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Synthesis of Slagenins A, B, and C

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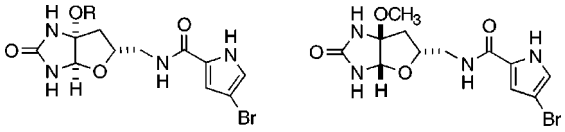
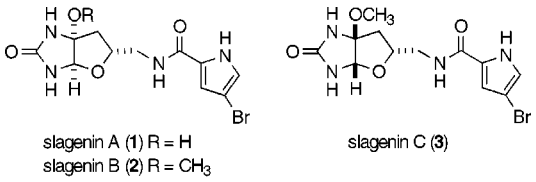
ABSTRACT



A short synthesis of the marine sponge metabolites slagenins A (1), B (2), and C (3) is described. The synthetic route features the preparation of β-hydroxyimidazolone 4 from ornithine and its subsequent oxidative cyclization to the slagenin core.

Slagenins A (**1**), B (**2**), and C (**3**) comprise a group of cytotoxic secondary marine metabolites recently isolated from the sponge *Agelas nakamurai*.[1] These structurally interesting natural products possess a highly functionalized tetrahydrofuro[2,3-*d*]imidazolidin-2-one core in which the relative stereochemistry was elucidated by 2D NMR spectroscopy. No prior synthesis of slagenins has appeared in the literature, and only one report describes the preparation of tetrahydrofuro[2,3-*d*]imidazolidin-2-one skeletons starting from urea and 2-aminosugars.[2] To our knowledge, the biosynthetic pathway to slagenins remains unknown but the amino acid ornithine appears to be an attractive precursor. In this Letter, we report a total synthesis of slagenins A, B, and C from intermediates derived from this hypothetical forerunner.



The synthetic approach centers on the introduction of the β-hydroxy substituent in imidazolone **4** and its subsequent oxidative cyclization to the requisite slagenin core (Figure 1). This strategy is based on the relevant transformation of 2-aminoimidazoles to dialkoxyimidazolines with NCS and alcohols (eq 1).[3] The success of this approach depends on the intramolecular cyclization of **4** and trapping the resulting reactive intermediate with methanol or water.

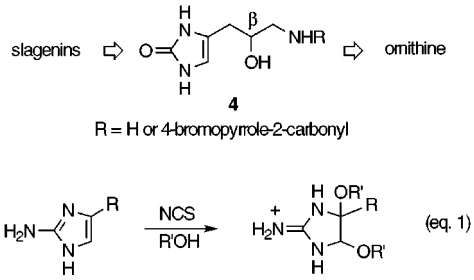


Figure 1. Synthetic plan.

Starting from commercially available ornithine, Fisher esterifcation afforded methyl ester **5** which upon reduction under Akabori conditions[4] followed by condensation with potassium cyanate produced imidazolone **6**[5] as a colorless

(1) Tsuda, M.; Uemoto, H.; Kobayashi, J. *Tetrahedron Lett.* **1999**, *40*, 5709.

(2) Avalos, M.; Babiano, R.; Cintas, P.; Jiménez, J. L.; Palacios, J. C.; Valencia, C. *Tetrahedron* **1993**, *49*, 2676.

(3) Olofson, A.; Yakushijin, K.; Horne, D. A. *J. Org. Chem.* **1998**, *63*, 1248.

(4) Initially performed with thiocyanate, see: (a) Akabori, S. *Ber.* **1933**, *66*, 157. (b) Lawson, A.; Morley, H. V. *J. Chem. Soc.* **1955**, 1695.

(5) All new compounds gave satisfactory spectral data (^{1}H and ^{13}C NMR and HRMS).

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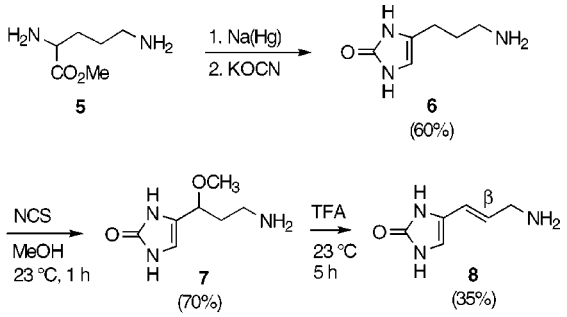
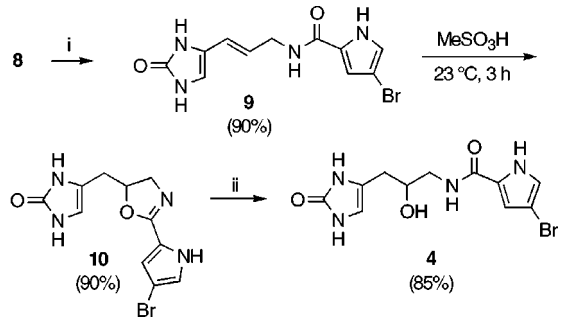
Scheme 1



solid (Scheme 1). Multigram quantities of **6** can be conveniently prepared by this method. Although the direct installment of the double bond in **8** from **6** proved to be problematic, treatment of **6** with NCS in methanol afforded α-methoxy derivative **7** in good yield. Trifluoroacetic acid caused elimination of MeOH which produced olefin **8** in modest amounts.[6]

The direct introduction of a hydroxyl substituent to the *β*-position in imidazolone **8** proved difficult. However, reports of allylic amides undergoing cyclization to oxazolines suggested an alternative solution.[7] Acylation of amine **8** with 4-bromo-2-(trichloroacetyl)pyrrole[8] gave amide **9** as a colorless solid (Scheme 2). With **9** in hand, conversion to oxazoline **10** in near quantitative yield was achieved in methanesulfonic acid. Aqueous acid caused cleavage of the oxazoline in **10**, producing alcohol **4** upon neutralization with

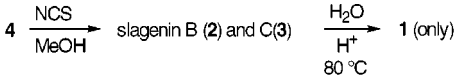
Scheme 2[a]



[a] (i) 4-Bromo-2-(trichloroacetyl)pyrrole, DMF, rt, 1 h; (ii) 5% HCl, reflux, 2 h, then neutralize with NaOH.

base.[9] When a methanol solution of **4** was treated with NCS (23 °C, 30 min), a 1:1 diastereomeric mixture of slagenins B (**2**) and C (**3**) was produced in 90% yield (Scheme 3).

Scheme 3



Pure samples of each were obtained through separation by flash chromatography. Upon heating in the presence of acid, both **2** and **3** were converted to slagenin A (**1**). Slagenin A, which bears an exo pyrrole carboxamide group, was obtained as the sole product and the presumably less stable endo diastereomer was not observed under these conditions. NMR, IR, and MS spectral data for synthetic slagenins A, B, and C were in satisfactory agreement with those reported for the natural material.[10]

In summary, a relatively short synthesis of slagenins A, B, and C has been accomplished from ornithine. The synthetic scheme incorporates several key steps that are conceivably biomimetic in nature. The genera *Agelas* is particularly known for its production of bioactive natural products that are related to oroidin.[11] The chemistry outlined here is entirely applicable to this closely related alkaloid family, and work in this area is currently in progress.

Acknowledgment. Financial support from the National Institutes of Health (GM 50929) is gratefully acknowledged.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for slagenins A (**1**), B (**2**), and C (**3**) and compounds **4** and **6**−**10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) Acid-facilitated dimerization of **7** and/or **8** predominates under these conditions. Current efforts are underway to optimize this step.

(7) MacManus, S. P.; Carroll, J. T. *J. Org. Chem.* **1970**, *35*, 3768.

(8) Keifer, P. A.; Schwartz, R. E.; Koker, M. E. S.; Hughes, R. G., Jr.; Rittschof, D.; Rinehart, K. L. *J. Org. Chem.* **1991**, *56*, 2965.

(9) Initial acid cleavage led to an intermediate ester which upon treatment with base facilited acyl transfer producing amide **4**.

(10) The following typographical errors for ^{13}C chemical shift values in ref 1 are noted in a personal communication from Professor Kobayashi: C2 of slagenin A should be 120.7 ppm and the listed values for C8 of slagenins B and C should be interchanged.

(11) Faulkner, D. J. *Nat. Prod. Rep.* **2000**, *17*, 7 and earlier reports in this series.