ORGANIC LETTERS

2008
Vol. 10, No. 1
149−152

Biomimetic Synthesis of the Shimalactones

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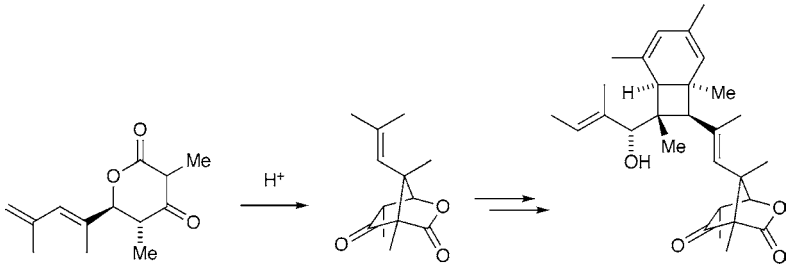
Received November 26, 2007

ABSTRACT



A biomimetic synthesis of shimalactone A and B is described. Its key features are an unprecedented acid-catalyzed cyclization of a dienyl β-ketolactone and a Stille coupling/8π-6π electrocyclization cascade to create the oxabicyclo[2.2.1]heptane and bicyclo[4.2.0]octadiene, respectively. The synthesis is convergent and void of protecting groups.

Natural products that arise from 8π-6π electrocyclization cascades have seen a remarkable surge in recent years. More than 20 years after the isolation of the endiandric acids, several pyrone polyketides featuring the bicyclo[4.2.0]-octadiene retron have been disclosed, occasionally in an oxidized form (Figure 1). These new natural products, represented by SNF4435 C, ocellapyrone A, and elysiapyrone A, have stimulated considerable synthetic activity, which has led to a deeper understanding of electrocyclization cascades and polyene chemistry in general.[1]

The shimalactones, a pair of neuritogenic natural products recently isolated from the cultured marine fungus *Emericella variecolor*, represent an interesting variation of this biosynthetic theme (Figure 1). These fascinating molecules contain an unprecented oxabicyclo[2.2.1]heptane moiety that is linked to a bicyclo[4.2.0]octadiene subunit through a trisubstituted double bond.[2] Taken together their two isolated bicyclic nuclei feature four quaternary stereocenters (two of them adjacent), which render the shimalactones a considerable synthetic challenge.

Biosynthetic considerations add to the attractiveness of the shimalactones as synthetic targets. In a recent review,[1b] we proposed that their biosynthesis could involve heptaenyl β-ketolactone **1** (Scheme 1). This hypothetical compound is a fairly regular polyketide that is related to previously isolated pyrones but has a higher degree of saturation in its heterocycle.

According to our hypothesis, **1** undergoes enzymatic epoxidation at the penultimate double bond to afford intermediate **2**. An acid-catalyzed epoxide opening would then form an undecapentaheptenyl cation **3**, which is eventually converted into its isomeric cation **4** as the positive charge is carried down the polyene chain. Notably, **3** and **4** are not resonance structures, since the numerous methyl

(1) (a) For a review of biosynthetic and biomimetic electrocyclizations, see: Beaudry, C. M.; Malerich, J. P.; Trauner, D. *Chem. Rev.* **2005**, *105*, 4757. (b) Miller, A. K.; Trauner, D. *Synlett* **2006**, *14*, 2295. (c) For a review of cascade reactions in synthesis, see: Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134−7186.

(2) (a) Wei, H.; Itoh, T.; Konishita, M.; Kotoku, N.; Kobayashi, M. *Tetrahedron* **2005**, *61*, 8054−8058. (b) Wei, H.; Itoh, T.; Konishita, M.; Kotoku, N.; Kobayashi, M. *Heterocycles* **2006**, *68*, 111−123.

10.1021/ol702806v CCC: $40.75
Published on Web 12/12/2007

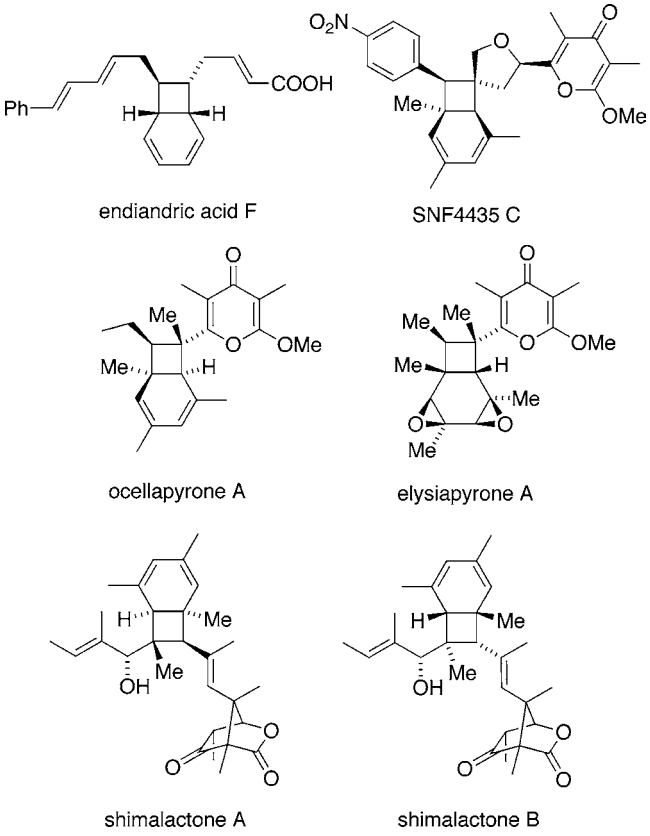
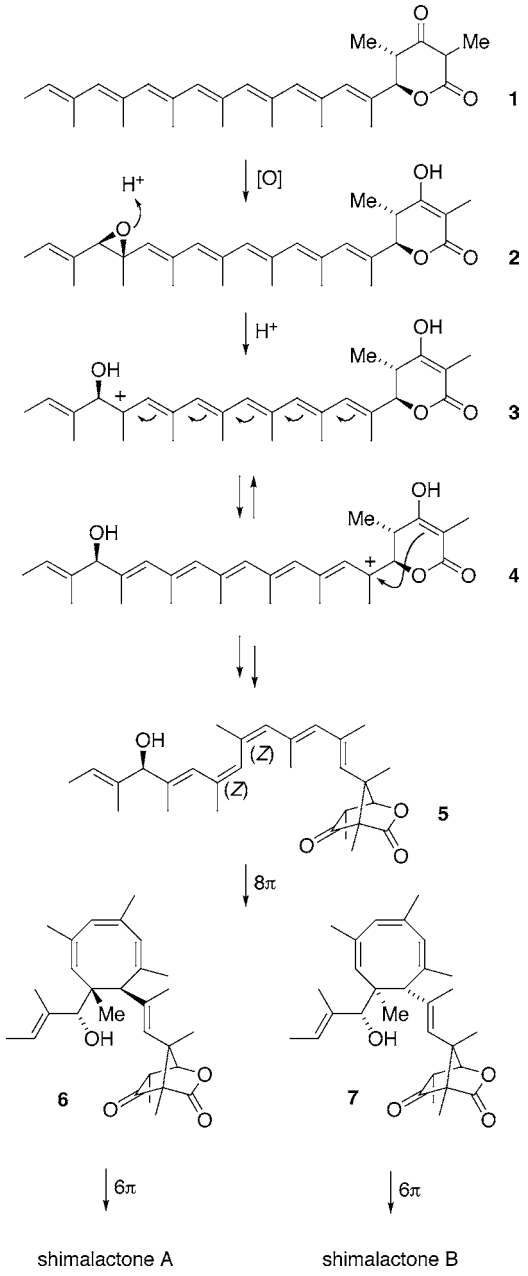


Figure 1. Natural products featuring the bicyclo[4.2.0]octadiene (or -octane) skeleton.

substituents on the polyene prevent the π-system from being planar due to A1,3-strain.[3] Once **4** is formed, it is intercepted by the enol form of the β-keto lactone moiety to form the oxabicyclo[2.2.1]heptane unit. The resulting conjugated pentaene moiety has to attain an (*E*,*E*,*Z*,*Z*,*E*)-configuration, which triggers an 8π-6π electrocyclization cascade (via **5** and **6**/**7**). In principle, the electrocyclization cascade could yield four diastereomeric shimalactones. However, since only two are found, it appears that the 6π-electrocyclization is highly diastereoselective, a scenario that has been noted before in the case of the SNF4435 compounds.[4] Of course, the double-bond isomer of **1** could be involved and the exact sequence of the electrocyclization cascade and oxabicyclo-[2.2.1]heptane formation could be reversed, i.e., the electrocyclization could take place at the stage of an undecapentaenyl cation, such as **4**.

We now present a total synthesis of the shimalactones that implements some of the elements of this biosynthetic proposal. Early in our investigations, however, we determined that the construction of epoxy hexaene **2** would present a very difficult synthetic challenge. We therefore decided to focus on the formation of the oxabicyclo[2.2.1]heptane moiety first and then use a Stille coupling/8π-6π electrocyclization cascade to assemble the bicyclo[4.2.0]octadiene unit of the natural product in a separate and final step.

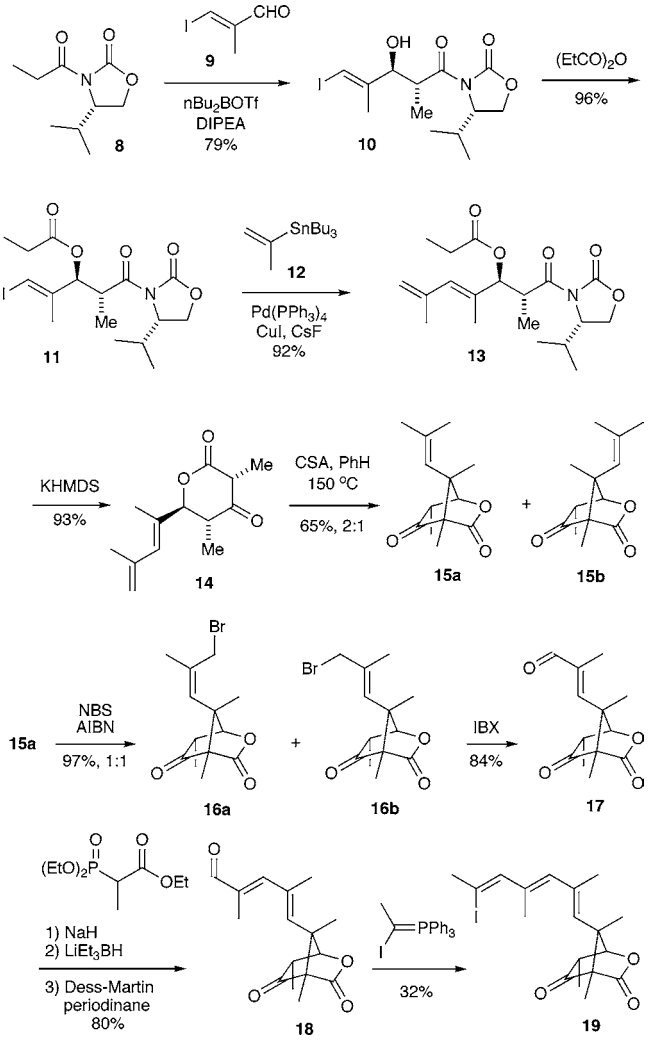
Scheme 1. Proposed Biosynthesis of Shimalactones



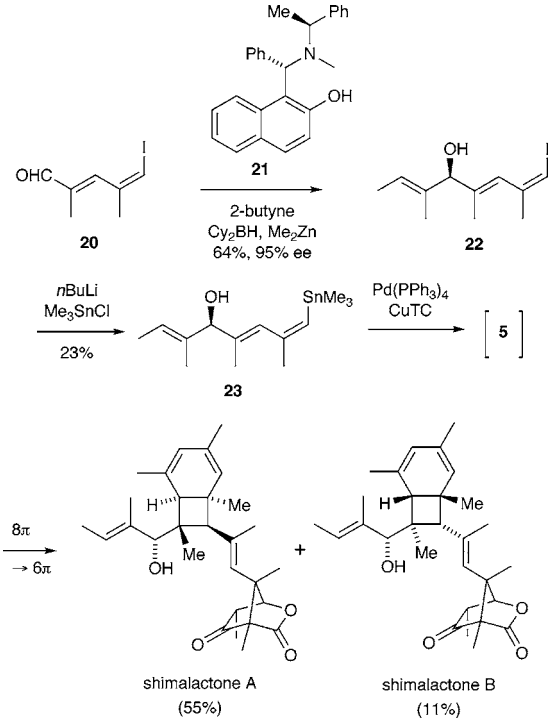
Accordingly, our synthesis of the shimalactones starts with a Heathcock anti-aldol addition of the boron enolate of **8** to iodoenal **9** to afford **10** (Scheme 2), the structure of which was confirmed by X-ray crystallography (see the Supporting Information).[5,6] Acylation with propionic anhydride gave **11**, which underwent Stille coupling with tributylisopropenylstannane (**12**) to yield **13**. A subsequent Dieckmann cyclization cleanly afforded β-ketolactone **14** as a single diastereomer.[7] After careful optimization, we found that treatment

(3) Jacobsen, M. F.; Moses, J. E.; Adlington, R. M.; Baldwin, J. E. *Org. Lett.* **2005**, *7*, 2473−2476.
(4) Beaudry, C. M.; Trauner, D. *Org. Lett.* **2005**, *7*, 4475−4477.
(5) Baker, R.; Castro, J. L. *J. Chem. Soc., Perkin Trans. I* **1990**, *1*, 47−65.
(6) (a) Raimundo, B. C.; Heathcock, C. H. *Synlett* **1995**, *12*, 1213−1214. (b) Walker, M.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 5747−5750.

Scheme 2. Preparation of the Oxabicyclo[2.2.1]heptane



Scheme 3. Total Synthesis of the Shimalactones



of **14** with camphorsulfonic acid (CSA) afforded strained oxabicyclo[2.2.1]heptanes **15a** and **15b** as a 2:1 mixture of diastereomers.

Our next challenge was the further functionalization of **15a**. While allylic oxidations failed, radical bromination cleanly gave a 1:1 mixture of allylic bromides **16a** and **16b**. Oxidation of **16b** with IBX yielded unsaturated aldehyde **17**, the structure of which was confirmed by X-ray crystallography.[8] Although **17** was extremely sensitive toward a variety of basic conditions, it could be elongated through a carefully optimized and highly efficient three-step sequence to afford dienal **18**. Stork−Zhao olefination of this aldehyde then gave the sensitive iodotriene **19**.

A second building block, **23**, was assembled through asymmetric addition of 2-butenyl methyl zinc to the known iododienal **20** to afford divinylcarbinol **22** (Scheme 3).[9] This could be achieved in high enantiomeric excess using the easily available aminophenol **21** as a catalyst.[10] Subsequent iodine−tin exchange afforded vinyl stannane **23**.

With both **19** and **23** in hand, the stage was set for the final Stille coupling/8π-6π electrocyclization cascade (Scheme 3). Indeed, this sequence could be achieved under modified Stille−Liebeskind conditions to afford the shimalactones as a 5:1 mixture of diastereomers. Whereas the major isomer, shimalactone A, could be fully purified, shimalactone B was obtained as a mixture with its diastereomer. All attempts to separate the two shimalactones further failed. Synthetic shimalactone A was identical in all respects (NMR, IR, MS, $[\alpha]_D$) with the natural product, thus confirming its absolute configuration. Notably, the two other diastereomers that could possibly result from the electrocyclization cascade were not observed. Therefore, the 6π branch of the cascade appears to be highly diastereoselective, as has been previously observed in related systems.[1a,b]

The electrocyclization cascade presumably proceeds through (*E*,*E*,*Z*,*Z*,*E*)-polyene **5**, which could never be isolated. Previous studies by Baldwin and our group have shown that polyenes of this type undergo facile isomerizations of their trisubstituted double bonds.[1b,11] Therefore, we decided to advance compound **16a** to the pentaene stage (Scheme 4). A sequence analogous to the one shown in Scheme 2 gave iodotriene **24**, which underwent cross coupling with stannane

(7) (a) Brandänge, S.; Leijonmarck, H. *Tetrahedron Lett.* **1992**, *33*, 3025−3028. (b) Vanderwal, C. D.; Vosburg, D. A.; Weiler, S.; Sorenson, E. J. *Org. Lett.* **1999**, *1*, 645−648. (c) Hinterding, K.; Singhanat, S.; Oberer, L. *Tetrahedron Lett.* **2001**, *42*, 8643−8645.

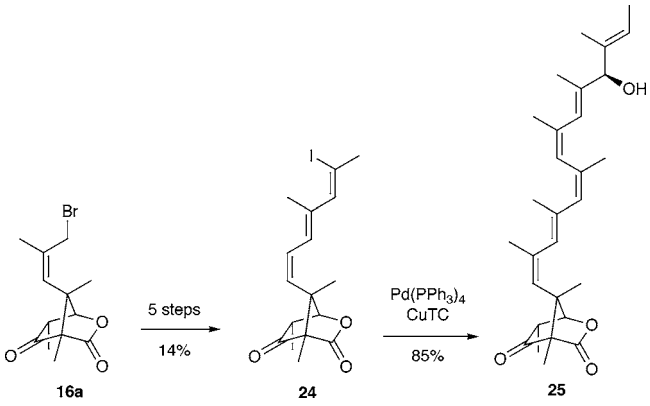
(8) Moorthy, J. N.; Singhal, N.; Senapati, K. *Tetrahedron Lett.* **2006**, *47*, 1757−1761.

(9) Barbarow, J. E.; Miller, A. K.; Trauner, D. *Org. Lett.* **2005**, *7*, 2901−2903.

(10) Ji, J.; Qiu, L.; Yip, C. W.; Chan, A. S. C. *J. Org. Chem.* **2003**, *68*, 1589−1590.

(11) Jacobsen, M. F.; Moses, J. E.; Adlington, R. M.; Baldwin, J. E. *Tetrahedron* **2006**, *62*, 1675−1689.

Scheme 4. An Isolable (*Z*,*E*,*Z*,*Z*,*E*)-Pentaene



23 to afford (*Z*,*E*,*Z*,*Z*,*E*)-pentaene **25**. Remarkably, this compound was found to resist 8π electrocyclization and could be isolated. Presumably, the bulk of the oxabicyclo-[2.2.1]heptaenyl substituent, which would be positioned endo in an 8π transition state, prevents **25** from undergoing the cyclization, in stark contrast to its isomer **5**. However, despite repeated attempts, **25** could not be isomerized to the shimalactones.

While our synthetic studies on the shimalactones were ongoing, the structures of two new natural products, coccidiostatin A and emecorrugatin A, were reported. Featuring an oxabicyclo[2.2.1]heptane moiety and a stable (*E*,*Z*,*Z*,*Z*,*Z*)-pentaene, these compounds show some interesting structural similarities to the shimalactones and stable pentane **25**, respectively.[12] It is conceivable that the biosynthesis of coccidiostatin A involves an analogous cationic cyclization of a polyenyl β-ketolactone, a reaction that is not possible in emerocorrugatin A due to the presence of a *gem*-dimethyl group.

In summary, we have achieved a convergent and protecting group-free synthesis of the shimalactones, which supports our biosynthetic hypothesis on the origin of these compounds. To this end we have developed a new acid-catalyzed key cyclization (**14**→**15a,b**), which generates two adjacent quaternary stereocenters in a strained bicyclic ring system. The scope and limitations of this reaction and its application to the synthesis of coccidiostatin A are under investigation.

Acknowledgment. This work was supported by National Institutes of Health Grant R01 GM067636. We thank Dr. Allen G. Oliver and Dr. Frederick J. Hollander (both from UC Berkeley) for the crystal structure determination of compounds **10** and **17**.

Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org. Crystallographic data (excluding structure factors) for compounds **10** and **17** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. 662079 and 662080. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223−336-033; e-mail: deposit@ccdc.cam.ac.uk).

OL702806V

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