Total Synthesis of the Indolizidinium Alkaloid Ficuseptine

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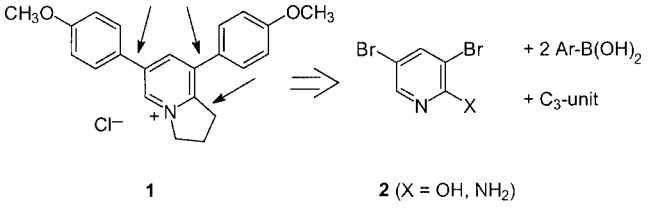
The first total synthesis of ficuseptine [4,6-bis(4-methoxyphenyl)-1,2,3-trihydroindolizidinium chloride] (**1**), an alkaloid from *Ficus septica*, is described. The crucial steps in this five-step synthesis are a palladium-catalyzed bis(arylation) of a dibromopyridine under Suzuki conditions and a palladium-catalyzed alkynylation of an iodopyridine under Sonogashira conditions, as well as a novel Sandmeyer-type iodination of a 2-aminopyridine derivative.

Introduction

In 1990, Rali and co-workers[1] reported on the isolation and characterization of the alkaloid ficuseptine (**1**) from *Ficus septica* Burm. F. (Moraceae). The antibacterial and antifungal activities of ficuseptine motivated us to work out a total synthesis. In order to develop a synthetic strategy that should also permit the convenient preparation of related compounds for the investigation of structure-activity relationships, we decided to start from a simple pyridine derivative and to build up the new carbon−carbon bonds (see arrows in Scheme 1) by means of palladium-catalyzed cross-coupling reactions. Firstly, the two 4-methoxyphenyl substituents were to be introduced into an appropriate dibromopyridine by a Suzuki coupling with an areneboronic acid. Then, introduction of the aliphatic C_3 unit should be accomplished by palladium-catalyzed alkynylation. Since handling of quaternary pyridinium compounds is somewhat tricky, we decided to perform the cyclization to the indolizidinium ring system as the last step in the synthetic sequence.



Scheme 1. Retrosynthetic analysis of ficuseptine (**1**): the carbon−carbon bonds to be built up by Pd-catalyzed cross-coupling reactions are marked with arrows

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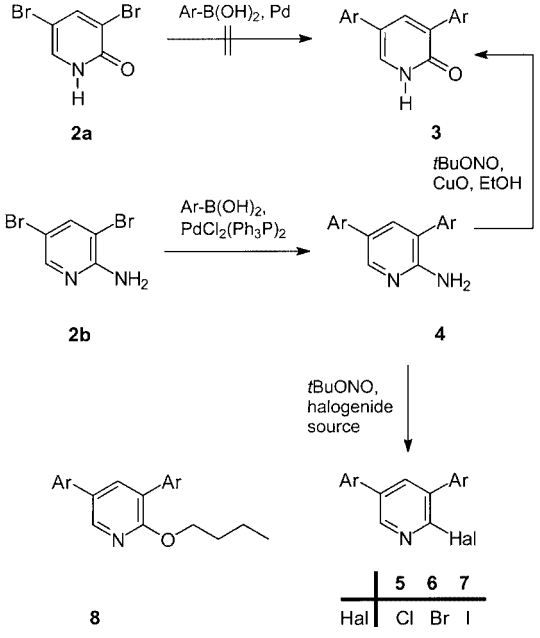
Results and Discussion

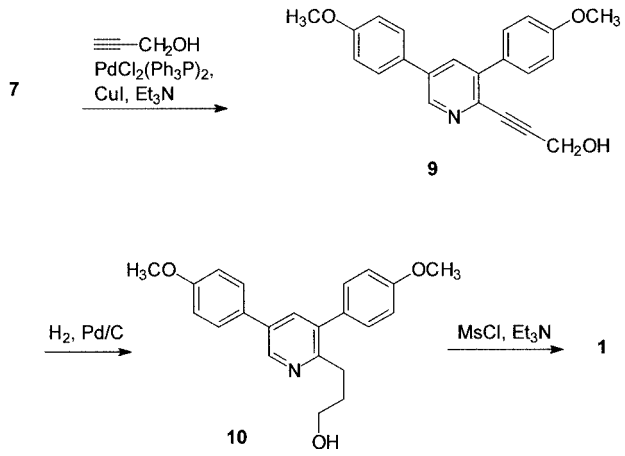
A 3,5-dibromopyridine with an additional substituent (OH, NH_2) in the 2-position, which could later be converted into a halogen substituent, appeared to be a suitable starting material for the synthesis of ficuseptine (**1**). In a first approach we tried to perform a palladium-catalyzed bis(arylation) of the known 3,5-dibromo-2(1*H*)-pyridone (**2a**)[2] with 4-methoxyphenylboronic acid[3] under Suzuki conditions,[4] but the reaction failed to give the desired pyridone **3**. Instead, we obtained 3- and 5-monoarylpyridones, with reductive elimination of the second bromo substituent. Problems in analogous syntheses of 5-aryl-2-hydroxypyridines have been discussed in the literature,[5] but the phenomenon of reductive debromination was not mentioned in that paper. Modified coupling conditions[6,7] also did not provide **3**. Under Gillmann's conditions[8] with Ag_2O as a base we even obtained 4,4′-dimethoxybiphenyl. In an alternative approach to an appropriate intermediate for further introduction of a C_3 unit at the 2-position of the pyridine ring we examined a palladium-catalyzed bis(arylation) of 2-amino-3,5-dibromopyridine (**2b**).[9] This reaction worked very well under Suzuki conditions to give compound **4**. Further transformation of this aminopyridine with nitrous acid prepared in situ[10] should give the desired 2-pyridone **3**, which then should be convertible into a 2-halogenated derivative under standard conditions. Surprisingly, diazotization of **4** in aqueous medium and heating did not give any **3**, so we examined the diazotation under non-aqueous conditions. Treatment of **4** with *tert*-butyl nitrite/$CuCl_2$ in 1-butanol/chloroform[11] gave moderate yields of two products, which were identified as the 2-chloro derivative **5** and the 2-butoxy derivative **8**. Consequent modification of the reaction conditions resulted in a method (*tert*-butyl nitrite/CuO in aqueous ethanol) that afforded the desired pyridone **3** in 50% yield. However, since direct preparation of 2-halogenated derivatives from aminopyridine **4** appeared to be even more

attractive than the pyridone route, we further modified the Sandmeyer-type reaction described above to find a direct approach to the bromo and iodo derivatives **6** and **7** (Scheme 2). Bromo compound **6** was obtained in 55% yield by treatment of **4** with *tert*-butyl nitrite/$CuBr_2$ in $CHBr_3$ as solvent. Interestingly, performing the same reaction in $CHCl_3$ instead of $CHBr_3$ gave a mixture of bromo compound **6** and chloro compound **5**, so $CuBr_2$ was not the only source of bromide in this reaction, but halogen from trihalomethanes could also be incorporated. Similar observations in chlorinations and brominations have been published previously.[12−14] Initial attempts to perform an iodination under analogous reaction conditions gave disappointing results; treatment of **4** with *tert*-butyl nitrite and CHI_3 in toluene or THF (a solvent was needed, since CHI_3 is a solid) with or without addition of CuI or I_2 resulted in complete decomposition. Finally, we found out that the iodopyridine **7** could be obtained by treatment of **4** with *tert*-butyl nitrite in diiodomethane (CH_2I_2) as solvent. The yield could even be enhanced by addition of I_2 to this reaction mixture, with **7** being obtained in 61% yield.



Scheme 2. Synthesis of 2-substituted 3,5-diarylpyridines (Ar = 4-methoxyphenyl); halide sources: $CuCl_2$ in *n*BuOH for **5**; $CuBr_2$ in $CHBr_3$ for **6**; I_2 in CH_2I_2 for **7**

The iodopyridine **7** was found to be a very useful intermediate for the introduction of a C_3 building block at the 2-position. Treatment with propargyl alcohol under palladium-catalyzed Sonogashira conditions[15−18] gave the alkynylated pyridine **9** in 81% yield (Scheme 3). Protection of the hydroxy group, as described in a recent publication,[19] was not necessary in this case. Catalytic hydrogenation of the triple bond afforded the pyridylpropanol **10**, which should allow the final cyclization to the indolizidinium ring system. We examined numerous literature methods[20−22] and found that treatment with mesyl chloride and triethylamine[19,23] in CH_2Cl_2 was most effective for obtaining alkaloid **1** in a single operation. Product **1** could efficiently be purified by extraction from an aqueous mixture with $CHCl_3$, followed by recrystallization.



Scheme 3. Total synthesis of ficuseptine (**1**)

Conclusion

In conclusion, we have developed an efficient five-step total synthesis of the alkaloid ficuseptine (**1**) by using palladium-catalyzed cross-coupling reactions as the crucial steps. Moreover, we have found a new modification of the Sandmeyer reaction for the preparation of 2-iodopyridines from corresponding aminopyridines. Ficuseptine showed potent antifungal activity in a preliminary screening. Work to evaluate the mechanism of the antifungal action is in progress.

Experimental Section

General: Melting points (uncorrected): Büchi SMP 20. Infrared spectra: Philips PU 9800 (FT-IR). NMR spectra: Bruker AM 400 (400.1 MHz for ^1H and 100.6 MHz for ^{13}C), $CDCl_3$ solutions with TMS as internal standard; δ values given in ppm. Mass spectra: Finnigan MAT 8430 (EI, 70 eV); fast atom bombardment (FAB): *m*-nitrobenzyl alcohol (NBA) as a matrix. Elemental analyses: Carlo Erba CHN Elemental Analyzer. Column chromatography: Merck Kieselgel 60 (230−400 mesh). Solvents were freshly distilled prior to use.

2-Amino-3,5-bis(4-methoxyphenyl)pyridine (4): 2-Amino-3,5-dibromopyridine hydrobromide (**2b**)[9] (6.66 g, 20.0 mmol) and 4-methoxyphenylboronic acid[3] (6.38 g, 42.0 mmol) were dissolved in methanol (50 mL). Na_2CO_3 (50 g) in water (100 mL) and then toluene (200 mL) were added, and the suspension was degassed with ultrasound for 5 min. $PdCl_2(PPh_3)_2$ (0.29 g, 0.41 mmol) was then added, and the mixture was heated under reflux under nitrogen with vigorous stirring for 65 h. The organic solvents were removed under reduced pressure, followed by extraction with ethyl acetate and column chromatography (diethyl ether). The product was recrystallized from methanol to give 4.37 g (71%) of **3** as a yellow powder, m.p. 165−166 °C. IR (KBr): $\tilde{\nu}$ = 1634, 1608, 1561, 1512, 1249, 828 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 3.84 (s, 3 H, OCH_3), 3.86

(s, 3 H, OCH_3), 4.61 (br. s, 2 H, NH_2), 6.96, 7.01, 7.42, and 7.46 (each br. d, J = 8.6 Hz, 4 × 2 H, Ar-H), 7.54 (d, J = 2.3 Hz, 1 H, 4-H), 8.25 (d, J = 2.3 Hz, 1 H, 6-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 55.4 (2 C), 114.4 (2 C), 114.6 (2 C), 121.5, 127.4 (2 C), 127.7, 129.9 (2 C), 130.2, 130.8, 136.3, 144.6, 154.9, 158.9, 159.3 ppm. MS (70 eV): *m*/*z* (%) = 306 (100) [M^+], 291 (25), 290 (11), 275 (5). $C_{19}H_{18}N_2O_2$ (306.36): calcd. C 74.49, H 5.92, N 9.14; found C 74.56, H 5.97, N 9.07.

3,5-Bis(4-methoxyphenyl)-1*H*-pyridin-2-one (3): *tert*-Butyl nitrite (0.16 g, 1.6 mmol) was added to a stirred suspension of aminopyridine **4** (0.30 g, 0.98 mmol) and CuO (0.10 g, 1.3 mmol) in ethanol (7.0 mL) and water (2.6 mL), and the reaction mixture was heated at 80 °C for 20 h while the color turned to reddish brown. K_2CO_3 (0.68 g, 4.9 mmol) in water (2.6 mL) and further *tert*-butyl nitrite (0.26 g, 2.5 mmol) were then added, and the mixture was heated at 100 °C for 18 h. After removal of the solvents under reduced pressure, the resulting residue was purified by column chromatography (ethyl acetate/triethylamine, 20:1), followed by recrystallization from ethanol, to give 0.15 g (50%) of **3** as light brown crystals, m.p. 201−202 °C (decomp.). IR (KBr): $\tilde{\nu}$ = 1644, 1610, 1560, 1509, 1246, 834 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 3.84 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 6.95, 6.99, and 7.38 (each br. d, J = 8.7 Hz, 3 × 2 H, Ar-H), 7.53 (d, J = 2.5 Hz, 1 H, 4-H), 7.73 (br. d, J = 8.7 Hz, 2 H, Ar-H), 7.81 (d, J = 2.5 Hz, 1 H, 6-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 55.3, 55.4, 113.9, 114.5 (2 C), 121.2, 127.0 (2 C), 129.0, 129.2, 129.8, 129.9 (2 C), 138.5, 159.1, 159.5 (2 C), 163.2, 179.7 ppm. MS (70 eV): *m*/*z* (%) = 307 (100) [M^+], 292 (18), 264 (10). $C_{19}H_{17}NO_3{\cdot}H_2O$ (325.36): calcd. C 70.14, H 5.89, N 4.30; found C 70.91, H 5.66, N 4.38.

2-Chloro-3,5-bis(4-methoxyphenyl)pyridine (5): A solution of aminopyridine **4** (0.61 g, 2.0 mmol) in $CHCl_3$ (5 mL) was added to a solution of anhydrous $CuCl_2$ (0.33 g, 2.5 mmol) in 1-butanol (11 mL) and *tert*-butyl nitrite (0.31 g, 3.0 mmol), and the mixture was stirred at room temperature for 3 h. To complete the reaction (TLC monitoring), further *tert*-butyl nitrite (up to 2 mL) was added and the reaction mixture was heated under reflux for a further 3 h. The reaction was stopped by addition of 25 mL of satd. Na_2CO_3 solution, followed by extraction with 3 × 50 mL of ethyl acetate. The combined organic layers were dried with Na_2SO_4 and concentrated. The residue was purified by column chromatography (diethyl ether) to give 0.15 g (23%) of **4** as light yellow crystals (from ethanol), m.p. 140−142 °C. IR (KBr): $\tilde{\nu}$ = 1607, 1515, 1245, 1031, 826 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 3.85 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 6.99 (m, 2 H, Ar-H), 7.01 (m, 2 H, Ar-H), 7.44 and 7.52 (each br. d, J = 8.8 Hz, 2 × 2 H, Ar-H), 7.79 (d, J = 2.5 Hz, 1 H, 4-H), 8.53 (d, J = 2.5 Hz, 1 H, 6-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 55.3, 55.4, 113.8 (2 C), 114.7 (2 C), 128.2 (2 C), 128.8, 129.8, 130.6 (2 C), 135.6, 136.3, 137.5, 145.7, 147.9, 159.7, 160.1 ppm. MS (70 eV): *m*/*z* (%) = 327 (34) [M^+], 325 (100) [M^+], 310 (20), 282 (11). $C_{19}H_{16}ClNO_2$ (325.79): calcd. C 70.05, H 4.95, N 4.30; found C 69.80, H 5.11, N 4.17.

2-Butoxy-3,5-bis(4-methoxyphenyl)pyridine (8): Further elution of the crude product described above with ethyl acetate gave 0.25 g (34%) of **8** as a light brown powder (from ethanol/water), m.p. 79 °C. IR (KBr): $\tilde{\nu}$ = 1610, 1561, 1513, 1449, 1246, 1180, 828 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 0.96 (t, J = 7.5 Hz, 3 H, CH_3), 1.47 (m, 2 H, CH_2−CH_3), 1.77 (m, 2 H, O−CH_2−CH_2), 3.84 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 4.39 (t, J = 6.7 Hz, 2 H, OCH_2), 6.97, 6.99, 7.49, and 7.57 (each br. d, J = 8.8 Hz, 4 × 2 H, Ar-H), 7.76 (s, 1 H, 4-H), 8.27 (s, 1 H, 6-H) ppm. ^{13}C NMR ($CDCl_3$,): δ = 13.9, 19.4, 31.2, 55.3, 55.4, 66.0 (O−CH_2), 113.6 (2 C), 114.4 (2 C), 123.9, 127.8 (2 C), 129.2, 130.0, 130.4 (2 C), 130.6, 136.8, 142.7, 159.1, 159.2, 159.8 ppm. MS (70 eV): *m*/*z* (%) = 363 (58) [M^+], 332 (10), 320 (22), 307 (100), 264 (10). $C_{23}H_{25}NO_3{\cdot}1/2H_2O$ (372.47): calcd. C 74.17, H 7.04, N 3.76; found C 74.55, H 6.76, N 3.74.

2-Bromo-3,5-bis(4-methoxyphenyl)pyridine (6): Anhydrous $CuBr_2$ (1.00 g, 4.48 mmol) and *tert*-butyl nitrite (1.16 g, 11.3 mmol) were added slowly to a solution of aminopyridine **4** (1.15 g, 3.75 mmol) in bromoform (15 mL), and the reaction mixture was stirred under reflux for 4 h. The reaction was stopped by addition of 25 mL of satd. Na_2CO_3 solution, followed by extraction with 3 × 50 mL of ethyl acetate. The combined organic layers were dried with Na_2SO_4 and concentrated. The residue was purified by column chromatography ($CHCl_3$/acetone, 100:3). Analytically pure product was obtained by further column chromatography (CH_2Cl_2), followed by recrystallization from acetone/water, to give 0.76 g (55%) of **6** as yellow needles, m.p. 163.5 °C. IR (KBr): $\tilde{\nu}$ = 1607, 1580, 1514, 1245, 1033, 825 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 3.85 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 6.99, 7.00, 7.41, and 7.52 (each br. d, J = 8.8 Hz, 4 × 2 H, Ar-H), 7.74 (d, J = 2.5 Hz, 1 H, 4-H), 8.51 (d, J = 2.5 Hz, 1 H, 6-H) ppm. ^{13}C NMR ($CDCl_3$,): δ = 55.3, 55.4, 113.8 (2 C), 114.7 (2 C), 128.2 (2 C), 128.7, 130.6 (2 C), 131.3, 135.8, 137.0, 139.1, 140.5, 146.1, 159.7, 160.1 ppm. MS (70 eV): *m*/*z* (%) = 371 (100) [M^+], 369 (98) [M^+], 290 (8), 275 (10). $C_{19}H_{16}BrNO_2$ (370.25): calcd. C 61.64, H 4.36, N 3.78; found C 62.59, H 4.55, N 3.53.

2-Iodo-3,5-bis(4-methoxyphenyl)pyridine (7): Aminopyridine **4** (2.25 g, 7.34 mmol) was dissolved in CH_2I_2 (21 mL), aided by ultrasound. *tert*-Butyl nitrite (1.19 g, 11.1 mmol) and I_2 (1.87 g, 7.37 mmol) were then added, and the reaction mixture was stirred at room temperature for 24 h under exclusion of light. To complete the reaction (TLC monitoring), addition of *tert*-butyl nitrite was repeated and the mixture was stirred for further 12 h. The reaction was stopped by addition of 50 mL of satd. Na_2CO_3 solution and an excess of solid $Na_2S_2O_3$. The solvents were evaporated to dryness under reduced pressure, followed by addition of water and extraction with 3 × 50 mL of ethyl acetate. The combined organic layers were dried with Na_2SO_4 and concentrated. The residue was purified by column chromatography (diethyl ether), followed by crystallization from acetone/water, to give 1.88 g (61%) of **7** as yellow needles, m.p. 164−165 °C. IR (KBr): $\tilde{\nu}$ = 1606, 1580, 1513, 1243, 1032, 824 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 3.84 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 6.98, 6.99, 7.34, and 7.50 (each br. d, J = 8.8 Hz, 4 × 2 H, Ar-H), 7.63 (d, J = 2.6 Hz, 1 H, 4-H), 8.49 (d, J = 2.6 Hz, 1 H, 6-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 55.3, 55.4, 113.7 (2 C), 114.7 (2 C), 120.4, 128.1 (2 C), 128.6, 130.6 (2 C), 133.8, 134.9, 135.6, 143.6, 146.7, 159.7, 160.1 ppm. MS (70 eV): *m*/*z* (%) = 417 (100) [M^+], 290 (34), 275 (13), 247 (11). $C_{19}H_{16}INO_2$ (417.25): calcd. C 54.69, H 3.87, N 3.36; found C 54.50, H 3.86, N 3.32.

3-[3,5-Bis(4-methoxyphenyl)pyridin-2-yl]-2-propyn-1-ol (9): CuI (0.050 g, 0.26 mmol) was suspended in triethylamine (5 mL) at 70 °C, and the suspension was cooled to room temperature with stirring. Propargyl alcohol (3 drops) was then added, and the yellow suspension was stirred for a further 10 min. $PdCl_2(Ph_3P)_2$ (0.10 g, 0.14 mmol), iodopyridine **7** (0.73 g, 1.8 mmol) in triethylamine (10 mL), and propargyl alcohol (0.51 g, 9.1 mmol) were then added under nitrogen, and the reaction mixture was stirred for a further 10 min at room temperature and then for 2 h under reflux. The reaction was stopped by addition of 10 mL of satd. $NaHCO_3$ solution and 40 mL of satd. NaCl solution, followed by extraction with 3 × 50 mL of ethyl acetate. The combined organic layers were dried with Na_2SO_4 and concentrated. The black residue was purified by

column chromatography (CH_2Cl_2, then ethyl acetate) and crystallized from ethanol/water to give 0.49 g (81%) of **9** as light brown crystals, m.p. 128 °C. IR (KBr): $\tilde{\nu}$ = 3275, 1611, 1513, 1450, 1250, 1027, 821 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 3.83 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 4.33 (br. s, 1 H, OH), 4.45 (s, 2 H, C*H*$_2$OH), 6.96, 6.98, 7.53, and 7.55 (each br. d, *J* = 8.8 Hz, 4 × 2 H, Ar-H), 7.80 (d, *J* = 2.0 Hz, 1 H, 4-H), 8.69 (d, *J* = 2.0 Hz, 1 H, 6-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 51.2, 55.3, 55.4, 84.3, 91.2, 113.8 (2 C), 114.7 (2 C), 128.2 (2 C), 129.2, 130.2, 130.4 (2 C), 134.5, 135.6, 138.3, 139.2, 146.0, 159.8, 160.1 ppm. MS (70 eV): *m*/*z* (%) = 345 (100) [M^+], 327 (21), 316 (29), 291 (21). $C_{22}H_{19}NO_3$ (345.39): calcd. C 76.50, H 5.54, N 4.06; found C 75.67, H 5.51, N 3.91.

3-[3,5-Bis(4-methoxyphenyl)pyridin-2-yl]-1-propanol (10): A solution of alkynol **9** (1.11 g, 3.21 mmol) in ethanol (50 mL) and water (15 mL), and palladium on charcoal (5%; 0.15 g) were shaken under hydrogen at room temperature. After complete conversion (TLC monitoring), the catalyst was filtered off, the solvents were removed under reduced pressure, and the residue was purified by column chromatography (ethyl acetate) to give 0.93 g (84%) of **10** as a light brown oil. IR (KBr): $\tilde{\nu}$ = 3357, 1610, 1513, 1453, 1247, 1033, 831 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.92 (m, 2 H, $CH_2-CH_2-CH_2$), 2.97 (t, *J* = 6.8 Hz, 2 H, Ar−C*H*$_2$), 3.67 (t, *J* = 5.8 Hz, 2 H, C*H*$_2$OH), 3.84 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 4.74 (br. s, 1 H, OH), 6.98, 6.99, 7.27, and 7.52 (each br. d, *J* = 8.7 Hz, 4 × 2 H, Ar-H), 7.68 (s, 1 H, 4-H), 8.67 (s, 1 H, 6-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 31.3, 32.4, 55.2, 55.3, 62.6, 113.9 (2 C), 114.5 (2 C), 128.0 (2 C), 129.7, 130.2 (2 C), 131.8, 133.7, 135.9, 136.7, 145.1, 156.9, 159.2, 159.7 ppm. MS (70 eV): *m*/*z* (%) = 349 (4) [M^+], 332 (6), 318 (12), 306 (24), 305 (100), 304 (98), 290 (4). $C_{22}H_{23}NO_3 \cdot H_2O$ (367.44): calcd. C 71.91, H 6.86, N 3.81; found C 72.86, H 6.58, N 3.68.

Ficuseptine (1): Mesyl chloride (0.53 g, 4.6 mmol) was added to an ice-cooled solution of alcohol **10** (0.80 g, 2.3 mmol) and triethylamine (0.71 g, 7.0 mmol) in dry CH_2Cl_2 (26 mL) with good stirring, and the mixture was allowed to warm up to room temperature over 2 h. The mixture was poured into satd. NaCl solution. The aqueous layer was washed with 3 × 15 mL of diethyl ether, followed by extraction with 3 × 50 mL of $CHCl_3$. The combined $CHCl_3$ layers were dried with $CaCl_2$ and concentrated to give, after recrystallization from 1-butanol/diethyl ether, 0.67 g (79%) of **1** as a light brown powder, m.p. 185−188 °C (dec.) (ref.:[1] 186−187 °C). IR (KBr): $\tilde{\nu}$ = 1607, 1519, 1480, 1253, 834 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.55 (m, 2 H, $CH_2-CH_2-CH_2$), 3.58 (t, *J* = 7.4 Hz, 2 H, Ar-C*H*$_2$), 3.79 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 5.44 (t, *J* = 7.4 Hz, 2 H, N−C*H*$_2$), 6.98, 7.07, 7.49, and 7.81 (each br. d, *J* = 8.7 Hz, 4 × 2 H, Ar-H), 8.18 (s, 1 H, 7-H), 9.98 (s, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.3, 32.4, 55.4, 55.5, 60.3, 114.8 (2 C), 115.0 (2 C), 125.2, 126.6, 128.9 (2 C), 129.9 (2 C), 138.0, 138.1, 138.8, 140.1, 153.0, 160.8, 161.2 ppm. MS (FAB, NBA, pos.): *m*/*z* (%) = 332 (100) [M^+] ppm. MS (70 eV): *m*/*z* (%) = 329 (100) [M^+ − 3 H], 314 (22), 286 (6). $C_{22}H_{22}NO_2Cl \cdot 2\,H_2O$ (406.91): calcd. C 65.42, H 6.49, N 3.47; found C 64.70, H 6.24, N 3.26.

Acknowledgments

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