Efficient synthesis of (±)-de-*O*-methyllasiodiplodin

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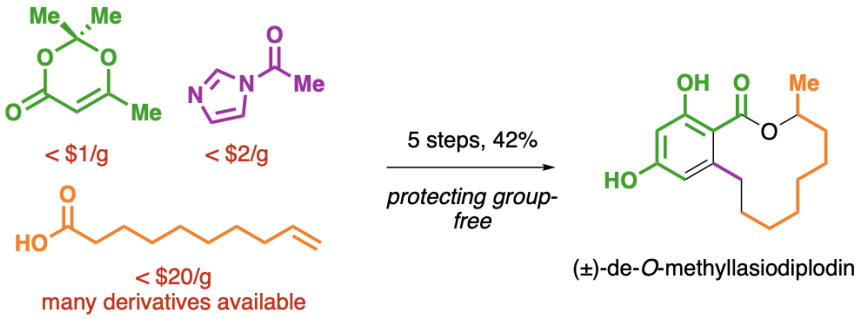
Abstract



Resorcinolic macrolides are a large class of fungal natural products with conserved resorcinolic ester cores within highly variable ten- to fourteen-membered macrocycles. They exhibit a broad range of biological activities, depending largely on the size and substitution on the macrocycle bridge. Here, we report a protecting group-free synthesis of (±)-de-*O*-methyllasiodiplodin, a minimal resorcinolic macrolide derived from the fungus *Lasiodiplodia theobromae*. The route proceeds in 42% yield over 5 steps (longest linear sequence) from 9-decenoic acid, a cheap and abundant starting material. Given the broad commercial availability of a variety of similar (terminal)-enoic acids, this route provides an entry to libraries of resorcinolic macrolides with highly variable macrocycle bridges.

1. Introduction

The resorcinolic macrolide (RM) class of natural products contains >50 members characterized by a resorcinolic ester within a macrocyclic lactone of varying size and substitution (Figure 1).[1] RMs exhibit diverse biological activities, and several have been shown to engage nucleotide binding sites with their resorcinolic ester core, which is highly conserved among family members with only minor structural variations such as chlorination or O-methylation. The macrocycle bridge, by contrast, shows a high degree of variability between family members and grants selectivity between binding sites. For example, radicicol (**1**) serves as an ATP mimic by binding to the Bergerat fold in Hsp90, but does not strongly engage other ATP-binding proteins.[2] Hypothemycin (**2**) covalently inhibits several human kinases[3] and CDXG kinases in *T. brucei,*[4] but has not been shown to inhibit Hsp90 or other proteins with Bergerat folds. Resorcinolic macrolides have generated significant interest from both academia and industry, with several detailed investigations into biological activity, synthesis, and structure–activity relationships recently reviewed.[1,5]

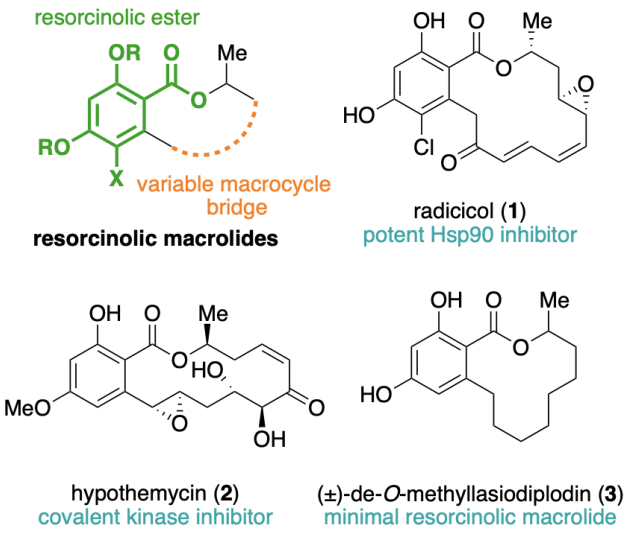


Figure 1. Resorcinolic macrolides: a structurally rich class with diverse biological activities.

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Lasiodiplodin and de-O-methyllasiodiplodin (**3**) are were isolated in 1971 from the fungus *Lasiodiplodia theobromae* (*Botrysdiplodia theobromae*)[6] and each have shown a variety of biological activities.[1] These structurally minimal resorcinolic macrolides have been the target of several synthetic studies over the past 50 years. Gerlach and Thalmann reported a ~9-step synthesis of (±)-lasiodiplodin in 1977.[7] Danishefsky and Etheredge[8] and Chan and Stossel[9] reported formal syntheses that intercepted Gerlach and Thalmann's intermediates. Syntheses of enantioenriched (R)- or (S)-lasiodiplodin have emerged from Gerlach,[10] Braun,[11] Bracher,[12] Solladié et al.[13] and Fürstner.[14–16] Catalytic asymmetric approaches have been reported by Jones and Huber[17] and Feringa.[18]

Four fully synthetic routes to de-*O*-methyllasiodiplodin (**3**), which lacks methylation on its resorcinol functionality, have been reported. The first synthesis, en route to lasiodiplodin, proceeded in 0.13% overall yield to (R)-**3** over 15 steps from 5-methylresorcinol, with a demethylation of the resorcinol as a limiting step (17% yield).[13] A shorter, 6-step route to (R)-**3** featuring an early application of ring-closing metathesis was reported by Fürstner and Kindler in 1996, but was limited by the same demethylation.[16] In 2011, (R)-**3** was synthesized via a more efficient route with nine steps in 28% overall yield by Guo and coworkers, owing to a more efficient deprotection of the methyl groups (57%).[19] This route enabled the synthesis of a small library of analogs, some of which exhibited improved antagonistic activity against mineralocorticoid receptor and other nuclear hormone receptors. Finally, Yadav and coworkers reported a synthesis of (R)-**3** that proceeds in 19% yield over 11 steps from 2,4,6-trihydroxybenzoic acid.[20] This synthesis stands apart from the others because it does not suffer from a low-yielding demethylation step. Herein we report an efficient, protecting group-free route to racemic **3** that proceeds in 5 steps and 42% overall yield.

2. Results and discussion.

In the design of our synthetic route, we had the following priorities: 1) starting materials for the macrocyclic bridge must be affordable and diversifiable, 2) protecting group usage should be minimized, 3) the route should have a low longest linear step count, and 4) the macrocyclization should be high-yielding and functional group-tolerant. With these considerations in mind, our retrosynthetic analysis of **3** as a representative RM is shown in Figure 2. Taking inspiration from elegant syntheses of zearalenone and LL-Z1640-2 by Miyatake-Ondozabal and Barrett,[21,22] we envisioned that the resorcinolic ester could arise from macrocyclization/aromatization of intermediate **4**. Macrolactonizations with 1,3-dioxin-4-ones precursors have been applied to the synthesis of hundreds of structurally diverse ketolides,[23] giving us confidence in the functional group tolerance of this transformation. Precursor **4** could be reached by allowing Weinreb amide **6** to react with the dienolate of intermediate **5**. It was unclear whether this step would require protection of the secondary alcohol. Ketone **5** could be

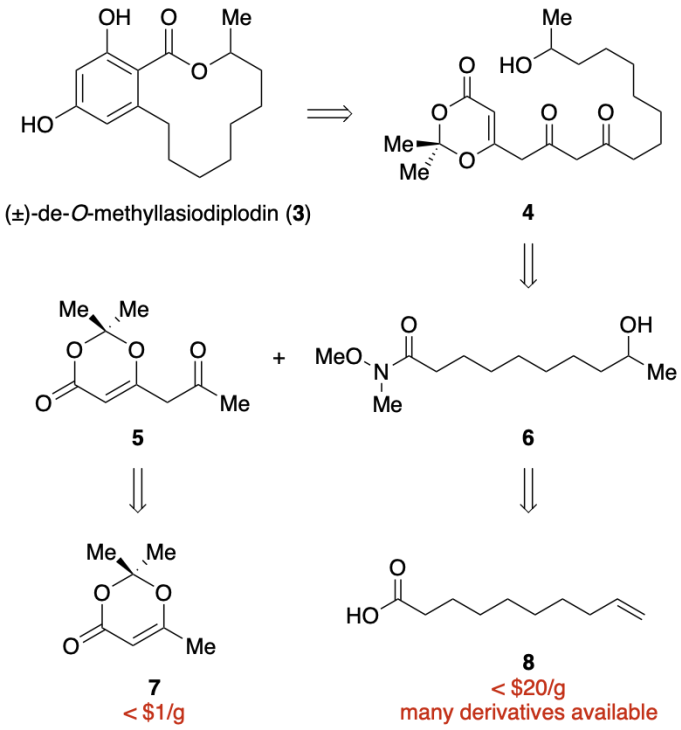
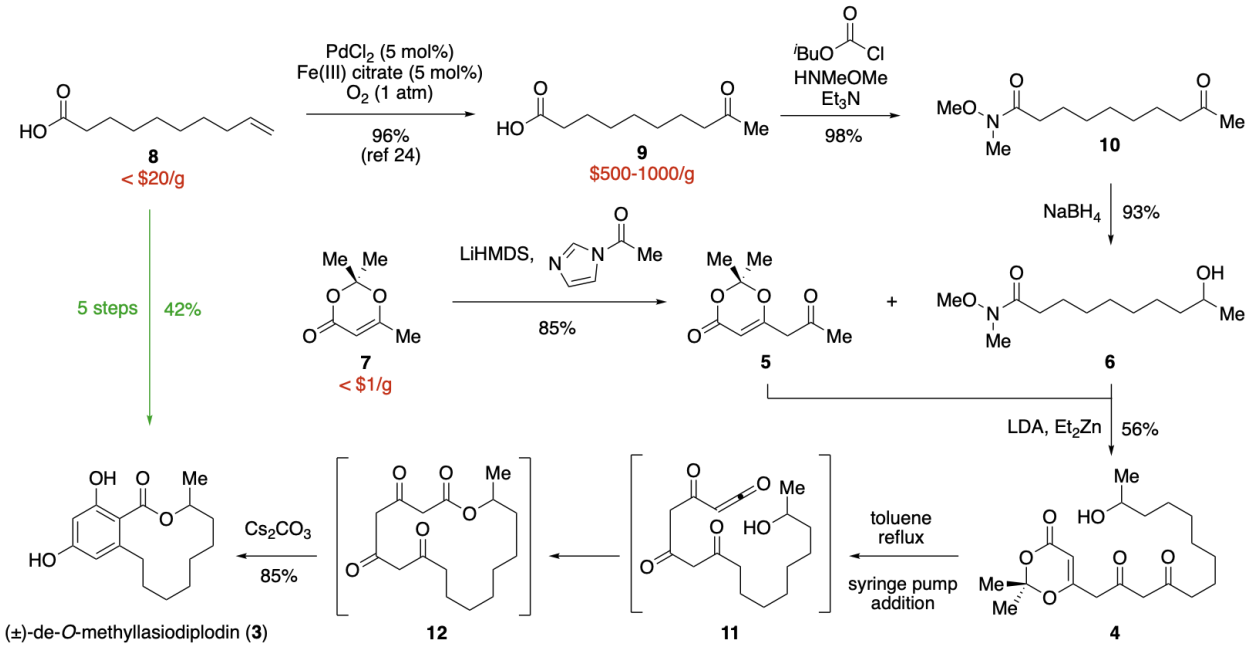


Figure 2. Retrosynthesis of de-*O*-methyllasiodiplodin (**3**).

synthesized in a single step from 4*H*-2,2,6-trimethyl-1,3-dioxin-4-one (**7**), which is cheap and abundant (< $1/g). A survey of commercially available building blocks led us to select 9-decenoic acid (**8**) as a precursor to **6**. This starting material is inexpensive (< $20/g) and, importantly, a variety of similar (terminal)-enoic acids are commercially available, enabling diversification of the macrocyclic linker by building block exchange.

Our synthesis of **3** is outlined in Scheme 1. Wacker oxidation of **8** under aqueous conditions with molecular oxygen as the terminal oxidant, developed by Miyazaki and Ura, provided **9** in excellent yield.[24] Subsequent Weinreb amide formation with isobutyl chloroformate and *N*,*O*-dimethylhydroxylamine proceeded in near quantitative yield to provide **10**. Sodium borohydride reduction provided racemic alcohol **6** in good yield. Attempts to render this step enantioselective using a Corey-Bakshi-Shibata (CBS) reduction failed to generate enantioenriched products. Methyl-(unbranched)alkyl ketones are known to be challenging substrates for enantioselective reductions, although recent advances in CBS catalyst design[25] and in catalytic hydrogenation[26] may grant avenues for future application in our system. Since natural RMs have both *R* and *S* stereochemistry at this center (see **1** and **2**, Figure 1), we chose to proceed with the racemic mixture in the current work.

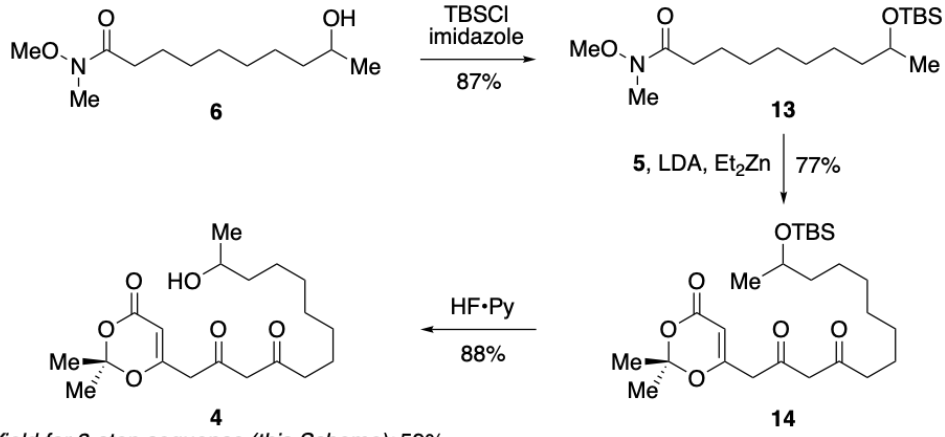


Scheme 1. Short, efficient, protecting group-free synthesis of de-*O*-methyllasiodiplodin (**3**). LDA = lithium diisopropylamide, LiHMDS = lithium hexamethyldisilazide.

Treatment of 4*H*-2,2,6-trimethyl-1,3-dioxin-4-one (**7**) with lithium hexamethyldisilazide (LiHMDS) followed by acetylimidazole provided ketone **5** in 85% yield. Coupling of **6** to **5** was accomplished with lithium diisopropylamide (LDA) and diethylzinc (Et_2Zn), delivering the macrocycle precursor **4** as a keto/enol mixture in 56% yield. We found that inclusion of diethylzinc was crucial for the yield of this transformation, perhaps due to conversion of the lithium dienolate to a less reactive zinc (di)enolate.[27] Macrocyclization was achieved using a modification of Barrett's protocol[28] wherein a solution of **4** was slowly added to refluxing toluene by means of syringe pump over 3 hours. Under these conditions, the intermediate **4** likely undergoes retro [4+2] cycloaddition to provide acyl ketene **11**, which is attacked intramolecularly by the secondary alcohol provided triketoester **12**. This intermediate exists as a mixture of several keto-enol tautomers by ^{1}H NMR analysis, and is not routinely isolated. Addition of cesium carbonate followed by

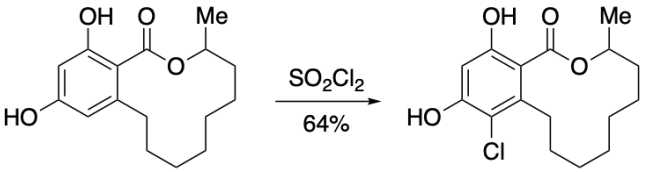
re-acidification with hydrochloric acid affected a cyclization/aromatization cascade, providing (±) -de-*O*-methyllasiodiplodin (**3**) in 85% yield in a one-pot operation from intermediate **4**.

The lowest yielding step in the sequence, coupling of fragments **5** and **6**, may be inefficient due to the unprotected secondary alcohol in **6** that is likely deprotonated by one equivalent of the dienolate of **5**. We hypothesized that the yield of this reaction could increase if the alcohol is shielded as its silyl ether. To test this hypothesis, we silylated **6** with *tert*-butyldimethylsilyl chloride (TBSCl) and imidazole to provide silyl ether **13** in 87% yield (Scheme 2). Coupling of **13** with **5** resulted in improved yield (77%) compared to **6** and **5** (56%). Desilylation of the resulting precursor **14** with Olah's reagent proceeded in 88% yield. Overall, the yield for this 3-step sequence was 59%, a moderate improvement over the 56% yield for the 1-step sequence.



Scheme 2. Evaluation of an alternative, 3-step sequence from **6** to **4**. Py = pyridine, TBS = *tert*-butyldimethylsilyl.

There is no indication that the de-*O*-methyllasiodiplodin (**3**) has been evaluated for its effects on Hsp90, a common target for RMs.[1] Radicicol (**1**) is a potent Hsp90 inhibitor, and its activity is dependent on chlorination of the resorcinol ring. We sought to develop a method for the introduction of this chlorine to **3** that could also be applied to other RMs to modulate their bioactivities.[29] We found that *N*-chlorosuccinimide (NCS) failed to produce any appreciable amount of **15**. However, sulfuryl chloride[30] was able to afford the correct chlorination in 64% yield with careful control of reaction duration and temperature to avoid dichlorination (Scheme 3). Due to challenges in separating **3** and **15** with column chromatography, it was important to drive the reaction to completion, and dichlorination accounted for the moderate yield.



Scheme 3. Chlorination of de-O-methyllasiodiplodin

3. Conclusion

We developed a 5-step synthesis of (±)-de-*O*-methyllasiodiplodin (**3**) that proceeds in 42% yield from affordable starting materials. The route proceeds without protecting groups and features a high-yielding (85%) macrocyclization/aromatization cascade directly providing the natural product. We have also developed a method for the direct chlorination of the resorcinol to mimic the halogenated members of the

class. This provides a scalable and efficient method for accessing **3** and its chlorinated derivative **15**, enabling further investigations into their biological activities. More broadly, this provides a general strategy for the synthesis of RMs with variable macrocycle bridges that complement the broad diversity found in nature.

Acknowledgements

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