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

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ABSTRACT

An efficient synthesis of the C4-epi lomaiviticin 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 C2-symmetric structures (Figure 1). They were isolated from a strain of actinomycetes, Micromonospora lomaivitiensis, and exhibit an array of biological activity.1 Lomaiviticin A (1) is potently cytotoxic toward 24 cultured cancer cell lines with IC50 values ranging from 0.007 to 72 nM. Furthermore, both 1 and lomaiviticin 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 lomaiviticin 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 lomaiviticin aglycon (3) is outlined in Scheme 1. We envisioned that the

(2) β-Alkoxyenone may undergo an elimination-aromatization pathway.
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 enolate dimerization of monomer 6. The oxanorbornanone system could be constructed from an intramolecular \textit{exo}-selective furan Diels–Alder reaction of a suitable precursor.

![Figure 2. Previous work from the Shair group.](image)

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). Benzyl protection of the secondary hydroxyl...
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)-enolate 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-selective13 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 LDA14 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.

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. Methanalysis 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 [Cp₂Fe]PF₆ 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 oxanorbornane carbon framework, the C4-substituent (pseudoauxial sulfone) plays a crucial role in reinforcing the exo-exo selectivity in our prior more complex polycyclic systems.4 Fortunately, 22 could be selectively equilibrated 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 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 systems4 (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 stereo-electronic consequences on the system. Unfortunately, all

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(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.


The authors declare no competing financial interest.

In all cases, either nonspecific decomposition or no reaction was observed.\textsuperscript{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 $S_{1}(1$-oxido-2-pyridinyl) 1,1,3,3-tetramethyl-thiouremine hexafluorophosphate (HOTT).\textsuperscript{17} Upon complete formation of the Barton ester, the reaction was saturated with O$_2$ and Sb(SPh)$_3$ was added.\textsuperscript{18} This protocol afforded alcohol 27 as a 2:1 mixture of diastereomers, favoring the desired epimer in 46\% isolated yield.\textsuperscript{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 \degree C, confirming our suspicion that the C4-stereocenter has far-reaching stereoelectronic effects. Bisenone product 32 was then converted to C4-\textit{epi}-lomaiviticin B core 34 in two steps, involving (1) dehydration of cyclic hydrate 32 in the presence of MgSO$_4$ to yield C4-\textit{epi}-lomaiviticin A core 33 and (2) stirring 33 with catalytic $p$-TsOH to provide C4-\textit{epi}-lomaiviticin B core 34 (62\%, three steps).

In summary, we have reported a synthesis of the C4-\textit{epi}-lomaiviticin A and B cores, the first time this has been achieved in our lab. Noteworthy transformations include an intramolecular exo-selective furan Diels–Alder reaction to construct the oxanorbornanone system, a stereo-selective 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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\textbf{Supporting Information Available.} Experimental procedures, spectroscopic data, and copies of \textsuperscript{1}H and \textsuperscript{13}C NMR. This material is available free of charge via the Internet at http://pubs.acs.org.

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