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Synthesis of the C4-*Epi*-Lomaivitician B Core Reveals Subtle Stereoelectronic Effects

Amy S. Lee and Matthew D. Shair*

Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford Street, Cambridge, Massachusetts 02138, United States

shair@chemistry.harvard.edu

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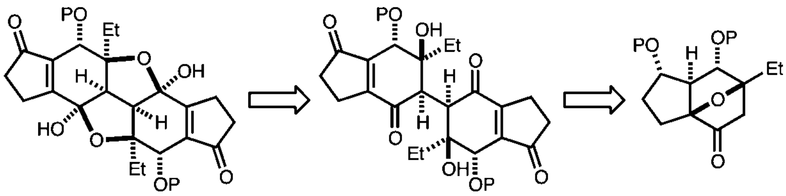
ABSTRACT



Lomaivitician B Core **Lomaivitician A Core**

An efficient synthesis of the C4-*epi*-lomaivitician B core is reported. The synthesis features a diastereoselective anionic formal furan Diels–Alder reaction and a stereoselective oxidative enolate dimerization. During the investigation, subtle yet critical stereoelectronic effects imparted by the C4-stereocenter were observed.

The lomaiviticins comprise a family of type-II polyketide natural products with remarkable C_2-symmetric structures (Figure 1). They were isolated from a strain of actinomycetes, *Micromonospora lomaivitiensis*, and exhibit an array of biological activity.[1] Lomaivitician A (**1**) is potently cytotoxic toward 24 cultured cancer cell lines with IC_{50} values ranging from 0.007 to 72 nM. Furthermore, both **1** and lomaivitician B (**2**) are antibiotics against Gram-positive bacteria.

The structural complexity of **1** and **2** poses several synthetic challenges. The highly oxidized carbon skeleton includes up to four 2-deoxyglycosides, and the central C2–C2′ bond links two densely functionalized halves to generate up to eight contiguous stereocenters. Each monomeric half possesses an unusual diazofluorene system, a naphthazarin, and a β-alkoxyenone subunit.[2] Altogether, these features render the lomaiviticins challenging targets.

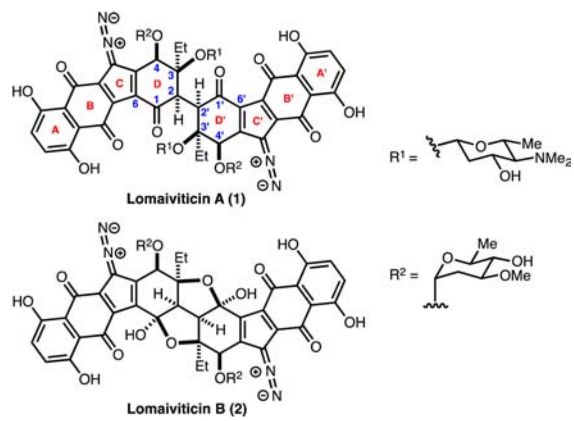


Figure 1. Structures of lomaivitician A (**1**) and B (**2**).

Indeed, despite efforts by various groups,[3,4] only one synthesis of the aglycon (**3**, Scheme 1) has been accomplished to date.[5]

Our retrosynthetic analysis of the lomaivitician aglycon (**3**) is outlined in Scheme 1. We envisioned that the

(1) (a) He, H.; 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. (b) Woo, C. M.; Beizer, N. E.; Janso, J. E.; Herzon, S. B. *J. Am. Chem. Soc.* **2012**, *134*, 15285–15288.

(2) β-Alkoxyenone may undergo an elimination–aromatization pathway.

(3) (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) Nicolaou, K. C.; Nold, A. L.; Li, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 5860–5863. (c) Zhang, W.; Baranczak, A.; Sulikowski, G. A. *Org. Lett.* **2008**, *10*, 1939–1941. (d) Feldman, K. S.; Selfridge, B. R. *Org. Lett.* **2012**, *14*, 5484–5487.

(4) (a) Krygowski, E. S.; Murphy-Benenato, K.; Shair, M. D. *Angew. Chem., Int. Ed.* **2008**, *47*, 1680–1684. (b) Lee, H. G.; Ahn, J. Y.; Lee, A. S.; Shair, M. D. *Chem. Eur. J.* **2010**, *16*, 13058–13062.

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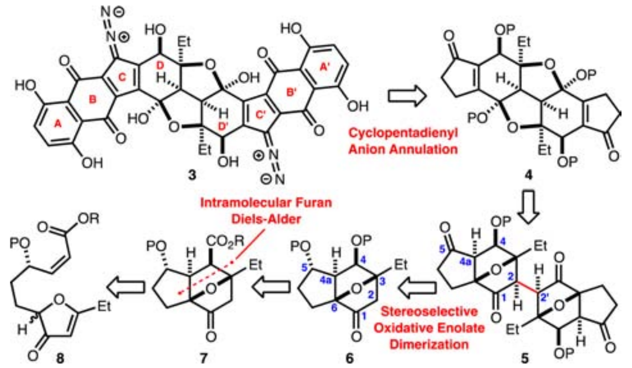
Scheme 1. Retrosynthetic Analysis of Lomaiviticin Aglycon (**3**)



AB/A′B′-naphthalenes of **3** could be constructed from lomaiviticin B core **4** via a late-stage cyclopentadienyl anion bisannulation.[6] **4** could arise from oxanorbornanone dimer **5**, where the key C2−C2′ bond would be established through a stereoselective oxidative enolate dimerization of monomer **6**. The oxanorbornanone system could be constructed from an intramolecular *exo*-selective furan Diels−Alder reaction of a suitable precursor.

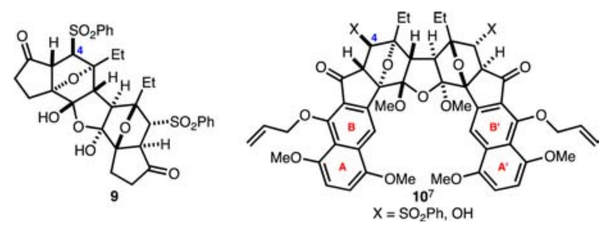
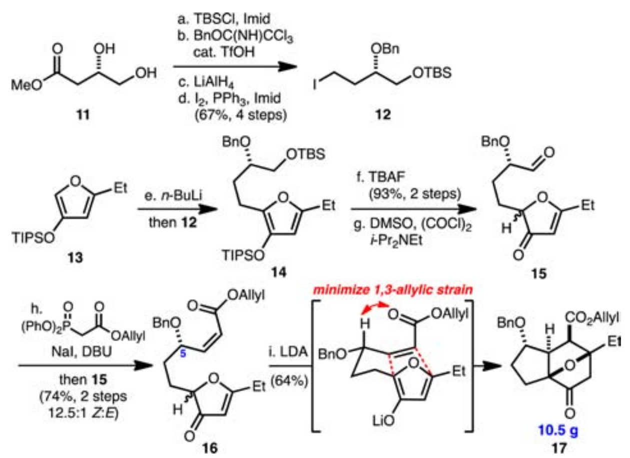


Figure 2. Previous work from the Shair group.[7,8]

Arguably, the stereoselective construction of the key C2−C2′ bond presents the most formidable obstacle in designing a route toward the lomaiviticins. Constructing the C2−C2′ bond via a dimerization strategy is complicated by two critical challenges: (1) a high potential for β-elimination of the C3-alkoxy group from a C1−C2 enolate and (2) difficulty in achieving stereoselective formation of the C2/C2′-stereocenters. To address this, our lab has developed a strategy utilizing the oxidative enolate dimerization of an oxanorbornanone system.[4] Stereoselective formation of the C2-stereocenter is controlled by dimerization of the enolate from the less hindered convex *exo* face of the oxanorbornanone. In the oxanorbornanone system, β-elimination is prevented due to the nearly orthogonal orientation of the endocyclic enolate (C1−C2) π-system with the antibonding σ^*-orbital of the bridging C−O bond (**6**, Scheme 1).[9] An exocyclic enolate (C5−C4a) of **5**, however, would have greater conformational flexibility and can thus achieve requisite orbital overlap for β-elimination.[10] We exploited this stereoelectronic dichotomy of the oxanorbornanone system successfully in our initial reported studies[4a] and achieved stereoselective oxidative enolate dimerization without β-elimination. Furthermore, we were able to subsequently fragment the oxygen bridge of **9** (Figure 2). However, displacement of the C4-phenylsulfone with various oxygen nucleophiles was low-yielding and the corresponding product could not be converted to the lomaiviticin core from the cyclic hydrate.

Unexpectedly, in our most recently published work,[4b] we were unable to fragment the oxygen bridge of the full aglycon carbon skeleton **10** (Figure 2). We attributed the unsuccessful fragmentation to the additional strain and rigidity that the AB/A′B′-naphthalenes introduce to the system. Predicated on the two aforementioned observations, we embarked on a new route to synthesize a substrate with the correct C4-stereochemistry (Scheme 1, **5**) and planned to introduce the naphthalene system after oxygen bridge fragmentation.

Scheme 2. Intramolecular *Exo*-Selective Furan Diels−Alder Reaction[a]



[a] Conditions: (a) TBSCl, Imid, CH_2Cl_2, 0 °C, 94%; (b) BnOC(NH)CCl_3, cat. TfOH, Et_2O, rt, 81%; (c) $LiAlH_4$, THF, −40 °C, 94%; (d) I_2, PPh_3, Imid, CH_2Cl_2, rt, 88%; (e) *n*-BuLi, THF, −78 → 0 °C; **12**, −78 → 0 °C; (f) TBAF, THF, 0 °C → rt, 93% (2 steps); (g) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C; *i*-Pr_2NEt, −78 → −20 °C; (h) NaI, DBU, THF, 0 °C; then **15**, −78 °C, 74% (2 steps, 12.5:1 *Z*:*E*); (i) LDA, THF, −78 °C, 64%.

The synthesis commenced with the selective TBS-protection of the primary hydroxyl of diol **11**, which can be readily synthesized in two steps from (*S*)-malic acid (Scheme 2).[11] Benzyl protection of the secondary hydroxyl

(5) (a) Herzon, S. B.; Lu, L.; Woo, C. M.; Gholap, S. L. *J. Am. Chem. Soc.* **2011**, *133*, 7260–7263. (b) Woo, C. M.; Gholap, S. L.; Lu, L.; Kaneko, M.; Li, Z.; Ravikumar, P. C.; Herzon, S. B. *J. Am. Chem. Soc.* **2012**, *134*, 17262–17273.

(6) Birman, V. B.; Zhao, Z.; Guo, L. *Org. Lett.* **2007**, *9*, 1223–1225.

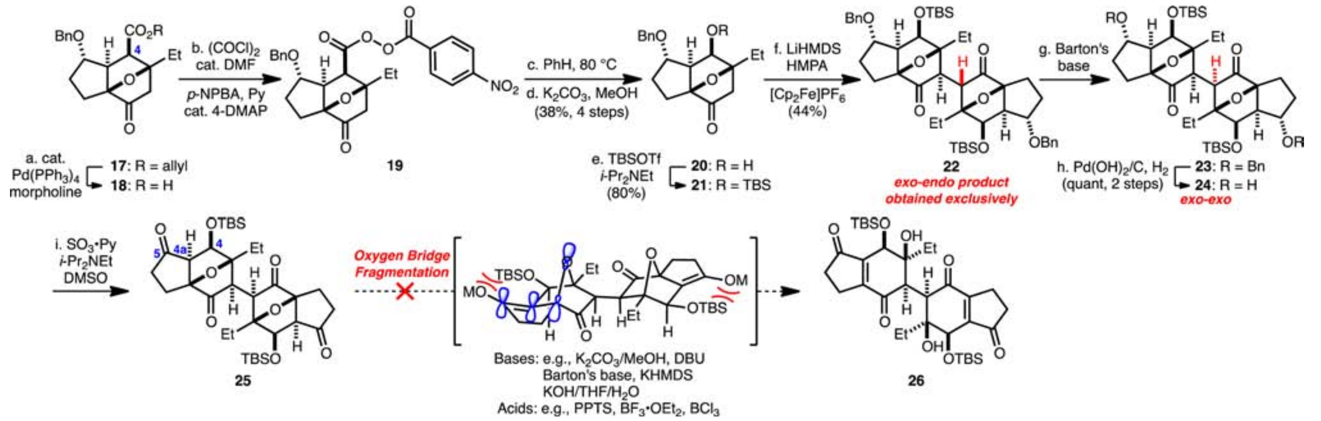
(7) Lee, H. G. Ph.D. Thesis, Harvard University, 2012.

(8) Compounds **9** and **10** have stereochemistry corresponding to the enantiomer of the natural product.

(9) (a) Tojo, S.; Isobe, M. *Synthesis* **2005**, 1237–1244. (b) Jackson, S. R.; Johnson, M. G.; Mikami, M.; Shiokawa, S.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 2694–2697. (c) Vogel, P.; Cossy, J.; Plumet, J.; Arjona, O. *Tetrahedron* **1999**, *55*, 13521–13642.

(10) (a) McMorris, T. C.; Staake, M. D.; Kelner, M. J. *J. Org. Chem.* **2004**, *69*, 619–623. (b) Jung, M. E.; Min, S. J. *Tetrahedron* **2007**, *63*, 3682–3701. (c) Krygowski, E. S. Ph.D. Thesis, Harvard University, 2008. See Supporting Information (Figure 1) for more details.

Scheme 3. Stereoselective Oxidative Enolate Dimerization and Attempted Oxygen Bridge Fragmentation[a]



[a] Conditions: (a) 10 mol % $Pd(PPh_3)_4$, morpholine, THF, rt; (b) $(COCl)_2$, cat. DMF; *p*-NPBA, Py, cat. 4-DMAP, CH_2Cl_2, 0 °C; (c) PhH, 80 °C; (d) K_2CO_3, MeOH, 0 °C, 38% (4 steps); (e) TBSOTf, *i*-Pr_2NEt, CH_2Cl_2, 0 °C → rt, 80%; (f) LiHMDS, HMPA, THF, −78 °C; then $[Cp_2Fe]PF_6$, −78 → −55 °C, 4 d, 44%; (g) 2-*tert*-butyl-1,1,3,3-tetramethylguanidine (Barton's base), MeCN, −5 °C; (h) $Pd(OH)_2/C$, H_2, THF, rt, quant (2 steps); (i) SO_3•Py, *i*-Pr_2NEt, DMSO, CH_2Cl_2, −10 °C.

group, reduction of the methyl ester, and formation of the corresponding iodide occurred smoothly to yield alkyl iodide **12**. Lithiation of furan **13**, followed by alkylation with **12**, afforded coupled product **14**, which upon global silyl deprotection with TBAF, provided the corresponding furanone alcohol (93%, two steps). Swern oxidation then cleanly delivered aldehyde **15**.

Aldehyde **15** was then converted to (*Z*)-enoate **16** (12.5:1 *Z*/*E*), the Diels−Alder substrate, via a *Z*-selective modified Horner−Emmons reaction.[12] We anticipated that the stereoselectivity of the *exo*-selective[13] intramolecular furan Diels−Alder reaction would be controlled by the single C5-stereocenter, which enforces a conformation where 1,3-allylic strain is minimized. Initial attempts to promote the Diels−Alder reaction by conventional thermal and Lewis acidic conditions failed to provide the desired cycloadduct in synthetically useful yields. We rationalized that tautomerization of the furanone to the requisite furan may be slow and that basic conditions may therefore promote the desired transformation. We discovered that treatment of **16** with LDA[14] provided the Diels−Alder product **17** in 64% yield as a 10:1 mixture of separable diastereomers, favoring the expected *cis*-5,5 fusion product. This process presumably occurs via a stepwise Michael−Michael reaction sequence. We were able to prepare over 10 g of **17** using this protocol.

(11) (a) Gaunt, M. J.; Jessiman, A. S.; Orsini, P.; Tanner, H. R.; Hook, D. F.; Ley, S. V. *Org. Lett.* **2003**, *5*, 4819–4822. (b) Saito, S.; Ishikawa, T.; Kuroda, A.; Koga, K.; Moriwake, T. *Tetrahedron* **1992**, *48*, 4067–4086.

(12) Ando, K.; Oishi, T.; Hirama, M.; Ohno, H.; Ibuka, T. *J. Org. Chem.* **2000**, *65*, 4745–4749.

(13) The *exo* transition state, which results in *cis*-5,5 fusion product **17**, should be favored over the *endo* transition state, which would result in a highly strained *trans*-5,5 fusion product.

(14) Caine, D. S.; Paige, M. A. *Synlett* **1999**, *9*, 1391–1394.

(15) (a) Denney, D. B.; Sherman, N. *J. Org. Chem.* **1965**, *30*, 3760–3761. (b) Fujimori, K.; Shigeru, O. *J. Chem. Soc., Perkin Trans. 2* **1989**, 1335–1348. (c) Meng, Z.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 1511–1513.

With **17** in hand, an oxidative "carboxy-inversion" sequence for converting the C4-ester to a hydroxyl with retention of configuration was required (Scheme 3).[15] First, the allyl ester of Diels−Alder product **17** was readily deprotected to carboxylic acid **18**. Next, *p*-nitroperbenzoic acid (*p*-NPBA) was coupled to carboxylic acid **18** via the acid chloride intermediate to afford crude diacyl peroxide **19**, which underwent an ionic rearrangement ("carboxy-inversion") upon heating to afford the corresponding acyl carbonate species. Methanolysis of this crude intermediate provided the desired secondary carbinol **20** as a single diastereomer (38%, four steps). Protection of **20** as a TBS ether yielded the dimerization precursor, monomer **21**. Utilizing the optimal oxidative enolate dimerization conditions developed in our group, ketone **21** was added to LiHMDS and HMPA in THF at −78 °C to generate the corresponding lithium enolate, which was then exposed to $[Cp_2Fe]PF_6$ and allowed to stir at −55 °C for 4 days. Contrary to our prior studies where only *exo*-*exo* dimerization was observed,[4] *exo*-*endo* dimer **22** was obtained exclusively (44%). It appears that although dimerization occurs with complete *exo* facial selectivity in the absence of any substitution on the oxanorbornanone carbon framework, the C4-substituent (pseudoaxial sulfone) plays a crucial role in reinforcing the *exo*-*exo* selectivity in our prior more complex polycyclic systems.[4] Fortunately, **22** could be selectively epimerized to the *exo*-*exo* dimer **23** by treatment with Barton's base.

With *exo*-*exo* dimer **23** in hand, the benzyl ethers were cleaved and the corresponding diol **24** was oxidized to afford 1,4-diketone dimer **25**. Fortuitously, **25** did not exist as a cyclic hydrate if silica gel column chromatography was avoided, which is in contrast to our previous systems[4] (Figure 2) where the analogous C5-ketone substrates existed exclusively as the cyclic hydrates. This suggests that the C4-stereochemistry has subtle yet far-reaching stereoelectronic consequences on the system. Unfortunately, all attempts to fragment the oxygen bridge were unsuccessful. In all cases, either nonspecific decomposition or no reaction was observed.[16] Surprisingly, deuterium incorporation studies (KOD in THF) revealed 100% deuterium incorporation at C4a of **25**. Unlike the original successful model studies where the dimer contained a pseudoaxial C4-phenylsulfone (Figure 2, **9**), we rationalized that fragmentation is disfavored due to a 1,3-allylic interaction between the enolate (C5–C4a) oxygen of **25** and the pseudoequatorial C4-TBS-ether that must occur during the transition state in order to achieve proper orbital overlap for fragmentation to occur. Unfortunately, moving to a sterically smaller protecting group (MOM) and even the free hydroxyl did not remedy this problem.

In line with our hypothesis, we rationalized that the C4-epimer of **25** would not suffer from an unfavorable 1,3-allylic-type interaction during oxygen bridge fragmentation. To this end, **18** was subjected to a one-pot Barton radical decarboxylation–oxidation reaction (Scheme 4). First, the Barton ester was formed from carboxylic acid **18** by using *S*-(1-oxido-2-pyridinyl) 1,1,3,3-tetramethylthiouronium hexafluorophosphate (HOTT).[17] Upon complete formation of the Barton ester, the reaction was saturated with O_2 and $Sb(SPh)_3$ was added.[18] This protocol afforded alcohol **27** as a 2:1 mixture of diastereomers, favoring the desired epimer in 46% isolated yield.[19] Protection of **27** as a TBS ether then yielded the dimerization precursor, monomer **28**.

Oxanorbornanone **28** underwent successful oxidative enolate dimerization to exclusively provide *exo*-*exo* dimer **29**. Benzyl ether cleavage and subsequent oxidation afforded cyclic hydrate **31**, which gratifyingly underwent successful fragmentation upon treatment with KOH at 0 °C, confirming our suspicion that the C4-stereocenter has far-reaching stereoelectronic effects. Bisenone product **32** was then converted to C4-*epi*-lomaiviticin B core **34** in two steps, involving (1) dehydration of cyclic hydrate **32** in the presence of $MgSO_4$ to yield C4-*epi*-lomaiviticin A core **33** and (2) stirring **33** with catalytic *p*-TsOH to provide C4-*epi*-lomaiviticin B core **34** (62%, three steps).

In summary, we have reported a synthesis of the C4-*epi*-lomaiviticin A and B cores, the first time this has been achieved in our lab. Noteworthy transformations include

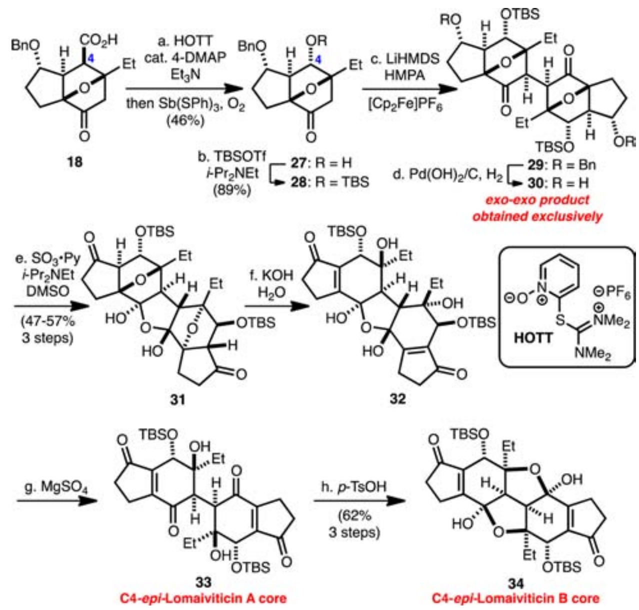
(16) Even the cyclic hydrate form of **25**, which can be readily accessed by exposure to KOH in H_2O/THF, did not undergo the desired fragmentation.

(17) Garner, P.; Anderson, J. T.; Dey, S. *J. Org. Chem.* **1998**, *63*, 5732–5733.

(18) (a) Barton, D. H. R.; Bridon, D.; Zard, S. Z. *Tetrahedron* **1989**, *45*, 2615–2626. (b) Zhu, J.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron* **1995**, *51*, 5099–5116.

(19) Use of the more conventional Barton radical decarboxylation–oxidation conditions (Barton ester formation, followed by exposure to O_2, *t*-BuSH, and a sunlamp, then reduction with PPh_3) afforded the alcohol product in a higher 4:1 dr, but in a somewhat lower isolated yield of the desired diastereomer (37–40%).

Scheme 4. Successful Oxygen Bridge Fragmentation and Conversion to C4-*Epi*-Lomaiviticin A (**33**) and B (**34**) Cores[a]



[a] Conditions: (a) HOTT, cat. 4-DMAP, Et_3N, THF; then $Sb(SPh)_3$, O_2, rt, 46%; (b) TBSOTf, *i*-Pr_2NEt, CH_2Cl_2, 0 °C → rt, 89%; (c) LiHMDS, HMPA, THF, −78 °C; then $[Cp_2Fe]PF_6$, −78 → −60 °C, 5 d; (d) $Pd(OH)_2$/C, H_2, THF, rt; (e) SO_3•Py, *i*-Pr_2NEt, DMSO, CH_2Cl_2, 0 °C → rt, 47–57% (3 steps); (f) KOH, 3:1 THF/H_2O, 0 °C; (g) $MgSO_4$, PhH, 80 °C; (b) *p*-TsOH, PhH, rt, 62% (3 steps).

an intramolecular *exo*-selective furan Diels–Alder reaction to construct the oxanorbornanone system, a stereoselective oxidative enolate dimerization to establish the key C2–C2′ bond, and successful oxygen bridge fragmentation to generate the lomaiviticin core. Crucial to the success of our oxygen bridge fragmentation was the discovery of a subtle stereoelectronic effect imparted by the C4-stereocenter, which necessitated the synthesis of a substrate with the opposite C4-stereochemistry to that found in the natural product. Current efforts are now focused on the elaboration of the lomaiviticin B core **34** to the full carbon skeleton of the aglycon and will be reported in due course.

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Supporting Information Available. Experimental procedures, spectroscopic data, and copies of ^1H and ^{13}C NMR. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.