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TOTAL SYNTHESIS OF PRODIGIOSIN

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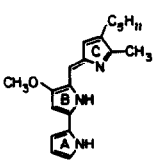
Abstract: *The total synthesis of prodigiosin (1), possessing the characteristic pyrrolylpyrromethene skeleton of a class of naturally-occurring polypyrroles, is detailed. The approach is based on the application of an inverse electron demand Diels-Alder reaction of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate in a 1,2,4,5-tetrazine → 1,2-diazine → pyrrole strategy for preparation of prodigiosin pyrrole ring B and the subsequent implementation of an intramolecular palladium(II)-promoted 2,2'-diaryl (2,2'-bipyrrole) coupling for construction of the prodigiosin 2,2'-bipyrrole AB ring system.*

Prodigiosin (1), a red pigment first isolated from *Serratia marcescens*, was the initial member of a class of naturally-occurring polypyrroles possessing a common, characteristic pyrrolylpyrromethene skeleton[2] which now include prodigiosene (2a), norprodigiosin (2b), undecylprodigiosin (2c), nonylprodigiosin (2d), cyclic nonylprodigiosin (3), cycloprodigiosin (4), metacycloprodigiosin (5), and 6, which have been shown to possess confirmed, potent antimicrobial and cytotoxic properties.[2e] Past efforts utilized in the preparation and structural confirmation of the naturally-occurring[2d] and synthetic[3] prodigiosenes have relied on conventional methods for monopyrrole preparation and the subsequent use of indirect approaches to electrophilic, intermolecular 2,2'-bipyrrole coupling for assemblage of the prodigiosin AB ring system.



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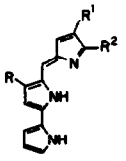

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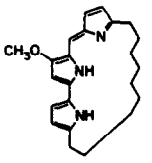

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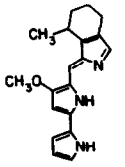

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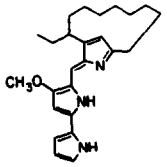

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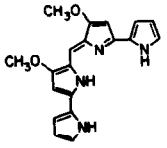


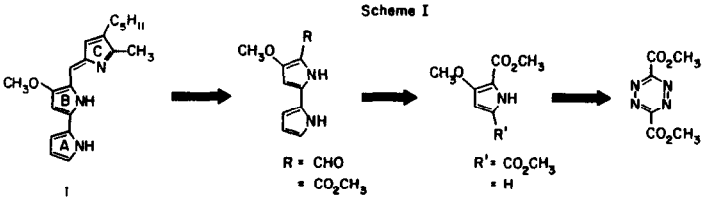
6

	R	R^1	R^2
2a	H	H	H
2b	OH	C_5H_{11}	CH_3
2c	OCH_3	H	$C_{12}H_{25}$
2d	OCH_3	H	C_9H_{19}

Herein we detail initial efforts on the development of a complementary approach to the construction of the pyrrolylpyrromethene skeleton characteristic of the prodigiosenes which have resulted in the total synthesis of prodigiosin (1). The approach is based on the application of an inverse electron demand Diels-Alder reaction[4] of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate in

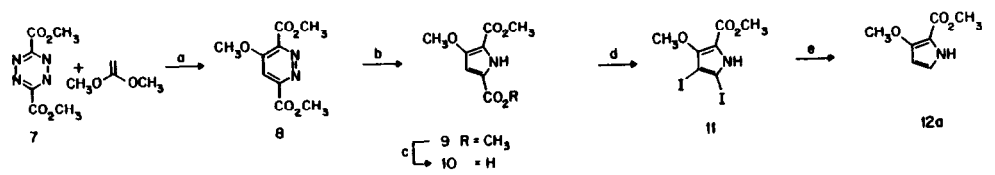
the implementation of a 1,2,4,5-tetrazine → 1,2-diazine → pyrrole strategy[5] for preparation of methyl 3-methoxypyrrole-2-carboxylate constituting prodigiosin ring B, Scheme I. A subsequent palladium(II)-promoted, intramolecular 2,2'-bipyrrole coupling proved suitable for construction of the prodigiosin 2,2'-bipyrrole AB ring system and provides a general solution to the preparation of mixed, electron-deficient 2,2'-bipyrroles.

Scheme I



Treatment of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate[6] (7) with 1,1-dimethoxyethylene provided the Diels-Alder cycloadduct **8** (25°C, 3 h, dioxane, 94%),[7] Scheme II. Reductive ring contraction of the electron-deficient 1,2-diazine **8** (10 equiv zinc, HOAc, 25°C) provided dimethyl 3-methoxypyrrole-2,5-dicarboxylate (**9**, 68%),[5] thus establishing the prodigiosin monopyrrole B ring by implementation of the 1,2,4,5-tetrazine → 1,2-diazine → pyrrole Diels-Alder strategy. Differentiation of the C-2/C-5 carboxylates of **9** effected by selective hydrolysis [1.0 equiv LiOH, THF-H_2O-CH_3OH, (3:1:1), 25°C, 78 h, 91%] of the electronically and sterically more accessible C-5 methoxycarbonyl cleanly provided 3-methoxy-2-methoxycarbonylpyrrole-5-carboxylic acid (**10**). Room temperature iodinative decarboxylation[8] of **10** and subsequent hydrogenolysis of the resulting pyrrole diiodide **11** provided 3-methoxy-2-methoxycarbonylpyrrole (**12a**).[9]

Scheme II[a]

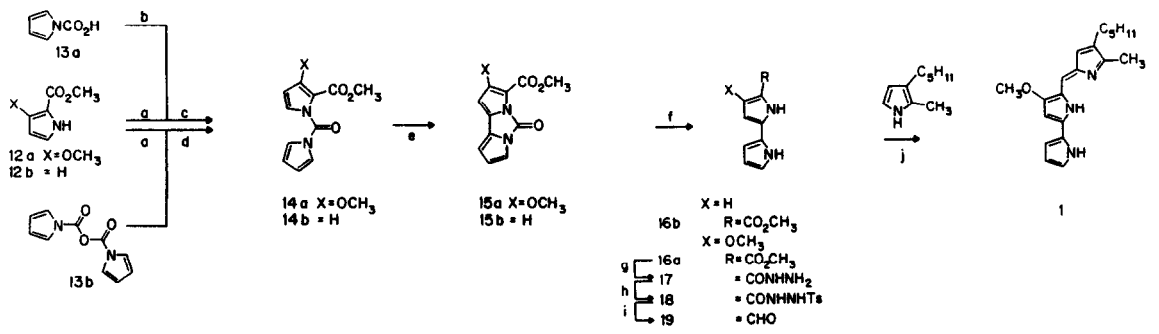


[a](a) 1.5 Equiv 1,1-dimethoxyethylene, dioxane, 25°C, 3 h, 94%. (b) 10 Equiv Zn, CH_3CO_2H, 25°C, 6 h, 68%. (c) 1.0 Equiv LiOH, THF-CH_3OH-H_2O (3:1:1), 25°C, 78 h, 91%. (d) 5.5 Equiv NaI, 6.2 equiv I_2, 9.2 equiv $NaHCO_3$, $ClCH_2CH_2Cl$-H_2O (1:1), 25°C, 12 h, 89%. (e) 5% Pd/C (cat.), H_2 (1 atm), 2 equiv K_2CO_3, CH_3OH, 25°C, 3 h, 96%.

Treatment of pyrrole-1-carboxylic acid (**13a**)[10] with triphenylphosphine-carbon tetrachloride (1.2 equiv-5.0 equiv, 3 h, 25°C, CH_3CN) followed by the addition of the sodium salt of pyrrole

12a or treatment of pyrrole-1-carboxylic acid anhydride (**13b**)[10] with the sodium salt of pyrrole **12a** provided the mixed 1,1'-carbonyldipyrrole **14a**, Scheme III. Intramolecular palladium(II)-promoted 2,2'-bipyrrole formation[11] provided **15a** and was found to be most effectively conducted using polymer-supported palladium(II) acetate [2-3% Pd, 1% cross-linked polystyrene].[12] Use of soluble palladium(II) acetate in acetic acid or palladium(II) trifluoracetate in trifluoroacetic acid provided excellent conversion of **14a,b** to **15a,b** based on the stoichiometric use of reagent in limiting quantities. However, attempts to promote the complete consumption of substrate **14a,b** led to competitive reactions of product 2,2'-bipyrroles **15a,b** with reagent at the expense of increased 2,2'-bipyrrole coupling. Use of polymer-supported palladium(II) acetate provided the 2,2'-bipyrrole coupling (**15a**: 96%; **15b**: 90%) with no evidence of competitive reaction of the electron-deficient 2,2'-bipyrroles with the polymer-supported reagent.

Scheme III[a]



[a](a) 1.0 Equiv NaH, THF; 25°, 15 min for **12b** and 65°C, 14 h for **12a**. (b) 4.0 Equiv **13a**, 8.0 equiv $(COCl)_2$, cat. DMF, THF, 25°C, 15 min (acid chloride formation) or 2.0 equiv **13a**, 1.95 equiv DCC, CH_2Cl_2, 25°C, 5 min (in situ anhydride formation). (c) THF, 25°C, 15 min; **14b** (89%, 67% resp.). (d) 1.2 Equiv **13b**, THF, 25°C, 15 min; **14b** (69%), **14a** (52%). (e) P-$Pd(OAc)_2$ (250 mg/mg substrate), CH_3COOH, 80°C, 12-36 h; 96% **15a**, 90% **15b**. (f) 1.0 Equiv $LiOCH_3$, CH_3OH, 25°C, 5 min; 88% **16a**, 95% **16b**. (g) NH_2NH_2, 25°C, 4 h, 98%. (h) 1.0 Equiv pTsCl, pyridine, 25°C, 15 min, 97%. (i) 3.5 Equiv Na_2CO_3, $HOCH_2CH_2OH$, 170°C, 5 min, 34%. (j) CH_3OH, cat. HCl, 25°C, 12 h, 59%.

Mild methanolysis of the labile urea of the 1,1'-carbonyl-2,2'-bipyrrole derivatives **15a,b** provided **16a,b** and completed the preparation of the prodigiosin and parent prodigiosene 2,2'-bipyrrole AB ring systems, respectively. Final conversion of **15a** to prodigiosin (1) via aldehyde 19 and its acid-catalyzed condensation with 2-methyl-3-pentylpyrrole followed the four-step sequence developed in the total syntheses of 1 detailed by Rapoport[2b] and Wasserman.[2a] Aldehyde **19** possessed the spectroscopic and physical properties described for synthetic,[2a,b] naturally-derived,[2g] and naturally-occurring material.[2g] Synthetic prodigiosin (1) and its hydrochloride proved identical in all comparable respects to samples of authentic, natural prodigiosin [^{1}H NMR (200 MHz), IR, EI/CIMS, HRMS, TLC] and prodigiosin hydrochloride [^{1}H NMR (200 MHz)].

Extensions of this approach to the preparation of additional members of the prodigiosene class of polypyrroles, a continued investigation of the scope of the polymer-supported palladium(II)-promoted 2,2'-biaryl (bipyrrole) coupling, and additional use of pyrrole-1-carboxylic acid anhydride are under current investigation.

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12. The polymer-supported palladium(II) acetate was prepared as follows: Bio Rad Bio Beads SX-resin (polystyrene- 1% divinylbenzene, 14,000 mol. wt. exclusion limit) was brominated and phosphinylated [Pittman, C. U., Jr.; Smith, L. R. *J. Am. Chem. Soc.* **1975**, *97*, 341] Anal. P, 1.45%; and subsequently loaded with palladium(II) by treatment with palladium(II) acetate in benzene, Anal. Pd, 2.79%.

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