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Synthesis of the Monomeric Unit of the Lomaiviticin Aglycon**

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Keywords

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Reported in 2001, lomaiviticins A (**1**) and B (**2**, Figure 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] apparently exerting their action through a novel mechanism involving DNA cleavage.[2] Their chemical synthesis presents a formidable challenge, and reports describing partial solutions have already appeared.[3] In this communication, we describe the total synthesis of the monomeric aglycon unit (**3**, Figure 1) of the lomaiviticins, which is reminiscent of the kinamycins (*i.e.* kinamycin C, **4**, Figure 1).

The dimeric structure of the lomaiviticins renders itself to a symmetrical retrosynthetic dissection through the center of the molecule, revealing monomeric unit **3** (see Figure 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 bromo-aldehyde **5** and iodo-enone **7** as the possible building blocks as shown in Figure 2), and involved an Ullmann coupling reaction and a benzoin-type cyclization as the main processes to construct its molecular framework. However, it required special design features (e.g. substrate **6**, vide infra, in order to achieve high regiocontrol) and the development of a novel samarium-mediated allylic hydroxyl group transposition (vide infra) that allowed significant shortening of the synthetic route.

The required building blocks **6** and **7** were synthesized from starting materials **5** and **8**, respectively, as summarized in Scheme 1. Thus, readily available bromo-aldehyde **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, iPr_2NEt, 92 % yield for two steps) to afford bromo-aldehyde **6**. On the other hand, and as shown in Scheme 1, 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 to its TMS-enol ether (TMSOTf,

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Et_3N), followed by 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 iodo-enone **7** in 91 % yield.

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, shown in Scheme 2, involved Ullmann coupling of benzyloxy bromo-aldehyde **5** with iodo-enone **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 previously observed in the kinamycin case.[4] However, and despite its efficiency (76 % combined yield), the latter reaction [**11** plus **12** (cat.), Et_3N] gave a disappointing ratio of the benzoin product **13a** and its isomer **13b** (1,4-addition, Stetter product, **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 shown conformation (see also Figure 3, calculated C_{4a}–C_5 distance 3.1 Å), thereby favoring the Stetter product **13b**. It was to avoid this predicament that we designed coupled product **14a** (from **6** and **7**, utilizing the same Ullmann coupling conditions, Scheme 3), whose preferred conformation was expected to be that shown in Scheme 3 (**14b**, see also Figure 3, calculated C_{4a}–C_5 distance 2.9 Å) due to the bulky OSEM group exerting its influence from six carbons away.

Thus, it was reasoned that by its mere presence at C_{10}, the OSEM group would force the OMe group at C_{11} towards the carbonyl moiety at C_{4a}, causing it to rotate with its carrier bicyclic ring system away and into a position to interact with the aldehyde group in the desired benzoin fashion (**14b**). Indeed, when ketoaldehyde **14a** was heated in refluxing CH_2Cl_2 in the presence of catalyst **12** and Et_3N, the OSEM group served its function well, with the desired benzoin product (**15**) forming in >20:1 selectivity (70 % yield, ca. 3:1 *dr* at C_{4a}) 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, since the corresponding C_{10}, C_7 bis-methoxy substrate (not shown) exhibits only a ca. 3:1 selectivity in favor of the desired benzoin product. Furthermore, it should be noted that Ullmann coupling substrates equipped at C_{10}, C_7 with bulkier groups than OSEM, such as OTES, OTIPS, and OBn, failed to couple with iodo-enone **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 reaction.

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** to hydroxyfluorenone **16** (Scheme 3). 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 reaction of **15** with SmI_2, followed by bubbling O_2 through the reaction mixture generated the desired fluorenone **16** directly, and in 76 % yield (ca. 1.5:1 *dr* at C_1).

The mechanism of this remarkably regioselective oxygenation at C_1 was probed through the use of $^{18}O_2$, and the results are shown in Scheme 4. Thus, exposure of hydroxy ketone **15** (ca. 3:1 *dr*) 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 C_1, the most reactive position of the enolate for radical chemistry, to afford, through the

intermediacy of peroxide species **21**[14] and upon work-up with aq. $Na_2S_2O_3$, hydroxy fluorenone **16**-O^{18} in 76% yield, along with ketone **23**-O^{18} (10 % yield). Although labile, the hydroperoxide species derived from aqueous work-up of **21** was detected by ^{1}H NMR spectroscopy and mass spectrometry. Interestingly, quenching the samarium enolate **20** with CSA, or Davis' oxaziridine, under anaerobic conditions[15] resulted in functionalization at C_{4a} (as is typically the case with extended enolates), rather than C_1, furnishing products **22** (72 % yield, ca. 1.5:1 *dr*)[16] and **15** (85 % yield, ca. 1.5:1 *dr*), respectively, as shown in Scheme 4.

The final steps of the synthesis of **3** (Scheme 3) involved initial hydrazone formation within fluorenenone **16** ($TsNHNH_2$, aq. HCl)[17] followed by an impressive performance by DMP, which concurrently oxidized the hydrazone, 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, an end towards which **17** was sequentially exposed to $Na_2S_2O_4$ and Ac_2O–Et_3N (91 % yield of acetonide bis-acetate) to afford, upon treatment with TMSOTf, dihydroxy bis-acetate **18** in 96 % yield. Finally, oxidation of **18** with CAN, followed by 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 technology 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 sig nificantly increased the overall yield (from 55 % over four steps to 83 % over one step, see Scheme 5).[4]

The described chemistry 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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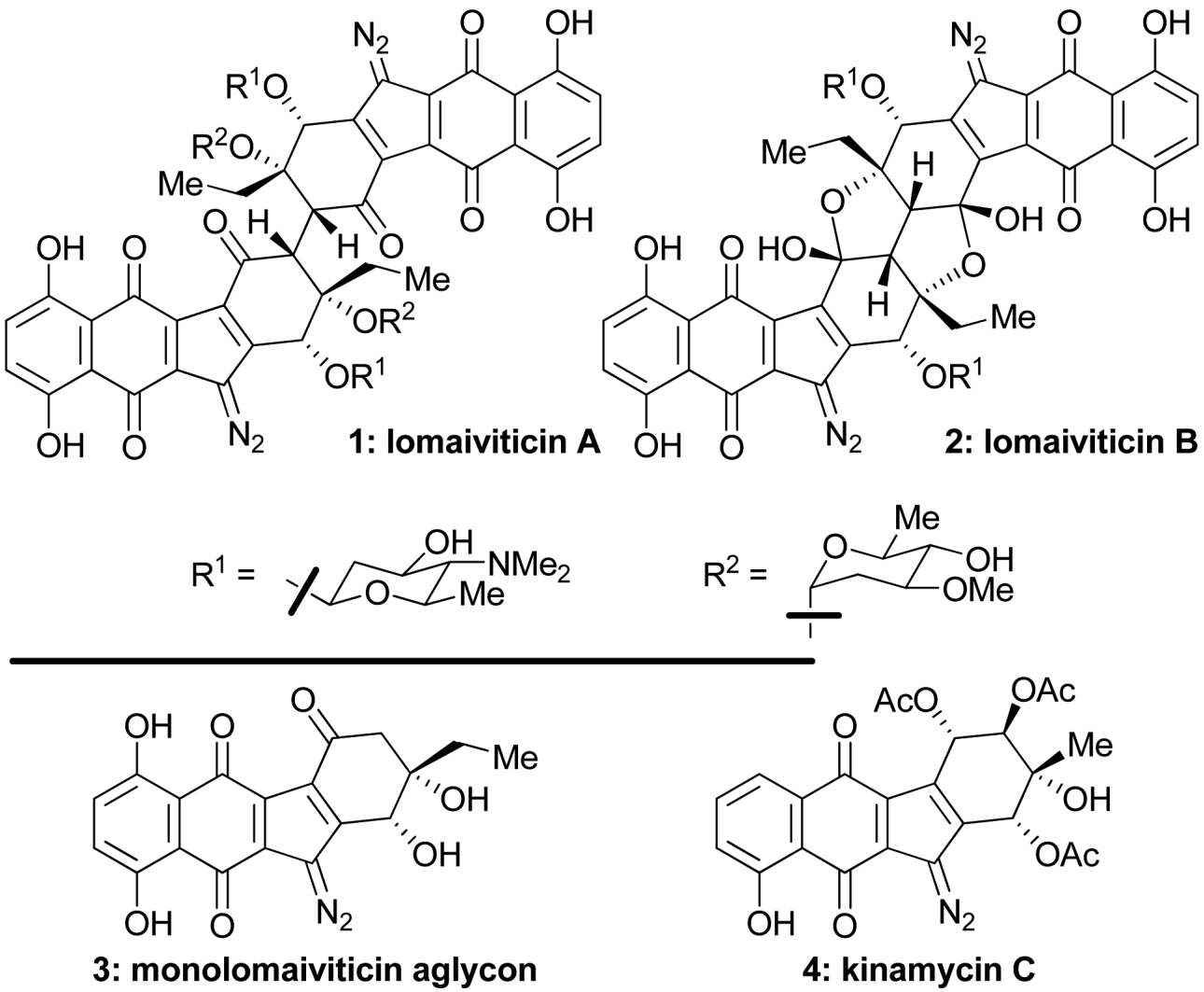


Figure 1.
Structures of lomaiviticins A (**1**) and B (**2**), their monomeric unit (**3**), and kinamycin C (**4**).

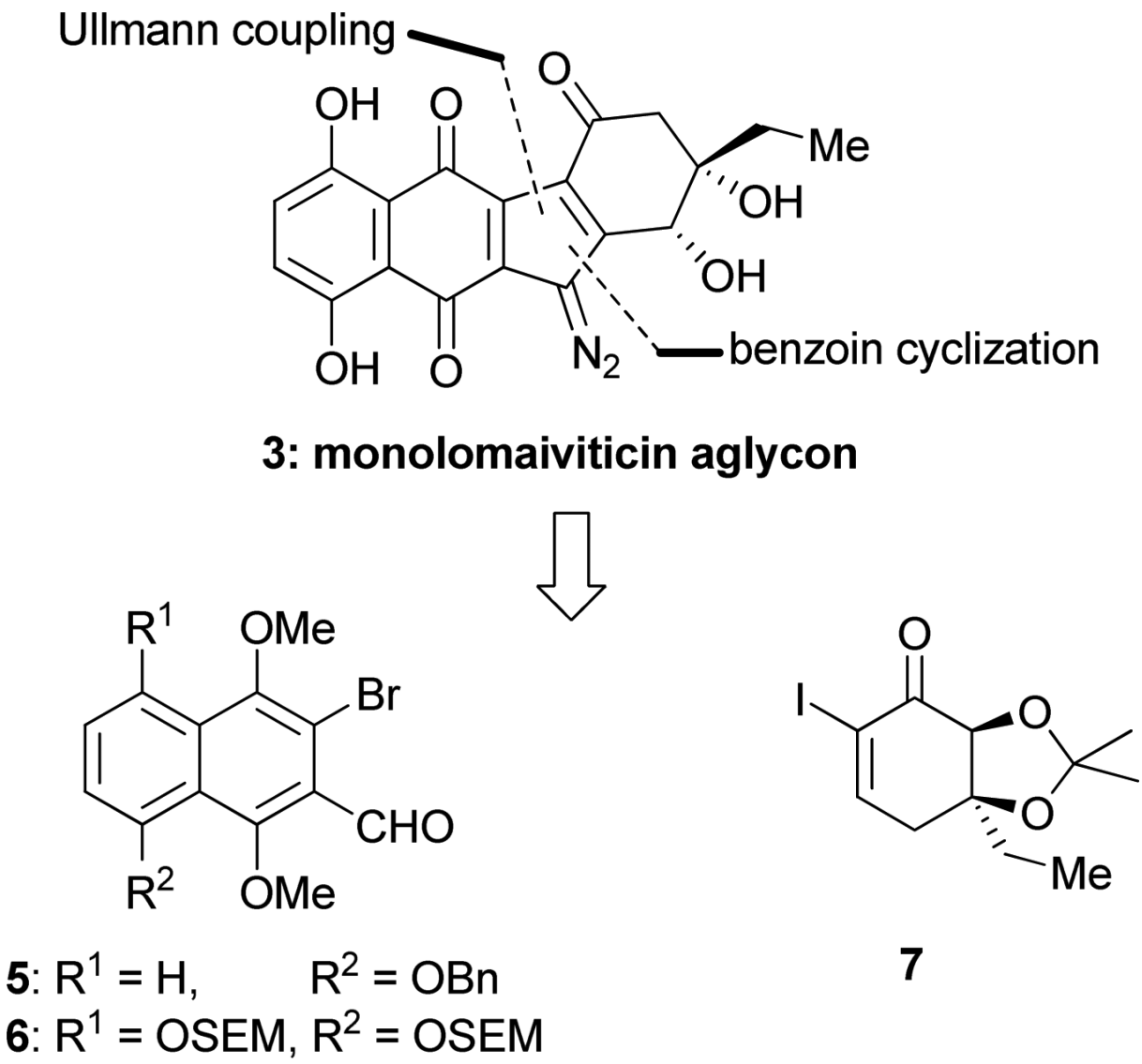
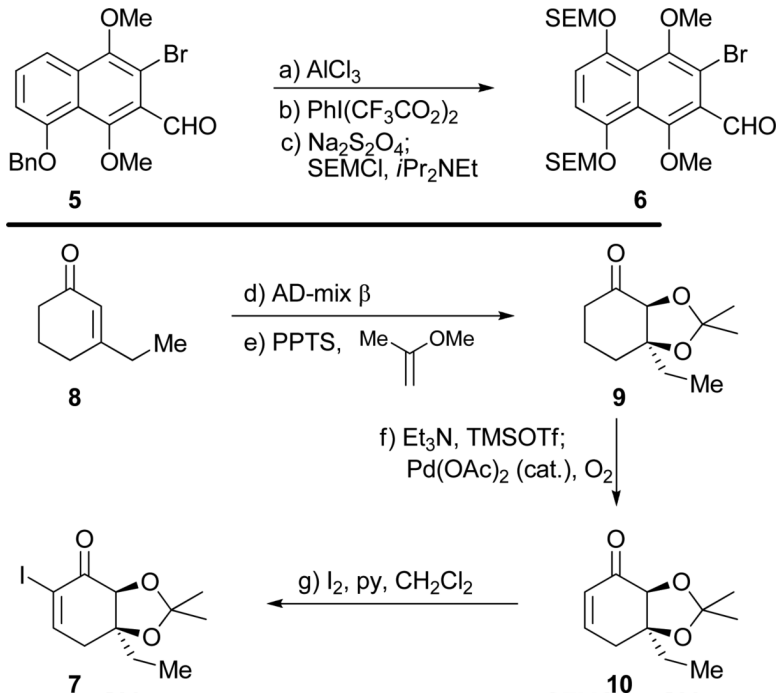
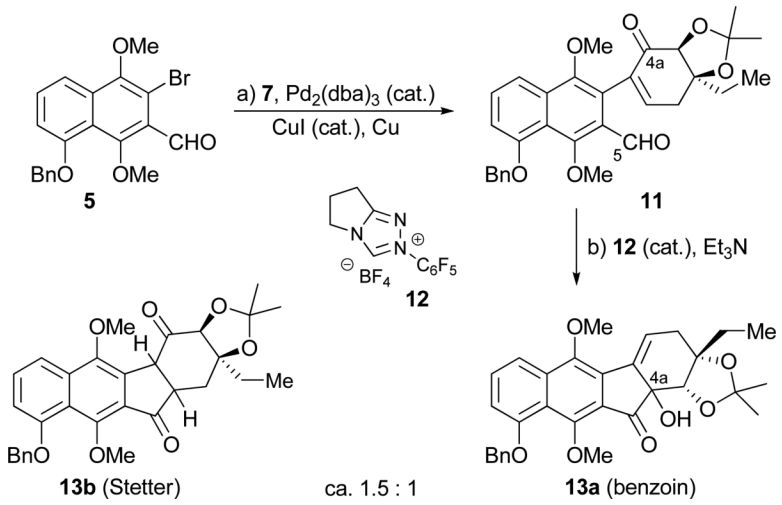


Figure 2.
Retrosynthetic analysis of lomaiviticin aglycon monomer **3**.



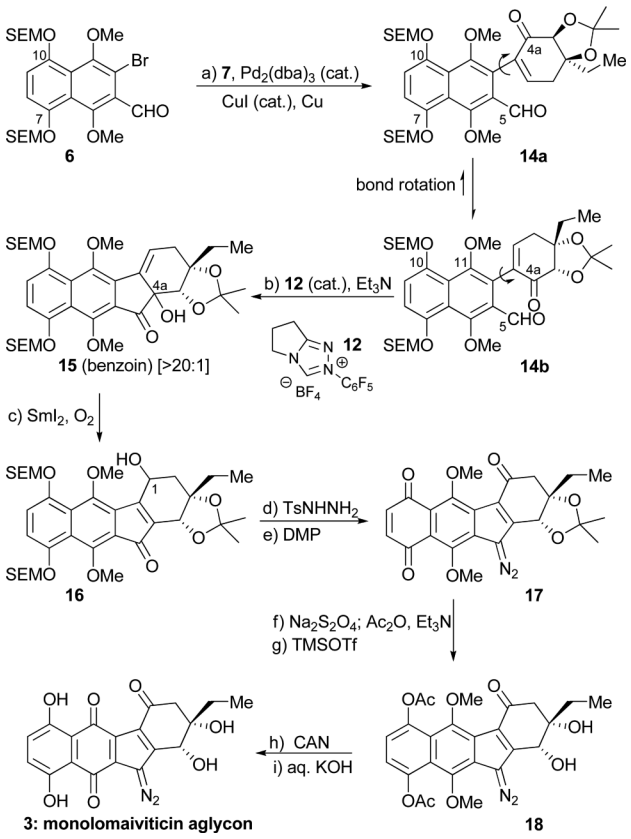
Scheme 1.

Construction of key buliding blocks bromo-aldehyde **6** and iodo-enone **7**. Reagents and conditions: a) $AlCl_3$ (1.2 equiv), CH_2Cl_2, 25 °C, 3 h, 80 %; b) $PhI(CF_3CO_2)_2$ (3.0 equiv), MeCN, H_2O, 25 °C, 30 min, 97 %; c) $Na_2S_2O_4$ (5.0 equiv), EtOAc, H_2O, 25 °C, 10 min; SEMCl (4.0 equiv), *i*Pr_2NEt (6.0 equiv), DMF, 25 °C, 18 h, 92 %; d) AD-mix-β (1.4 equiv), H_2NSO_2Me (1.0 equiv), $NaHCO_3$ (3.0 equiv), tol., *t*BuOH, H_2O, 0 °C, 36 h, 69 %, >95 % *ee*; e) 2-methoxypropene (5.0 equiv), PPTS (0.1 equiv), CH_2Cl_2, 25 °C, 18 h, 94 %; f) TMSOTf (1.35 equiv), Et_3N (1.5 equiv), THF, 0 °C, 30 min; $Pd(OAc)_2$ (0.1 equiv), O_2 (balloon), DMSO, 25 °C, 18 h, 83 %; g) I_2 (3.0 equiv), CH_2Cl_2, py, 25 °C, 30 min, 91 %. Bn = benzyl, MeCN = acetonitrile, OAc = acetate, SEM = 2-(trimethylsilyl) ethoxymethyl, DMF = dimethylformamide, tol = toluene, *t*Bu = *tert*-butyl, PPTS = pyridinium, 4-toluenesulfonate, TMS = trimethylsilyl, Tf = trifluoromethanesulfonyl, DMSO = dimethyl sulfoxide, py = pyridine.



Scheme 2.

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_3N (2.0 equiv), CH_2Cl_2, 42 °C, 18 h, 76 %, ca. 1:1.5 benzoin:Stetter. dba = dibenzylideneacetone.



Scheme 3.

Completion of the synthesis of 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:Stetter; c) SmI_2 (4.0 equiv), MeOH (10.0 equiv), THF, –78 °C, 5 min; –78→25 °C; 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; 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 %. Ts = 4-toluenesulfonyl, DMP = Dess–Martin periodinane, Ac_2O = acetic anhydride, DMAP = 4-dimethylaminopyridine, CAN = cerium ammonium nitrate.

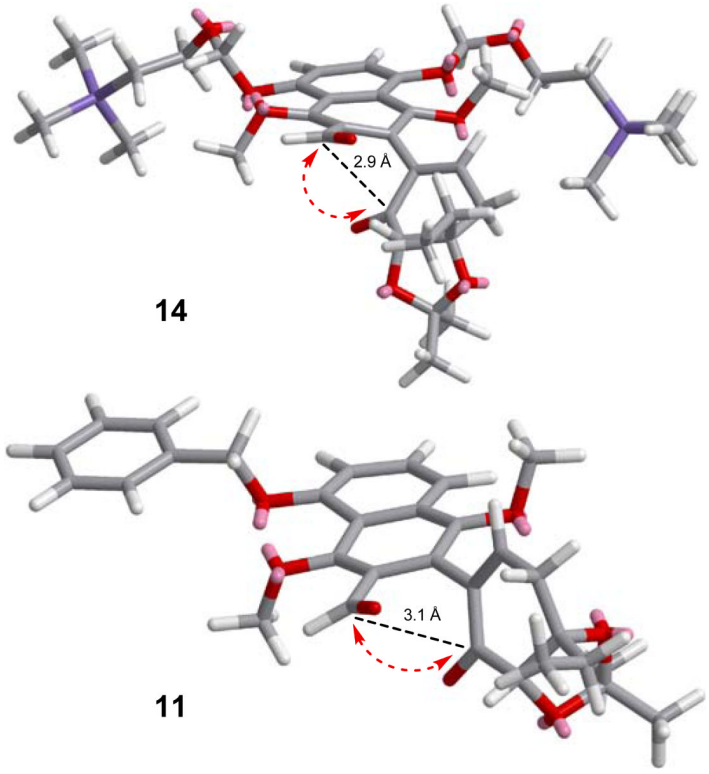
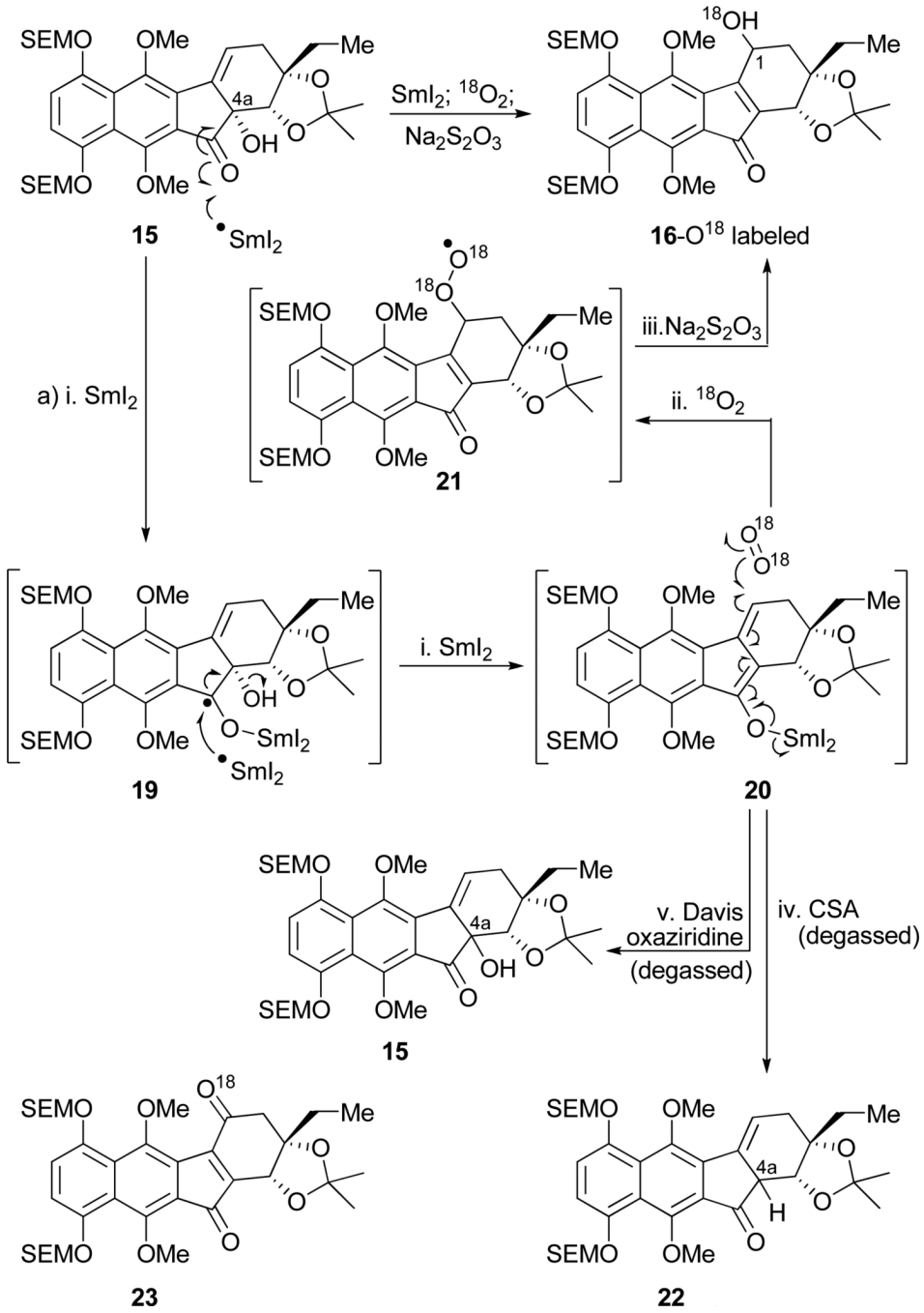
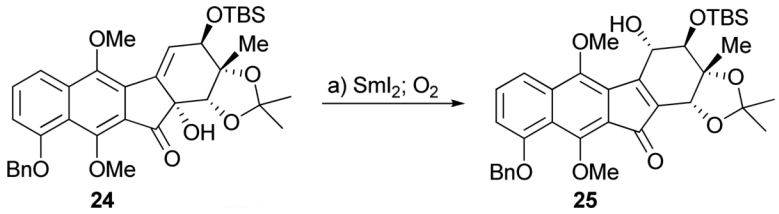


Figure 3.
Calculated preferred conformations of **14** and **11** (Chem3D MM2).



Scheme 4.

$^{18}O_2$ Studies elucidating the samarium-induced 1,3-allylic alcohol transposition reaction (**15→16**). Reagents and conditions: a) i. SmI_2 (4.0 equiv), MeOH (10.0 equiv), THF, –78 °C, 5 min; – 78→25 °C; ii. $^{18}O_2$ (balloon), 25 °C, 18 h; iii. aq. $Na_2S_2O_3$, 25 °C, 30 min, 76 %, 1.5:1 mixture of diastereomers; iv. CSA, (5.0 equiv), – 78→25 °C, 10 min, 72 % 1.5:1 mixture of diastereomers; v. Davis oxaziridine (2.0 equiv), THF, 0 °C, 2 h, 85 %, 1.5:1 mixture of diastereomers.



Scheme 5.

Streamlining the kinamycin samarium-mediated allylic alcohol transposition. Reagents and conditions: a) SmI_2 (4.0 equiv), MeOH (10.0 equiv), THF, –78 °C, 5 min; –78→25 °C; O_2 (balloon), 25 °C, 18 h, 83 %, single diastereomer.