SYNTHESIS OF BENZO[*c*]PHENANTHRIDINE ALKALOIDS, CHELERYTHRINE AND NITIDINE, USING A NOVEL PALLADIUM-PHOSPHINE COMBINATION SYSTEM –$Pd(OAc)_2$, DPPP, AND Bu_3P–

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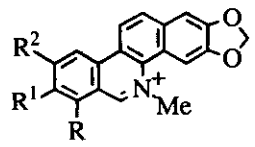
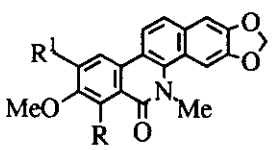
Abstract - Total synthesis of chelerythrine (**1**) and nitidine (**4**) was accomplished *via* the aryl-aryl cyclization reaction using a novel Pd reagent prepared from $Pd(OAc)_2$, DPPP, and Bu_3P. The present method was very versatile for coupling reaction not only between aromatic triflate and arene but also between aromatic halide and arene.

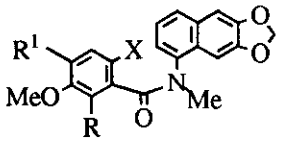
Fully aromatized benzo[*c*]phenanthridine alkaloids have attracted considerable attention because of their potent pharmacological and biological activities.[1] It was recently found that, among these alkaloids, chelerythrine (**1**),[1e] isofagaridine (**2**),[1d] and sanguinarine (**3**)[1f-1h] inhibited protein kinase C, DNA topoisomerase I, and lipoxygenase, respectively, and nitidine (**4**) showed a strong antileukemic activity.[1, 2b] Extensive efforts have been directed toward the development of a convenient method for synthesizing benzo[*c*]phenanthridine alkaloids.[1a, 1b, 2] However, the reported methods involved several disadvantages



$R = R^1 = OMe$, $R^2 = H$ chelerythrine (**1**)
$R = OMe$, $R^1 = OH$, $R^2 = H$ isofagaridine (**2**)
$R, R^1 = OCH_2O$, $R^2 = H$ sanguinarine (**3**)
$R = H$, $R^1 = R^2 = OMe$ nitidine (**4**)

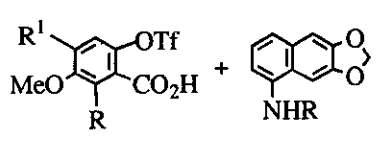


oxychelerythrine (**5**)
$R = OMe$, $R^1 = H$
oxynitidine (**6**)
$R = H$, $R^1 = OMe$



7 : $R = OMe$, $R^1 = H$
8 : $R = H$, $R^1 = OMe$

X = OTf, I or Br



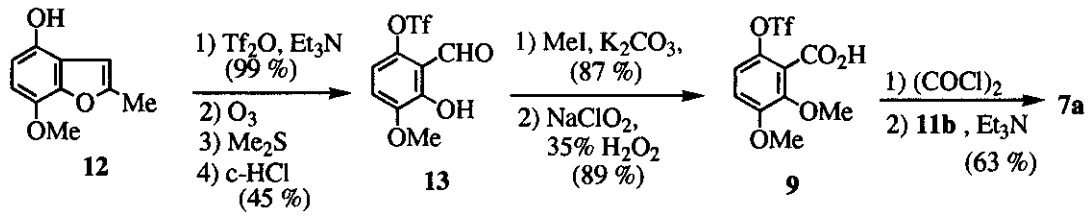
9 : $R = OMe$, $R^1 = H$
10 : $R = H$, $R^1 = OMe$

11a : R=H
11b : R=Me

Scheme 1

such as numerous steps, low total yield and/or absence of generality. Therefore, we developed a versatile method of synthesizing these alkaloids. Recently, we succeeded in the total synthesis of **1** and **4** using an internal biaryl coupling reaction of halo amides (**7b** and **7c**, and **8b**) by palladium.[3] Subsequently, we investigated a biaryl cyclization reaction of amide possessing a triflate group instead of a halogen group as a leaving group and found a novel palladium reagent system prepared from $Pd(OAc)_2$, DPPP [1,3-bis-(diphenylphosphino)propane] and Bu_3P for this purpose.[4] Moreover, this method was proven to be effective not only for the triflate group but also the halogen group as a leaving group.[4] In this communication, we describe the total synthesis of **1** and **4** using this novel method.

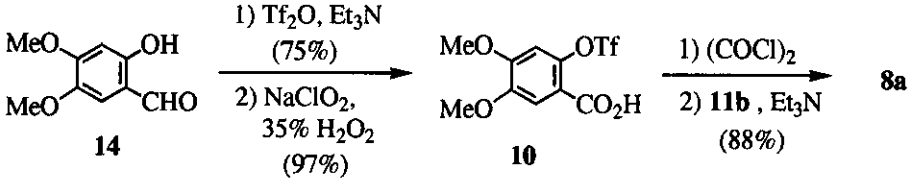
We designed a common synthesis plan for **1** and **4** as shown in Scheme 1. The monomethylnaphthylamine (**11b**) was synthesized from 1-naphthylamine (**11a**)[3a] in a 75% total yield *via* trifluoroacetylation, *N*-methylation with MeI in the presence of NaH, and hydrolysis with alkaline. Triflate acid (**9**) for synthesis of **1** was prepared as shown in Scheme 2. Thus, reaction of benzofuran (**12**)[5] with Tf_2O and successive treatment with ozone, Me_2S and hydrochloric acid provided salicylaldehyde (**13**), which was methylated and then oxidized to afford **9**. Finally, reaction of acid chloride of **9** with **11b** afforded triflate-amide (**7a**). Then, cyclization reaction of **7a** by the our novel palladium-phosphine combination system[4] was examined. As seen in Table 1, oxychelerythrine (**5**)[3a] was obtained in a higher yield using $^iPr_2NEt$ as base (see runs 1 and 2). Moreover, on applying the novel method to halo amides (**7b** and **7c**),[3a] both amides gave **5** in excellent yields (see runs 3-6 in Table 1).



Scheme 2

Next, triflate amide (**8a**) for synthesis of **4** was prepared as shown in Scheme 3. Thus, reaction of salicylaldehyde (**14**)[6] with Tf_2O followed by oxidation gave triflate acid (**10**), acid chloride of which was treated with **11b** to afford **8a**. Cyclization reaction of **8a** by the novel palladium-phosphine combination system provided oxynitidine (**6**)[3b] in an excellent yield (see run 1 in Table 2). Iodo amide (**8b**)[3b] also provided **6** in a high yield (see runs 2 and 3 in Table 2).

Synthetic samples (**5** and **6**) were identical with the authentic samples, which had already been converted to **1**[2a] and **4**[2c], respectively.



Scheme 3

Consequently, the novel combination system consisting of $Pd(OAc)_2$, DPPP, Bu_3P, and base was very efficient and powerful for an internal aryl-aryl coupling reaction involving not only triflate but halogen as a leaving group.

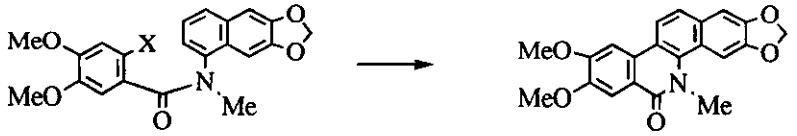
7a X=OTf
7b X=I
7c X=Br

5

Table 1. Results of Cyclization Reaction of 6-Substituted 2,3-Dimethoxy-*N*-methyl-*N*-(6,7-methylenedioxy-1-naphthyl)benzamide (**7**)[a] to Oxychelerythrine (**5**)

X	run	$Pd(OAc)_2$ (eq.)	ligand	Bu_3P (eq.)	base	time	yield (%) **5**
7a	1	1.0	DPPP	1.0	$^iPr_2NEt$	30 min	73
	2	1.0	DPPP	1.0	Ag_2CO_3	4 h	53[b]
7b	3	1.0	DPPP	1.0	$^iPr_2NEt$	15 min	85
	4	1.0	DPPP	1.0	Ag_2CO_3	15 min	95
7c	5	1.0	DPPP	1.0	$^iPr_2NEt$	30 min	79
	6	1.0	DPPP	1.0	Ag_2CO_3	30 min	89

a) All reaction were carried out using $Pd(OAc)_2$ and ligand in a molar ratio of 1 : 1 and 2 equivalents of base in DMF under reflux. b) Detriflyloxy amide (**7**, X=H) was obtained in 17% yield.



8a X=OTf
8b X=I

6

Table 2. Results of Cyclization Reaction of 6-Substituted 3,4-Dimethoxy-*N*-methyl-*N*-(6,7-methylenedioxy-1-naphthyl)benzamide (**8**)[a] to Oxynitidine (**6**)

X	run	$Pd(OAc)_2$ (eq.)	ligand	Bu_3P (eq.)	base	time	yield (%) **6**
8a	1	1.0	DPPP	1.0	$^iPr_2NEt$	30 min	93
8b	2	1.0	DPPP	1.0	$^iPr_2NEt$	30 min	94
	3	1.0	DPPP	1.0	Ag_2CO_3	30 min	88

a) All reaction were carried out using $Pd(OAc)_2$ and ligand in a molar ratio of 1 : 1 and 2 equivalents of base in DMF under reflux.

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