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A New Method for the Synthesis of β,γ-Unsaturated Amides from Allylic Carbonate Catalyzed by Palladium in the presence of Carbon Monoxide and Amine: Studies Towards the Total Synthesis of Antillatoxin

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Abstract

The reaction of α,β-unsaturated carbonates was carried out in DMF in the presence of $PdCl_2$/dppb (5 mol%), CO and L-alanine at 65 °C for 4 days to give the β, γ-unsaturated amide intermediate of antillatoxin in good yield.

Keywords : Palladium and compounds; Carbonylation; Amides.

Antillatoxin (**1**)[1], a newly isolated ichthyotoxic natural product possesses the β,γ-unsaturated amide fragment **2** whose access normally involves a one-carbon elongation method to form the corresponding acid followed by the coupling of the amine to obtain the amide.[2,3,4] However, all these methods suffer from low yields due to the unstable nature of the β,γ-unsaturated system under basic or acidic conditions. A particularly attractive approach to antillatoxin[5,6,7,8,9] involves the palladium catalyzed reaction of an allylic carbonate with a free amine in the presence of carbon monoxide. Although the use of secondary amines in this type of reaction has been demonstrated by Tsuji et al.[10,11,12], as far as we know, the use of primary amines has not been evaluated. To explore the scope and limitations of this process as well as its ability to facilitate the synthesis of antillatoxin, we systematically investigated the reaction of various allylic carbonates with primary amines using palladium catalysts in the presence of carbon monoxide. In this paper, we describe an efficient synthesis of the advanced intermediate **2** of antillatoxin based on a new palladium catalyzed reaction[12,13,14] of the

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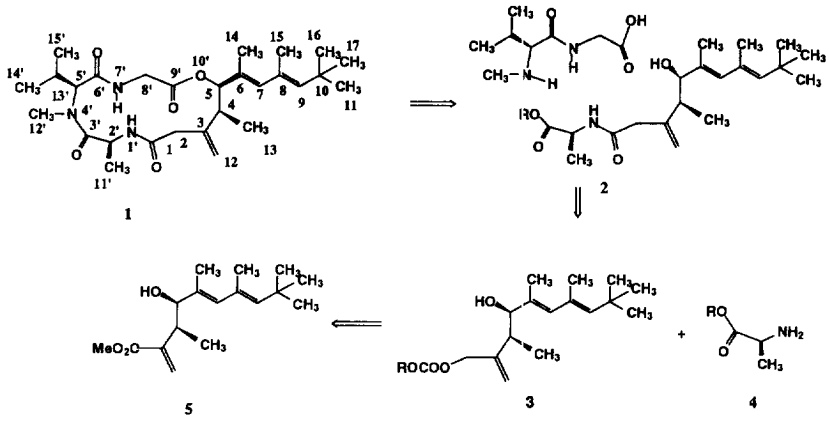
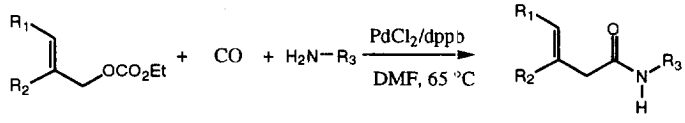
allylic carbonate **3** derived from **5** with L-alanine in the presence of carbon monoxide at atmospheric pressure.



Scheme 1

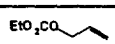
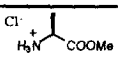
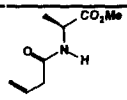
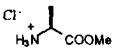
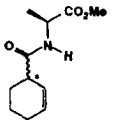
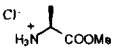
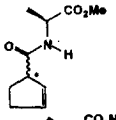
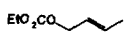
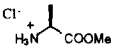
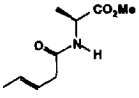
Before we embarked on the more complex system, we first performed several model studies using simple substrates. Thus, a wide variety of allylic carbonates were subjected to the reaction using Pd(0) (5 mol%), alanine and CO in DMF under atmospheric pressure at 65 °C. The results are summarized in Table 1.



In all cases, the desired β,γ-unsaturated amides were obtained in moderate to good yields. When a racemic mixture of cyclopentene carbonate and cyclohexene carbonate are used, the products were obtained as a 1:1 diastereomeric ratio. Of special interest is that reaction with an unsymmetrical allylic carbonate afforded the product with high regioselectivity (Table 1, entry 4).

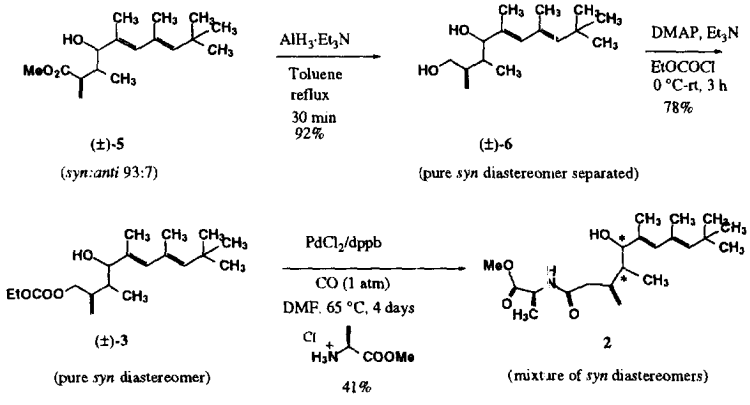
With the success of this new one carbon elongation using a primary amine, we applied this methodology to the synthesis of antillatoxin. In our previous work, we have developed a highly *syn*-selective and efficient approach for the synthesis of its C1-C11 segment **5**, possessing two stereogenic centers in the target molecule[7].

Table 1. Palladium-catalyzed carbonylation with alanine

Entry	Allylic Carbonate	H_2NR	Conditions	Product	Yield[a]
1			$CO/dppb/PdCl_2$ (5 mol%), DMF, 65 °C, DIEA, 24 h		52%
2	 (±)		$CO/dppb/PdCl_2$ (5 mol%), DMF, 65 °C, DIEA, 24 h		56%
3	 (±)		$CO/dppb/PdCl_2$ (5 mol%), DMF, 65 °C, DIEA, 24 h		69%
4			$CO/dppb/PdCl_2$ (5 mol%), DMF, 65 °C, DIEA, 24 h		62%

a. Isolated yield * Diastereomeric ratio 50:50

The allylic carbonate (±)-**3** was synthesized in 2 steps from (±)-**5** which was prepared according to our previously reported procedure[7]. Reduction of the α,β-unsaturated ester **5** with $AlH_3 \cdot Et_3N$[15] in toluene under reflux for 30 min afforded the corresponding alcohol **6** in 92% yield. Subsequently, selective protection of the primary alcohol **6** with ethyl chloroformate in the presence of DMAP and triethylamine at 0 °C for 3 h afforded the mono-protected alcohol **3** in 78% yield.



Scheme 2

Thus, the coupling of (±)-**3** with commercially available alanine methyl ester was carried out in DMF in the presence of $PdCl_2$/1,4-bis(diphenyphosphino)butane (dppb) (5 mol%), CO at 65 °C for 4 days to give the β, γ-unsaturated amide **2** in 41% yield.

In summary, we have developed a short and efficient synthesis of **2**. A 1-carbon elongation of allylic carbonate **3** using CO in the presence of palladium catalyst followed by the coupling with L-alanine has been accomplished in a single step to afford the β,γ-unsaturated amide **2** which is the key intermediate for the synthesis of antillatoxin. The experimental protocol is simple without the need to carry out the experiment under strictly anhydrous conditions[16].

References and Notes:

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