Improved Synthetic Route to C-Ring Ester-Functionalized Prodigiosenes

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Received 18 August 2010

Abstract: An efficient, optimized, and scalable process for the synthesis of C-ring ester-functionalized prodigiosenes has been developed by (i) exploiting a silylative Mukaiyama aldol strategy for the condensation of alkyl 5-formyl-2,4-dimethylpyrrole-3-carboxylate and 4-methoxy-3-pyrrolin-2-one to form the corresponding ester-functionalized dipyrrinone analogues, and (ii) developing a facile synthesis of stable bromodipyrrin analogues for the use in formal Suzuki coupling reactions. The process was applied to the synthesis of three C-ring ester-functionalized prodigiosenes in multigram scales (up to 6.5 g prodigiosene free-base) with useful yields (35–56% overall yields over three steps starting from the 2-formyl pyrroles).

Key words: prodigiosin, prodigiosene, bromodipyrrin, dipyrrinone, bromination

Prodigiosenes belong to a family of tripyrrolic red pigments with important biological properties.[1] Thus several investigations have been focused on the structure–activity relationships in prodigiosenes.[2] Recently, we have discovered that C-ring functionalized prodigiosenes exhibit efficient anticancer properties in effective doses.[3,4] These discoveries stimulated the development of an expedient synthetic strategy to prepare novel analogues with potent anticancer properties (Figure 1) and to prepare highly active derivatives on a multigram scale.

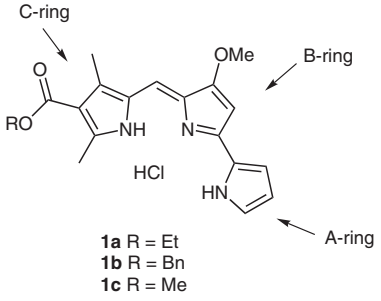


Figure 1 C-Ring ester-functionalized prodigiosenes

Two main synthetic strategies for the synthesis of the tripyrrolic skeleton of prodigiosenes have been reported: (i) the condensation of a bipyrrole unit with the C-ring moiety (path A and path B, Scheme 1),[5,6] and (ii) the coupling of a dipyrrin unit with the A-ring (path C, Scheme 1).[7]

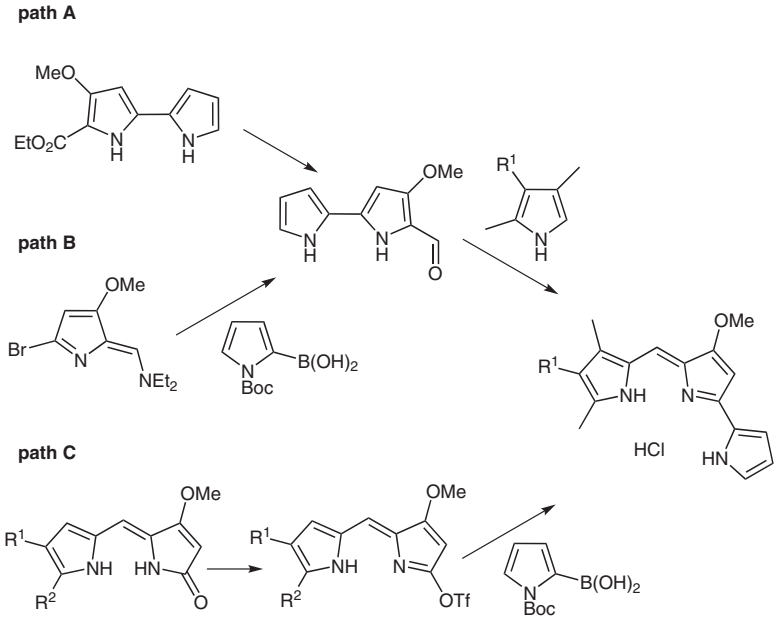
Path A suffered from low yields as the bipyrrolic unit was consistently synthesized using a low yielding McFayen–Stevens reduction.[5] An alternative strategy to generate the bipyrrolic unit was recently developed by Dairi et al. (path B, Scheme 1) and involves the synthesis of a 2-formyl bipyrrole in a two-step route from 4-methoxy-3-pyrrolin-2-one.[8,9] Unfortunately, this process was not successful in our hands as the 2-formyl bipyrrole could only be isolated in low and irreproducible yields.

Path C is relatively more convenient and has traditionally relied on a base-promoted condensation of a 2-formyl pyrrole with a pyrrolin-2-one to generate the dipyrrinone unit, followed by formation of the triflated analogues and then Suzuki coupling to the final pyrrolyl-dipyrrin skeletons.[3] However, the base-promoted condensation step of this process to generate the dipyrrinones suffers serious limitations due to the equilibrium between the retro 2-formyl pyrrole in the presence of strong base, as observed by others during the synthesis of metacycloprodigiosin.[10] Once synthesized, the dipyrrinone is converted into a triflate analogue, which, depending on the substituent at R^1, has limited thermal stability. The low thermal stability of these analogues renders purification of multigram quantities problematic.

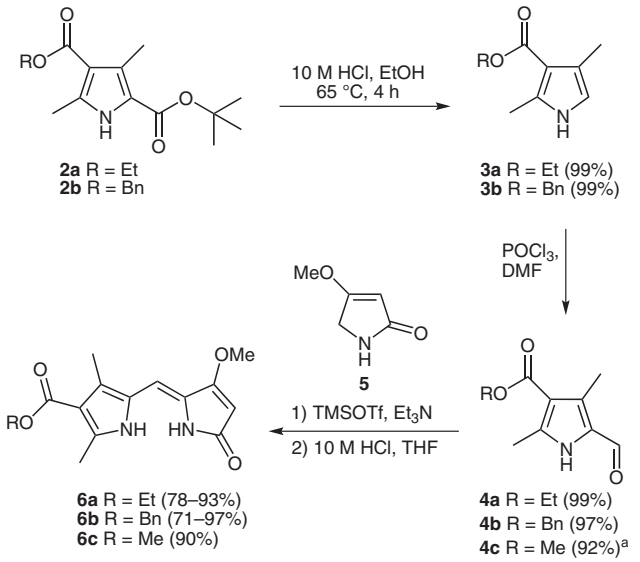
As part of our studies towards mapping the SAR profile of C-ring ester-functionalized prodigiosenes with optimized immunosuppressive properties, we needed an improved synthetic process with (i) a short reaction sequence, (ii) an alternative condensation step to form the dipyrrinone unit, and (iii) a stable analogue for use in the formal Suzuki diheteroaryl coupling reactions with BOC-protected pyrrole 2-boronic acid. We anticipate that addressing these issues would result in a scalable synthetic process. Our investigations in this regard are discussed herein.

Our synthetic strategy (Scheme 2) involved starting with 2-formyl pyrroles **4**, synthesized by following a slight modification of a reported protocol.[11] Knorr pyrrole 5-*tert*-butyl esters **2a**,**b** were subjected to acid-promoted hydrolysis, decarboxylation to give **3a**,**b**, then Vilsmeier formylation to give **4a–c** in almost quantitative overall yields (Scheme 2). Based on the understanding that the base-promoted condensation of **4a–c** and **5** suffers several drawbacks due to a reversible retro 2-formyl pyrrole generation in the presence of a strong base,[10] we used an alternative strategy involving dual Lewis acid–Lewis base activation using a silylative Mukaiyama aldol strategy.[10,12] Acid-promoted elimination of the OTMS functionality gave the dipyrrinone analogues **6a–c** in moderate to good yields (Scheme 2).

SYNLETT 2010, No. 17, pp 2561–2564
Advanced online publication: 30.09.2010
DOI: 10.1055/s-0030-1258769; Art ID: S05110ST



Scheme 1 Synthetic strategies for the synthesis of prodigiosenes



Scheme 2 Preparation of ester-functionalized dipyrrinone analogues. [a]**4c** was prepared using an esterification strategy (see Supporting Information for more details).

The dipyrrinones **6a–c** were observed to form as a mixture of distinguishable isomers **I** and **II** depending on the reaction conditions, that is, acid concentration and dilution. The structural assignment for the isomeric dipyrriones **I** and **II** was executed using NOESY (Figure 2). In the NOESY spectrum, the correlation between NH/NH of the major isomer **I** indicated the *Z*-configuration at the dipyrrin moiety, and the correlation between NH/*meso*-H of the minor isomer **II** indicated the *E*-configuration (Figure 2).

The structure of the major isomer was further confirmed by the isolation of the major isomer in pure form by altering the reaction conditions. The structure of benzyl ester dipyrrinone **6b** was confirmed by an X-ray crystal structure (Figure 3).

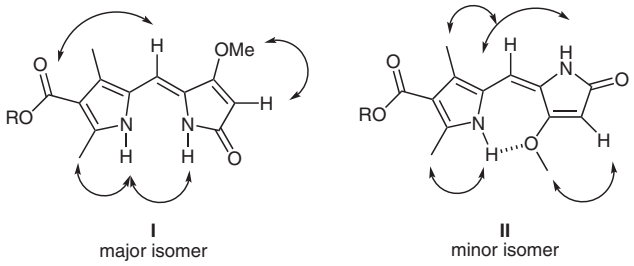


Figure 2 NOESY correlations observed for the dipyrrinones **I** and **II**

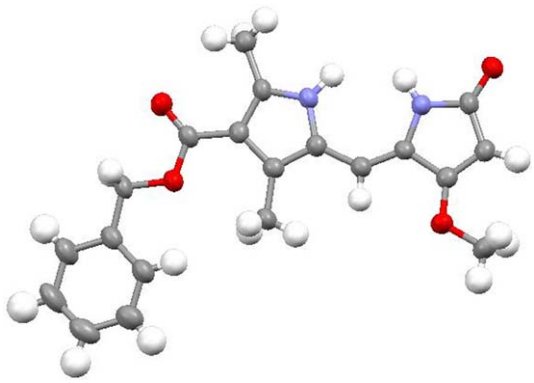


Figure 3 X-ray crystal structure of **6b**

In our previous work with prodigiosenes, we noted that several triflate analogues were thermally unstable.[3] In one case, a symmetrical dipyrrin byproduct was isolated from the triflation reaction mixture. The generation of this symmetrical dipyrrin byproduct **8**[13] (Figure 4) is probably due to the hydrolysis of the dipyrrinone as its triflate in the presence of even trace amounts of moisture, followed by acid-catalyzed self-condensation.

With the knowledge that triflate analogues had proven problematic, our modified strategy for the synthesis of C-ring ester-functionalized prodigiosenes focused on the

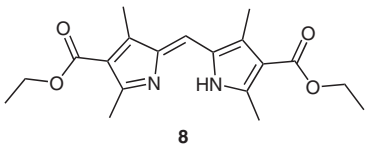


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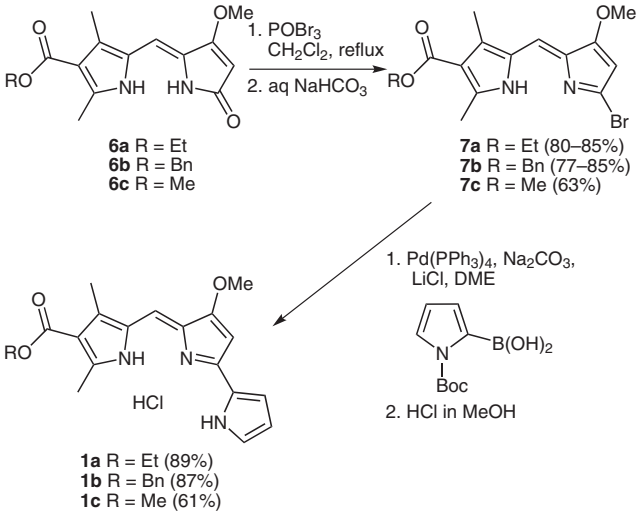
Figure 4 The symmetrical dipyrrin byproduct **8**

analogous bromodipyrrin analogues **7a–c**. Bromination of the dipyrrinone using $POBr_3$ was thought to be a viable alternative based on the work of Dairi,[8] who used $POBr_3$ to brominate pyrrolinones, and Rapoport,[14] who used $POCl_3$ to chlorinate pyrrolinones.

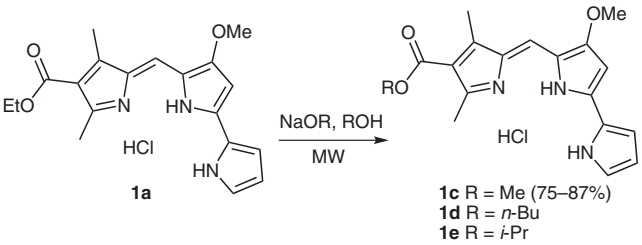
Regardless of isomeric ratios, when the dipyrrinones **6a–c** were treated with $POBr_3$, isomers **I** and **II** react to generate a single isomer of the corresponding bromodipyrrins (Scheme 3). The bromodipyrrins were obtained as HBr salts, which, upon basic workup, gave free bases **7a–c** in good yields (up to 85%). These *meso*-unsubstituted bromodipyrrins are stable at room temperature under air and can be used in bench-top operations, making them feasible intermediates for the large-scale production of prodigiosenes.

Finally, the Suzuki coupling reaction of bromodipyrrins **7a–c** with *N*-Boc-protected pyrrole-2-boronic acid worked well as for the triflated analogues, and was used effectively for the large-scale synthesis of prodigiosenes **1a–c** (up to 6.5 g prodigiosene free base) in good yields (35–56% overall yields over three steps starting from the 2-formyl pyrroles; Scheme 3).



Scheme 3 Preparation of ester-functionalized prodigiosenes

In addition, we investigated a convergent hydrolysis/esterification approach to a series of new prodigiosene esters using **1a**[15] and **1b**. Several attempts were made to hydrolyze the ethyl ester of **1a** and, although the required crude carboxylic acid product was observed using mass spectrometry, it was unstable and could not be isolated. Hydrogenolysis of the benzyl-ester functional group of **1b** followed by esterification of the crude acid reaction mixture was similarly unsuccessful, probably due to the low stability of the carboxylic acid. As another alternative method, direct transesterification of ethyl ester prodigiosene **1a** was attempted. High-pressure microwave-promoted reaction conditions were used for the transesterification of ethyl ester prodigiosene **1a** in attempts to generate the methyl ester **1c**, the *n*-butyl ester **1d**, and the 2-propyl ester prodigiosene **1e**. The results of experiments towards these transformations are shown in Scheme 4 with the investigated conditions listed in Table 1.



Scheme 4 Microwave-promoted transesterification of prodigiosene **1a**

Table 1 Conditions for the Microwave-Promoted Transesterification of Prodigiosene **1a**

R	Conditions	Results
Me	NaOMe (1.2 equiv), MeOH, 125 °C, 10 min	**1a** and **1c**
	NaOMe (1.5 equiv), MeOH, 125 °C, 20 min	**1c** 75–87%
	NaOMe (1.5 equiv), MeOH, reflux,[a] 20 min	**1a** recovered
n-Bu	NaO*n*-Bu (15 equiv), *n*-BuOH, 200 °C, 40 min	**1a** and **1d**
i-Pr	NaO*i*-Pr (125 equiv), *i*-PrOH, 140 °C, 40 min	**1a** and **1e**

[a] Without using microwave.

The ethyl ester prodigiosene **1a** was successfully transesterified to give the methyl ester prodigiosene **1c**, in high yields, by treating it with 1.5 equivalents of sodium methoxide and heating the reaction to 125 °C for 20 minutes in methanol under microwave irradiation. When the same reaction was carried out under reflux conditions, **1a** was recovered quantitatively, thus identifying the microwave promotion to be key for the transesterification to be successful. When this method was adapted to *n*-butyl and 2-propyl alkoxides, ^{1}H NMR spectroscopic analysis showed the presence of the desired product along with remaining starting material, even though large excesses of the alkoxides were used. Re-subjection of these mixtures to the reaction conditions did not noticeably improve the ratio of starting material to product, and the mixtures of starting material and product could not be adequately separated using column chromatography. Although this method produced the methyl ester derivative **1c** in good yield, it was not general for other esters and not a synthetically viable method for synthesizing prodigiosene C-ring esters.

In conclusion, we have developed an efficient method for the multigram synthesis of functionalized prodigiosenes using a silylative Mukaiyama aldol strategy to generate dipyrrinone intermediates and using stable bromodipyrrins in place of triflates in the final Suzuki coupling reaction to generate the prodigiosene targets. The process was successfully applied to the total synthesis of three C-ring ester-functionalized prodigiosenes.

General Procedures and Representative Data

Compounds **2a**,**b**,[11] **3a**,**b**,[11] **4a**,**b**,[11] **4c**,[16] and **6a–c**[10,12] were prepared following modified literature procedures.

Procedure for the Synthesis of Bromodipyrrins (7)

To a stirred suspension of **6a** (3.4 g, 11.7 mmol) in dry CH_2Cl_2 (250 mL) was added $POBr_3$ (6.70 g, 23.37 mmol). The resulting solution was heated at reflux temperature under nitrogen for 17 h. After the reaction mixture was cooled to r.t., sat. $NaHCO_3$ (500 mL) was added at 0 °C, and the organic layer was separated, washed with brine and H_2O, dried using anhyd Na_2SO_4, filtered, and the solvent was evaporated in vacuo. The crude product was purified by passing a solution in EtOAc through a pad of silica gel eluting with 20% hexane in EtOAc to give the title compound **7a** as bright orange yellow solid (3.30 g, 80%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 11.20 (1 H, br s), 6.94 (1 H, s), 5.59 (1 H, s), 4.29 (2 H, q, *J* = 7.0 Hz), 3.85 (3 H, s), 2.59 (3 H, s), 2.40 (3 H, s), 1.36 (3 H, t, *J* = 7.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.5, 165.4, 147.2, 144.1, 139.2, 134.1, 126.5, 115.9, 114.1, 100.2, 59.7, 58.7, 15.2, 14.6, 11.6. HRMS (ESI$^+$): *m/z* calcd for $C_{15}H_{18}BrN_2O_3$ [M$^+$]: 353.0495; found: 353.0482.

Procedure for the Synthesis of Prodigiosenes (1)

Compound **7a** (3.20 g, 9.06 mmol), LiCl (1.16 g, 27.36 mmol), 1-*N*-Boc-pyrrole-2-boronic acid (2.32 g, 10.99 mmol), and $Pd(PPh_3)_4$ (1.05 g, 0.91 mmol) were dissolved in 1,2-dimethoxyethane (180 mL), and the solution was purged by bubbling with nitrogen for 10 min. A solution of Na_2CO_3 (2 M, 18.2 mL, 36.4 mmol) was then added, and the reaction mixture was stirred at 85 °C for 24 h. After cooling to r.t. the reaction mixture was poured into H_2O. Extraction with EtOAc (3 × 100 mL), followed by washing of the combined organic fractions with brine (150 mL), drying with anhyd Na_2SO_4, filtration, and evaporation of the solvent in vacuo gave the crude product that was purified using flash chromatography on neutral aluminum oxide (grade III) using a gradient of EtOAc–hexane (10:90 to 20:80) as eluent to give the prodigiosene free base (2.73 g, 89%). Then a solution of HCl in MeOH (0.75 M, 1.5 equiv) was added to a solution of the free base in MeOH–$CHCl_3$ (20:1) to give **1a** as deep pink solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 12.90 (1 H, br s), 12.69 (1 H, br s), 12.64 (1 H, br s), 7.28 (1 H, s), 7.09 (1 H, s), 6.98 (1 H, s), 6.37 (1 H, s), 6.09 (1 H, s), 4.30 (2 H, d, *J* = 7.0 Hz), 4.04 (3 H, s), 2.80 (3 H, s), 2.50 (3 H, s), 1.37 (3 H, t, *J* = 7.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.7, 164.7, 150.4, 150.1, 140.6, 128.5, 123.5, 122.5, 122.1, 119.1, 115.9, 113.0, 112.5, 93.5, 60.1, 59.2, 14.9, 14.5, 12.0. UV/vis: λ_{max} ($CHCl_3$) = 528 (ε = 108017), 500 (ε = 51587). HRMS (ESI$^+$): *m/z* calcd for $C_{19}H_{22}N_3O_3$ [M + H]$^+$: 340.1656; found: 340.1637.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

This work was supported by the Canadian Institutes for Health Research (CIHR) and the Canadian Breast Cancer Foundation-Atlantic Region. S.M.C. thanks the Natural Sciences and Engineering Research Council of Canada (NSERC) for a graduate scholarship. We offer our gratitude to Carlie Charlton for her help in this research.

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