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Synthesis of the Monomeric Unit of the Lomaiviticin Aglycon**

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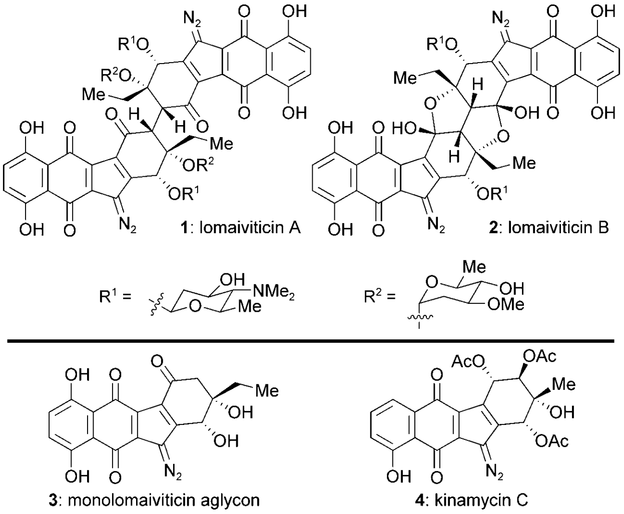
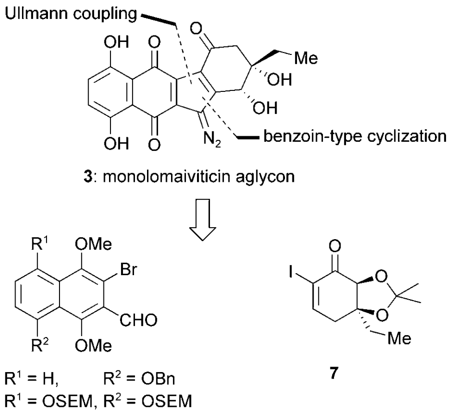
Reported in 2001, lomaiviticins A (**1**) and B (**2**; Scheme 1) were isolated from *Micromonospora lomaivitiensis* and demonstrated striking molecular architectures and impressive antitumor and antibiotic activities against a variety of cancer cell lines and bacteria.[1] These natural products apparently exert their action through a novel mechanism involving the cleavage of DNA.[2] Their chemical synthesis presents a formidable challenge, and reports describing partial success have already appeared.[3] Herein, we describe the synthesis of the monomeric aglycon unit of the lomaiviticins (**3**; Scheme 1), which is reminiscent of the kinamycins (i.e. kinamycin C (**4**); Scheme 1).



Scheme 1. Structures of lomaiviticins A (**1**) and B (**2**), their monomeric unit (**3**), and kinamycin C (**4**).

The dimeric structure of the lomaiviticins renders itself to a symmetrical retrosynthetic dissection through the center of the molecule. This dissection reveals monomeric unit **3** (Scheme 2) as a possible precursor to both **1** and **2**—a scenario that might not be so dissimilar to their biosynthetic pathway. Our approach to enantiopure pre-lomaiviticin structure **3** followed our general strategy towards the kinamycins[4] (defining bromoaldehyde **5** and iodoenone **7** as the possible building blocks as shown in Scheme 2), and involved an Ullmann coupling reaction and a benzoin-type cyclization as the main processes to construct its molecular framework. However, the approach required special design features (e.g. substrate **6**, see below, to achieve high regiocontrol) and the development of a novel samarium-mediated 1,3-allylic hydroxy group transposition (see below) that allowed significant shortening of the synthetic route.



Scheme 2. Retrosynthetic analysis of lomaiviticin aglycon monomer **3**. Bn = benzyl, SEM = 2-(trimethylsilyl)ethoxymethyl.

The required building blocks **6** and **7** were synthesized from starting materials **5** and **8**, respectively, as summarized in Scheme 3. Thus, readily available bromoaldehyde **5**[4] was debenzylated ($AlCl_3$, 80 % yield)[5] and selectively oxidized with $PhI(CF_3CO_2)_2$[6] to the expected *p*-quinone (97 % yield), which was reduced with $Na_2S_2O_4$ to the corresponding dihydroquinone and protected with SEM groups (SEMCl, $i Pr_2NEt$, 92 % yield for two steps) to afford bromoaldehyde **6**. Meanwhile, enantioselective asymmetric dihydroxylation of enone **8**[7] (AD-mix-β, single recrystallization, 69 % yield, > 95 % *ee*)[8] afforded the corresponding 1,2-diol, whose protection (2-methoxypropene, PPTS) furnished acetonide **9** in 94 % yield. Conversion of the latter into its TMS enol ether (TMSOTf, Et_3N), and subsequent exposure to O_2 in the presence of catalytic amounts of $Pd(OAc)_2$,[9] led to enone **10** (83 % yield), whose iodination (I_2, py) afforded iodoenone **7** in 91 % yield.

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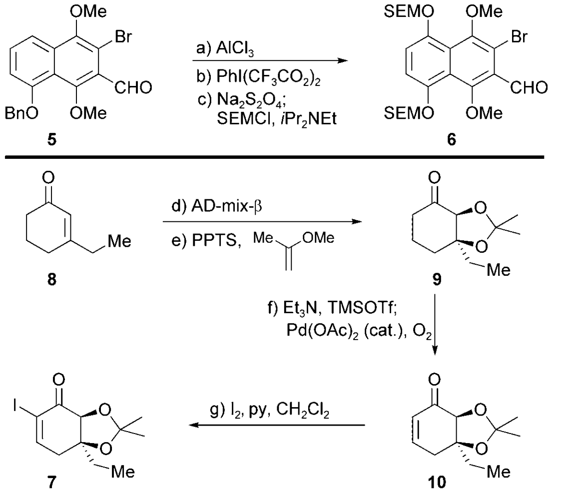
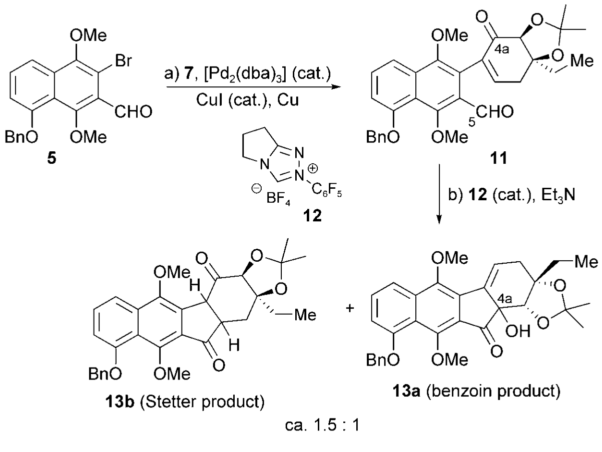


Scheme 3. Construction of key building blocks bromoaldehyde **6** and iodoenone **7**. Reagents and conditions: a) AlCl$_3$ (1.2 equiv), CH$_2$Cl$_2$, 25 °C, 3 h, 80%; b) PhI(CF$_3$CO$_2$)$_2$ (3.0 equiv), MeCN, H$_2$O, 25 °C, 30 min, 97%; c) Na$_2$S$_2$O$_4$ (5.0 equiv), EtOAc, H$_2$O, 25 °C, 10 min; then SEMCl (4.0 equiv), *i*Pr$_2$NEt (6.0 equiv), DMF, 25 °C, 18 h, 92%; d) AD-mix-β (1.4 equiv), H$_2$NSO$_2$Me (1.0 equiv), NaHCO$_3$ (3.0 equiv), toluene, *t*BuOH, H$_2$O, 0 °C, 36 h, 69%, >95% *ee*; e) 2-methoxypropene (5.0 equiv), PPTS (0.1 equiv), CH$_2$Cl$_2$, 25 °C, 18 h, 94%; f) TMSOTf (1.35 equiv), Et$_3$N (1.5 equiv), THF, 0 °C, 30 min; then Pd(OAc)$_2$ (0.1 equiv), O$_2$ (balloon), DMSO, 25 °C, 18 h, 83%; g) I$_2$ (3.0 equiv), CH$_2$Cl$_2$, py, 25 °C, 30 min, 91%. DMF = *N*,*N*-dimethylformamide, DMSO = dimethyl sulfoxide, PPTS = pyridinium 4-toluenesulfonate, py = pyridine, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.

With ample quantities of **5**, **6**, and **7** available, we proceeded to explore ways to advance them to the target molecule **3**. Our initial foray, as shown in Scheme 4, involved Ullmann coupling of benzyloxy bromoaldehyde **5** with iodoenone **7** ([[Pd$_2$(dba)$_3$] (cat.), CuI (cat.), Cu)[10] to afford coupling product **11** in 83% yield, whose intramolecular benzoin-type reaction with Rovis catalyst **12**[11] was expected to afford desired tetracyclic structure **13a** (as was previously observed in the kinamycin case).[4] However, despite its efficiency (76% combined yield), the latter reaction [**11** plus **12** (cat.), Et$_3$N] gave a disappointing ratio of the benzoin product **13a** and its isomer **13b** (Stetter product resulting from 1,4-addition; **13a**/**13b** ca. 1:1.5).[12] We attributed the formation of the latter compound to the preference of cyclization precursor ketoaldehyde **11** and its latent reaction species to reside in the conformation shown (see also Figure 1, the calculated C4a–C5 distance for **11** is 3.1 Å), thereby favoring the Stetter product **13b**. To avoid this predicament, we designed coupled product **14a** (from **6** and **7**, utilizing the same Ullmann coupling conditions; Scheme 5), whose preferred conformation was expected to be that shown in Scheme 5 (**14b**, see also Figure 1, the calculated C4a–C5 distance for **14** is 2.9 Å) owing to the bulky OSEM group exerting its influence six carbon atoms away.



Scheme 4. Failure of the original synthetic plan. Reagents and conditions: a) **5** (1.0 equiv), **7** (1.5 equiv), CuI (0.4 equiv), [Pd$_2$(dba)$_3$] (0.1 equiv), Cu (10.0 equiv), DMSO, 65 °C, 2.5 h, 83%; b) **12** (0.2 equiv), Et$_3$N (2.0 equiv), CH$_2$Cl$_2$, 42 °C, 18 h, 76%, ca. 1:1.5 benzoin product/Stetter product. dba = *trans*,*trans*-dibenzylideneacetone.

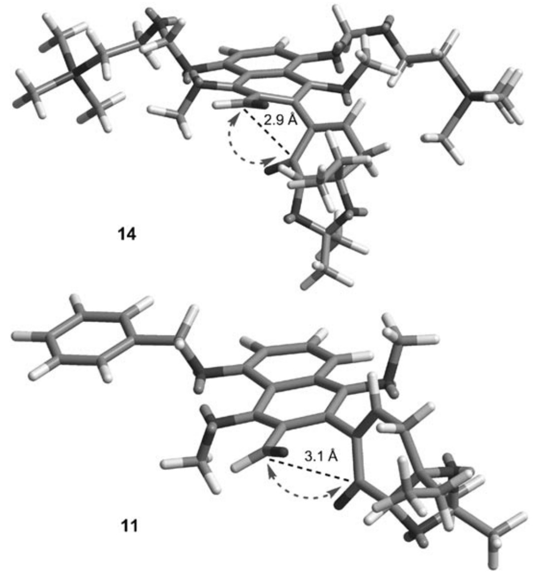
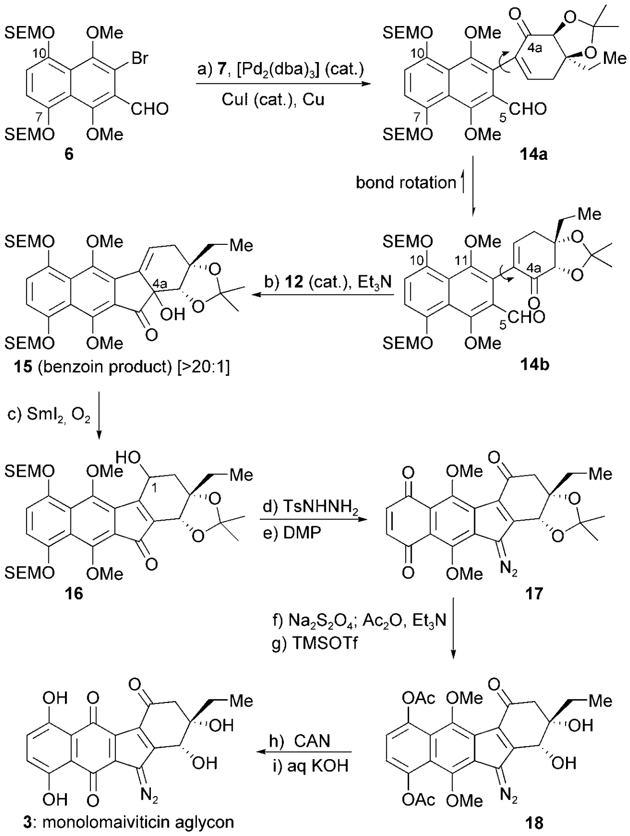


Figure 1. Calculated preferred conformations of **11** and **14** (Chem3D MM2).

Thus, it was reasoned that by its mere presence at C10, the OSEM group would force the OMe group at C11 towards the carbonyl moiety at C4a, thus causing the OSEM group to rotate (with its carrier bicyclic ring system) away and into a position to interact with the aldehyde group in the desired fashion to give the benzoin product (**14b**). Indeed, when ketoaldehyde **14a** was heated in CH$_2$Cl$_2$ at reflux in the presence of catalyst **12** and Et$_3$N, the OSEM group served its function well, and the desired benzoin product **15** was formed with greater than 20:1 selectivity (70% yield, ca. 3:1 d.r. at C4a) over its Stetter counterpart. We believe that the beneficial effect of the OSEM group in this cyclization stems primarily from its steric bulk rather than its electron-donating nature, as the corresponding C10, C7 bis(methoxy) substrate (not shown) exhibits only about 3:1 selectivity in favor of the desired benzoin product. Furthermore, it should be noted that Ullmann coupling substrates equipped at C10

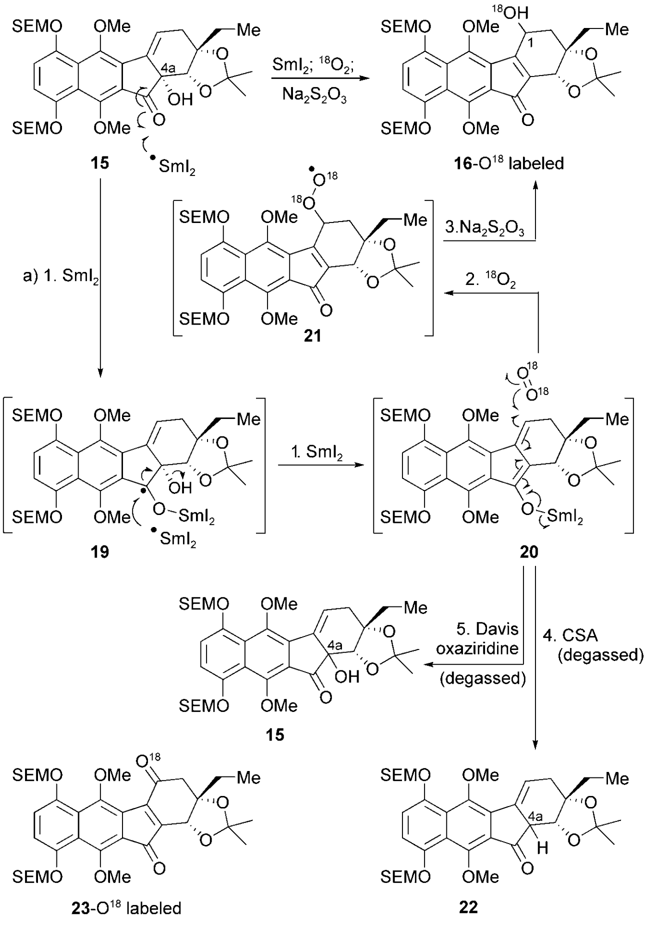


Scheme 5. Completion of the synthesis of the monolomaiviticin aglycon (**3**). Reagents and conditions: a) **6** (1.0 equiv), **7** (1.5 equiv), CuI (0.4 equiv), $[Pd_2(dba)_3]$ (0.1 equiv), Cu (10.0 equiv), DMSO, 65 °C, 3 h, 69%; b) **12** (0.2 equiv), Et_3N (2.0 equiv), CH_2Cl_2, 42 °C, 18 h, 70%, 3:1 mixture of diastereomers, >20:1 benzoin product/Stetter product; c) SmI_2 (4.0 equiv), MeOH (10.0 equiv), THF, −78 °C, 5 min; then −78→25 °C; then O_2 (balloon), 25 °C, 18 h, 76%, 1.5:1 mixture of diastereomers; d) $TsNHNH_2$ (5.0 equiv), aq HCl (1 M)/*i*PrOH (1:100), 25 °C, 18 h, 91%, 1:1 mixture of *E*/*Z* isomers of a 1.5:1 mixture of diastereomers; e) DMP (5.0 equiv), CH_2Cl_2, 25 °C, 1.5 h, 62%; f) $Na_2S_2O_4$ (5.0 equiv), EtOAc, H_2O, 25 °C, 5 min; then Ac_2O (10.0 equiv), Et_3N (10.0 equiv), DMAP (1.0 equiv), CH_2Cl_2, 25 °C, 20 min, 91%; g) TMSOTf (5.0 equiv), CH_2Cl_2, 25 °C, 20 min, 96%; h) CAN (3.0 equiv), MeCN, pH 7 phosphate buffer, 25 °C, 20 min, 96%; i) aq KOH (1 M), THF, H_2O, 25 °C, 30 min, 95%. CAN = cerium ammonium nitrate, DMAP = 4-dimethylaminopyridine, DMP = Dess–Martin periodinane, THF = tetrahydrofuran, Ts = 4-toluenesulfonyl.

and C7 with groups that are bulkier than OSEM, such as OTES, OTIPS, and OBn, failed to couple with iodoenone **7** under the same reaction conditions employed for **5** and **6**, thus precluding them from serving as viable precursors. These observations underscore the importance of the OSEM group as a unique design feature to ensure the sequential success of both the Ullmann coupling and the benzoin-like cyclization reactions.

With the first hurdle in the synthesis behind us, we were now faced with a second challenge, that of improving our previously devised allylic alcohol transposition to convert **15** into hydroxyfluorenone **16** (Scheme 5). Although our originally employed four-step protocol[4] for this transformation formed the desired product (**16**) in only 42% overall yield, it provided an important hint (in the form of trace amounts of the desired product (**16**) in the samarium-mediated step), namely that the sequence could be replaced with a one-step procedure. Indeed, exposure of hydroxy ketone **15** to the SmI_2 conditions[13] resulted in 10% yield of the desired rearranged alcohol **16**. Our initial suspicions of this process occurring through an intramolecular delivery of oxygen were dispelled when a single diastereomer of **15** led to a mixture of epimeric alcohols (**16**). We soon realized that the reaction of **15** with SmI_2, and subsequent bubbling of O_2 through the reaction mixture directly generated the desired fluorenone **16** in 76% yield (ca. 1.5:1 d.r. at C1).

The mechanism of this remarkably regioselective oxygenation at C1 was probed through the use of $^{18}O_2$, and the results are shown in Scheme 6. Thus, exposure of hydroxy ketone **15** (ca. 3:1 d.r.) to SmI_2/MeOH likely forms extended enolate **20** (through two sequential single-electron transfers). This species reacts with $^{18}O_2$ regioselectively (but not stereoselectively) at C1 (which is the most reactive position of the

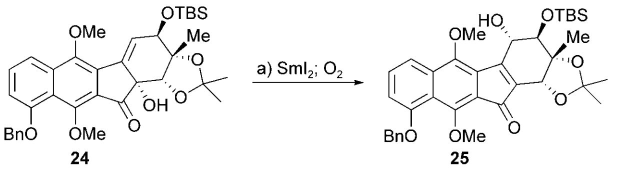


Scheme 6. $^{18}O_2$ labeling studies to elucidate the samarium-mediated 1,3-allylic alcohol transposition reaction (**15**→**16**). Reagents and conditions: a) 1. SmI_2 (4.0 equiv), MeOH (10.0 equiv), THF, −78 °C, 5 min; then −78→25 °C; 2. $^{18}O_2$ (balloon), 25 °C, 18 h; 3. aq $Na_2S_2O_3$, 25 °C, 30 min, 76%, 1.5:1 mixture of diastereomers; 4. CSA, (5.0 equiv), −78→25 °C, 10 min, 72% 1.5:1 mixture of diastereomers; 5. Davis oxaziridine (2.0 equiv), THF, 0 °C, 2 h, 85%, 1.5:1 mixture of diastereomers. CSA = 10-camphorsulfonic acid.

enolate for radical chemistry) to afford, through the intermediacy of peroxide species **21**[14] and upon work-up with aqueous $Na_2S_2O_3$, hydroxyfluorenone **16**-O^{18} in 76 % yield, along with ketone **23**-O^{18} (10 % yield). Although labile, the hydroperoxide species derived from the aqueous work-up of **21** was detected by ^{1}H NMR spectroscopy and mass spectrometry. Interestingly, by quenching the samarium enolate **20** with CSA, or Davis' oxaziridine, under anaerobic conditions[15] resulted in functionalization at C4a (as is typically the case with extended enolates), rather than C1, to furnish products **22** (72 % yield, ca. 1.5:1 d.r.)[16] and **15** (85 % yield, ca. 1.5:1 d.r.), respectively.

The final steps of the synthesis of **3** (Scheme 5) involved initial formation of a hydrazone within fluorenenone **16** ($TsNHNH_2$, aq HCl)[17] and subsequent treatment with DMP, which concurrently oxidized the hydrazone moiety, the secondary alcohol, and the bis(SEM) aromatic system to afford diazo quinone **17** in 56 % overall yield. The quinone structural motif within the latter needed to be transposed to its proper position; to this end, **17** was sequentially exposed to $Na_2S_2O_4$ and Ac_2O/Et_3N [91 % yield of acetonide bis(acetate)] and afforded, upon treatment with TMSOTf, dihydroxy bis(acetate) **18** in 96 % yield. Finally, oxidation of **18** with CAN and subsequent deacetylation (aq KOH) led to the coveted lomaiviticin aglycon monomer (−)-**3** in 91 % overall yield.

The application of the developed samarium-mediated 1,3-allylic alcohol transposition procedure to our kinamycin synthesis[4] reduced the previously employed sequence (involving Ac_2O, Et_3N, DMAP; SmI_2, MeOH; Et_3N; SeO_2) to a single operation, and significantly increased the overall yield (from 55% over four steps to 83% over one step; Scheme 7).[4]



Scheme 7. Streamlining the kinamycin samarium-mediated 1,3-allylic alcohol transposition. Reagents and conditions: a) SmI_2 (4.0 equiv), MeOH (10.0 equiv), THF, −78 °C, 5 min; then −78→25 °C; then O_2 (balloon), 25 °C, 18 h, 83 %, single diastereomer. TBS = *tert*-butyldimethylsilyl.

The chemistry described here provides a rapid entry into the monomeric unit of the lomaiviticins that should facilitate further synthetic, biosynthetic, and biological studies within this important area of investigation. It also demonstrates the power of remote group interactions and cascade reactions[18] in achieving control and efficiency in chemical synthesis.

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Keywords: antibiotics · antitumor agents · natural products · samarium diiodide · Ullmann reaction

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