A Facile Biogenetic Synthesis of Pulcheotine A

Prasad B. Wakchaure, Narshinha P. Argade*

Division of Organic Chemistry, National Chemical Laboratory, Pune 411008, India
E-mail: np.argade@ncl.res.in

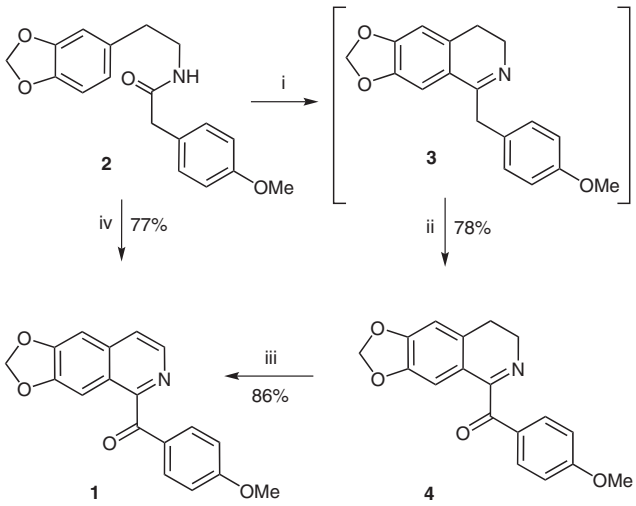
Received 31 March 2008; revised 21 April 2008

Abstract: Starting from homopiperonylamine and 4-methoxyphenylacetic acid, a facile biogenetic route to naturally occurring pulcheotine A has been demonstrated via Pictet–Spengler cyclization and two different air oxidation processes.

Key words: homopiperonylamine, 4-methoxyphenylacetic acid, Pictet–Spengler cyclization, regioselective air oxidations, pulcheotine A

Pulcheotine A (**1**) has been isolated from *Ocotea pulchella*.[1] Pulcheotine and its congeners have been synthesized from the coupling reaction of an appropriate amine with vicinal tricarbonyl compounds,[2] α-chloro-α-phenyl thioketones,[3] or phenylglyoxal.[4] The air oxidation of the benzylic methylene group to the corresponding carbonyl compound in the presence of platinum-on-charcoal is known in the literature.[5] We reasoned and proposed that 4-methoxyphenylacetic acid would be the best biogenetic precursor for the synthesis of **1**. Herein we report the direct and stepwise synthesis of **1** via Pictet–Spengler cyclization and two very regioselective air oxidation reactions (Scheme 1).

The carbodiimide-induced dehydrative coupling reaction of homopiperonylamine with 4-methoxyphenylacetic acid furnished the required amide **2** in 86% yield. The amide **2**, on treatment with phosphorus oxychloride, gave the desired intermediate dihydroisoquinoline **3** via dehydrative intramolecular cyclization. Herein, we confirmed the formation of **3** only by thin layer chromatography; we did not isolate **3** because of its instability to silica gel column chromatography. We proposed that the doubly activated (allylic and benzylic) methylene will undergo a rapid air oxidation process proving that the simple 4-methoxyphenylacetic acid is the better precursor for the synthesis of **1**. As expected the dihydroisoquinoline **3** on treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene at 25 °C for two hours, almost exclusively furnished the expected ketone **4** in 78% yield via a facile regioselective base-catalyzed air oxidation process. The dihydroisoquinoline **4** again on treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene at 25 °C for 24 hours, underwent a smooth second air oxidation process and gave the expected natural product pulcheotine A (**1**) in 86% yield. The repetition of both the Pictet–Spengler cyclization and two air oxidation steps in one pot also furnished **1** in 77% yield. We surmise that herein both the oxidation processes, viz. methylene to carbonyl and dihydroisoquinoline to isoquinoline, occur by the base-catalyzed formation of corresponding peroxy linkages.



Scheme 1 *Reagents and conditions*: (i) $POCl_3$, benzene, 80 °C, 2 h; (ii) DBU, CH_2Cl_2, r.t., 2 h, 78%; (iii) DBU, CH_2Cl_2, r.t., 24 h, 86%; (iv) $POCl_3$, benzene, 80 °C, 2 h, then DBU, CH_2Cl_2, r.t., 24 h, 77%.

In summary, we have completed the direct and stepwise efficient synthesis of pulcheotine A by taking advantage of two facile air oxidations. We feel that the present approach is general in nature and it will be useful for the design of focused combinatorial libraries of natural and unnatural isoquinoline analogues and congeners for the study of structure–activity relationships.

^{1}H NMR spectra were recorded on a Bruker AC 200 (200 MHz) spectrometer using TMS as an internal standard. ^{13}C NMR spectra were recorded on a Bruker AC 200 (50 MHz) spectrometer. FT-IR spectra were recorded on a Shimadzu FT-IR-8300 spectrophotometer. Column chromatographic separations were carried out on silica gel (60–120 mesh); PE = petroleum ether (bp 60–80 °C).

***N*-[2-(1,2-Benzodioxol-5-yl)ethyl]-2-(4-methoxyphenyl)acetamide (2)**

To a stirred soln of 4-methoxyphenylacetic acid (1 g, 6.02 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added EDCI (1.26 g, 6.66 mmol) and a catalytic amount of DMAP (20 mg). The mixture was stirred under an inert atmosphere for 20 min. Homopiperonylamine (993 mg, 6.02 mmol) in CH_2Cl_2 (7 mL) was added to this mixture in a dropwise fashion over 10 min and it was further stirred at 25 °C for 4 h. The mixture was diluted with H_2O (25 mL) and extracted with EtOAc (3 × 25 mL). The organic layer was washed with H_2O and brine and dried (Na_2SO_4). Concentration of the organic layer in

SYNTHESIS 2008, No. 15, pp 2321–2322
Advanced online publication: 08.07.2008
DOI: 10.1055/s-2008-1067162; Art ID: Z07108SS

vacuo followed by column chromatographic purification of the obtained residue (silica gel, PE–EtOAc, 1:1) gave **2** as a white crystalline solid (1.61 g, 86%); mp 86–88 °C.

IR (Nujol): 3248, 1641, 1610 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.64 (t, *J* = 6 Hz, 2 H), 3.41 (q, *J* = 6 Hz, 2 H), 3.51 (s, 2 H), 3.81 (s, 3 H), 5.62 (br s, 1 H), 5.92 (s, 2 H), 6.45 (dd, *J* = 8, 2 Hz, 1 H), 6.53 (d, *J* = 2 Hz, 1 H), 6.66 (d, *J* = 8 Hz, 1 H), 6.85 (d, *J* = 8 Hz, 2 H), 7.09 (d, *J* = 8 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 35.0, 40.8, 42.6, 55.2, 100.8, 108.2, 108.9, 114.3, 121.5, 126.4, 130.5, 132.2, 146.0, 147.6, 158.8, 171.6.

Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 69.11; H, 6.04; N, 4.39.

(7,8-Dihydro-1,3-dioxolo[4,5-*g*]isoquinolin-5-yl)(4-methoxyphenyl)methanone (4)

To a stirred soln of amide **2** (750 mg, 2.39 mmol) in benzene (25 mL) at 25 °C was added $POCl_3$ (1.37 mL, 14.37 mmol) in a dropwise fashion. The mixture was heated at 80 °C for 2 h under N_2. The mixture was then cooled to 25 °C and excess $POCl_3$ and solvent were removed in vacuo. The thus formed yellow-colored residue was dissolved in CH_2Cl_2 (20 mL) and DBU (1.00 mL, 7.17 mmol) was added, the mixture was stirred at 25 °C for 2 h, and it then was concentrated in vacuo. The obtained residue was purified by column chromatography (silica gel, PE–EtOAc, 3:2) to provide **4** as a yellow crystalline solid (580 mg, 78%); mp 130–132 °C.

IR (Nujol): 1651, 1599 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.90 (dd, *J* = 8, 8 Hz, 2 H), 3.88 (s, 3 H), 3.95 (dd, *J* = 8, 8 Hz, 2 H), 6.00 (s, 2 H), 6.77 (s, 1 H), 6.85 (s, 1 H), 6.96 (d, *J* = 8 Hz, 2 H), 7.98 (d, *J* = 8 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 25.8, 46.5, 55.5, 101.5, 107.2, 108.3, 113.9, 120.2, 128.0, 132.7, 133.2, 146.6, 150.3, 164.4, 165.0, 191.8.

Anal. Calcd for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.88; N, 4.52. Found: C, 69.70; H, 4.99; N, 4.38.

(1,3-Dioxolo[4,5-*g*]isoquinolin-5-yl)(4-methoxyphenyl)methanone (Pulcheotine A, 1)

Method A: To a stirred soln of **4** (300 mg, 0.97 mmol) in CH_2Cl_2 (10 mL) was added DBU (0.44 mL, 2.91 mmol) and the mixture was stirred at 25 °C for 24 h. The mixture was concentrated in vacuo and the obtained residue was purified by column chromatography (silica gel, PE–EtOAc, 7:3) to give **1** as a yellow crystalline solid (256 mg, 86%).

Method B: Compound **1** can also be directly synthesized in 77% yield by repeating the above imine preparation and air oxidation procedures in one pot; mp 150–151 °C (Lit.[1a] 152–153 °C).

IR ($CHCl_3$): 1661, 1599 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.81 (s, 3 H), 6.06 (s, 2 H), 6.88 (d, *J* = 8 Hz, 2 H), 7.11 (s, 1 H), 7.38 (s, 1 H), 7.62 (d, *J* = 6 Hz, 1 H), 7.84 (d, *J* = 8 Hz, 2 H), 8.38 (d, *J* = 6 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 55.5, 101.8, 102.1, 102.7, 113.7, 121.8, 123.7, 129.4, 133.1, 135.6, 139.9, 149.3, 151.2, 154.4, 164.0, 193.2.

Anal. Calcd for $C_{18}H_{13}NO_4$: C, 70.35; H, 4.26; N, 4.55. Found: C, 70.42; H, 4.17; N, 4.42.

Acknowledgement

P.B.W. thanks CSIR, New Delhi, for the award of a research fellowship.

References

(1) (a) Botega, C.; Pagliosa, F. M.; Boizani, V. D. S.; Yoshida, M.; Gottlieb, O. R. *Phytochemistry* **1993**, *32*, 1331. (b) Marsaioli, A. J.; Magalhaes, A. F.; Ruveda, E. A.; Reis, F. D. A. M. *Phytochemistry* **1980**, *19*, 995.
(2) Wasserman, H. H.; Amici, R.; Frechette, R.; Duzer, J. H. V. *Tetrahedron Lett.* **1989**, *30*, 869.
(3) (a) Silveira, C. C.; Bernardi, C. R.; Braga, A. L.; Kaufman, T. S. *Synlett* **2002**, 907. (b) Silveira, C. C.; Bernardi, C. R.; Braga, A. L.; Kaufman, T. S. *Tetrahedron Lett.* **2001**, *42*, 8947.
(4) Yang, M.-L.; Kuo, P.-C.; Damu, A. G.; Chang, R.-J.; Chiou, W.-F.; Wu, T.-S. *Tetrahedron* **2006**, *62*, 10900.
(5) McMahon, R. M.; Thornber, C. W.; Ruchirawat, S. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2163.