Natural Product Synthesis

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Enantioselective Synthesis of the Central Ring System of Lomaiviticin A in the Form of an Unusually Stable Cyclic Hydrate**

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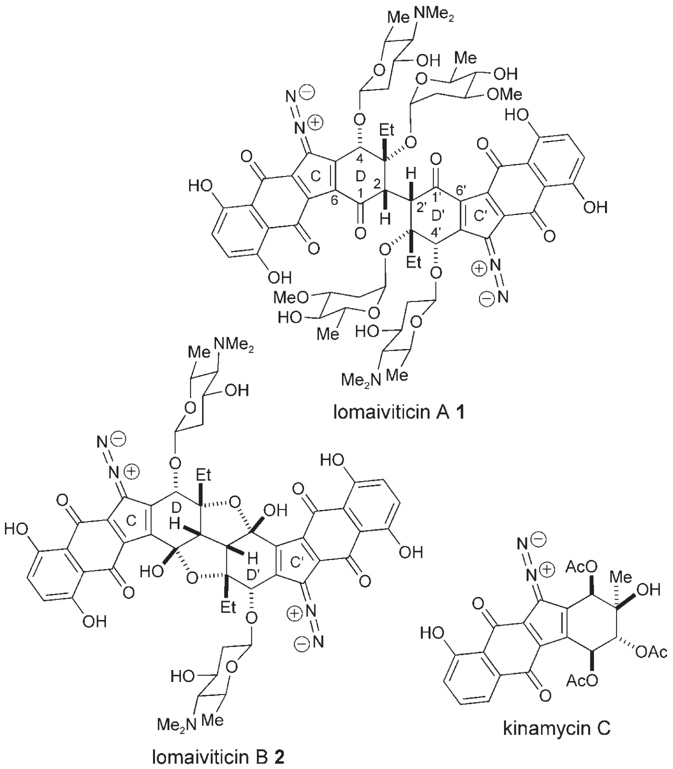
The lomaiviticin family of natural products are potent cytotoxic molecules with remarkable C_2-symmetric structures (Scheme 1). They were isolated from a strain of actinomycetes, *Micromonospora lomaiviitiensis*, which was itself isolated from the inner core of a host ascidian.[1] The GI_{50} values of **1** against a panel of 24 cultured cancer cell-lines are 0.007–72 nM, and both **1** and **2** are potent antibiotics against Gram-positive bacteria. He et al.[1] reported that **1** and **2** damage DNA, although detailed studies of their interactions with nucleic acids or other biopolymers have not been disclosed. The diazobenzofluorene ring system of the lomaiviticins would appear to be responsible for their cytotoxicity.[2] This rare ring system has only ever been found in the kinamycin family of antibiotics (see kinamycin C in Scheme 1),[3] which resemble the monomeric subunits of the lomaiviticins.



Scheme 1. Structures of lomaiviticins A (**1**) and B (**2**) as well as a related kinamycin.

Compounds **1** and **2** are daunting synthetic targets because of their size, potential lability, and juxtaposition of diverse functional groups. Of particular complexity are the central CD/C′D′-ring systems of the lomaiviticins. These rings are linked by a sterically congested and synthetically challenging C2–C2′ σ bond, the center of which is the axis of symmetry for **1** and **2**. To date, Nicolaou et al. have reported the only approach to the lomaiviticins with the syntheses of model D/D′-ring systems of **1** and **2**.[4]

Considering a global strategy for syntheses of **1** and **2**, we concluded that the most convergent approach to prepare these C_2-symmetric molecules would be to stereoselectively form the C2–C2′ bond at the latest possible stage, thereby reducing the amount of double processing (Scheme 2). Since the C2–C2′ bond is part of a 1,4-diketone (C1-C2-C2′-C1′), our desire was to link the two tetracyclic "halves" of **1** and **2** in a late-stage stereoselective oxidative enolate coupling reaction (see **3** in Scheme 2). However, this transformation has two serious problems. Firstly, the ketone enolate **4** will be prone to β elimination, thus leading to aromatization of the D ring. Secondly, there is no obvious means of controlling the configurations of the newly formed stereocenters at C2 and C2′. Our hypothesis is that linking the C3 tertiary carbinol to C6 and forming the 7-oxanorbornanone **5** will resolve both issues. β Elimination of the C3 alkoxy group is prevented in enolates of **5** by the nearly orthogonal orientation of the enolate π system and the antibonding σ* orbital of the bridging C–O bond.[5] Oxidative enolate coupling should also be stereoselective in this system, with dimerization occurring from the convex, α faces (*syn* to the oxygen bridge), thus delivering the desired α,α stereochemistry across the C2–C2′ bond. Herein we report the synthesis of the central ring system of lomaiviticin A (**1**) using this strategy.

Initially, we sought to determine whether oxidative enolate coupling of 7-oxanorbornanones could be accomplished stereoselectively and without β elimination. Conversion of **6** (85 % *ee*)[6] into **7** and exposure to Ag_2O in DMSO[7] at 100 °C afforded the desired oxidative enol coupling adduct

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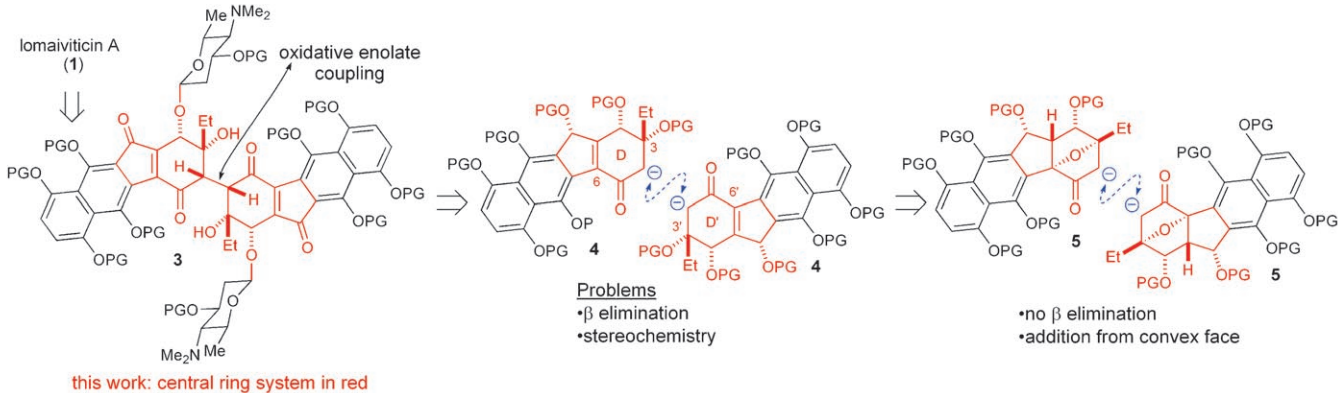
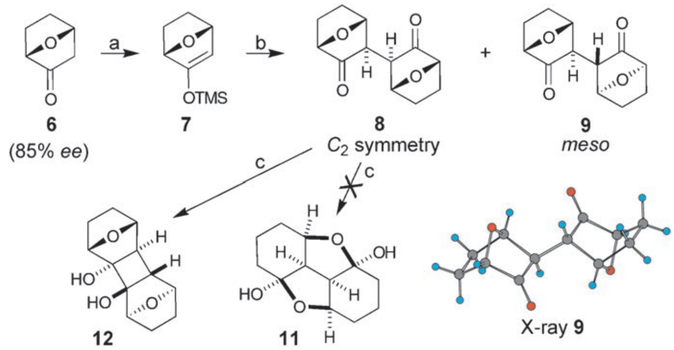


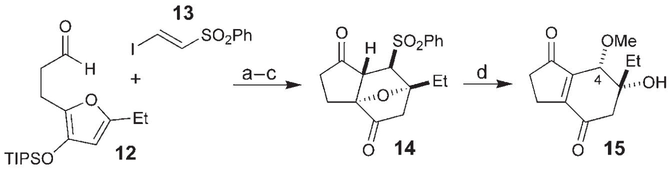
Scheme 2. Retrosynthesis of lomaiviticin A showing a strategy based on oxidative enolate coupling of a 7-oxanorbornanone. PG = protecting group.

as a 7:1 mixture of the C_2-symmetric and *meso* products, **8** and **9**,[8] respectively (Scheme 3). Gratifyingly, the reaction occurred with complete facial selectivity from the convex, *exo* faces of both bicycles. Attempted reductive cleavage of the ether bridge, between the C6 and C6′ carbons, with SmI_2 did not afford **10**, the central ring system of **2**, but instead delivered cyclobutanediol **11**. Apparently, the close proximity of the ketones renders pinacol coupling a faster process than C−O bond cleavage.

We then tested an oxygen-bridge-opening strategy that did not rely on generating reactive intermediates of the C1 ketone, thereby avoiding proximity-induced reactions like the aforementioned pinacol coupling. A model substrate was constructed (Scheme 4) by performing a tandem Kishi–Nozaki–Hiyama coupling/intramolecular furan Diels–Alder reaction between aldehyde **12** and vinyl iodide **13**,[9] to afford cycloadduct **14** after alcohol oxidation and enol silane hydrolysis. In an attempt to β-eliminate the phenylsulfonyl group, we were surprised yet happy to discover that treatment of **14** with K_2CO_3 in MeOH at 0 °C led to **15** in 95 % yield. The



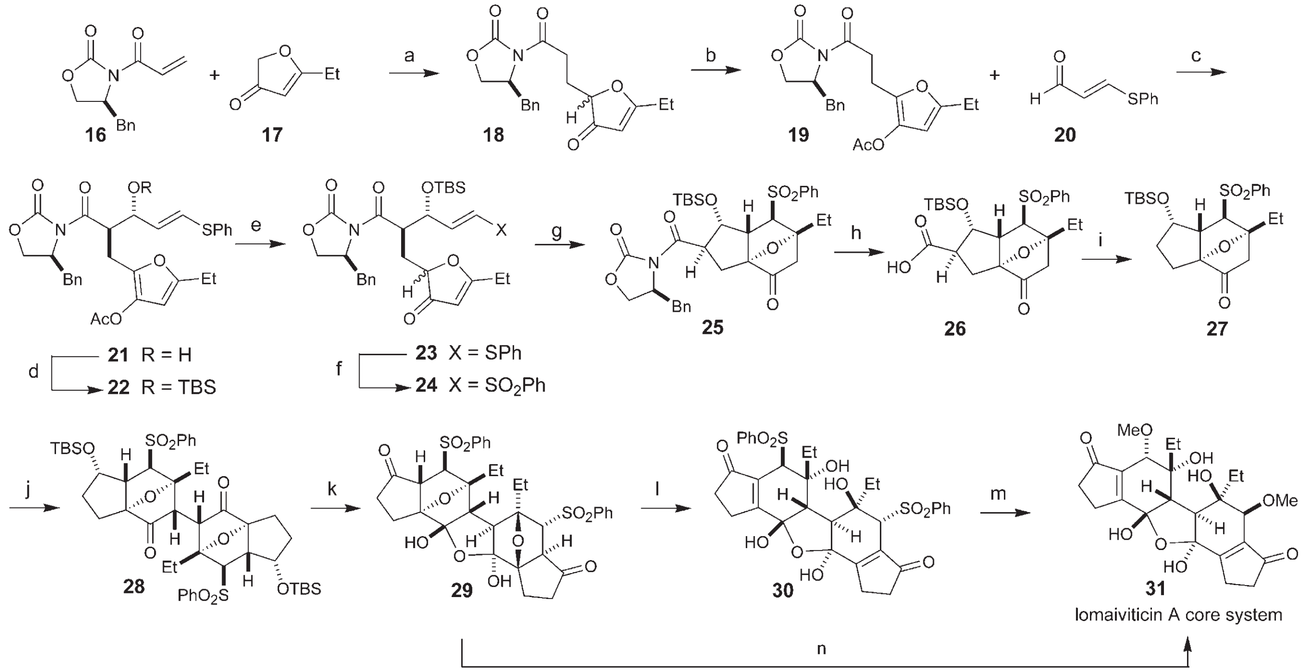
Scheme 3. Stereoselective dimerization of 7-oxanorbornanone. Reagents and conditions: a) LDA (1.3 equiv), TMSCl (8 equiv), THF, −78 °C, 5 min; b) Ag_2O (1.2 equiv), DMSO, 100 °C, 2 h, 85 % over 2 steps; c) SmI_2 (6 equiv), THF/MeOH (3:1), −78 °C, 20 min, 60 %. DMSO = dimethyl sulfoxide, LDA = lithium diisopropylamide, TMS = trimethylsilyl.



Scheme 4. Cleavage of the oxygen bridge using an exocyclic enolate. Reagents and conditions: a) $NiCl_2$ (5 mol %), $CrCl_2$ (6 equiv), **13** (1.2 equiv), THF, 23 °C, 18 h, 35 %; b) TPAP (2.5 mol %), NMO (1.5 equiv), 4-Å M.S., CH_2Cl_2, 23 °C, 1 h, 77 %; c) TFA, CH_2Cl_2, 0 °C, 58 %; d) K_2CO_3 (3 equiv), MeOH, 0 °C, 10 min, 95 %. M.S. = molecular sieves, NMO = *N*-methylmorpholine-*N*-oxide, TFA = trifluoroacetic acid, TIPS = triisopropylsilyl, TPAP = tetrapropylammonium perruthenate.

ether bridge opened as desired and the C4 oxygen was installed with the desired *syn* relationship to the C3 tertiary carbinol. Following the discovery of this cascade reaction we then sought to apply the same transformation to a C_2-symmetric dimer of **15**, which represents the central ring system of the lomaiviticins.

An enantioselective synthesis of the central ring system of lomaiviticin A began with Michael addition of the lithium enolate of furanone **17**[10] to the oxazolidinone acrylate **16**,[11] to deliver **18** in 88 % yield as a 1:1 mixture of diastereomers (Scheme 5). To prevent the furanone of **18** from participating in the ensuing aldol addition reaction, it was protected as the acetoxyfuran **19.** Using the Evans protocol,[12] a Mg^{II}-catalyzed anti-aldol reaction was performed between **19** and β-thiophenylacrolein (**20**).[13] Following TBS protection of the aldol adduct **21**, acetoxyfuran **22** was isolated as a separable 5.5:1 mixture of anti-aldol diastereomers in 60 % yield over two steps. Conversion of **22** to furanone **23** was accomplished by exposure to catalytic potassium cyanide in *i*PrOH. The same reaction in EtOH resulted in competitive opening of the oxazolidinone. Treatment of **23** with *m*CPBA oxidized the vinyl sulfide to afford vinyl sulfone **24**. Upon gentle warming **24** underwent tautomerization, intramolecular furan Diels–Alder cycloaddition, and enol tautomerization to afford **25** as a 3:1 mixture of separable diastereomers in 53 % overall yield from **22**. The furan Diels–Alder reaction afforded only *endo*



Scheme 5. Enantioselective synthesis of the central ring system of lomaiviticin A. Reagents and conditions: a) LDA (1 equiv), THF, −78 °C, 30 min; then **16** (0.5 equiv), THF, −78 °C, 3 h, 90%; b) Ac_2O (6 equiv), DMAP (10 mol%), pyr, 23 °C, 48 h, 92%; c) $MgCl_2$ (10 mol%), $NaSbF_6$ (30 mol%), Et_3N (2 equiv), TMSCl (1.5 equiv), **20** (1.5 equiv), EtOAc, 23 °C, 5 days, d.r. 5.5:1, 60–77%; d) TBSCl (3 equiv), imidazole (6 equiv), DMAP (5 mol%), DMF, 23 °C, 14 h, 78%; e) KCN (10 mol%), *i*PrOH, 50 °C, 3 days, 70–95%; f) *m*CPBA (3 equiv), CH_2Cl_2, 23 °C, 20 min; g) neat, 50 °C, 3 days, d.r. 3:1, 53% over 2 steps; h) 1. 1,4-dioxane/water/conc. HCl (4:4:1), 100 °C, 2 days; 2. TBSOTf (3 equiv), *i*Pr_2NEt (6 equiv), CH_2Cl_2; 3. K_2CO_3 (5 equiv), THF/MeOH/water (2:1:1), 23 °C, 30 min, 71% over 3 steps; i) 1. oxalyl chloride (3 equiv), DMF (3 equiv), C_6H_6, 23 °C, 2 h; 2. 2-mercaptopyridine-1-oxide sodium salt (1.2 equiv), *t*BuSH (10 equiv), DMAP (20 mol%), C_6H_6, 80 °C, *hν*, 50 min, 64% over 2 steps; j) LiHMDS (1.7 equiv), HMPA (5 equiv), THF, −78 °C, 1.5 h; then $[Cp_2Fe]PF_6$ (3 equiv), −20 °C, 20 h, 45–51%; k) 1. 48% aq. HF (20 equiv), MeCN, 23 °C, 3 d; 2. DMP (3 equiv), CH_2Cl_2, 23 °C, 3 h, 26% over 2 steps (four reactions); l) K_2CO_3 (6 equiv), MeOH, 0 °C, 30 min, 85%; m) K_2CO_3 (6 equiv), MeOH, 23 °C, 2 h, 17%; n) K_2CO_3 (6 equiv), MeOH, 0 °C to 23 °C, 3 h, 14%. Bn = benzyl, $[Cp_2Fe]PF_6$ = ferrocenium hexafluorophosphate, DMAP = 4-dimethylaminopyridine, DMF = dimethylformamide, DMP = Dess–Martin periodinane, HMDS = hexamethyldisilazane, HMPA = hexamethylphosphoramide, *m*CPBA = 3-chloroperbenzoic acid, pyr = pyridine, TBS = *tert*-butyldimethylsilyl.

cycloadducts; unlike most furan Diels–Alder reactions that typically afford *exo* cycloadducts because they are reversible and under thermodynamic control.[14] Exposure of the minor diastereomer from the furan Diels–Alder reaction to the above reaction conditions only led to starting material, thus suggesting that this furan Diels–Alder reaction is not reversible and therefore not susceptible to equilibration. This may result from the low propensity of **25** to enolize under the reaction conditions, a requirement for retrocycloaddition.

Unfortunately, attempts to generate carboxylic acid **26** directly from **25** by treatment with either lithium hydroperoxide or hydroxide led to undesired reactions involving the oxygen bridge. However, the oxazolidinone auxiliary could be removed with concomitant TBS removal using aqueous acid. Reintroduction of the TBS group and decarboxylation using the Barton conditions[15] delivered **27** in 64% yield.

Following our earlier success with 7-oxanorbornanone, we initially attempted to achieve oxidative dimerization of the enol silane of **27**, but this failed and gave primarily starting material. The lithium enolate of **27** could be generated using LHMDS, but further exposure to common oxidants used for such reactions, including copper(II) salts, iron(III) salts, and iodine, which all required warming to 0 °C or higher, consistently led to products in which the oxygen bridge had been compromised. From these experiments we learned that the lithium enolate of **27** was not stable above −20 °C, and we reasoned that an oxidant capable of electron transfer below −20 °C would be required to achieve dimerization of **27**. With this in mind, the powerful oxidant $[Cp_2Fe]PF_6$ was exposed to the lithium enolate of **27** at −20 °C for 20 h to finally afford the C_2-symmetric molecule **28** as a single diastereomer.[16] The oxidative enolate coupling was fully stereoselective and afforded only the desired α,α adduct. The ^1H and ^{13}C NMR spectra of **28** clearly indicates that a C_2-symmetric compound had been formed. A strong NOE (% enhancement) between H2 and the phenylsulfonyl group, which is also possible with H2 in an *endo* orientation, supported the stereochemical assignment at C2 and C2′. Compound **28** is only moderately stable to silica gel chromatography, which affected the yield of isolated product.

Double processing of **28** commenced with desilylation using aqueous HF in acetonitrile followed by oxidation with Dess–Martin periodinane to afford **29**. To our surprise, a water molecule added to the C1 and C1′ ketones, forcing compound **29** to exist as a cyclic hydrate. Apparently, the cyclic hydrate has a stabilizing effect because, unlike **28**, compound **29** is now stable to silica gel chromatography.

X-ray crystallographic analysis provided confirmation of structure **29**, most importantly the stereochemical assignment at C2 and C2′ and the presence of the cyclic hydrate (Figure 1).[17]

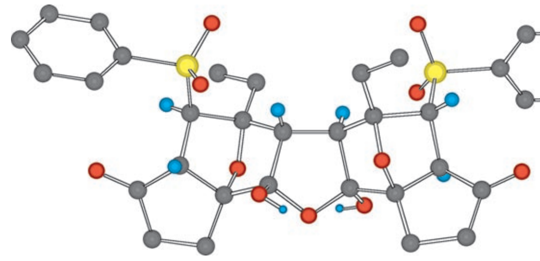
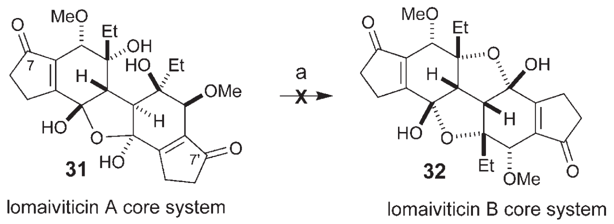


Figure 1. Representation of **29** derived from X-ray crystallographic analysis (some hydrogen atoms are omitted). C gray, H blue, O red, S yellow.

Three transformations are required to convert **29** to the central ring structure found in **1**: installation of the C5–C6 double bond, fragmentation of the C6–O bond, and conversion of the C4 phenylsulfonyl group to an ether with inversion of configuration. Based upon studies on the monomeric model system (**14**), we found that all three transformations can be achieved by exposure to K_2CO_3 in methanol. Treatment of **29** with K_2CO_3/MeOH at 0°C→23°C afforded **31** in 14% yield. Insight into the sequence of events for conversion of **29** to **31** came from conducting the reaction at 0°C, which cleanly afforded the E2 reaction product **30** in 85% yield (Scheme 5). Re-exposure of **30** to K_2CO_3 in MeOH at 23°C induced displacement of the allylic phenylsulfonyl groups with inversion of configuration to afford **31** in 17% yield (41% over two S_N2 reactions). Similar to **29**, the cyclic hydrate of **31** is stable to silica gel chromatography. In fact, attempts to dehydrate compound **31** with acid catalysis and convert it to **32**, the core system of lomaiviticin B, have only led to recovery of starting material, or if more forcing conditions were applied, they led to decomposition (Scheme 6). We cannot exclude the possibility that equilibrium is established between **31** and **32** under acid catalysis, favoring **31**, and eventually decomposition pathways predominate under harsh conditions. We suspect that the stability of the cyclic hydrate of **31** results from a combination of effects: the C1 and C1′ ketones are held in close proximity, and they



Scheme 6. Attempted dehydration of the lomaiviticin A central ring system. Reagents and conditions: a) $Sc(OTf)_3$ (cat.), MeOH, 65°C or TsOH (cat.), 4-Å M.S., C_6H_6, 80°C. TsOH = *p*-toluenesulfonic acid.

are part of a vinylogous 1,2-diketone system. Also, 1,2-diketones are known to have a higher propensity for hydration.[18] In order to convert **31** (a lomaiviticin A-type system) into **32** (a lomaiviticin B-type system) it may be necessary to remove the C7 and C7′ ketones, thereby reducing the propensity for hydration at C1 and C1′.

In conclusion, an enantioselective synthesis of the central ring system of lomaiviticin A has been achieved using a stereoselective oxidative enolate coupling of a 7-oxanorbornanone to solve the problems of β elimination and facial selectivity. One important discovery from this study is that $[Cp_2Fe]PF_6$ promotes oxidative enolate coupling at low temperature before oxygen-bridge-opening occurs; these mild conditions will be useful in a total synthesis involving more complex units. The resulting C_2-symmetric molecule was converted to the central ring system of lomaiviticin A using a mild base-initiated cascade reaction. Our discovery that the lomaiviticin A central ring system forms a stable cyclic hydrate may also prove to be useful in a total synthesis of **1** since it effectively prevents interconversion to the lomaiviticin B structure, thus allowing the C3 and C3′ tertiary carbinols to remain free for eventual glycosylation. We are using the reactions and strategies reported herein to achieve total syntheses of **1** and **2**, which will enable more careful scrutiny of their chemical and biological properties.

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