Enantioselective Synthesis of the Lomaiviticin Aglycon Full Carbon Skeleton Reveals Remarkable Remote Substituent Effects During the Dimerization Event

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Lomaiviticin A (1) and lomaiviticin B (2) are novel C2-symmetric diazobenzofluorene glycoside marine natural products (Figure 1).[1] Lomaiviticin A (1) potently inhibits the growth of cultured cancer cell lines (GI50 values ranging from 0.007 nM to 72.0 nM), and both 1 and 2 exhibit impressive growth inhibition activity against Gram-positive bacteria. Compound 1 causes damage to DNA in vitro. It has been speculated that a reactive species derived from the diazenobenzofluorenone of 1 and 2 causes damage to nucleic acids, leading to the cytotoxic activities of these molecules. Experimental studies have provided support for the formation of reactive species from diazenofluorenone structures.[2] However, it remains to be determined how the full structures of 1 and 2 react under physiologically relevant conditions and what cellular components are perturbed by 1 and 2.

The structures of 1 and 2 are unprecedented and striking. The unusual structures of 1 and 2 pose interesting questions about how they are biosynthesized, especially how the C2-C2' bond is made, and questions about how to achieve syntheses of these molecules. Although a synthesis of 1 or 2 has not yet been achieved, many approaches to these molecules have been reported,[3] including our own enantioselective synthesis of the central (C-D-D'-C') ring system of 1.[4] A synthesis of the full carbon skeleton of 1 and 2 has not yet been accomplished. To achieve syntheses of 1 and 2, there are significant challenges to overcome; the most difficult of which is likely formation of the C2-C2' o-bond (Figure 1, see red bond). The C2-C2' bond links two highly functionalized ‘halves’ of 1 and 2, which closely resemble the related natural product kinamycins.[5] The congested environment surrounding the C2-C2' bond, stereochemical control during bond formation, and the potential lability of the D and D' rings render the formation of this bond extremely challenging. Late-stage dimerization and formation of the C2-C2' bond, in which double-processing is kept at a minimum, would be the most efficient means of synthesizing 1 and 2. Since the C2-C2' bond in 1 and 2 is part of a 1,4-diketone (C1-C2-C2'-C1'), a late-stage oxidative enolate coupling would be the ideal reaction to construct this bond. However, the high potential for β-elimination of the C3 tertiary carbonyl from a C1-C2 enolate, coupled with the likely poor stereoselectivity of such an oxidative enolate coupling reaction, renders this approach unattractive. To circumvent these obstacles, we developed a strategy utilizing the oxidative enolate coupling of 7-oxanorbornanones to achieve the first enantioselective synthesis of the central ring system of the aglycon of 1 (Scheme 1, see black structures in brackets). The 7-oxanorbornanone structure prevents β-elimination at C3 due to stereoelectronic effects, and it provides perfect diastereoselectivity during the formation of the C2-C2' bond due to double diastereodifferentiation in the dimerization event. Herein we report stereoselective coupling of the monomeric units of 1 and 2 leading to the first synthesis of the full carbon skeleton of the aglycons of 1 and 2. During the course of these studies, remarkable remote substituent effects during the key dimerization reaction have been observed, which may further complicate future syntheses of 1 and 2.

As stated, our synthesis plan is to perform an oxidative dimerization of the enolate of 4 to afford 3 (Scheme 1). An annulation reaction[3] between enone 5 and a known cyanophthalide reagent[6] would provide access to 4 (Scheme 3, 12). Enone 5 would be accessible from intermediate 6, a compound for which we had previously developed an enantioselective synthesis. Initially, an anionic annulation reaction on an enone similar to 5, but with C1 at the ketone oxidation state,
was attempted. Unfortunately, the basic conditions of the annulation were not compatible with the C1 ketone. Therefore, we were forced to use NaBH₄ to reduce the ketone (Scheme 2). Surprisingly, 7 was obtained as the major product when the reduction was performed in allyl alcohol solvent (Scheme 2). We speculate that transesterification of the oxazolidinone chiral auxiliary occurs from the boronate of allyl alcohol. Quenching the remaining borohydride with acetone allowed us to isolate 7 in 89% yield. Protecting group manipulation of 7 afforded 8. The C5 carbonyl of compound 8 was then oxidized under standard Swern conditions. Surprisingly, the product was obtained as the chlorinated β-ketoester 9 [7].

The reductive dechlorination of 9 with Zn afforded β-ketoester 10, which underwent decarboxylative deallylation [8] upon exposure to PdCl₂(PPh₃)₄ and nBu₂SnH, furnishing ketone 11 in 85% yield. Finally, α-phenylselenation of the enolate of 11, followed by oxidation, delivered enone 5 [9].

Scheme 3. Synthesis of dimerization precursors 16a and 16b. Reagents and conditions: a) NaBH₄, allyl alcohol, –78 °C, 5 min; then acetone, 23 °C, 15 min, 89%; b) PivCl, pyridine, CH₂Cl₂, 40 °C, 24 h; c) TBAF, THF, 23 °C, 16 h, 91% over two steps; d) DMSO, (COCl)₂, –78 °C 30 min; then Et₃N, 23 °C, 30 min; e) Zn dust, AcOH, 23 °C, 2 h, 96% over two steps; f) PdCl₂(PPh₃)₄, nBu₂SnH, AcOH, toluene, 0 °C, 36 min; then 110 °C, 30 min, 85%; g) LHMDS, THF, –78 °C, 30 min; then PhSeBr, –78 °C, 5 min; then H₂O₂, CH₂Cl₂/THF (1:1), 0 °C, 45 min, 73%. Piv = trimethylacetyl, TBAF = tetrabutylammonium fluoride, THF = tetrahydrofuran, DMSO = dimethyl sulfoxide, LHMDS = lithium bis(trimethylsilyl)amide.

For the key annulation reaction, we used the cyanophthalide method developed by Kraus [10] (Scheme 3). Addition of the anion of 12 to enone 5 afforded hydroquinone 13a in 85% yield. The C5 ketone of 13a was protected as a dioxolane. [11] Protection of the two phenols of 14a as their corresponding allyl ethers (compound 15a), followed by reductive cleavage of the pivaloyl group, and subsequent oxidation at C1 afforded ketone 16a, setting the stage for the key oxidative enolate coupling.

For synthesis of the C-D-D'-C' central ring system of 1 and 2, we had developed conditions for the oxidative enolate coupling reaction involving deprotonation of the ketone with LHMDS at –78 °C, addition of Cp₃FePF₃, and warming to –60 °C. [12] We then applied these conditions to the oxidative dimerization of ketone 16a (Scheme 4). Unfortunately, none of the desired dimer (17a) was formed under these conditions, and only starting material 16a or decomposed material was isolated (Scheme 4).

Scheme 4. Attempted oxidative dimerization of 16a. Reagents and conditions: a) LHMDS, HMPA, THF, –78 °C, 2 h; then Cp₃FePF₃, –60 °C, 72 h, 0%. LHMDS = lithium bis(trimethylsilyl)amide, HMPA = hexamethylphosphoramide, Cp₃FePF₃ = ferrocenium hexafluorophosphate.

In light of these disappointing results, we tried to rationalize why our C-D ring system published earlier underwent successful dimerization, but the A-D ring system here failed to dimerize. We speculated that non-bonded interactions may be developing in the
transition state, which could be inhibiting dimerization. Since little is known about the mechanism of this reaction and the trajectory by which substrates approach each other, we attempted to understand possible developing non-bonded interactions in the transition state by studying the ground state conformations of the desired product (compound 17a).\cite{13}

We examined compound 17a (Figure 2) and each of the three staggered conformations about the C2-C2' bond, specifically H2-H2' dihedral angles of 60°, 180°, and −60° (see Figure 2). The conformation with a H2-H2' dihedral angle of 180° adopted an ‘n’ conformation, the name of which is given because the shape of the conformer resembles that of the letter ‘n’. This conformer appeared to be very high in energy and unlikely to be a relevant conformer since the C3 and C3' ethyl groups were suffering from severe non-bonded interactions. The 60° H2-H2' dihedral angle conformation also exists in an ‘n’ conformation, but it does not suffer from the destabilizing C3-C3' ethyl interactions. However, we did notice potential non-bonded interactions between the C11 and C11' allyloxy groups (see red arrow). Finally, the −60° H2-H2' dihedral angle conformation exists in a ‘z’ conformation, which was also given due to the resemblance to the letter ‘z’ in shape, and in this conformation non-bonded interactions may develop between C11 (and C11') allyloxy groups and the C3' (and C3) ethyl groups. Since in both the ‘n’ and ‘z’ conformations, the C11 (and C11') allyloxy groups may be preventing dimerization, we decided to synthesize the tetracyclic dimerization precursor where the C11 allyloxy group is replaced with a hydrogen atom (16b, R= H). This forced us to devise a new annulation strategy to access this structure from enone 5.

Figure 2. Postulated steric interactions in the dimeric products.

To construct 16b, where the C11 substituent is a hydrogen atom, we synthesized Hauser-type sulfoxide annulation partner 18 (Scheme 3).\cite{14}

Deprotonation of 18 with LHMDS at −60 °C, followed by exposure to enone 5, delivered phenol 13b in 79% yield. It is worth noting that the use of the phenyl ester of 18, compared to the more commonly used methyl ester, dramatically enhanced the rate and yield of the annulation reaction—a finding that may be useful in other applications of this reaction.\cite{15}

Following the process we developed previously, 13b was converted to dioxolane 14b. Allyl protection of the phenol to afford 15b, followed by cleavage of the C1 pivaloyl group, and subsequent oxidation, delivered ketone 16b. With ketone 16b in hand, we again attempted to perform oxidative enolate coupling under identical conditions (LHMDS, HMPA, Cp3FePF6, −60 °C, THF). We were gratified to find that oxidative dimerization of 16b afforded 17b in 80% yield as a single diastereomer (Scheme 5).

To confirm the relative stereochemistry at C2 and C2’, and to determine the conformation of dimeric structure 17b, we set out to obtain an X-ray crystal structure. Fortunately, we discovered that removal of the allyl groups of 17b afforded 19 as a crystalline solid (Scheme 5), which was subjected to X-ray crystallographic analysis to provide the structure shown in Figure 3.\cite{16} The crystal structure confirmed that the correct C2-C2’ stereochemistry had been established and also that the compound can exist in an ‘n’ conformation.

Closer inspection of the X-ray crystal structure revealed that the C11 hydrogen atom is in close proximity to the C1’ ketone oxygen atom (and conversely the C1’ hydrogen and C1 ketone oxygen; see Figure 4). In fact, the interatomic distance between H11 and O1’ (and H11’ and O1) is only 0.29 Å greater than the sum of their van der Waals radii. This close contact between the C11 substituent and O1’ (as well as C11’ and O1) may explain why the first attempted oxidative dimerization with a C11 allyloxy group failed. If, as in our first attempted dimerization, C11 bears an oxygen atom, its greater van der Waals radii of 1.52 Å would have suffered a non-bonded interaction with O1’.

Interestingly, although our analysis of ground state conformations

Scheme 5. Oxidative dimerization of 16b. Reagents and conditions: a) LHMDS, HMPA, THF, −78 °C, 2 h; then Cp3FePF6, −60 °C, 72 h, 80%; b) PdCl2(PPh3)2, nBu3SnH, AcOH, CH2Cl2, 0 °C, 30 min, 90%. LHMDS = lithium bis(trimethylsilyl)amide, HMPA = hexamethylphosphoramide, Cp3FePF6 = ferrocenium hexafluorophosphate.

Figure 4. Interatomic distance of C11 hydrogen and C1’ oxygen.

Figure 3. X-ray crystal structure of 19.
Financial support for this project was provided by a grant from the NIH (CA125240). A.S.L. acknowledges financial support from an NDSEG fellowship. H.L. and J.A. acknowledge Sanofi-Aventis and Eli Lilly, respectively, for graduate fellowships.

Shao-Liang Zheng is acknowledged for X-ray crystallographic analysis.

**Keywords:** annulation • antitumor agents • natural products • remote steric effect • total synthesis


[12] It is crucial to keep the reaction temperature below -60 °C to suppress undesired β-elimination.

[13] The analyses were made by a simple hand-held plastic model. For more clear 3D representations of each staggered conformation, see the Supporting information.


[16] CDCC 77057 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request cif.

Received: ((will be filled in by the editorial staff))
Revised: ((will be filled in by the editorial staff))
Published online: ((will be filled in by the editorial staff))
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A full carbon skeleton of natural product lomaivitin has been synthesized. The approach features anionic annulation reactions to deliver A and B rings of the natural product, and stereoselective oxidative enolate coupling to form the central C2-C2’ σ-bond. In the course of the investigation, a remarkable substituent effect at C11 position was observed.