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Two-step synthesis of the bipyrrole precursor of prodigiosins

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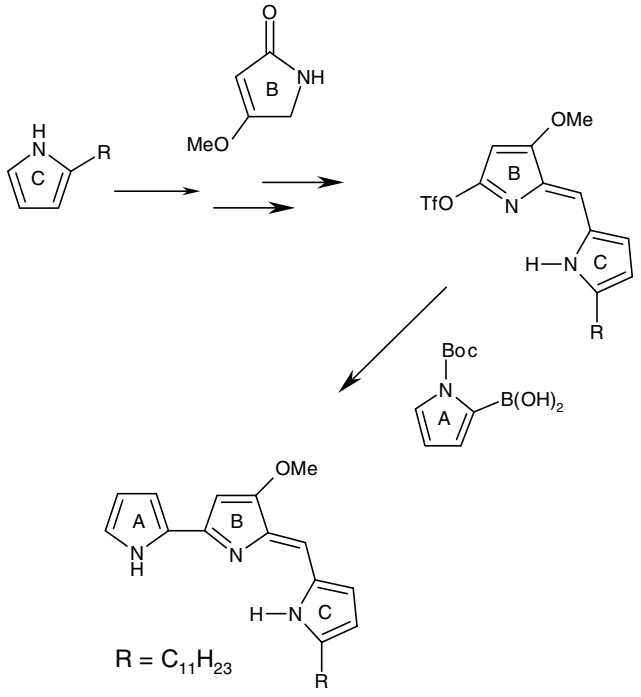
Abstract—The key intermediate in the synthesis of prodigiosins, 4-methoxy-2,2′-bipyrrole-5-carboxaldehyde, has been prepared in two steps and 65% overall yield from the commercially available 4-methoxy-3-pyrrolin-2-one.

4-Methoxy-2,2′-bipyrrole-5-carboxaldehyde is the key intermediate in the biosynthesis of many polypyrrole natural products such as the prodigiosins and tambjamines.[1] Although its chemical structure is relatively simple and known for more than 40 years, only three groups have reported its total synthesis with modest overall yields.[2] In 1996, a new alternative approach for the synthesis of prodigiosins was reported by D'Alessio and Rossi.[3] In contrast with biomimetic routes in which the B ring was first coupled to the A ring, they have first condensed the C ring to B ring (Scheme 1) and completed the synthesis through a Suzuki cross-coupling reaction with ring A. Although the synthesis is very short, efficient, and scalable, it does not give access to the natural bipyrrole aldehyde precursor of prodigiosins.

In this present letter, we wish to report a two-step synthesis of 4-methoxy-2,2′-bipyrrole-5-carboxaldehyde (**3**).[4] Using the same building blocks as D'Alessio and Rossi, we have reorganized the reaction sequence in order to get access to the natural biomimetic precursor. The commercially available 4-methoxy-3-pyrolin-2-one (**1**) (Scheme 2) was treated with the Vislmeier–Haack reagent (3 equiv) derived from diethylformamide to produce the bromo pyrrole enamine **2** in 70% yield.[5,6] Using the original procedure with dimethylformamide, proceeded in only 30% yield despite the use of various experimental conditions. This key haloformylation reaction has been previously reported by Von Dobeneck and Schnierler in 1966 on a dialkylpyrrolinone derivative[7] but to our knowledge, it has never been applied to the synthesis of prodigiosins. The Suzuki cross-coupling reaction between **2** and the Boc-pyrrole boronic acid[3,8] led to the desired natural bipyrrole aldehyde **3** in 95% yield.[9] The ^{1}H NMR, FT-IR, HRMS and TLC were



Scheme 1.

Keywords: Natural product; Prodigiosins; Tambjamines; Haloformylation; Bipyrrole; Suzuki coupling.
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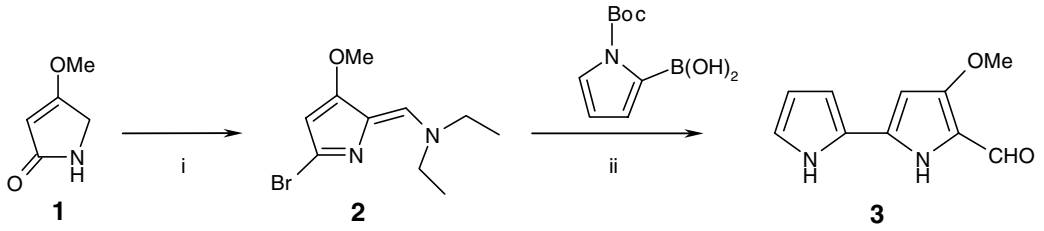

Scheme 2. Reagents and conditions: (i) $POBr_3$ (3 equiv), diethylformamide (3 equiv), chloroform, reflux, 5 h, 70%. (ii) Boc pyrrole boronic acid (1.5 equiv), $Pd(PPh_3)_4$, dioxane, H_2O, Na_2CO_3, reflux, 2.5 h, 95%.

in perfect agreement with the reported spectroscopic data and with those recorded from an authentic sample obtained by fermentation.[10]

Using the final condensation step described by Rapoport and Holden[2a] with different pyrroles, compound **3** and also other dipyrrole derivatives were converted to prodigiosin analogues.[11] This new approach has been adapted and used on kg scale to support the development of GX15-070,[12] the first prodigiosin derivative to reach clinical trials in oncology.

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2. (a) Rapoport, H.; Holden, J. *Am. Chem. Soc.* **1962**, *84*, 635–642; (b) Boger, D. L.; Patel, M. *J. Org. Chem.* **1988**, *53*, 1405–1415; (c) Wasserman, H. H.; Lombardo, L. J. *Tetrahedron Lett.* **1989**, *30*, 1725–1728; (d) Wasserman, H. H.; Petersen, A. K.; Xia, M.; Wang, J. *Tetrahedron Lett.* **1999**, *40*, 7587–7589.
3. D'Alessio, R.; Rossi, A. *Synlett* **1996**, 513–514.
4. Attardo, G.; Dairi, K.; Lavallee, J.-F.; Rioux, E.; Tripathy, S. WO 2004106328; PCT Int. Appl. 2004; 172 pp.
5. It has been previously shown that increasing the size of R groups in the formylating reagent can be beneficial for controlling regioselectivity and change the ratio of the possible products: For example: Pansare, S.; Ravi, G. *Synlett* **1994**, *10*, 823–824.
6. Preparation of compound **2**: To a mixture of diethylformamide (3 equiv, 5.8 mL) and chloroform (5 mL) at 0 °C was added dropwise a solution of phosphorus oxybromide (2.5 equiv, 12.6 g) in chloroform (15 mL). The resulting suspension was stirred at 0 °C for 30 min, and the solvent was removed by rotary evaporation to obtain the Vilsmeier complex as a white solid. After drying in vacuo for 20 min, chloroform (10 mL) was added to the solid and cooled to 0 °C. A solution of 4-methoxy-3-pyrrolin-2-one (**1**) (2 g, 17.7 mmol) in chloroform (20 mL) was added dropwise and the mixture was warmed to room temperature, and then heated at 60 °C for 5 h. The mixture was poured onto ice (75 mL), and the pH of the aqueous solution was adjusted to pH 7–8 by treatment with NaOH 2 N. EtOAc (40 mL) was added to the resulting precipitate and the mixture was filtered over Celite® to remove the black solid containing phosphorus salts. The two layers were separated and the aqueous layer was extracted with EtOAc (3×100 mL). The organic layers were combined, washed with brine (3×200 mL), dried over Na_2SO_4, filtered and the solvent was removed by rotary evaporation to furnish the crude bromo enamine **2**. The residue was filtered over a pad of silica gel (50 mL) using a 10% EtOAC/hexanes as eluent to obtain the enamine as an oil, which upon drying in vacuo led to a beige solid. Yield: 3.20 g, 70%. Mp: 38–40 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.24–1.37 (6H, m), 3.31–3.46 (2H, q, $J = 7.1$), 3.76 (3H, s), 4.03–4.18 (2H, q, $J = 7.1$), 5.58 (1H, s), 6.98 (1H, s). HRMS; *m/z*: 259.0440 [M+1]. Found: 259.0443.
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9. Preparation of compound **3**: To a degassed solution of toluene (1.5 mL) were added $Pd(OAc)_2$ (0.1 equiv, 86 mg) and PPh_3 (0.45 equiv, 456 mg). The mixture immediately became bright yellow and was stirred at 70 °C for 20 min under N_2. A solution of bromo pyrrole enamine **2** (1 g, 3.86 mmol) and *N*-Boc-pyrroleboronic acid (1.5 equiv, 1.22 g) in 10% water/dioxane (15 mL) was degassed and purged with N_2. The solution was transferred to the suspension of $Pd(PPh_3)_4$ in toluene followed by the addition of Na_2CO_3 (3.0 equiv, 1.23 g). The mixture was stirred for 90 min at 100 °C and then poured onto water (100 mL), the pH of the solution was lowered to pH 7 with 2 N HCl. The brown precipitate was recovered by filtration over a fritted disc funnel and washed with water then acetone. The yellow solid was washed with 10 mL of $CHCl_3$ then 2×10 mL Et_2O. The desired 4-methoxy-2,2′-bipyrrole-5-carboxaldehyde (**3**) is obtained as a yellow solid and used without further purification. Yield: 700 mg, 95%. Mp: 224–227 °C (dec.). IR (Neat, cm^{-1}): 3244, 3196, 1607, 1360. ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 3.82 (3H, s), 6.10 (1H, t, $J = 2.9$), 6.26 (1H, s), 6.73 (1H, d, $J = 2.6$), 6.89 (1H, br s), 9.27 (1H, s), 11.13–11.29 (1H, br s), 11.32–11.49 (1H, br s). HRMS; *m/z*: 191.0815 [M+1]. Found: 191.0807.
10. Produced by MDS Pharma Services, South Bothell WA, USA.
11. For recent examples see: Baldino, C. M.; Parr, J.; Wilson, C. J.; Ng, S.-C.; Yohannes, D.; Wasserman, H. H. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 701–704.
12. 2-[2-[(3,5-Dimethyl-1*H*-pyrrol-2-yl)methylene]-3-methoxy-2*H*-pyrrol-5-yl]-1*H*-indole.