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Stereocontrolled Assembly of the C3/C3′ Dideoxy Core of Lomaiviticin A/B and Congeners

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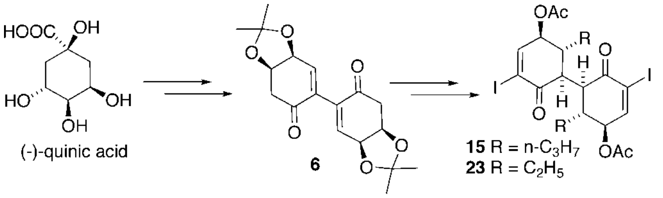
ABSTRACT



The dideoxy core (23) of lomaiviticinone and congener 15 were derived starting from (−)-quinic acid in a stereocontrolled fashion.

Lomaiviticins A and B are novel dimeric diazobenzofluorene glycosides isolated from the microorganism *Micromonospora lomaivitiensis* in 2001 (Figure 1),[1] reminiscent of the kinamycin family of antibiotics.[2] The more abundant lomaiviticin A demonstrated broad cytotoxicity (0.01 to 98 ng/mL) against a 24-cancer cell line panel in addition to displaying potent activity against Gram-positive bacteria. Based on their common structural characteristics, the lomaiviticins and kinamycins likely share a biosynthetic ancestry with the former incorporating a higher level of complexity by dimerization of the common tetracyclic ring system.[3] Unique to the kinamycin and lomaiviticin secondary metabolites is the incorporation of a diazoparaquinone functionality, presumably associated with the reported DNA damaging properties of lomaiviticins A and B.

The inspiring structure and biological properties of the lomaiviticins have not only drawn attention to these natural products but also rekindled interest in the chemical synthesis[4] and mechanism(s) of action[5] of the kinamycins. The remarkable architectural complexity exhibited by the lomaiviticins coupled with a need to provide further insight into the molecules' unique mode of action prompted our own efforts aimed at the total synthesis of these compounds and

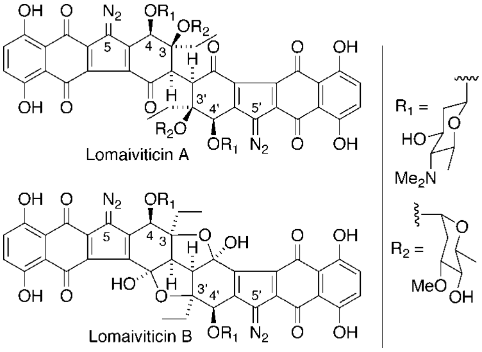


Figure 1. Structures of lomaiviticin A and B.

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(1) He, H. Y.; Ding, W. D.; Bernan, V. S.; Richardson, A. D.; Ireland, C. M.; Greenstein, M.; Ellestad, G. A.; Carter, G. T. *J. Am. Chem. Soc.* **2001**, *123*, 5362–5363.

(2) Marco-Contelles, J.; Molina, M. T. *Curr. Org. Chem.* **2003**, *7*, 1433–1442.

(3) Gould, S. J. *Chem. Rev.* **1997**, *97*, 2499–2509.

(4) (a) Lei, X. G.; Porco, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 14790–14791. (b) Nicolaou, K. C.; Li, H. M.; Nold, A. L.; Pappo, D.; Lenzen, A. *J. Am. Chem. Soc.* **2007**, *129*, 10356–10400. (c) Kumamoto, T.; Kitani, Y.; Tsuchiya, H.; Yamaguchi, K.; Seki, H.; Ishikawa, T. *Tetrahedron* **2007**, *63*, 5189–5199.

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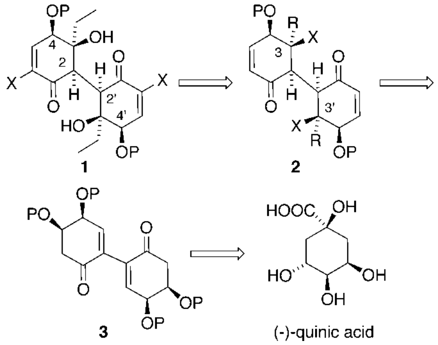
congeners. Herein, we describe a stereocontrolled assembly of the dideoxy core of the lomaiviticins and derivatives.

From a strategic standpoint, a total synthesis of lomaiviticinone (the aglycone of lomaiviticins A and B) requires two major issues to be addressed: these are assembly of the tetracyclic diazobenzofluorene ring system and stereocontrolled introduction of the central carbon−carbon bond. Recently, two groups have reported the total synthesis of kinamycin C demonstrating synthetic approaches to the tetracyclic ring system common to the kinamycins and lomaiviticins.[4a,b] In addressing the central carbon−carbon bond of the lomaiviticins, Nicolaou and Shair have independently described elegant stereocontrolled approaches toward core structures of lomaiviticinone.[6] A retrosynthetic representation of our approach to the central core **1** starting from (−)-quinic acid via bisenone **3** is shown in Scheme 1.

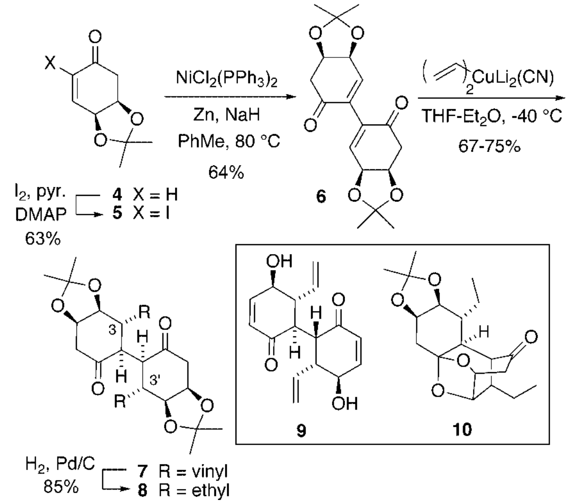
Scheme 1



We anticipated that local stereochemistry in bisenone **3** would assist in the stereocontrolled introduction of the C3/C3′ stereocenters. *As illustrated in Scheme 1, control of the C2−C2′ relative stereochemistry would rely on stereoselective protonation of intermediate enol(ate)s generated during the course of a conjugate addition of an organometallic reagent to bisenone* **3**.

Our synthesis began from (−)-quinic acid, which was converted to cyclohexenone **4** following a known five-step reaction sequence (Scheme 2).[7] α-Iodination[8] of **4** provided iodoenone **5** which was subject to a nickel(0)-catalyzed homocoupling employing reaction conditions described by Lin and Hong[9] to provide bisenone **6** in 64% yield. Addition of a higher-order cuprate derived from vinyllithium to **6** provided diketone **7** as a single stereoisomer (Scheme 2). Hydrogenation [H_2 (1 atm), 10% Pd/C, EtOAc] of **7** afforded **8** in 85% yield. Having served the purpose of enforcing stereoselectivity in the cuprate conjugate addition reaction, we planned to liberate the acetonide group by a base-induced elimination with simultaneous introduction of unsaturation appropriately positioned for bidirectional annulation of the remaining tetracyclic ring system. Surprisingly, treatment of diketones **7** and **8** with base resulted in quite different reaction pathways. First, treatment of **7** with DBU in benzene resulted in elimination of the acetonide group accompanied by epimerization of the C2 carbon to provide unsymmetrical bisenone **9** in 56% yield. In contrast, treatment of diketone **8** under identical reaction conditions produced the unusual cage compound **10** (49% yield), a product of interrupted bisfragmentation by Michael capture of an intermediate hemiacetal.[10]

Scheme 2



Based on the observation that minor differences in substituents located at C3/C3′ (i.e., vinyl versus ethyl) led to distinctive reaction pathways, we examined alternative approaches to the introduction of the C3/C3′ ethyl group and elimination of the acetonide group. To this end, conjugate addition of allyltributylstannane promoted by TBSOTf to bisenone **6** afforded bis-silylenol ether **11** in over 90% yield (Scheme 3).[11] Hydrogenation of **11** proceeded smoothly to provide the *n*-propyl derivative **12** in high yield. *We were pleased to discover treatment of* **12** *with an excess of TBAF in tetrahydrofuran afforded diol* **13**, *possessing the desired lomaiviticinone core stereochemistry.* Acetylation of **13** followed by iodination then delivered bisenone **15**. The structure of **15** was confirmed by single-crystal X-ray analysis.

Our next goal was to adjust this reaction sequence to deliver the C3/C3′ ethyl and hydroxyl groups common to lomaiviticinone. To this end, we examined a reaction sequence that would convert the allyl group to an ethyl group

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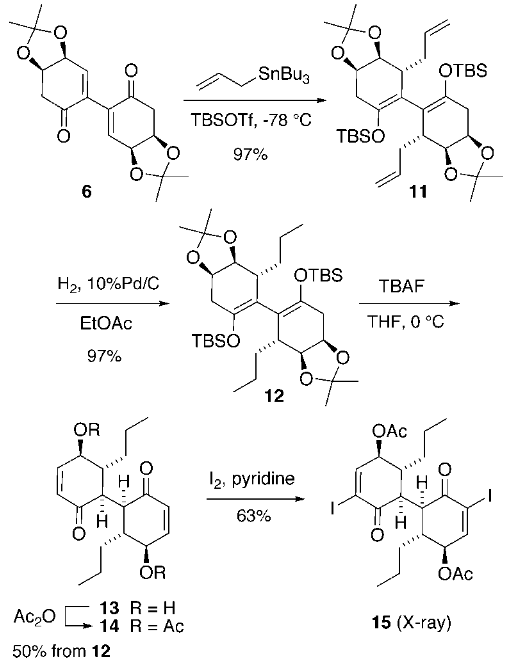
(5) (a) Laufer, R. S.; Dmitrienko, G. I. *J. Am. Chem. Soc.* **2002**, *124*, 1854–1855. (b) Feldman, K. S.; Eastman, K. J. *J. Am. Chem. Soc.* **2005**, *127*, 15344–15345. (c) Feldman, K. S.; Eastman, K. J. *J. Am. Chem. Soc.* **2006**, *128*, 12562–12573. (d) Zeng, W.; Ballard, T. E.; Tkachenko, A. G.; Burns, V. A.; Feldheim, D. L.; Melander, C. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5148–5151. (e) O'Hara, K. A.; Wu, X.; Patel, D.; Liang, H.; Yalowich, J. C.; Chen, N.; Goodfellow, V.; Adedayo, O.; Dmitrienko, G. I.; Hasinoff, B. B. *Free Radical Biol. Med.* **2007**, *43*, 1132–1144.

(6) (a) Nicolaou, K. C.; Denton, R. M.; Lenzen, A.; Edmonds, D. J.; Li, A.; Milburn, R. R.; Harrison, S. T. *Angew. Chem., Int. Ed.* **2006**, *45*, 2076–2081. (b) Krygowski, E. S.; Murphy-Benenato, K.; Shair, M. D. *Angew. Chem., Int. Ed.* **2008**, *47*, 1680–1684.

(7) Audia, J. E.; Boisvert, L.; Patten, A. D.; Villalobos, A.; Danishefsky, S. J. *J. Org. Chem.* **1989**, *54*, 3738–3740.

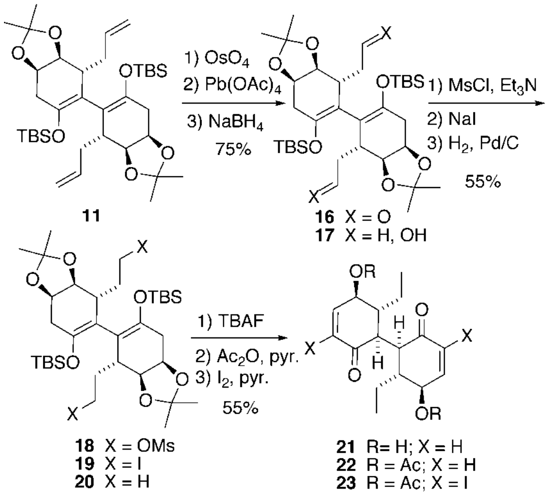
(8) Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W.; Wovkulich, P. M.; Uskokovic, M. R. *Tetrahedron Lett.* **1992**, *33*, 917–918.

Scheme 3



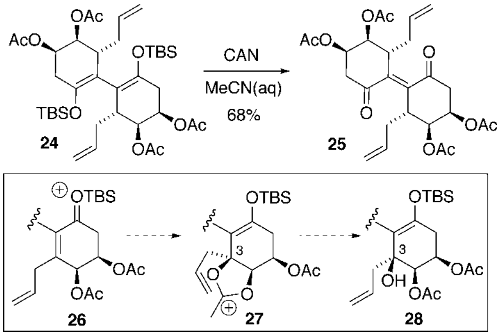
starting with a dihydroxylation/lead tetraacetate oxidation and reduction to afford diol **17** in 75% yield.[12] Mesylation of **17** followed by iodide substitution under Finkelstein conditions provided diiodide **19**, and hydrogenolyis (H_2, Pd/C) completed conversion of the allyl group to an ethyl substituent.[13] Treatment of **20** with excess tetrabutylammonium fluoride afforded **21**. Acetylation followed by iodination of **21** gave **23**, the core of dideoxy lomaiviticinone (Scheme 4).

Scheme 4



We examined introduction of the C3/C3′ hydroxyl groups by a novel oxidation−hydrolysis reaction to access the complete lomaiviticin core structure. Magnus has reported that the oxidation of hydrolytically stable silyl enol ethers leads to intermediate oxonium ions following proton loss that can be trapped by nucleophiles.[14] With this in mind, we examined CAN oxidation of bisacetate **24** (derived from **11** in two steps) with the expectation that the neighboring acetate group would participate in the solvolysis and lead to **28** via intermediate cation **27**. Unfortunately, the only isolated product was enone **25**, a result of oxidative desilylation (Scheme 5).

Scheme 5



In summary, we have developed a synthetic sequence leading to the stereocontrolled construction of the dideoxy core of lomaiviticin as well as various congeners (cf. **15**). We are currently pursuing the total synthesis of dideoxy lomaiviticinone. We anticipate, based on the excellent cytotoxic properties and unique mode of action of lomaiviticinone, that these deriviatives will provide insight into the biological properties of this unique natural product.

Acknowledgment. We thank the National Institutes of Health (GM067726-05) for their support of this research. We also thank Joseph Reibenspies (Center for Chemical Characterization and Analysis, Texas A&M University) for determining the X-ray crystal structure of **15**.

Supporting Information Available: Experimental procedures, complete spectroscopic data, and ^{1}H and ^{13}C NMR spectra for all new compounds and CIF files for **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Lin, G. Q.; Hong, R. *J. Org. Chem.* **2001**, *66*, 2877–2880.

(10) The structure of **10** was assigned based on extensive NMR analysis. See Supporting Information for full details.

(11) Kim, S.; Lee, J. M. *Synth. Commun.* **1991**, *21*, 25–29.

(12) (a) Wipf, P.; Kim, Y.; Goldstein, D. M. *J. Am. Chem. Soc.* **1995**, *117*, 11106–11112. (b) Ginn, J. D.; Padwa, A. *Org. Lett.* **2002**, *4*, 1515–1517.

(13) To date, attempts to convert **6** directly to **20** by cuprate conjugate addition and trapping of the intermediate enolate with a silylating agent have failed.

(14) Magnus, P.; Lacour, J.; Evans, P. A.; Roe, M. B.; Hulme, C. *J. Am. Chem. Soc.* **1996**, *118*, 3406–3418.