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Total Synthesis of Amaryllidaceae Alkaloid Buflavine

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Abstract: A concise synthesis of the amaryllidaceae alkaloid buflavine (**1**) and its regioisomer (**2**) involving sequential Meyers' biaryl coupling, enecarbamate formation, and hydrogenation followed by ultimate intramolecular reductive amination is presented.

Buflavine **1** constitutes an eminent example of the odd natural amaryllidaceous alkaloids that have been isolated from *Boophane flava*, an endemic Amaryllidaceae species growing in the winter rainfall area in Southern Africa.[1] This alkaloid possesses an unique 5,6,7,8-tetrahydrobenzo[*c*,*e*]azocine skeleton present in the apogalanthamine series[2] and seems to be endowed with an interesting profile of biological activities, namely adrenolytic and anti-serotonin properties.[3] As far as we are aware, the first synthesis of buflavine **1** was incidentally reported 25 years ago,[4] but curiously, this report predated its isolation and structural elucidation.[1] Consequently, the skillful synthetic approach recently reported by Snieckus et al.[5] can arguably be deemed as the first total synthesis of this natural product.

Herein, we delineate a tactically new six-step total synthesis of the alkaloid buflavine **1** that relies upon our long-standing experience in the field of *N*-acylenamine chemistry,[6] and we wish to disclose the success of our concept by describing the synthesis of its regioisomer **2**.

A contentious issue in the elaboration of the target compounds **1** and **2** was judging the proper strategy for the formation of the heteroring unit embedded in the polyhydrobenzoazocine skeleton. The formation of the eight-membered ring could be a priori triggered by the ring closure of the arylmethylarylethylamine derivatives **3** and **4** equipped with appropriate functionalities liable to secure the biaryl coupling reaction (retrosynthetic Scheme 1, path a). However, rare literature precedent[2] did not give sound support to the feasibility of such an approach, and it was decided to adopt the alternative synthetic tactic depicted in the retrosynthetic Scheme 1 (path b).

Critical to the success of this strategy then was the ability to identify a temporary auxiliary Z in the diarylalkylamines **5** and **6** that could be capable not only of allowing and, if feasible, facilitating the aryl−aryl bond formation but also could serve as a latent functionality to react ultimately with a remote alkylamino group. Our synthetic approach was dictated by reliance on the elegant Meyers' protocol[7] and an oxazoline-mediated unsymmetrical biaryl coupling was then employed to form the pivotal biaryl carbon−carbon bond of the benzo[*c*,*e*]azocine system.

The first facet of the synthesis then started with the assembly of the biphenyl derivatives **10** and **11** equipped with the appropriate functionalities (Scheme 2). This operation was readily accomplished when the 2-aryl-4,4-dimethyl-2-oxazolines **8** and **9** readily obtained from the corresponding benzoic acids[7] were allowed to react with the Grignard reagent derived from the acetal **7** of 2-bromobenzaldehyde. The bulky size of the different substituents at the 2 and 2′ positions had no steric impact on the biaryl coupling reaction since usual workup and chromatography provided the corresponding biaryls **10** and **11** in excellent yields of 76% and 81%, respectively. Regeneration of the carboxaldehyde function delivered almost quantitatively the corresponding benzaldehyde derivatives **12** and **13**. Horner reaction between the metalated carbamate **15** obtained by coupling *N*-[(diphenylphosphinoyl)methyl]-*N*-methylamine **14** with di-*tert*-butyl dicarbonate and compounds **12** and **13** proceeded uneventfully to furnish the enecarbamates **16** and **17**, which were isolated in high yields (85% and 81%, respectively) as a mixture of *Z* and *E* isomers with the *E* isomer predominating by a large margin (>90%) (Scheme 3). Hydrogenation[8] of the polysubstituted enecarbamates **16** and **17** delivered the protected biarylalkylamines **18** and **19** with very good yields (97% and 95%, respectively).[9] Gratifyingly, all these operations spared the oxazoline unit and its presence in the elaborated models was rewarded here: reductive cleavage of the oxazoline ring of **18** and **19** following the mild high-yield procedure developed by Meyers[10] gave rise to the benzaldehyde derivatives **20** and **21** in satisfactory yields (79% and

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(2) Kihara, M.; Itoh, J.; Iguchi, S.; Imakura, Y.; Kobayashi, S. *J. Chem. Res., Synop.* **1988**, 8.
(3) (a) Ishida, Y.; Sasaki, Y.; Kimura, Y.; Watanabe, K. *J. Pharmacobio-Dyn.* **1985**, *8*, 917; *Chem. Abstr.* **1986**, *104*, 45660. (b) Manoury, P. M.; Binet, J. L.; Dumas, A. P.; Lefevre-Borg, F.; Cavero, I. *J. Med. Chem.* **1986**, *29*, 19. (c) Campbell, S. F.; Davey, M. J.; Hardstone, J. D.; Lewis, B. N.; Palmer, M. J. *J. Med. Chem.* **1987**, *30*, 49.
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(5) Patil, P. A.; Snieckus, V. *Tetrahedron Lett.* **1998**, *39*, 1325.
(6) (a) Couture, A.; Lebrun, S.; Deniau, E.; Grandclaudon, P. *Eur. J. Org. Chem.* **1999**, 2345. (b) Couture, A.; Deniau, E.; Grandclaudon, P.; Hoarau, C. *Tetrahedron* **2000**, *56*, 1491. (c) Hoarau, C.; Couture, A.; Deniau, E.; Grandclaudon, P. *J. Org. Chem.* **1998**, *63*, 3128. (d) Hoarau, C.; Couture, A.; Cornet, H.; Deniau, E.; Grandclaudon, P. *J. Org. Chem.* **2001**, *66*, 8064.
(7) For leading references and examples, see: Hutchings, R. H.; Meyers, A. I. *J. Org. Chem.* **1996**, *61*, 1004.
(8) (a) Sonesson, C.; Wikstroem, H.; Smith, M. W.; Svensson, K.; Carlsson, A.; Waters, N. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 241. (b) Couture, A.; Deniau, E.; Grandclaudon, P.; Lebrun, S.; Leonce, S.; Renard, P.; Pfeiffer, B. *Bioorg. Med. Chem.* **2000**, *8*, 2113.
(9) Attempts to assemble compounds **18** and **19** by applying the Meyers' coupling reaction to **8**, **9** and *N*-methyl-*N*-*tert*-butoxycarbonyl-2-bromophenethylamine met with limited success since the preparation of the Grignard reagent was accompanied by the formation of undesirable inter- and intra-self-condensation products.
(10) Meyers, A. I.; Willemsen, J. J. *Tetrahedron* **1998**, *54*, 10493.

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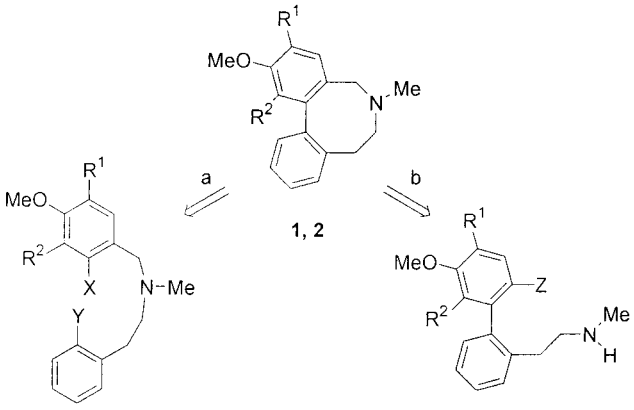
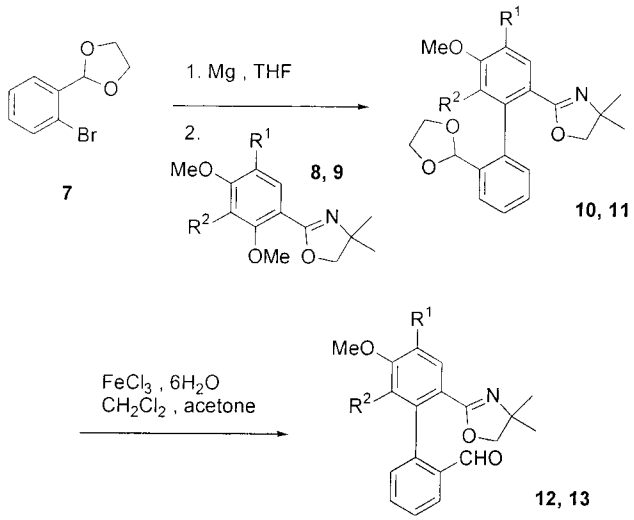
SCHEME 1



	R^1	R^2
1, 3, 5, 8, 10, 12, 16, 18, 20	OCH_3	H
2, 4, 6, 9, 11, 13 ,17, 19, 21	H	OCH_3

SCHEME 2. Meyers' Coupling Reaction



77%, respectively). This protocol allowed the tailored incorporation of a carboxaldehyde function into the dimethoxylated aromatic part of the models (compared to **12** and **13**). N-Deprotection of carbamates **20** and **21** with trifluoroacetic acid and subsequent reductive amination[11] afforded straightforwardly the target natural product buflavine **1** and its regioisomer **2** with overall yields of 35% and 33% for the seven steps (starting from the precursors of **8** and **9**).

In summary, the new synthetic protocol consisting of sequential Meyers' biaryl coupling reaction, enecarbamate formation, subsequent hydrogenation, and ultimate reductive amination has been applied to an efficient construction of the 5,6,7,8-tetrahydrodibenzo[*c*,*e*]azocine framework, and the synthetic potential of this method has been illustrated by the second known total synthesis of the alkaloid buflavine.

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Experimental Section

General Methods. All reactions were conducted under an argon atmosphere with magnetic stirring. Solvents were dried according to established protocols by distillation under argon from an appropriate drying agent. Dichloromethane and dichloroethane were distilled from CaH_2. Tetrahydrofuran (THF) was distilled over sodium benzophenone ketyl and stored over sodium before use. Methanol and ethanol were distilled from magnesium turnings. ^1H, ^{13}C, and ^{31}P NMR spectra were recorded at 300, 75, and 121 MHz, respectively. Elemental analyses were performed by the CNRS microanalysis center. For flash chromatography, Merck silica gel 60 (230−400 mesh ASTM) was used.

Materials. Compounds **7**,[12] **8**,[13] **9**,[10] and phosphorylated amine **14**[14] were synthesized according to already reported procedures.

***N*-(*tert*-Butoxycarbonyl)-*N*-[(diphenylphosphinoyl)methyl]methylamine (15).** A solution of di-*tert*-butyl dicarbonate (12 g, 55 mmol) in THF (10 mL) was added dropwise to a solution of the phosphorylated amine **14** (12.25 g, 50 mmol) in THF (20 mL), and the mixture was refluxed for 3 h under Ar. The solvent was removed under vacuum, and recrystallization of the residue from hexane−toluene afforded the phosphorylated carbamate **15** as a white solid (13.45 g, 78%): mp 83−84 °C; ^1H NMR ($CDCl_3$, mixture of rotational isomers, 75:25) δ (major rotational isomer) 1.23 (s, 9H), 2.97 (s, 3H), 4.18 (d, J = 4.4 Hz, 2H), 7.33−7.56 (m, 6H), 7.66−7.90 (m, 4H); δ (minor rotational isomer) 1.16 (s, 9H), 3.00 (s, 3H), 4.12 (d, J = 4.2 Hz, 2H), 7.33−7.56 (m, 6H), 7.66−7.90 (m, 4H); ^{13}C NMR ($CDCl_3$) δ (major rotational isomer) 28.1, 35.8, 48.7 (d, J_{CP} = 79.5 Hz), 80.1, 128.5 (d, J_{CP} = 11 Hz), 131.0 (d, J_{CP} = 97 Hz), 131.1 (d, J_{CP} = 10 Hz), 132.0 (d, J_{CP} = 2.5 Hz), 155.4; ^{31}P NMR ($CDCl_3$, mixture of rotational isomers, 75:25) δ (minor rotational isomer) 31.0, δ (major rotational isomer) 27.6. Anal. Calcd for $C_{19}H_{24}NO_3P$: C, 66.08; H, 7.00; N, 4.06. Found: C, 66.30; H, 6.91; N, 3.89.

Synthesis of the Biaryls 10, 11. To a suspension of the bromo derivative **7** (2.5 g, 10.9 mmol) and granular magnesium (292 mg, 12 mmol) in THF (10 mL) was added 1,2-dibromotetrafluoroethane (1.3 g, 5 mmol) in portions over a period of 1 h. The resulting Grignard reagent was transferred via cannula to a solution of the oxazoline **8**, **9** (2.9 g, 10.9 mmol) in THF (10 mL), and the reaction mixture was stirred overnight. The reaction was quenched with saturated aqueous NH_4Cl and filtered over a Celite pad. Water was added, and the reaction mixture was extracted with AcOEt (3 × 20 mL), dried over $MgSO_4$, and concentrated in vacuo to give the crude biaryl, which was purified by silica gel column chromatography (acetone/hexanes, 40:60) to afford **10** and **11** as light yellow solid. Final purification was carried out by recrystallization from EtOH.

2-(2-(2-[1,3]Dioxol-2-ylphenyl)-4,5-dimethoxyphenyl)-4,4-dimethyl-4,5-dihydro[1,3]oxazole (10): 3.17 g, 76%; mp 114−115 °C; ^1H NMR ($CDCl_3$) δ 1.15 (s, 3H), 1.17 (s, 3H), 3.53 (d, J = 8.0 Hz, 1H), 3.66 (d, J = 8.0 Hz, 1H), 3.73−4.04 (m, 2H), 3.82 (s, 3H), 3.90 (s, 3H), 3.97−4.04 (m, 2H), 5.47 (s, 1H), 6.76 (s, 1H), 7.11 (dd, J = 1.8, 6.6 Hz, 1H), 7.24−7.31 (m, 2H), 7.30 (s, 1H), 7.58 (dd, J = 1.8, 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 27.8, 28.1, 55.9, 56.0, 65.1, 65.3, 66.8, 79.2, 101.4, 112.0, 114.2, 120.5, 126.0, 127.3, 128.3, 129.5, 132.8, 134.9, 141.3, 147.7, 149.7, 163.2. Anal. Calcd for $C_{22}H_{25}NO_5$: C, 68.91; H; 6.57; N, 3.65. Found: C, 69.04; H, 6.72; N, 3.51.

2-(2-(2-[1,3]Dioxol-2-ylphenyl)-3,4-dimethoxyphenyl)-4,4-dimethyl-4,5-dihydro[1,3]oxazole (11): 3.38 g, 81%; mp 104−105 °C; ^1H NMR ($CDCl_3$) δ 1.12 (s, 3H), 1.18 (s, 3H), 3.47 (s, 3H), 3.55 (d, J = 8.0 Hz, 1H), 3.63 (d, J = 8.0 Hz, 1H), 3.80−3.83 (m, 2H), 3.89 (s, 3H), 3.98−4.03 (m, 2H), 5.55 (s, 1H), 6.91 (d, J = 8.6 Hz, 1H), 7.15 (dd, J = 1.8, 6.8 Hz, 1H), 7.32−7.37 (m, 2H), 7.56 (d, J = 8.6 Hz, 1H), 7.61 (dd, J = 1.8, 7.6 Hz, 1H);

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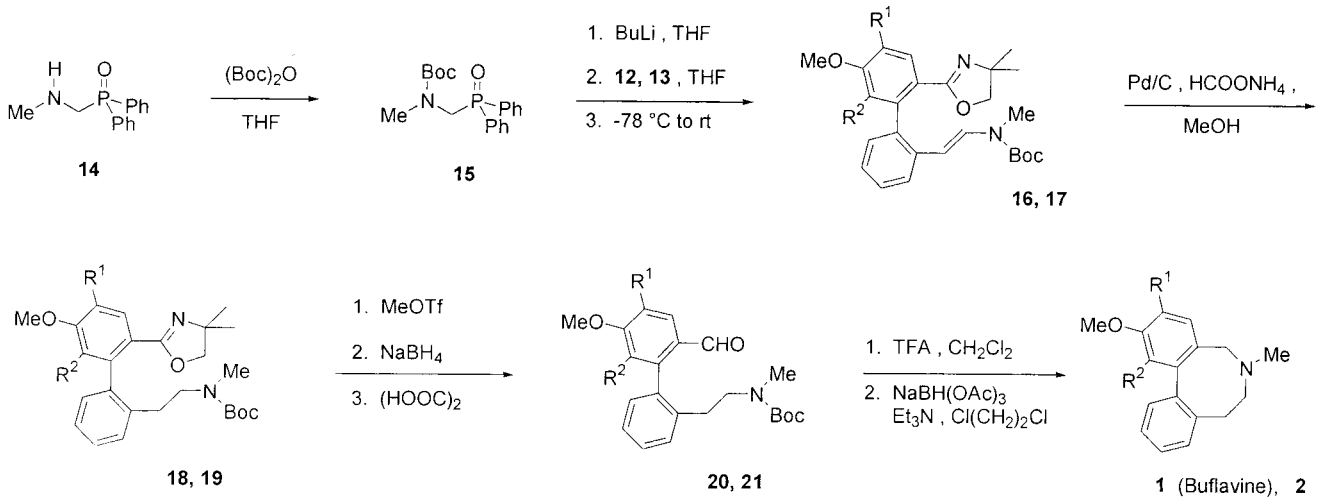
SCHEME 3. Total Synthesis of Buflavine



^{13}C NMR ($CDCl_3$) δ 27.8, 28.1, 55.8, 60.4, 65.2, 66.7, 79.3, 101.6, 111.1, 122.0, 125.8, 126.1, 127.5, 128.0, 129.9, 134.3, 135.7, 136.3, 146.5, 154.6, 163.0. Anal. Calcd for $C_{22}H_{25}NO_5$: C, 68.91; H, 6.57; N, 3.65. Found: C, 68.80; H, 6.74; N, 3.79.

Synthesis of the Biarylcarboxaldehydes 12, 13. A solution of the biaryl **10**, **11** (3 g, 7.8 mmol) and iron(III) chloride hexahydrate (6 g, 22.2 mmol) in a mixture acetone/dichloromethane (1:4, 50 mL) was vigorously stirred over a period of 2 h at room temperature. The crude mixture was poured onto a saturated aqueous NH_4Cl solution (20 mL), filtered on Celite, and extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were washed successively with water and brine and dried over $MgSO_4$. The solvents were removed in vacuo, and the crude residue was recrystallized from hexane−toluene to afford **12** and **13** as colorless powder.

2-(2-(4,4-Dimethyl-4,5-dihydro[1,3]oxazol-2-yl)-4,5-dimethoxyphenyl)benzaldehyde (12): 2.43 g, 92% after recrystallization; mp 87−88 °C; ^{1}H NMR ($CDCl_3$) δ 1.08 (s, 3H), 1.10 (s, 3H), 3.57 (d, J = 8.1 Hz, 1H), 3.61 (d, J = 8.0 Hz, 1H), 3.82 (s, 3H), 3.91 (s, 3H), 6.70 (s, 1H), 7.26 (d, J = 7.4 Hz, 1H), 7.33 (s, 1H), 7.39 (t, J = 7.5 Hz, 1H), 7.51 (t, J = 7.4 Hz, 1H), 7.89 (d, J = 7.7 Hz, 1H), 9.76 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 27.9, 28.0, 56.0, 56.1, 67.2, 79.1, 112.1, 113.7, 121.2, 126.4, 127.6, 130.5, 130.8, 133.0, 134.2, 148.4, 150.2, 154.2, 162.1, 192.0. Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.92; H, 6.29; N, 3.97.

2-(2-(4,4-Dimethyl-4,5-dihydro[1,3]oxazol-2-yl)-3,4-dimethoxyphenyl)benzaldehyde (13): 2.35 g, 89% after recrystallization; mp 109−110 °C; ^{1}H NMR ($CDCl_3$) δ 1.08 (s, 3H), 1.10 (s, 3H), 3.44 (s, 3H), 3.48 (d, J = 8.0 Hz, 1H), 3.64 (d, J = 8.0 Hz, 1H), 3.82 (s, 3H), 6.98 (d, J = 8.6 Hz, 1H), 7.24 (dd, J = 1.1, 7.6 Hz, 1H), 7.45 (dt, J = 0.9, 7.5 Hz, 1H), 7.53 (dt, J = 0.9, 7.5 Hz, 1H), 7.57 (d, J = 8.6 Hz, 1H), 7.97 (dd, J = 1.1, 7.7 Hz, 1H), 9.78 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 27.8, 28.0, 55.9, 60.3, 67.2, 79.1, 111.8, 122.2, 126.0, 126.5, 127.8, 130.7, 132.7, 134.2, 134.4, 140.5, 146.7, 154.6, 162.0, 192.0. Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.98; H, 6.10; N, 4.05.

Synthesis of Enecarbamates 16, 17. A solution of BuLi (3.6 mL, 1.6 M in hexanes, 5.8 mmol) was added dropwise to a solution of the phosphorylated carbamate **15** (2 g, 5.8 mmol) in THF (50 mL) at −78 °C under Ar. The orange solution was kept at this temperature for 15 min, and a solution of the biarylcarboxaldehyde **12**, **13** (1.97 g, 5.8 mmol) in THF (5 mL) was then added by syringe. The reaction mixture was allowed to warm to room temperature over a period of 2 h followed by addition of aqueous NH_4Cl and extraction with Et_2O (3 × 25 mL). The organic layer was purified by flash column chromatography with acetone/hexanes (70:30) as eluent to afford **16** and **17** as a mixture of *E* and *Z* isomers.

2-(4,5-Dimethoxy-2-(2-(2-methyl-*tert*-butoxycarbonylamino-(*E*)-1-ethenyl)phenyl)phenyl)-4,4-dimethyl-4,5-dihydro-[1,3]oxazole (16): 2.30 g, 85%; ^{1}H NMR ($CDCl_3$) δ 1.18 (s, 6H), 1.48 (s, 9H), 2.90 (s, 3H), 3.55−3.72 (m, 2H), 3.87 (s, 3H), 3.98 (s, 3H), 5.52 (d, J = 14.6 Hz, 1H), 6.73 (s, 1H), 7.19 (s, 1H), 7.18−7.29 (m, 2H), 7.42−7.55 (m, 2H), 7.68 (d, J = 14.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 28.0, 28.2, 34.2, 56.0, 56.1, 66.8, 79.5, 81.4, 107.3, 112.2, 113.7, 120.2, 123.6, 125.5, 127.4, 129.4, 129.8, 134.3, 135.5, 139.6, 147.7, 150.2, 154.9, 163.2.

2-(3,4-Dimethoxy-2-(2-(2-methyl-*tert*-butoxycarbonylamino-(*E*)-1-ethenyl)phenyl)phenyl)-4,4-dimethyl-4,5-dihydro-[1,3]oxazole (17): 2.19 g, 81%; ^{1}H NMR ($CDCl_3$) δ 1.12 (s, 6H), 1.46 (s, 9H), 2.86 (s, 3H), 3.46 (s, 3H), 3.56−3.61 (m, 2H), 3.90 (s, 3H), 5.46 (d, J = 14.6 Hz, 1H), 6.91 (d, J = 8.6 Hz, 1H), 7.14−7.15 (m, 2H), 7.25−7.30 (m, 1H), 7.40−7.59 (m, 2H), 7.53 (d, J = 8.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 28.0, 28.2, 34.0, 55.8, 60.5, 67.5, 79.5, 81.2, 107.5, 110.9, 123.4, 123.5, 125.0, 125.9, 127.5, 129.3, 130.2, 135.4, 135.8 (two peaks overlapping), 146.8, 154.8, 155.4, 162.9.

Synthesis of the Carbamates 18, 19. A solution of compound **16**, **17** (1.4 g, 3 mmol) in MeOH (100 mL) was stirred with activated Pd/C (10%, 50 mg) and ammonium formate (1.90 g, 3 mmol) was added portionwise. The reaction mixture was refluxed for 0.5 h, filtered on Celite, and evaporated to dryness. The crude residue was dissolved in CH_2Cl_2 (100 mL), and the organic phase was washed with water, dried ($MgSO_4$), and concentrated in vacuo to afford the carbamates **18** and **19** as colorless oils that were sufficiently pure to be used directly for the next step without further purification.

2-(4,5-Dimethoxy-2-(2-(2-methyl-*tert*-butoxycarbonylaminoethyl)phenyl)phenyl)-4,4-dimethyl-4,5-dihydro[1,3]-oxazole (18): 1.36 g, 97%; ^{1}H NMR ($CDCl_3$) δ 1.15 (s, 3H), 1.16 (s, 3H), 1.40 (s, 9H), 2.45 (s, 3H), 2.59−2.61 (m, 2H), 3.13−3.18 (m, 2H), 3.59 (s, 2H), 3.84 (s, 3H), 3.90 (s, 3H), 6.64 (s, 1H), 7.08 (s, 1H), 7.06−7.20 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 28.0, 28.3, 31.5, 33.9, 50.1, 56.0, 56.1, 66.8, 79.0, 79.2, 112.1, 113.3, 120.2, 125.5, 127.3, 129.2, 129.6, 134.4, 137.0, 141.1, 147.6, 150.1, 155.4, 163.5. Anal. Calcd for $C_{27}H_{36}N_2O_5$: C, 69.21; H, 7.74; N, 5.98. Found: C, 69.14; H, 7.61; N, 6.15.

2-(3,4-Dimethoxy-2-(2-(2-methyl-*tert*-butoxycarbonylaminoethyl)phenyl)phenyl)-4,4-dimethyl-4,5-dihydro[1,3]-oxazole (19): 1.33 g, 95%; ^{1}H NMR ($CDCl_3$) δ 1.12 (s, 3H), 1.13 (s, 3H), 1.40 (s, 9H), 2.55 (s, 3H), 2.47−2.63 (m, 2H), 3.21−3.23 (m, 2H), 3.48 (m, 4H), 3.63−3.65 (m, 1H), 3.92 (s, 3H), 3.93 (d, J = 8.6 Hz, 1H), 7.09−7.23 (m, 4H), 7.51 (d, J = 8.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 27.9, 28.0, 28.4, 32.2, 34.2, 49.6, 55.8, 60.5, 66.9, 78.9, 79.1, 110.9, 122.2, 125.1, 125.8, 127.4, 128.8, 129.6, 135.6, 136.2, 137.9, 146.2, 154.5, 155.6, 162.8. Anal. Calcd for $C_{27}H_{36}N_2O_5$: C, 69.21; H, 7.74; N, 5.98. Found: C, 69.40; H, 7.89; N, 6.02.

Synthesis of the Formylated Carbamates 20, 21. To a flame-dried flask containing a solution of oxazoline **18**, **19** (1.40 g, 3 mmol) in CH_2Cl_2 (25 mL) was added methyl trifluoromethanesulfonate (985 mg, 0.68 mL, 6 mmol), and the solution was stirred at room temperature overnight. The solution was cooled to 0 °C and treated dropwise with a solution of $NaBH_4$ (226 mg, 6 mmol) in THF/MeOH (4:1, 30 mL). After the mixture was stirred for 1 h, saturated aqueous NH_4Cl (30 mL) was added. The layers were separated, the organic layer was washed with CH_2Cl_2 (3 × 25 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated to dryness. Filtration through a short plug of silica and evaporation of the solvent left a crude residue that was dissolved in a solution of THF/H_2O (4:1, 50 mL) and treated with oxalic acid dihydrate (1.0 g, 8 mmol). The solution was stirred overnight, Et_2O (50 mL) was added, and then the solution was washed successively with saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to provide a colorless oil that was finally purified by flash column chromatography using acetone/hexanes (1:1) as eluent.

4,5-Dimethoxy-2-(2-(2-methyl-*tert*-butoxycarbonylaminoethyl)phenyl)benzaldehyde (20): 945 mg, 79%; ^{1}H NMR ($CDCl_3$) δ 1.20 (s, 9H), 2.47 (s, 3H), 2.59−2.61 (m, 2H), 3.09−3.30 (m, 2H), 3.92 (s, 6H), 6.68 (s, 1H), 7.13−7.32 (m, 4H), 7.46 (s, 1H), 9.50 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 28.2, 31.3, 34.0, 50.3, 56.0, 56.3, 79.2, 107.9, 112.8, 126.0, 127.2, 128.5, 129.8, 130.7, 137.2, 138.0, 140.3, 148.7, 153.5, 155.3, 190.7. Anal. Calcd for $C_{23}H_{29}NO_5$: C, 69.15; H, 7.32; N, 3.51. Found: C, 68.98; H, 7.20; N, 3.73.

3,4-Dimethoxy-2-(2-(2-methyl-*tert*-butoxycarbonylaminoethyl)phenyl)benzaldehyde (21): 920 mg, 77%; ^{1}H NMR ($CDCl_3$) δ 1.36 (s, 9H), 2.45−2.59 (m, 5H), 3.11−3.18 (m, 2H), 3.52 (s, 3H), 3.97 (s, 3H), 7.05 (d, J = 8.6 Hz, 1H), 7.15 (d, J = 7.4 Hz, 1H), 7.23−7.29 (m, 2H), 7.35 (d, J = 6.7 Hz, 1H), 7.83 (d, J = 8.6 Hz, 1H), 9.46 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 28.3, 32.0, 34.2, 49.7, 56.0, 60.7, 79.1, 111.4, 124.7, 125.8, 128.2, 128.5, 129.6, 130.6, 132.8, 138.3, 139.4, 146.0, 155.5, 157.7, 190.6. Anal. Calcd for $C_{23}H_{29}NO_5$: C, 69.15; H, 7.32; N, 3.51. Found: C, 69.05; H, 7.44; N, 3.56.

Synthesis of the Tetrahydrodibenzo[*c,e*]azocines 1, 2. To a solution of the formylated carbamate **20**, **21** (40 mg, 0.1 mmol) in CH_2Cl_2 (10 mL) was added, by syringe under Ar, trifluoroacetic acid (114 mg, 1 mmol), and the mixture was stirred for 2 h. The solvent and excess reagent were removed under vacuum, and the crude salt was dissolved in $Cl(CH_2)_2Cl$ (50 mL). Sequential addition of Et_3N (101 mg, 1 mmol) and $NaBH(OAc)_3$ (25 mg, 0.12 mmol) was followed by stirring at room temperature under Ar for 12 h. The reaction mixture was then treated with saturated aqueous $NaHCO_3$ (2 × 10 mL) and washed with water and brine. The organic phase was dried over $MgSO_4$ and concentrated in vacuo, and the crude product was purified by chromatography on silica gel (eluent CH_2Cl_2/MeOH, 90:10) to afford the annulated product **1**, **2**, which was finally recrystallized from hexane.

2,3-Dimethoxy-6-methyl-5,6,7,8-tetrahydrodibenzo[*c,e*]azocine (Buflavine, 1): 24.3 mg, 86%; mp 106−107 °C (lit.[1] mp 106−108 °C). Analytical and spectral data matched those reported for the natural product.

1,2-Dimethoxy-6-methyl-5,6,7,8-tetrahydrodibenzo[*c,e*]azocine (2): 23.5 mg, 83%; mp 62−63 °C; ^{1}H NMR ($CDCl_3$) δ 2.41 (s, 3H), 2.47−2.51 (m, 2H), 2.65−2.69 (m, 1H), 2.98 (d, J = 13.5 Hz, 1H), 3.17−3.20 (m, 1H), 3.44 (s, 3H), 3.47 (d, J = 13.5 Hz, 1H), 3.88 (s, 3H), 6.92 (d, J = 8.4 Hz, 1H), 7.10 (d, J = 8.4 Hz, 1H), 7.21−7.24 (m, 2H), 7.31−7.33 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 35.3, 45.6, 55.9, 57.5, 58.9, 60.4, 111.7, 125.3, 126.1, 126.3, 129.2, 130.5, 131.6, 134.5, 135.1, 141.5, 146.1, 151.9. Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.30; H, 7.47; N, 4.94. Found: C, 76.46; H, 7.30; N, 5.09.

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