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

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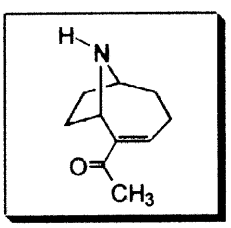
Abstract: 9-Azabicyclo[4.2.1]nonane skeleton **3a** was prepared by intramolecular aminocarbonylation of **2a** catalyzed by palladium. In three steps **3a** was transformed into **8** which had previously been transformed into anatoxin-a, thus completing the formal total synthesis.

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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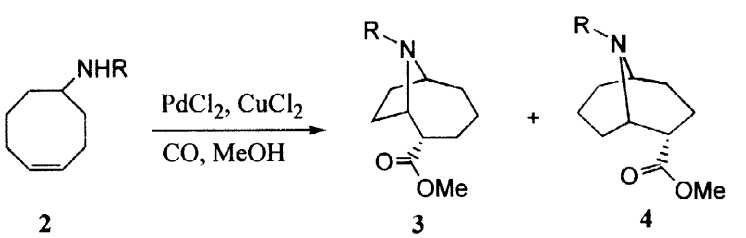

2 3 4

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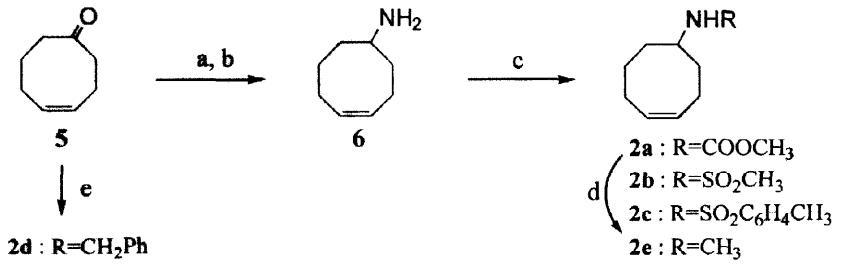
The cyclization precursors, **2a-e** were readily prepared from the known ketone **5**[6] as illustrated in **Scheme 1**.



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.

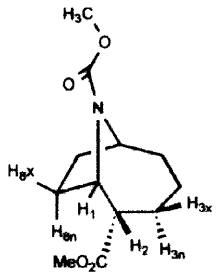
Substrate	time[a]	yield(%)[b]	ratio(3 : 4)[c]
2a	24h	61	72 : 28
2b	48h	66	47 : 53
2c	48h	52	55 : 45
2d	48h	47	3 : 97
2e	48h	no reaction	

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

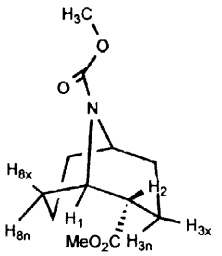
c. The ratio was determined by ^{1}H-NMR(500MHz) and HPLC analysis

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

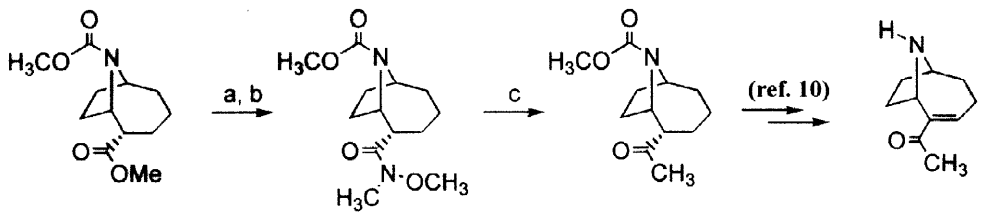


	J(Hz)
J1,8x	5.2
J1,8n	1.0
J1,2	**5.0**
J2,3x	**5.1**
J2,3n	**12.9**

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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7. The assignment of 9-azabicyclo[4.2.1]- and 9-azabicyclo[3.3.1] nonane ring system for **3a-c** and **4a-d** on their respective ^{1}H-NMR and ^{13}C-NMR. **3a, rotamer** : ^{1}H-NMR(500MHz, $CDCl_3$): δ 4.65(0.5H, m), 4.55(0.5H, m), 4.36(0.5H, br t), 4.24(0.5H, br t), 3.71, 3.69, 3.67, 3.66(1.5H × 4, 4s), 3.09(0.5H, m), 2.93(0.5H, m), 2.2 ~ 1.35(10H, m); ^{13}C-NMR(75.5MHz, $CDCl_3$) : δ 174.9, 155.1, 58.2, 57.8, 55.9, 55.6, 53.0, 52.9, 52.3, 52.2, 48.5, 47.2, 35.4, 34.6, 33.1, 32.3, 27.0, 26.7, 26.1, 23.1; **4a, rotamer** : ^{1}H-NMR(500MHz, $CDCl_3$) : δ 4.62(0.5H, br), 4.51(0.5H, br), 4.33(0.5H, br), 4.21(0.5H, br), 3.72, 3.72, 3.71, 3.70(1.5H × 4, 4s), 2.83(1H, m), 2.32(1H, m), 2.02 ~ 1.54(9H, m); ^{13}C-NMR(75.5MHz, $CDCl_3$) : δ 172.7, 154.8, 53.2, 52.4, 48.5, 47.8, 46.8, 46.1, 45.7, 45.2, 29.9, 29.6, 27.2, 26.8, 26.5, 23.0, 20.5; **3b** : ^{1}H-NMR(300MHz, $CDCl_3$) : δ 4.50(1H, m), 4.20(1H, br t), 3.61(3H, s), 2.90(1H, m), 2.77(3H, s), 2.10 ~ 1.37(10H, m); ^{13}C-NMR(75.5MHz, $CDCl_3$) : δ 173, 60.0, 58.3, 51.7, 49.6, 38.1, 35.9, 33.0, 27.0, 26.0, 22.5; **4b** : ^{1}H-NMR(300MHz, $CDCl_3$) : δ 4.26(1H, br), 3.99(1H, br), 3.64(3H, s), 2.98(1H, m), 2.91(3H, s), 2.31(1H, m), 2.10 ~ 1.37(9H, m); ^{13}C-NMR(75.5MHz, $CDCl_3$) : δ 173, 52.1, 49.0, 47.6, 45.1, 41.7, 29.4, 26.3, 22.1, 19.5; **3c** : ^{1}H-NMR(300MHz, $CDCl_3$) : δ 7.71(2H, d), 7.25(2H, d), 4.54(1H, br q), 4.25(1H, br t), 3.65(3H, s), 2.96(1H, m), 2.10 ~ 1.36(10H, m) ; ^{13}C-NMR(75.5MHz, $CDCl_3$) : δ 173.9, 143.2, 137.2, 129.7, 126.9, 126.7, 60.3, 58.6, 51.7, 49.7, 36.0, 32.4, 26.8, 26.1, 22.5, 21.5; **4c** : ^{1}H-NMR(300MHz, $CDCl_3$) : δ 7.69(2H, d), 7.20(2H, d), 4.29(1H, br), 4.03(1H, br), 3.62(3H, s), 2.81(1H, m), 2.35(3H, s), 2.20(1H, m), 1.97 ~ 1.41(9H, m); ^{13}C-NMR(75.5MHz, $CDCl_3$) : δ 173.2, 142.9, 138.8, 129.7, 126.9, 51.8, 48.9, 47.5, 44.5, 29.0, 28.9, 25.9, 22.1, 21.5, 19.5; **4d** : ^{1}H-NMR(300MHz, $CDCl_3$) : δ 7.29 ~ 7.11(5H, m), 3.78(2H, d), 3.55(3H, s), 3.03(1H, br), 2.99(1H, m), 2.66(1H, br), 2.21(1H, m), 1.99 ~ 1.35(9H, m); ^{13}C-NMR(75.5MHz, $CDCl_3$) : δ 175.5, 140.0, 128.2, 126.7, 56.7, 53.0, 51.4, 49.5, 41.4, 27.6, 25.2, 24.5, 22.7, 20.2.
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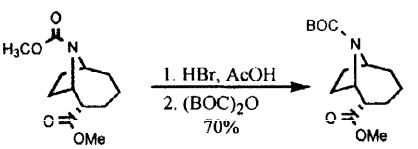

3a **9**

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