ORGANIC LETTERS

2010
Vol. 12, No. 5
1048−1051

Evaluation of the Biosynthetic Proposal for the Synthesis of Marineosins A and B

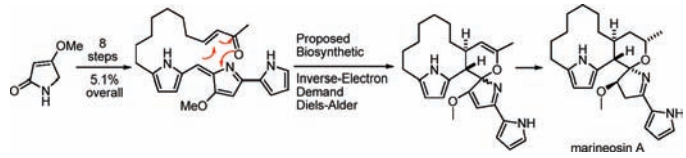
Leslie N. Aldrich, Eric S. Dawson, and Craig W. Lindsley*

Departments of Chemistry and Pharmacology, Vanderbilt Institute of Chemical Biology, Vanderbilt University Medical Center, Nashville, Tennessee 37232

craig.lindsley@vanderbilt.edu

Received January 7, 2010

ABSTRACT



The first synthetic efforts toward marineosins A and B, novel spiroaminals from a *Streptomyces* actinomycete, are described by evaluation of the proposed biosynthesis. The hypothesized biosynthetic C1−C25 Diels−Alder substrate was prepared in 8 steps in 5.1% overall yield; however, the proposed biomimetic inverse-electron-demand hetero-Diels−Alder reaction failed to deliver the marineosin core. Molecular mechanics supports this observation.

Recently, Fenical and co-workers reported on the isolation, characterization, and biological evaluation of two novel spiroaminals, marineosins A (**1**) and B (**2**), from a marine-derived *Streptomyces*-related actinomycete (Figure 1).[1] Biosynthetically, **1** and **2** appear to be derived from previously unknown modifications within the prodigiosin-like pigment pathways,[2] and both displayed inhibition of human colon carcinoma (HCT-116 IC_{50}'s of 0.5 and 46 μM, repsectively), with **1** significantly more potent.[1] Fenical also proposed a possible biosynthesis of **1** and **2** via an inverse-electron-demand hetero-Diels−Alder reaction on acyclic C1−C25 substrate **5** that would form the pyran ring and spiroaminal in a single step (Figure 2).[1] On the basis of the novel structure, the biological activity, and the enticing biosynthetic proposal for **1** and **2**, efforts toward a biomimetic total synthesis of **1** and **2** were pursued in order to test the proposed biosynthesis.

Synthetic efforst focused on the biosynthesis proposed by Fenical in which a condensation between the C1−C9 bis-pyrrole **3** and the enone-containing C10−C24 pyrrole **4** was envisioned to deliver the Diels−Alder substrate **5**. An intramolecular inverse-electron-demand hetero-Diels−Alder reaction would then provide in a single step the spiroaminal pyranyl core **6**. Subsequent reduction across C22−C23 and C6−C7 would provide marineosins A (**1**) and B (**2**). In this Letter, we describe the synthesis of **5**, the acyclic C1−C25 biosynthetic intermediate, and attempts toward a biomimetic synthesis of **1** and **2**; unfortuately, the biosynthetic proposal could not be validated in the laboratory.

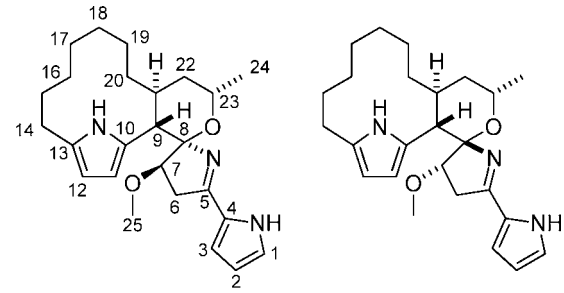


Figure 1. Structures of marineosins A (**1**) and B (**2**).

Synthetic efforts focused on the construction of the key C1−C9 bis-pyrrole **3** and the enone-containing C10−C24

(1) Boonlarppraadab, C.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *Org. Lett.* **2008**, *10*, 5505–5508.
(2) Fuerstner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3582–3603.

10.1021/ol100034p
Published on Web 02/08/2010

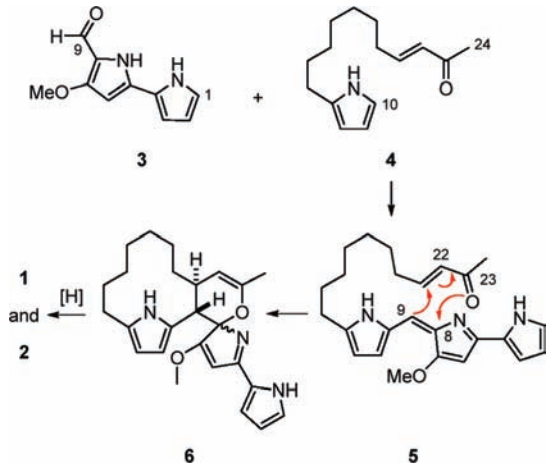
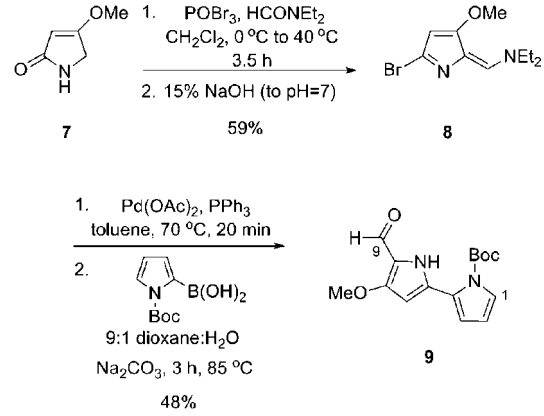


Figure 2. Proposed biosynthesis of marineosins A (**1**) and B (**2**) from the condensation of **3** and **4** to deliver **5**, followed by a inverse-electron-demand Diels−Alder reaction to produce **6**.

pyrrole **4**. The synthesis of **3** proved to be starightforward following literature methods utilized in the synthesis of structurally similar tamajamines and the BcI inhibitor obatoclax.[3,4] As shown in Scheme 1, a Vilsmeier−Haack

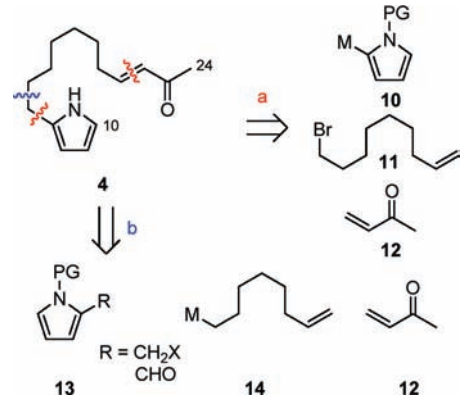
Scheme 1. Synthesis of C1−C9 Protected Bis-pyrrole **9**



haloformylation was performed on 4-methoxy-3-pyrrolin-2-one **7** to provide bromoenamine **8** in 59% yield. Suzuki coupling with Boc-1*H*-pyrrol-2yl boronic acid delivered the Boc-protected analogue **9** of the C1−C9 **3** in 48% yield.

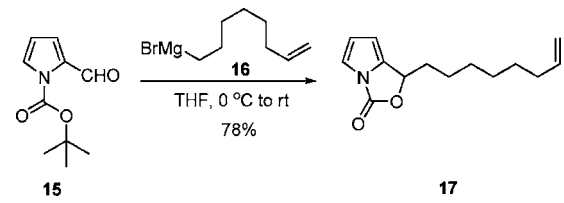
Retrosynthesis of the enone-containing C10−C24 pyrrole **4** led to a number of reasonable approaches (Scheme 2). In both disconnection routes a and b, the enone was envisioned to be installed through a cross-metathasis with **12**. Disconnection pathway a led to the 2-pyrrole organometallic (Li

Scheme 2. Retrosynthesis of C10−C24 Fragment **4**



or $B(OH)_2$) **10** and 9-bromo-1-nonene **11**. Both sp^2-sp^3 Suzuki couplings and S_N2 reactions between **10** and **11** failed to afford the desired product. Similarly, via pathway b, wherein the R in **13** was a CH_2Br or CH_2OMs, S_N2 chemistry also failed with organometallic reagents **14**. Ultimately, addition of an octenyl Grignard to a protected pyrrole-2-carboxaldehyde proved effective, but with quite unexpected results.

Scheme 3. Grignard Addition to Aldehyde **15**



As shown in Scheme 3, treatment of Boc-protected pyrrole-2-carboxaldehyde **15** with Gringard **16** provided the unexpected oxazolidinone **17**, resulting from 1,2-addition, followed by cyclization, in 78% yield. Although this was not a productive venue to access **4**, it led us to hypothesize a one-pot addition, rearrangement, deoxygenation, and deprotection cascade based on the precendent set forth by Muchowski.[5] In 1985, Muchowski demonstrated that $NaBH_4$ reduction of phenylsulfonamide-protected 2-carboxypyrroles **18** led directly to deoxygenated and deprotected congeners **23** (Scheme 4).[5] Thus, we postulated that addition of Gringard **16** to pyrrole **24**, followed by $NaBH_4$, may lead directly to the desired **25** in a single pot. In the event, **25** was indeed produced in the one-pot cascade, but the major product **26** was delivered in a 1:10 ratio (**25**:**26**) in 70% yield.

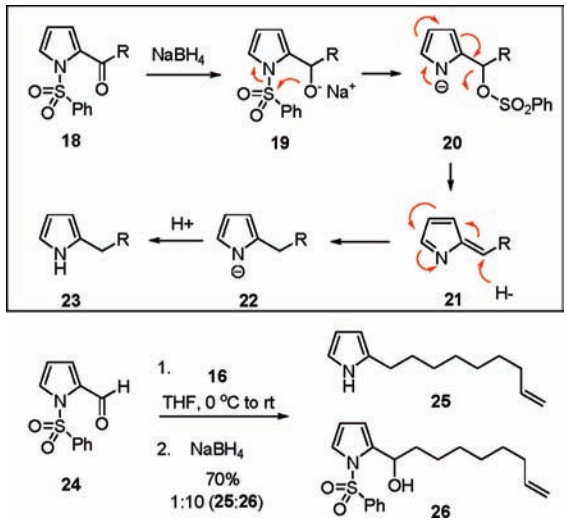
Ultimately, **25** could be delivered in high yield by a three-step sequence involving Grignard **16** addition to pyrrole aldehyde **24** to provide secondary alochol **26**. Ley oxidation

(3) Dari, K.; Yao, Y.; Faley, M.; Tripathy, S.; Rioux, E.; Billot, X.; Rabouin, D.; Gonzalez, G.; Lavalle, J. F.; Attardo, G. *Org. Process Res. Dev.* **2007**, *11*, 1051–1057.

(4) Pinkerton, D. M.; Banwell, M. G.; Willis, A. C. *Org. Lett.* **2007**, *9*, 5127–5130.

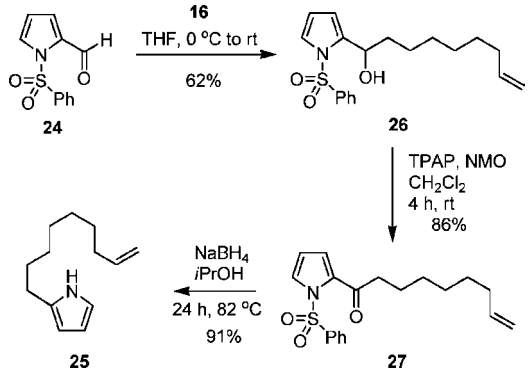
(5) Greenhouse, R.; Ramirez, C.; Muchowski, J. M. *J. Org. Chem.* **1985**, *50*, 2961–2964.

Scheme 4. One-Pot Addition, Rearrangement, Deoxygenation, and Elimination



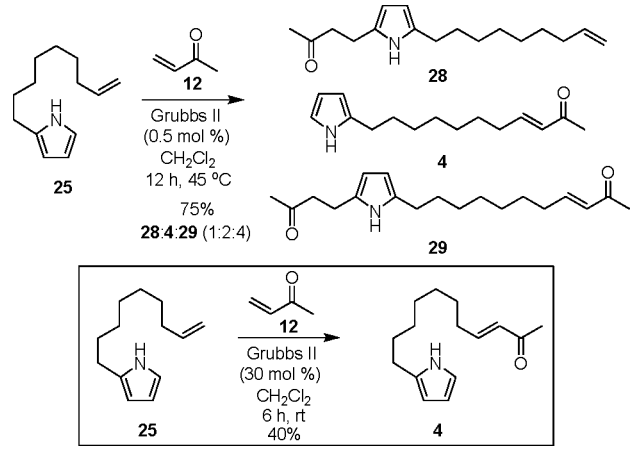
affords the corresponding ketone **27**, and application of Muchowski's one-pot cascade delivers **25** in 48% for the three steps (Scheme 5).

Scheme 5. Synthesis of C10−C21 Fragment **25**



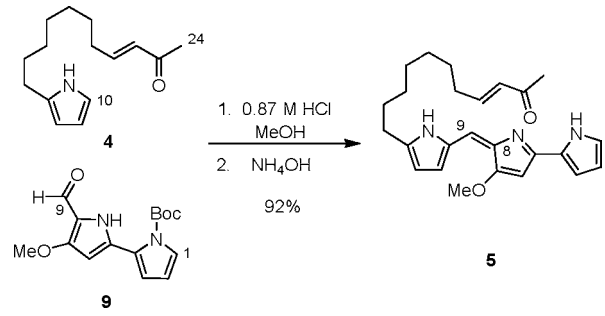
With **25** in hand, the stage was set for the cross-metathasis reaction to assemble the C10−C24 fragment **4**.[6] Once again, this "straightforward" approach provided unexpected results. Under standard cross-metathasis conditions with catalytic Grubbs II, **25**, and **12** (Scheme 6), the desired **4** was produced as a minor product along with conjugate addition products **28** and **29**. To the best of our knowledge, this is the first account of Grubbs II catalyzing 1,4-conjugate additions, and the reaction is quite general with respect to both electron-rich pyrroles and acyclic Michael acceptors.[7] However, increasing catalyst loading from 0.5 to 30 mol % concomitant with lowering the temperature from 40 °C to room temperature allowed the cross-metathasis product **4** to be isolated in 40% yield.

Scheme 6. Synthesis of C10−C24 Fragment **4**



With the two biosynthetic fragments, **9**, the C1−C9 Boc-protected **3**, and the C10−C24 enone **4** in hand, an acid-mediated condensation smoothly formed the C9−C10 bond, delivering the C1−C25 acyclic precursor **5** for the proposed inverse-electron-demand hetero-Diels−Alder reaction in 92% yield (Scheme 7). Isolation of this highly colored poly pyrrole was difficult and required significant refinement to the isolation and purification steps, but **5** could ultimately be produced, purified via reverse phase chromatography, and stored in gram quantities. It is known that **5** and related prodigiosins exist as two stable isomers about the C8−C9 bond in solution, and the equilibrium distribution is dependent on both solvent and pH. For clarity as a DA substrate, we depicted a single isomer **5**.[8] At this point, we had completed the synthesis of the key biosynthetic precursors **3**−**5** prescribed by Fenical and were ready to attempt the proposed inverse-electron-demand hetero-Diels−Alder reaction.

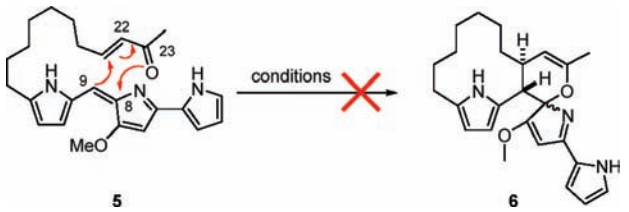
Scheme 7. Synthesis of C1−C25 Diels−Alder Substrate **5**



As shown in Scheme 8, the proposed inverse-electron-demand hetero-Diels−Alder reaction of **5** to deliver **6** proved unsuccessful. Over months of study and hundreds of reaction

(6) Chatterge, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783–3786.
(7) Manuscript in preparation.

Scheme 8. Attempted Inverse-Electron-Demand Hetero-Diels−Alder Reaction of **5** To Afford **6**



5 **6**

conditions (heat, microwave, photochemical, Lewis acid catalysis, mineral acid catalysis, solvent, and additives), we were unable to effect the conversion of **5** to **6** in anything other than presumed trace amounts detected only by LCMS.[9] On the basis of these results, we enlisted molecular modeling in an attempt to understand why the Diels−Alder reaction failed. Molecular mechanics sampling for **5** was conducted starting from the hypothesized transition geometry using both stochastic and systematic conformer searches and gradient energy minimization with the Merck MMFF94 forcefield as implemented in the MOE software package (Chemical Computing Group).[10] Analysis of the top 10,000 conformers with the lowest relative energies (20 kcal from lowest energy conformer) indicated a failure to identify favorable Diels−Alder transition state geometries. Out of 10,000 systematic search conformers generated for **5**, less than 15% of the structures sampled have a folded topology, and the key atoms remained separated by almost 5 Å (Figure 3). Of those conformers with a "folded" topology, 15% form intramolecular hydrogen bonds.[8] Thus, as a result of intramolecular hydrogen bonds and a large degree of conformational flexibility present in the long, alkyl linker moeity, the intramolecular Diels−Alder mechanism is likely energetically disfavored. Moreover, attempts at intermolecular variants[9] proved equally unsuccessful, suggesting the C8−C9 olefin of the extended poly pyrrole π-system is not a competent dienophile.

In summary, we evaluated the biosynthetic proposal put forth by Fenical and co-workers for marineosins A and B.

(8) Furstner, A.; Grabowski, J.; Lehman, C. W. *J. Org. Chem.* **1999**, *64*, 8275–8280.

(9) See Supporting Information.

(10) Vainio, M. J.; Johnson, M. S. *J. Chem. Inf. Model.* **2007**, *47*, 2462–2474.

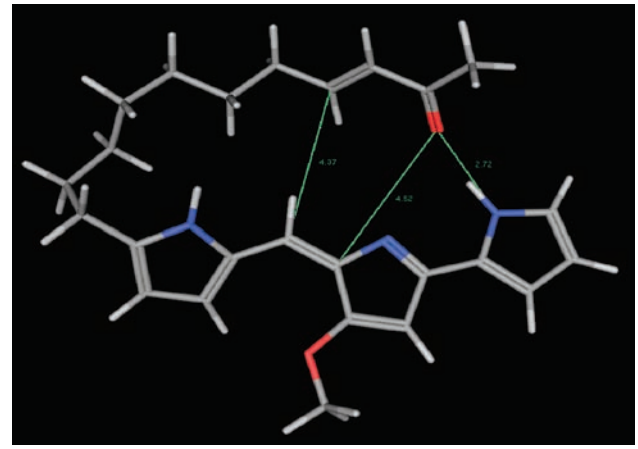


Figure 3. Mist favored Merck MMFF94 minimized conformer of **5**.

In short order, we prepared the proposed biosynthetic building blocks **3** and **4** and synthesized the key C1−C25 inverse-electron-demand hetero-Diels−Alder substrate **5** in 8 steps (5.1% overall yield). Hundreds of reaction conditions were explored, but the proposed biomimetic intramolecular inverse-electron-demand hetero-Diels−Alder reaction was not successful. Modeling studies supported the inability of **5** to affect this transformation. Thus, a fundamentally new synthetic strategy is now underway to synthesize marineosines A and B. In the course of this work, we also discovered a novel Grubbs II catalyzed 1,4-conjugate addition reaction. While synthetically we could not validate the biosynthetic proposal, an enzyme-templated process in nature may still align **5** in a manner conducive for the Diels−Alder reaction to occur.

Acknowledgment. The authors acknowledge the Department of Pharamcology for support of this research. L.N.A. acknowledges the Vanderbilt Institute of Chemical Biology (VICB) for a predoctoral fellowship.

Supporting Information Available: Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for all new compounds **4**, **5**, **8**, **9**, **17**, **25**−**28**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL100034P