Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 46 (2005) 6823–6825
Tetrahedron Letters

# Palladium-catalyzed intramolecular γ-lactam formation of an aryl halide and an enolate: synthesis of isoindolobenzazepine alkaloids, lennoxamine, 13-deoxychilenine, and chilenine

Toshio Honda* and Yoshiaki Sakamaki

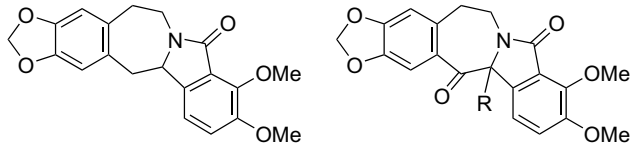
*Faculty of Pharmaceutical Sciences, Hoshi University, Ebara 2-4-41, Shinagawa, Tokyo 142-8501, Japan*

Received 19 July 2005; revised 29 July 2005; accepted 4 August 2005
Available online 19 August 2005

**Abstract**—A facile synthetic path to isoindolobenzazepine alkaloids, lennoxamine, 13-deoxychilenine, and chilenine, was established by employing a palladium-catalyzed intramolecular α-arylation of the ketone, as the key step.


Palladium-catalyzed intramolecular α-arylation of ketones, esters, and amides is recognized as one of the most promising procedures for constructing polycyclic compounds, including heterocycles.[1] Recently, we have demonstrated the versatility and utility of the methodology in the synthesis of isoquinoline alkaloids, chellyrine, and latifine, in which δ-lactam formation was involved, as a key step.[2] As part of our continuing exploration of palladium-catalyzed intramolecular carbon–carbon bond formation of aryl halides and enolates, we were interested in the synthesis of natural isoindolobenzazepine alkaloids, lennoxamine, 13-deoxychilenine, and chilenine, aiming at the construction of an isoindolobenzazepine ring by this reaction.

Lennoxamine **1**, 13-deoxychilenine **2**, and chilenine **3** were isolated from *Berbelis darwinii*,[3] *Berbelis actinacantha*,[4] and *Berbelis empetrifolia*[5] as racemic forms, respectively. Since these alkaloids have relatively simple structural features, a number of total syntheses of **1**[6] and **3**[6c,d,7] have been achieved by application of newly developed synthetic strategy and methodology. However, the synthesis of **2** has not been reported yet (Fig. 1).




**1.** Lennoxamine

**2.** 13-Deoxychilenine: R = H
**3.** Chilenine: R = OH

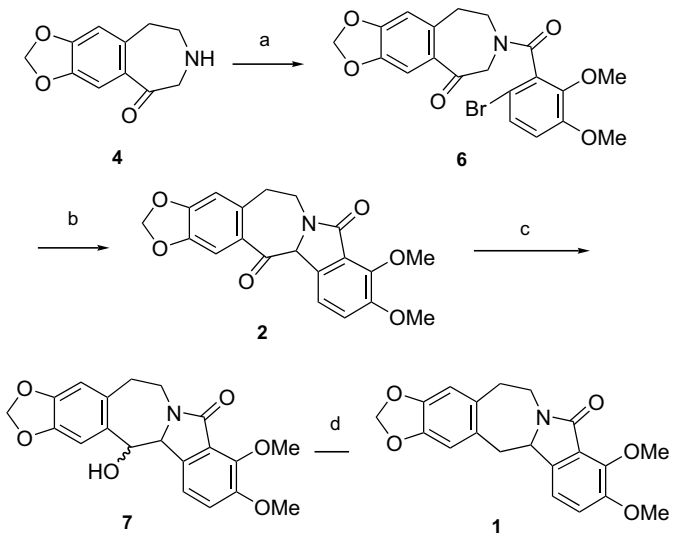
**Figure 1.** Structures of isoindolobenzazepine alkaloids.

Our synthesis of isoindolobenzazepine alkaloids starts from Schotten–Baumann acylation of the known benzazepinone derivative **4**[8] with 6-bromo-2,3-dimethoxybenzoyl chloride **5**[9] to afford the corresponding amide **6** in 91% yield. With screening of a variety of reaction conditions, such as the species of palladium catalysts, ligands, and solvents, for a palladium-catalyzed intramolecular α-arylation of **6**, we found proper reaction conditions for obtaining the desired cyclization product in reasonable yield, as follows (Scheme 1).

The Pd-catalyzed intramolecular coupling reaction of **6** in the presence of 5 mol % of $Pd_2(dba)_3{\cdot}CHCl_3$, 10 mol % of (±)-BINAP, and 1.5 equiv of KO*t*-Bu in refluxing dioxane proceeded smoothly to give the desired lactam **2** in 65% yield, together with a debromo-compound (18%). The spectroscopic data[10] of the synthesized compound **2**, mp 156–157 °C (lit.,[4] mp 156–157 °C), were identical with those reported in the literature.[4]

*Keywords*: Lennoxamine; 13-Deoxychilenine; Chilenine; Palladium-catalyzed intramolecular α-arylation; Isoindolobenzazepine alkaloid.
* Corresponding author. Tel.: +81 3 5498 5791; fax: +81 3 3787 0036; e-mail: honda@hoshi.ac.jp

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.08.025



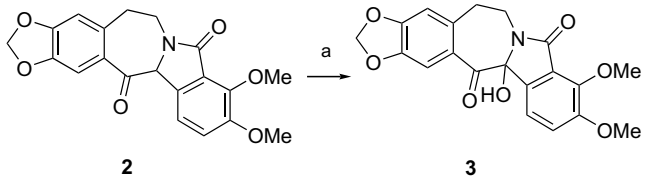

**Scheme 1.** Reagents and conditions: (a) 6-bromo-2,3-dimethoxybenzoyl chloride **5**, aq $NaHCO_3$, $Et_2O$, 0 °C (91%); (b) $Pd_2(dba)_3/CHCl_3$, BINAP, KO*t*-Bu, dioxane, reflux (65%); (c) $NaBH_4$, EtOH, rt; (d) $Et_3SiH$, $BF_3/OEt_2$, $CH_2Cl_2$, rt (67% from **2**).

Thus, we were able to establish the facile first synthesis of 13-deoxychilenine in short steps. Although the coupling reaction was carried out in the presence of chiral ligand (*S*)-BINAP under the same reaction conditions as above, directed at its chiral synthesis, the product was found to be racemate, probably due to the presence of the easily enolizable benzylic ketone in the cyclization product **2**.[10]

In order to establish the synthesis of lennoxamine, the 13-deoxychilenine **2** was converted to the alcohol **7** on reduction with sodium borohydride. Further reduction of **7** with triethylsilane in the presence of boron trifluoride etherate furnished lennoxamine **1** in 67% yield from **2**. The spectroscopic data of **1**, mp 228–229 °C (lit.,[11] mp 228–229 °C), were identical with those reported in the literature[6d,10] (Scheme 2).

Synthesis of chilenine **3** was also achieved by direct oxidation of 13-deoxychilenine **2** with Davis' reagent [racemic 3-phenyl-2-(phenylsulfonyl)oxaziridine] in the presence of sodium hexamethyldisilazide, as the base, in 95% yield. Again, the spectroscopic data of **3**, mp 157–158 °C (lit.,[6d] mp 157–158 °C), were identical with those reported in the literature.[6d]

In summary, we were able to establish the concise synthesis of isoindolobenzazepine alkaloids, lennoxamine **1**, 13-deoxychilenine **2**, and chilenine **3**, by employing palladium-catalyzed intramolecular α-arylation of the ketone **6** as the key step. The strategy developed here provides a further useful example of the palladium-catalyzed coupling reaction of aryl halides with enolates, and seems to be widely applicable to the synthesis of a number of biologically active compounds, including natural products.




**Scheme 2.** Reagents and conditions: (a) Davis reagent (4 equiv), NaHMDS, THF, −78 °C to rt (95%).

## Acknowledgments

This work was supported in part by a grant from the Ministry of Education, Culture, Sports, Science, and Technology of Japan.

## References and notes

1. Reviews, see: (a) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234–245; (b) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127–2198. For the Pd-catalyzed intramolecular coupling of aryl halides and enolates, see: (c) Muratake, H.; Natsume, M. *Tetrahedron Lett.* **1997**, *38*, 7581–7582; (d) Shaughnessy, K. H.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1998**, *63*, 6546–6553; (e) Muratake, H.; Nakai, H. *Tetrahedron Lett.* **1999**, *40*, 2355–2358. For the Pd-catalyzed intermolecular coupling of aryl halides and enolates, see: (f) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360–1370, and references cited therein.
2. Honda, T.; Namiki, H.; Satoh, F. *Org. Lett.* **2001**, *3*, 631–633.
3. Valencia, E.; Freyer, A. J.; Shamma, M.; Fajardo, V. *Tetrahedron Lett.* **1984**, *25*, 599–602.
4. Valencia, E.; Weiss, I.; Firdous, S.; Freyer, A. J.; Shamma, M. *Tetrahedron* **1984**, *40*, 3957–3962.
5. Fajardo, V.; Elango, V.; Cassels, B. K.; Shamma, M. *Tetrahedron Lett.* **1982**, *23*, 39–42.
6. Recent synthesis of (+)- and racemic lennoxamine, see: (a) Comins, D. L.; Schilling, S.; Zhang, Y. *Org. Lett.* **2005**, *7*, 95–98; (b) Sahakitpichau, R.; Ruchirawat, S. *Tetrahedron* **2004**, *60*, 4169–4172; (c) Kim, G.; Kim, J. H.; Kim, W.-j.;

Kim, Y. A. *Tetrahedron Lett.* **2003**, *44*, 8207–8209; (d) Koseki, Y.; Katsura, S.; Kusano, S.; Sakata, H.; Sato, H.; Monzene, Y.; Nagasaka, T. *Heterocycles* **2003**, *59*, 527–540; (e) Fuchs, J. R.; Funk, R. L. *Org. Lett.* **2001**, *3*, 3923–3925, and references cited therein.

7. Recent synthesis of chilenine, see: (a) Yoda, H.; Inoue, K.; Ujihara, Y.; Mase, N.; Tanabe, K. *Tetrahedron Lett.* **2003**, *44*, 9057–9060; (b) Yoda, H.; Nakahara, A.; Koketsu, T.; Tanabe, K. *Tetrahedron Lett.* **2002**, *43*, 4667–4669; (c) Koseki, Y.; Kusano, S.; Sakata, H.; Nagasaka, T. *Tetrahedron Lett.* **1999**, *40*, 2169–2172; (d) Kessar, S. V.; Singh, T.; Vohra, R. *Indian J. Chem. Sec. B* **1991**, *30B*, 299–301; (e) Ishibashi, H.; Kawanami, H.; Iriyama, H.; Ikeda, M. *Tetrahedron Lett.* **1995**, *36*, 6733–6734; (f) Fang, F. G.; Danishefsky, S. J. *Tetrahedron Lett.* **1989**, *30*, 2747–2750.
8. Zhao, Y.; Xi, S.; Song, A.; Ji, G. *J. Org. Chem.* **1984**, *49*, 4549–4551.
9. Kametani, T.; Sugai, T.; Shoji, Y.; Honda, T.; Satoh, F.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1151–1155.
10. Selected data for **2**: mp 156–157 °C; $^{1}$H NMR (270 MHz, $CDCl_3$) $\delta$: 3.00 (ddd, 1H), 3.39 (ddd, 1H), 3.57 (ddd, 1H), 3.83 (s, 3H), 3.92 (s, 3H), 4.15 (ddd, 1H), 4.72 (s, 1H), 5.93 (d, 1H), 5.95 (d, 1H), 6.65 (s, 1H), 6.74 (s, 1H), 6.98 (d, 1H), 7.40 (d, 1H); $^{13}$C NMR (67.5 MHz, $CDCl_3$) $\delta$: 30.92, 37.85, 56.30, 62.31, 90.38, 101.74, 108.66, 109.41, 116.29, 119.41, 122.57, 129.92, 133.76, 135.58, 145.71, 146.71, 151.31, 153.85, 166.10, 201.96; IR (thin film) 1690, 1610 $cm^{-1}$; HRMS *m/z* (EI): calcd for $C_{20}H_{17}NO_6$ ($M^+$) 367.1056. Found 367.1043.
11. (a) Teitel, S.; Klötzer, W.; Borgese, J.; Brossi, A. *Can. J. Chem.* **1972**, *50*, 2022–2024; (b) Napolitano, E.; Spinelli, G.; Fiaschi, R.; Marsili, A. *J. Chem. Soc., Perkin Trans. 1* **1986**, 785–787.