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Total Synthesis of the Proposed Structure of Marineosin A

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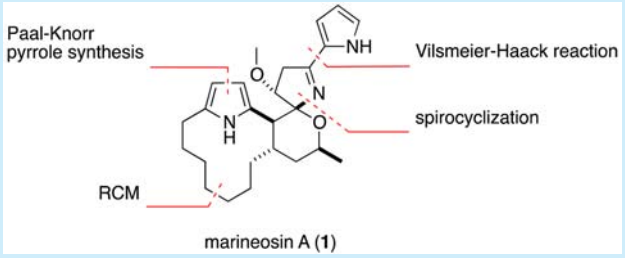
Supporting Information

ABSTRACT: A total synthesis of a proposed structure of marineosin A has been achieved. The key steps involve Lewis acid catalyzed spirocyclizaton, ring-closing metathesis, Paal–Knorr pyrrole synthesis, and a Vilsmeier–Haack type reaction with Tf_2O.



In 2008, Fenical and co-workers reported the isolation of two novel spiroiminals from a marine-derived Streptomyces-related actinomycete, designated as marineosins A (**1**) and B (**2**) (Figure 1).[1] These two compounds have been shown to possess significant anticancer activities toward human colon carcinoma (HCT-116) (IC_{50} = 0.5 μM for **1** and IC_{50} = 46 μM for **2**).[1] Marineosins A and B contain a *trans*-fused macrocyclic ring, a spiro tetrahydropyran-dihydropyrrole iminal moiety, and two pyrroles. The structural difference of these two compounds lies in the stereochemistry of the MeO group in the dihydropyrrole and the spiroiminal center. The intriguing structures along with the promising biological activities make marineosins attractive synthetic targets. Several synthetic approaches toward marineosins have been reported. In 2010, Lindsley and co-workers reported their biomimetic approach to these two molecules via the inverse-electron-demand hetero-Diels–Alder process.[2] Subsequently, they also reported the synthesis of a macrocyclic pyrrole and functionalized spiroaminals.[3] In 2010, Snider and co-workers reported an alternative proposal for the biosynthesis of the marineosins and described their synthesis of the spiroiminal moiety.[4] A macrocyclic pyrrole was synthesized in their further studies.[5] Recently, Reynolds and co-workers reported the elucidation of the biosynthetic pathway for marineosins with the relevant gene cluster.[6] To date, no total synthesis of any member of marineosins has been reported. The unique combination of a macrocyclic pyrrole and a pyrrole-containing spiroiminal presents a synthetic challenge. Herein, we wish to report the first total synthesis of the proposed structure of marineosin A.

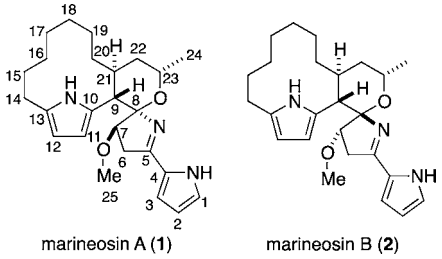
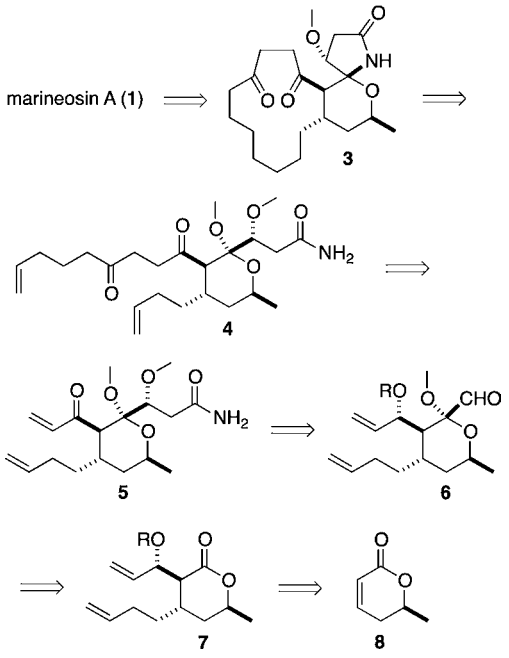


Figure 1. Structures of marineosins A and B.

Our retrosynthetic plan is shown in Scheme 1. The sensitive pyrroles were planned to be installed in a late stage via Paal–Knorr pyrrole synthesis and a Vilsmeier–Haack type reaction

Scheme 1. Retrosynthetic Analysis of Marineosin A



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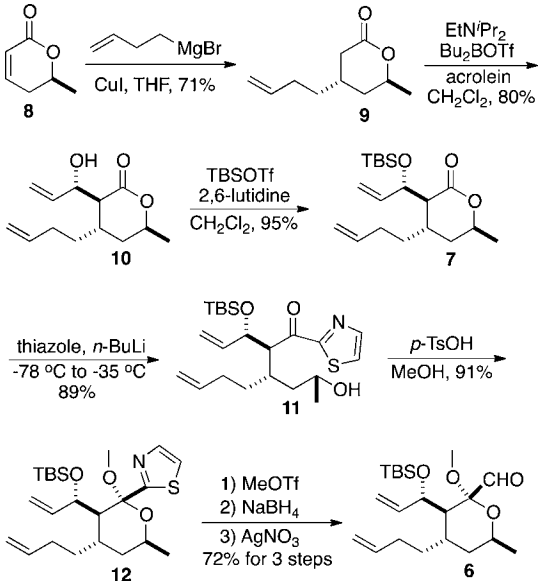
from spiro lactam **3**,[7] which could be obtained from spiroketal **4** via an acid-catalyzed cyclization and ring-closing metathesis (RCM). Compound **4** could be generated from ketone **5** via Stetter reaction. The amide in **5** could be introduced by the addition of $LiCH_2CN$ to aldehyde **6**, followed by a hydrolysis of the resulting nitrile. Aldehyde **6** could be derived from lactone **7** with a masked formyl anion equivalent. Lactone **7** may be prepared from pyranone **8** via conjugate addition of a 3-butenyl group and an aldol addition reaction with acrolein.

Our synthesis started with readily available pyranone **8** (Scheme 2).[8] Subjecting **8** to 3-butenylmagnesium bromide

Scheme 2. Synthesis of Aldehyde 6



and CuI led to lactone **9** in 71% yield.[9] Compound **9** was treated with dibutylboron triflate and EtN^{i}Pr$_2$ to form the corresponding boron enolate, which reacted with acrolein diastereoselectively to give alcohol **10** in 80% yield.[10] Compound **10** was protected with a TBS group (95% yield)[11] and subsequently reacted with lithium thiazole to give ketone **11** in 89% yield.[12] Treating **11** with a catalytic amount of *p*-TsOH (0.15 equiv) in MeOH at room temperature led to cyclic ketal **12** in 91% yield.[13] The stereochemistry of **12** was confirmed by the X-ray structure (Figure 2). The thiazole **12** was subsequently converted to aldehyde **6** in 72% overall yield via a three-step process with MeOTf, $NaBH_4$, and $AgNO_3$ (Scheme 2).[14]

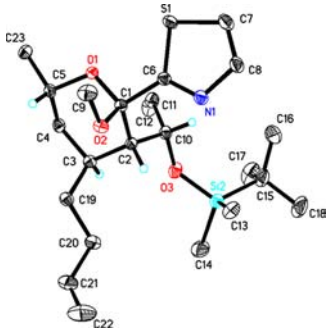
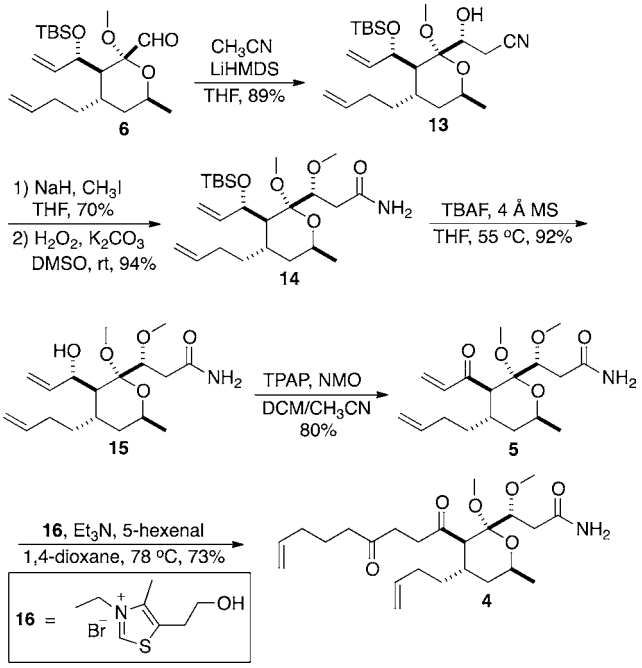


Figure 2. X-ray structure of compound **12**.

The conversion of aldehyde **6** to 1,4-diketone **4** is shown in Scheme 3. Treating **6** with $LiCH_2CN$ at −78 °C gave *β*-

Scheme 3. Synthesis of 1,4-Diketone 4



hydroxynitrile **13** as a single diastereomer in 89% yield.[15] Upon methylation[4] with NaH and CH_3I (70% yield), the *β*-hydroxynitrile was hydrolyzed to amide **14** in 94% yield with H_2O_2 and K_2CO_3 in DMSO at room temperature.[16] The desilylation of **14** with TBAF in the presence of 4 Å molecular sieves gave alcohol **15** (92% yield),[17] whose structure was further confirmed by the X-ray diffraction (Figure 3). The

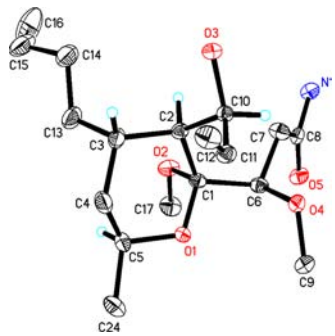


Figure 3. X-ray structure of compound **15**.

allylic alcohol was oxidized to enone **5** in 80% yield with TPAP and NMO.[18] The Stetter reaction of enone **5** was accomplished with 5-hexenal, 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide (**16**), and Et_3N in 1,4-dioxane at 78 °C, giving 1,4-diketone **4** in 73% yield (Scheme 3).[19]

With 1,4-diketone **4** in hand, the cyclization was subsequently investigated (Scheme 4). The macrocyclization of compound **4** was initially attempted. However, no desired product was obtained under various ring-closing metathesis (RCM) conditions. At this point, it was decided that the spirocyclization would be carried out first with the hope that the resulting spiro lactam could be a better substrate for the ring-closing metathesis. In the event, the spirocyclization of

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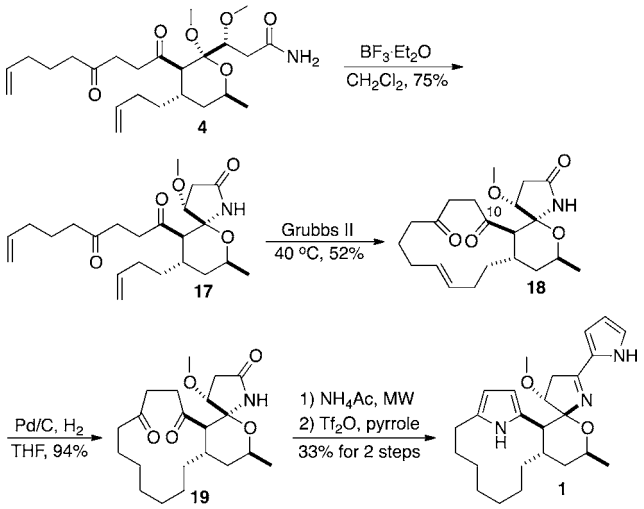
Scheme 4. Completion of Marineosin A



compound **4** was accomplished with $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at room temperature to give spiro lactam **17** in 75% yield (Scheme 4).[20] To our delight, the lactam was indeed more suited for the ring-closing metathesis. Treating **17** with Grubbs II catalyst (10 mol %) in CH_2Cl_2 at reflux under diluted conditions led to macrocyclic compound **18** in 52% yield.[21,19b] The hydrogenation of **18** with Pd/C (10%) under a H_2 atmosphere (with a balloon) provided compound **19** in 94% yield.[19b]

The X-ray structure of **18** showed that the tetrahydropyran ring adopted a chair conformation in which the amide N atom and the macrocyclic side chains were in the axial positions in the solid state (Figure 4). At this moment, it is not clear if the

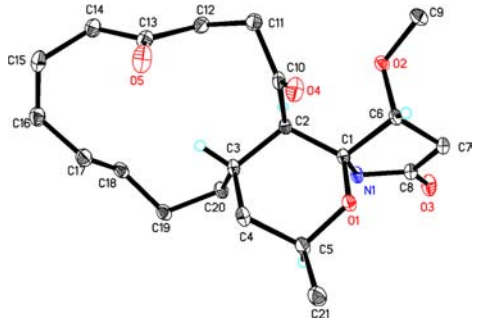


Figure 4. X-ray structure of compound **18**.

stereochemistry of the spiro lactam was established during the spirocyclization or was formed in the subsequent RCM reaction via isomerization to avoid the repulsion between the amide carbonyl group and the carbonyl group at C-10.[22] Once the double bond was hydrogenated, the macrocyclic ring became more flexible as indicated by the X-ray structure of **19** (Figure 5), and the tetrahydropyran ring adopted a boat conformation with the amide N atom being in the axial position and the macrocyclic side chains being in equatorial positions.

The installation of two pyrroles into compound **19** was eventually accomplished with a microwave-assisted Paal–Knorr process[3b,23] and a subsequent Vilsmeier–Haack type reaction,[3a,7,24] giving marineosin A (**1**) as a white solid in 33% overall yield over two steps. The structure of the synthesized compound is consistent with the proposed structure of

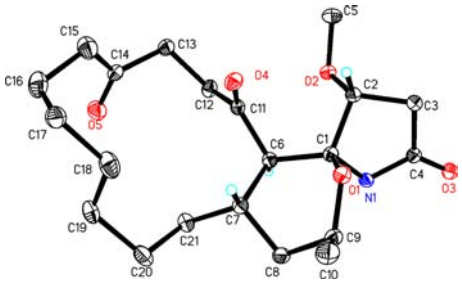


Figure 5. X-ray structure of compound **19**.

marineosin A as indicated by the X-ray structure (Figure 6). Interestingly, the stereochemistry of the spiroiminal was

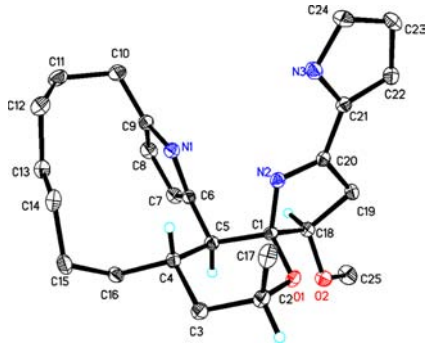


Figure 6. X-ray structure of the synthesized marineosin A (**1**).

inversed as compared to compound **19**. It is not clear if the inversion process occurred during the Paal–Knorr pyrrole synthesis or during the Vilsmeier–Haack reaction, or during the purification process. As indicated by the X-ray structure, the tetrahydropyran ring in compound **1** adopted a chair conformation with the imine N atom in the axial position and the macrocyclic side chains in the equatorial positions (Figure 6). While the NMR spectra of the synthetic compound exhibit great similarity to those of the isolated marineosin A, there are also noticeable differences for these two compounds. For example, the CH_2 on C-6 appeared at 2.80 (dd, J = 16.0, 7.5 Hz, 1H) and 2.71 (dd, J = 15.5, 8.0 Hz, 1H) for the synthetic compound while the same CH_2 appeared at 2.88 (dd, J = 16.0, 8.5 Hz, 1H) and 1.88 (dd, J = 16.0, 8.5 Hz, 1H) for the isolated one. The synthetic compound is a white solid while the isolated one is a colorless oil. In addition, the optical rotation of these two compounds showed opposite signs in MeOH. It appears that the synthetic compound and the isolated compound are not exactly the same. These two compounds could be atropisomers or diastereoisomers or structural isomers. Further structural elucidation will be facilitated by the synthesis of other members of marineosins such as **2**, **20**, and **21** (Figures 1 and 7).

In summary, the total synthesis of the proposed structure of marineosin A has been accomplished from readily available (*S*)-6-methyl-5,6-dihydro-2-pyrone (**8**) in 19 steps with 1.2% overall yield. The key synthetic transformations include Lewis acid catalyzed spirocyclizaton, ring-closing metathesis, Paal–Knorr pyrrole synthesis, and a Vilsmeier–Haack type reaction with Tf_2O. The structure of the synthetic marineosin A was established by X-ray analysis. The current work presents the first synthesis for any member of marineosins, which provides a good foundation for the synthesis and structural elucidation of

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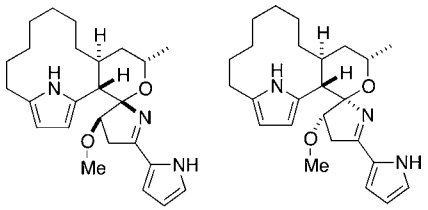

Figure 7. Structures of marineosins A′ and B′.

other members of this family of compounds as well as for the biological studies of these molecules and their analogues.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00632.

Experimental procedures, characterization data, and NMR spectra (PDF)
X-ray structures of **1** (CIF)
X-ray structures of **12** (CIF)
X-ray structures of **15** (CIF)
X-ray structures of **18** (CIF)
X-ray structures of **19** (CIF)

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Notes

The authors declare no competing financial interest.

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