Efficient Entry to the Pyrroloquinoline Core of *Martinella* Alkaloids via Novel Base-catalyzed Mukaiyama–Mannich Reaction

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An efficient enantiocontrolled entry to *Martinella* alkaloids was achieved based on the unexpected discovery that a catalytic amount of KH/dicyclohexyl-18-crown-6 induced an intramolecular Mukaiyama–Mannich reaction of imine **3**, leading to a cascade sequence involving a novel silyl group migration to furnish the pyrroloquinoline core **6**.

Since its disclosure in 1995,[1] the hexahydropyrrolo[3,2-*c*]-quinoline core of martinelline (**1**) and martinellic acid (**2**) has posed a considerable challenge to the synthetic community (Figure 1). More than 20 successful approaches[2] have been documented on the synthesis of the unique heterocyclic system, several of which culminated in the total syntheses of the natural products.[3] However, few of them allow efficient construction of the ring system in an enantiocontrolled manner.[2b,2d,3a–3c]

We recently reported a novel protocol for the synthesis of hexahydropyrrolo[3,2-*c*]quinoline **6** from imine **3**,[4] where $BF_3 \cdot OEt_2$ promoted the tandem Mukaiyama–Mannich/hemiaminalization sequence (Scheme 1). During this investigation, we reconfirmed Aubé's crucial note[2a] indicating that the intramolecular hydrogen bonding between the imine and the carbamate N–H is formed in closely related substrates and suggesting that such interaction would render the imine moiety inactive toward external activation.

We indeed had trouble in controlling the specific activation

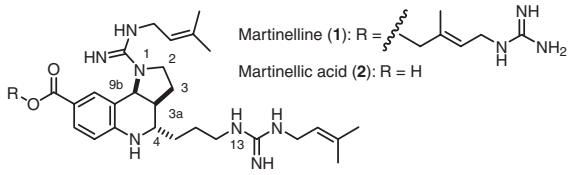
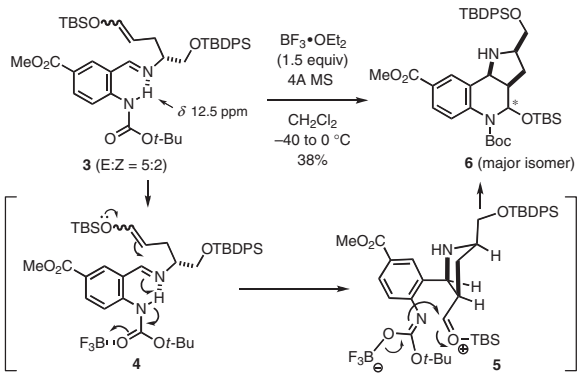
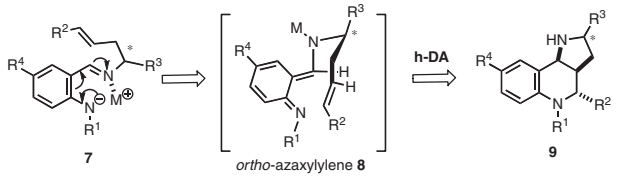


Figure 1. Structure of *Martinella* alkaloids.



Scheme 1. Previous result.



Scheme 2. Synthetic plan for the tricyclic core system.

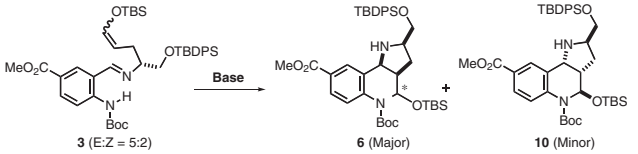
of imine **3** in a productive way: the reaction always gave a significant amount of unidentifiable decomposed products. Learning from these studies, we hypothesized that deprotonation from the carbamate N–H by a suitable base could give rise to isomerization of **7** to *ortho*-azaxylylene **8** which would then participate in the subsequent intramolecular hetero-Diels–Alder (h-DA) reaction (Scheme 2).

Efforts to identify conditions that realize the projected isomerization/h-DA reaction led us to the novel base-catalyzed reaction system that enables a much more efficient and diastereoselective conversion of **3** to **6** as presented in the following.

As shown in Table 1, our investigations commenced with low-nucleophilic strong base NaHMDS, but no reaction was observed (Entry 1). When **3** was treated with a stoichiometric amount of KH in THF (Entry 2), evolution of H_2 was observed and the color of the solution turned bright yellow. Despite the marked change in appearance, the expected reaction had not occurred and **3** was recovered. It was suggested that the deprotonation from the carbamate N–H was surely achieved, but in both cases, the resulting anion formed a stable chelate with the counter cation, maintaining a situation similar to that of the parent imine (cf. **13** in Scheme 3). To break down this situation, we added dicyclohexyl-18-crown-6 (Cy_2-18-crown-6)[5] and found its marked effect. Thus, the combination of KH (1.5 equiv) and Cy_2-18-crown-6 (1.5 equiv) provided the desired cycloadducts [**6** (41%) and **10** (5%)] (Entry 3). After considerable experimentation, we found that the use of a catalytic amount of KH/Cy_2-18-crown-6 (0.1 equiv each) gave optimal and reproducible results, providing **6** and **10** in good yield (81%, dr = 77:4, Entry 4). Gratifyingly, both the yield and the stereoselectivity were markedly improved compared with our previously reported protocol [$BF_3 \cdot OEt_2$ (1.5 equiv), 4A MS, CH_2Cl_2]. The diastereomeric ratio of the products did not reflect the E:Z ratio of the substrate, which provided insight into the reaction mechanism (vide infra). Use of Lewis bases such as AcOK, AcOLi,[6a] and KF resulted in zero conversion (Entries 5–7). The corresponding products were also obtained using KOH, albeit in low yield (Entry 8).

To gain insight into the reaction mechanism, we carried out complementary experiments, using other imines **11** and **12** (Chart 1) having an alkyl enol ether or an (*E*)-alkenyl substituent. In both cases, no reaction was observed under the optimized

Table 1. Base-promoted annulations of imine **3**



Entry	Base /equiv	Additive /equiv	Solvent	Temp /°C	Time /h	Yield/% 6/10
1	NaHMDS (1.2)	—	THF	−78 to rt	2	0/0
2	KH (1.5)	—	THF	0 to rt	2.5	0/0
3	KH (1.5)	Cy_2-18-crown-6 (1.5)	THF	0 to rt	3	41/5
4	KH (0.1)	Cy_2-18-crown-6 (0.1)	THF	0 to rt	10.5	77/4
5	AcOK (0.1)	Cy_2-18-crown-6 (0.1)	DMF	rt	12	0/0
6	AcOLi (1.1)	TMEDA (1.15)	DMF	rt to 40	48	0/0
7	KF (0.1)	Cy_2-18-crown-6 (0.1)	THF	rt	2.5	0/0
8	KOH (0.45)	Cy_2-18-crown-6 (0.2)	THF	rt	1.5	30/6

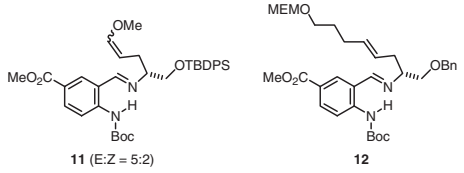
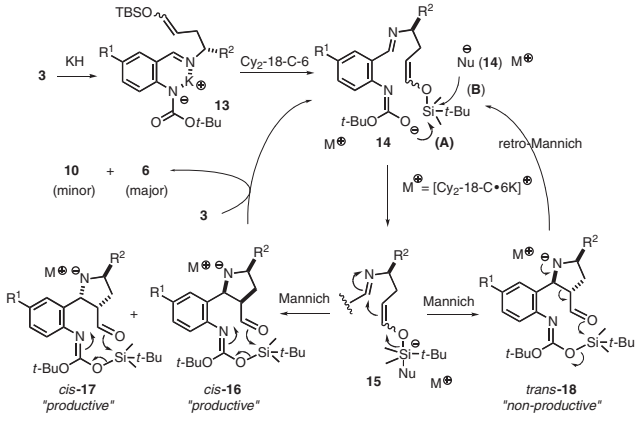


Chart 1.

condition,[7,10] which suggested that the silyl enol ether was essential for the base-catalyzed cyclization reaction.

We suppose the following mechanism of the base-catalyzed cyclization, where TBS groups play a crucial role (Scheme 3). The deprotonation from the carbamate N–H provides anion **13** with a potassium cation stabilized by chelation. The addition of Cy_2-18-crown-6 drives dissociation of the counter cation to release anion **14**. Under the reaction conditions, highly nucleophilic[6a,6b] pentavalent silicate **15** would be generated via an intramolecular (**A**) or intermolecular activation (**B**). The resulting silicate **15** would undergo a tandem Mukaiyama–Mannich/hemiaminalization reaction to afford the desired tricyclic products.[8] Resilylation might be achieved via either an internal or an external pathway.[9] We assume that the basic conditions allowed the first Mannich-type adducts to enjoy an equilibrium between *cis*-**16**, -**17**, and *trans*-**18**, this may be the main reason why the marked improvement in terms of yield and stereoselectivity was realized in comparison with the reaction under Lewis acidic conditions, despite using the same substrate.



Scheme 3. Plausible reaction mechanism.

In summary, we have reported a novel and efficient protocol for the stereoselective synthesis of the hexahydropyrrolo-[3,2-*c*]quinoline core by tandem anionic cyclizations with a catalytic KH/Cy_2-18-crown-6 system. This work demonstrates the first Mukaiyama–Mannich reaction between a less reactive aldimine and silyl enol ether. Efforts to extend synthetic scope of the base-catalyzed Mukaiyama–Mannich reaction are now under way in our laboratory.

References and Notes

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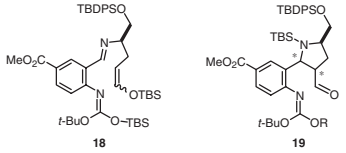
7 One-tenth- equiv KH/Cy_2-18-crown-6, THF, 0 °C to rt; Although we tried a stoichiometric amount of KH/Cy_2-18-crown-6 and reflux condition in toluene or xylene, no reaction was observed.

8 To the best of our knowledge, the base-catalyzed Mukaiyama–Mannich reaction requires activated imine acceptors such as Ts-imines.[6a,6b] This is the first example in which a non-activated alkyl-aldimine worked as an electrophile.

9 For instance, two species (*O*-silyl **18** or *N*-silyl **19**) can be considered as silylating agents in an external process.



10 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

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