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Total Syntheses of the Resorcylic Acid Lactones Paecilomycin F and Cochliomycin C Using an Intramolecular Loh-Type α-Allylation Reaction for Macrolide Formation

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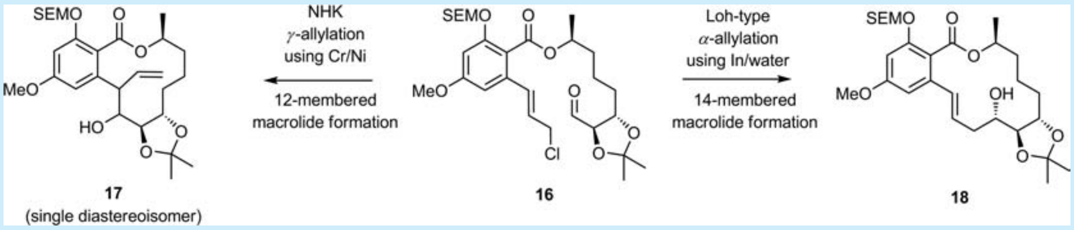
Supporting Information

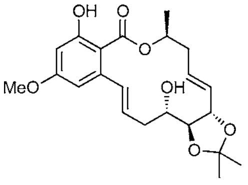


ABSTRACT: Subjection of the resorcylic ester **16** to a Nozaki–Hiyama–Kishi reaction afforded the 12-membered lactone **17**, while treatment of it under the Loh-type α-allylation conditions using indium metal gave the isomeric, 14-membered macrolide **18**. Compound **18** was readily elaborated to the resorcylic acid lactone type natural products paecilomycin F and cochliomycin C.

The resorcylic acid lactones (RALs) are a large and ever-growing group of mycotoxins that embody a β-resorcylic acid residue annulated to a 14-membered macrolactone.[1,2] Many of these natural products display a range of potent biological properties, perhaps most notably powerful and selective inhibitory activities against ATPases and kinases as well as, inter alia, antifungal, antiparasitic, antimalarial, and/or antifouling effects.[1] As a consequence, considerable effort has been devoted to their synthesis.[1] Arguably the most challenging aspect of these endeavors has been the assembly of the macrolide ring, and a significant range of techniques has been developed for this purpose. Macrolactonization,[3] ring-closing metatheses (RCMs),[4] intramolecular nucleophilic addition reactions (including NHK and HWE olefinations),[5] intramolecular nucleophilic substitution,[6] and cross-coupling processes[7] as well as radical cyclization[8] and ring contraction[9] reactions represent just some of the numerous techniques used.[10] Herein, we detail a versatile new means for constructing the macrocyclic ring of RALs and its exploitation in the synthesis of the title natural products, namely paecilomycin F and cochliomycin C.

The cochliomycins are a series of six RALs isolated from the marine-derived fungus *Cochliobolus lunatus*[11] that display notable antifouling and/or fungicidal properties.[12] The structures of the first three members of the family, namely cochliomycins A–C (**1**–**3**, respectively), are shown in Figure 1. The isomeric natural products **1** and **2** each incorporate acetonide residues, while congener **3** is a chlorinated derivative of paecilomycin F (**4**), another RAL that has been isolated from a filamentous fungus collected in Southern China and shown to display antimalarial activity.[13]

In seeking to extend our recently reported[5d] preparations of compounds **1** and **2** to congeners **3** and **4**, we have now identified a hitherto unexploited but highly effective means for assembling the macrolactone ring associated with the RALs. The pivotal bond-forming events associated with the route reported here are shown in Figure 2 with the most important being an intramolecular α-allylation reaction that was used to close the 14-membered ring.



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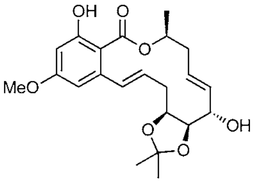

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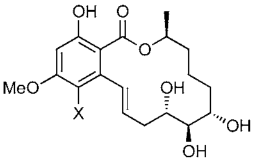

3 (X = Cl)
4 (X = H)

Figure 1. Cochliomycins A–C and paecilomycin F (**1**–**4**, respectively).

To the best of our knowledge, this approach to the construction of RALs has not been examined previously, perhaps in part because of potential competition from formation of the presumably kinetically more favorable 12-

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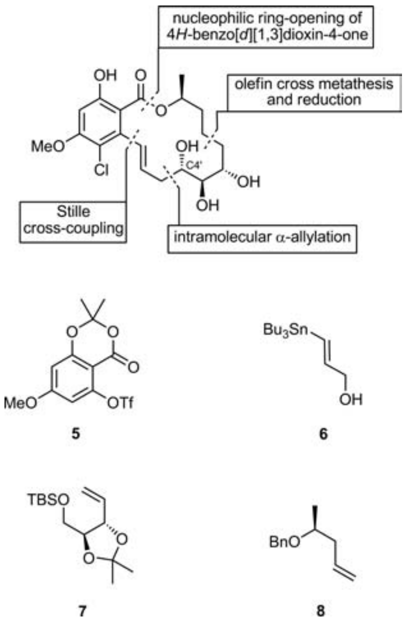


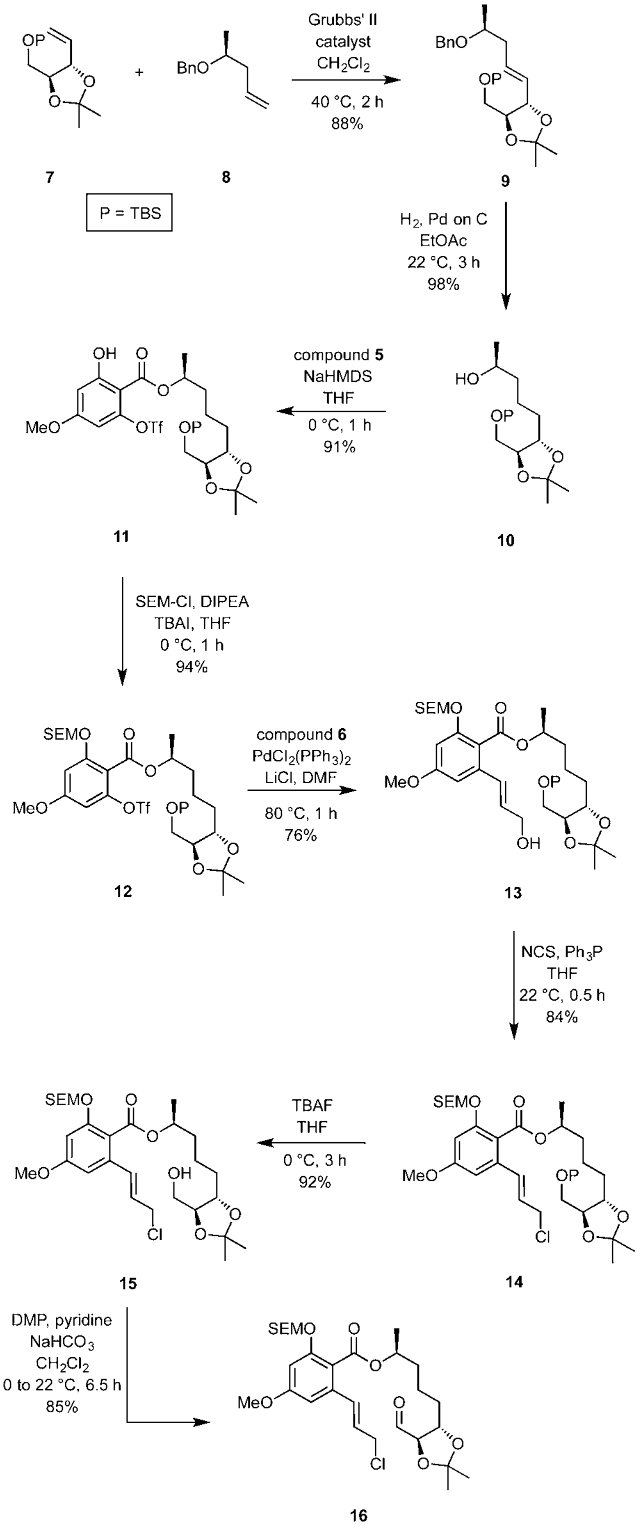
Figure 2. Key bond-forming events associated with the assembly of cochliomycin C (**3**) and the key building blocks, **5**−**8**, used.

membered ring lactone. The building blocks required for the purposes of investigating this approach were compounds **5**−**8**.

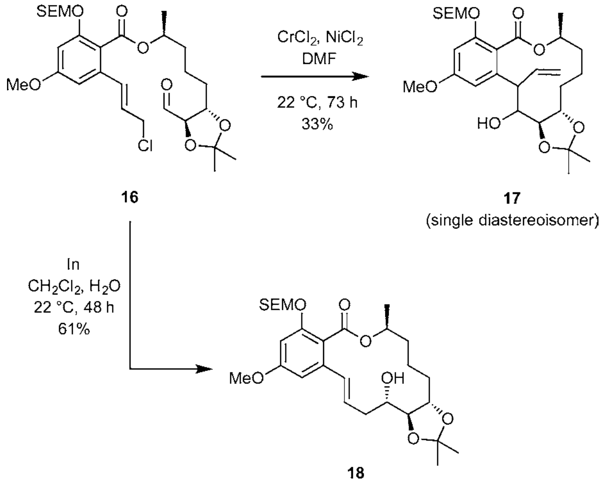
The synthetic sequence used to assemble these building blocks in readiness for exploring the intramolecular allylation reaction is shown in Scheme 1 and started with the olefin cross metathesis (OCM) of compounds **7**[14] and **8**,[15] using Grubbs' second-generation catalyst,[16] to form the *E*-olefin **9** (88%). This was reacted with dihydrogen in the presence of palladium on carbon so as to effect concurrent reduction of the C−C double bond and hydrogenolytic cleavage of the benzyl ether, thus forming alcohol **10** in 98% yield. Reaction of this last compound with building block **5**[5d] in the presence of sodium hexamethyldisilazide (NaHMDS) resulted in the anticipated *trans*-esterification reaction to produce compound **11** (91%) that was immediately protected as the corresponding 2-(trimethylsilyl)ethoxymethyl or SEM ether **12** (94%) under standard conditions. A Stille cross-coupling reaction[17] between this last compound and building block **6**[18] gave the cinnamyl alcohol **13** (76%) that was readily converted into the corresponding chloride **14** (84%) on reaction with *N*-chlorosuccinimide (NCS) and triphenylphosphine. In the final steps used to assemble the substrate required for examining the foreshadowed ring-closing (intramolecular) allylation reaction, the TBS ether **14** was cleaved with tetra-*n*-butylammonium fluoride (TBAF) and the resulting alcohol **15** (92%) oxidized with the Dess−Martin periodinane (DMP)[19] to give the target aldehyde **16** in 85% yield. All of the spectral data acquired on compound **16** were in complete accord with the assigned structure. Most notably, the presence of an aldehyde residue was evident in the IR and NMR spectra while the mass spectrum established that the compound contained one chlorine atom.

That variant of the intramolecular NHK reaction wherein the organochromium(III) reagent derived from an alkenyl iodide is added to a pendant aldehyde has been successfully exploited in the assembly of the 14-membered lactone rings of RALs.[5b,d] In contrast, the allyl variant has not, perhaps because of the potential for competing formation of the corresponding 12-membered macrolide. Consistent with such possibilities, when compound **16** was subjected (Scheme 2) to reaction with an excess of chromium(II) chloride in the presence of 6 mol % nickel(II) chloride in *N*,*N*-dimethylformamide (DMF), the only isolable product of reaction was compound **17**. This was obtained as a single diastereoisomer in 33% yield. Product **17** results from a so-called γ- rather than α-allylation reaction.[20] A

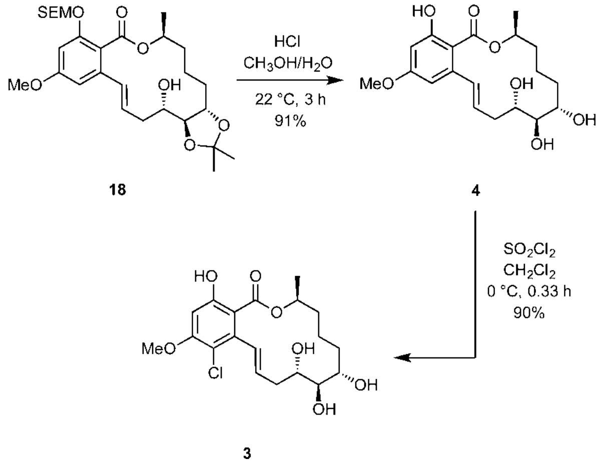
Scheme 1. Assembly of Building Blocks 5−8 in the Formation of Compound 16



Scheme 2. Intramolecular Allylation Reactions of Compound 16



Scheme 3. Completion of Syntheses of Paecilomycin F (4) and Cochliomycin C (3)



trans-relationship between the adjacent vinyl and hydroxyl groups is tentatively assigned on the basis of a consideration of the transition state likely to be operative in the cyclization reaction.[21]

Loh and co-workers have described[20] a method wherein allyl indium reagents[22] can be regioselectively engaged in α- rather than γ-allylation reactions (through careful control of the amount of water added to the reaction medium), although this protocol does not appear to have been applied to macrocyclization processes. Accordingly, it was pleasing to observe that when compound **16** was treated with a suspension of indium metal in dichloromethane containing 11 molar equiv of water then the desired mode of cyclization took place, thereby producing macrolide **18** in an unoptimized yield of 61%. No evidence was obtained for the formation of the previously observed compound **17**, the *Z*-isomer of product **18**, or its C4′-epimer. Confirmation of the illustrated structure of product **18** follows from an X-ray analysis of a derivative as detailed below. A Felkin–Anh-type transition state would account for the observed diastereoselectivity of this macrocyclization reaction.[22b]

The conversion of macrolide **18** into the title natural products **4** and **3** was effected using the straightforward procedures shown in Scheme 3. Specifically, both the SEM and acetonide protecting groups associated with compound **18** could be cleaved on treatment with HCl in aqueous methanol and paecilomycin F (**4**)[23] thus obtained in 91% yield. All of the NMR spectral data acquired on compound **4** matched those reported for the natural product (see Table S1 for some relevant comparisons) as did the specific rotation [$[\alpha]_D^{20}$ −103.3 (*c* 0.6, methanol) vs lit.[13a] $[\alpha]_D^{24}$ −106.4 (*c* 0.28, methanol)]. The regioselective aromatic monochlorination of RAL **4** was readily effected using sulfuryl chloride in dichloromethane[23e] and cochliomycin C (**3**)[23] obtained in 90% yield.

Not only did all of the spectral data acquired on this synthetically derived compound (viz. **3**) compare favorably with those reported[11a] for the natural product (see the Supporting Information), but a single-crystal X-ray analysis served to confirm its structure and, therefore, that of the natural product.

The work reported here highlights the capacity of Loh's indium-mediated α-allylation protocol to effect macrocyclization reactions in a predictable fashion and to introduce functionality relevant to the synthesis of RALs and related natural products. As such, this procedure, which proceeds under mild conditions in an aqueous environment, warrants further attention in macrolide synthesis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01963.

Experimental procedures, spectroscopic and analytical data, and NMR spectra of new compounds (PDF)
X-ray data for compound **3** (CIF)

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Notes

The authors declare no competing financial interest.

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