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

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, CH₂Cl₂/MeOH 9:1). After 20 hours the mixture was filtered, the solvent evaporated and flash purification was performed (flash silica gel, CH₂Cl₂/MeOH 92:8). The desired product was obtained as an orange oil (690 mg – 1.26 mmol – 75%). Rf = 0.40 (silica gel, CH₂Cl₂/MeOH 9:1); IR (film, CHCl₃): νmax = 2937, 1585, 1260, 1030 cm⁻¹; ¹H NMR (400 MHz, CDCl₃), δ 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); ¹³C NMR (100 MHz, CDCl₃), δ 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⁺), 440 (10), 426 (100); HRMS (ES) calcd for C₃₆H₃₆NO₄⁺: 546.2639, found: 546.2642.

It is interesting to note that the signal at about δ 1.25 (2 H, s), attributable to H₂6, should have been expected at approximately δ 3.50. This phenomenon might be explained by anisotropic effects, either inter- or intramolecular. It is possible to consider that the two H₂6 are in the shielding region of ring C (see Figure S1-a-), and even in that of ring B (see Figure S1-b-).¹

Figure S1

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%). Rf = 0.30 (silica gel, CH2Cl2/MeOH 85:15); IR (film, CH3OH): νmax = 3061, 2926, 1589, 1029 cm–1; 1H NMR (400 MHz, CD3OD), δ 1.25 (2 H, s), 3.35 (2 H, t partially hidden by CD3OD signal, J ~ 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); 13C NMR (100 MHz, CD3OD), δ 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 (M+), 398 (10), 384 (100); HRMS (ES) calcd for C32H28NO4+: 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, CH2Cl2/MeOH 99:1) and the desired product was obtained as a yellow varnish (5 mg – 0.009 mmol – 10%). Due to the overlap of 1H 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. Rf = 0.70 (silica gel, CH2Cl2/MeOH 95:5); IR (film, CHCl3): νmax = 3010, 1579, 1300, 1108 cm–1; 1H NMR (400 MHz, CDCl3), δ 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); 13C NMR (100 MHz, CDCl3), δ 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 ([M + H]+), 444 (100); HRMS (ES) calcd for C36H39NO4H+: 550.2919, found: 546.2922.