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A brief total synthesis of fumaramidine

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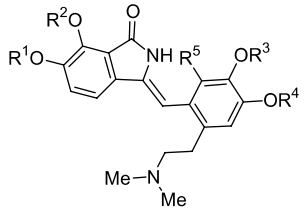
Abstract—The first total synthesis of the alkaloid fumaramidine is reported. The synthetic tactics involve the sequential construction of the isoindolinone template by a Parham cyclization process followed by benzylic lactam deprotonation, interception with the suitable carboxaldehyde and ultimate E1cb elimination. Final *N*-lactam deprotection completes the synthesis of the *Z* configured title compound.

1. Introduction

The creeper *Fumaria parviflora Lam* (*Fumariaceae*) is widespread in Pakistan where it is commonly known as Pit Papra and where its extracts are used in folk medicine as a blood purifier and as an anthelmintic, as well as in the treatment of skin diseases and diarrhea.[1] The crude alkaloidal extracts have initially indicated the presence of 17 isoquinoline bases[2] and additionally four enelactams, that is, fumaramidine **1**, fumaramine **2**, fumaridine **3** and narceine imide **4** (Fig. 1) were isolated from the strongly basic ethanolic extracts of dried plant material.[3]

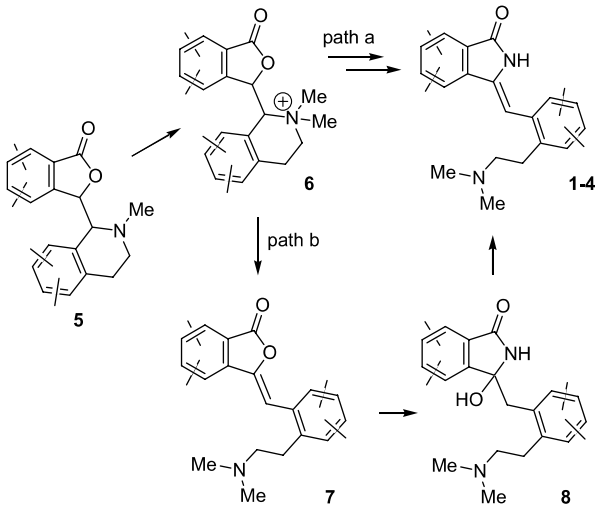


1	Fumaramidine	$R^1,R^2 = -CH_2-$; $R^3 = R^4 = Me$; $R^5 = H$
2	Fumaramine	$R^1,R^2 = R^3,R^4 = -CH_2-$; $R^5 = H$
3	Fumaridine	$R^1 = R^2 = Me$; $R^3,R^4 = -CH_2-$; $R^5 = H$
4	Narceine imide	$R^1 = R^2 = Me$; $R^3,R^4 = -CH_2-$; $R^5 = OMe$

Figure 1.

However, their presence in the natural source is not guaranteed and is still a subject for discussion. They can indeed be formed by a logical biogenetic sequence involving N-methylation of the phthalideisoquinolines **5** to their quaternary analogs **6** followed by unspecified rearrangements including Hoffmann elimination (Scheme 1, path a).[4]

But it has also been conjectured that the transformation of **6** to **1**–**4** might be performed with ammonium hydroxide usually used in the course of their isolation since it has been shown that enol lactones **7** react with ammonia to form hydroxylactams **8** liable to undergo facile dehydration to the enelactams **1**–**4** (Scheme 1, path b).[5] Until and unless the presence of hydroxyl and enelactams **8** and **1**–**4**, respectively is conclusively demonstrated in the plant extracts prior to strongly base treatments it can be concluded that these enelactams are artifacts and not true alkaloids. This problem



Scheme 1.

Keywords: Alkaloids; Parham procedure; Ene lactams; Isoindolinones.
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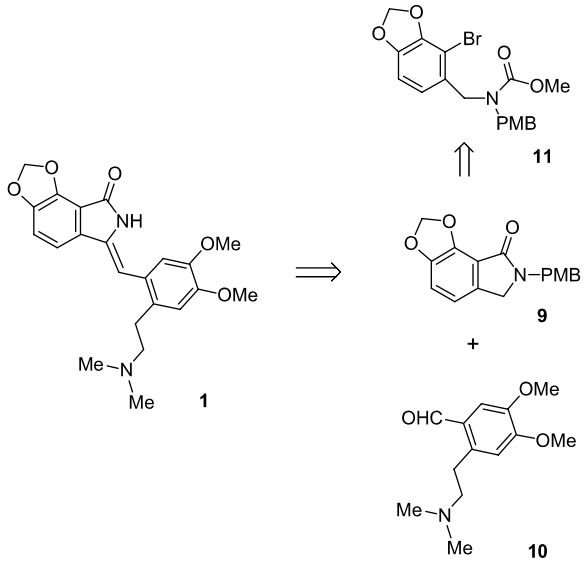
prompted us to launch a project related to the total synthesis of these highly conjugated models and we delineate in this paper a tactically new synthesis of the exemplary representative fumaramidine **1** that relies upon our long-standing experience in the field of *N*-acylenamine and isoindoline chemistry.[6,7]

2. Results and discussion

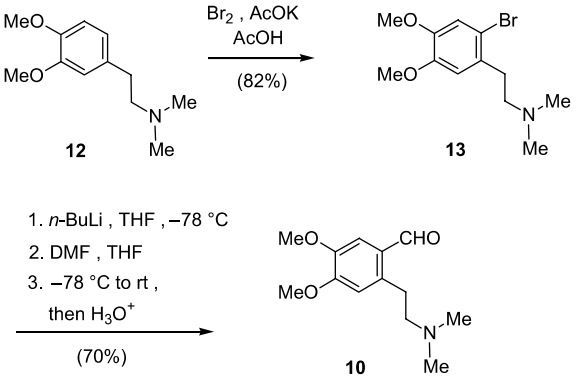
A swift skimming over the structural composition of this enelactam reveals that this alkaloid can be regarded as having a *Z* configured stilbenoid system fused with a lactam ring. But besides it turns out that a number of synthetic issues has also to be addressed such as (i) the connection of diverse and dense functionalities on the environmentally different aromatic units and in particular the assemblage of an unsymmetrically disubstituted isoindolinone and (ii) the presence of an unsubstituted nitrogen lactam, which may require a problematic deprotection step for such models with a high degree of conjugation.[8] As far as we are aware no total synthesis of **1** has appeared in print. For the elaboration of compound **1** we opted for the synthetic route depicted in the retrosynthetic Scheme 2.



Scheme 2.

We assumed that fumaramidine **1** would be conceivably assembled by sequential basic treatment of the protected isoindolinone **9**, quenching with the poly and differentially substituted benzaldehyde **10** followed by dehydration of the primary adduct and ultimate deprotection. We envisaged building up the parent isoindolinone **9** by reliance on the Parham cyclization process involving the tetrasubstituted aromatic carbamate **11**. Literature precedents gave support to the feasibility of this synthetic approach. Isoindolinones have been successfully metalated at the benzylic position of the heteroring system thus allowing the connection of a range of electrophiles.[9] E1cb elimination from *erythro* and *threo* isoindolinones equipped with an *O*-alkoxybenzyl appendage on the lactam ring has been shown to be particularly efficient owing to the highly conjugated character of the resulting enelactams.[10] And finally, application of the Parham cyclization process for the elaboration of five-membered lactams are scarce but a number of structurally related systems have been successfully prepared under the agency of this process.[11]

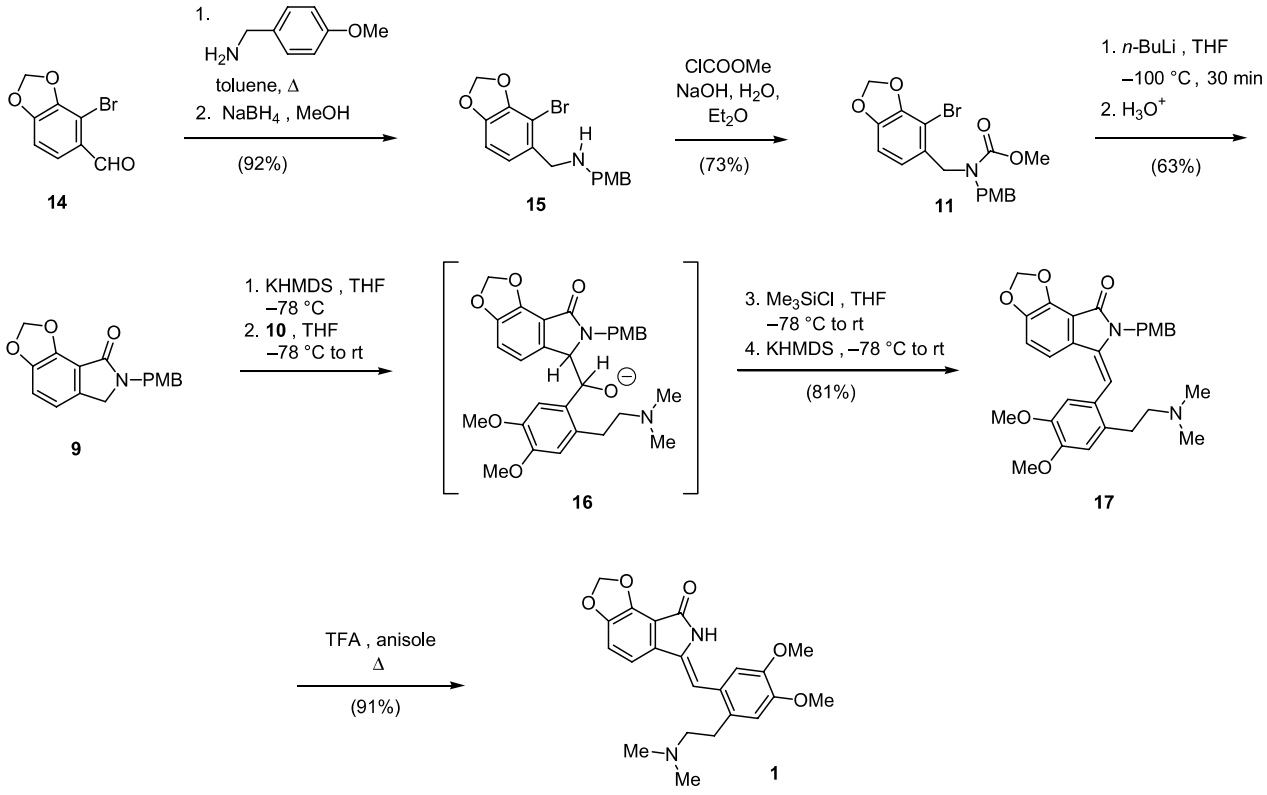
The first facet of the synthesis was then the elaboration of the polyfunctionalized aldehyde **10**. This compound was readily obtained by regioselective bromination of the dimethoxylated phenethylamine derivative **12** and the subsequent installation of the formyl functionality was achieved by bromine/lithium interconversion from **13** and subsequent trapping with DMF as the formylating agent (Scheme 3).



Scheme 3.

The elaboration of the second partner of the synthesis, that is, isoindolinone **9**, required the preliminary preparation of the bromoarylcarbamate **11**. This compound was readily obtained by the two-step sequence portrayed in Scheme 4. Reductive amination involving the easily available bromopiperonal **14** and *para*-methoxybenzylamine delivered the secondary amine **15** incorporating the nitrogen protecting group *para*-methoxybenzyl (PMB). Treatment of **15** with methyl chloroformate provided the carbamate **11** candidate for the planned Parham cyclization process. This annulation technique hinges upon aromatic lithiation and subsequent trapping with an internal electrophile. Carbamate **11** was then exposed to *n*-BuLi at −100 °C to ensure halogen/lithium interconversion and the intramolecular ring closure was instantaneous since the annulated compound **9** was solely obtained in an excellent yield upon immediate aqueous work up (scheme 4).

The final installation of the pendant arylmethylene unit on the isoindolinone framework required four phases, which could be fortunately performed as a single one-pot reaction. For this purpose compound **9** was smoothly deprotonated with KHMDS in THF at −78 °C and subsequently allowed to react with the appropriate aldehyde **10** (Scheme 4). To trigger off the E1cb elimination process the transient oxanion **16** was *O*-silylated in situ with TMSCl and subsequently treated in the sequel with KHMDS at −78 °C. Warming to 0 °C was followed by acidic aqueous work up and gratifyingly



Scheme 4.

conducting this reaction according to this procedure afforded straightforwardly and solely the protected arylmethylideneisoindolinone **17** with an excellent yield. Compound **17** was obtained exclusively with the undesired *E* geometry and configurational assignments were determined by NOE experiments. However, at this stage stereochemical considerations about the central double bond were not crucial for the ultimate formation of the *Z* configured target product. Indeed removal of the selected benzyl protection of the nitrogen lactam of **17** is usually achieved by treatment in boiling TFA in the presence of anisole as cation scavenger.[12] These conditions are appropriate to favor the formation of the thermodynamically more stable stereoisomer with the mandatory *Z* configuration and the target product **1** was obtained exclusively and in an excellent yield by this technique. The constitution and stereochemistry of this synthetic enelactam **1** agree with those reported for the alkaloid extracted from natural sources.[4]

3. Conclusion

In conclusion, a simple and efficient first total synthesis of the enelactam fumaramidine from *fumariceae* species has been disclosed. The advantages of this synthesis, which lie mainly in the small number of steps, their procedural simplicity and high efficiency provide a strong incentive for the elaboration of similar structurally modified alkaloids as well as their biogenetically related congeners.

4. Experimental

4.1. General

Tetrahydrofuran (THF) was pre-dried with anhydrous Na_2SO_4 and distilled over sodium benzophenone ketyl under Ar before use. DMF, CH_2Cl_2, NEt_3, and toluene were distilled from CaH_2. Dry glassware was obtained by oven drying and assembly under dry Ar. The glassware was equipped with rubber septa and reagent transfer was performed by syringe techniques. For flash chromatography, Merck silica gel 60 (40–63 μm; 230–400 mesh ASTM) was used. The melting points were obtained on a Reichert-Thermopan apparatus and are not corrected. NMR spectra: Bruker AM 300 (300 and 75 MHz, for ^1H, and ^{13}C), $CDCl_3$ as solvent, TMS as internal standard. Microanalyses were performed by the CNRS microanalysis center.

N,*N*-Dimethyl-3,4-dimethoxy-β-phenethylamine **12**[13] and 2-bromopiperonal **14**[14] were synthesized according to literature methods.

4.2. Synthesis of the benzaldehyde derivative 14

4.2.1. *N*,*N*-Dimethyl-3,4-dimethoxy-5-bromo-β-phenethylamine (13). Bromine (7.6 mmol, 0.4 mL) was added dropwise under stirring to a solution of *N*,*N*-dimethyl-3,4-dimethoxy-β-phenethylamine **12** (800 mg, 3.8 mmol) and potassium acetate (560 mg, 3.8 mmol). Stirring was maintained for 16 h at room temperature, the solution was concentrated under vacuum and the residue was dissolved in

CH_2Cl_2 (60 mL). The solution was washed successively with saturated aqueous Na_2CO_3 (20 mL), aqueous sodium thiosulfate (10%, 20 mL), and brine. The organic layer was dried (Na_2SO_4) and the solvent was evaporated under vacuum. The crude oily residue was purified by column chromatography using AcOEt–hexanes–NEt_3 (80/10/10) as eluent to deliver the amine **13** as a yellow oil. Yield 921 mg (82%); ^{1}H NMR (δ_H) 2.30 (s, 6H, 2×NCH_3), 2.44–2.49 (m, 2H, CH_2), 2.79–2.84 (m, 2H, CH_2), 3.81 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 6.72 (s, 1H aromatic H), 6.96 (s, 1H, aromatic H) ppm; ^{13}C NMR (δ_C) 34.1, 45.3, 56.0, 56.1, 59.7, 113.1, 114.1, 115.6, 131.5, 147.9, 148.4 ppm. Anal. Calcd for $C_{12}H_{18}BrNO_2$ (288.2): C, 50.01; H, 6.30; N 4.86%. Found: C, 50.25; H, 4.63; N 4.67%.

4.2.2. 2-(2-Dimethylaminoethyl)-4,5-dimethoxybenzaldehyde (10). A solution of *n*-BuLi (1.64 mL, 1.6 M in hexane, 2.6 mmol) was added dropwise by syringe at −78 °C under Ar to a solution of amine **13** (550 mg, 2.0 mmol) in dry THF (50 mL). The reaction mixture was stirred at −78 °C for 15 min and DMF (140 mg, 0.2 mL, 2.6 mmol) was added. The solution was stirred at −78 °C for 1 h, then at room temperature for an additional 1 h and treated with saturated aqueous NH_4Cl (5 mL). The mixture was diluted with water (10 mL), extracted with Et_2O (3×50 mL) and the combined organic extracts were dried ($MgSO_4$). Evaporation of solvents in vacuo left an oily residue, which was purified by flash column chromatography with AcOEt–hexanes–NEt_3 (80/10/10) as eluent to furnish **10** as a yellow solid. Yield 331 mg (70%); mp 54–55 °C (from hexane–toluene); ^{1}H NMR (δ_H) 2.25 (s, 6H, 2×NCH_3), 2.43–2.48 (m, 2H, CH_2), 3.03–3.08 (m, 2H, CH_2), 3.85 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 6.68 (s, 1H, aromatic H), 7.24 (s, 1H, aromatic H), 10.12 (s, 1H, CH═O) ppm; ^{13}C NMR (δ_C) 30.1, 45.3, 55.9, 56.0, 62.0, 111.1, 113.0, 126.8, 138.3, 147.6, 153.6, 189.5 (CHO) ppm. Anal. Calcd for $C_{13}H_{19}NO_3$ (237.3): C, 65.80; H, 8.07; N 5.90%. Found: C, 66.01; H, 8.03; N 6.05%.

4.3. Synthesis of the isoindolinone 9

4.3.1. *N*-(4-Bromobenzo[1,3]dioxol-5-ylmethyl)-*N*-(4-methoxybenzyl)amine (15). A solution of 2-bromopiperonal (4.85 g, 20 mmol) and 4-methoxybenzylamine (2.74 g, 20 mmol) in toluene (70 mL) was refluxed in the Dean–Stark apparatus for 3 h. Evaporation of the solvent under vacuum left quantitatively the [1-(4-bromobenzo-[1,3]dioxol-5-ylmethyl)methylidene]-(4-methoxybenzyl)-amine as a yellow oil, which was treated in the next step without further purification. (6.98 g); ^{1}H NMR (δ_H) 3.79 (s, 3H, CH_3), 4.75 (s, 2H, NCH_2), 6.07 (s, 2H, OCH_2O), 6.77 (d, J=8.3 Hz, 1H, aromatic H), 6.88 (d, J=8.3 Hz, 2H, aromatic H), 7.24 (d, J=8.3 Hz, 2H, aromatic H), 7.65 (d, J=8.3 Hz, 1H, aromatic H), 8.60 (s, 1H, CH═N) ppm; ^{13}C NMR (δ_C) 55.3, 64.5, 103.8, 104.0, 107.8, 113.9, 122.9, 128.4, 129.1, 131.3, 146.1, 149.4, 158.7, 159.1 (CH═N) ppm. Sodium borohydride (832 mg, 22 mmol) was added portionwise to a solution of the crude imine (6.98 g, 20 mmol) in MeOH (100 mL). The reaction mixture was then stirred at room temperature for 30 min and then concentrated under vacuum. The oily residue was dissolved in CH_2Cl_2 (100 mL). The solution was washed with water (2×30 mL), brine and dried (Na_2SO_4). After evaporation of the solvent, the crude oily residue was purified by column chromatography using AcOEt–NEt_3 (90/10) as eluent to deliver the amine **15** as a light yellow oil. Yield 6.45 mg (92%); ^{1}H NMR (δ_H) 1.71 (br s, 1H, NH), 3.70 (s, 2H, NCH_2), 3.78 (s, 5H, NCH_2+OCH_3), 6.02 (s, 2H, OCH_2O), 6.71 (d, J=7.8 Hz, 1H, aromatic H), 6.82–6.87 (m, 3H, aromatic H), 7.25 (d, J=8.3 Hz, 2H, aromatic H) ppm; ^{13}C NMR (δ_C) 52.1, 52.2, 55.3, 101.4, 102.7, 107.0, 113.7, 123.0, 129.4, 132.3, 132.6, 146.3, 146.7, 158.6 ppm. Anal. Calcd for $C_{16}H_{16}BrNO_3$ (350.2): C, 54.87; H, 4.61; N 4.00%. Found: C, 54.65; H, 4.92; N 4.11%.

4.3.2. Methyl *N*-(4-bromobenzo[1,3]dioxol-5-ylmethyl)-*N*-(4-methoxbenzyl)carbamate (11). Methyl chloroformate (1.04 g, 11 mmol) was added slowly under stirring to a cooled (0 °C) solution of amine **15** (3.51 g, 10 mmol) in Et_2O (50 mL) followed by a solution of NaOH (440 mg, 11 mmol) in water (5 mL). The mixture was stirred at 0 °C for 30 min and the ethereal layer was separated, washed with aqueous HCl (4 M; 3×30 mL), water (30 mL) and dried (Na_2SO_4). After evaporation of the solvent, the crude oily residue was purified by column chromatography using AcOEt–hexanes (40/60) as eluent to deliver the carbamate **11** as a colorless oil. Yield 2.98 g (73%); ^{1}H NMR (δ_H) 3.78 (s, 6H, 2×OCH_3), 4.37–4.46 (m, 4H, 2×NCH_2), 6.02 (s, 2H, OCH_2O), 6.62–6.73 (m, 3H, aromatic H), 6.83 (d, J=8.5 Hz, 2H, aromatic H), 7.13 (d, J=11.5 Hz, 2H, aromatic H) ppm; ^{13}C NMR (δ_C) 48.5, 49.2, 53.0, 55.3, 101.5, 107.3, 113.9, 120.8, 122.2, 128.8, 129.3, 129.5, 146.3, 146.9, 157.3, 159.0 ppm. Anal. Calcd for $C_{18}H_{18}BrNO_5$ (408.2): C, 52.96; H, 4.44; N 3.43%. Found: C, 53.09; H, 4.33; N 3.27%.

4.3.3. 7-(4-Methoxybenzyl)-6,7-dihydro[1,3]dioxolo[4,5-*e*]-isoindol-8-one (9). A solution of *n*-BuLi (3.6 mL, 1.6 M in hexane, 5.76 mmol) was added dropwise by syringe at −90 °C under Ar to a solution of carbamate **11** (1.96 g, 4.8 mmol) in dry THF (50 mL). The reaction mixture was stirred at −90 °C for 20 min then allowed to warm to −40 °C over a period of 30 min followed by addition of saturated aqueous NH_4Cl (5 mL). The mixture was diluted with water (20 mL), extracted with Et_2O (3×25 mL) and the combined organic layers were dried ($MgSO_4$). Evaporation of the solvent in vacuo left an oily residue, which was purified by flash column chromatography with AcOEt–hexanes (60/40) as eluent to furnish the isoindolinone **9** as a yellow oil. Yield 898 mg (63%); ^{1}H NMR (δ_H) 3.74 (s, 3H, OCH_3), 4.14 (s, 2H, NCH_2), 4.62 (s, 2H, NCH_2), 6.07 (s, 2H, OCH_2O), 6.72 (d, J=7.8 Hz, 1H, aromatic H), 6.80 (d, J=8.5 Hz, 2H, aromatic H), 6.86 (d, J=7.8 Hz, 1H, aromatic H) 7.19 (d, J=8.5 Hz, 2H, aromatic H) ppm; ^{13}C NMR (δ_C) 45.7, 49.4, 55.3, 102.6, 111.0, 114.1, 115.2, 129.0, 129.5, 130.2, 134.3, 143.4, 148.3, 159.1, 165.8 (CO) ppm. Anal. Calcd for $C_{17}H_{15}BrNO_4$ (297.3): C, 68.68; H, 5.09; N 4.71%. Found: C, 68.46; H, 5.39; N 4.82%.

4.4. Synthesis of fumaramidine (1)

4.4.1. 6-{1-[2-(2-Dimethylaminoethyl)-4,5-dimethoxyphenyl]meth-(*E*)-ylidene}-7-(4-methoxybenzyl)-6,7-dihydro[1,3]dioxolo[4,5-*e*]isoindo-8-one (17). A solution of KHMDS (2.2 mL, 0.5 M in toluene, 1.1 mmol) was

added dropwise at −78 °C under Ar to a stirred solution of isoindolinone **9** (297 mg, 1 mmol) in THF (50 mL). After stirring at −78 °C for 10 min a solution of benzaldehyde derivative **10** (260 mg, 1.1 mmol) in THF (10 mL) was added dropwise. The resulting solution was allowed to warm to room temperature over 15 min then recooled to −78 °C. Chlorotrimethylsilane (119 mg, 1.1 mmol) was added and the mixture was allowed to warm slowly to room temperature and recooled to −78 °C. KHMDS (2.2 mL, 0.5 M in toluene, 1.1 mmol) was then added and warming to room temperature over 30 min allowed the completion of E1cb elimination reaction. Saturated aqueous NH_4Cl (5 mL) was added and the mixture was diluted with water (20 mL), extracted with Et_2O (3×20 mL). After drying of the combined organic layers (Na_2SO_4), evaporation of solvent in vacuo left an oily residue, which was purified by flash column chromatography with AcOEt–NEt_3 (90/10) as eluent to furnish the arylmethyleneisoindolinone **17** as a yellow oil. Yield 418 mg (81%); ^{1}H NMR (δ_H) 1.90 (s, 6H, 2×NCH_3), 2.11 (t, J=7.5 Hz, 2H, CH_2), 2.41 (t, J=7.5 Hz, 2H, CH_2), 3.63 (s, 3H, OCH_3), 3.64 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.95 (s, 2H, NCH_2), 6.13 (s, 2H, OCH_2O), 6.36 (s, 1H, CH═), 6.69–6.74 (m, 3H, aromatic H), 6.82 (s, 1H, aromatic H), 7.14–7.21 (m, 3H, aromatic H), 7.25 (m, 1H, aromatic H) ppm; ^{13}C NMR (δ_C) 31.7 (CH_2Ar), 45.1 (2×NCH_3), 42.6 (CH_2, PMB), 55.0 (OCH_3, PMB), 55.8 (OCH_3), 55.9 (OCH_3), 60.3 (NCH_2), 100.6 (OCH_2O), 110.1 (CH═), 112.6 (CH), 113.3 (CH), 113.4 (CH), 114.1 (2×CH, PMB), 123.2 (CH), 125.7 (C), 127.3 (2×CH, PMB), 129.1 (C), 130.1 (C), 132.1 (C), 135.1 (C), 136.0 (C), 144.3 (C), 147.1 (C), 148.8 (C), 149.3 (C), 158.8 (C), 166.6 (CO) ppm. Anal. Calcd for $C_{30}H_{32}N_2O_6$ (516.6): C, 69.75; H, 6.24; N 5.42%. Found: C, 69.58; H, 6.11; N 5.17%.

4.4.2. Fumaramidine (1). A solution of the arylmethylene isoindolinone **17** (260 mg, 0.5 mmol) and anisole (540 mg, 5.0 mmol) in trifluoroacetic acid (10 mL) was refluxed under Ar for 24 h. The reaction mixture was concentrated under vacuum, the residue was dissolved in CH_2Cl_2 (20 mL) and NEt_3 (0.5 mL) was added with stirring. Water (3× 50 mL) was then added, and the organic layer was washed with brine, dried ($MgSO_4$) and concentrated to yield an oily residue. Purification by flash column chromatography using AcOEt–NEt_3 (95/5) as eluent and recrystallization from EtOH gave a yellow solid: mp 266–267 °C (dec). The spectral data of synthetic **1** (180 mg, 91%) matched those reported for the natural product.[3,4] ^{1}H NMR (δ_H) 2.24 (s, 6H, 2×NCH_3), 2.46 (t, J=7.9 Hz, 2H, CH_2), 2.77 (t, J= 7.9 Hz, 2H, CH_2), 3.86 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 6.14 (s, 2H, OCH_2O), 6.43 (s, 1H, CH═), 6.74 (s, 1H, aromatic H), 6.82 (s, 1H, aromatic H), 7.02 (d, J=8.0 Hz, aromatic H), 7.25 (d, J=8.0 Hz, aromatic H), 8.34 (br s, 1H, NH) ppm; ^{13}C NMR (δ_C) 31.8 (CH_2Ar), 45.5 (2×NCH_3), 55.9 (OCH_3), 56.2 (OCH_3), 60.7 (NCH_2), 103.0 (CH═), 103.1 (OCH_2O), 111.7 (CH), 112.0 (CH) 113.1 (CH), 113.2 (CH), 125.6 (C), 131.8 (C), 132.0 (C), 133.3 (C), 143.4 (C), 147.7 (C), 148.7 (C), 149.3 (C), 166.1 (CO) ppm.

Acknowledgements

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