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Cascade Approach toward the Core Structure of Neosarpagine

Xuebin Liao,[†] Shengming Huang,[†] Hao Zhou,[†] Damon Parrish,[‡] and James M. Cook*,[†]

Department of Chemistry and Biochemistry, University of Wisconsin—Milwaukee, 3210 North Cramer Street, Milwaukee, Wisconsin 53211, and Laboratory for the Structure of Matter, Naval Research Laboratory, Washington, D.C. 20375

capncook@uwm.edu

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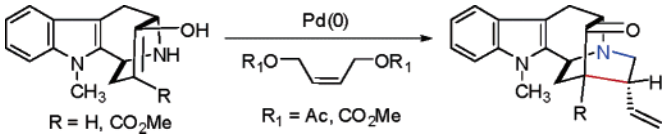
ABSTRACT



A palladium-catalyzed domino sequence was developed to rapidly construct the core structure of neosarpagine and other quinuclidine-related alkaloids. The cyclization of ketone 11 to ethylidene 4 with $Pd(dba)_2$, DPEphos, LiHMDS, and $ZnCl_2$ in THF represents a new domino process wherein a nonstabilized enolate served as a nucleophile.

During the past decade, domino or cascade reactions have been intensively studied because they are well-suited for the rapid construction of complex natural products and drug candidates.[1−3] Among these, those mediated by transition metals, especially palladium-catalyzed tandem reactions, have been widely investigated.[4,5] Allylic systems are among the most frequently employed in palladium-catalyzed domino or cascade reactions because either or both allylic positions can be employed to generate an olefin moiety, which can be further transformed by subsequent bond-forming processes. An example of sequential allylic substitution in an intermolecular−intramolecular fashion with 1,4-diacetoxy *cis*-2-butene by Hayashi and co-workers[6] has been reported, reminiscent of the early work of Trost et al. Recently, we have begun a study of this type of process as an entry into quinuclidine-related alkaloids such as neosarpagine **1**. Pillay reported the isolation of neosarpagine **1** from *Rauwolfia micrantha* in 1960.[7,8] To our knowledge, the stereochemistry at the ethylidene function in **1** remains unknown. The proposed structure of neosarpagine **1** attracted our attention due to the terminal olefin at C(20); moreover, if the C(20)−N_b bond in **1** could be broken via a Hoffman elimination process, this would lead to macroline-related alkaloids (Figure 1). Described in this communication is a simple process to provide the quinuclidine core structure of **1**. Furthermore, this strategy could be employed for the

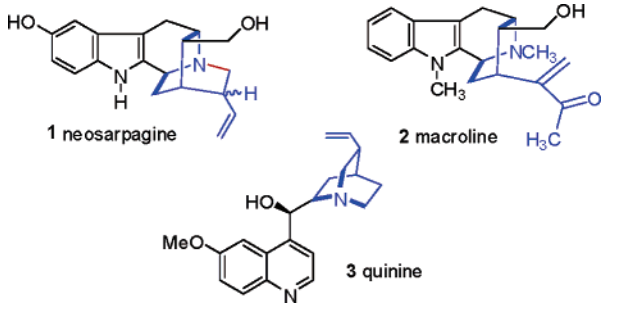


Figure 1. Structures of macroline- and quinuclidine-containing alkaloids.

[†] University of Wisconsin—Milwaukee.
[‡] Naval Research Laboratory.

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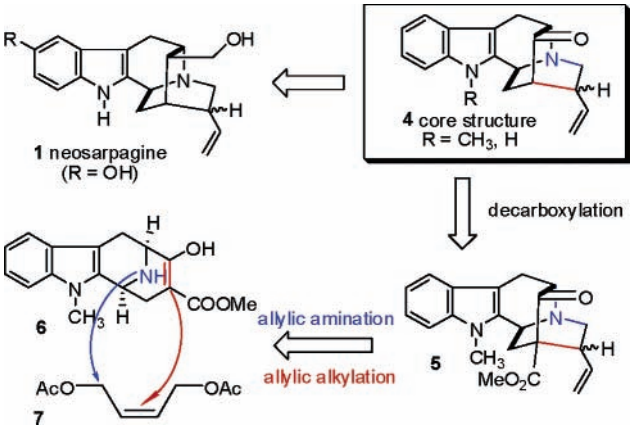
synthesis of macroline **2**, as well as the quinuclidine-related alkaloid quinine **3**.

As illustrated in Scheme 1, it was felt that a sequential

Scheme 1. Retrosynthetic Analysis of Neosarpagine



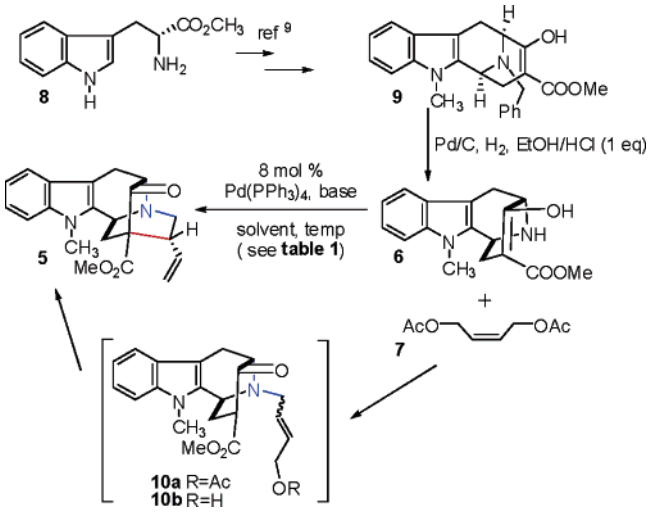
allylic substitution could be effected in which initially the allylic amination would be followed by allylic alkylation in a one-pot process. This would provide **4** with the correct core framework. Although this intermolecular−intramolecular allylic substitution with 1,4-diacetoxy *cis*-2-butene has been reported previously,[6] the combination of allylic amination and alkylation has not been reported.

The synthesis began with the β-keto ester **9** readily available on a 300−600 gram scale; it was prepared in three reaction vessels from tryptophan methyl ester **8** as reported.[9] The β-keto ester **9** was subjected to the conditions of catalytic hydrogenolysis to remove the benzyl group to provide the N_b−H derivative **6** (Scheme 2).

It was felt that a sequential allylic amination and alkylation process could be accomplished by the control of the rate of allylic amination vs attack of the stabilized enolate on the developing π-allyl Pd complex. In 1997, Tietze et al.[10] reported a highly efficient synthesis of cephalotaxine which involved an allylic amination. When these original conditions[10] were employed with enol **6** and bisacetate **7**, the quinuclidine system **5** was obtained in 60% yield.

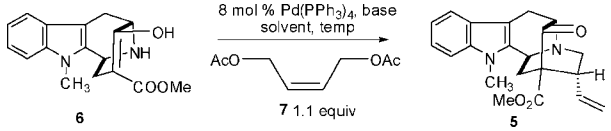
When the process was carried out in THF, a better yield of **5** was obtained (see Table 1). When the more hindered base, DIPEA, was employed, the process took longer to go to completion and some of the product of allylic amination was isolated after 12 h, which indicated the allylic alkylation was slower in the presence of the hindered base. However, the yield in this case was 70%. Execution of the process at a lower temperature further improved the yield, although the reaction time was much longer. Because the presence of allylic alcohol **10b** was observed, it was felt that an additive

Scheme 2. Synthesis of Ethylidene **5**



(Et_3B) was required to coordinate the hydroxyl group[11] and promote the desired allylic alkylation (Table 1). Under

Table 1. Conditions for the Palladium-Catalyzed Cascade Formation of Ethylidene **5**



	base	solvent	temp (°C)	yield (%)
1	Et_3N	CH_3CN	50	60
2	Et_3N	THF	50	63
3	DIPEA	THF	80	70
4	DIPEA	THF	50	75[a]
5	DIPEA	THF	rt to 80	85[b]

[a] Full conversion to **5** took 24 h. [b]Process stirred at room temperature overnight; then Et_3B was added as an additive and stirring was continued at 80 °C for 6 h.

optimized conditions, the desired ketone **5** was obtained in 85% yield (Table 1) in the presence of Et_3B. The structure of ester **5** was confirmed by X-ray crystallography (Figure 2). A similar strategy has been employed by Trost,[12] Williams,[13] and Padwa[14] for the construction of quinuclidine alkaloids.

With the desired ring system **5** in hand, it could be converted into the key intermediate **4**, which is related to the core structure of neosarpagine by a hydrolysis and

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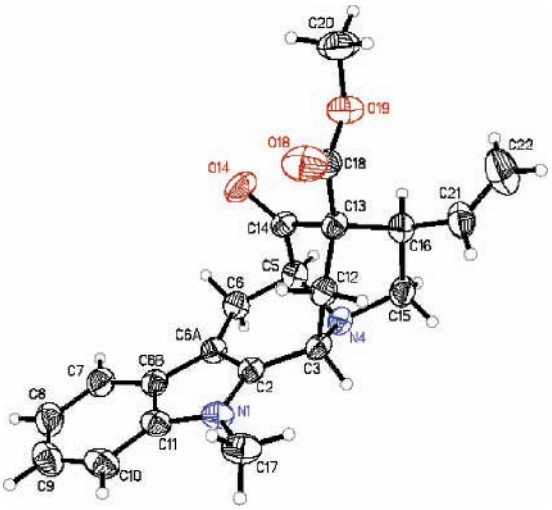
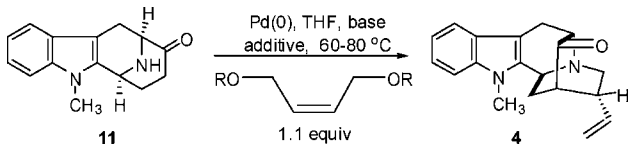


Figure 2. Structural representation of ketone **5** from the ORTEP.

decarboxylation process.[15] Moreover, analogous to the chemistry of Liu,[15] the key intermediate **5** could be converted into N_a-methyl-isokoumidine if desired. However, decarboxylation of the bridgehead carboxylic acid group is not trivial and would require radical-induced Barton decarboxylation conditions,[16,17] analogous to the work of Liu.[15] To circumvent this obstacle, the original strategy was altered to employ ketone **11** instead which was devoid of the ester function (see Table 2). This approach required the allylic amination, followed by direct attack on the π-allyl Pd(II) complex by a carbanion rather than the soft carbon nucleophile (β-keto ester). Although nonstabilized metal ketone enolates as nucleophiles are quite limited and usually not successful,[18−20] there are two advantages here: (1) it would be easier to control the sequence of allylic amination, followed by alkylation and (2) the decarboxylation step would be avoided. Initial efforts began with the weak base, Cs_2CO_3, in DMF from which a trace of the desired **4** was isolated (see Table 2). Encouraged by this result, lithium or sodium enolates were attempted as nucleophiles; however, yields were poor even in the presence of Et_3B. Recently, Kazmaier[21,22] reported the use of chelated zinc enolates or their derivatives as nucleophiles. These zinc enolates[21,22] reacted under much milder conditions than the corresponding lithium or sodium enolates. After screening several ligands and the Pd complex, it was found that the desired cyclization of ketone **11** to ethylidene **4** was obtained in 55% yield with $Pd(dba)_2$, DPEphos, and the combination of LiHMDS and $ZnCl_2$ in THF (Table 2). To our knowledge, this represents the first domino reaction which involved a nonstabilized enolate as a nucleophile. Further optimization and generalization of this process are under investigation.

Table 2. Conditions for the Palladium-Catalyzed Formation of Ketone **4**



	Pd(0)/L	base	additive	RO⁄\OR	yield (%)
1	$Pd(PPh_3)_4$	NaO^tBu	no	R = Ac	<5
2	$Pd(PPh_3)_4$	K_3PO_4	Et_3B	R = Ac	0
3	$Pd(dba)_2$/dppe	NaHMDS	Et_3B	R = CO_2Me	10
4	$Pd(dba)_2$/DPEphos	LiHMDS	$ZnCl_2$	R = CO_2Me	55

In summary, a domino sequence was developed to rapidly construct the quinuclidine core structure of neosarpagine as well as sarpagine alkaloids. In addition, this one-pot reaction could be exploited for the synthesis of *Cinchona* alkaloids. The application of this process to alkaloid total synthesis will be reported in due course.

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