Acid-Catalyzed Rearrangement of 5-Bromo-3-[1-allyl-2-(3,5-dimethoxyphenyl)-ethyl]-2-cyanopyridine

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Introduction

Tricyclic heterocycles **1** are an important class of chemical structures that display biological activity in several therapeutic areas.[1−4] A convenient synthesis of these compounds starts with the electrophilic cyclization of 2-cyanopyridine **2a** followed by hydrolysis of the intermediate imine to afford the versatile tricyclic ketone **3a**.[3,5] As part of a synthetic effort to develop more potent compounds related to our lead farnesyl protein transferase inhibitor **1b**,[1,4] we were interested in obtaining the 3,8-dihalo-5-allyl tricyclic ketone **3b**. Attempted synthesis of **3b** by cyclization of the appropriately substituted cyanopyridine **2b** showed that this substrate undergoes a complex acid-catalyzed chemical rearrangement. We report here a novel tetracyclic rearrangement product **4** that is formed in the electrophilic cyclization of **2b** (Figure 1) as well as the identification of the intermediate products and a possible reaction mechanism for the formation of the rearrangement products.

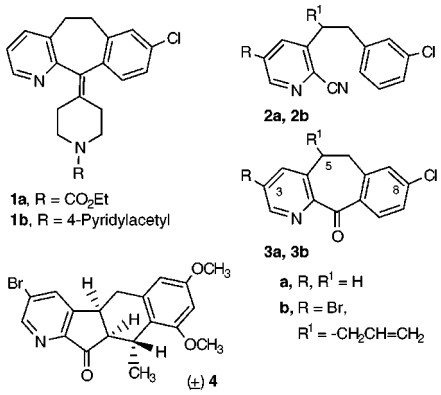
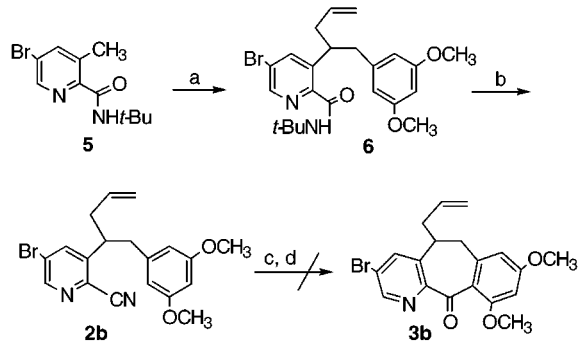


Figure 1.

Results and Discussion

The precursor allyl cyanopyridine **2b** was obtained by applying previously described methodology for the preparation of this class of compounds.[3] Thus, alkylation of 3-bromopyridine **5** using LDA and 3,5-dimethoxybenzyl chloride followed by alkylation of the intermediate product with allyl bromide afforded **6**. The *tert*-butylamide **6** was converted to nitrile **2b** with phosphorus oxychloride. Triflic acid-mediated electrophilic cyclization of **2b** followed by hydrolysis did not afford[6] the desired tricyclic ketone **3b** (Scheme 1).

Scheme 1[a]



[a] Key: (a) (i) LDA, THF, −78 °C, then 3,5-dimethoxybenzyl chloride, (ii) LDA, THF, −78 °C, then allyl bromide; (b) $POCl_3$, $PhCH_3$, 110 °C; 9c) CF_3SO_3H, 20 °C; (d) 2 N HCl, 110 °C.

Scheme 2 summarizes the reaction course that this cyclization/hydrolysis follows. Treatment of **2b** with triflic acid afforded a mixture of three products that were isolated and characterized as **7** (28%), **8** (35%), and **9** (11%). The isolation of these compounds required flash chromatography to afford the nonpolar nitrile **9** followed by preparative TLC to isolate the bicyclo amine **7** and the imine **8**. Hydrolysis of **8** in refluxing 2 N hydrochloric acid led to the formation of the ketone **4**, which contains a new tetracyclic ring system. The same ketone **4** was also obtained by refluxing a solution of **7**, or a mixture of **7** and **8**, in 2 N hydrochloric acid. Treatment of **2b** with triflic acid followed by refluxing a solution of the crude product in 2 N hydrochloric acid afforded, after flash chromatography, the tetracyclic ketone **4** (65%) and **9** (10%). The isolation of the components from this mixture was uneventful since compound **9** is relatively

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(1) For example, Loratidine (**1a**) is a potent nonsedating antihistamine drug in current medicinal use.[2] Dual PAF/histamine antagonists have been reported for analogues of **1**.[3] More recently, **1b** has been reported by our laboratories as a lead Ras farnesyl protein transferase (FPT) inhibitor;[4] such inhibitors are of interest for the development of antitumor agents.

(2) (a) Villani, F. J.; Magatti, C. V.; Vashi, D. B.; Wong, J.; Popper, T. L. *Arzneim.-Forsch/Drug Res.* **1986**, *36*(II), 1311. (b) Barnett, A.; Iorio, L. C.; Kreutner, W.; Tozzi, S.; Ahn, H. S.; Gulbenkian, A. *Agents Actions* **1984**, *14*, 590. (c) *Drugs Future* **1987**,*12*, 544.

(3) (a) Wong, J. K.; Piwinski, J. J.; Green, M. J.; Ganguly, A. K.; Anthes, J. C.; Billah, M. M. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1073. (b) Piwinski, J. J.; Wong, J. K.; Chan, T. M.; Green, M. J.; Ganguly, A. K. *J. Org. Chem.* **1990**, *55*, 3341.

(4) (a) Bishop, R. W.; Bond, R.; Petrin, J.; Wang, L.; Patton, R.; Doll, R.; Njoroge, G.; Cattino, J.; Schwartz, J.; Windsor, W.; Syto, R.; Schwartz, J.; Carr, D.; James, L.; Kirshmeier, P. *J. Biol. Chem.* **1995**, *270*, 30611.(b) For more recent references see Kelly, J.; Wolin, R.; Connolly, M.; Afonso, A.; James, L.; Kirshmeier, P.; Bishop, W. R.; McPhail, A. T. *Bioorg. Med. Chem.* **1998**, *6*, 673.

(5) (a) Villani, F. J.; Daniels, P. J. L.; Ellis, C. A.; Mann, T. A.; Wang, K.-C. *J. Heterocycl. Chem.* **1971**, *8*, 73. (b) Piwinski, J. J.; Wong, J. K.; Green, M. J.; Ganguly, A. K.; Billah, M. M.; West, R. E.; Kreutner, W. *J. Med. Chem.* **1991**, *34*, 457.

(6) Our initial experiment (Scheme 1) involved the reaction of **2b** with triflic acid followed by hydrolysis of the crude intermediate with aqueous hydrochloric acid and isolation of the single major product (65% yield) by chromatography. The NMR spectrum of the product showed a methyl doublet at δ 1.32, which was not consistent with the desired structure **3b**. Further NMR studies elucidated the structure of the reaction product as **4**. The interesting and complicated nature of this new tetracyclic ring system arising from a simple precursor prompted us to study the electrophilic cyclization reaction of **2b** in greater detail.

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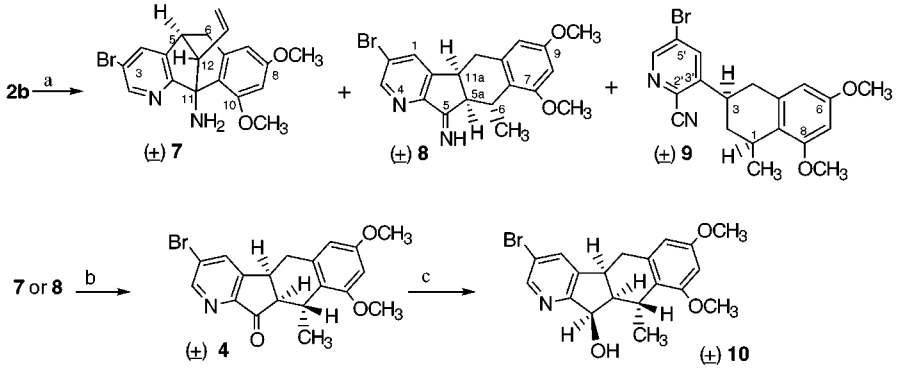
Scheme 2[a]



[a] Key: (a) CF_3SO_3H, 20 °C; (b) 2 N HCl, 110 °C; (c) $NaBH_4$, EtOH, 0 °C.

much less polar than **4**. Sodium borohydride reduction of the ketone **4** proceeded stereoselectively to afford exclusively one diastereoisomer, which was characterized as the alcohol **10**.

Structure Assignments.[7] Proton NMR data of **9** indicated the presence of resonances at δ 1.30 (d, CH_3), 3.79, 3.83 (s, OCH_3), 3.24, 2.88 (m, $H_{4,4}$), 1.58, 2.38 (m, $H_{2,2}$), 2.88 (m, H_3), 3.24 (m, H_1), and aromatic protons at δ 8.62 ($H_{6'}$), 7.92 ($H_{4'}$), 6.21 (H_5), and 6.36 (H_7); 2D (^{1}H−^{1}H) COSY, NOSEY, and HMBC data led to the assignment of structure **9** for this product. The relative stereochemical assignment at H_3 is based on the absence of an observable NOE between the methyl doublet at δ 1.30 and the methine multiplet at δ 2.88. ^{1}H NMR spectra of **7** indicated the presence of a vinylic function at δ 5.52, 5.36, 5.24 and an isolated methine proton at δ 3.13 (J = 9.0 Hz). The relative stereochemistry of H_{12} was assigned as cis to H_5 since a coupling between these protons was not measurable. In the ^{13}C NMR spectra, the resonance at δ 65.2 was assigned to the C_{11} quaternary carbon bearing an amino group. The carbon atoms were easily assignable using standard NMR techniques. Detailed NMR studies were performed for the structure elucidation of **4**. ^{1}H NMR data of **4** indicated the presence of resonances due to a methyl group, a methylene function, three methine moieties, and two methoxyl groups. In addition, there were four aromatic proton resonances. 2D (^{1}H−^{1}H) COSY and NOESY spectra led to the chemical shift assignments shown in Table 1.

HMBC and SINEPT studies confirmed all of the ^{13}C assignments. The relative stereochemistry of H_{5a} and H_{11a} was assigned as cis (J = 8.0 Hz) and that of H_{5a} and H_6 as trans (J = 1.6 Hz). Some of the relevant NOESY and HMBC connectivities for compound **4** are shown in Figure 2.

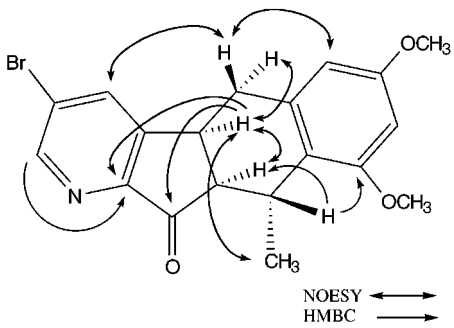


Figure 2. Selected NOESY/HMBC correlations in **4**.

The structures of the imine **8** and the borohydride reduction product **10** were assigned on the basis of NMR resonance correlations with those of the corresponding ketone **4** (Table 1). Specifically, the ^{1}H NMR spectrum of **10** indicated the presence of a methine proton at δ 5.13 (doublet J = 8.0 Hz) and a ^{13}C NMR resonance at δ 75.2 ppm. The relative stereochemistry of H_5 was assigned as cis to H_{5a}.

Most importantly, the structure and relative stereochemistry of **10** were confirmed by X-ray crystallography;[8] this determination also confirms the structure and stereochemical assignments for compounds **4** and **8**.

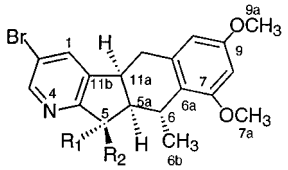
Mechanism. The formation of the minor product **9** is not unexpected since the substrate **2b** can undergo an electrophilic cyclization between the olefinic substituent and the phenyl ring to afford this product.

The formation of **4**, on the other hand, is a more complex process. The isolation of the amine **7** in the acid-catalyzed rearrangement of **2b** to **4** enables us to postulate a reaction mechanism to rationalize the formation of these products (Scheme 3). The postulated pathway involves three sequential electrophilic cyclizations starting with the initial formation of **11**, the expected imine intermediate formed in cyclizations of 2-cyanopyridines **2**.[5] This is followed by a prototropic rearrangement of the allyl group at C_5 of **11** to a 5-*trans*-propenyl group affording **12**, a key intermediate in this mechanism. Intermediate **12** undergoes a second electrophilic cyclization between the propenyl group and the protonated imine leading to the formation of the vinyl bicyclo intermediate **7,** which was isolated and characterized as the cis diastereoisomer. The exclusive diastereoselectivity observed for the formation of **7** may suggest that the conversion of **12** to **7** is a reversible process, thereby allowing for the equilibration of the possible *trans*-diastereoisomer (vinyl group oriented toward the pyridine ring) to **7**; the electron-rich phenyl ring would have a stabilizing effect on the cationic species of the propenyl, thereby favoring the observed orientation for the resulting vinyl group in **7**. The final step in the rearrangement of **7** to **8** requires the 1,3-bond migration of 10a−11 → 10a−13, which may be facilitated by the amino group. Alternatively, the vinyl group of **7** could undergo a third electrophilic cyclization facilitated by the aromatic methoxyl group, resulting in the highly strained transient

(7) Atom numbering used for listing NMR data and for the nomenclature of these compounds is shown in Scheme 2.

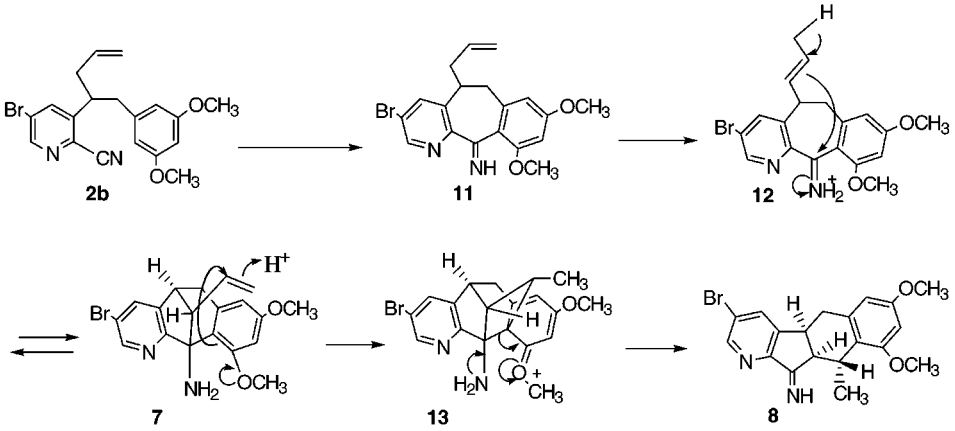
(8) An ORTEP diagram and X-ray crystallography data are included in the Supporting Information.

Table 1. NMR Data in $CDCl_3$



	compd **8** R_1R_2 = NH		compd **4** R_1R_2 = O		compd **10** R_1 = H, R_2 = OH	
atom no.	^{1}H δ (mult, J (Hz))	^{13}C δ	^{1}H δ (mult, J (Hz))	^{13}C δ	^{1}H δ (mult, J (Hz))	
1	7.70 (dd 2.0, 1.0)	136.7	8.12 (dd 2.0, 0.9)	135.7	7.68 (d 2.0)	
2		126.2		123.0		
3	8.40 (dd 2.0, 0.5)	152.5	8.69 (dd 2.0, 0.7)	148.7	8.38 (d 2.0)	
4a		152.5		162.3		
5		206.0		75.2	5.13 (d 8)	
5a	2.68 (m)	28.7	2.96 (dd 8, 1.6)	23.3	2.95 (dt 8, 8. 1.7)	
6	3.63 (dq 7.5, 0.5)	52.4	4.14 (dq 7.5, 1.6)	48.2	3.79 (dq 7.5,1.7)	
6a		121.0		120.4		
6b	1.31 (d 7.5)	20.1	1.32 (d 7.5)	22.3		
7		157.2		157.3		
7a	3.86 (s)	55.7	3.73 (s)	55.5	3.75 (s)	
8	6.10 (d 2.0)	96.9	6.20 (d 2.2)	96.9	6.24 (d 2.5)	
9		158.9		158.4		
9a	3.70 (s)	55.2	3.66 (s)	55.2	3.73 (s)	
10	6.23 (d 2.0)	105.2	6.04 (d 2.2)	105.2	6.16 (d 2.5)	
10a		134.6		136.0		
11	2.70 (m)	32.9	2.88 (dd 15.4, 1.2)	32.6	2.87 (dd 16, 3)	
	3.30 (dd 16.0, 4.5)		3.47 (ddd 15.4, 7.7, 0.9)		3.26 (dd 16, 7)	
11b		154.1		141.8		
11a	3.40 (m)	35.6	4.01 (dt 7.8, 7.7, 1.0)	38.9	3.73 (m)	

Scheme 3



intermediacy of a cyclobutane **13** which then undergoes cleavage of the 10a−11 bond and rearomatization to afford **8** which is the final stable product in the sequence. The exclusive diasteroselectivity observed for **8,** is derived from the vinyl−phenyl π-overlap in **7** required for the 10a−13 bond formation of **13**. Hydrolysis of the imine **8** then leads to the formation of the tetracyclic ketone **4**.

In summary, we report here the acid-catalyzed rearrangement of the allyl cyanopyridine **2b**, which affords the novel tetracyclic structures **7**, **8**, and **4**; the rearrangement proceeds with a high degree of stereoselectivity, resulting in the formation of these products as single diastereoisomers. Dibenzo ring system analogues of **7** have been reported previously;[9] however, the tetracyclic product **7** is the first example of a compound containing a 6,11-dihydro-5,11-methano-5*H*-benzo[5.6]-cyclohepta[1,2-*b*]pyridine ring system. The 5,6,11,11a-tetrahydro-5*H*-benzo[5.6]indeno[2,1-*b*]pyridine ring system of the products **8**, **4**, and **10** is new and has not been reported previously.[10]

Experimental Section

Melting points are uncorrected. Column chromatography was performed on silica gel (Selecto, 32-63 mesh), and reactions were monitored by TLC on silica gel plates (Analtech).

3-[1-Allyl-2-(3,5-dimethoxyphenyl)ethyl]-*N*-(1,1-dimethylethyl)-2-pyridinecarboxamide (6). *n*-Butyllithium in hexanes (2.5 M, 18.33 mL, 45.83 mmol) was added to a solution of diisopropylamine (6.85 mL, 50.33 mmol) in THF (40 mL) at −78 °C, and the mixture stirred at that temperature for 15 min and at 0 °C for 15 min. The reaction mixture was cooled to −78 °C,

(9) For references on compounds containing the corresponding 10,11-dihydro-5,10-methano-5*H*-dibenzo[*a*,*d*]cycloheptene ring system, see: (a) Hagishita, S.; Kuriyama, K. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2790. (b) Cristol, S. J.; Aeling, E. O.; Heng, R. *J. Am. Chem. Soc.* **1987**, *109*, 830.

(10) The ring system of these compounds is not listed in the *Ring Systems Handbook* (Chemical Abstracts Service) published by the American Chemical Society, 1997; Suppl. 8. Conventional nomenclature guidelines were followed in naming compounds **4**, **8**, and **10**.

and a solution of the *tert*-butylamide **5** (5.0 g, 18.45 mmol)[3] in THF (20 mL) was added dropwise. The resulting purple solution was stirred at this temperature for 1 h, and then 3,5-dimethoxybenzyl chloride (4.6 g, 24.65 mmol) in THF (20 mL) was added at −78 °C. The dry ice−acetone bath was replaced with an ice−water bath, and the light brown solution was stirred at 0 °C for 3 h. The reaction was quenched by addition of water (150 mL) and then extracted with EtOAc (2 × 200 mL). The organic extracts were combined, dried over $MgSO_4$, and filtered, and the solvent evaporated, yielding a red oil that was chromatographed on silica gel. Elution with 20% v/v EtOAc/hexanes yielded **3-[2-(3,5-dimethoxyphenyl)ethyl]-*N*-(1,1-dimethylethyl)-2-pyridinecarboxamide (5a)** as a colorless oil: 5.5 g (84%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.43 (s,9H), 2.90 (t, 2H), 3.50 (t, 2H), 3.75 (s, 6H), 6.30 (s, 1H), 6.35 (s, 2H), 7.55 (s, 1H), 7.75 (bs, 1H), 8.40 (s, 1H); MS (FAB) *m*/*z* 421 (MH^+).

n-Butyllithium in hexanes (2.5 M, 12 mL, 30 mmol) was added to a solution of diisopropylamine (4.20 mL, 32.5 mmol) in THF (30 mL) at −78 °C, and the mixture was stirred at that temperature for 30 min and at 0 °C for 15 min. The reaction was cooled to −78 °C, and a solution of **5a** (5.0 g, 11.85 mmol) in THF (20 mL) was added dropwise. The resulting purple solution was stirred at −78 °C for 1 h, and then allyl bromide (2.5 mL, 28.8 mmol) was added dropwise. The dry ice−acetone bath was replaced with an ice−water bath, and the light brown solution was stirred at 0 °C for 2 h. The reaction was quenched by addition of water (150 mL) and then extracted with EtOAc (2 × 200 mL). The organic extracts were combined, dried over $MgSO_4$, and filtered, and the solvent was evaporated, yielding an oil that was chromatographed on silica gel. Elution with 20% EtOAc/hexanes yielded the title product **6** as a colorless oil: 4.9 g (90.7% yield); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.43 (s,9H), 2.40 (m, 2H), 2.84 (m, 2H), 3.75 (s, 6H), 4.75 (m, 1H), 4.92 (dd, 2H), 5.70 (m, 1H), 6.25 (s, 3H), 7.28 (b, 1H), 7.77 (s, 1H), 8.35 (s,1H); HRMS (FAB) calcd for $C_{23}H_{30}N_2O_3Br$ 461.1440, found 461.1434.

3-[1-Allyl-2-(3,5-dimethoxyphenyl)ethyl]-*N*-(1,1-dimethylethyl)-2-pyridinecarbonitrile (2b). A solution of **6** (5 g, 10.8 mmol) and phosphorus oxychloride (15 mL) in toluene (15 mL) was stirred at 110 °C for 5 h. The reaction was cooled to room temperature and evaporated under reduced pressure. Water (200 mL) was added, and the mixture was basified by addition of 10% NaOH and then extracted with CH_2Cl_2 (2 × 200 mL). The organic extracts were combined, dried over $MgSO_4$, filtered, and evaporated, yielding an oil that was chromatographed on silica gel. Elution with 20% EtOAc/hexanes yielded **2b** as a pale yellow solid: 4.0 g (95% yield); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.25 (m, 1H), 2.55 (m, 1H), 2.80 (m, 1H), 3.0 (m, 1H), 3.55 (m, 1H), 3.77 (s, 6H), 5.0 (dd, 2H), 5.65 (q, 1H), 6.22 (s, 2H), 6.28 (s, 1H), 7.80 (s,1H), 8.55 (s,1H); HRMS (FAB) calcd for $C_{19}H_{20}N_2O_2Br$ 387.0708, found 387.0700.

3-Bromo-12*(RS)*-ethenyl-6,11-dihydro-8,10-dimethoxy-5*(RS)*,11-methano-5*H*-benzo[5.6]cyclohepta[1,2-*b*]pyridin-11*(SR)*-amine (7), 2-Bromo-5a*(RS)*,6,11,11a*(SR)*-tetrahydro-7,9-dimethoxy-6*(RS)*-methyl-5*H*-benzo[5.6]indeno[2,1-*b*]pyridin-5-imine (8), and 5′-Bromo-3′-(1,2,3,4-tetrahydro-6,8-dimethoxy-1*(SR)*-methyl-3*(RS)*-naphthalenyl)-2′-pyridinecarbonitrile (9). The nitrile **2b** (2.7 g, 6.99 mmol) was added portionwise with stirring during 10 min to triflic acid (25 mL) at 20 °C, and the solution was stirred overnight at room temperature. The reaction mixture was then poured into ice (200 g) and basified with 10% NaOH. The precipitated solid was filtered, washed with water (50 mL), dried, and chromatographed on silica gel. Elution with 10% EtOAc/hexanes yielded compound **9** as a low-melting amorphous resin: mp 55−57 °C; 0.3 g (11% yield); IR (CH_2Cl_2) 2235 cm^{-1}; ^{1}H NMR data are included in the text; ^{13}C NMR ($CDCl_3$, 100.62 MHz) δ 150.1 ($C_{6'}$),[7] 125.2 ($C_{5'}$), 137.2 ($C_{4'}$), 131.7 ($C_{3'}$), 37.4 (C_3), 37.9 (C_4), 136.0 (C_{4a}), 104.3 (C_5), 158.5 (C_6), 97.3 (C_7), 159.3 (C_8), 121.3 (C_{8a}), 29.5 (C_1), 40.5 (C_2), 115.8 ($C_{2'}$-CN), 147.9 ($C_{2'}$), 55.3 ($C_{6/8}$-OCH_3), 22.7 (C_1-CH_3); HRMS (FAB) calcd for $C_{19}H_{20}N_2O_2$-Br 389.0688, found 389.0670 (MH^+). Anal. Calcd for $C_{19}H_{19}N_2O_2$-Br: C, 58.92; H, 4.94; N, 7.23. Found: C, 59.06; H, 5.03; N, 7.24. Further elution with 5% methanol/ethyl acetate yielded a mixture of compounds **7** and **8** (1.89 g, 70% yield). The mixture **7** and **8** (100 mg) was purified by preparative TLC (Analtech silica gel plates 20 × 20 × 0.1 cm), eluting with EtOAc to yield compound **7** as a colorless foam (40 mg, 28% yield) and the slower eluting compound **8** as an amorphous powder (50 mg, 35% yield).

7: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.75 (dd 17, 1.5, H_6), 3.47 (dd 17, 5.0, H_6), 3.13 (d 9.0, H_{12}), 3.26 (dd 5.0, 1.5, H_5), 3.70 (s, C_8−OCH_3), 3.88 (s, C_{10}−OCH_3), 5.36 (dd 17, 2, H_{14}), 5.24 (dd 10, 2, H_{14}), 5.52 (ddd 17, 10, 9 H_{13}), 6.16 (d 2.0, H_7), 6.29 (d 2.0, H_9), 7.65 (d 2.0, H_4), 8.32 (d 2.0, H_2); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 36.0 (C_6), 41.9 (C_{12}), 55.3 (C_8-OCH_3), 56.3 (C_{10}-OCH_3), 61.7 (C_5), 65.2 (C_{11}), 98.1 (C_9), 106.4 (C_7), 120.5 (C_{14}), 135.1 (C_4), 135.4 (C_{13}), 135.7 (C_{6a}), 138.9 (C_{4a}), 148.0 (C_{11a}), 148.9 (C_2), 158.1 (C_{10}), 159.9 (C_8); HRMS (FAB) calcd for $C_{19}H_{20}N_2O_2Br$ 387.0708, found 387.0702 (MH^+).

8: NMR data are included in Table 1; HRMS (FAB) calcd for $C_{19}H_{20}N_2O_2Br$ 387.0708, found 387.0714 (MH^+).

2-Bromo-5a*(RS)*,6,11,11a*(SR)*-tetrahydro-7,9-dimethoxy-6*(RS)*-methyl-5*H*-benzo[5.6]indeno[2,1-*b*]pyridin-5-one (4). A. From 7. A solution of **7** (1.0 g, 2.59 mmol) was refluxed overnight in 2 N HCl (10 mL) and then cooled to 0 °C and basified with 2 N NaOH. The mixture was extracted with CH_2Cl_2 (100 mL), dried over $MgSO_4$, and filtered, and the extract was evaporated, yielding a residue that was chromatographed on silica gel. Elution with 5% EtOAc/CH_2Cl_2 yielded the title compound **4** as a white crystalline solid: 800 mg (80%); mp 225−227 °C; NMR data are included in Table 1; IR (CH_2Cl_2) 1727, 1607 cm^{-1}; HRMS (FAB) calcd for $C_{19}H_{19}NO_3Br$ 388.0548, found 388.0551 (MH^+). Anal. Calcd for $C_{19}H_{18}NO_3Br\cdot 0.25H_2O$: C, 58.10; H, 4.75; N, 3.57. Found: C, 58.19; H, 4.59; N, 3.95.

B. From 8. From procedure A, substituting compound **8** (100 mg) for **7**, the title compound **4** was obtained: 85 mg (85%), data (mp, TLC, NMR) identical with **4** prepared above from **7**.

C. From a Mixture of 7 and 8. From procedure A, substituting the mixture of **7** and **8** (1.7 g) for compound **7**, the title compound **4** was obtained: 1.36 g (80%), data (mp, TLC, NMR) identical with **4** prepared above from **7**.

D. From 2b. The crude product obtained from the reaction of **2b** (3.0 g) in triflic acid (30 mL) was hydrolyzed in 2 N HCl using procedure A to afford **9** (0.3 g, 10% yield) and **4** (1.96 g, 65% yield).

2-Bromo-5a*(RS)*,6,11,11a*(SR)*-tetrahydro-7,9-dimethoxy-6*(RS)*-methyl-5*H*-benzo[5.6]indeno[2,1-*b*]pyridin-5*(RS)*-ol (10). Sodium borohydride (500 mg, 13.51 mmol) was added to a suspension of **4** (500 mg, 1.288 mmol) in EtOH (15 mL) at 0 °C and stirred at this temperature for 1 h and at room temperature for 1 h. The solvent was evaporated, the residue was extracted with CH_2Cl_2 (50 mL), washed with H_2O (50 mL), dried over $MgSO_4$, and filtered, and the solvent was evaporated, yielding a white solid (500 mg, 100%) that was homogeneous on TLC (silica gel, 40% EtOAC/hexanes). Recrystallization from hot EtOAc/acetone furnished the title compound **10** as white crystals: 410 mg (82%); mp 204−205 °C; NMR data are included in Table 1; IR (CH_2Cl_2) 3565, 1607 cm^{-1}; HRMS (FAB) calcd for $C_{19}H_{21}NO_3Br$ 390.0705, found 390.0700 (MH^+). Anal. Calcd for $C_{19}H_{20}NO_3Br$: C, 58.47; H, 5.16; N, 3.59. Found: C, 58.33; H, 5.21; N, 3.75.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR, correlation spectra for compounds **2b**, **4**, **6**, **7**, **9**, and **10**, and an ORTEP diagram and X-ray crystallographic data for compound **10** (31 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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