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Synthesis of Isoindolobenzazepine Alkaloids Based on Radical Reactions or Pd(0)-Catalyzed Reactions

Yu Onozaki, Nobuhito Kurono,† Hisanori Senboku,† Masao Tokuda, and Kazuhiko Orito*

Laboratory of Organic Synthesis, Division of Molecular Chemistry, Graduate School of Engineering, Hokkaido University, Sapporo 060-8628, Japan.† Present address: Division of Chemical Process Engineering.

orito@eng.hokudai.ac.jp

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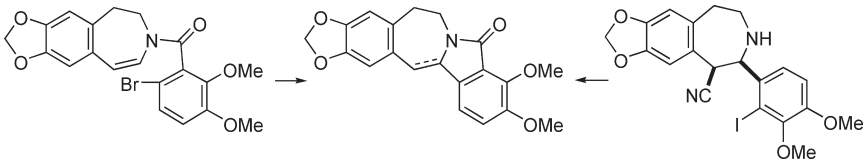

Methods for synthesis of a ring system characteristic of isoindolobenzazepine alkaloids were studied. Synthesis of lennoxamine and a formal synthesis of chelenine were accomplished in a short route via radical or Pd(0)-catalyzed cyclization as the key step. An altenative approach based on a radical migration of a cyano group or Pd(0)-catalyzed carbonylation was also developed for both alkaloids.

Introduction

Lennoxamine (**1**) and chilenine (**2**)[1] occur together with some isoquinoline alkaloids in nature.[1] The ring system, isoindolo[1,2-*b*][3]benzazepine, has been completed by cyclization that forms a C−C or C−N bond at a,[2] b,[3] c,[4] d,[5] e,[6] or f[7] at the final stage of the synthesis. Conversion of dehydrolennoxamine (**3**) into chilenine[3d] and lennoxamine[2e,3g] has been achieved (Scheme 1). We were interested in the synthetic routes via a ring-closure at e, f, or g, which leads to the isoindolinone ring formation, and examined the validity of the methodologies based on Pd-catalyzed cyclizations

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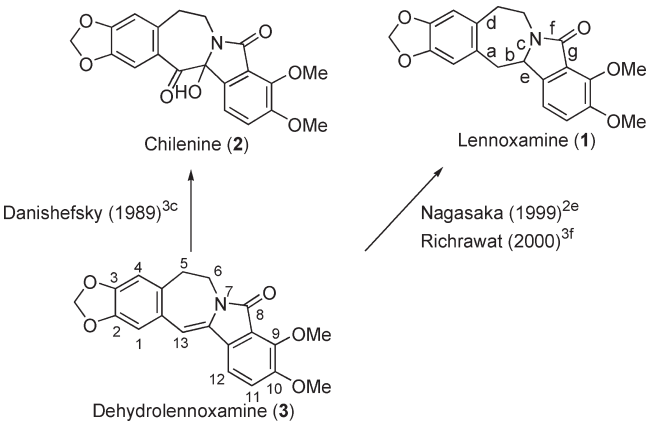
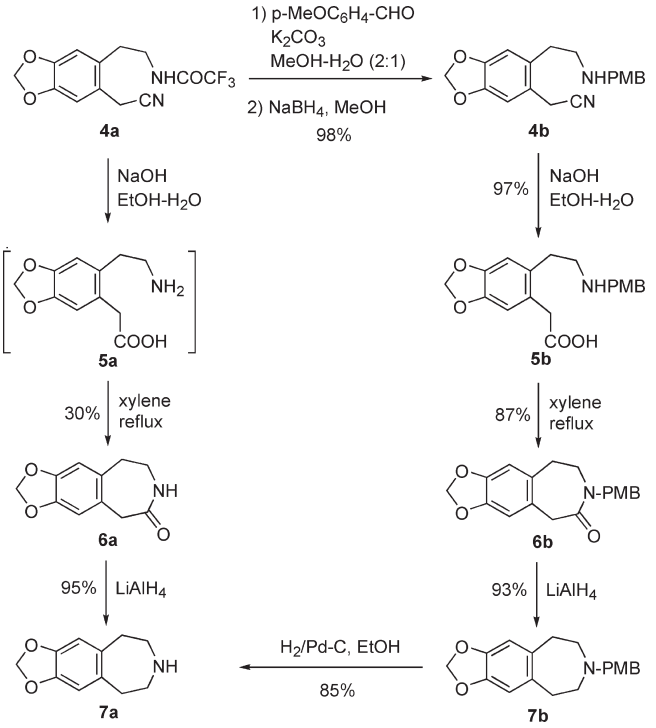
SCHEME 1. Isoindolobenzazepine Alkaloids



SCHEME 2. Preparation of Tetrahydro-3*H*-3-benzazepine 7a



involving Heck reaction[8] or Mori−Ban carbonylation,[9,10] or aryl radical reactions[11] using 3-benzazepines with a haloaryl group as the substrates.

Results and Discussion

Preparation and reactions of 3-benzazepine intermediates **8** and **10** are first examined on the basis of the reported method.[12] 3-Benzazepin-2-one **6a** was prepared via *primary*-amino acid **5a** from **4a** in a low yield of 30% but was smoothly reduced with $LiAlH_4$ to tetrahydro-3*H*-3-benzazepine **7a** in good yield. Introduction of a *p*-methoxybenzyl group on the nitrogen atom improved the yield for the intramolecular condensation (**5b** → **6b**) to 87%, although reaction steps for the benzylation and debenzylation were required to give **7a** (Scheme 2).

As shown in Scheme 3, benzapine **7a** was then treated with 6-bromo-2,3-dimethoxybenzoyl chloride[2b] to give 3-benzoyl-3*H*-3-benzazepine **8** in 95% yield. A radical cyclization via a 1,5-hydrogen atom migration[13] followed by an insertion of the generated α-acylamino radical[6c] to an internal phenyl group for the conversion of **8** to lennoxamine **1** [**8** → **i** → **ii** → **1**] was unsuccessful, and only debrominated reactant **9** was formed in 94% yield. Attempts at conversion of **8** into its dehydro-derivative **10** by dehydrogenation with DDQ or Pd−C or similar functionalization at C-1 by other methods, including NBS/$(PhCOO)_2$ or *hν*, or CrO_3 oxidation were unsuccessful.

Another route to dihydro-3*H*-3-benzazepine **10** was examined. *N*-Alkylation of phenethylamine **11**[14] with $BrCH_2$-$(OMe)_2$ (K_2CO_3, in DMF at 80 °C) produced acetal **12** almost quantitatively, as shown in Scheme 4. Successive *N*-benzoylation with 6-bromo-2,3-dimethoxybenzoyl chloride[2b] (Py in C_6H_6, rt) gave benzamide **13** (61%). An attempt to induce cyclization of **13** by a method using AcCl−$ZnCl_2$[5c] resulted in recovery of the corresponding aldehyde. Courture's conditions with H_2SO_4−AcOH (5:3 v/v)[5e] caused decomposition of the substrate to give a complex mixture. The effect of reduction in the amount of H_2SO_4 was attempted. The use of a 1:3 v/v H_2SO_4−AcOH solution yielded the desired **10** in 45% yield, together with a significant amount of the aldehyde. Addition of $MgSO_4$, Ac_2O, or MS did not improve the reaction, but the addition of a small amount of MeOH (half volume of H_2SO_4), which was expected to reproduce the acetal group, markedly improved the low cyclization efficiency to 82% yield of **10** in two steps. In addition, treatment of acetal **12** with H_2SO_4−AcOH (1:4 v/v) at 40 °C produced dihydroazepine **14** in 77% yield, but its *N*-acylation with 6-bromo-2,3-dimethoxybenzoyl chloride failed to give **10**, and a complex mixture was obtained.

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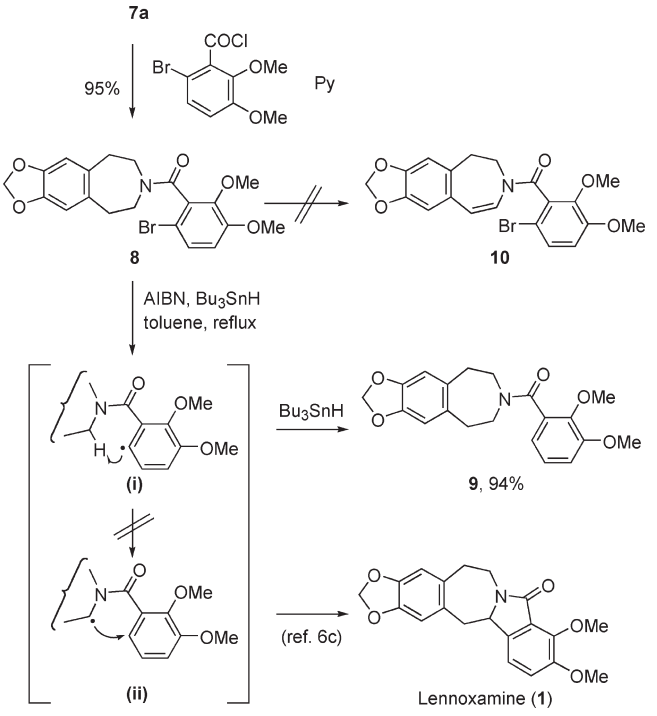
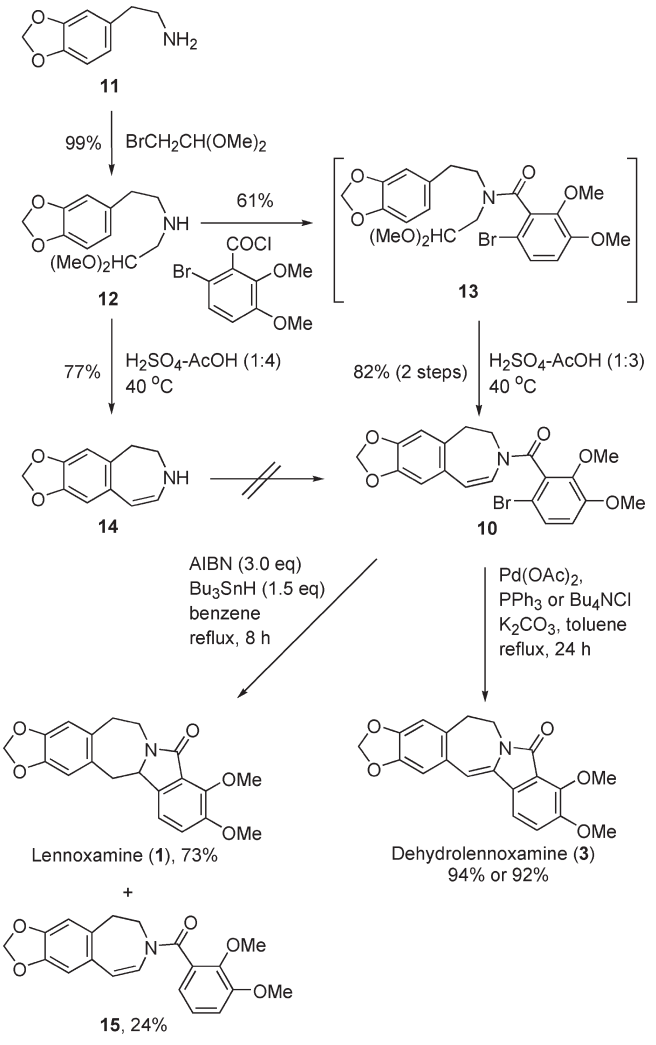
SCHEME 3. Attempts at Conversion of 8 to Lennoxamine (1)



To examine the e-bond formation, radical cyclization of dihydro-3*H*-3-benzazepine **10** to lennoxamine **1** was examined. Funk has already reported the conversion affording **1** in 58% yield under standard conditions using a catalytic amount of AIBN (0.15 mol equiv),[6b] and a radical cyclization of *o*-bromobenzylamine derivative was also reported by Hanaoka.[6a] The use of excess AIBN (3.0 mol equiv) together with Bu_3SnH (1.5 mol equiv) in boiling benzene for 8 h produced **1** in 73% yield together with the debrominated reactant (**15**) (24%). The use of a smaller amount of AIBN (1 mol equiv) resulted in the formation of a larger amount of **15** (>30%). An alternative procedure utilizing AIBN (4 mol equiv) and $AllylSnBu_3$ (4 mol equiv) resulted in complete suppression of the debromination, but the cyclization proceeded slowly to give a 1:1 mixture of the unchanged reactant **10** and **1** even after 4 days.

On the other hand, Heck cyclization[15a] of **10** with $Pd(OAc)_2$ (20 mol %) and PPh_3 (40 mol %) in the presence of K_2CO_3 (10 mol equiv) heated in boiling toluene for 24 h gave dehydrolennoxamine (**3**) in 94% isolated yield, as shown in entry 1 (Table 1). Tertiary amine (Et_3N) used instead of K_2CO_3 was not effective at all (entry 2).[16] The use of Bu_4NCl (2 mol equiv)[17] instead of PPh_3 resulted in exclusive Heck

SCHEME 4. Preparation of 10 and Synthesis of 1 and Dehydrolennoxamine (3)



cyclization via trans-elimination of $HPdBr$[15b−g] to give **3** in DMF (entry 3) or better in toluene (92% isolated yield) (entry 4 in Table 1). In view of the previous conversion of **3** into lennoxamine (**1**)[2e,3g] and chilenine (**2**),[3d] this constitutes a formal synthesis of these alkaloids, providing a new example for Heck cyclization versus radical cyclization.[18]

The previously reported one-pot method with EtONa in EtOH affords 1-cyano-2-phenyl-3-benzazepines in low yield of about 30%.[19] Therefore, according to the aforementioned procedure for the preparation of **4b**, trifluoroacetamide **4a** was first treated with bromobenzaldehyde **16a**[20] and K_2CO_3 in $MeOH-H_2O$ (1:1) in the presence of 3 Å molecular sieves

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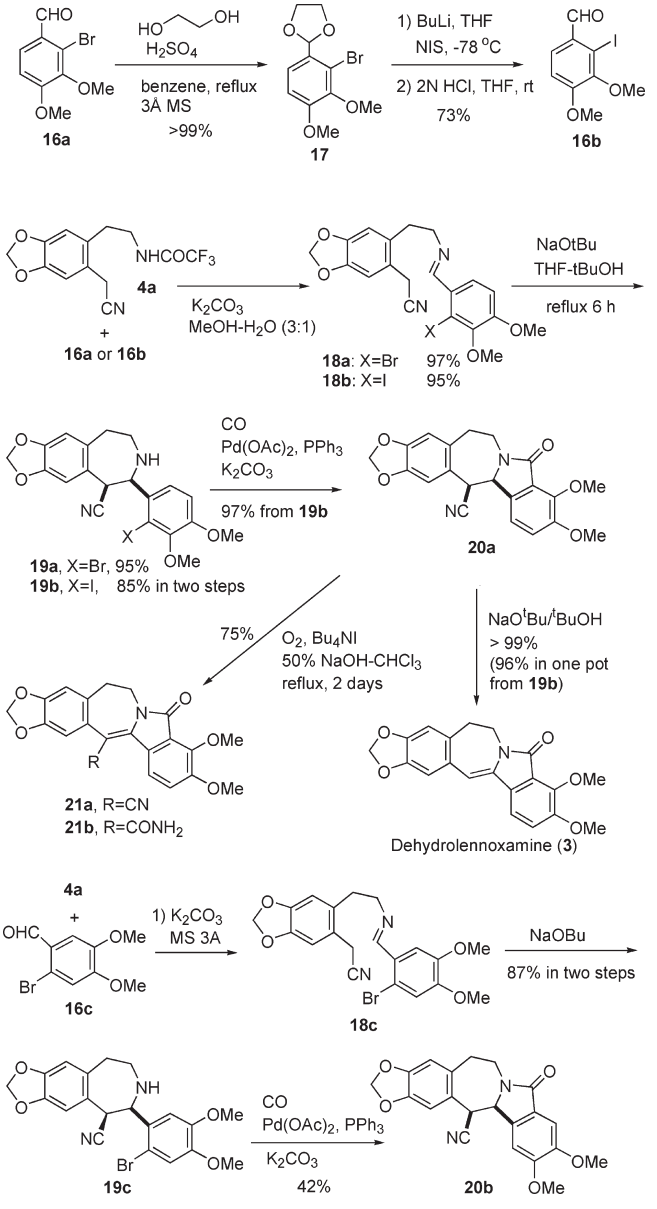
TABLE 1. Heck Cyclization of Dihydro-3*H*-3-benzazepine 10

entry	solvent	catalyst (mol %)/ligand (mol %)	base (mol equiv)	additive (mol equiv)	**10**:**3**	yield of **3** (%)
1	toluene[a]	$Pd(OAc)_2$ (20)/PPh_3 (40)	K_2CO_3 (10)		0:100	94
2	toluene[a]	$Pd(OAc)_2$ (20)/PPh_3 (40)	Et_3N (3)		100:0	
3	DMF[b]	$Pd(OAc)_2$ (20)	K_2CO_3 (10)	Bu_4NCl (2)	15:85	
4	toluene[a]	$Pd(OAc)_2$ (20)	K_2CO_3 (10)	Bu_4NCl (2)	0:100	92

[a]Refluxed under argon for 24 h. [b]Heated at 90 °C under argon for 24 h.

SCHEME 5. Synthesis of 3 via Pd-Catalyzed Carbonylation



at rt for 12 h, to afford imine **18a** (97%), as shown in Scheme 5. An attempt to prepare iodobenzaldehyde **16b** by direct treatment of bromide **16a** with CuI/KI/TMEDA,[21] LDA/I_2, or NIS failed. A halogen exchange on ethylene acetal **17** (99%) with BuLi and NIS,[22] followed by deacetalization with 2 N HCl solution, produced iodobenzaldehyde **16b** (73%), which was similarly subjected to condensation with **4a** to give imine **18b** (95%).

A combination of EtONa (1.1 equiv) with an ethanolic solvent such as EtOH, THF−EtOH (entries 1 and 2 in Table 2), or dioxane−EtOH (entry 3) did not give good results for the conversion of imine **18a** to 3-benzazepine **19a**. The use of a 3-fold greater amount of the base resulted in the better formation of the desired azepine **19a** (entry 4). When a more basic alkoxide, *t*-BuONa, was used in THF−*t*-BuOH, the cyclization proceeded smoothly, and 80% of **19a** was formed after 3 h (entry 5). It was isolated almost quantitatively in the best isolated yield of 95% after 6 h (entry 6). Thus,**18b** was also heated with *t*-BuONa (1.1 equiv) in THF−*t*-BuOH (2:1) for 6 h to afford benzazepine **19b** (85% in two steps).

As shown in Scheme 5, Pd(0)-catalyzed carbonylation of iodobenzazepine **19b** [CO (1 atm), $Pd(OAc)_2$ (20 mol %), PPh_3 (40 mol %), K_2CO_3 (2 mol equiv)] in boiling toluene (12 h) produced cyanolennoxamine **20a** in 97% yield. Under the same conditions, bromobenzazepine **19a** failed to produce **20a**, but its 4′,5′-dimethoxy derivative **19c** underwent carbonylation to give **20b** (42%), which is a regioisomer to **20a**. To generate a vicinal ketol system such as that in **2**, **20a** was subjected to oxidative decyanation with Bu_4NI (10 equiv) by treatment in a refluxing 50% NaOH−$CHCl_3$ solution under oxygen for 2 days.[23] However, neither **2** nor other oxygenated compounds were formed, and unsaturated cyanolennoxamine **21a** was instead obtained in 75% yield. The use of Bu_4NBr in place of Bu_4NI resulted in complete recovery of **20a**. Further attempts at dioxygenation of an unsaturated system in **21a** by using a dual-oxygenation reagent, such as dimethyldioxirane,[3d,24] OsO_4,[3d,25] H_2O_2,[26] *t*-BuOOH,[26] or $KMnO_4$,[27] have so far been unsuccessful. For instance, treatment of **21a** with H_2O_2 in the presence of Bu_4NF[26] afforded amide **21b** in 48% yield. The cyano group of **20a** was quantitatively removed in a boiling *t*-BuOH−THF (3:2) solution containing *t*-BuONa (1.5 equiv), and the aforementioned synthetic precursor **3** of lennoxamine (**1**) or chilenine (**2**) was obtained. Execution of this two-step procedure on **19b** in one pot resulted in the formation of **3** in 96% yield.

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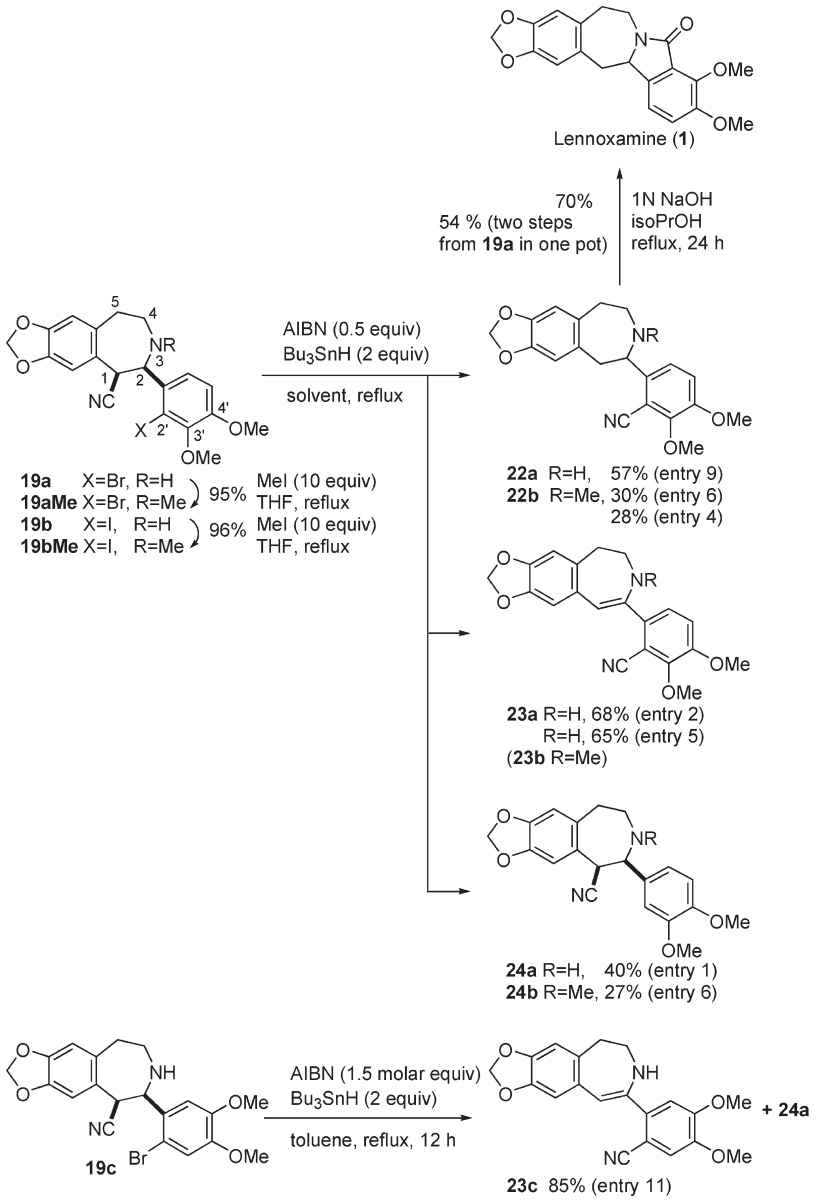
TABLE 2. Cyclization of Imine 18a to 3-Benzazepine 19a[a]

entry	base (equiv)	solvents	temp, °C	time, h	**18a**:**19a**[b]	yield of **19a**, %
1	EtONa (1.1)	THF/EtOH (2:1)	reflux	3	4:1	
2	EtONa (1.1)	THF/EtOH (2:1)	50	20	a complex mixture	
3	EtONa (1.1)	dioxane/EtOH (2:1)	50	3	1: 1	
4	EtONa (3.0)	THF/EtOH (2:1)	50	3	1:2	
5	^{t}BuONa (1.1)	THF/^{t}BuOH (2:1)	50	3	1:4	
6	^{t}BuONa (1.1)	THF/^{t}BuOH (2:1)	50	6	0:10	95

[a]Reactions were carried out under argon. [b]Determined by ^{1}H NMR analysis.

SCHEME 6. Radical 1,4-Cyano Migration of 3-Benzazepines 19 and Synthesis of 1



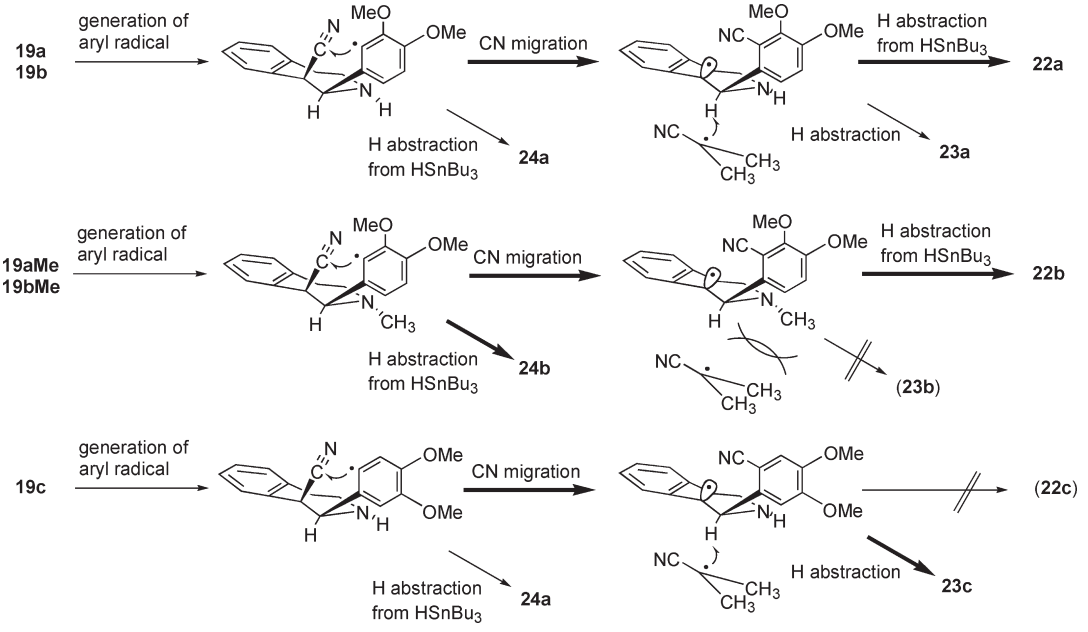
To obtain 3-benzazepine **22a**, a 1,4-cyano migration via a 5-*exo* radical cyclization onto the halogenated aryl carbon was examined (Scheme 6).[28] When iodide **19b** in a 0.02 M boiling benzene solution was treated with AIBN (1.5 equiv) and Bu_3SnH (2 equiv) for 12 h, only deiodination occurred in 50% conversion to give **24a** (entry 1 in Table 3). Replacement of the solvent with boiling toluene afforded an unsaturated cyano migrated product **23a** over **24a** in a ratio of 2:1 from both iodide **19b** and bromide **19a** (entries 2 and 4). Reaction in boiling xylene gave a complex mixture (entry 3). Similar treatments of *N*-Me derivatives (**19bMe** and **19aMe**) of **19b** and **19a** in boiling toluene produced a saturated cyano migration product, 2-(2-cyanophenyl)-3*H*-3-benzazepine **22b** and dehalogenated reactant **24b** in a 1:1 ratio in a dark brown reaction mixture, respectively (entries 5 and 6). In entries 7 and 8, the amount of the

TABLE 3. Radical 1,4-Cyano Migration of 3-Benzazepines 19[a]

entry	substrate	R	X	AIBN/Bu_3SnH, mol equiv	concn, M	solvent	NMR mol ratio **19**:**22**:**23**:**24**	yield
1[b]	**19b**	H	I	1.5/2.0	0.02	benzene	1:0:0:1	**24a** (40%)
2[b]	**19b**	H	I	1.5/2.0	0.02	toluene	0:0:2:1	**23a** (65%)
3[b]	**19b**	H	I	1.5/2.0	0.02	xylene	a complex mixture	
4[b]	**19a**	H	Br	1.5/2.0	0.02	toluene	0:0:2:1	**23a** (63%)
5[b]	**19bMe**	Me	I	1.5/2.0	0.02	toluene	0:1:0:1	**22b** (28%)
6[b]	**19aMe**	Me	Br	1.5/2.0	0.02	toluene	0:1:0:1	**22b** (30%) **24b** (27%)
7[c]	**19a**	H	Br	0.5/2.0	0.02	toluene	0:2:0.1:1	**22a** (40%)[d]
8[c]	**19a**	H	Br	0.1/2.0	0.02	toluene	0:3:0:1	**22a** (51%)[d]
9[c]	**19a**	H	Br	0.5/2.0	0.01	toluene	0:4:0.2:1	**22a** (57%)[d]
10[c]	**19a**	H	Br	0.1/2.0	0.01	toluene	1.5:3:0.3:1	**22a** (44%)[d]
11[b]	**19c**	H	Br	1.5/2.0	0.02	toluene	0:0:15:1	**23c** (85%)

[a]All reactions were carried out in an appropriate boiling solvent under Ar. [b]The reaction was carried out with 0.05 mmol of each substrate in a solvent (2.5 mL). [c]The reaction was carried out with 1 mmol of **19a**. [d]Isolated as an HBr salt.

SCHEME 7. Radical 1,4-Cyano Migration of 3-Benzazepines 19



radical initiator AIBN in the reaction of bromide **19a** was reduced to 0.5 or 0.1 molar equiv, the 0.5 molar equiv giving the desired product **22a** together with a small amount of its 1,2-unsaturated derivative **23a** and the 0.1 molar equiv giving a greater amount of **22a** without forming **23a**. The use of 0.5 molar equiv of AIBN in a diluted system (0.01 M toluene solution, entry 9) resulted in more efficient 1,4-cyano migration (>80%) to produce 2-(2-cyanophenyl)-3*H*-3-benzazepine **22a** in 57% isolated yield accompanied by its 1,2-unsaturated derivative **23a** and debrominated reactant **24a** in a ratio of 4:0.2:1 (entry 9). In another diluted system containing 0.1 molar equiv of AIBN (entry 10) some of the reactant remained unchanged. Successive treatment of **22a** with 1 N NaOH solution in boiling isoPrOH (1:5 vol %) for 24 h produced lennoxamine (**1**) in 70% yield. A one-pot procedure for these conversions gave **1** in a better yield (54%). Thus, the first natural product synthesis through a cyano migration[28] was accomplished. In addition, bromide 19c gave an unsaturated cyano migration product **23c**, together with a small amount of **24a** in a ratio of 15:1, in 85% isolated yield (entry 11) under the same conditions as those in entry 2.

Scheme 7 shows processes for radical cyano migration followed by abstraction of a hydrogen atom. In the radical reaction of **19b**, which has an NH group, a greater amount of AIBN causes a hydrogen abstraction at the C_2 position by a generated isobutyronitrile radical after cyano migration to form a double bond in an unsaturated azepine **23a**. In contrast, in the case of its *N*-Me derivatives, **19aMe** and **19bMe**, the attack of the isobutyronitrile radical to the C-2 hydrogen is blocked with a barricade of an *N*-Me group, and an unsaturated azepine depicted as **23b** was not formed. The radical at C-1 abstracts a hydrogen atom from Bu_3SnH to give a saturated azepine **22b**, as shown in entries 5 and 6. Moreover, the cyano migration proceeded more slowly with a sterically hindered aryl radical generated from the 2′-halo-3′,4′-dimethoxyphenyl group in **19a** or **19b** compared with that from the 2′-halo-4′,5′-dimethoxy group in **19c**, and the hindered aryl radical tended to abstract a hydrogen atom intermolecularly from Bu_3SnH to give **24a** or **24b**. This is the reason why **19c** gave the cyano migration product (**23c**) in greater amount. Thus, the desired compound **22a** was more efficiently formed in a diluted solution of **19a** in order to suppress an intermolecular hydrogen abstraction of the C-2′

aryl radical from Bu_3SnH to **24a** and an intermolecular hydrogen abstraction at C-2 by an isobutyronitrile radical to **23a**.

In summary, methods for synthesis of a ring system characteristic of isoindolobenzazepine alkaloids were studied. Synthesis of lennoxamine and a formal synthesis of chelenine were accomplished in a short route via radical or Pd(0)-catalyzed cyclization as the key step. An alternative access based on a radical migration of a cyano group also led to the synthesis of lennoxamine.

Experimental Section

3-(6-Bromo-2,3-dimethoxybenzoyl)-7,8-(methylenedioxy)-1,2,4,5-tetrahydro-3*H*-3-benzazepine (8). To a stirred solution of **7a** (442 mg, 2.31 mmol) and pyridine (1.5 mL) in benzene (10 mL) at rt was dropwise added 6-bromo-2,3-dimethoxybenzoyl chloride[2b,15g] (700 mg, 2.5 mmol) {freshly prepared from 6-bromo-2,3-dimethoxybenzoic acid [prepared by bromination of 2,3-dimethoxybenzoic acid with 1,3-dibromo-5,5-dimethylhydantoin, mp 81−83 °C (benzene−hexane), ^{1}H NMR δ 3.88 (s, 3H), 3.93 (s, 3H), 6.86 (d, J = 8.6 Hz, 1H), 7.28 (d, J = 8.6 Hz, 1H)] and excess $SOCl_2$} in benzene (10 mL). The mixture was stirred for 12 h and then washed with aq 2 N HCl (3×25 mL), aq 2 N NaOH (3 × 25 mL), and water (3 × 50 mL), then dried (Na_2SO_4). The solvent was evaporated, and the residue was crystallized from benzene −hexane to give **8** (963 mg, 95%), mp 201−203 °C, as dark gray crystals: IR (Nujol) ν_{max} 1628, 1490 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.83 (dd, J = 6.3, 3.0 Hz, 2H), 2.95 (t, J = 4.6 Hz, 2H), 3.33 (dd, J = 6.3, 4.6 Hz, 2H), 3.87 (s, 3H), 3.88 (s, 3H), 3.70−4.10 (m, 2H), 5.91 (s, 2H), 6.54 (s, 1H), 6.68 (s, 1H), 6.80, 7.26 (AB type, J = 8.6 Hz, each 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 37.0, 37.3, 44.5, 49.7, 56.0, 61.7, 100.9, 109.2, 11.1, 110.2, 113.6, 128.2, 133.4, 133.7, 134.4, 145.6, 145.8, 152.2, 165.5, 183.7; EI-MS m/z (rel intensity) 435 (M^+, 31), 433 (M^+, 32), 354 (68), 243 (100). Anal. Calcd for $C_{20}H_{20}BrNO_5$: C, 55.31; H, 4.64; Br, 18.40; N, 3.23. Found: C, 55.56; H, 4.79; Br, 18.43; N, 3.15.

Treatment of 8 with Bu_3SnH and AIBN. A stirred solution of **8** (30.4 mg, 0.07 mmol), AIBN (11.5 mg, 0.07 mmol), and Bu_3SnH (40.7 mg, 0.14 mmol) in toluene (2 mL) was heated at reflux for 4 h. The reaction mixture was concentrated. The residue was dissolved in CH_3CN (10 mL), then washed with hexane (3×20 mL). Evaporation of CH_3CN afforded an oil (34 mg), which was subjected to preparative TLC with 3% $MeOHCH_2Cl_2$. A band with R_f 0.6 afforded **9** as colorless crystals (21 mg, 94%), mp 151−152 °C (Et_2O) (lit.[6c] mp 151−152 °C).

Preparation of 3-(6-Bromo-2,3-dimethoxybenzoyl)-7,8-(methylenedioxy)-1,2-dihydro-3*H*-3-benzazepine (10). A mixture of phenethylamine **11** (2.48 g, 15 mmol), bromoacetaldehyde dimethylacetal (2.53 g, 15 mmol), and K_2CO_3 (10.3 g, 75 mmol) in DMF (50 mL) was stirred at 80 °C for 12 h. The mixture was poured into water (80 mL), then extracted with ether (3 × 40 mL). The combined extracts were washed with saturated brine (5 × 50 mL), dried ($MgSO_4$), and concentrated to give acetal **12** (3.83 g, 99%) as a colorless oil: IR (Nujol) ν_{max} 3328, 1609, 1502 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.75, 2.85 (each t, J = 5.6 Hz, each 2H), 3.37 (s, 6H), 4.45 (t, J = 5.6 Hz, 1H), 5.92 (s, 2H), 6.64 (dd, J = 7.9, 1.7 Hz, 1H), 6.69 (d, J = 1.7 Hz, 1H), 6.73 (d, J = 7.9 Hz, 1H); EI-MS m/z (rel intensity) 253 (M^+, 7), 190 (15), 149 (55), 118 (100). HRMS calcd for $C_{13}H_{19}NO_4$ 253.1314, found 253.1316. To a stirred suspension of **12** (128 mg, 0.5 mmol), Et_3N (91 mg, 0.9 mmol), and anhydrous $MgSO_4$ (100 mg) in CH_2Cl_2 (7 mL) at rt was added dropwise 6-bromo-2,3-dimethoxybenzoyl chloride[2b,15g] (0.24 g, 0.6 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred for 12 h, and then washed with water (3×50 mL) and aq 2 N NaOH (3×25 mL) and dried (Na_2SO_4). The solvent was evaporated to give amide **13** (290 mg, 61%) as a light brown oil. This was dissolved in a mixture of MeOH (0.5 mL) and acetic acid (3 mL) and cooled to 0 °C. After concd H_2SO_4 (1.0 mL) was added dropwise, the mixture was stirred at rt for 24 h and poured slowly into concd NH_4OH (15 mL). The mixture was extracted with CH_2Cl_2 (3×15 mL). The combined extracts were washed with water (3×20 mL), dried (Na_2SO_4), and concentrated to give an oil (281 mg), which was purified by preparative TLC on silica gel developed with 1% $MeOHCH_2Cl_2$. A main band with R_f 0.6 gave 3-benzazepine **10** (186 mg, 85% in 2 steps) as a colorless oil: IR (Nujol) ν_{max} 1661, 1636, 1505 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.96−3.13 (m, 2H), 3.62, 4.11 (2:1, each t, J = 5.0, 4.0 Hz, 1H), 3.96 (s, 3H), 3.88 (s, 3H), 4.01−4.36 (m, 1H), 5.40, 5.80 (2:1, each d, J = 10.6, 2:1, 1H), 5.92 (s, 2H), 6.20, 7.42 (2:1, each d, J = 10.6 Hz, 1H), 6.50, 6.61, 6.64, 6.71 (1:2:2:1, each s, 2H), 6.83, 6.85 (2:1. each d, J = 8.9 Hz, 1H), 7.30, 7.36 (2:1, each s, 1H); EI-MS m/z (rel intensity) 433 (M^+, 29), 431 (M^+, 30), 243 (100). HRMS calcd for $C_{20}H_{18}BrNO_5$ 431.0396, found 431.0382.

Preparation of 7,8-Methylenedioxy-4,5-dihydro-3*H*-3-benzazepine (14) and an Attempt To Obtain Its *N*-Benzoyl Derivative 10. To a stirred solution of acetal **12** (127 mg, 0.5 mmol) in AcOH (2 mL) was added concd H_2SO_4 (0.5 mL). The mixture was warmed at 40 °C for 15 h, then poured slowly into concd NH_4OH solution (10 mL). The mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with water (3 × 10 mL), dried (Na_2SO_4), and concentrated to give enamine **14** as an oil (73 mg, 77%); IR (Nujol) ν_{max} 3310, 1628, 1502 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.39−2.97 (m, 2H), 3.42−3.47 (m, 1H), 3.91 (br s, 1H), 4.95 (d, J = 9.9 Hz, 1H), 5.87 (s, 2H), 6.11 (dd, J = 9.9, 5.9 Hz, 1H), 6.50 (s, 1H), 6.56 (s, 1H); EI-MS (rel intensity) 189 (M^+, 100). HRMS calcd for $C_{20}H_{18}BrNO_5$ 189.0790, found 189.0783. This was dissolved in benzene (2 mL) containing pyridine (0.5 mL) and treated with 6-bromo-2,3-dimethoxybenzoyl chloride[2b,15g] (137 mg, 0.49 mmol) in benzene (1 mL) at rt for 12 h. The reaction mixture was diluted with Et_2O (15 mL), washed with water (3× 10 mL) and aq 2 N NaOH (3×10 mL), and dried (Na_2SO_4). The solvent was evaporated to give an oil (127 mg), ^{1}H NMR spectrum of which showed mainly the presence of 6-bromo-2,3-dimethoxybenzoic acid but not the desired amide **10**.

Radical Cyclization of 10: Synthesis of Lennoxamine (1). A solution of **10** (30 mg, 0.07 mmol), AIBN (36 mg, 0.21 mmol), and Bu_3SnH (30 mg, 2.3 mmol) in dry benzene (12 mL) under nitrogen was refluxed with stirring for 8 h. The solvent was evaporated. The residue was dissolved in CH_3CN (10 mL) and washed with hexane (3 × 20 mL). The CH_3CN layer was separated and concentrated to give an oil (35 mg), which was purified by preparative TLC on silica gel developed with 3% MeOH−CH_2Cl_2. A main band with R_f 0.6 was crystallized from MeOH to give lennoxamine (**1**) (18 mg, 73%), mp 229−230 °C (lit.[1e] mp 225 °C; lit.[2c] mp 223−225 °C; lit.[6b] mp 223−226 °C; lit.[3j] mp 226−227 °C; lit.[5h] 226−228 °C; lit.[6c] mp 227−228 °C; lit.[5c,7a] mp 228−229 °C; lit.[2d] mp 229−230 °C; lit.[5f] mp 235−235.5 °C), as colorless crystals. A band with R_f 0.8 gave the debrominated reactant **15** (6 mg, 24%) as a pale yellow oil: IR (neat) ν_{max} 2938, 2240, 1659 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.94−3.03 (m, 2H), 3.70−4.33 (m, 2H), 3.85 (s, 3H), 3.90 and 3.91 (2:1, each s, 3H), 5.36 and 5.75 (2:1, each d, J = 10.6 Hz, 1H), 5.92 (s, 2H), 6.29 and 7.43 (2:1, each d, J = 10.6 Hz, 1H), 6.51, 6.60, 6.64, 6.71 (1:2:2:1, each s, 2H), 6.83−6.88 (m, 1H), 6.98 (dd, J = 8.3, 1.7, 1H), 7.09−7.16 (m, 1H); EI-MS m/z (rel intensity) 353 (M^+, 1), 91 (31). HRMS calcd for $C_{20}H_{17}NO_5$ 353.1263, found 353.1260.

Heck Cyclization of Benzazepine 10: Synthesis of Dehydrolennoxamine (3). A stirred mixture of benzazepine **10** (15 mg, 0.035 mmol), $Pd(OAc)_2$ (1.6 mg, 0.007 mmol), PPh_3 (3.7 mg, 0.014 mmol), and

K_2CO_3 (48 mg, 0.35 mmol) in toluene (2 mL) was refluxed under argon for 24 h. The reaction mixture was cooled to rt and filtered through a Celite pad. The filtrate was concentrated. The residue (18 mg) was purified by preparative TLC developed with 3% MeOH−CH_2Cl_2. A main band with R_f 0.3 was crystallized from MeOH to give **3** (12 mg, 94%) as yellow crystals, mp 210−211 °C (lit.[3j] mp 208−209 °C; lit.[2b] mp 209−211 °C; lit.[5f] mp 213−214 °C).

Preparation of 2-Iodo-3,4-dimethoxybenzaldehyde (16b). A mixture of 2-bromo-3,4-dimethoxybenzaldehyde (**16a**)[20] (2.45 g, 10 mmol), ethylene glycol (5.68 mL, 0.1 mol), and concd H_2SO_4 (0.5 mL) in dry benzene (50 mL) was refluxed with a DeanStark water separator under argon for 12 h. After cooling, the mixture was diluted with Et_2O (50 mL), washed with water (3 × 30 mL), and dried (Na_2SO_4). The solvent was evaporated to give [1,3]dioxolane **17** (2.93 g, >99%) as a crystalline solid. An analytical sample was prepared by recrystallization from benzene−hexane; mp 72−73 °C; IR (Nujol) ν_{max} 1594, 1495 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.85 (s, 3H), 3.88 (s, 3H), 4.03−4.18 (m, 4H), 6.07 (s, 1H), 6.89 (d, J = 8.9 Hz, 1H), 7.34 (d, J = 8.9 Hz, 1H); EI-MS m/z (rel intensity) 290 (M^+, 88), 289 [(M + H)$^+$, 100], 288 (M^+, 90), 257 (28), 243 (30), 216 (54). Anal. Calcd for $C_{11}H_{13}BrO_4$: C, 45.70; H, 4.53; Br, 27.64. Found: C, 45.81; H, 4.58; Br, 27.57. To a stirred solution of this dioxolane (4.34 g, 15 mmol) in dry THF (100 mL) under argon at −78 °C was added dropwise *n*-BuLi (1.5 M hexane solution, 12 mL). After 20 min, a solution of *N*-iodosuccinimide (4.39 g, 19.5 mmol) in dry THF (100 mL) was added dropwise. The mixture was stirred at −78 °C for 2 h, and then at rt for 3 h. The resulting mixture was quenched with aq 2 N HCl (10 mL), stirred for 2 h, extracted with CH_2Cl_2 (3 × 30 mL), washed with saturated brine (3 × 30 mL), and dried (Na_2SO_4). The solution was concentrated to dryness. The residue (4.19 g) was subjected to column chromatography on silica gel with CH_2Cl_2 as eluent to give iodide **16b** (3.18 g, 73%) as a crystalline solid. An analytical sample was prepared by recrystallization from EtOH; mp 77−78 °C; IR (Nujol) 1677, 1579 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.87 (s, 3H), 3.96 (s, 3H), 6.97 (d, J = 8.6 Hz, 1H), 7.73 (d, J = 8.6 Hz, 1H), 10.02 (s, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 56.2, 60.4, 100.3, 111.8, 127.4, 128.9, 148.7, 157.7, 194.9; EI-MS m/z (rel intensity) 292 (M^+, 100), 277 (11), 248 (3). Anal. Calcd for $C_9H_9BrO_3$: C, 44.11; H, 3.70; Br, 32.60. Found: C, 44.04; H, 3.85; Br, 32.48.

2-Cyanomethyl-*N*-(2-bromo-3,4-dimethoxybenzylidene)-4,5-(methylenedioxy)phenethylamine (18a): General Procedure. A mixture of trifluoroacatamide **4a** (600 mg, 2.0 mmol), 2-bromo-3,4-dimethoxybenzaldehyde (**16a**) (490 mg, 2.0 mmol), K_2CO_3 (1.38 g, 10 mmol), water (5 mL), and MeOH (15 mL) was stirred at rt overnight. MeOH was then evaporated, and the residue was treated with water (20 mL) and CH_2Cl_2 (20 mL). The organic layer was washed with water (3 × 20 mL), dried (Na_2SO_4), and concentrated. The residue was crystallized from EtOH to give imine **18a** (836 mg, 97%) as colorless crystals; mp 108−109 °C; IR (Nujol) ν_{max} 1639, 1589 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.93 (t, J = 6.6 Hz, 2H), 3.71 (s, 2H), 3.85 (s, 3H), 3.91 (s, 3H), 3.85 (t, J = 6.9 Hz, 2H), 5.96 (s, 2H), 6.75 (s, 1H), 6.83 (s, 1H), 6.91 (d, J = 8.9 Hz, 1H), 7.72 (d, J = 8.9 Hz, 1H), 8.42 (s, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 21.4, 33.9, 56.1, 60.5, 62.4, 101.3, 108.9, 110.2, 111.3, 118.2, 121.1, 121.4, 124.0, 127.5, 131.6, 146.0, 146.5, 147.6, 155.5, 160.6; EIMS m/z (rel intensity) 433 (M^+, 14), 431 (M^+, 15), 256 (37), 200 (50), 177 (100). Anal. Calcd for $C_{20}H_{19}BrN_2O_4$: C, 55.70; H, 4.44; Br, 18.53; N, 6.50. Found: C, 55.63; H, 4.57; Br, 18.28; N, 6.34.

2-Cyanomethyl-*N*-(2-iodo-3,4-dimethoxybenzylidene)-4,5-(methylenedioxy)phenethylamine (18b): colorless crystals (99%), mp 128−130 °C (EtOH); IR (Nujol) ν_{max} 1634, 1582, 1505 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.94 (t, J = 6.6 Hz, 2H), 3.70 (s, 2H), 3.83 (s, 3H), 3.86 (t, J = 6.9 Hz, 2H), 3.91 (s, 3H), 5.95 (s, 2H), 6.74 (s, 1H), 6.83 (s, 1H), 6.92 (d, J = 8.9 Hz, 1H), 7.67 (d, J = 8.9 Hz, 1H), 8.26 (s, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 21.4, 33.9, 56.0, 60.3, 62.1, 99.6, 101.3, 108.9, 110.2, 112.3, 118.2, 121.4, 124.5, 129.9, 131.5, 146.5, 147.6, 148.3, 154.6, 165.0; EI-MS m/z (rel intensity) 478 (M^+, 76), 304 (33), 177 (100). Anal. Calcd for $C_{20}H_{19}IN_2O_4$: C, 50.22; H, 4.00; I, 26.53; N, 5.86. Found: C, 50.29; H, 4.03; I, 26.78; N, 5.78.

2-Cyanomethyl-*N*-(2-bromo-4,5-dimethoxybenzylidene)-4,5-(methylenedioxy)phenethylamine (18c): colorless crystals (93%), mp 109−110 °C (EtOH); IR (Nujol) ν_{max} 2256, 1634, 1598, 1509 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.94 (t, J = 6.9 Hz, 2H), 3.72 (s, 2H), 3.84 (t, J = 6.9 Hz, 2H), 3.91 (s, 3H), 3.94 (s, 3H), 5.96 (s, 2H), 6.76 (s, 1H), 6.84 (s, 1H), 6.98 (s, 1H), 7.48 (s, 1H), 8.37 (s, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 21.4, 34.0, 56.1, 56.2, 62.1, 101.3, 109.0, 109.6, 110.3, 115.0, 116.7, 118.1, 121.3, 126.5, 131.5, 146.6, 147.7, 148.7, 151.7, 160.6; EI-MS m/z (rel intensity) 433 (M^+, 49), 431 (M^+, 50), 256 (31), 200 (44), 177 (100). Anal. Calcd for $C_{20}H_{19}BrN_2O_4$: C, 55.70; H, 4.44; Br, 18.53; N, 6.50. Found: C, 55.47; H, 4.59; Br, 18.70; N, 6.42.

2-(2-Bromo-3,4-dimethoxyphenyl)-1-cyano-7,8-(methylenedioxy)-1,2,4,5-tetrahydro-3*H*-3-benzazepine (19a): General Procedure. A solution of **18a** (431 mg, 1.0 mmol) and *t*-BuONa (105 mg, 1.1 mmol) in dry THF (30 mL) and dry *t*-BuOH (15 mL) was refluxed under argon for 10 h. The cooled reaction mixture was concentrated and dissolved in CH_2Cl_2 (20 mL), washed with water (3 × 20 mL), dried (Na_2SO_4), and concentrated. The residue was crystallized from EtOH to give 3-benzazepine **19a** (409 mg, 95%) as colorless crystals, mp 208−209 °C; IR (Nujol) ν_{max} 1600, 1504 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.17 (br. s, 1H), 2.73 (dd, J = 15.2, 5.6 Hz, 1H), 2.87 (t, J = 12.2 Hz, 1H), 3.42−3.55 (m, 2H), 3.87 (s, 3H), 3.90 (s, 3H), 3.94 (d, J = 1.0 Hz, 1H), 4.34 (d, J = 1.0 Hz, 1H), 5.97, 5.98 (each d, J = 1.3 Hz, each 1H), 6.68 (s, 1H), 6.70 (s, 1H), 6.96 (d, J = 8.6 Hz, 1H), 7.51 (d, J = 8.6 Hz, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 37.5, 47.4, 48.9, 56.1, 60.5, 62.5, 101.4, 110.4, 111.1, 111.6, 117.7, 118.5, 122.4, 127.3, 133.5, 136.3, 136.0, 146.4, 147.4, 153.3; EI-MS m/z (rel intensity) 433 (M^+, 22), 431 (M^+, 24), 430 (92), 390 (12), 256 (50), 244 (100), 200 (95), 177 (94). Anal. Calcd for $C_{20}H_{19}BrN_2O_4$: C, 55.70; H, 4.44; Br, 18.53; N, 6.50. Found: C, 55.53; H, 4.31; Br, 18.72; N, 6.36.

1-Cyano-2-(2-iodo-3,4-dimethoxyphenyl)-7,8-(methylenedioxy)-1,2,4,5-tetrahydro-3*H*-3-benzazepine (19b): colorless crystals (85% in two steps from **4** and **16b** through **18b**), mp 219−223 °C (EtOH); IR (Nujol) ν_{max} 2236, 1587, 1504 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.13 (br. s, 1H), 2.74 (dd, J = 15.2, 5.6 Hz, 1H), 2.88 (t, J = 12.2 Hz, 1H), 3.48 (m, 2H), 3.85 (s, 3H), 3.89 (s, 3H), 3.91 (s, 1H), 4.24 (s, 1H), 5.97, 5.98 (each s, each 1H), 6.68 (s, 1H), 6.76 (s, 1H), 6.97 (d, J = 8.6 Hz, 1H), 7.51 (d, J = 8.6 Hz, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 37.5, 47.4, 48.9, 56.1, 60.3, 67.0, 98.4, 101.4, 110.8, 111.1, 112.6, 117.7, 123.1, 127.3, 136.4, 136.4, 146.0, 147.5, 148.7, 152.4; EI-MS m/z (rel intensity) 478 (M^+, 100), 438 (15), 304 (37), 256 (50), 215 (14), 177 (87). Anal. Calcd for $C_{20}H_{19}IN_2O_4$: C, 50.22; H, 4.00; I, 26.53; N, 5.86. Found: C, 50.18; H, 4.00; I, 26.47; N, 5.77.

2-(2-Bromo-4,5-dimethoxyphenyl)-1-cyano-7,8-(methylenedioxy)-1,2,4,5-tetrahydro-3*H*-3-benzazepine (19c): colorless crystals (87% in two steps from **4** and **16c** through **18c**), mp 213-215 °C (EtOH); IR (Nujol) ν_{max} 1504 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.0−2.2 (br, 1H), 2.75 (dd, J = 15.2, 5.6 Hz, 1H), 2.88 (t, J = 12.2 Hz, 1H), 3.42−3.57 (m, 2H), 3.89 (s, 4H), 3.96 (s, 3H), 4.30 (s, 1H), 5.97, 5.98 (each d, J = 2.0 Hz, each 1H), 6.67 (s, 1H), 6.69 (s, 1H), 7.04 (s, 1H), 7.39 (s, 1H); EI-MS m/z (rel intensity) 433 (M^+, 17), 431 (M^+, 20), 430 (76), 390 (11), 256 (42), 244 (40), 200 (32), 177 (100). Anal. Calcd for $C_{20}H_{19}BrN_2O_4$: C, 55.70; H, 4.44; Br, 18.53; N, 6.50. Found: C, 55.67; H, 4.48; Br, 18.37; N, 6.41.

Preparation of 13-Cyannolenoxamine (20a): General Procedure. A mixture of iodide **19b** (954 mg, 2.0 mmol), PPh_3 (210 mg, 0.80 mmol), $Pd(OAc)_2$ (45 mg, 0.20 mmol), and K_2CO_3 (1.93 g,

14 mmol) in toluene (120 mL) was refluxed under CO for 12 h. The precipitates were removed by filtration with a Celite pad, and the filtrate was concentrated. The residue (1.49 g) was chromatographed on silica gel with 3% MeOH−CH_2Cl_2 as eluents to give a crude product. Crystallization from EtOAc−hexane gave **20a** (730 mg, 97%) as colorless crystals, mp 270−272 °C; IR (Nujol) ν_{max} 2242, 1693, 1504 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.85 (dd, J = 15.2, 4.3 Hz, 1H), 2.96 (t, J = 12.2 Hz, 1H), 3.34−3.45 (m, 1H), 3.93 (s, 3H), 4.12 (s, 3H), 4.22 (d, J = 2.3 Hz, 1H), 4.53 (d, J = 2.3 Hz, 1H), 4.80 (m, 1H), 6.00, 6.02 (each d, J = 1.3 Hz, each 1H), 6.75 (s, 1H), 6.76 (s, 1H), 7.15, 7.19 (AB type, J = 8.3 Hz, each 1H); EI-MS m/z (rel intensity) 378 (M^+, 100), 338 (28), 205 (51), 192 (72). Anal. Calcd for $C_{21}H_{18}N_2O_5$: C, 66.66; H, 4.79; N, 7.40. Found: C, 66.52; H, 4.75; N, 7.32.

13-Cyano-10,11-dimethoxy-5,6,12b,13-tetrahydro-8*H*-2,3-(methylenedioxy)isoindolo[1,2-*b*][3]benzazepin-8-one (20b). Bromide **19c** (22 mg, 0.05 mmol) on carbonylation under a similar manner for 24 h gave colorless crystals of **20b** (8 mg, 42%), mp 276−278 °C (AcOEt−hexane); IR ($CHCl_3$) ν_{max} 2242, 1693, 1504 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.87−3.03 (m, 3H), 3.97 (s, 3H), 4.04 (s, 3H), 4.06 (d, J = 7.9 Hz, 1H), 4.41 (d, J = 7.9 Hz, 1H), 4.73−4.81 (m, 1H), 6.01, 6.03 (each d, J = 1.0 Hz, each 1H), 6.75 (s, 1H), 7.30 (s, 1H), 7.33 (s, 1H), 7.49 (s, 1H); EI-MS m/z (rel intensity) 378 (M^+, 100), 352 (31), 338 (23), 205 (98), 192 (87). Anal. Calcd for $C_{21}H_{18}N_2O_5$: C, 66.66; H, 4.79; N, 7.40. Found: C, 66.45; H, 4.76; N, 7.41.

Synthesis of 3 by Dehydrocyanation of 20a. A mixture of **20a** (38 mg, 0.1 mmol) and *t*-BuONa (15 mg, 0.15 mmol) in *t*-BuOH (3 mL) and THF (2 mL) was refluxed under Ar for 1 h. The cooled mixture was concentrated, then treated with CH_2Cl_2 (10 mL) and water (10 mL). The CH_2Cl_2 layer was washed with water (10 mL), dried (Na_2SO_4), and concentrated to give **3** as a solid (35 mg), which showed one spot (R_f 0.6) on silica gel TLC developed with 3% MeOH−CH_2Cl_2. The reaction mixture obtained from carbonylation of **19b** (48 mg, 0.1 mmoL) followed by the above-mentioned dehydrocyanation in one pot was filtered through a Celite pad. The filtrate was subjected to silica gel TLC (3% MeOH−CH_2Cl_2), and a band with R_f 0.6 gave **3** (34 mg, 96%) as colorless crystals, mp 208−209 °C (MeOH).

13-Cyano-9,10-dimethoxy-5,6-dihydro-8*H*-2,3-(methylenedioxy)isoindolo[1,2-*b*][3]benzazepin-8-one (21a). A mixture of **20a** (378 mg, 1.0 mmol), Bu_4NI (3.69 g, 10 mmol), and 50 wt % aqueous NaOH solution (5 mL) in $CHCl_3$ (50 mL) was refluxed under oxygen for 48 h. After cooling, Et_2O (100 mL) was added, and the mixture was washed with saturated brine (6 × 50 mL), dried ($MgSO_4$), and concentrated. The residue was chromatographed on a silica gel column with 3% MeOH−CH_2Cl_2 as eluents to give a crude product, which was crystallized from CH_2Cl_2−hexane to give **21a** (266 mg, 75%) as yellow crystals, mp 280−281 °C; IR (Nujol) ν_{max} 2202, 1712, 1578, 1511 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.00 (dd, J = 5.3, 4.3 Hz, 2H), 3.97 (s, 3H), 4.08 (s, 3H), 3.90−4.20 (br m, 2H), 6.02 (s, 2H), 6.66 (s, 1H), 7.17 (d, J = 8.9 Hz, 1H), 7.36 (s, 1H), 8.57 (d, J = 8.9 Hz, 1H); EI-MS m/z (rel intensity) 376 (M^+, 100), 361 (38), 347 (22). Anal. Calcd for $C_{21}H_{16}N_2O_5$: C, 67.02; H, 4.28; N, 7.44. Found: C, 66.88; H, 4.27; N, 7.51.

13-Carbamoyl-9,10-dimethoxy-5,6-dihydro-8*H*-2,3-(methylenedioxy)isoindolo[1,2-*b*][3]benzazepin-8-one (21b). A solution of **21a** (38 mg, 0.1 mmol), H_2O_2 (30 wt % solution in water, 0.34 mL), and Bu_4NF (1.0 M solution in THF, 3 mL) in DMSO (15 mL) was stirred at rt for 3 h. The resulting mixture was diluted with Et_2O (30 mL) and washed with saturated brine (6 × 300 mL), dried ($MgSO_4$), and concentrated to give a crude product, which was purified by preparative TLC on silica gel developed with 3% MeOH−CH_2Cl_2. A main band with R_f 0.5 gave **21b** (16 mg, 48%) as yellow crystals, mp 245−250 °C (EtOH); IR ($CHCl_3$) ν_{max} 3334, 2930, 1697, 1501 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.95 (t, J = 4.3 Hz, 2H), 3.54−3.66 (m, 2H), 3.87 (s, 3H), 3.97 (s, 3H), 5.98 (s, 2H), 6.15, 6.60 (each br s, each 1H), 6.63 (s, 1H), 7.01 (d, J = 8.6 Hz, 1H), 7.15 (s, 1H), 7.74 (d, J = 8.6 Hz, 1H); EI-MS m/z (rel intensity) 394 (M^+, 100), 365 (19), 350 (40). Anal. Calcd for $C_{21}H_{18}N_2O_6$: C, 63.96; H, 4.60; N, 7.10. Found: C, 63.69; H, 4.58; N, 6.98.

2-(2-Bromo-3,4-dimethoxyphenyl)-1-cyano-3-methyl-7,8-(methylenedioxy)-1,2,4,5-tetrahydro-3*H*-3-benzazepine (19aMe): General Procedure. A mixture of **19a** (86 mg, 0.20 mmol) and CH_3I (0.12 mL, 2.0 mmol) in THF (3 mL) was refluxed for 8 h. The resulting mixture was treated with 1.0 M aqueous K_2CO_3 solution (10 mL), extracted with CH_2Cl_2 (3 × 10 mL), washed with water (3 × 20 mL), dried (Na_2SO_4), and concentrated. The residue was crystallized from CH_2Cl_2−EtOH−hexane to give **19aMe** (71 mg, 95%) as colorless crystals, mp 212−213 °C (EtOH); IR ($CHCl_3$) ν_{max} 2238, 1593, 1506 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.14 (s, 3H), 2.42 (t, J = 11.6 Hz, 1H), 2.80 (dd, J = 15.8, 4.0 Hz, 1H), 3.37 (dd, J = 12.9, 6.0 Hz, 1H), 3.49 (d, J = 1.3 Hz, 1H), 3.61 (dd, J = 15.8, 10.6 Hz, 1H), 3.80 (d, J = 1.3 Hz, 1H), 3.89 (s, 3H), 3.91 (s, 3H), 5.96, 5.99 (each d, J = 1.3 Hz, each 1H), 6.66 (s, 1H), 6.67 (s, 1H), 6.99 (d, J = 8.9 Hz, 1H), 7.64 (d, J = 8.9 Hz, 1H); EI-MS m/z (rel intensity) 446 (M^+, 99), 444 (M^+, 100), 404 (29), 270 (51), 229 (58). Anal. Calcd for $C_{21}H_{21}BrN_2O_4$: C, 56.64; H, 4.75; Br, 17.94; N, 6.29. Found: C, 56.72; H, 4.79; Br, 17.78; N, 6.14.

1-Cyano-2-(2-iodo-3,4-dimethoxyphenyl)-3-methyl-7,8-(methylenedioxy)-1,2,4,5-tetrahydro-3*H*-3-benzazepine (19bMe): colorless crystals (96%), mp 213-215 °C (EtOH); IR (Nujol) ν_{max} 2236, 1587, 1504 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.13 (s, 3H), 2.43 (t, J = 11.6 Hz, 1H), 2.78 (dd, J = 15.8, 6.9 Hz, 1H), 3.37 (ddd, J = 12.9, 6.9, 1.3 Hz, 1H), 3.63 (dd, J = 15.8, 9.9 Hz, 1H), 3.76 (s, 2H), 3.87 (s, 3H), 3.91 (s, 3H), 5.97, 5.98 (d, J = 1.3 Hz, each 1H), 6.68 (s, 1H), 6.71 (s, 1H), 7.01 (d, J = 8.6 Hz, 1H), 7.61 (d, J = 8.6 Hz, 1H); EI-MS m/z (rel intensity) 492 (M^+, 100), 452 (31), 365 (17), 318 (36), 277 (50). Anal. Calcd for $C_{21}H_{21}IN_2O_4$: C, 51.23; H, 4.30; I, 25.78; N, 7.95. Found: C, 51.28; H, 4.28; I, 25.61; N, 8.00.

2-(2-Cyano-3,4-dimethoxyphenyl)-3-methyl-7,8-(methylenedioxy)-1,2,4,5-tetrahydro-3*H*-3-benzazepine (22b): General Procedure for Radical 1,4-Cyano Migration (Entries 1−6 and 11 in Table 3). A stirred solution of bromide **19aMe** (44 mg, 0.10 mmol), AIBN (24 mg, 0.15 mmol), and Bu_3SnH (58 mg, 0.20 mmol) in dry toluene (6 mL) was refluxed for 12 h under argon (entry 6). The resulting mixture was concentrated, dissolved in CH_3CN (10 mL), washed with hexane (3 × 20 mL), and concentrated. The residue was subjected to preparative TLC on silica gel developed with 3% MeOH−CH_2Cl_2 to show two bands at R_f 0.5 and 0.35 in a 1:1 ratio. A mobile band with R_f 0.5 gave **22b** (10 mg, 30%) as a light brown oil; IR ($CHCl_3$) ν_{max} 2224, 1573, 1488, 1041 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.07 (s, 3H), 2.38−2.52 (m, 1H), 2.63 (d, J = 14.9 Hz, 1H), 2.75 (dd, J = 7.3, 14.9 Hz, 1H), 3.12−3.28 (m, 3H), 3.51 (d, J = 9.2, 1H), 3.90 (s, 3H), 4.03 (s, 3H), 5.90 (s, 2H), 6.58 (s, 1H), 6.63 (s, 1H), 7.11 (d, J = 8.9 Hz, 1H), 7.24 (d, J = 8.9 Hz, 1H); EI-MS m/z (rel intensity) 366 (M^+, 100), 351 (23), 310 (49), 217 (37). HR-MS calcd for $C_{21}H_{22}N_2O_4$ 366.1579, found 366.1574. A less mobile band with R_f 0.35 gave **24b**, mp 175−178 °C (95% EtOH), as colorless crystals (9 mg, 27%, R_f 0.35); IR ($CHCl_3$) ν_{max} 2242, 1603, 1590, 1517 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.13 (s, 3H), 2.41 (t, J = 11.7 Hz, 1H), 2.84 (dd, J = 15.6, 6.8 Hz, 1H), 3.29 (br d, J = 15.6 Hz, 1H), 3.55 (br s, 1H), 3.55 (br t, J = 12.7 Hz, 1H), 3.89, 3.90 (each s, each 3H), 3.93 (br s, 1H), 5.94, 5.96 (each d, J = 1.5 Hz, each 1H), 6.55, 6.58 (each s, each 1H), 6.83 (d, J = 7.8 Hz, 1H), 6.85 (dd, J = 7.8, 2.0 Hz, 1H), 7.10 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.5, 46.3, 46.3, 55.9, 55.9, 57.2, 71.3, 101.3, 109.9, 110.0, 110.3, 118.9, 119.8, 127.0, 134.1, 135.4, 146.1, 147.6, 148.8, 149.2; EI-MS m/z

(rel intensity) 366 (M^+, 94), 192 (100), 178 (50), 151 (82). Anal. Calcd for $C_{21}H_{22}N_2O_4$: C, 68.84; H, 6.05; N, 7.65. Found: C, 68.76; H, 5.98; N, 7.42.

1-Cyano-2-(3.4-dimethoxyphenyl)-7,8-(methylenedioxy)-1,2,3,4-tetrahydro-3*H*-3-benzazepine (24a): colorless crystals (7 mg, 40%, R_f 0.2), mp 209−211 °C (95% EtOH), from **19b** (24 mg, 0.05 mmol) (entry 1); IR ($CHCl_3$) ν_{max} 3320, 2232, 1606, 1593, 1519 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.20 (br s, 1H), 2.74 (dd, J = 15.1, 5.4 Hz, 1H), 2.85 (t, J = 12.2 Hz, 1H), 3.43 (ddd, J = 12.2, 5.4, 2.0 Hz, 1H), 3.52 (ddd, J = 15.1, 12.2, 2.0 Hz, 1H), 3.89 (d, J = 1.0 Hz, 1H), 3.93 (s, 3H and hiding 1H), 3.97 (s, 3H), 5.95, 5.97 (each d, J = 1.5 Hz, each 1H), 6.59, 6.68 (each s, each 1H), 6.86 (d, J = 8.3 Hz, 1H), 6.99 (dd, J = 8.3, 2.0 Hz, 1H), 7.18 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.5, 48.9, 49.0, 56.0, 56.0, 65.1, 101.4, 109.3, 110.4, 111.2, 111.3, 118.4, 118.5, 127.8, 135.2, 136.2, 146.0, 147.5, 149.0, 149.3; EI-MS m/z (rel intensity) 352 (M^+, 57), 178 (100). Anal. Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 67.98; H, 5.54; N, 7.69.

2-(2-Cyano-3.4-dimethoxyphenyl)-7,8-(methylenedioxy)-4,5-dihydro-3*H*-3-benzazepine (23a): brown oil (11 mg, 65%, R_f 0.2) from **19b** (25 mg, 0.05 mmol) (entry 2); IR ($CHCl_3$) 3318, 1625, 1500 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.06 (t, J = 4.6 Hz, 2H), 3.93 (s, 3H), 4.02 (s, 3H), 3.80−4.30 (br m, 2H), 5.95 (s, 2H), 6.16 (s, 1H), 6.66 (s, 1H), 6.77 (s, 1H), 7.08 (d, J = 8.3 Hz, 1H), 7.38 (d, J = 8.3 Hz, 1H); EI-MS m/z (rel intensity) 350 (M^+, 96), 335 (100), 319 (12). HRMS calcd for $C_{20}H_{18}N_2O_4$ 350.1266, found 350.1260.

2-(2-Cyano-3,4-dimethoxyphenyl)-7,8-(methylenedioxy)-1,2,4,5-tetrahydro-3*H*-3-benzazepine (22a) and Its Hydrobromide (22a-HBr): General Procedure for Radical 1,4-Cyano Migration (Entries 7−9 in Table 3). A stirred solution of **19a** (432 mg, 1.0 mmol), AIBN (82 mg, 0.50 mmol), and Bu_3SnH (0.54 mL, 2.0 mmol) in dry toluene (100 mL) was refluxed under Ar for 12 h (entry 9). The solvent was evaporated to give an oil, which showed a 4:0.2:1 ratio of **22a-HBr**, **23a**, and **24a** in its ^1H NMR spectrum, and was dissolved in CH_3CN (30 mL), washed with hexane (3 × 60 mL), and concentrated. The residue was treated with CH_2Cl_2 to give **22a-HBr** (246 mg, 57%) as yellow crystals, mp 220−225 °C dec; IR ($CHCl_3$) ν_{max} 3398, 2244, 1679, 1609 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.90 (dd, J = 15.1, 10.2 Hz, 1H), 3.07−3.20 (m, 3H), 3.35−3.41 (m, 1H), 3.96 (s, 3H), 4.15 (s, 3H), 4.63 (d, J = 10.2 Hz, 1H), 5.61 (br d, J = 15.2 Hz, 1H), 5.96, 5.97 (each s, each 1H), 6.73 (s, 1H), 6.74 (s, 1H), 7.23, 7.29 (AB type, J = 8.3 Hz, each 1H); EI-MS m/z (rel intensity) 352 [($M - HBr$)$^+$, 100], 335 (53), 191 (87), 94 (53). Anal. Calcd for $C_{20}H_{21}BrN_2O_4$: C, 55.44; H, 4.89; Br, 18.44; N, 6.47. Found: C, 55.20; H, 4.89; Br, 18.76; N, 6.37. A mixture of **22a-HBr** (43 mg, 0.1 mmol) and K_2CO_3 (138 mg, 1 mmol) in MeOH (10 mL) was stirred at rt for 3 h. The resulting mixture was concentrated, and the residue was dissolved in CH_2Cl_2, washed with water (20 mL), dried (Na_2SO_4), and concentrated to give **22a** (35 mg, >99%) as a pale brown oil; IR ($CHCl_3$) ν_{max} 3398, 1678, 1630 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.84−3.09 (m, 5H), 3.92 (s, 3H), 4.04 (s, 3H), 4.39 (d, J = 9.9 Hz, 1H), 5.01 (br d, J = 12.2 Hz, 1H), 5.94, 5.95 (each d, J = 1.3 Hz, each 1H), 6.72 (s, 1H), 6.75 (s, 1H), 7.10 (d, J = 8.3 Hz, 1H), 7.16 (d, J = 8.3 Hz, 1H); EI-MS m/z (rel intensity) 352 (M^+, 100), 335 (26), 191 (96). HRMS calcd for $C_{20}H_{20}N_2O_4$ 352.1424, found 352.1423.

2-(2-Cyano-4,5-dimethoxyphenyl)-7,8-(methylenedioxy)-4,5-dihydro-3*H*-3-benzazepine (23c): dark yellow oil (16 mg, 85%, R_f 0.2) from **19c** (22 mg, 0.05 mmol) (entry 11); IR ($CHCl_3$) 2228, 1626, 1613, 1497 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.08 (t, J = 4.6 Hz, 2H), 3.99 (s, 3H), 4.03 (s, 3H), 3.85−4.30 (br m, 2H), 5.96 (s, 2H), 6.14 (s, 1H), 6.67 (s, 1H), 6.80 (s, 1H), 7.11 (s, 1H), 7.14 (s, 1H); EI-MS m/z (rel intensity) 350 (M^+, 100), 335 (99), 319 (16). HRMS calcd for $C_{20}H_{18}N_2O_4$ 350.1266, found 350.1289.

Preparation of 1 from 22a-HBr. 22a-HBr (78 mg, 0.2 mmol) was dissolved in a solution of KOH (112 mg, 2 mmol) in isoPrOH (5 mL) and H_2O (1 mL) was refluxed for 24 h. The reaction mixture was acidified with 2 N HCl (10 mL) and extracted with CH_2Cl_2 (2 × 10 mL). The extracts were washed with saturated brine (10 mL), dried (Na_2SO_4), and concentrated. The residue was crystallized from CH_2Cl_2−hexane to give **1** (49 mg, 70%) as colorless crystals, mp 228−230 °C (MeOH). A one-pot two-step procedure starting with **19a** (43 mg) gave **1** (20 mg) in 56% yield.

Supporting Information Available: Experimental procedures for the preparation of benzazepine **7a**, and copies of ^1H NMR spectra of every compound except **5a** and **5b** and ^{13}C NMR spectra of compounds **4a**, **6b**, **8**, **16b**, **18a**, **18b**, **18c**, **19a**, **19b**, **24a**, and **24b**. This material is available free of charge via the Internet at http://pubs.acs.org.