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Communication

Alkaloids

Studies on Pumiliotoxin A Alkaloids: An Approach to Preparing the Indolizidinic Core by Intramolecular Diastereoselective N-Heterocyclic Carbene Catalyzed Benzoin Reaction

José Tiago M. Correia,[a] Laís V. Acconcia,[a] and Fernando Coelho*[a]

Abstract: In this article, we describe the development of a convergent organocatalytic strategy to prepare the indolizidinic core of the pumiliotoxin A alkaloid family. The key step of the proposed strategy is based on a diastereoselective N-heterocyclic carbene catalyzed benzoin reaction, in which the Breslow intermediate generated from an enal moiety (umpolung a^1 to d^1 – acyl anion equivalent) attacks a ketone moiety intramolecularly to provide the indolizidinone core in good yield with good selectivity.

Introduction

The indolizidine ring stands out among all the heterocyclic scaffolds present in nature, because it is present in the primary structures of several biologically active natural products.[1] One of the largest classes of indolizidinic alkaloids is the pumiliotoxin A class, which is subdivided into pumiliotoxins **1** and allopumilioxins **2**; this class contains chemical-defense compounds that are isolated from the skin of Central American dart poison frogs (dendrobatidae) (Figure 1).[2] Despite their toxicity, these compounds are known for their cardiotonic and insecticide activities[3] as well as for their unique structures, which have attracted the attention of synthetic, medicinal, and pharmaceutical chemistry groups. The first synthetic studies were developed independently by the groups of Overman and Kibayashi, in collaboration with Daly, to assign certain structural aspects and to obtain sufficient synthetic material for biological assays.[4,5] Since those preliminary contributions, many other groups have attempted to develop new strategies to synthesize these compounds. However, to date, only noncatalyzed and organometallic-catalyzed transformations have been used as key methodologies to prepare these indolizidinic cores.[6] Because organocatalysis has become a well-established field in homogeneous catalysis during the past 15 years,[7] an organocatalyzed strategy represents a promising alternative for further applications.

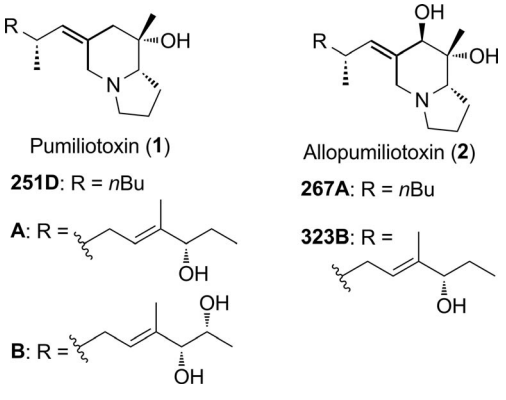

Figure 1. Pumiliotoxin A alkaloids.

N-Heterocyclic carbene (NHC) organocatalysis has reached its most sophisticated level over the past 10 years. Many reactivities have been improved or disclosed by combining these highly reactive catalysts with structurally different aldehydes, activated esters, or anhydrides.[8] The application of NHC catalysis in total synthesis was recently reviewed by Scheidt and coworkers,[9] who identified the robustness of this catalytic strategy.

Inspired by the unconventional disconnection approach allowed by umpolung transformations mediated by NHCs, we performed our retrosynthesis, recognizing that acyloin **3**, a simplified analogue of a well-known intermediate to access allopumiliotoxin's dihydroxylated indolizidinic core **2**,[6a,6c] could be prepared from keto enal **4** by diastereoselective intramolecular benzoin condensation promoted by an NHC precatalyst (Scheme 1). This reactivity goes against the natural behavior of enals, which usually react as homoenolate equivalents (umpolung a^1 to d^3) under NHC-catalyzed reactions.[10] To the best of our knowledge, although inter- and intramolecular benzoin reactions involving aliphatic and aromatic aldehydes attacking ketones have been widely reported,[11] only few intermolecular versions of benzoin reactions involving Breslow intermediates (umpolung a^1 to d^1) generated from enals have been described by using imines and non-enolizable ketones as electrophiles.[12] Additionally, some examples of intramolecular and intermolec-

[a] *Institute of Chemistry, University of Campinas*
P. O. Box 6154, 13083-970 Campinas, São Paulo, Brazil
E-mail: coelho@iqm.unicamp.br
www.iqm.unicamp.br
www.unicamp.br

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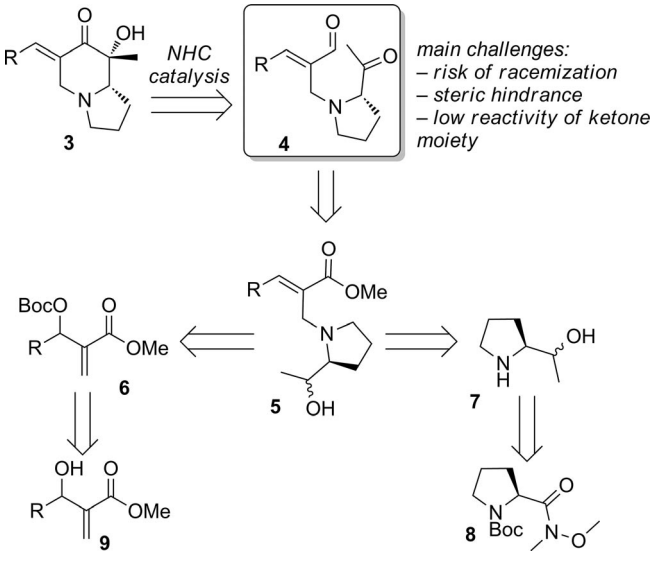
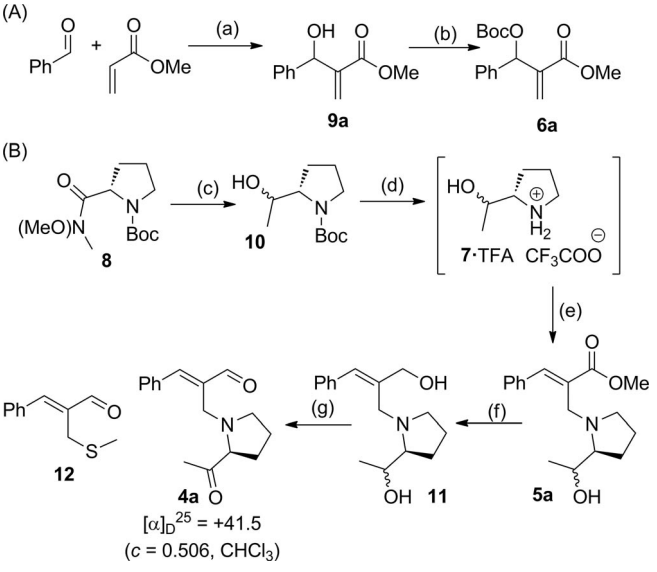
ular Stetter reactions involving Breslow intermediates from enals can be found in the literature, which reinforces the feasibility of our strategy.[13] Intermediate **4** could be prepared from a diastereoisomeric mixture of esters **5** through a reduction–oxidation sequence. Finally, **5** could be prepared through nucleophilic substitution between Morita–Baylis–Hillman carbonate **6** and a diastereoisomeric mixture of 2-(1-hydroxyethyl)pyrrolidine (**7**). In this step, the (*E*) double-bond configuration, which is an important structural aspect in the structure of the target, would be highly favored. Another important aspect of the proposed strategy of this study is that the stereocenter present at C2 of **7** serves as a stereochemistry-controlling element for cyclization.[9] Considering the versatility of this convergent strategy, we assumed that starting from an appropriated enantiopure α-methylated aldehyde,[4–6,14] access to any of the allopumiliotoxins would be allowed.



Scheme 1. Retrosynthetic analysis of the proposed strategy.

Results and Discussion

Carbonate **6a**, the first building block in the proposed strategy, was easily prepared in two steps in an overall yield of 58 % by a Morita–Baylis Hillman reaction/*tert*-butoxycarbonyl (Boc) activation sequence,[15] as shown in Scheme 2 (part A). The second building block, a diastereoisomeric mixture of (2*S*)-*N*-Boc-2-(1-hydroxyethyl)pyrrolidine (**10**), was prepared from commercially available (2*S*)-*N*-Boc-(*N*-ethoxy-*N*-methyl)prolinamide (**8**, Weinreb amide) also in two steps (86 % overall yield), which started with the addition of methylmagnesium bromide to **8** at 10 °C to afford (2*S*)-*N*-Boc-2-acetylpyrrolidine in 93 % yield. This intermediate was reduced in the presence of $LiAlH_4$ to provide **10** as a diastereoisomeric mixture (1:1) in 92 % yield [Scheme 2 (part B)].[16] With these building blocks (i.e., compounds **6a** and **10**), the next step was removal of the protecting group in **10** to obtain 2-(1-hydroxyethyl)-substituted pyrrolidine **7**. Thus, pyrrolidine **10** was treated with trifluoroacetic acid (TFA) in dichloromethane to afford **7** as its TFA salt. The crude salt was neutralized with a saturated solution of NH_4OH and was then treated with adduct **6a**[17] in MeOH by a vinylogous allylic substitution to provide **5a** (Scheme 2).[18] At this stage, all carbon atoms that would constitute the indolizinic core were incorporated. However, the maximum overall yield achieved in this sequence after chromatographic purification was 45 % for these two steps.



Scheme 2. Reagents and conditions: (a) 1,4-diazabicyclo[2.2.2]octane (DABCO, 1 equiv.), THF/H_2O (1:1), 48 h, 70 %; (b) Boc_2O (1.1 equiv.), 4-(dimethylamino)pyridine (DMAP, 0.2 equiv.), CH_2Cl_2, 90 min, 83 %; (c) 1. MeMgCl (3 M), THF, 10 °C to r.t., 18 h, 93 %; 2. $LiAlH_4$ (0.3 equiv.), CH_2Cl_2, –78 °C, 50 min; (d) TFA (14 equiv.), CH_2Cl_2, 1 h; (e) 1. Et_3N (5 equiv.), **6a** (1 equiv.), MeOH, 3 h; 2. NH_4OH (70 % from **10**); (f) DIBAL-H (4.5 equiv.), CH_2Cl_2, –78 °C, 3 h, 60 %; (g) 1. $(COCl)_2$, DMSO, –78 °C, 30 min; 2. *N*,*N*-diisopropylethylamine (DIPEA), –78 °C to r.t., 40 %. Major byproduct **12** was detected in the oxidation step.

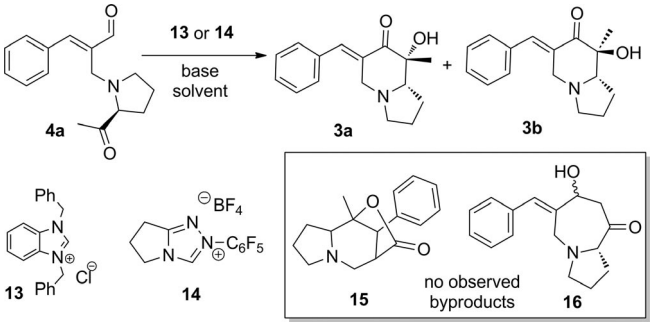
To circumvent this issue and by assuming that a loss of **7** might have occurred during its isolation, we changed the sequence. Thus, in a one-pot sequence, the TFA salt of **7** was dissolved in MeOH and treated with an excess amount of triethylamine (5 equiv.) prior to its reaction with **6a**. Under this protocol, **5a** was produced in a higher yield (95 %) after filtration through a pad of silica gel; however, unfortunately, analysis by NMR spectroscopy detected contamination with unreacted **10**. To our surprise, we were not able to eliminate **10** by standard chromatographic separation. Unfortunately, **5a** and **10** presented the same chromatographic profile in several different eluent mixtures. This purification issue was overcome by removing residual **10** from the crude reaction product mixture by using the same experimental protocol as that used to isolate **7**[17] before proceeding to column purification (Scheme 2b). This one-pot sequence and "scavenging" of remaining unprotected starting material **10** afforded the pure mixture of diastereoisomers in 70 % yield from **10**. During these studies, we were able to isolate a small amount of one of the diastereoisomers of product **5a**, which proved to be very useful during NMR spectroscopic characterization of the mixture (see pages S14–S17 in the Supporting Information). Intermediate **5a** was easily reduced with diisobutylaluminum hydride (DIBAL-H) in toluene to produce diol **11** in 60 % yield; the other DIBAL-H solutions

investigated in this study did not produce complete reduction, even if used in excess amount (Scheme 2b). Again, isolation and characterization of a small enriched sample of one of the diastereoisomers of **11** was possible (see pages S20–S21).

In the next step, intermediate **11** was converted into keto enal **4a** by Swern oxidation {$[\alpha]_D^{25}$ = +41.5 (*c* = 0.5, CH_2Cl_2)}.[19] Following the assumed rationalization and on the basis of literature precedent, this methodology proved to be the best choice to oxidize both the primary allylic and secondary hydroxy groups simultaneously. Sequential oxidation would not be a good strategy owing to the high risk of hemiketal formation and consecutive oxidation, which would produce a lactone. Dicarbonyl compound **4a** proved to be highly unstable primarily under acidic conditions; therefore, its isolation required caution. Although analysis of the crude product by NMR spectroscopy demonstrated that dicarbonyl compound **4a** presented an acceptable degree of purity, certain additional spots were seen by TLC analysis. To mitigate the acid instability of **4a**, the silica gel used for purification was doped with Et_3N. However, after chromatography, we isolated only 40 % of **4a** and a major byproduct that was characterized as mercaptan **12** (Scheme 2b).

A rapid comparison between the spectra showed that the ^{1}H NMR signals of **12** were completely superimposed with the signals of **4a** in the crude product with the exception of the characteristic signal of the aldehyde group, which was marginally higher in field. To improve this yield, we tested Dess–Martin periodinane (DMP) as an oxidant. Unfortunately, a lower yield accompanied by a complex mixture of byproducts was obtained. Therefore, despite this challenging oxidation step, we decided to continue the study and start the screening of the key step of intramolecular benzoin condensation. The screening was guided by the limited number of reports concerning NHC-catalyzed reactions involving acyl anion Breslow intermediates from enals.[12,13] Two of the most popular nonchiral precatalysts were tested: benzimidazolium salt **13**, which was used by Yadav in the nucleophilic substitution of α-brominated ketones with benzaldehydes and cinnamaldehyde;[20] and triazolium tetrafluoroborate **14**, a precatalyst that has been widely used in several NHC-catalyzed transformations.[6] Precatalyst **14** has the advantage of being activated by weak bases, which would avoid racemization of pH-sensitive substrates, such as **4**, as well as a possible aldol side reaction, which would produce byproduct **16** (see the scheme of Table 1). Initially, we were interested in seeing how far the transfer of chirality to a neighbor stereocenter could go. Depending on this result, chiral precatalysts would be applied in future studies. These results are summarized in Table 1. Unfortunately, catalyst **13** failed in all attempts (Table 1, Entries 1–3); only messy reaction mixtures were observed after 96 h by analysis of the crude product mixture by TLC and ^{1}H NMR spectroscopy, which indicated that side reactions and degradation of the starting material had occurred. The strong basicity of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) likely contributed to that result. The desired product could only be detected when we changed the catalyst to **14** and used potassium carbonate (30 mol-%) as a base. At that point, we also discov-

Table 1. Diastereoselective NHC-catalyzed intramolecular benzoin reaction.[a]

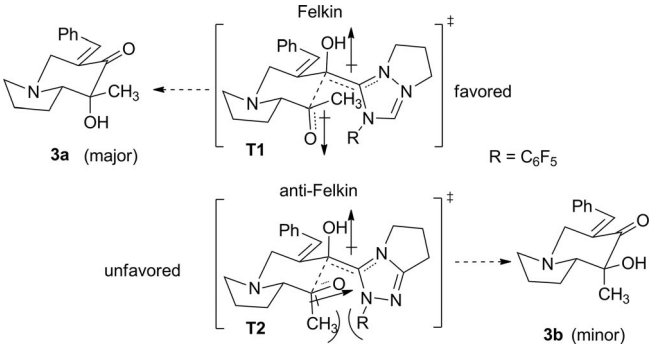


Entry	Catalyst (mol-%)	Base (equiv.)	Solvent	*t* [h]	Yield [%]	*dr*[b] (**3a**/**3b**)
1	**13** (30)	DBU (0.3)	THF	96	n.d.[c]	–
2	**13** (30)	DBU (0.3)	CH_2Cl_2	96	n.d.[c]	–
3	**13** (30)	DBU (0.3)	CH_3CN	96	n.d.[c]	–
4	**14** (20)	K_2CO_3 (0.3)	THF	120	(55)[d]	50:50
5	**14** (30)	AcONa (1.0)	THF	120	(58)[d]	40:60
6	**14** (30)	AcONa (1.0)	CH_2Cl_2	120	69[e,f]	75:25
7	**14** (15)	AcONa (1.0)	CH_2Cl_2	120	56[f]	75:25
8	**14** (30)	AcONa (1.0)	toluene	120	49[f]	75:25
9	**14** (30)	AcONa (1.0)	CH_2Cl_2	48	59[f]	75:25

[a] All reactions were performed at room temperature. [b] The diastereomeric ratio (*dr*) was determined by ^{1}H NMR spectroscopy. [c] n.d.: not determined, as decomposition of the starting material was observed. [d] The yield was determined by ^{1}H NMR spectroscopy by using 1,2,4,5-tetramethylbenzene as an internal standard. [e] A CH_2Cl_2 solution (0.5 mL) of catalyst **14** (30 mol-%) and AcONa (1.0 equiv.) was stirred at room temperature for 1 h. After that time, a CH_2Cl_2 solution (0.5 mL) of **4a** was added, and the mixture was stirred for 120 h. The organic solution was diluted, washed with distilled water, and purified by silica-gel column chromatography. [f] Yield of isolated product.

ered that the chromatographic profiles of the starting material and the product were similar upon using Et_3N-doped TLC. Therefore, TLC could not be used to monitor the evolution of the reaction to its completion. The yield and diastereoselectivity of the reaction with catalyst **14** and potassium carbonate were determined by analysis of the crude product by NMR spectroscopy (Table 1, Entry 4). Although, the yield seemed promising, no diastereoselectivity was observed; therefore, we decided to test sodium acetate as a base. This salt is hygroscopic and is a weaker base than those commonly used; thus, we decided to increase its stoichiometry to 1 equiv. to drive the equilibrium toward the direction of the carbene. Under these conditions, we observed no modification to the reaction yield, but marginal diastereoselectivity favoring undesired diastereoisomer **3b** was observed (Table 1, Entry 5). The effect of the solvent was also considered in this study of this reaction. To our surprise, we observed an increase in the yield and diastereoselectivity in favor of desired diastereoisomer **3a** upon using dichloromethane in the reaction with catalyst **14** (Table 1, Entry 6). The use of a smaller amount of catalyst (15 mol-%) in the reaction in CH_2Cl_2 significantly decreased the yield, although the diastereoselectivity remained the same (Table 1, Entry 7). In toluene, a heterogeneous reaction took place, and after 5 d of reaction, the product was recovered in a lower yield with the same diastereoselectivity (Table 1, Entry 8). To optimize the experimental conditions, we interrupted the reaction in CH_2Cl_2 after 48 h. In this case, full conversion was observed, as determined by NMR spectroscopy, but only 59 % of the product was recovered. A plausible explanation for this moderate yield can be attributed to decomposition of the products during the purification steps. Neither compound **15** nor aldol product **16** was detected under any of the described conditions.

The relative configurations of both diastereoisomers were determined by a sequence of two-dimensional NMR spectroscopy analyses. Compounds **3a** and **3b** were easily separated by using preparative thin-layer chromatography (see the Supporting Information for details). Diastereoisomer **3a** has the same relative configuration as that exhibited by most natural pumiliotoxins. The transition state can be simply rationalized by considering two possible chairlike transition states and seems to suffer some influence of the solvent used, although further studies must be performed to confirm this proposal (Scheme 3). Felkin-type approach **T1**, which produces **3a**, seems to be more stable in less polar media given that the dipole moments of the carbonyl groups subtract from each other. On the other hand, in anti-Felkin-type approach **T2**, the dipole moments of the carbonyl groups add to each other, which makes it more polar; therefore, **T2** is less stabilized than **T1** in solvents with lower polarities (Scheme 3). The fact that products **15a**/**15b** are not formed can be explained by the high steric hindrance between the catalyst and the pyrrolidine moiety, which prevents the required alignment of the orbitals; therefore, electronic conjugation necessary to activate the β-carbon atom cannot occur.[21] This property is another advantage of the proposed strategy of this study, because electronic effects of the side chain through π-conjugation would be minimized, and only inductive effects would be present.[9]



Scheme 3. Possible transition states for the intramolecular benzoin condensation key step.

Conclusions

We developed a new strategy to prepare the indolizidinic core of pumiliotoxin A alkaloids. This strategy begins with a Morita–Baylis–Hillman adduct and employs a diastereoselective NHC-catalyzed intramolecular benzoin condensation as its key step. The indolizidinic core was produced in an overall yield of 12 % over eight steps from Weinreb amide **8**. To the best of our knowledge, this is the first application of Morita–Baylis–Hillman and NHC catalysis toward the preparation of this class of alkaloids. With this strategy in hand, further work envisioning the total synthesis of pumiliotoxin A alkaloids are ongoing in our laboratory.

Acknowledgments

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Keywords: Alkaloids · Carbenes · Diastereoselectivity · Organocatalysis · Umpolung

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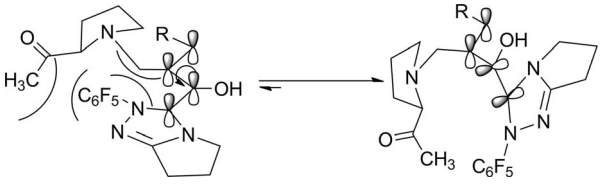
[21] A possible representation of this behavior can be:



This behavior was previously discussed: S. S. Sohn, J. W. Bode, *Org. Lett.* **2005**, *7*, 3873.

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