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Gold-Catalyzed Cycloisomerization of *N*-Propargylindole-2-carboxamides: Application toward the Synthesis of Lavendamycin Analogues

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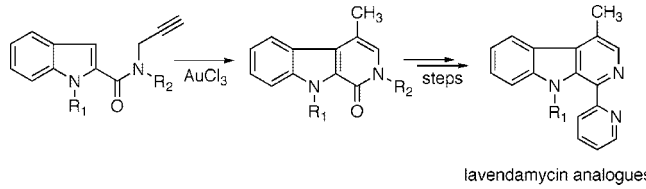
ABSTRACT



A series of *N*-propargylindole-2-carboxamides were found to undergo a $AuCl_3$-catalyzed cycloisomerization to give β-carbolinones in high yield. The corresponding β-chlorocarboline derivative was prepared and used for Pd(0)-catalyzed cross-coupling chemistry directed toward the synthesis of lavendamycin analogues.

The number of reports describing the utility of gold complexes as homogeneous catalysts for the formation of C−X and C−C bonds has dramatically increased in recent years.[1] Gold catalysts can be considered as powerful soft Lewis acids for the activation of C−C triple bonds toward nucleophilic attack.[2] A variety of nucleophilic reagents, such as H_2O/alcohols,[3] alkynes,[4] azides,[5] and carbonyl groups,[6] have been utilized. These catalytic cyclization reactions generally proceed under extremely mild conditions and are characterized by high turnover numbers. Gold complexes are also particularly active in promoting the intermolecular and intramolecular hydroarylation of alkynes[7] and allenes.[8] Recently, the Echavarren group reported that indoles react intramolecularly with alkynes in the presence of gold catalysts to give six- to eight-membered ring annulated

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compounds.[9,10] We envisioned taking advantage of a somewhat related cycloisomerization for a synthesis of various analogues of the antitumor antibiotic lavendamycin.

Lavendamycin (**1**) was isolated and characterized in 1981 by Doyle from the fermentation broths of *Streptomyces lavendulae*[11] and is structurally and biosynthetically related to streptonigrin (**2**),[12] another potent antitumor antibiotic (Figure 1). Both of these compounds have been shown to possess cytotoxic properties and exhibit significant activity against topoisomerases.[13] Consequently, these target molecules have been the focus of much synthetic effort since their initial structural identification.[14] A limitation to exploiting the biological properties of lavendamycin is its toxicity that may be partly due to the presence of the quinone moiety in the A-ring. Synthetic approaches toward lavendamycin and its structural analogues generally involve either a Bischler−Napieralski cyclodehydration[15] or a Pictet−Spengler cyclization to build the C-ring.[16] The Boger group's synthesis of **1** was based upon the formation of the B-ring by a Friedlander condensation.[17] Still another approach that had been used involves a modified Knoevenagel−Stobbe pyridine formation and further D-ring construction by a thermolytic nitrene insertion.[18] Herein, we describe a highly efficient route toward the synthesis of various lavendamycin analogues utilizing a gold-catalyzed cycloisomerization of *N*-propargylindole-2-carboxamides.

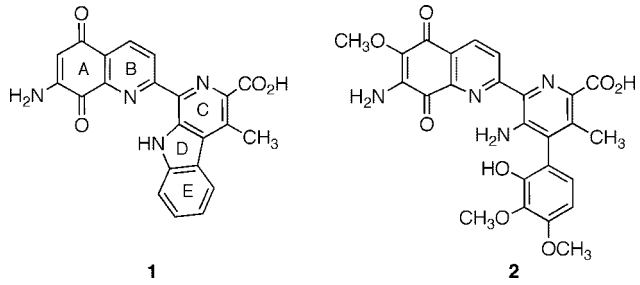
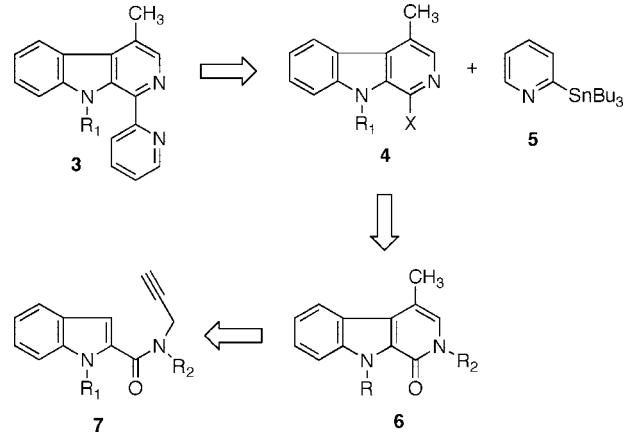


Figure 1. Some potent antitumor antibiotics.

Scheme 1



Our synthetic plan is shown in antithetic format in Scheme 1. Thus, a retrosynthetic analysis of the much simpler

Scheme 2

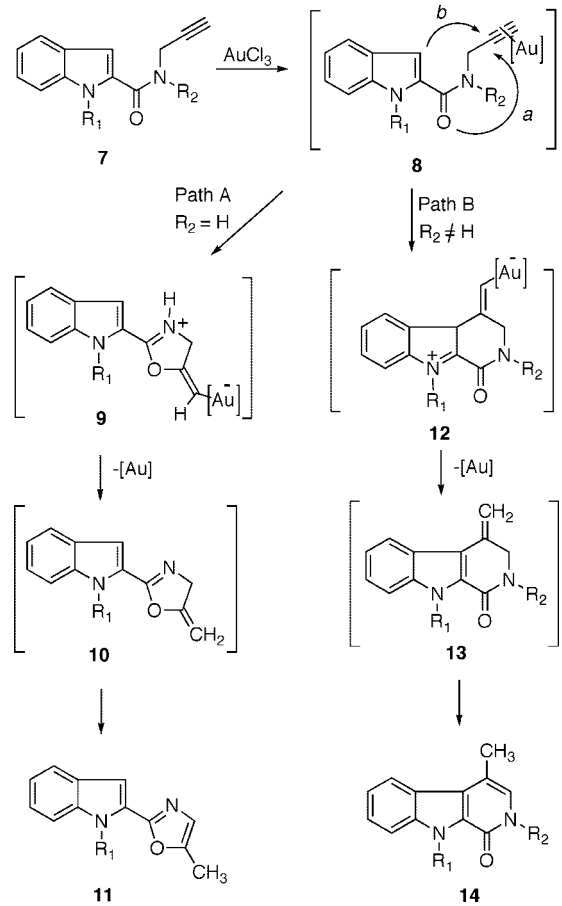


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Table 1. Cycloisomerization of Indolo-Substituted Propargylcarboxamides

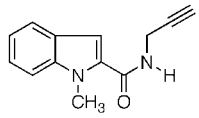
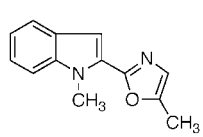
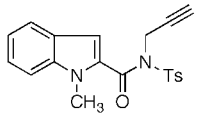
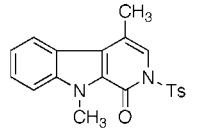
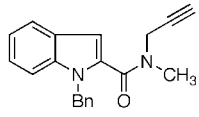
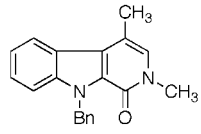
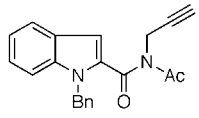
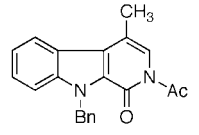
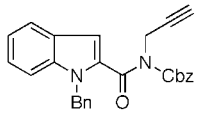
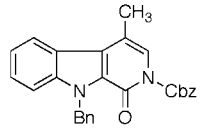
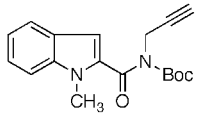
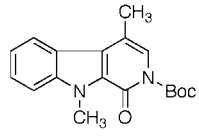
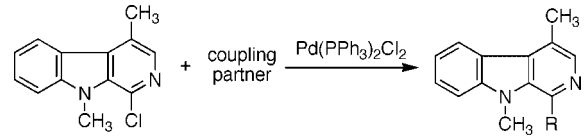
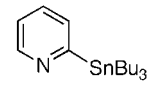
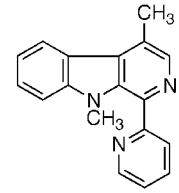
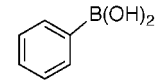
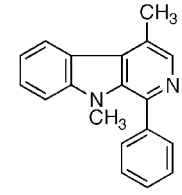
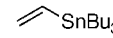
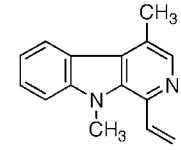
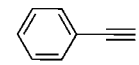
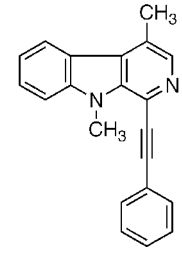
entry	indole	product (%)
1	 **7a**	 **11a**; 75%
2	 **7b**	 **14b**; 85%
3	 **7c**	 **14c**; 87%
4	 **7d**	 **14d**; 78%
5	 **7e**	 **14e**; 65%
6	 **7f**	 **14f**; 60%

Table 2. Cross-Coupling Reactions of β-Chorocarboline **15**



15

entry	coupling partner	product (%)
1		 **16**; 79%
2		 **17**; 77%
3		 **18**; 56%
4		 **19**; 88%

β-carboline CDE ring system of lavendamycin (i.e., **3**) revealed to us that this skeletal framework could be obtained from a cross-coupling reaction of two key intermediates, namely the β-substituted carboline **4** and pyridinylstannane **5**. Compound **4** was envisioned to result from 1*H*-pyrido-[3,4-*b*]indol-1-one **6**, which in turn would arise from a gold-catalyzed intramolecular cycloisomerization of *N*-(prop-2-ynyl)-1*H*-indole-2-carboxamide **7**. Finally, a Pd-catalyzed cross-coupling of **4** and **5** would lead to the synthesis of various lavendamycin analogues.

On the basis of earlier reports in the literature dealing with the cyclization reactions of *N*-propargylcarboxamides,[19] we reasoned that treating carboxamide **7** with a Au(III) catalyst would result in an initial activation of the triple bond by the electrophilic metal species. Two modes of cycloisomerization are possible depending on the nature of the R_2 substituent (Scheme 2). In the case where R_2 = H, backside attack by the amide carbonyl group on the π-coordinated alkyne complex **8** via path A would eventually produce oxazole **11** by a protodemetalation of the aurated enol ether species **9** followed by a subsequent isomerization of a transient 5-methylene-substituted 4,5-dihydrooxazole **10**. This type of reactivity has been described by both Hashmi[20] and Echavarren.[9] However, if the amido nitrogen atom contains a substituent other than hydrogen, we envisioned that a 6-*exo-dig* cyclization reaction would occur by attack at the C_3-position of the indole ring via path B. Following protodemetalation of **12** and isomerization of **13**, carbolinone **14** would be produced.

In the first study that was carried out, treating a sample of *N*-(prop-2-ynyl)-1*H*-indole-2-carboxamide **7a** with a catalytic

quantity of $AuCl_3$ in CH_2Cl_2 at 25 °C led to the exclusive formation of the expected oxazole **11a** in 75% overall yield. Gratifyingly, the related *N*-substituted propargylcarboxamide **7b** underwent smooth cycloisomerization in the presence of catalytic $AuCl_3$ to give the desired β-carbolinone **14b** in 85% yield using similar reaction conditions. The scope of the cyclization was further studied, and the results obtained with amides **7c**−**f** are shown in Table 1. Various protecting groups on the amido nitrogen were allowed, and in all cases, the cyclization proceeded with good to excellent efficiencies.

The next phase of our investigations was aimed at both developing the chemistry required to construct the requisite β-carboline coupling partner **4** and determining the functional group compatibility of this methodology. β-Chlorocarboline **15** was synthetically more accessible from pyridoindolone **14f** than its triflate analogue and was therefore chosen as the prime coupling partner to be used for the synthesis of various lavendamycin analogues. Thus, the reaction of carboxamide **7f** with $AuCl_3$ gave carbolinone **14f** in 60% yield. Deprotection of the Boc group with trifluoroacetic acid followed by reaction with phosphorus oxychloride gave **15** in 80% yield over the two steps. The transition-metal-catalyzed cross-coupling of organometallic reagents with aryl halides represents a powerful method for the preparation of substituted biaryls.[21] The synthesis of various heterobiaryls by Pd(0) cross-coupling using halopyridine derivatives is also known but has not been as well documented.[22] We were pleased to discover that β-chlorocarboline **15** underwent smooth coupling with 2-(tributylstannyl)pyridine under classic Stille conditions to give β-carboline **16** in 79% yield (Table 2). The coupling of **15** with phenylboronic acid under traditional Suzuki conditions also gave the related β-phenyl-substituted carboline **17** in 77% yield. Cross-coupling of **15** with both tributyl(vinyl)stannane and phenyl acetylene also proceeded smoothly and afforded carbolines **18** (56%) and **19** (88%).

In conclusion, we have developed a simple, efficient method for the synthesis of various lavendamycin type analogues in good yield via the $AuCl_3$-catalyzed cycloisomerization of *N*-propargylindole-2-carboxamides. The resulting β-carbolinone system was used for subsequent cross-coupling chemistry. Application of the methodology toward lavendamycin is currently under investigation, the results of which will be disclosed in due course.

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Supporting Information Available: Spectroscopic data and experimental details for the preparation of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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