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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.

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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) (Calvciphvlline 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 coworkers, 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 onegram 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 H₂O₂ 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-2butene,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/K₂CO₃/HCO₂Na,^{8a} PdCl₂(CH₃CN)₂/ HCO₂H/DIPEA,^{8b} AIBN/Bu₃SnH, Ni(cod)₂/Et₃SiH/Et₃N, 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 NaHCO₃ 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/HCO₂Na/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 $\mathbf{8}$) 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 Et₃N was added to the reaction system, this unexpected double-bond isomerization process still occurred. If inorganic base such as K₂CO₃ 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 AgNO₃, Ag₂CO₃ 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



Scheme 2. Synthesis of the intermediate 18.

Table 1Initial attempts to the cyclization



Entry	Conditions	Solvent ^a	Temp (°C)	Product
1	Pd(OAc) ₂ , K ₂ CO ₃ , TBAC, HCO ₂ Na	DMF	60	17 (14%)
				20 (<5%)
2	Pd(OAc) ₂ , PPh ₃ , TBAC, HCO ₂ Na	DMF	80	20 (78%)
3	Pd ₂ (dba) ₃ , DIPEA, HCO ₂ Na	DMF	120/MW	20 (8%)
4	Pd(PPh ₃) ₄ , HCO ₂ Na	CH ₃ CN	80	20 (60%)
5	PdCl ₂ (CH ₃ CN) ₂ , HCO ₂ H, DIPEA	DMF/CH ₃ CN	80	NR
6	Et ₃ B, air, Bu ₃ SnH	Toluene	rt	20 (<5%)
7	AIBN, Bu ₃ SnH or TMSSH	Toluene	Reflux	20 (<5%)
8	Ni(cod) ₂ , Et ₃ SiH, Et ₃ N	CH₃CN	rt	Decomposed

^a Extra dry solvents were used unless otherwise noted.



Figure 2. Plausible conformational interconversion of [4,3,0]-bicyclic framework 18.

energies of the stationary points on the potential energy surface were calculated using the DFT (X3LYP) and *into* (MP2) methods in conjunction with the 6-311++G(d,p) basis sets. The calculated relative energies suggest the compound **28** is lower than that of **8**. The value is about $-7.20 \text{ kcal} \cdot \text{mol}^{-1}$ at MP2/6-311++G(2d,2p) level as shown in Table 3. These results indicated that *exo* double-bond of compound **8** was catalyzed by palladium species again to afford the more stable analogue **28**.



Scheme 3. Preparation of the decarboxylation substrates.

Table 2Study on the reductive heck cyclization



Entry	Catalyst	Base	Additive	Yield ^a (%)
1	$Pd(OAc)_2$	_	TBAC	52
3	$Pd(OAc)_2$	Et₃N	TBAB	33
4	$Pd(OAc)_2$	K ₂ CO ₃	TBAC	Decomposed
5	$Pd(OAc)_2$	_	PPh_3	Complex
6	Pd ₂ (dba) ₃	_	-	25
7	$Pd(PPh_3)_4$	_	-	Decomposed
8	$Pd(PPh_3)_4$	_	-	Decomposed ^b
9	$Pd(OAc)_2$	-	$AgNO_3$	45
10	$Pd(OAc)_2$	-	Ag ₂ CO ₃	29

 $^{\rm a}$ All reactions were conducted in extra dry DMF at 60 °C, using HCO_2Na as reducing reagent.

^b 10% H₂O was used as co-solvent.

 Table 3

 X3LYP and MP2-calculated absolute and relative energies (kcal·mol⁻¹) at 6-311++G (2d,2p) basis set

Compound	E ^a	ΔE^{a}	$E^{\mathbf{b}}$	ΔE^{b}
8 28	-374844.0711 -374852.5993	-8.53	-372595.73 -372602.93	-7.20

^a Calculated **8** and **28** with X3LYP/6-311++G(2d,2p).

^b Calculated **8** and **28** with MP2/6-311++G(2d,2p).

Conclusion

In summary, we have developed a novel and practical stereoselectively synthetic approach to accomplish aza-[6,5,6]-tricyclic skeletons **28** which were widespread in various natural alkaloids. This synthetic route involved twelve linear step sequence from the readily available α , β -unsaturated ketone **12**. Most of the synthetic steps could be conducted on multi-gram scale and in good yields. Meanwhile, the double-bond and carbonyl group provide the chance for further functionalities and chemical transformations to synthesize many different types of natural alkaloids. The reported protocols would also allow for the preparation of their derivatives for biological studies.

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Supplementary data

Supplementary data (experimental and characterization data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.08.017.

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