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Formal amide insertion strategy for the synthesis of anatoxin-a using rhodium catalysis

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ABSTRACT

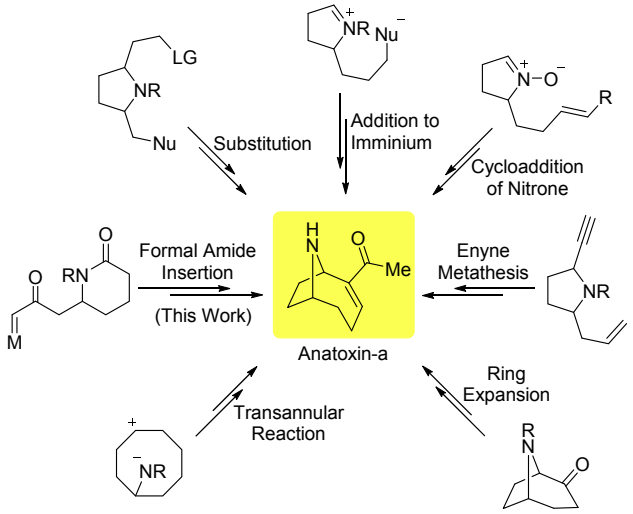
A formal synthesis of anatoxin-a was accomplished by using rhodium-catalyzed formal amide insertion reaction. The key reaction was performed on a gram scale using 0.4 mol % of $Rh_2(NHCO^tBu)_4$ catalyst, affording a 9-azabicyclo[4.2.1]nonane derivative in good yield. The nitrogen-bridged molecule was converted to Wiseman's intermediate through diastereoselective reduction, site-selective deoxygenation and functional group interconversions.

1. Introduction

Anatoxin-a was discovered in North America in the 1970s in the toxic bloom of the blue-green algae *Anabaena flos aquae* (Lyngb.) de Bréb,[1] which periodically kills wildlife. The structure of this natural product was determined in 1976,[2] although X-ray crystallographic analysis of its *N*-acetyl derivative was reported already in 1972.[3] Anatoxin-a is a strong nicotinic acetylcholine receptor agonist that kills mice within only a few minutes by interfering with neurotransmission. Anatoxin-a and its derivatives are useful biologic tools for investigations of neurologic disorders.[4] In addition to the pharmaceutical potential stemming from its potent bioactivity, anatoxin-a has attracted organic chemists due to its characteristic and challenging 9-azabicyclo[4.2.1]nonane structure, which is a suitable synthetic target to evaluate the usefulness of newly developed reactions. Various syntheses of anatoxin-a have been reported using intramolecular addition to iminium cation,[5] substitution reaction,[6] ring expansion,[7] cycloaddition of nitrone,[8] transannular reaction of nitrogen nucleophile,[9] and enyne metathesis[10] (Scheme 1).

We recently developed a rhodium-catalyzed formal carbenoid insertion into amide C–N bonds for the construction of diverse nitrogen-bridged bicyclic systems.[11] Azabicyclo[4.2.1]nonane skeletons, the core structure of anatoxin-a, were accessible in good to excellent yields from the corresponding lactam derivatives with a diazocarbonyl unit using this methodology.

The proposed reaction pathway is outlined in Scheme 2. The generation of rhodium carbenoids from substrates with



Scheme 1. Various strategies toward the synthesis of anatoxin-a.

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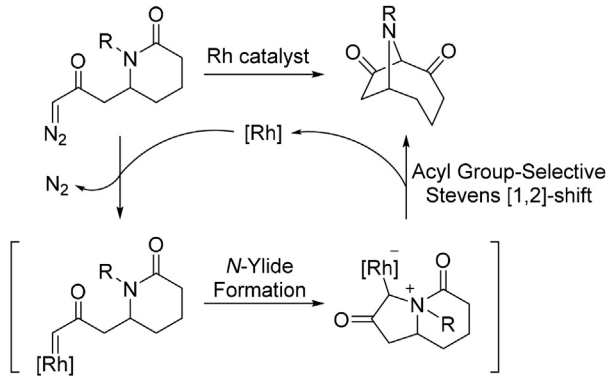
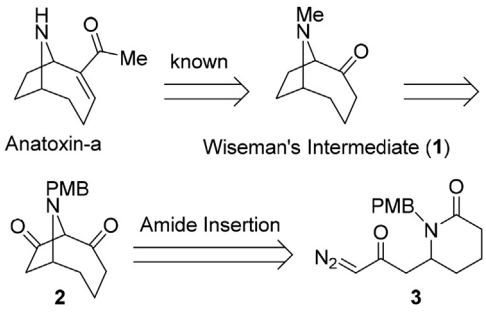


Scheme 2. Reaction process of the formal amide insertion.

a diazocarbonyl motif, followed by addition of the amide nitrogen to the carbenoid intermediates, results in the formation of rhodium-associated *N*-ylides. An acyl group-selective Stevens [1,2]-shift from the nitrogen to the carbon associated with rhodium metal occurs subsequently to give the nitrogen-bridged bicyclic compounds. We hypothesized that the present rhodium catalysis would be applicable to the synthesis of anatoxin-a. In this article, we report a de novo synthetic pathway to anatoxin-a through a rhodium-catalyzed formal amide insertion reaction.

2. Results and discussion

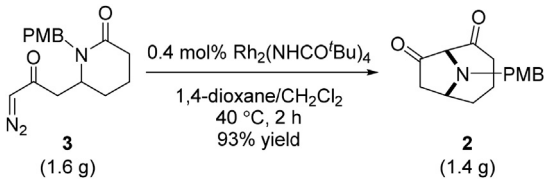
The plan for the synthesis of anatoxin-a is shown in Scheme 3. Our retrosynthetic analysis began with compound **1**, which was utilized as the key intermediate in a previous total synthesis by Wiseman's group.[9c] We assumed that compound **1** would be accessible if the two ketones in **2** could be distinguished by a site-selective deoxygenation process. The nitrogen-bridged bicyclic molecule **2** bearing the core structure of anatoxin-a could be synthesized from the lactam derivative with a diazocarbonyl unit **3** through the above-mentioned rhodium-catalyzed formal amide insertion reaction.



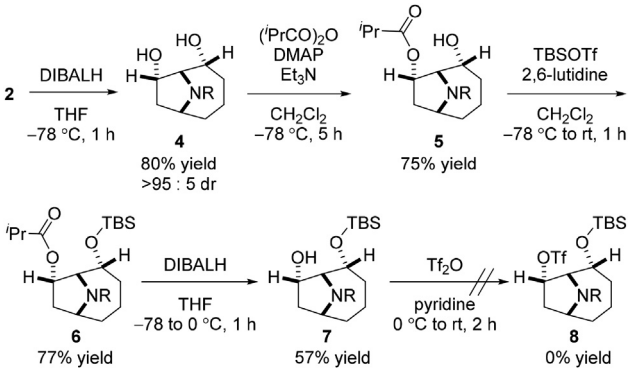
Scheme 3. Retrosynthetic analysis of anatoxin-a.

Our synthetic study began with the large-scale production of **2** under the previously optimized conditions.[11] A solution of **3** (1.6 g) in 1,4-dioxane/CH_2Cl_2 mixed solvent was stirred for 2 h at 40 °C in the presence of 0.4 mol % $Rh_2(NHCO^tBu)_4$ catalyst, affording 1.4 g of **2** in 93% yield (Scheme 4).

We next examined the differentiation between the two ketones using a site-selective functionalization process (Scheme 5). We first investigated the selective functionalization of the ketone in the pyrrolidine ring via an enol triflate formation, hydrosilylation, acetalization, and transition metal-catalyzed hydrogenation. All examinations, however, led to unsuccessful results. In addition,



Scheme 4. Gram scale synthesis of **2**.



Scheme 5. Site-selective transfomations of the two-carbonyl group. R=PMB.

gradual decomposition of **2** via a ring opening reaction with nucleophiles such as methanol was observed.[12] Thus, we turned our attention to the use of the corresponding diol for this purpose. Several trials revealed that reduction of **2** with DIBALH at −78 °C proceeded in a highly diastereoselective manner (>95: 5 dr), providing 1,3-diol **4** in 80% yield. The relative stereochemistry of the major isomer was determined by X-ray crystallographic analysis[11] and the obtained diol was utilized as the substrate for site-selective acylation reaction. Acylation of **4** with acetic anhydride gave a monoacetylated product in 56% yield, accompanied by the formation of the diacetylated product and the recovery of **4**. The use of isobutyric anhydride increased the yield of monoacylated compound **5** to 75%. No reaction occurred when $(^tBuCO)_2O$ was used as a more bulky acylation reagent.

To remove the oxygen functional group from the pyrrolidine framework, we investigated protection of the other hydroxyl group with a TBS group. Although the reaction did not proceed under standard conditions using TBSCl and imidazole, the use of TBSOTf afforded the corresponding product **6** in 77% yield. Subsequent removal of the acyl group using DIBALH gave compound **7** in 57% yield. Introduction of a sulfonate group to the alcohol in **7** was examined for reductive removal of the oxygen. The reaction of **7** with highly electrophilic Tf_2O, however, resulted in complex mixtures, possibly due to the reactive lone pair of tertiary amines.

The reactivity problem derived from the nitrogen atom led us to change the protective group from a PMB group to a Boc group to prevent undesired side reactions (Scheme 6). In addition, the Boc group can be transformed into a methyl group by reduction with lithium aluminum hydride (LAH) in the latter step, enabling efficient access to Wiseman's intermediate. The PMB group was successfully transformed into a Boc group by treating **6** with $Pd(OH)_2$ and $(Boc)_2O$ under H_2 gas (1 atm) in one-pot, providing **9** in a quantitative yield. After removal of the acyl group using a DIBALH reduction, the resulting alcohol **10** was reacted with Tf_2O in pyridine to give compound **11** in 62% yield (2 steps). Reductive removal of the triflate group in **11** was performed using Super-Hydride. Deprotection of the TBS group was also conducted during the