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A Formal Total Synthesis of (±)-Anatoxin-a by an Intramolecular Pd-Catalyzed Aminocarbonylation Reaction

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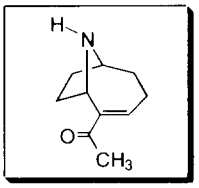
Abstract: 9-Azabicyclo[4.2.1]nonane skeleton **3a** was prepared by intramolecular aminocarbonylation of **2a** catalyzed by palladium. In three steps **3a** was transformed into **8** which had previously been transformed into anatoxin-a, thus completing the formal total synthesis.

Certain strains of the fresh green algae *Anabaena flos-aquae* produce a potent toxin which has been responsible for numerous incidents of live stock and water poisoning in the Midwestern United States and Canada.[1] An alkaloidal toxin identified from these sources was shown to be 2-acetyl-9-azabicyclo[4.2.1]non-2-ene(anatoxin-a, **1**) also designated "Very Fast Death Factor"(VFDF).[2]

Anatoxin-a mimics the neurotransmitter acetylcholine and acts as a potent agonist for the nicotinic acetylcholine receptor(nAChR).[3] As a consequence, this molecule has proved to be an important pharmacological probe and is providing valuable information about the mechanism of intramuscular neurotransmission. Since anatoxin-a has the 9-azabicyclo-[4.2.1]nonane ring system, its unusual bicyclic ring structure and its biological properties have stimulated the interest of many synthetic organic chemists.[4] Intramolecular aminocarbonylation has been proved to be an efficient method for constructing biologically important alkaloids and related compounds. There are many examples of the cyclization of unsaturated amine compounds.[5] The key step in our approach involves an intramolecular palladium-catalyzed aminocarbonylation reaction to form the desired bicyclic ring skeleton **3** which might be converted to (±)-anatoxin-a.



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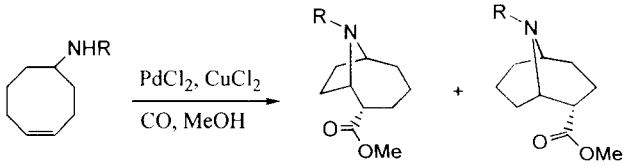

2 3 4

a: R=CO_2CH_3, b: R=SO_2CH_3, c: R=$SO_2C_6H_4CH_3$, d: R=CH_2Ph, e: R=CH_3

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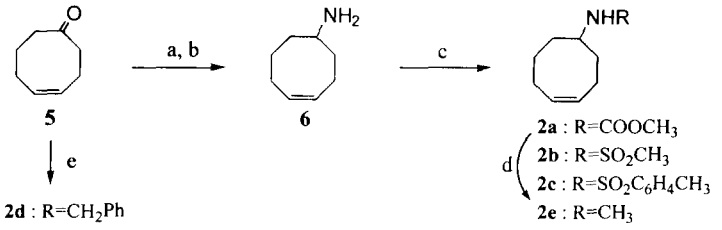
The cyclization precursors, **2a-e** were readily prepared from the known ketone **5**[6] as illustrated in **Scheme 1**.



Scheme 1

Reagents and Conditions: a) NH_2OH-HCl, Na_2CO_3, MeOH, reflux, 80%, b) LAH, THF, reflux, 66%, c) $ClCO_2CH_3$, Et_3N, CH_2Cl_2, 51% for **2a**; MsCl, Et_3N, CH_2Cl_2, 53% for **2b**; TsCl, Et_3N, CH_2Cl_2, 55% for **2c**, d) LAH, THF, reflux, 79%, e) $PhCH_2NH_2$, $NaCNBH_3$, MeOH, pH5, 45%

We examined the intramolecular palladium-catalyzed aminocarbonylation reaction of the carbamate **2a**, the sulfonamides **2b**, **2c**, and the amines **2d**, **2e** in the presence of copper(II) chloride as an oxidant. These reactions were carried out in methanol under 1 atm of carbon monoxide at room temperature as shown in **Table 1**.

Table 1. Intramolecular Pd-catalyzed aminocarbonylation reaction.

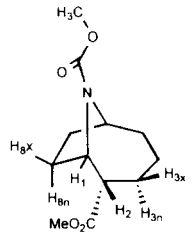
Substrate	time[a]	yield(%)[b]	ratio(3 : 4)[c]
2a	24h	61	72 : 28
2b	48h	66	47 : 53
2c	48h	52	55 : 45
2d	48h	47	3 : 97
2e	48h	no reaction	

a. Reactions were performed as follows : **2**(1 mmol), $PdCl_2$(0.1 mmol), $CuCl_2$(3 mmol), CO(1 atm) in dry MeOH at RT

b. Yields refer to isolated and chromatographically pure products

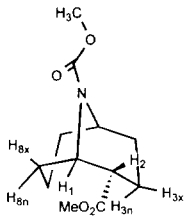
c. The ratio was determined by ^{1}H-NMR(500MHz) and HPLC analysis

In the course of the transannular cyclization, we found that the regiochemistry of the reaction can be controlled by the nature of the N-substituent of **2a-d**. Palladium induced cyclization of the carbamate **2a** proceeded smoothly to afford a 72 : 28 mixture of **3a** and **4a** in favor of **3a** as the desired isomer. The cyclization of the sulfonamides **2b** or **2c** yielded at a 47 : 53 mixture of **3b** and **4b** or 55 : 45 mixture of **3c** and **4c**. On the other hand, cyclization of the N-benzyl amine **2d** gave a 3 : 97 mixture of **3d** and **4d** under the same condition. As we expected, this cyclization was totally stereoselective[5i]; only one stereoisomer (only the α-ester isomers) was found in the mixture as proved by ^{1}H-NMR spectra.[7] For example, the stereochemistry of **3a** was deduced from ^{1}H-NMR; the diagnostic proton H-2 exhibited coupling constant of 8 and 4.9Hz with H-3n and H-1, respectively. The structure of bicycle **3a** was confirmed by comparison with spectroscopic data in the literature[8], in which the stereochemistry of the ester group was trans to the nitrogen. The configuration of **4a** was also assigned based on the proton H-2 coupling constant of 12.9 and 5Hz with H-3n and H-1. (**Figure 1**.)



	J(Hz)
J1,8x	9.1
J1,8n	2.7
J1,2	**4.9**
J2,3x	**6.0**
J2,3n	**8.0**

3a

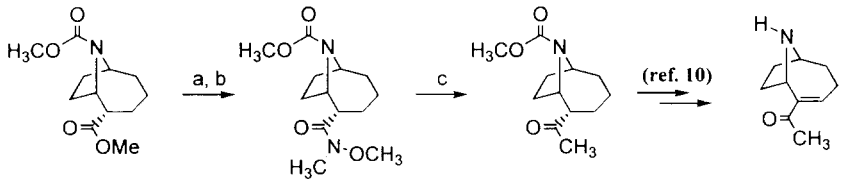


	J(Hz)
J1,8x	5.2
J1,8n	1.0
J1,2	**5.0**
J2,3x	**5.1**
J2,3n	**12.9**

4a

Figure 1. Assignment of coupling constants of **3a** and **4a** (for one rotamer)

Compound **3a** was treated with potassium hydroxide to afford the corresponding acid, which was reacted with N,O-dimethylhydroxylamine hydrochloride in the presence of EDCI and HOBT in CH_2Cl_2.[9] The resulting amide was reacted with methylmagnesium bromide at 0 ℃ to give the known ketone **8** in 72% overall yield. The conversion of **8** to (±)-**1** has been earlier reported by the Skrinjar group.[10]



3a **7** **8** **(±)-1**

Scheme 2

Reagents and Conditions: a) KOH, MeOH, reflux, 98%; b) $HNCH_3(OCH_3)$, EDCI, HOBT, CH_2Cl_2, 87%; c) CH_3MgBr, THF, 0 ℃, 85%

In summary, a new synthesis of (±)-anatoxin-a (**1**) was accomplished by using the intramolecular Pd-catalyzed aminocarbonylation reaction of **2a** as a key step.

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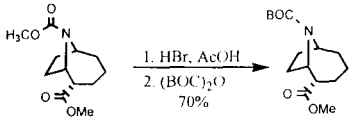

3a **9**

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