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# A Concise Synthesis of Butylcycloheptylprodigiosin

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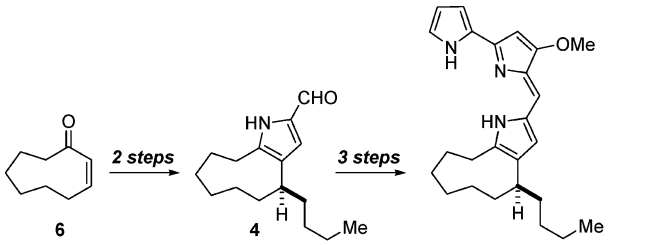
## ABSTRACT




**A short and efficient total synthesis of the tripyrrole alkaloid butylcycloheptylprodigiosin is described. Key to the brevity of the approach is a two-step synthesis of macrocyclic formylpyrrole 4 from cyclononenone 6.**

The prodigiosins are a family of intensely pink/red alkaloids with a common pyrrolylpyrromethene chromophore.[1,2] These natural products display a broad range of biological activity, and synthetic analogues have shown promising immunosuppressive and anticancer effects.[3] Butylcycloheptylprodigiosin (**1**, Figure 1) was isolated in 1975 by Gerber from a strain of bacteria (*Streptomyces* sp. Y-42) found in leaf and grass compost.[4] Ten years later, Floss and co-workers noted the formation of **1** in the fermentation of mutant strains of

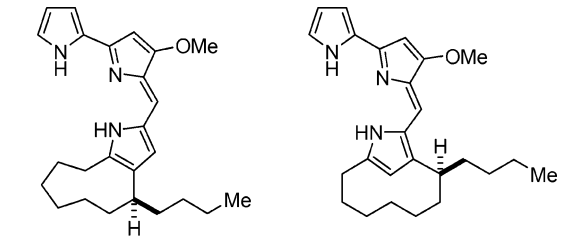



**Figure 1.** Butylcycloheptylprodigiosin and Streptorubin B.

*Streptomyces coelicolor*.[5] In 1991, Weyland and co-workers suggested **1** was actually the meta-bridged isomer streptorubin B (**2**) on the basis of comparison of NMR data.[6] Gerber's original structural assignment was confirmed, however, by the pioneering total synthesis of **1** by Fürstner and colleagues in 2005.[7] Although elegant, this synthesis required 16 linear steps from 1,4-cyclononadien-3-one, thereby rendering the

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production of large quantities of **1** (and analogues) for further biological evaluation challenging. It appeared that our recently disclosed methodology for preparation of 2-formyl-4,5-disubstituted pyrroles could enable a much shorter synthesis of **1**.[8] Herein is described the application of this procedure to a concise (five steps from cyclononenone) synthesis of **1**.

The retrosynthetic analysis of **1** was guided by the efficient three-step sequence employed by Fürstner and co-workers for late stage pyrrolylpyrromethene installation.[7,9,10] Thus, an *O*-triflation/Suzuki cross-coupling simplifies **1** to lactam **3**, from which a condensation transform leads to the key formylpyrrole **4** (Figure 2).

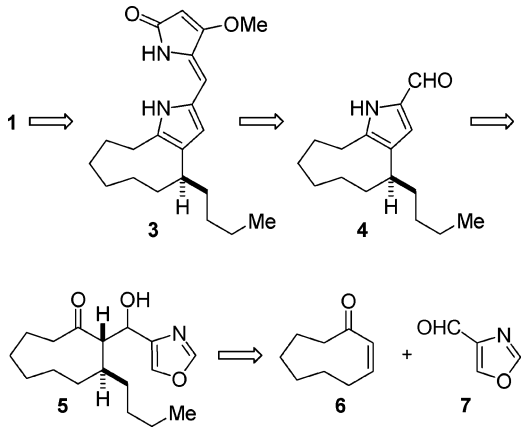



**Figure 2.** Retrosynthetic analysis.

In our previous report, we described a novel synthesis of 4,5-disubstituted-2-formylpyrroles from aldol adducts of ketones and 4-formyloxazole.[8] This one-pot conversion, illustrated in Figure 3, involves initial dehydration to give a

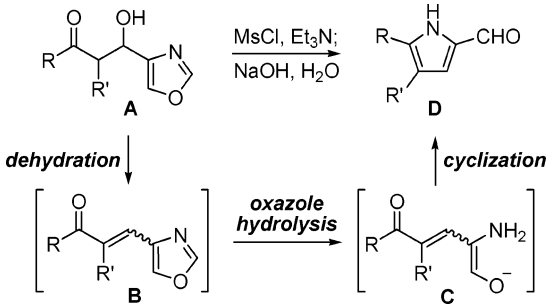
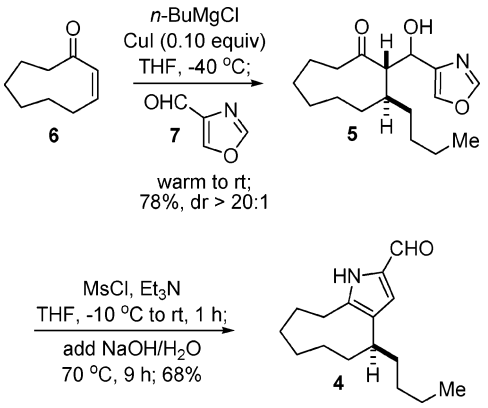



**Figure 3.** One-pot conversion of $\beta$-hydroxy-$\beta$-(4-oxazolyl) ketones (**A**) to 4,5-disubstituted-2-formylpyrroles (**D**).

$\beta$-(4-oxazolyl)enone (**B**), which on treatment with aqueous alkali undergoes hydrolysis of the oxazole ring to generate **C** (or an equivalent tautomeric structure). Dehydrative cyclization of the amino group yields the product pyrrole **D**. The application of this transform to **4** gives the aldol **5**, which could be derived from a conjugate addition/aldol trapping reaction of cyclononenone **6** with *n*-BuMgCl and 4-formyloxazole **7**.

Cyclononenone (**6**) was obtained by oxidation of commercially available cyclononanone with IBX (*o*-iodoxybenzoate) as described by Nicolaou and co-workers.[11] 4-Formyloxazole (**7**) was obtained as previously described by partial reduction of commercially available ethyl 4-oxazolecarboxylate.[8] With building blocks **6** and **7** in hand, investigation of the conjugate addition/aldol reaction was initiated. Although numerous variations of reaction conditions (organocopper reagent, solvent, additive) have been described for conjugate addition/enolate trapping reactions, it was found that simple CuI-catalyzed addition of *n*-BuMgCl to **6** proceeded efficiently in THF at −40 °C in the absence of additives (Scheme 1).[12] The resultant enolate was trapped with **7** to

**Scheme 1.** Two-step Synthesis of Macrocyclic Formylpyrrole **4**




give crystalline adduct **5** in 78% yield as a single diastereomer by $^1$H NMR and HPLC analysis of the crude reaction mixture. While the expected trans relationship of the *n*-butyl and (4-oxazolyl)hydroxymethyl groups was evident from $^1$H NMR and NOESY data, the relative stereochemistry of the exocyclic carbinol (which is ultimately of no consequence) could not be definitively assigned from NMR methods.[13]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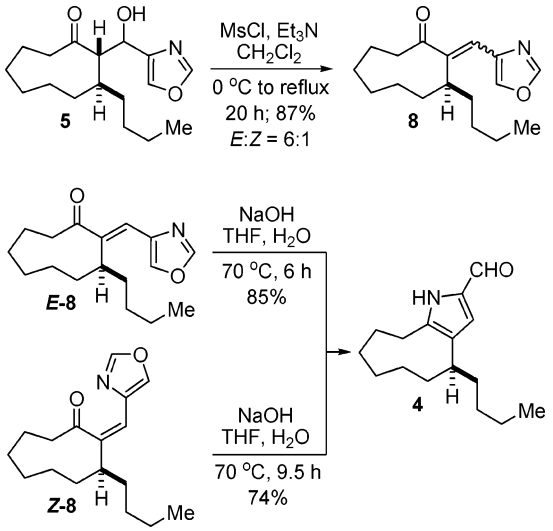
Aldol **5** was subjected to the previously optimized conditions for pyrrole formation. Thus, treatment with MsCl/$Et_3N$ in THF, addition of aqueous NaOH on completion of the mesylation (as monitored by HPLC) and finally heating at 70 °C for 9 h produced the desired formylpyrrole **4** in 68% isolated yield. The powerful combination of a conjugate addition/aldol reaction and a one-pot dehydration/oxazole hydrolysis/pyrrole formation had enabled a *two-step synthesis* of **4** from cyclononenone **6**. By way of comparison, preparation of *N*-Boc **4** required 13 steps from 1,4-cyclononadien-3-one in the previous synthesis.[7]

To ascertain the effect of olefin geometry of the intermediate enone on the rate of oxazole hydrolysis, **5** was dehydrated to enone **8**, formed as a 6:1 mixture of separable *E*/*Z* isomers (Scheme 2). Olefin geometries were unambiguously assigned

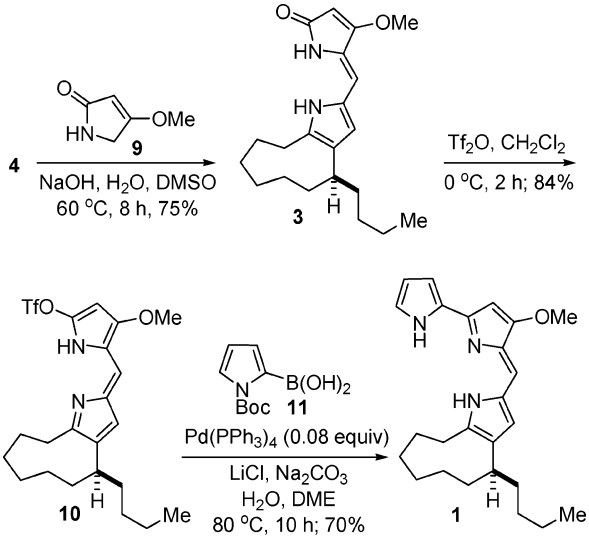
**Scheme 2.** Convergent Hydrolysis of ***E*-8** and ***Z*-8** to **4**




from COSY and NOESY NMR analyses. Individual hydrolysis of the isomeric enones, monitored by HPLC analysis, showed that ***E*-8** converted more quickly to **4** than ***Z*-8**. The attenuated reactivity of ***Z*-8** may be attributable to poorer conjugation of the ketone with the oxazole ring relative to ***E*-8** due to torsional strain and, thus, decreased electrophilicity of the oxazole toward hydrolytic attack at $C_2$.[14]

Elaboration of **4** into **1** was accomplished in three steps as outlined in Scheme 3. Condensation of **4** with commercially available pyrrolinone **9** gave **3** as a bright yellow solid in 75% yield.[7] The preparation of **3** constituted a formal total synthesis of **1**, and conversion of **3** to **1** followed directly from the procedures of Fürstner and co-workers.[7,9] *O*-Sul-

**Scheme 3.** Completion of the Total Synthesis of **1**




fonylation of **3** with $Tf_2O$ gave triflate **10** in 84% yield. Suzuki cross-coupling of **10** with commercially available boronic acid **11** with concomitant hydrolysis of the Boc group furnished (±)-butylcycloheptylprodigiosin (**1**) in 70% yield.[15] Spectral data of **1** (IR, $^1H$ and $^{13}C$ NMR, HRMS) were in excellent agreement with data from Fürstner's synthetic material[7] and available data from the natural product.[5]

In summary, a concise total synthesis of (±)-butylcycloheptylprodigiosin (**1**) has been described. The use of a conjugate addition/aldol reaction in conjunction with the application of our methodology for synthesis of 2-formyl-4,5-disubstituted pyrroles from *β*-hydroxy-*β*-(4-oxazolyl) ketones was key to the brevity of the route (five steps, 23% overall yield versus 16 steps, 1.5% overall yield for the previous synthesis).[7] The approach outlined herein should be of general use for the synthesis of other prodigiosin alkaloids as well as analogues and may assist further investigations of their medicinal potential.

**Acknowledgment.** Prof. Heinz G. Floss (University of Washington) is thanked for a copy of the $^1H$ NMR spectrum of butylcycloheptylprodigiosin. Prof. Alois Fürstner (Max-Planck Institut für Kohlenforschung) is thanked for helpful discussions. Mr. Scot J. Campbell and Dr. Heewon Lee are thanked for assistance with 2-D NMR and HRMS analysis, respectively.

**Supporting Information Available:** Experimental procedures, characterization data and copies of $^1H$ and $^{13}C$ NMR spectra for **1**, **3**−**5**, **8** and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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