

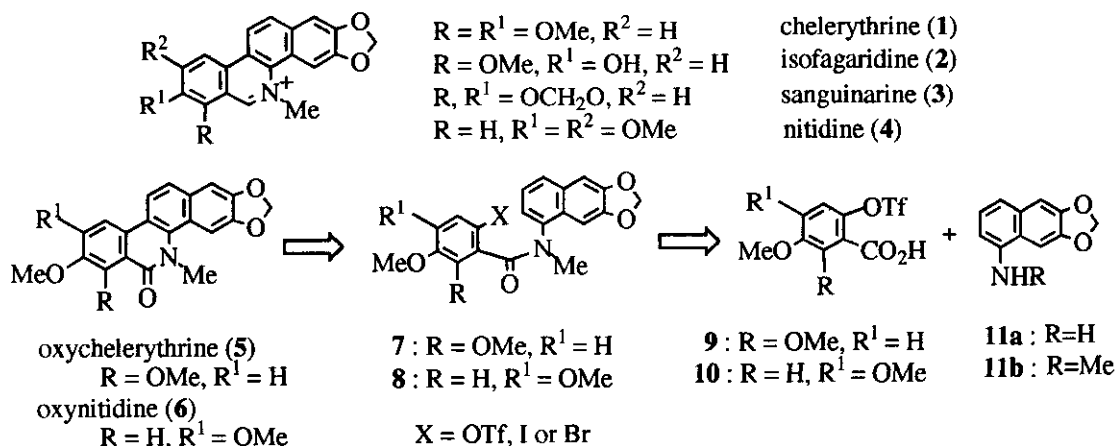
**SYNTHESIS OF BENZO[*c*]PHENANTHRIDINE ALKALOIDS,  
CHELERYTHRINE AND NITIDINE, USING A NOVEL  
PALLADIUM-PHOSPHINE COMBINATION SYSTEM  
–Pd(OAc)<sub>2</sub>, DPPP, AND Bu<sub>3</sub>P–**

Takashi Harayama,\* Toshihiko Akiyama, Yuichiro Nakano, and  
Kentaro Shibaie

*Faculty of Pharmaceutical Sciences, Okayama University, Tsushima-naka  
1-1-1, Okayama 700-8530, Japan*

**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)<sub>2</sub>, DPPP, and Bu<sub>3</sub>P. The present method was very versatile for coupling reaction not only between aromatic triflate and arene but also between aromatic halide and arene.

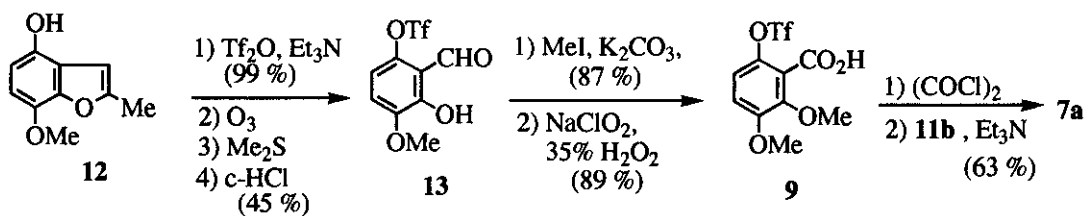
Fully aromatized benzo[*c*]phenanthridine alkaloids have attracted considerable attention because of their potent pharmacological and biological activities.<sup>1</sup> It was recently found that, among these alkaloids, chelerythrine (1),<sup>1e</sup> isofagaridine (2),<sup>1d</sup> and sanguinarine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



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.<sup>3</sup> 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)<sub>2</sub>, DPPP [1,3-bis-(diphenylphosphino)propane] and Bu<sub>3</sub>P for this purpose.<sup>4</sup> Moreover, this method was proven to be effective not only for the triflate group but also the halogen group as a leaving group.<sup>4</sup> In this communication, we describe the total synthesis of **1** and **4** using this novel method.

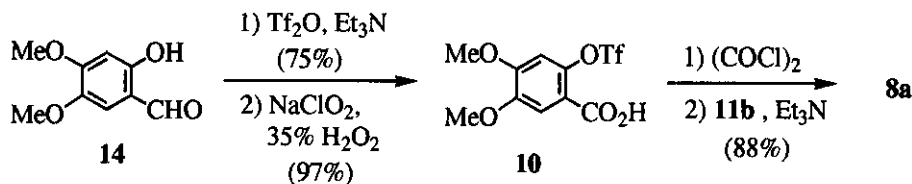
We designed a common synthesis plan for **1** and **4** as shown in Scheme 1. The monomethylnaphthylamine (**11b**) was synthesized from 1-naphthylamine (**11a**)<sup>3a</sup> in a 75% total yield *via* trifluoroacetylation, *N*-methylation with MeI in the presence of NaH, and hydrolysis with alkaline. Triflate acid (**9**) for synthesis of **1** was prepared as shown in Scheme 2. Thus, reaction of benzofuran (**12**)<sup>5</sup> with Tf<sub>2</sub>O and successive treatment with ozone, Me<sub>2</sub>S 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<sup>4</sup> was examined. As seen in Table 1, oxchelerythrine (**5**)<sup>3a</sup> was obtained in a higher yield using <sup>i</sup>Pr<sub>2</sub>NEt as base (see runs 1 and 2). Moreover, on applying the novel method to halo amides (**7b** and **7c**),<sup>3a</sup> both amides gave **5** in excellent yields (see runs 3-6 in Table 1).



Scheme 2

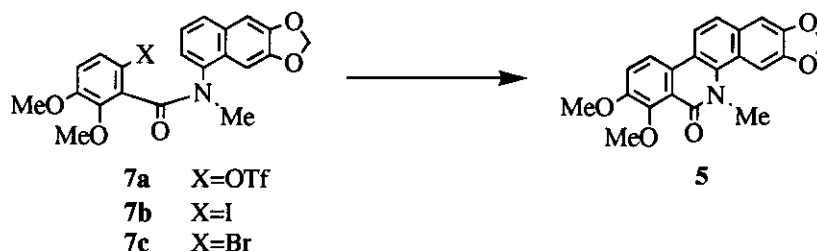
Next, triflate amide (**8a**) for synthesis of **4** was prepared as shown in Scheme 3. Thus, reaction of salicylaldehyde (**14**)<sup>6</sup> with Tf<sub>2</sub>O followed by oxidation gave triflate acid (**10**), acid chloride of which was treated with **11b** to afford **8a**. Cyclization reaction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



Scheme 3

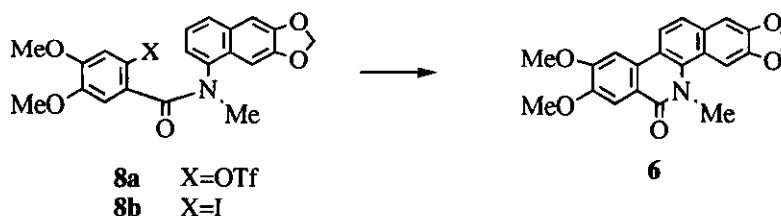
Consequently, the novel combination system consisting of  $\text{Pd}(\text{OAc})_2$ , DPPP,  $\text{Bu}_3\text{P}$ , and base was very efficient and powerful for an internal aryl-aryl coupling reaction involving not only triflate but halogen as a leaving group.



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

X	run	$\text{Pd}(\text{OAc})_2$ (eq.)	ligand	$\text{Bu}_3\text{P}$ (eq.)	base	time	yield (%)
							<b>5</b>
<b>7a</b>	1	1.0	DPPP	1.0	<sup>i</sup> Pr <sub>2</sub> NEt	30 min	73
	2	1.0	DPPP	1.0	Ag <sub>2</sub> CO <sub>3</sub>	4 h	53 <sup>b</sup>
<b>7b</b>	3	1.0	DPPP	1.0	<sup>i</sup> Pr <sub>2</sub> NEt	15 min	85
	4	1.0	DPPP	1.0	Ag <sub>2</sub> CO <sub>3</sub>	15 min	95
<b>7c</b>	5	1.0	DPPP	1.0	<sup>i</sup> Pr <sub>2</sub> NEt	30 min	79
	6	1.0	DPPP	1.0	Ag <sub>2</sub> CO <sub>3</sub>	30 min	89

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



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

X	run	$\text{Pd}(\text{OAc})_2$ (eq.)	ligand	$\text{Bu}_3\text{P}$ (eq.)	base	time	yield (%)
							<b>6</b>
<b>8a</b>	1	1.0	DPPP	1.0	<sup>i</sup> Pr <sub>2</sub> NEt	30 min	93
<b>8b</b>	2	1.0	DPPP	1.0	<sup>i</sup> Pr <sub>2</sub> NEt	30 min	94
	3	1.0	DPPP	1.0	Ag <sub>2</sub> CO <sub>3</sub>	30 min	88

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

## ACKNOWLEDGEMENTS

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## REFERENCES

- 1 a) V. Simanek, "The Alkaloids," Vol. 26, ed. by Brossi A., Academic Press. Inc., New York, 1983, pp. 185–240; b) J. Dostal and M. Potacek, *Coll. Czech. Chem. Commun.*, 1990, **55**, 2840; c) W. M. Suffiness and G. A. Gordell, "The Alkaloids," Vol. 25, ed. by Brossi A., Academic Press. Inc., New York, 1983, pp. 178–188; d) S. -D. Fang, L. -K. Wang, and S. M. Hecht, *J. Org. Chem.*, 1993, **58**, 5025; e) J. M. Herert, J. M. Augereau, J. Gleye, and J. P. Maffrand, *Biochem. Biophys. Res. Commun.*, 1990, **172**, 993; f) C. Vavreckova, I. Gawlik, and K. Müller, *Planta Medica*, 1995, **62**, 397; g) *Idem, ibid.*, 1996, **62**, 491; h) T. Schmeller, B. Latz-Bruning, and M. Wink, *Phytochemistry*, 1997, **44**, 257.
- 2 Reviews: a) I. Ninomiya and T. Naito, *Recent Dev. Chem. Nat. Carbon Comp.*, 1984, **10**, 9; b) H. Ishii, Y. Ichikawa, E. Kawanabe, M. Ishikawa, T. Ishikawa, K. Kuretani, M. Inomata, and A. Hoshi, *Chem. Pharm. Bull.*, 1985, **33**, 4139. Recent papers for synthesis of benzo[c]phenanthridine alkaloids: c) M. Hanaoka, H. Yamagishi, M. Marutani, and C. Mukai, *Chem. Pharm. Bull.*, 1987, **35**, 2348 and references cited therein; d) J. H. Rigby and D. D. Holsworth, *Tetrahedron Lett.*, 1991, **32**, 5757; e) G. Martin, E. Guitian and L. Castedo, *J. Org. Chem.*, 1992, **57**, 5907; f) D. Perez, E. Guitian, and L. Castedo, *J. Org. Chem.*, 1992, **57**, 5911; g) D. Seraphin, M. A. Lynch, and O. Duval, *Tetrahedron Lett.*, 1995, **36**, 5731; h) T. Minami, A. Nishimoto, and M. Hanaoka, *Tetrahedron Lett.*, 1995, **36**, 9505 and references cited therein; i) M. A. Lynch, O. Duval, P. Pochet, and R. D. Waigh, *Bull. Soc. Chim. Fr.*, 1994, **131**, 718; j) T. A. Olugbade, R. D. Waigh, and S. P. Mackay, *J. Chem. Soc., Perkin Trans. 1*, 1990, 2657; k) S. V. Kessar, Y. P. Gupta, P. Balakishnan, K. K. Sawal, T. Mohammad, and M. Dutt, *J. Org. Chem.*, 1988, **53**, 1708; l) G. R. Geen, I. S. Mann, M. Mullane, and A. McKillop, *J. Chem. Soc., Perkin Trans. 1*, 1996, 1647; m) J. Smidrkal, *Coll. Czech. Chem. Commun.*, 1984, **49**, 1412; n) M. Hanaoka, T. Motonishi, and C. Mukai, *J. Chem. Soc., Perkin Trans. 1*, 1986, 2253; o) H. Ishii, T. Ishikawa, S. Takeda, M. Suzuki, and T. Harayama, *Chem. Pharm. Bull.*, 1992, **40**, 2002.
- 3 a) T. Harayama, T. Akiyama, and K. Kawano, *Chem. Pharm. Bull.*, 1996, **44**, 1634; b) T. Harayama and K. Shibaie, *Heterocycles*, 1998, **49**, in press.
- 4 T. Harayama, T. Akiyama and Y. Nakano, *Chem. Pharm. Bull.*, 1997, **45**, 1723.
- 5 H. Ishii, K. Kenmotsu, W. Döpke, and T. Harayama, *Chem. Pharm. Bull.*, 1992, **40**, 1770.
- 6 A. K. Sihakabu and R. T. Borchardt, *J. Org. Chem.*, 1983, **48**, 1941.

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