

## Biogenetic hypothesis and first steps towards a biomimetic synthesis of haouamines

Edmond Gravel, Erwan Poupon,\* Reynald Hocquemiller

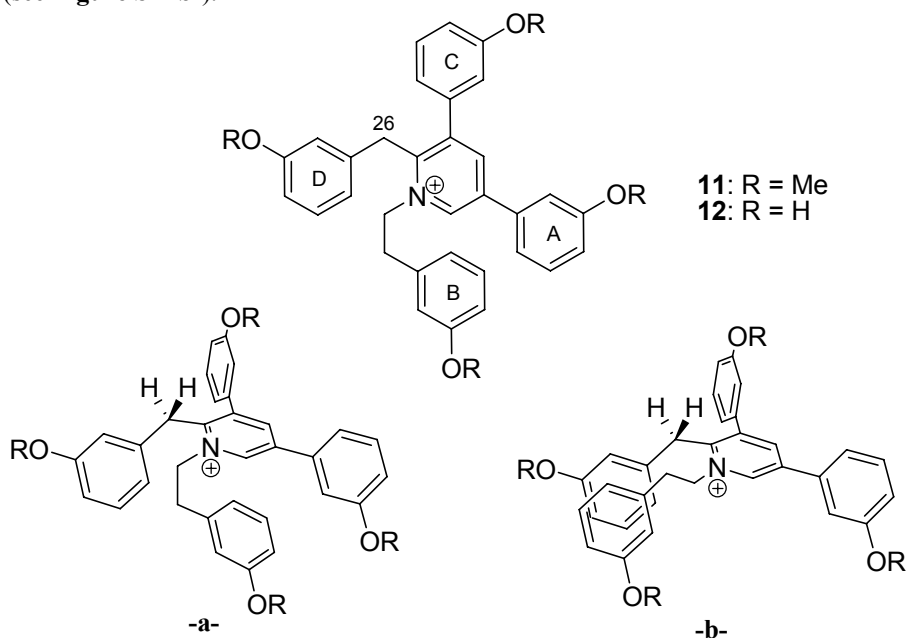
Laboratoire de Pharmacognosie associé au CNRS (UMR 8076 – BioCIS), Centre d'Études Pharmaceutiques, Université Paris-Sud 11, 5, rue Jean-Baptiste Clément, 92290, Châtenay-Malabry, France. Fax: +33 1 46 83 55 99; Tel: +33 1 46 83 55 86; E-mail: [erwan.poupon@cep.u-psud.fr](mailto:erwan.poupon@cep.u-psud.fr)

### Electronic Supplementary Information

#### Experimental procedures and spectral data for compounds 11, 12 and 14:

**One step assembly of pyridinium 11** : To a stirred solution of 3-methoxyphenylacetaldehyde (800 mg – 5.3 mmol) in methylene chloride (8 mL), ytterbium triflate (300 mg – 0.5 mmol) was added, followed by 3-methoxyphenylethylamine (250 mg – 1.7 mmol). The reaction was carried out at room temperature and monitored by TLC (silica gel, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9:1). After 20 hours the mixture was filtered, the solvent evaporated and flash purification was performed (flash silica gel, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 92:8). The desired product was obtained as an orange oil (690 mg – 1.26 mmol – 75%). *R*<sub>f</sub> = 0.40 (silica gel, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9:1); IR (film, CHCl<sub>3</sub>):  $\nu_{\max}$  = 2937, 1585, 1260, 1030 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>),  $\delta$  1.25 (2 H, s), 3.27 (2 H, t, *J* = 6.5 Hz), 3.67 (6 H, s), 3.86 (6 H, s), 5.15 (2 H, t, *J* = 6.5 Hz), 6.55–7.45 (16 H, m), 8.47 (1 H, s), 8.75 (1 H, s); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>),  $\delta$  29.6, 37.8, 55.1, 55.7, 63.5, 112.5, 113.5, 114.2, 116.6, 118.2, 119.6, 121.1, 122.6, 130.2, 130.8, 134.0, 136.9, 139.8, 140.5, 141.3, 160.2, 160.6; MS (ES) *m/z* 546 (M<sup>+</sup>), 440 (10), 426 (100); HRMS (ES) calcd for C<sub>36</sub>H<sub>36</sub>NO<sub>4</sub><sup>+</sup>: 546.2639, found: 546.2642.

It is interesting to note that the signal at about  $\delta$  1.25 (2 H, s), attributable to H<sub>26</sub>, should have been expected at approximately  $\delta$  3.50. This phenomenon might be explained by anisotropic effects, either inter- or intramolecular. It is possible to consider that the two H<sub>26</sub> are in the shielding region of ring C (see **Figure S1 -a-**), and even in that of ring B (see **Figure S1 -b-**).<sup>1</sup>



**Figure S1**

<sup>1</sup> Haouamine A itself shows unusually shielded protons, see ref 1 : L. Garrido, E. Zubía, M. J. Ortega, and J. Salvá, *J. Org. Chem.*, 2003, **68**, 293.

**Phenol deprotection of 11 to yield 12** : A solution of **11** (50 mg – 0.09 mmol) in methylene chloride (1 mL) was cooled to – 78 °C under nitrogen atmosphere and tribromoborane (94 mg – 0.37 mmol – 4.1 equiv.) was added dropwise. The mixture was then brought back to room temperature and stirred for 3 hours after which it was poured into ice water (1 mL) and stirred for 30 additional minutes. The biphasic system was extracted with ethyl acetate (3 × 2 mL) and the organic phases were combined. After solvent removal under reduced pressure, the desired product was obtained as a brown varnish (38 mg – 0.08 mmol – 85%).  $R_f = 0.30$  (silica gel,  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  85:15); IR (film,  $\text{CH}_3\text{OH}$ ):  $\nu_{\text{max}} = 3061, 2926, 1589, 1029 \text{ cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ ),  $\delta$  1.25 (2 H, s), 3.35 (2 H, t partially hidden by  $\text{CD}_3\text{OD}$  signal,  $J \sim 6.6$  Hz), 4.97 (2 H, t,  $J = 6.6$  Hz), 6.55–7.45 (16 H, m), 8.78 (1 H, s), 8.88 (1 H, s);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CD}_3\text{OD}$ ),  $\delta$  30.8, 38.4, 64.4, 115.4, 115.6, 117.0, 117.2, 118.4, 119.7, 121.1, 121.3, 131.3, 131.9, 136.0, 138.5, 141.5, 141.9, 142.8, 159.3, 159.8; MS (ES)  $m/z$  490 ( $\text{M}^+$ ), 398 (10), 384 (100); HRMS (ES) calcd for  $\text{C}_{32}\text{H}_{28}\text{NO}_4^+$  : 490.2013, found : 490.2015.

**Reduction of pyridinium 11 to tetrahydropyridine 14** : An excess of sodium borohydride was slowly added to a solution of **11** (50 mg – 0.09 mmol) in methanol (20 mL). The mixture was stirred at room temperature for an hour and then refluxed for 3 hours. After solvent evaporation *in vacuo* the residue was dissolved in ethyl acetate (5 mL) and washed with a solution of sodium hydroxide 1 M (2 × 2 mL). Flash chromatography was then performed (flash silica gel,  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  99:1) and the desired product was obtained as a yellow varnish (5 mg – 0.009 mmol – 10%). Due to the overlap of  $^1\text{H}$  NMR signals in the 2.75–3.05 ppm region, it was impossible to clearly establish the stereochemistry of the product but it is likely to be a mixture of *cis/trans* isomers, with the *trans* being predominant.  $R_f = 0.70$  (silica gel,  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  95:5); IR (film,  $\text{CHCl}_3$ ):  $\nu_{\text{max}} = 3010, 1579, 1300, 1108 \text{ cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ),  $\delta$  2.52 (2 H, d,  $J = 12$  Hz), 2.75–3.05 (7 H, m), 3.25 (1 H, d,  $J = 14.5$  Hz), 3.82 (12 H, m), 6.26 (1 H, s), 6.75–7.30 (16 H, m);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$  30.2, 39.5, 40.1, 55.3, 58.9, 62.6, 66.0, 111.2, 111.4, 113.2, 114.4, 117.4, 117.8, 117.9, 128.5, 129.4, 129.7, 139.8, 141.3, 141.4, 159.8; MS (ES)  $m/z$  550 ( $[\text{M} + \text{H}]^+$ ), 444 (100); HRMS (ES) calcd for  $\text{C}_{36}\text{H}_{39}\text{NO}_4\text{H}^+$  : 550.2919, found: 546.2922.

