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Enantioselective synthesis of metacycloprodigiosin via the “Wasserman pyrrole”

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Abstract

A concise, nine-step enantioselective total synthesis of metacycloprodigiosin is reported. The synthesis provides increased step-efficiency over the previous racemic and enantioselective syntheses of this compound. Key features of the work include investigations into a convergent oxidative coupling reaction and subsequent ring-closing metathesis to deliver an advanced pyrrole intermediate we name the “Wasserman pyrrole” that can be converted to metacycloprodigiosin in one step.

Keywords

Prodigiosin alkaloids; Metacycloprodigiosin; Oxidative coupling; Ring-closing metathesis

The prodigiosin alkaloids (Figure 1) have attracted significant attention from the scientific community due to their unique structures, interesting biosynthesis, and biological activity.¹ This potent combination of attributes has led to numerous research programs aimed at devising efficient routes to their total synthesis,² and also spawned a successful medicinal chemistry program at Gemin X.³ Amongst the prodigiosin family, metacycloprodigiosin (**1**), along with streptorubin B (**2**), occupies a special position due to its highly strained pyrrolophane structure⁴ and unusual biosynthesis.⁵

Isolated from *Streptomyces longisporus ruber* (strain M-3), the structure of metacycloprodigiosin (**1**) was first reported by Wasserman and coworkers in 1969.⁴ In the following journal article, they also reported the first total synthesis of racemic metacycloprodigiosin (**1**) by a 14-step route that involved the late-stage union of pyrrole **5** (i.e., the “Wasserman pyrrole”) with bis-pyrrole aldehyde **6**.⁶ Fürstner and his group reported the second synthesis of the racemate via **5** in a formal sense in 1998 (10-steps), and again in 1999 (20-steps, also via **5**).⁷

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Supplementary Material: Experimental procedures and spectral data for all new compounds.

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In 2009, our own group completed the first enantioselective synthesis of metacycloprodigiosin (**1**), which ultimately enabled the absolute configuration of the natural product to be assigned some 40 years after its initial structure determination.⁸ Our synthesis targeted pyrrole **7** as a key late-stage intermediate, which could be formed in seven steps from simple starting materials. Conversion of **7** into the target molecule required five additional steps, however, which greatly reduced the overall efficiency of our route. The methyl substituent on the pyrrole within **7**, which was required for an earlier oxidative coupling reaction,⁹ meant that we could not utilize the same convergent coupling that Wasserman reported for pyrrole **5**. While we were pleased that our route delivered metacycloprodigiosin (**1**) and was flexible enough to also produce the related natural product, prodigiosin R1, we wished to devise a route that would be shorter than the current 13-step synthesis. Herein we report the development of a new enantioselective synthesis of metacycloprodigiosin (**1**) that proceeds via enantioenriched “Wasserman pyrrole” **5** in just nine total steps.

Our first approach to a new synthesis of **1** commenced with the preparation of enoate **9** in 85% yield by the oxidation of terminal alcohol **8** followed by a Wittig olefination (Figure 3). A Feringa asymmetric addition¹⁰ of ethylmagnesium bromide gave rise to ester **10** in 69% yield and with good levels of stereoselectivity (94:6 er).¹¹ Exhaustive reduction of the ester **10** to the corresponding alcohol with lithium aluminum hydride (LiAlH₄), followed by a Parikh–Doering oxidation¹² afforded the desired aldehyde **11** (80% over two steps). We next sought to prepare 1,4-dicarbonyl **11** by way of an oxidative cross-coupling reaction of aldehyde **11** with the silyl enol ether **12**. In 1992, Narasaka and coworkers had reported the selective oxidative cross-coupling of silyl enol ethers with preformed enamines derived from morpholine or pyrrolidine.¹³ Subsequent contributions by the MacMillan lab substantially enhanced the utility of this process by rendering the transformation enantioselective through the use of enamine catalysis.¹⁴ Attempts at conducting the oxidative cross-coupling using a Narasaka-type protocol involving the initial stoichiometric generation of an enamine from aldehyde **11** with pyrrolidine or morpholine were unsuccessful, so we turned to MacMillan's conditions. After considerable experimentation we found that imidazolidinone *rac*-**13** provided the greatest yield of the desired 1,4-dicarbonyl adduct **14**. Thus, treatment of aldehyde **11** with 0.5 equivalents of **13** in the presence of 2.0 equivalents of enol silane **12** and 2.0 equivalents of ceric ammonium nitrate (CAN) provided coupled product **14** in 75% yield. Attempts to use lower loadings of **13** led to diminished yields of **14**, while use of either individual enantiomer of **13** was found to have no appreciable impact on the reaction outcome.

The gratification that the efficiency of this oxidative coupling gave us was soon extinguished when we began to explore the subsequent formation of the desired 12-membered ring using ring-closing metathesis. We were initially encouraged when exposure of **14** to Grubbs II catalyst¹⁵ produced a compound whose ¹H NMR spectrum displayed peaks in line with the desired enone **15**. Reduction of this putative structure over Pd/C and subsequent exposure to ammonium acetate (NH₄OAc) gave rise to a material whose NMR spectra were different from those reported for the Wasserman pyrrole **5**.^{4,6,7} Most puzzling was the missing diagnostic signal at –1.88 ppm in the ¹H NMR spectrum of our isolated

material, which within **5** is attributed to an anisotropic shielding of the saturated hydrocarbon ring by the meta-fused pyrrole. This analysis, in conjunction with mass spectral data, led us to conclude that the ring-closing metathesis of **14** was probably generating dimeric structures instead of the more strained 12-membered ring.

Failure of this initially promising route led us to consider an alternative approach with a modified set of precursors (Figure 4). In this new approach, the alkene formed during 12-membered ring formation would be two carbon atoms removed from the ketone in much the same fashion as in our published first generation synthesis. Synthesis of the requisite homologous aldehyde **19** proceeded in a similar fashion to that developed for **11**, although the use of diisobutylaluminum hydride (DIBAL) to directly reduce ester **18** to the aldehyde allowed for an increased step-efficiency. Thus, aldehyde **19** was obtained in 96:4 er over four steps from commercially available diol **16**.¹¹ Frustratingly, oxidative coupling of aldehyde **19** with enol silane **20** led to lower yields of the desired 1,4-dicarbonyl **21** than had been obtained in our initial route. Under our best set of conditions, which used a full equivalent of imidazolidinone **13**, a 22% isolated yield of 1,4-dicarbonyl **21** was obtained. Control experiments using aldehyde **11** and enol silane **20**, which gave rise to 62% yield of the corresponding adduct (not shown), indicated that the issue with this reaction most likely lay with the structure of the aldehyde.¹⁶ As we found for aldehyde **11**, use of either enantiomer of imidazolidinone **13** rather than the racemate also provided no enhancement in yield. Despite this setback, the reaction could be conducted on sufficient scale to provide material for advancement of our synthesis and to test the now even more critical ring-closing metathesis reaction.

Unlike 1,4-dicarbonyl **14**, which did not participate in the desired ring-closure to generate the target 12-membered ring, homologous aldehyde **21** underwent ring-closing metathesis using 10 mol% of Grubbs catalyst to allow isolation of **22** in 50% yield. Hydrogenation followed by condensation with ammonium acetate (NH₄OAc) yielded pyrrole (*R*)-**5**, which possessed identical NMR spectral characteristics to the “Wasserman pyrrole” including the key upfield resonance at –1.88 ppm. Wasserman and coworkers had reported the synthesis of metacycloprodigiosin (**1**) from **5** by condensation with bis-pyrrole aldehyde **6** (see Figure 2),⁵ but recent synthetic investigations have demonstrated that improved variations of this coupling can be achieved using the Boc-protected derivative **23**.¹⁷ Thus, the conclusion of our synthesis was met with the HCl-mediated union of pyrrole (*R*)-**5** with aldehyde **23**, followed by the addition of sodium methoxide to cleave the Boc-group. In this way, (*R*)-metacycloprodigiosin (**1**) was produced in 68% isolated yield and shown to possess identical properties (¹H NMR, ¹³C NMR, IR, CD) to those reported for the natural product.^{4,8a}

In conclusion, we have executed a short, nine-step enantioselective total synthesis of (*R*)-metacycloprodigiosin (**1**) that takes advantage of the convergent late-stage union of a bis-pyrrole aldehyde (i.e., **23**) with an optically enriched meta-fused macrocyclic pyrrole (i.e., the “Wasserman pyrrole” (*R*)-**5**). An initially promising, yet ultimately unsuccessful, route highlights the challenges associated with ring-closing metathesis approaches for generating strained medium-sized rings. By utilizing an isomeric species with the terminal alkenes located in different positions, this challenge of ring-closure was overcome and a successful

synthesis achieved. Ultimately, this new route has improved the step-count for the enantioselective synthesis of metacycloprodigiosin from 13-steps to 9-steps.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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***metacycloprodigiosin* (1)**

***streptorubin B* (2)**

***methylcyclooctylprodigiosin* (3)**

***cycloprodigiosin* (4)**

Figure 1.
Characteristic prodigiosin alkaloids.

Figure 2.
Key pyrrole species in previous syntheses of **1**.

Figure 3. Initial, unsuccessful route to metacycloprodigiosin (1)

Figure 4. Concise route to metacycloprodigiosin (1)