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Diastereoselective organocatalytic Mannich access to azacyclic system en route to lyconadin A

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ABSTRACT

Organocatalytic and stereoselective Mannich coupling of hindered and chiral cyclohexylcarboxaldehyde is described for a synthetic approach to the pyrrolidine core of lyconadin A. The strategy led concisely and stereoselectively to complex azaheterocyclic system containing up to five stereocenters.

Lyconadin A (**1**) is an alkaloid isolated from *Lycopodium complanatum*. Its peculiar structure features pyrrolidine and 2-pyridone rings embedded into a complex polycyclic carbon framework (Scheme 1).[1] This challenging skeleton has inspired elegant total syntheses from Smith,[2] Sarpong,[3] Fukuyama,[4] and Dai,[5] using innovative methodologies and disconnections to solve the complexity of the target. Additionally, Castle disclosed a synthetic approach to the bicyclo[5.4.0]undecane framework of lyconadin A.[6] In connection with our program of organocatalytic access to chiral pyrrolidines containing basic *N*-heteroaryl substituents, we sought to explore a new disconnection toward the core of lyconadin A.[7] We report herein a stereoselective organocatalytic access to a highly substituted azapolycyclic framework.

Our initial retrosynthetic analysis was based on a Mannich reaction of chiral aldehyde **5** and imine **4a** entailing the key methoxypyridine as a protected precursor of 2-pyridone (Scheme 1). Structural modifications of the resulting adduct **3** would involve decarbonylation and hemiaminal reduction followed by the construction of the piperidine scaffold to give **2**. Unveiling the 2-pyridone ring of **1** by demethylation of **2** according to Sarpong would conclude the synthesis.

Diastereoselective organocatalytic Mannich coupling of aldehyde is scarcely documented.[8] The objective was therefore to evaluate the ability of catalyst **6** based on the 3-aminopyrrolidine scaffold to forge two new stereocenters that would match the required configuration of the natural product (Scheme 2). Our stereochemical analysis was based on the fact that aldehyde **5** has two stereocenters at C12 and C7 that are epimerizable. While the C7 stereocenter is irrelevant for the stereochemical outcome of the reaction due to the enamine formation, the C12 stereocenter was projected to direct the stereoselectivity of the coupling at C7 by favoring one approach of the electrophile but also by hampering the (*E*/*Z*)-isomerization of the enamine moiety. The C6 stereocenter was expected to be controlled by the organocatalyst through H-bonding as in **7**. Then at a further stage, we anticipated inverting the C12 stereocenter of **3** to match the configuration of the target by controlled epimerization.

To add to the challenge of building a stereogenic quaternary carbon in a crowded structural environment, we anticipated a low reactivity of imine **4a** for electronic reasons. Yet, a recent report about a Mannich coupling promoted by proline involving a structurally close imine (**4c** in Scheme 3) and glutaraldehyde was encouraging for our synthetic plan.[9]

Thus, the synthesis of aldehyde **5** was carried out from rac-**8**, itself prepared in one step from ethylacetoacetate and crotonaldehyde and for which an asymmetric synthesis is known

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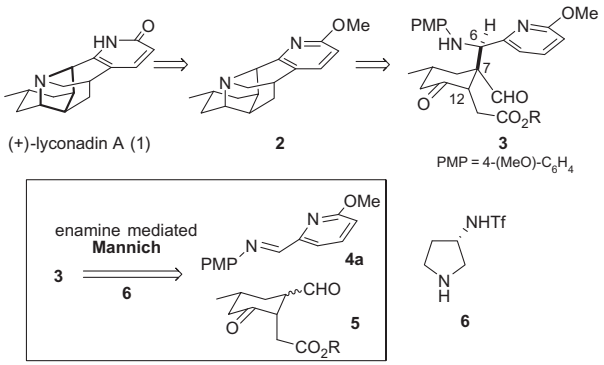


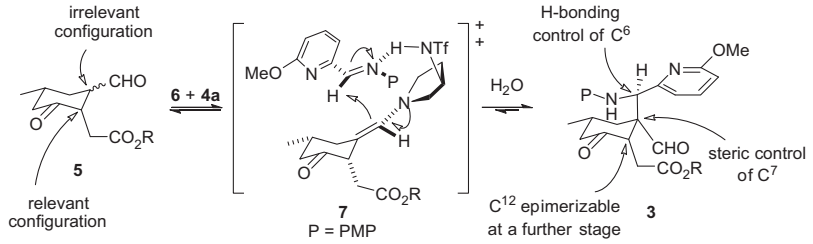
Scheme 1. Retrosynthetic analysis of **1**.

(Scheme 3).[10] The 1,4-addition of vinylmagnesium bromide in the presence of CuI led to the intermediate enolate **9** that was intercepted with bromo *t*-butylacetate in HMPA to give **10a**.[11] To our knowledge, 1,4-additions to 5-methylcyclohex-2-en-1-one followed by stereoselective alkylation of the resulting enolate are not trivial.[12] Pleasingly though, this 2-step process delivered trisubstituted cyclohexanone **10a** in 40% yield with a good anti-selectivity of 9:1 between the two newly created 2,3-stereogenic centers, which giving the level of substitution and functionalization could certainly find applications in other contexts. Interestingly, trapping enolate **9** with bromo acetonitrile led to **10b** with a substantial drop of selectivity (dr = 3:1). Oxidative cleavage of the olefin (98%) completed the stereoselective preparation of the Mannich partner **5a**. NOESY analysis confirmed the 3,5-*trans* configuration of the major isomer of cyclohexanone **5a**.

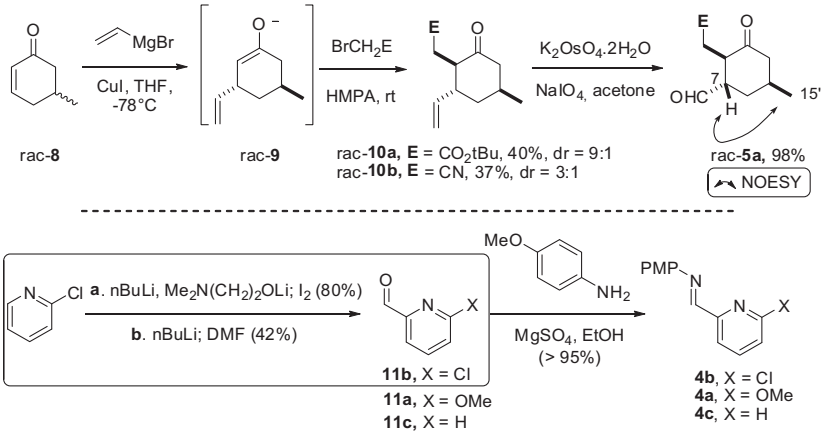
With the objective of testing imines with different electronic properties and reactivity, pyridine carboxaldehydes **11a**–**c** were treated with anisidine to generate the corresponding imines **4a**–**c**.[13] While **11a**,**c** are commercially available, the 6-chloropicolinaldehyde **11b** was prepared in two steps by lithiation of 2-chloropyridine and quenching with I_2 (80%).[14] The resulting 2-chloro-6-iodopyridine was then lithiated (*n*BuLi) and treated with *N*,*N*-dimethylformamide to provide aldehyde **11b** in 42% (Scheme 3).

The Mannich coupling was investigated using an organocatalyst based on the recently unveiled 3-aminopyrrolidine scaffold which has the advantages of being reactive and readily available.[15] In order to avoid a match/mismatch effect, the study was carried out with the racemic catalyst since racemic aldehyde was employed. Resorting to reaction parameters in line with our previous studies, all attempts to couple aldehyde **5a** with **4a** met with failure (Scheme 4). Unfortunately, swapping to imines **4b** and **4c** did not improve the outcome of the reaction. In all cases, the ^{1}H NMR monitoring of the reaction indicated hydrolysis of the imine and degradation of the aldehyde. The same result was obtained with proline as the catalyst. With the objective of decreasing the LUMO of imine **4a**, the coupling was attempted in the presence of a Brønsted acid co-catalyst. Thus, several acids (CF_3CO_2H, 2,5-dinitrobenzoic, 2,6-difluorobenzoic, benzoic and acetic acid) of variable strengths were tested (1.1 equiv) with the degradation of imine **4a** as the sole result.

To evaluate the reactivity of aldehyde **5a**, the reaction was eventually tested with more reactive electrophile **12** derived from ethyl glyoxalate (Scheme 5). Interestingly, the reaction proceeded to completion with a stoichiometric ratio of reagents **5a** and **12** but the presence of a Brønsted acid was required. Hence, the combination of catalyst **6** and a substoichiometric amount of CF_3CO_2H (0.8 equiv) was needed to prepare **13a** in 42% alongside degradation products.[16] Mannich adduct **13a** was directly isolated as a stable hemiaminal, probably because the dehydration would give an *anti*-Bredt iminium. Importantly, the stereoselectivity of the reaction reached a promising value of 6:1. The reaction worked likewise with the simplified aldehyde **5b** (dr = 9:1), prepared from cyclohex-2-en-1-one, giving the corresponding Mannich adduct **13b** in 39% (dr = 6:1). ^{1}H NMR NOESY analysis of **13a** confirmed



Scheme 2. Steric and H-bonding control of Mannich coupling.



Scheme 3. Synthesis of the Mannich coupling partners.