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TOTAL SYNTHESIS OF ISOINDOLOBENZAZEPINE ALKALOIDS, LENNOXAMINE AND CHILENINE, BASED ON PALLADIUM-CATALYZED REDUCTION OF ALKENYL PHOSPHATES

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Dedicated to Professor Ryoji Noyori on the occasion of his 70th birthday.

Abstract – An efficient method for the synthesis of enol ethers and enecarbamates has been developed based on palladium(0)-catalyzed chemoselective reduction of alkenyl phosphates. This method has been applied successfully to the total synthesis of two isoindolobenzazepine alkaloids, lennoxamine and chilenine.

INTRODUCTION

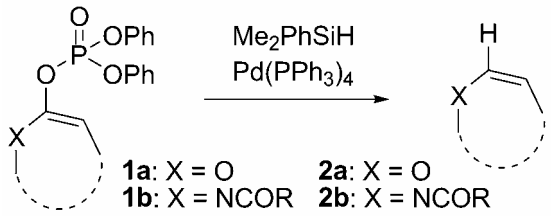
The significance of palladium-catalyzed reactions in modern organic synthesis is well recognized by virtue of their exceptional ability to build up complex molecules, remarkable functional group tolerance and chemoselectivity, and mild reaction conditions.[1] Alkenyl trifluoromethanesulfonates (triflates) have successfully expanded the scope of palladium-catalyzed reactions because of their easy accessibility from the parent phenolic or carbonyl compounds and their sufficient reactivity. At the same time, however, the instability of alkenyl triflates is sometimes problematic, especially in the case of α-heteroatom substituted alkenyl triflates. In general, α-heteroatom substituted alkenyl triflates are difficult to isolate by aqueous workup and to purify by silica gel chromatography, because they are readily hydrolyzed or decomposed during these manipulations. The unstable nature of alkenyl triflates becomes even more problematic when a palladium-catalyzed reaction necessitates an elevated reaction temperature and/or the addition of a base (e.g., Suzuki-Miyaura reaction,[2] Sonogashira reaction[3]). Additionally, preparation of alkenyl triflates requires expensive reagents such as trifluromethanesulfonic anhydride or *N*-phenyl bis(trifluoromethanesulfonyl)imide. In contrast, alkenyl phosphates are more stable and easier-to-handle

than their triflate counterparts, so they can be easily isolated by aqueous workup and purified by silica gel chromatography. Furthermore, alkenyl phosphates can be synthesized using less expensive reagents such as diphenylphosphoryl chloride. These features of alkenyl phosphates make them attractive alternatives to the triflate counterparts as electrophiles in palladium-catalyzed reactions. However, after pioneering works by Oshima and co-workers,[4] little attention was paid to the application of palladium-catalyzed reactions of alkenyl phosphates in organic synthesis until Nicolaou and co-workers demonstrated their power and usefulness in the context of heterocyclic chemistry in the late 1990s.[5,6]

Since the development of a convergent strategy for the synthesis of marine polycyclic ether natural products based on Suzuki-Miyaura coupling of lactone-derived enol phosphates,[7-9] we have been interested in expanding the scope of palladium-catalyzed reactions of alkenyl phosphates.[10] In this paper, we describe an efficient method for the synthesis of enol ethers and enecarbamates based on palladium(0)-catalyzed hydrosilane reduction of alkenyl phosphates and its application to the total synthesis of two isoindolobenzazepine alkaloids, lennoxamine[11] and chilenine.[12,13]

RESULTS AND DISCUSSION

Stille and co-workers have reported that alkenyl triflates can be reduced to the corresponding alkenes under the influence of a palladium(0) catalyst and a hydride source such as Et_3SiH or *n*-Bu_3SnH.[14] Meanwhile, Greene et al. have described a palladium-catalyzed reduction of α-alkoxy-substituted alkenyl phosphates using triethylaluminum, giving the corresponding enol ethers in moderate to good yields.[15,16] We envisioned that α-heteroatom-substituted alkenyl phosphates **1a** and **1b** can be reduced with a combination of a hydrosilane and a palladium(0) catalyst under neutral conditions to deliver the corresponding enol ether **2a** and enecarbamate **2b**, respectively (Scheme 1).

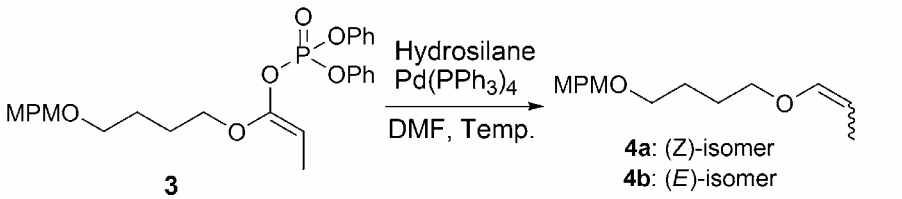


Scheme 1. Concept of the present work

We first investigated the reduction of alkenyl phosphate **3**, which was derived from the corresponding ester by treatment with LDA followed by diphenylphosphoryl chloride. Reduction of **3** was examined under a variety of conditions, and the results are summarized in Table 1. Upon exposure of **3** to 5 equiv of Et_3SiH and 10 mol% of $Pd(PPh_3)_4$ in DMF at 60 °C, an approximately 2:1 mixture of enol ethers **4a** and **4b** was isolated in 86% combined yield (entry 1). Among the hydrosilanes examined, Me_2PhSiH turned

was isolated in 86% combined yield (entry 1). Among the hydrosilanes examined, Me_2PhSiH turned out to be the best hydride source. Thus, treatment of **3** with 5 equiv of Me_2PhSiH and 10 mol% of $Pd(PPh_3)_4$ (DMF, 60 °C) provided a ca 5.6:1 mixture of **4a,b** in 89% combined yield (entry 2). When the reaction was performed using Me_2PhSiH at room temperature, further improvement of the stereoselectivity was attained, although the net yield decreased (entry 3). The use of $MePh_2SiH$, Ph_3SiH, or Ph_2SiH_2 resulted in significant isomerization of the double bond (entries 4-6), while $(Me_3Si)_3SiH$ was found to be ineffective (entry 7). We have also attempted to utilize *n*-Bu_3SnH, which is one of the effective hydride sources in palladium(0)-catalyzed reduction of alkenyl triflates.[14] However, we found that homocoupling of *n*-Bu_3SnH predominates over the reduction of **3**. *n*-Bu_3GeH was likewise ineffective. In addition, the addition of inorganic salts, such as lithium chloride or copper(I) iodide, was examined, but these additives completely retarded the reaction.[17] We have also screened several catalysts including, $Pd(PPh_3)_4$, $Pd(OAc)_2$/tri(2-furyl)phosphine, $Pd(OAc)_2$/tricyclohexylphosphine, and $Pd(OAc)_2$/(*o*-dicyclohexylphosphino)biphenyl, and found that $Pd(PPh_3)_4$ was the catalyst of choice for the present reaction.

Table 1. Optimization of reaction conditions[a]



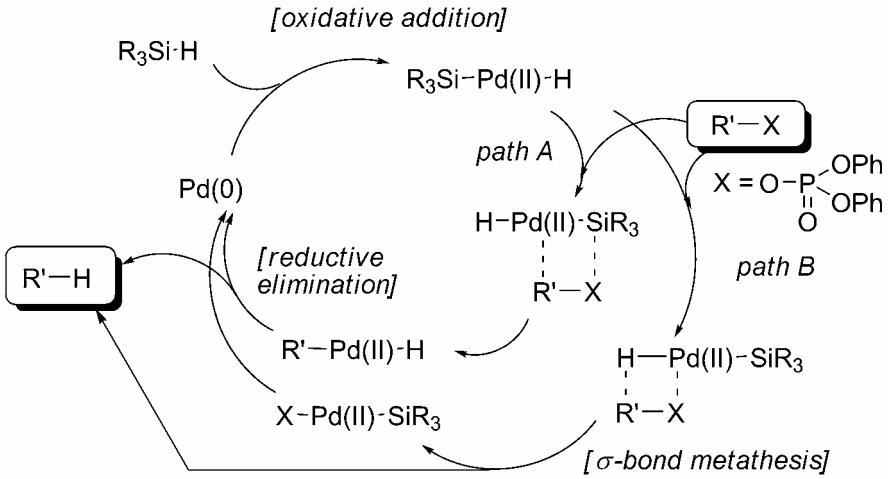
3

Entry	Hydrosilane	Solid angle (deg)	*D* (Si-H) (kJ mol^{-1})	Temp. (°C)	Yield (%)	*Z*:*E*[b]
1	Et_3SiH	132	398.0	60	86	2.0:1
2	Me_2PhSiH	122	364.0	60	89	5.6:1
3	Me_2PhSiH	122	364.0	rt	70	9.1:1
4	$MePh_2SiH$	136	359.2	60	78	2.5:1
5	Ph_3SiH	145	354.8	60	87	1.3:1
6	Ph_2SiH_2		377.8	60	89	1.4:1
7	$(Me_3Si)_3SiH$	182	351.0	60	trace	N/A

[a]All reactions were carried out using hydrosilane (5 equiv) and $Pd(PPh_3)_4$ (10 mol%) in DMF. [b]The ratio of isomers was determined by ^1H NMR (500 MHz) of a purified mixture of **4a,b**.

A plausible reaction mechanism of the present reaction precedents is summarized in Scheme 2.[18] The catalytic cycle starts with the oxidative addition of a hydrosilane (R_3SiH) into a palladium(0) complex to generate a R_3Si—Pd(II)—H intermediate. Two possible pathways, A and B, can be considered for association of the intermediate with R'—X and subsequent σ-bond metathesis. Reductive elimination

finally provides the product R'—H and regenerates the initial palladium(0) complex. Another catalytic cycle involving the oxidative addition of R'—X into a palladium(0) complex, transmetallation of the resultant R'—Pd(II)—X with hydrosilane, and reductive elimination may also be considered. We could not rule out the possibility of the latter catalytic cycle operating in the present reaction. However, Masuda and co-workers have shown that the oxidative addition of a Si—H bond into a palladium(0) complex must be the key for the catalytic silylation of aryl iodides with triethoxysilane.[18c] We postulated that this is also the case with our reaction. The observed stereochemical scrambling of the double bond of **3** can be explained by re-addition of the R_3Si—Pd(II)—H intermediate to the product followed by elimination. Interestingly, it seems that the degree of isomerization of the double bond of **3** moderately correlates with the steric property of the hydrosilanes,[19] except for Ph_2SiH_2. The ratio of **4a**/**4b** decreases with the increase in the steric bulkiness of the hydrosilanes (Me_2PhSiH > $MePh_2SiH$, Et_3SiH > Ph_3SiH). On the other hand, the bond strength of the hydrosilanes (dissociation energy of Si—H bonds (*D* (Si—H))[20] does not correlate with the observed stereoselectivity.

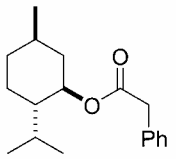
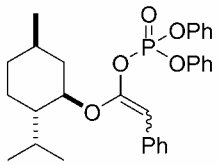
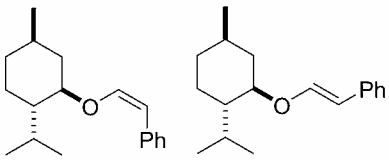
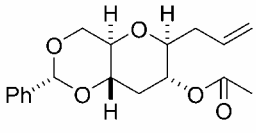
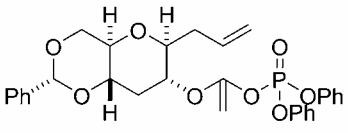
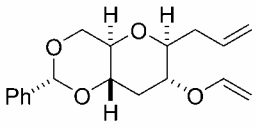
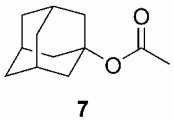
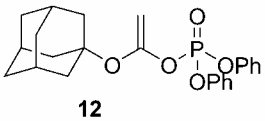
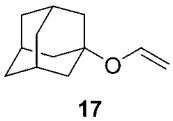
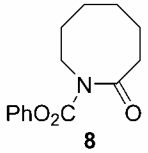
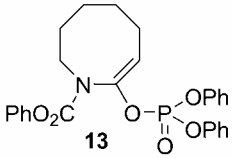
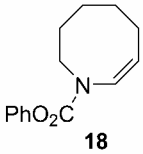
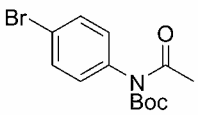
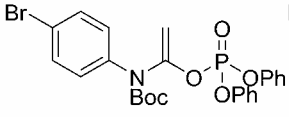
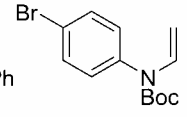
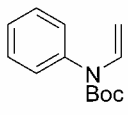


Scheme 2. A proposed reaction mechanism

We next applied the optimized conditions to the reduction of a variety of α-heteroatom substituted alkenyl phosphates (**10a,b-14**) readily derived from the corresponding esters and imides (**5-9**). The results are summarized in Table 2. When an approximately 1:1 mixture of **10a** and **10b** was reduced with Me_2PhSiH in the presence of $Pd(PPh_3)_4$ in DMF at 60 °C, selective reduction of the sterically less encumbered (*E*)-isomer **10a** took place to give (*Z*)-enol ether **15a** in 36% yield along with (*E*)-enol ether **15b** in 9% yield, while (*Z*)-isomer **10b** was recovered in 43% yield (entry 1). The less reactive **10b** was reduced by elevating the reaction temperature to 135 °C, giving **15a** in 58% yield and **15b** in 19% yield (entry 2). Alkenyl phosphate **11** derived from acetate **6** was elaborated to vinyl ether **16** in 82% yield with no sign of potentially competitive intramolecular Heck cyclization of **11** (entry 3). Sterically hindered

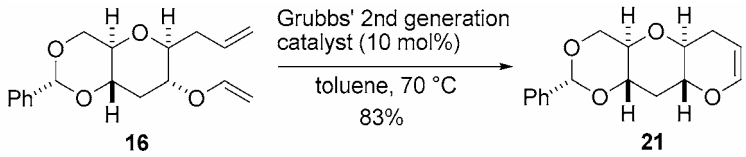
alkenyl phosphate **12** was also reduced to vinyl ether **17**[21] in good yield (entry 4). The endocyclic alkenyl phosphate **13**, prepared from medium-sized lactam **8**, was efficiently transformed to endocyclic enecarbamate **18** (entry 4). We observed an interesting chemoselectivity between aryl bromide and alkenyl phosphate functionalities when the reaction of alkenyl phosphate **14** was carried out in DMF at 60 °C. Under these conditions, a mixture of enecarbamates **19** (55%) and **20** (11%) was produced, which were readily separable by silica gel flash chromatography. This result suggested that our method is able to reduce an alkenyl phosphate in the presence of an aryl bromide. Eventually, we found that chemoselective reduction of **14** could be achieved by performing the reaction at room temperature, affording **19** in 73% yield. This unexpected chemoselectivity of the reduction was successfully applied to the total synthesis of isoindolobenzazepine alkaloid natural products (*vide infra*). In some cases, a small amount (~5%) of the corresponding over-reduced product was also detected, although the mechanism underlying its formation remains elusive.[22]

Table 2. Application to a variety of substrates[a]

Entry	Substrate	Alkenyl phosphate	Product(s)	%Yield
1	 **5**	 **10a** (*E*) : **10b** (*Z*) = *ca.*1:1	 **15a** **15b**	**15a**: 36 **15b**: 9[d]
2[b]				**15a**: 58 **15b**: 19
3	 **6**	 **11**	 **16**	82
4	 **7**	 **12**	 **17**	63
5	 **8**	 **13**	 **18**	68
6	 **9**	 **14**	 **19**  **20**	**19**: 55 **20**: 11
7[c]				**19**: 73

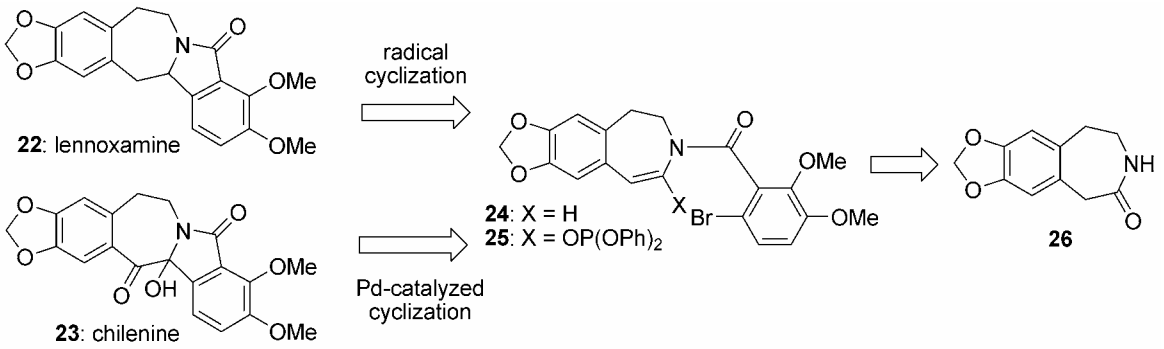
[a]Reaction conditions: (i) KHMDS, $(PhO)_2P(O)Cl$, THF/HMPA, −78 °C; (ii) Me_2PhSiH (5 equiv), $Pd(PPh_3)_4$ (10 mol%), DMF, 60 °C. [b]The reaction was performed at 135 °C. [c]The reaction was performed at room temperature. [d]**10b** was recovered in 43% yield.

The vinyl ether **16**, for example, is a versatile intermediate for the synthesis of polycyclic ethers (Scheme 3). Treatment of **16** with 10 mol% of the Grubbs' second generation catalyst in toluene at 70 °C smoothly delivered dihydropyran **21** in 83% yield.[23] Thus, our method for the synthesis of enol ethers coupled with ring-closing metathesis may constitute an efficient entry to marine polycyclic ether natural products.[24,25]



Scheme 3. Ring-closing metathesis of enol ether **16**

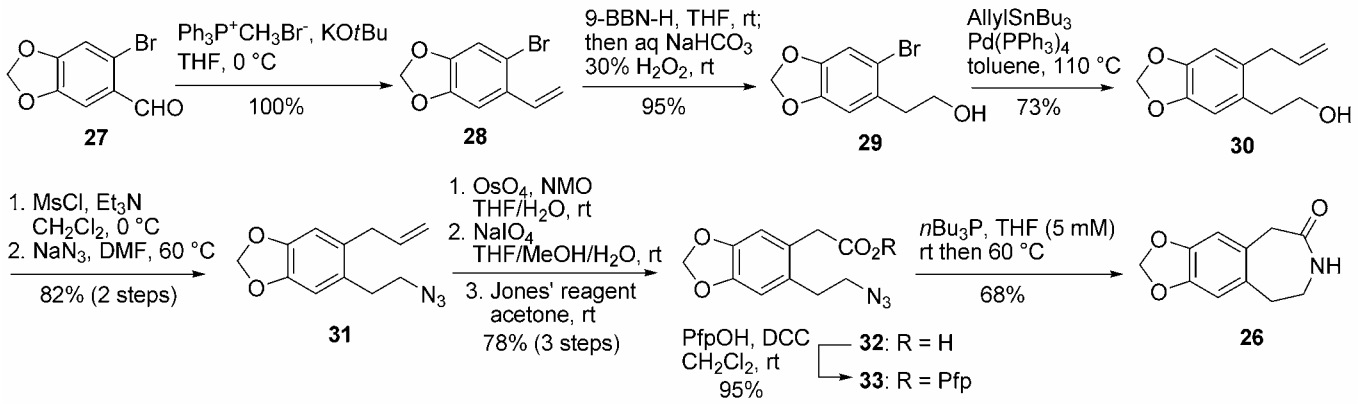
Finally, we applied our method to the total synthesis of lennoxamine[11] and chilenine,[12] isoindolobenzazepine alkaloids isolated from Chilean barberries *Berberis darwinii* and *Berberis empetrifolia*, respectively. Due to their intriguing structures, these natural products are continuously attracting the attention of organic chemists, and a number of synthetic efforts to synthesize them have been reported to date.[26,27] We envisioned that isoindolinone moieties of **22** and **23** could be constructed by radical cyclization[28] and palladium-catalyzed cyclization,[29] respectively, from a common intermediate, i.e., enamide **24**. In turn, we planned to prepare the enamide **24** based on chemoselective reduction of alkenyl phosphate **25**, which in turn could be derived from seven-membered lactam **26**.



Scheme 4. Synthesis plan for isoindolobenzazepine alkaloid natural products, lennoxamine and chilenine, via a common intermediate **24**

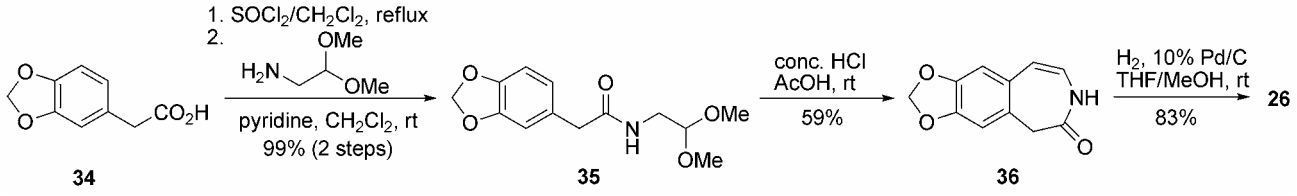
Our first approach toward lactam **26** featured an intramolecular Staudinger-aza-Wittig cyclization of ω-azido pentafluorophenyl (pfp) ester **33** (Scheme 5).[30] Wittig methylenation of 6-bromopiperonal **27** gave olefin **28** in quantitative yield. Hydroboration of **28** using 9-BBN-H afforded alcohol **29** in 95% yield. Stille coupling of **29** with allyl tri-*n*-butyltin in the presence of $Pd(PPh_3)_4$ in toluene at 110 °C led to olefin **30** in 73% yield, which was converted to azide **31** via the corresponding mesylate in 82% yield for the two steps. Oxidative cleavage of the double bond, followed by Jones oxidation of the derived

aldehyde, led to acid **32** in 78% yield for the three steps. Coupling of **32** with pentafluorophenol using DCC delivered pentafluorophenyl ester **33**. Treatment of **33** with tri-*n*-butylphosphine in THF (5 mM, room temperature then 60 °C) directly afforded lactam **26** in 68% yield. On the other hand, when the reaction was performed in toluene (10 mM, 100 °C), a complex mixture of products was obtained, from which the desired lactam **26** was isolated in only 20% yield.



Scheme 5. Synthesis of lactam **26** via an intramolecular Staudinger-aza-Wittig cyclization

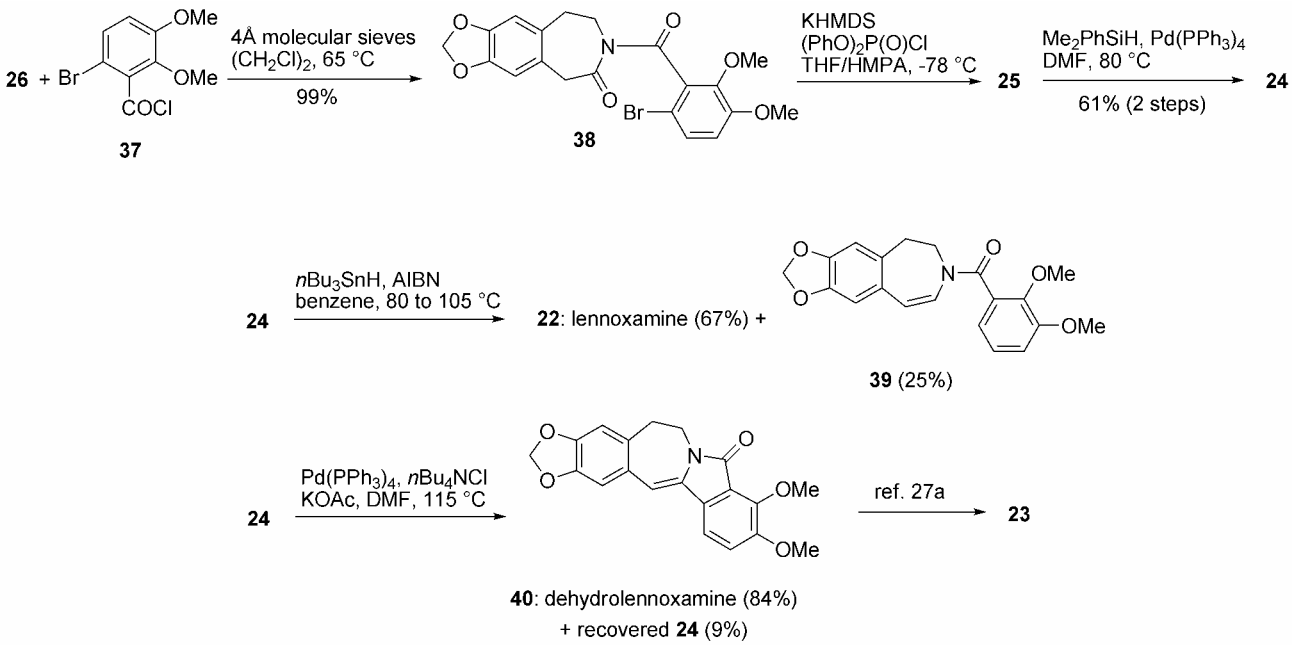
We have also examined the synthesis of lactam **26** employing a Pomeranz-Fritsch-type cyclization[31] of amide **35** as a key step (Scheme 6). Treatment of 3,4-methylenedioxyphenylacetic acid **34** with thionyl chloride, followed by condensation with aminoacetaldehyde dimethylacetal, provided amide **35** in 99% yield (two steps). Exposure of **35** to concentrated HCl in AcOH at room temperature gave enamide **36** in moderate yield. Hydrogenation of the double bond within **36** afforded lactam **26** in 83% yield. Thus, the benzazepine framework was expeditiously constructed in just four steps from a commercially available material.



Scheme 6. Synthesis of lactam **26** via an acid-mediated cyclization of **35**

Completion of the total synthesis of **22** and **23** is illustrated in Scheme 7. Although *N*-acylation of **26** using 2-bromo-5,6-dimethoxybenzoyl chloride **37** and a base such as *n*-BuLi, LHMDS, or NaH was ineffective in our hands, treatment of **26** with **37** in the presence of molecular sieves in 1,2-dichloroethane at 65 °C cleanly provided the desired imide **38** in an almost quantitative yield. Enolization of **38** with KHMDS in the presence of $(PhO)_2P(O)Cl$ gave alkenyl phosphate **25**, which, without purification, was

reacted with $Me_2PhSiH/Pd(PPh_3)_4$ in DMF at 85 °C to furnish enamide **24** in 61% yield for the two steps. According to Funk's procedure,[26i] exposure of **24** to *n*-Bu_3SnH in the presence of AIBN in refluxing benzene delivered lennoxamine **22** in 67% yield along with **39**[26i] in 25% yield. The spectroscopic data (^1H, ^{13}C NMR, HRMS) as well as the melting point of synthetic **22** were in full accordance with those reported in the literature.[26m] Thus, the total synthesis of lennoxamine **22** was efficiently achieved in seven steps from **34** (20% overall yield). On the other hand, palladium(0)-catalyzed cyclization of **24** afforded dehydrolennoxamine **40** in 84% yield (recovered starting material, 9%). The spectroscopic data (^1H, ^{13}C NMR, HRMS) and melting point of synthetic **40** matched the reported data.[26m] Since the transformation of **39** into chilenine **23** has been reported by Danishefsky and Fang,[27a] the present synthesis constitutes a formal total synthesis of this natural product (seven steps, 25% overall yield).



Scheme 7. Completion of the total synthesis of lennoxamine and chilenine

In conclusion, we have demonstrated that the palladium-catalyzed reduction of α-heteroatom-substituted alkenyl phosphates using Me_2PhSiH as a hydride source efficiently provides enol ethers and enecarbamates in good to excellent yields. Our method has been applied successfully to the total synthesis of two isoindolobenzazepine alkaloids, lennoxamine and chilenine, based on its useful level of chemoselectivity. Further studies on the exploitation of palladium-catalyzed reactions of alkenyl phosphates are currently underway and will be reported in due course.

EXPERIMENTAL

General remarks. All reactions sensitive to moisture and/or air were carried out under a slightly positive

pressure of argon using oven-dried glassware unless otherwise noted. Anhydrous tetrahydrofuran (THF), dichloromethane (CH_2Cl_2) and *N*,*N*-dimethylformamide (DMF) were purchased from Kanto Chemical Co., Inc. and used as received. Hexamethylphosphoramide (HMPA) was distilled over calcium hydride under reduced pressure. Tetrakis(triphenylphosphine)palladium(0) was prepared according to the procedure (D. R. Coulson, *Inorg. Synth.*, 1972, **13**, 121.). All other chemicals were purchased at highest commercial grade and used as received. Analytical thin-layer chromatography was performed using Merck pre-coated analytical plates, 0.25 mm-thickness, silica gel 60 F254. Flash column chromatography was carried out using Fuji Silysia silica gel BW-300 (200-400 mesh). Preparative HPLC was performed on Japan Analytical Industries, Co. Ltd. LC-9201 system. Melting points were measured on a Yanagimoto melting points apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity INOVA-500 spectrometer. Chemical shift values were reported in δ (ppm) downfield from tetramethylsilane with reference to internal residual solvent [^{1}H NMR, C*H*Cl_3 (7.24), C_6HD_5 (7.15); ^{13}C NMR, $CDCl_3$ (77.0), C_6D_6 (128.0)]. Coupling constants (*J*) were reported in hertz (Hz). Following abbreviations were used to designate the multiplicities: s = singlet; d = doublet; t = triplet; m = multiplet; br = broad. EI and FAB mass spectra were recorded on a JEOL JMS-700 spectrometer and ESI mass spectra were measured on a Bruker microTOFfocus spectrometer.

General procedure for the preparation of alkenyl phosphates and their palladium(0)-catalyzed reduction: The synthesis of compound **16** is representative. To a solution of acetate **6** (46.6 mg, 0.147 mmol) in THF (4 mL) were added HMPA (0.127 mL, 0.730 mmol) and $(PhO)_2P(O)Cl$ (0.152 mL, 0.733 mmol). The resultant mixture was cooled to −78 °C and treated with KHMDS (0.5 M solution in toluene, 0.88 mL, 0.44 mmol). After being stirred at −78 °C for 0.5 h, the reaction mixture was quenched with 3% NH_4OH, diluted with diethyl ether, and allowed to warm to rt over 20 min. The resultant mixture was extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide crude alkenyl phosphate **11**, which was passed through a short pad of Florisil column and used immediately in the next reaction. To a solution of **11** in DMF (2 mL) were added Me_2PhSiH (0.112 mL, 0.731 mmol) and $Pd(PPh_3)_4$ (16.9 mg, 0.0146 mmol). After being stirred at 60 °C for 1 h, the reaction mixture was cooled to rt, diluted with EtOAc, washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (5 to 10% diethyl ether/hexanes) gave **16** (36.1 mg, 82%) as a colorless oil.

Compounds **4a,b** (an inseparable mixture, data for (*Z*)-isomer **4a**): ^{1}H NMR (500 MHz, C_6D_6) δ 7.21 (d, *J* = 7.5 Hz, 2H), 6.81 (d, *J* = 7.5 Hz, 2H), 5.82 (apparent d, *J* = 4.0 Hz, 1H), 4.39 (apparent t, *J* = 7.0 Hz,

1H), 4.29 (s, 2H), 3.45 (m, 2H), 3.30 (s, 3H), 3.26 (m, 2H), 1.74 (d, *J* = 7.0 Hz, 3H), 1.59 (m, 4H); ^{13}C NMR (125 MHz, C_6D_6) δ 159.6, 146.1, 131.4, 129.3 (× 2), 114.0 (× 2), 100.5, 72.6, 71.8, 69.7, 54.7, 27.1, 26.6, 9.6; HRMS (EI) calcd for $C_{15}H_{22}O_3$ (M^+) 250.1569, found 250.1574.

Compound **15a**: ^{1}H NMR (500 MHz, C_6D_6) δ 7.84 (d, *J* = 7.5 Hz, 2H), 7.27 (t, *J* = 7.5 Hz, 2H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.02 (d, *J* = 7.5 Hz, 1H), 5.26 (d, *J* = 7.5 Hz, 1H), 3.24 (dt, *J* = 11.0, 4.5 Hz, 1H), 2.26 (m, 1H), 1.86 (m, 1H), 1.47—1.44 (m, 2H), 1.35 (m, 1H), 1.08 (m, 1H), 0.98 (ddd, *J* = 12.0, 12.0, 11.5 Hz, 1H), 0.85 (d, *J* = 7.0 Hz, 3H), 0.80 (d, *J* = 6.0 Hz, 3H), 0.76 (d, *J* = 6.5 Hz, 3H), 0.66 (m, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 146.4, 137.1, 128.6, 128.5, 128.5, 125.8, 105.7, 83.8, 48.0, 42.1, 34.4, 31.6, 26.3, 23.7, 22.2, 20.9, 16.6 (one carbon signal is missing due to solvent overlapping); HRMS (EI) calcd for $C_{18}H_{26}O$ (M^+) 258.1984, found 258.1985.

Compound **15b**: ^{1}H NMR (500 MHz, C_6D_6) δ 7.18—7.12 (m, 4H), 7.02 (m, 1H), 6.86 (d, *J* = 13.0 Hz, 1H), 6.16 (d, *J* = 13.0 Hz, 1H), 3.39 (dt, *J* = 10.5, 4.0 Hz, 1H), 2.30 (m, 1H), 1.97 (m, 1H), 1.49—1.46 (m, 2H), 1.37 (m, 1H), 1.13 (m, 1H), 1.00 (ddd, *J* = 12.0, 11.5, 11.5 Hz, 1H), 0.90 (d, *J* = 7.0 Hz, 3H), 0.82 (d, *J* = 6.5 Hz, 3H), 0.81 (d, *J* = 7.0 Hz, 3H), 0.68 (m, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 147.9, 137.3, 128.8, 125.7, 125.4, 118.1, 107.7, 81.4, 48.1, 41.6, 34.5, 31.6, 26.2, 23.8, 22.2, 20.9, 16.7 (one carbon signal is missing due to solvent overlapping); HRMS (EI) calcd for $C_{18}H_{26}O$ (M^+) 258.1984, found 258.1987.

Compound **16**: ^{1}H NMR (500 MHz, C_6D_6) δ 7.64 (d, *J* = 6.5 Hz, 2H), 6.08 (dd, *J* = 14.0, 6.0 Hz, 1H), 5.93 (m, 1H), 5.33 (s, 1H), 5.12-5.06 (m, 2H), 4.40 (dd, *J* = 14.0, 2.0 Hz, 1H), 4.18 (dd, *J* = 10.0, 4.0 Hz, 1H), 3.99 (dd, *J* = 6.5, 1.5 Hz, 1H), 3.46—3.39 (m, 2H), 3.24 (ddd, *J* = 12.0, 7.0, 3.0 Hz, 1H), 3.14—3.04 (m, 2H), 2.55 (m, 1H), 2.43 (ddd, *J* = 8.0, 4.0, 4.0 Hz, 1H), 2.23 (m, 1H), 1.62 (ddd, *J* = 11.5, 11.0, 10.0 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 150.5, 138.5, 134.5, 129.0, 128.5 (× 2), 126.7 (× 2), 117.5, 101.6, 89.2, 79.9, 76.4, 75.8, 73.4, 69.4, 36.2, 35.1; HRMS (FAB) calcd for $C_{18}H_{23}O_4$ [$(M + H)^+$] 303.1596, found 303.1597.

Compound **18**: ^{1}H NMR (500 MHz, C_6D_6) δ 7.15—6.72 (m, 6H), 4.74 (m, 1H), 3.69—3.62 (m, 2H), 2.08—2.01 (m, 2H), 1.62—1.55 (m, 2H), 1.55—1.40 (m, 4H); HRMS (FAB) calcd for $C_{14}H_{18}NO_2$ [$(M + H)^+$] 232.1337, found 232.1344.

Compound **19**: ^{1}H NMR (500 MHz, C_6D_6) δ 7.59 (dd, *J* = 15.5, 8.5 Hz, 1H), 7.15 (d, *J* = 8.0 Hz, 2H), 6.64 (d, *J* = 8.0 Hz, 2H), 4.13 (d, *J* = 8.5 Hz, 1H), 3.83 (d, *J* = 15.5 Hz, 1H), 1.26 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 152.0, 137.8, 135.1, 132.6 (× 2), 130.9 (× 2), 121.4, 93.5, 81.2, 28.0 (× 3); HRMS (FAB)

calcd for $C_{13}H_{18}{}^{79}BrNO_2Na$ [$(M + Na)^+$] 322.0419, found 322.0419.

Dihydropyran **21**: To a solution of enol ether **16** (55.6 mg, 0.184 mmol) in toluene (10 mL) was added a solution of Grubbs' 2nd generation catalyst (15.6 mg, 0.0184 mmol) in toluene (2 mL). The resulting mixture was heated at 70 °C for 45 min. After cooling to rt, the resulting solution was concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, 10% diethyl ether/hexanes) gave dihydropyran **21** (41.7 mg, 83%) as a colorless crystal: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50—7.49 (m, 2H), 7.39—7.34 (m, 3H), 6.33 (d, *J* = 6.0 Hz, 1H), 5.55 (s, 1H), 4.70 (ddd, *J* = 6.0, 2.0, 1.5 Hz, 1H), 4.33 (dd, *J* = 11.0, 5.0 Hz, 1H), 3.71 (dd, *J* = 11.0, 10.0 Hz, 1H), 3.65 (ddd, *J* = 11.5, 8.5, 3.5 Hz, 1H), 3.61—3.52 (m, 2H), 3.48 (ddd, *J* = 10.0, 9.5, 5.0 Hz, 1H), 2.54 (ddd, *J* = 11.5, 4.5, 4.0 Hz, 1H), 2.31 (m, 1H), 2.07 (m, 1H), 1.82 (ddd, *J* = 11.5, 11.5, 11.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.2, 137.3, 129.1, 128.3 (× 2), 126.1 (× 2), 101.8, 98.5, 76.7, 75.1, 73.5, 73.4, 69.1, 34.5, 26.7; HRMS (EI) calcd for $C_{16}H_{18}O_4$ (M^+) 274.1205, found 274.1208.

Olefin **28**: To a suspension of $Ph_3P^+CH_3Br^-$ (21.3 g, 59.6 mmol) in THF (150 mL) cooled to 0 °C was added KO*t*-Bu (5.72 g, 51.0 mmol). The resultant slurry was stirred at the same temperature for 20 min. To this suspension was added 6-bromopiperonal **27** (9.73 g, 42.5 mmol), and the resultant mixture was stirred at 0 °C for 20 min before it was quenched with saturated aqueous NH_4Cl. The mixture was extracted with diethyl ether, washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, 5% EtOAc/hexanes) gave olefin **28** (9.61 g, 100%) as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.01 (s, 1H), 6.98 (s, 1H), 6.96 (dd, *J* = 17.6, 10.7 Hz, 1H), 5.95 (s, 2H), 5.55 (d, *J* = 17.6 Hz, 1H), 5.25 (d, *J* = 10.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.0, 147.7, 135.4, 130.8, 114.9, 114.7, 112.6, 105.9, 101.8; HRMS (EI) calcd for $C_9H_7O_2{}^{79}Br$ (M^+) 225.9644, found 225.9625.

Alcohol **29**: To a flask containing olefin **28** (4.61 g, 20.4 mmol) was added 9-BBN-H (0.5 M solution in THF, 81.6 mL, 40.3 mmol), and the solution was stirred at rt for 3 h. The resultant mixture was cooled to 0 °C and treated with saturated aqueous $NaHCO_3$ (40 mL) and 30% H_2O_2 (30 mL). After being stirred at rt overnight, the resultant mixture was extracted with EtOAc, washed with saturated aqueous Na_2SO_3 and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, 15 to 30% EtOAc/hexanes) gave alcohol **29** (4.73 g, 95%) as a colorless crystal: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99 (s, 1H), 6.75 (s, 1H), 5.94 (s, 2H), 3.82 (t, *J* = 6.5 Hz, 2H), 2.92 (t, *J* = 6.5 Hz, 2H), 1.36 (br, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.3, 147.1, 130.7, 114.6, 112.8, 110.7, 101.6, 62.2, 39.1; HRMS (EI) calcd for $C_9H_9O_3{}^{79}Br$ (M^+) 243.9735, found 243.9739.

Olefin **30**: To a solution of alcohol **29** (96.4 mg, 0.395 mmol) in toluene (4 mL) were added allyl tri-*n*-butyltin (0.150 mL, 0.484 mmol) and $Pd(PPh_3)_4$ (45.7 mg, 0.0395 mmol). The resultant mixture was heated at 110 °C for 18 h. After cooling, the reaction mixture was concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, 25% EtOAc/hexanes) gave olefin **30** (59.5 mg, 73%) as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.68 (s, 1H), 6.65 (s, 1H), 5.91 (m, 1H), 5.89 (s, 2H), 5.04 (d, *J* = 10.0 Hz, 1H), 4.98 (d, *J* = 17.5 Hz, 1H), 3.77 (t, *J* = 7.0 Hz, 2H), 3.32 (d, *J* = 6.0 Hz, 1H), 2.79 (t, *J* = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.2, 146.0, 137.3, 131.3, 129.3, 115.7, 110.0, 109.9, 100.8, 63.3, 36.9, 35.7; HRMS (EI) calcd for $C_{12}H_{14}O_3$ (M^+) 206.0943, found 206.0947.

Azide **31**: To a solution of olefin **30** (2.48 g, 12.0 mmol) in CH_2Cl_2 (60 mL) cooled at 0 °C were added Et_3N (5.02 mL, 36.0 mmol) and MsCl (1.90 mL, 24.5 mmol). After being stirred at 0 °C for 1 h, the resultant mixture was diluted with EtOAc, washed with 1 M aqueous HCl, saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residual crude mesylate was used in the next reaction without further purification.

To a solution of the above mesylate in DMF (60 mL) was added NaN_3 (2.34 g, 36.0 mmol). After being stirred at 60 °C for 75 min, the reaction mixture was cooled to rt, diluted with EtOAc, washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, 5% diethyl ether/hexanes) gave azide **31** (2.28 g, 82% for the two steps) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.649 (s, 1H), 6.646 (s, 1H), 5.90 (s, 2H), 5.89 (m, 1H), 5.05 (m, 1H), 4.98 (m, 1H), 3.39 (t, *J* = 8.0 Hz, 2H), 3.30 (m, 1H), 2.79 (t, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.5, 146.2, 137.1, 131.1, 129.0, 115.9, 110.1, 109.7, 100.9, 52.1, 36.9, 32.1; HRMS (EI) calcd for $C_{12}H_{13}O_2N_3$ (M^+) 231.1008, found 231.1009.

Acid **32**: To a solution of azide **31** (110.1 mg, 0.4766 mmol) in 1:1 THF/H_2O (6 mL) were added NMO (167.5 mg, 1.430 mmol) and a crystal of OsO_4. After being stirred at rt overnight, the reaction mixture was diluted with EtOAc, washed with saturated aqueous Na_2SO_3 and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residual crude diol was used in the next reaction without further purification.

To a solution of the above diol in 1:1:1 THF/MeOH/H_2O (6 mL) was added $NaIO_4$ (203.9 mg, 0.9533 mmol). After being stirred at rt for 30 min, the mixture was extracted with EtOAc, washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residual crude aldehyde was used in the next reaction without further purification.

To a solution of the above aldehyde in acetone (6 mL) cooled to 0 °C was added Jones' reagent (2.6 M solution in acetone). After being stirred at rt for 45 min, the reaction mixture was treated with *i*-PrOH and

diluted with H_2O. The resultant mixture was repeatedly extracted with $CHCl_3$, and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, 5% MeOH/$CHCl_3$) gave acid **32** (83.3 mg, 70% for the three steps) as a pale yellow crystal: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.71 (s, 1H), 6.68 (s, 1H), 5.92 (s, 2H), 3.60 (s, 2H), 3.44 (t, *J* = 7.5 Hz, 2H), 2.80 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.5, 147.3, 146.7, 130.1, 124.9, 110.7, 109.8, 101.2, 52.0, 38.1, 32.2; HRMS (EI) calcd for $C_{11}H_{11}O_4N_3$ (M^+) 249.0726, found 249.0757.

Pentafluorophenyl ester **33**: To a solution of acid **32** (2.12 g, 8.51 mmol) in CH_2Cl_2 (50 mL) were added pentafluorophenol (1.72 g, 9.34 mmol) and DCC (2.11 g, 10.2 mmol). After being stirred at rt overnight, the reaction mixture was diluted with diethyl ether and filtered through a plug of cotton. The filtrate was concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, 5 to 8% EtOAc/hexanes) gave pentafluorophenyl ester **33** (3.34 g, 95%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.78 (s, 1H), 6.71 (s, 1H), 5.95 (s, 2H), 3.92 (s, 2H), 3.48 (t, *J* = 7.0 Hz, 2H), 2.84 (t, *J* = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 147.7, 146.9, 130.3, 123.6, 110.6, 109.9, 101.4, 52.1, 37.4, 32.2; HRMS (EI) calcd for $C_{17}H_{10}O_4N_3F_5$ (M^+) 415.0592, found 415.0592.

Lactam **26**: A solution of pentafluorophenyl ester **33** (222.0 mg, 0.5349 mmol) in THF (30 mL) was added dropwise to a solution of *n*-Bu_3P (0.67 mL, 2.68 mmol) in THF (80 mL) over a period of 1 h. The resultant solution was stirred at rt for 1 h and then at 60 °C for 2.5 h. After cooling to rt, the reaction mixture was concentrated under reduced pressure. The residual crystals were washed thoroughly with *i*-Pr_2O and dried to give lactam **26** (75.0 mg, 68%) as a colorless crystal: mp 222—224 °C (MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.61 (s, 1H), 6.59 (s, 1H), 6.10 (br, 1H), 5.90 (s, 2H), 3.72 (s, 2H), 3.52 (q, *J* = 6.0 Hz, 2H), 3.02 (t, *J* = 6.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.8, 146.3, 138.8, 130.1, 125.0, 110.4, 109.6, 101.0, 41.9, 33.0; HRMS (EI) calcd for $C_{11}H_{11}NO_3$ (M^+) 205.0749, found 205.0736.

Amide **35**: A suspension of 3,4-methylenedioxyphenylacetic acid **34** (2.00 g, 11.1 mmol) in CH_2Cl_2 (10 mL) was added thionyl chloride (10 mL), and the mixture was heated under reflux for 1 h. After cooling to rt, the resultant mixture was concentrated under reduced pressure to give 3,4-methylenedioxyphenylacetyl chloride, which was used in the next reaction without purification.

To a solution of aminoacetaldehyde dimethylacetal (0.97 g, 9.23 mmol) in CH_2Cl_2 (50 mL) were added pyridine (0.90 mL, 11.1 mmol) and 3,4-methylenedioxyphenylacetyl chloride prepared as above. The reaction mixture was stirred at rt for 80 min. The resultant mixture was quenched H_2O and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure.

Purification of the residue by flash chromatography (silica gel, 50% EtOAc/hexanes to EtOAc) gave amide **35** (2.43 g, 99%) as an oil, which upon standing crystallized: mp 66—67 °C (EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.77 (d, *J* = 8.0 Hz, 1H), 6.72 (s, 1H), 6.68 (d, *J* = 8.0 Hz, 1H), 5.94 (s, 2H), 5.61 (br, 1H), 4.30 (t, *J* = 5.0 Hz, 1H), 3.46 (s, 2H), 3.35—3.33 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 148.0, 146.9, 128.3, 122.5, 109.7, 108.6, 102.6, 101.1, 54.5, 43.3, 41.1; HRMS (FAB) calcd for $C_{13}H_{18}NO_5$ [$(M + H)^+$] 268.1185, found 268.1191.

Enamide **36**: To a solution of amide **35** (1.55 g, 5.81 mmol) in AcOH (10 mL) was added concentrated HCl (10 mL). After being stirred at rt for 23 h, the resulting mixture was poured into ice-cold water (60 mL) and the precipitates were collected by filtration under reduced pressure. Recrystallization from $CHCl_3$ gave enamide **36** (0.70 g, 59%) as a colorless crystal: mp 200—201 °C ($CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (br, 1H), 6.73 (s, 1H), 6.67 (s, 1H), 6.24 (d, *J* = 9.5 Hz, 1H), 6.16 (dd, *J* = 9.5, 4.5 Hz, 1H), 5.95 (s, 2H), 3.39 (s, 2H); HRMS (EI) calcd for $C_{11}H_9NO_3$ (M^+) 203.0574, found 203.0585.

Lactam **26**: To a solution of enamide **36** (0.70 g, 3.45 mmol) in 2:1 THF/MeOH (45 mL) was added 10% Pd/C (0.25 g), and the resulting suspension was stirred at rt overnight under an atmosphere of hydrogen. The mixture was filtered through Celite and the filtrate concentrated under reduced pressure. Recrystallization from MeOH gave lactam **26** (0.59 g, 83%) as a colorless crystal. The spectroscopic data matched those of the sample prepared above.

Imide **38**: To a solution of lactam **26** (67.6 mg, 0.330 mmol) in 1,2-dichloroethane (5 mL) were added activated molecular sieves 4A (200 mg) and 2-bromo-5,6-dimethoxybenzoyl chloride [prepared from 2-bromo-5,6-dimethoxybenzoic acid (383 mg, 1.47 mmol) and thionyl chloride (5 mL) under reflux for 2.5 h]. After being stirred at 65 °C for 1 day, the resultant mixture was cooled to rt, filtered through Celite, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 30 to 40% EtOAc/hexanes) gave imide **38** (145.3 mg, 99%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (d, *J* = 9.0 Hz, 1H), 6.74 (d, *J* = 9.0 Hz, 1H), 6.58 (s, 1H), 6.49 (s, 1H), 5.90 (s, 2H), 4.45 (brm, 2H), 3.93—3.83 (m, 2H), 3.79 (s, 3H), 3.64 (s, 3H), 3.23 (brm, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 166.6, 151.7, 147.3, 146.1, 145.3, 135.0, 128.6, 127.4, 122.1, 113.5, 110.9, 109.9, 107.7, 101.1, 61.0, 55.9, 44.7, 40.6, 32.7; HRMS (EI) calcd for $C_{20}H_{18}{}^{79}BrNO_6$ (M^+) 447.0318, found 447.0318.

Enamide **24**: To a solution of imide **38** (449.2 mg, 1.005 mmol) in THF (12 mL) were added HMPA (0.52 mL, 2.99 mmol) and $(PhO)_2P(O)Cl$ (0.25 mL, 1.23 mmol). The resultant mixture was cooled to −78 °C and treated with KHMDS (0.5 M solution in toluene, 2.41 mL, 1.21 mmol). After being stirred

at −78 °C for 40 min, the reaction mixture was quenched with 3% NH_4OH, diluted with diethyl ether, and allowed to warm to rt over 20 min. The resultant mixture was extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide crude alkenyl phosphate **25**, which was used immediately in the next reaction. To a solution of **25** in DMF (12 mL) were added Me_2PhSiH (0.77 mL, 5.02 mmol) and $Pd(PPh_3)_4$ (116.1 mg, 0.100 mmol). After being stirred at 80 °C for 100 min, the reaction mixture was cooled to rt, diluted with EtOAc, washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (3% diethyl ether/benzene) followed by preparative HPLC gave **24** (262.3 mg, 61% for the two steps) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$, 293 K, exists as an approximately 7:3 mixture of rotational isomers) δ 7.41 (d, *J* = 11.0 Hz, 0.3H), 7.26 (d, *J* = 7.0 Hz, 0.7H), 6.84 (d, *J* = 7.0 Hz, 0.7H), 6.83 (m, 0.3H), 6.68 (s, 0.3H), 6.61 (s, 0.7H), 6.59 (s, 0.7H), 6.48 (s, 0.3H), 6.18 (d, *J* = 10.0 Hz, 0.7H), 5.90 (s, 2H), 5.78 (d, *J* = 11.0 Hz, 0.3H), 5.39 (s, 0.7H), 4.30 (dd, *J* = 13.0, 7.0 Hz, 0.7H), 4.04 (dd, *J* = 13.0, 7.0 Hz, 0.7H), 3.86 (s, 3H), 3.83 (s, 3H), 3.59 (t, *J* = 4.5 Hz, 0.3H × 2), 3.05-2.96 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, 293 K, exists as an approximately 7:3 mixture of rotational isomers) δ 164.8, 152.3, 146.3, 146.2, 146.1, 133.8, 133.5, 132.2, 128.2, 128.1, 128.1, 128.0, 124.9, 122.6, 114.3, 114.0, 112.3, 110.1, 110.3, 110.2, 109.4, 109.2, 101.0, 61.7, 61.6, 56.0, 56.0, 48.1, 42.8, 36.8, 36.2; HRMS (ESI) $C_{20}H_{18}{}^{79}BrNO_5Na$ [$(M + Na)^+$] 454.0267, found 454.0266.

Lennoxamine **22**: To a solution of enamide **24** (25.7 mg, 0.0596 mmol) in benzene (2 mL) were added a solution of *n*-Bu_3SnH (0.035 mL, 0.130 mmol) and AIBN (3.0 mg, 0.018 mmol) in benzene (2 mL). After being stirred at 80 °C for 8 h, additional portion of a solution of *n*-Bu_3SnH (0.035 mL, 0.130 mmol) and AIBN (3.0 mg, 0.018 mmol) in benzene (2 mL) was added, and the mixture was heated at 105 °C for 12 h. The resultant mixture was concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, 25 to 75% EtOAc/hexanes) gave lennoxamine **22** (14.0 mg, 67%) along with debrominated **39** (5.3 mg, 25%). **22**: mp 229—230 °C (MeOH) (lit.,[26m] 229—230 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (d, *J* = 8.5 Hz, 1H), 7.11 (d, *J* = 8.5 Hz, 1H), 6.75 (s, 1H), 6.68 (s, 1H), 5.93 (d, *J* = 5.0 Hz, 1H), 5.93 (d, *J* = 5.0 Hz, 1H), 4.72 (m, 1H), 4.28 (apparent d, *J* = 10.0 Hz, 1H), 4.08 (s, 3H), 3.89 (s, 3H), 3.09 (dd, *J* = 14.5, 1.5 Hz, 1H), 2.92—2.85 (m, 2H), 2.83—2.76 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 152.6, 147.2, 146.3, 146.1, 138.2, 134.8, 130.9, 124.2, 117.1, 116.1, 110.3 (× 2), 101.0, 62.5, 60.1, 56.7, 42.7, 41.1, 35.9; HRMS (ESI) calcd for $C_{20}H_{19}NO_5Na$ [$(M + Na)^+$] 376.1161, found 376.1166. **39**: ^{1}H NMR (500 MHz, $CDCl_3$, exists as an approximately 2:1 mixture of *cis*-*trans* isomers) δ 7.46 (d, *J* = 11.0 Hz, 0.33H), 7.15—7.12 (m, 1H), 7.00 (d, *J* = 8.5 Hz, 1H), 6.87 (m, 1H), 6.72 (s, 0.33H), 6.65 (s, 0.67H), 6.62 (s, 0.67H), 6.52 (s, 0.33H), 6.31 (d, *J* = 10.5 Hz, 0.67H), 5.94 (s, 2H), 5.78 (d, *J* = 11.0 Hz, 0.33H), 5.37 (d, *J* = 10.5 Hz, 0.67H), 4.28 (br, 0.67H), 4.08 (br, 0.67H), 3.92 (s, 1H), 3.91 (s,

2H), 3.87 (s, 3H), 3.78 (m, 0.33H), 3.55 (m, 0.33H), 3.05 (m, 1.33H), 2.95 (m, 0.67H); HRMS (ESI) calcd for $C_{20}H_{19}NO_5Na$ [$(M + Na)^+$] 376.1161, found 376.1161.

Dehydrolennoxamine **40**: To a solution of enamide **24** (25.8 mg, 0.0599 mmol) in DMF (1.5 mL) were added *n*-Bu_4NCl (16.6 mg, 0.0597 mmol), KOAc (14.7 mg, 0.150 mmol), and $Pd(PPh_3)_4$ (6.9 mg, 0.00597 mmol). After being stirred at 110 °C overnight, the resulting mixture was cooled to rt and diluted with EtOAc. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, 30% EtOAc/hexanes) gave dehydrolennoxamine **40** (17.6 mg, 84%) along with recovered enamide **24** (2.4 mg, 9%). **40**: mp 212—214 °C (EtOAc/hexane) (lit.,[26m] 209—211 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.0 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 1H), 6.78 (s, 1H), 6.64 (s, 1H), 6.30 (s, 1H), 5.94 (s, 2H), 4.08 (s, 3H), 3.90 (s, 3H), 4.20—3.80 (m, 2H), 3.01 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.7, 152.9, 146.91, 146.85, 146.6, 133.9, 133.3, 131.1, 127.8, 120.3, 116.3, 114.3, 110.3, 110.2, 104.9, 101.2, 62.5, 56.7, 41.8, 35.5; HRMS (ESI) calcd for $C_{20}H_{17}NO_5Na$ [$(M + Na)^+$] 374.1004, found 374.1004.

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