undergo the designed transannular cyclization too. We inferred that the conformation of tertiary amine **18** might be critical to the cyclization (Fig. 2). It was possible that steric interactive effects between the *N*-side chain and ester group dominated the favored conformation. The iodide-substituted side chain was pushed toward the *exo*-face of [4,3,0]-bicyclic framework, leading to the two reactive sites (*N*-side chain and cyclohexene) far away from each other. We supposed that removal of the methyl ester will facilitate the *N*-side chain approach the cyclohexene.

As shown in Scheme 3, the removal of the hindered methyl ester group was conducted through three-step sequences, involving basic hydrolysis of the ester group, oxidative decarboxylation,[17] and reduction. The bicyclic unit **23** was smoothly obtained via merely one flash column chromatography isolation in 92% total yield over three-step. Then the *N*-Cbz group was removed under the same conditions as in Scheme 2 to deliver the amine **24**. We noticed that little amount of the olefin over-reducing by-product was generated during the hydrogenation, and it was difficult to be removed by column chromatography. However, we found that the by-product was inert to the following TBAF-mediated desilication and thus could be easily separated in the following step. After *N*-alkylation and removal of the TBS group, the alcohol **26** was obtained as pure product in 59% yield. Finally, alcohol **26** was treated with Dess–Martin periodinane in the presence of excessive $NaHCO_3$ to afford α,β-unsaturated ketone **27**.

All of the three compounds **25**, **26,** and **27** could be served as cyclization substrates. However, none of the cyclization products were detected when compounds **25** and **26** were conducted. When compound **27** was treated with $Pd(OAc)_2/HCO_2Na$/TBAC in heated anhydrous DMF, a single product was obtained in good yields (Table 2, entry 1). This compound was identified as compound **28** where the transannular cyclization occurred. It's interesting that the double-bond shifted from the exocyclic position (as the structure of compound **8**) to the intracyclic position.[18] Although this compound possessed the desired [6,5,6]-tricyclic skeletons, we wanted to figure out the reason why the double-bond shifted and whether it could be inhibited. According to the representative mechanism of reductive Heck reaction as well as the nature of Pd catalyst, we supposed that the isomerization raised from readdition–elimination of [HPdX] species toward the *exo* double-bond.[19] We inferred that this kind of undesired double-bond isomerization could be prohibited when the hydrohalic acid generated in situ was trapped under basic conditions. However, when excessive Et_3N was added to the reaction system, this unexpected double-bond isomerization process still occurred. If inorganic base such as K_2CO_3 was used as an alternative, the starting material decomposed very quickly under these conditions. There were several examples that olefin isomerization could be extensively restrained by utilizing $AgNO_3$, Ag_2CO_3 either as base or as additive under Heck conditions.[20] Guided by the literature, substantial experimentations were explored but failed too. Olefin isomerization compound **28** was still obtained as a single product.

To investigate the reason why only the double-bond shifted compound **28** was generated, both of the two isomers **8** and **28** were calculated for their potential energies. Their geometries were fully optimized without imposing any symmetry constraints. The