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Biomimetic synthetic studies on lactonamycin: an expedient synthesis of dihydroxy-isoindolinone-carboxylates

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ABSTRACT

The synthesis of dihydroxy-isoindolinone-carboxylates from a dioxinone keto-ester and N-protected sarcosine without the use of phenolic protection is described. Base-induced aromatization of the dioxinone diketo-ester followed by lactamization furnished the desired dihydroxy-isoindolinone moiety, which could be used as an EF-ring precursor toward the synthesis of lactonamycin.

Introduction

Lactonamycin (**1**) possesses several intriguing structural features (Fig. 1).[1] The novel, highly functionalized hexacyclic aglycone core, contains, in the western half, a highly-oxygenated fused perhydrofuran-furanone ring with a labile tertiary methoxy group, and in the eastern half, a naphtha[*e*]isoindole ring system. In addition to its interesting structure, the biological evaluation of lactonamycin (**1**) against Gram-positive bacteria showed significant levels of antimicrobial activity.[2] It was especially active against clinically isolated methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE) with minimum inhibitory concentration levels of 0.39 and 0.20 μg/mL, respectively. Lactonamycin (**1**) also showed significant levels of cytotoxicity against various tumor cell lines.[2]

We[3] and others[4] have reported studies on the syntheses of the ABCD and CDEF ring systems of **1**. Our approach was based on the use of an intramolecular Friedel–Crafts acylation of acid **3**, which was synthesized from bromide **4** and triflate **5** via a Suzuki coupling reaction (Scheme 1).[3b] Although the original route provided sufficient quantities of triflate **5**, the synthesis was insufficiently concise and, therefore, we have investigated alternative routes toward the synthesis of triflate **5**.

Simple phthalimidines **6**[5](Fig. 2) are typically synthesized from 2-methylbenzoyl ester derivatives via radical benzylic bromination followed by condensation with a primary amine and cyclization;[6] condensation of isobenzofuran-1(3*H*)-one derivatives[7] or *o*-phthalaldehyde derivatives[8] with a primary amine; nitrile reduction of 2-cyanobenzoyl ester derivatives and subsequent lactamization;[9] palladium-catalyzed reactions,[10] and finally the reduction of phthalimide derivatives.[11] Albeit usually high yielding, many of these conditions are often not suitable for phthalimidine derivatives bearing sensitive substituents on the aromatic ring.

We recently published the biomimetic synthesis of several resorcylate natural products by late-stage aromatization reactions from triketo-ester derivatives.[12] Based on this methodology,[13] we sought a second-generation biomimetic approach toward the synthesis of triflate **5**. Herein, we report the synthesis of an advanced intermediate toward triflate **5** using a late-stage base-induced aromatization of dioxinone diketo-ester.

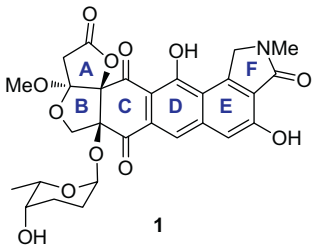

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Figure 1. Structure of lactonamycin (**1**).

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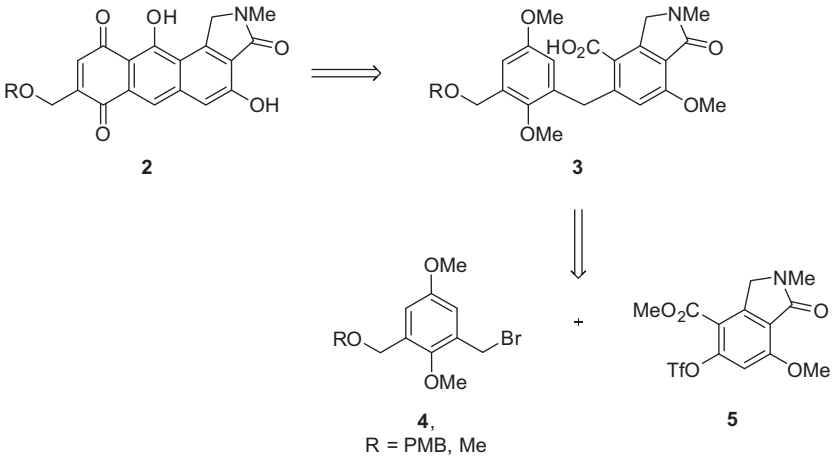


Scheme 1. Retrosynthetic analysis of model CDEF tetracyclic target **2**.

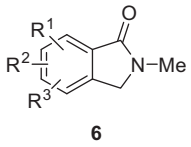


Figure 2. Generic structure of phthalimidine derivatives **6**.

Results and discussion

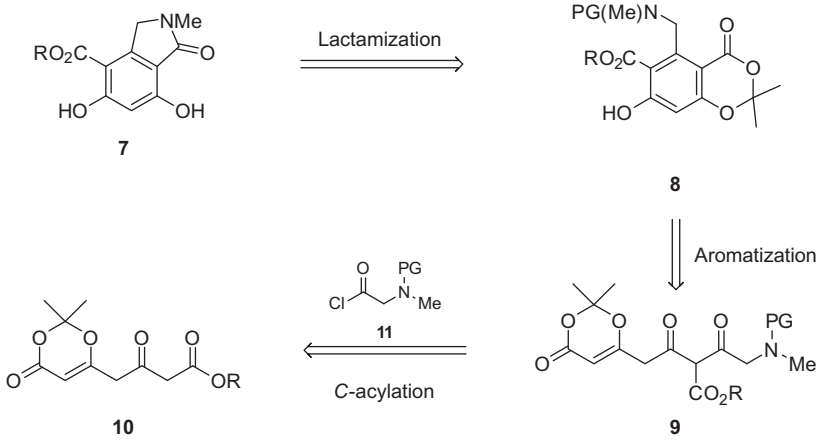
Our retrosynthesis is illustrated in Scheme 2. Dihydroxy-isoindolinone-carboxylates **7** should be available by deprotection followed by lactamization from isopropylidene-protected resorcylates **8**, which in turn could be prepared from dioxinone diketo-esters **9** by base-induced aromatization. Finally, C-acylation between keto-ester dioxinones **10** and acid chloride **11** derived from N-protected sarcosine could generate dioxinone diketo-esters **9**.

Reaction of Meldrüm's acid **12** with *tert*-butanol at 100 °C gave the half malonate ester **13** in 52% yield (Scheme 3).[14] The corresponding acid chloride **14a**, synthesized with oxalyl chloride, was allowed to react with the lithium enolate **15a** derived from dioxinone **15** by treatment with lithium hexamethyldisilazide to afford keto-ester dioxinone **10a** in 76% yield. In a similar manner, keto-ester dioxinone **10b** was prepared from acid chloride **14b**[15] in a lower yield of 35%.

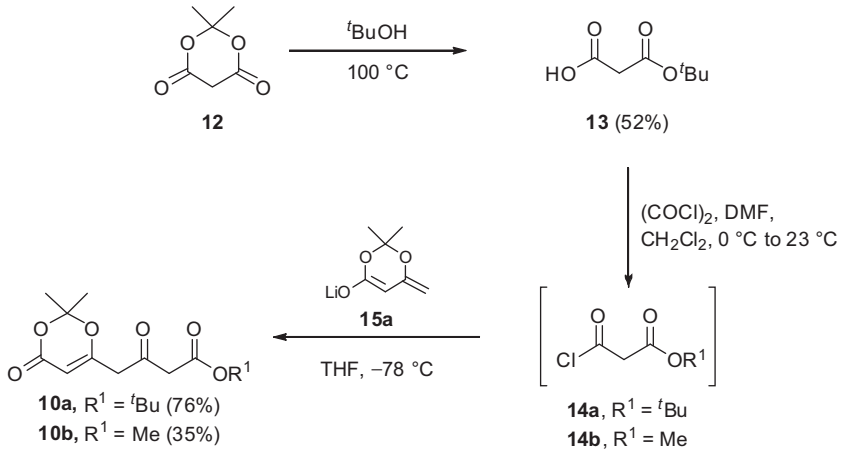
The next step involved the key C-acylation of keto-ester dioxinones via Mg-enolate formation (Scheme 4). Sarcosine (**16**) was protected by sequential reaction with trimethylsilyl chloride[16] and 2-$Me_3SiCH_2CH_2SO_2Cl$ (SESCl) followed by de-trimethylsilylation upon acid work-up to give **17**.[17] Upon treatment with oxalyl chloride, SES-protected sarcosine **17** was converted into the corresponding acid chloride **11a**, which was directly allowed to react with the Mg-enolates **18a** and **18b** of **10a** and **10b** to form dioxinone diketo-esters **9a** and **9b**.[12] These crude adducts were unstable and, therefore, were directly cyclized using triethylamine[18] to give resorcylates **8a** and **8b** in moderate yields of 49% and 30% over three steps, respectively.

Methanolysis of **8a** and **8b** in the presence of cesium carbonate gave methyl esters **19a** and **19b** in good yields (Scheme 5).[18] The deprotection of the SES group with Bu_4NF was followed by subsequent lactamization to give dihydroxy-lactams **7a** and **7b** in 78% and 65% yields, respectively.[19]

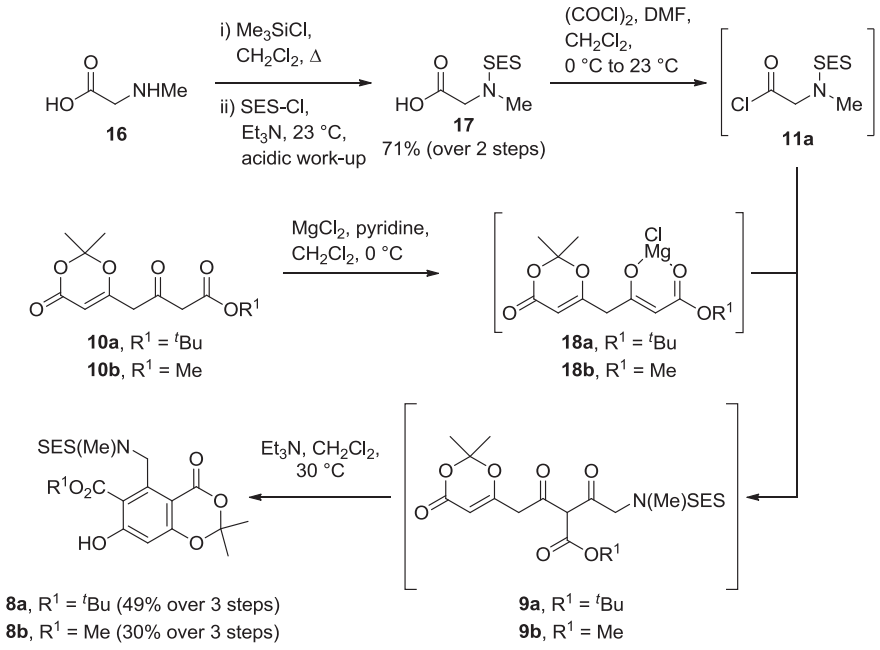
In summary, we have developed a concise five-step synthesis to dihydroxy-isoindolinone-carboxylates **8a** and **8b** in good yield. Both could serve as potential precursors toward the synthesis of the EF-ring system of lactonamycin (**1**). This methodology could be further applied for the synthesis of a wider range of dihydroxy-isoindolinone derivatives starting from different amino acids or dioxinone keto-esters.



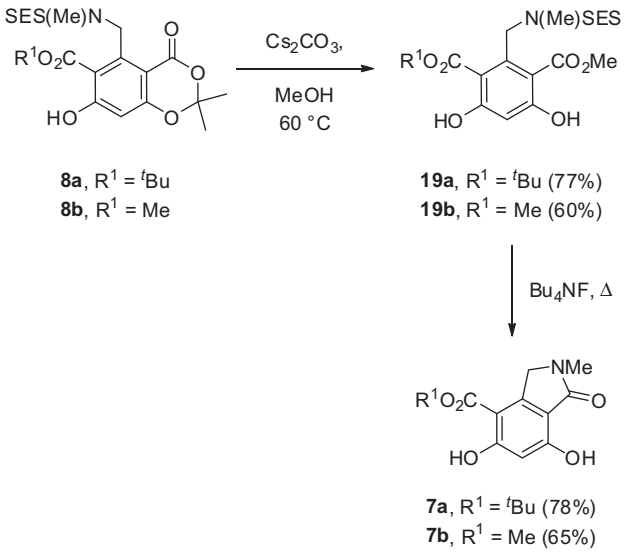
Scheme 2. Retrosynthetic analysis.



Scheme 3. Synthesis of dioxinone keto-esters **10a** and **10b**.



Scheme 4. Synthesis of resorcylates **8a** and **8b**.



Scheme 5. Synthesis of dihydroxy-isoindolinone-carboxylates **7a** and **7b**.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures, characterization data and copies of ^{1}H and ^{13}C NMR spectra for all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.08.173.

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