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A Concise Synthesis of Butylcycloheptylprodigiosin

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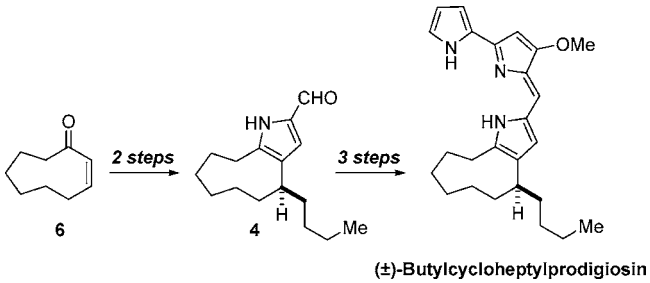
ABSTRACT



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

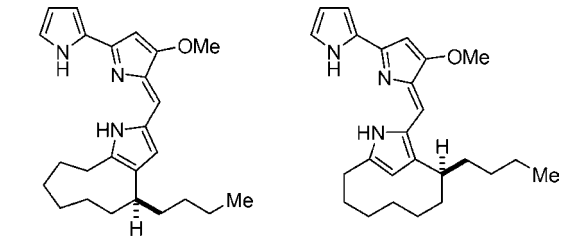


Figure 1. Butylcycloheptylprodigiosin and Streptorubin B.

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).

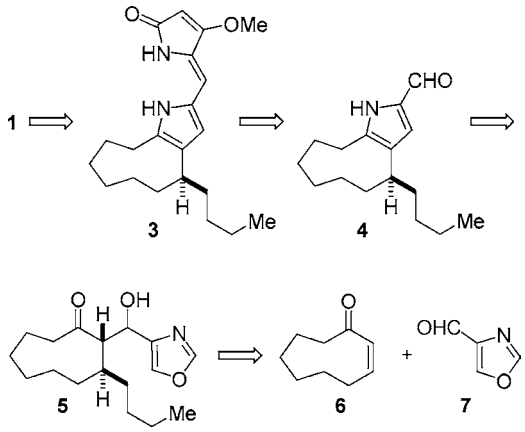


Figure 2. Retrosynthetic analysis.

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

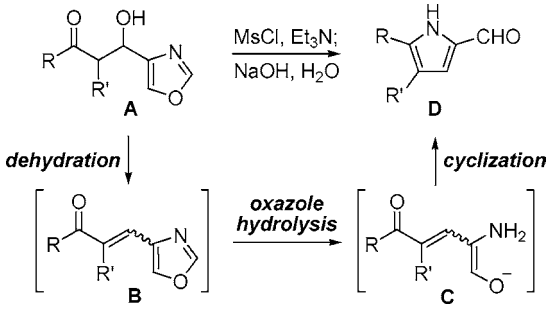
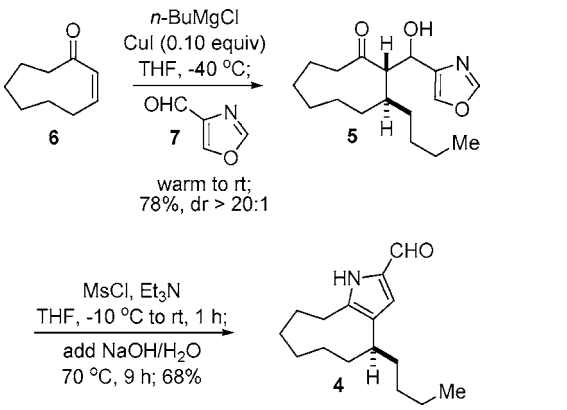


Figure 3. One-pot conversion of β-hydroxy-β-(4-oxazolyl) ketones (**A**) to 4,5-disubstituted-2-formylpyrroles (**D**).

β-(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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(7) (a) Fürstner, A.; Radkowski, K.; Peters, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 2777−2781. (b) Fürstner, A.; Radkowski, K.; Peters, H.; Seidel, G.; Wirtz, C.; Mynott, R.; Lehmann, C. W. *Chem. Eur. J.* **2007**, *13*, 1929−1945.

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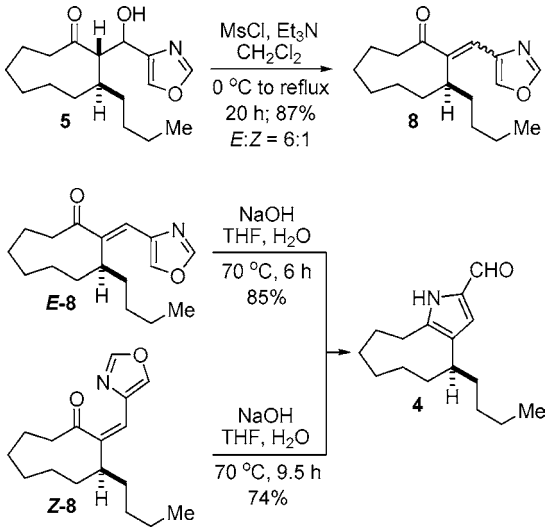
Aldol **5** was subjected to the previously optimized conditions for pyrrole formation. Thus, treatment with MsCl/Et_3N in THF, addition of aqueous NaOH on completion of the mesylation (as monitored by HPLC) and finally heating at 70 °C for 9 h produced the desired formylpyrrole **4** in 68% isolated 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

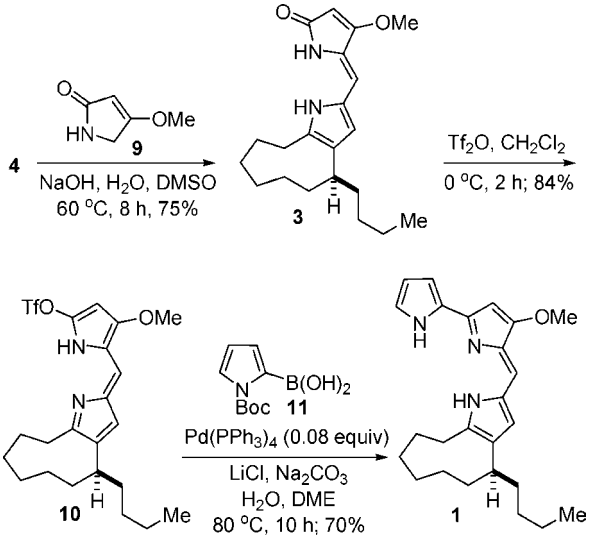
Scheme 2. Convergent Hydrolysis of ***E*-8** and ***Z*-8** to **4**



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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