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Synthesis of the C1−C10 Fragment of Madeirolide A

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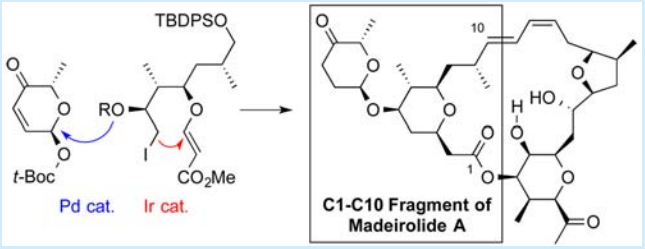
Supporting Information

ABSTRACT: The synthesis of a fully elaborated C1−C10 fragment of madeirolide A has been achieved via a strategy based on a series of stereospecific processes. The concise synthetic route also features an iridium-catalyzed visible light induced radical cyclization for construction of the THP ring and a palladium-catalyzed glycosylation for formation of the α-cineruloside linkage.



Madeirolides are a family of glycosylated macrolides isolated by Wright and Winder from a *Leiodermatium* species harvested from the deep sea off the coast of Madeira, Portugal (Figure 1).[1] Both congeners A (**1**) and B (**2**) were

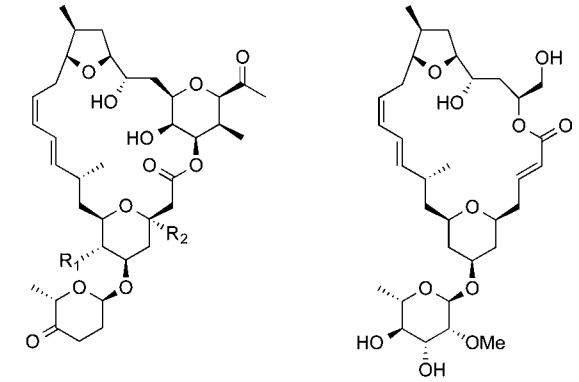


Figure 1. Madeirolides and mandelalide A.

shown to possess inhibitory activity against the fungal pathogen *Candida albicans* with fungicidal MIC values of 12.5 and 25 μg/mL, respectively. Structurally, madeirolides belong to a group of macrolides that feature one or multiple bicyclic ether units embedded within a stereochemically decorated macrolactone scaffold. Differing in the pentasubstituted tetrahydropyran and glycone domains, these sponge-derived polyketides bear considerable structural resemblance to the mandelalide family of macrolides isolated from a species of *Lissoclinum* ascidian.[2] Indeed, madeirolide A (**1**) and the recently revised structure of mandelalide A (**3**) share a nearly identical substructure encompassing 20 carbon atoms of the 24-membered macrolactone backbone.[3] Since these secondary metabolites originate from marine invertebrates yet of distinctive phyla, it remains a possibility that a common microbial symbiont may be involved in their biogenesis.[4] The remarkable structural homology, however, is incommensurate with their antitumor activity profiles: whereas mandelalides exhibited nanomolar cytotoxicity against tumor cell lines, no appreciable antiproliferative activity was detected from madeirolides. Given the difficulties associated with detailed bioassays of madeirolides due to the scarcity of the sponge isolates, along with the interesting issues regarding their stereostructure, biogenetic origin, and biological profile, we embarked on a total synthesis investigation of madeirolides that could enable full-scale biological evaluations.[5] Reported here is the first account of our endeavor accomplishing the synthesis of the fully functionalized C1−C10 fragment of madeirolide A.

Our synthesis strategy arose from the notion that the lactone and (*E*,*Z*)-diene linkages could serve as staging points for macrocyclization (Scheme 1).[3,6] In this plan targeting a penultimate intermediate (e.g., **1′**), it was anticipated that both the C1 ester and the C10−C13 moiety, in the form of a diene or an enyne, would also lend themselves to strategic junctures at which the elaborated fragments **4** and **5** could be conjoined in a convergent manner with flexibility to probe the relative stereochemistry with regard to each domain. An additional element of consideration in the design of the synthesis plan was the prospect of assembling the oxacyclic subunits by way of catalytic methods developed in our laboratory. In particular, the 2,6-*cis*-THP skeleton of **5** was envisioned to be built through a free radical-mediated cyclization of iodide **6** under visible light induced photoredox conditions,[7,8] while the α-cinerulose 5,1′-glycosidic linkage would be established with control of anomeric configuration via the palladium-catalyzed glycosylation[9] with pyranone **7**.[10] With this disconnection relying on the two catalytic events for the critical bond formations, the synthesis problem presented by the aglycon of **5** was essentially reduced to the stereoselective preparation of the C4−C10 subunit **8** possessing four stereocenters, which in turn could be derived from the aldol

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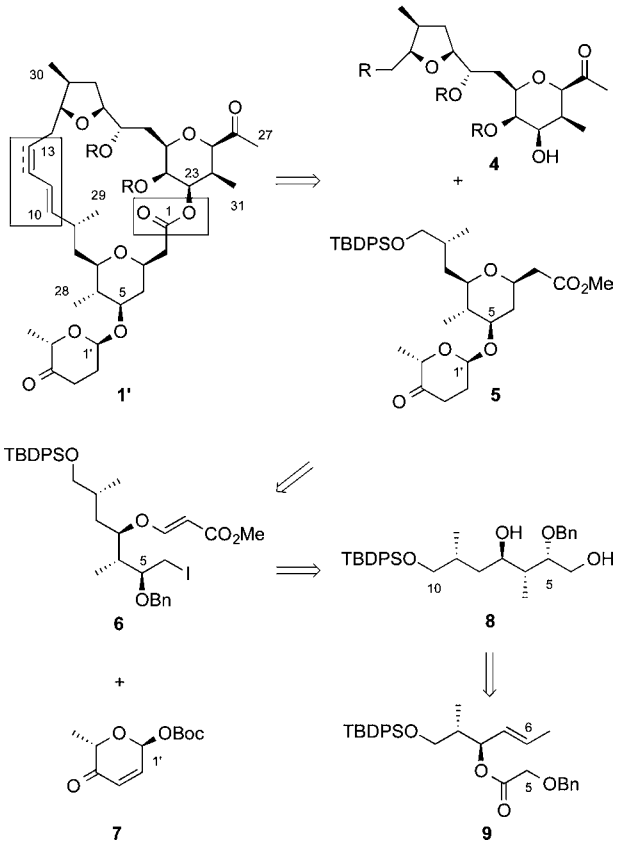
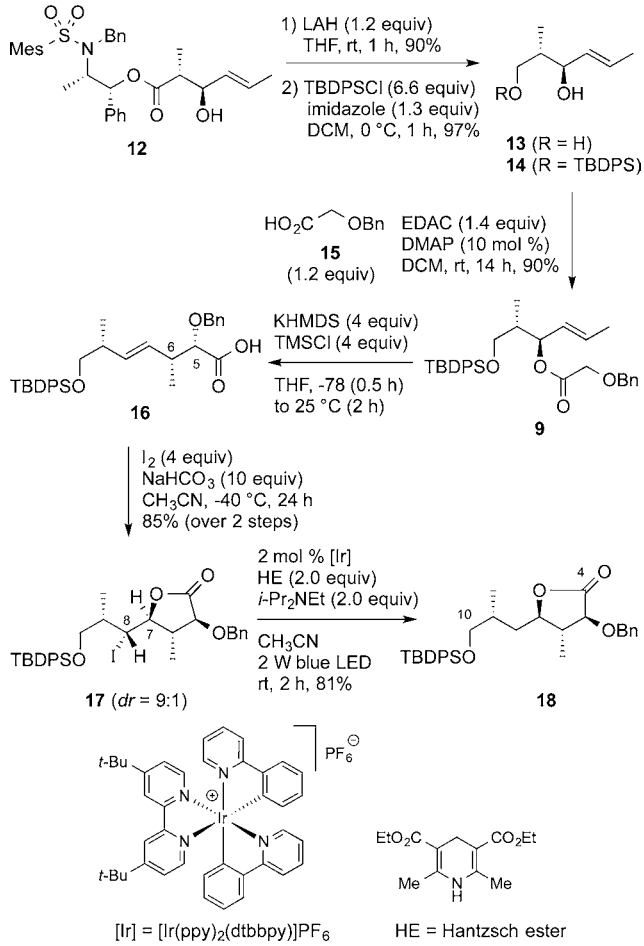
Scheme 1. Retrosynthetic Analysis of Madeirolide A



Scheme 2. Synthesis of C4−C10 Lactone 18



adduct **9** through a sequence involving stereospecific [3,3] sigmatropic rearrangement and alkene hydroxylation reactions.

Based on a synthetic roadmap aimed at establishing all of the stereocenters in the C1−C10 chain of madeirolide A via a series of diastereoselective processes, our synthesis started with the known Abiko−Masamune *anti*-aldol product **12** derived from crotonaldehyde (Scheme 2).[11] Following reductive detachment of the chiral auxiliary, the resulting diol **13** was silylated selectively at the primary hydroxyl group to give TBDPS ether **14**, which was then condensed with acid **15** to give the allylic ester **9**. The Ireland−Claisen rearrangement of **9** took place smoothly with excellent stereoselectivity to provide acid **16** as a single stereoisomer, thus transferring the chirality of the allylic center to the stereochemistry of C5 and C6 centers with concomitant two-carbon chain elongation.[12] In order to install the C7 hydroxyl group via a π-facial selective alkene addition reaction, acid **16** was subjected to a sequence of iodolactonization and deiodination reactions. While literature precedents suggested the halolactonization of γ,δ-unstaturated acids with an intervening substitution at the α and/or β position such as **16** to be straightforward,[13] the strong dependence of the stereochemical outcome on the solvent as well as temperature was noted.[14] After considerable experimentation, it was found that the desired iodide **17** could be obtained in excellent yield (85% over two steps) and diastereoselectivity (dr = 9:1) by performing the reaction at −40 °C using acetonitrile as the solvent. The iodide was then subjected to reductive deiodination to provide lactone **18**. In this radical-mediated hydrodeiodination, visible light photocatalytic conditions gave higher yields of **18** than traditional organosilane and organotin-based methods.[15] However, the established catalytic systems, such as $[Ir(ppy)_2(dtbbpy)]PF_6$/DIPEA[7] and *fac*-$Ir(ppy)_3$/Hantzsch ester/Bu_3N,[16] did not fare well. A brief survey of various conditions for hydrodehalogenation revealed the combination of $[Ir(ppy)_2(dtbbpy)]PF_6$ catalyst and both DIPEA and Hantzsch ester as the reductants to be optimal, affording lactone **18** in 81% yield.

Having prepared the C4−C10 sector **18** equipped with four stereocenters, we then set out to advance it to β-alkoxyacrylate **6** en route to tetrahydropyran aglycon **22** (Scheme 3). For the installation of a β-alkoxyacrylate group at the C7 hydroxyl, lactone **18** was first reduced to diol **8a** and monosilylated to TBS ether **8b** (TBSCl, imidazole, DCM, 90%). Our initial attempts at employing well-established protocols for the Michael reaction with propiolates,[17] however, met with little success, indicating that steric congestion around the C7 alcohol essentially was prohibitive. Despite screening a wide variety of conditions, **21b** could be produced only in unsustainable yield (ca. 5%) from reactions run at elevated temperatures for prolonged reaction times (>48 h). Thus, an alternative approach was sought in which the requisite β-alkoxyacrylate would arise from the selective elimination of cyclic acetal **20**, which could be accessed from diol **8a** via transacetalization with dimethyl acetal **19**. Gratifyingly, when a diastereomeric mixture of cyclic acetal **20** (dr = 1.7:1) was treated with LHMDS at −78 °C, selective ring-opening elimination occurred smoothly to furnish acrylate **21a** as an *E*-isomer exclusively.[18] The ensuing primary alcohol was then converted to iodide **6** poised for a free radical mediated cyclization.[19] In the presence of the iridium

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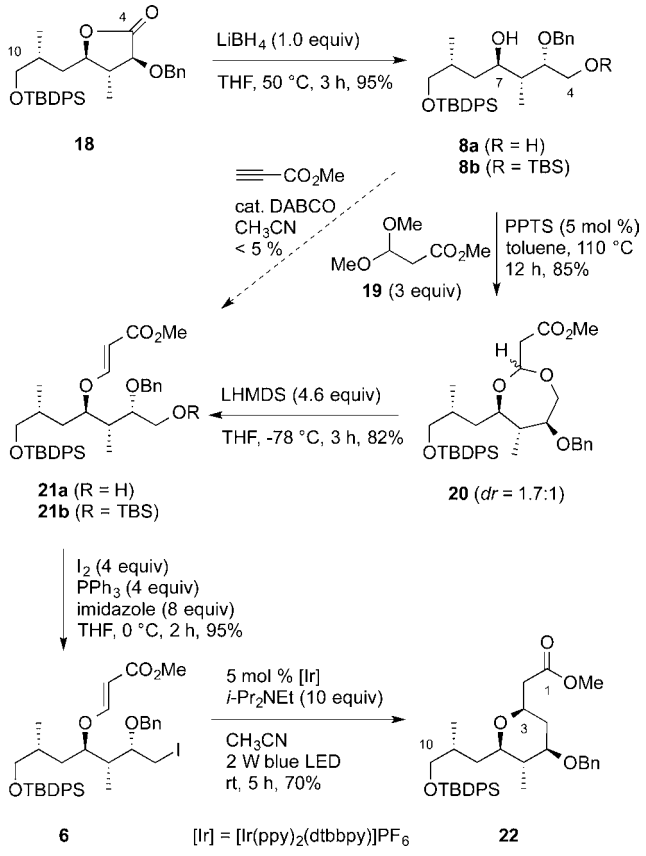
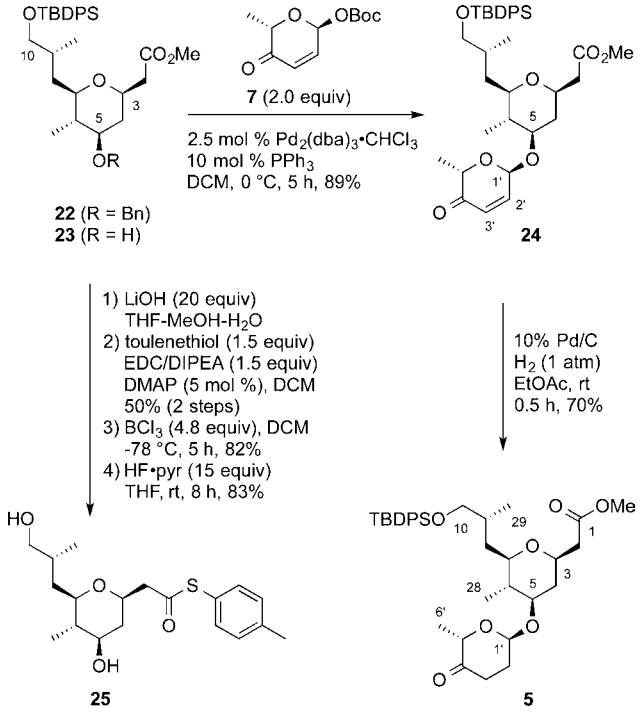
Scheme 3. Synthesis of C1−C10 Aglycon 22



Scheme 4. Completion of the C1−C10 Glycoside 5



catalyst in conjunction with DIPEA, irradiation of **6** with a 2 W blue LED (λ_{max} = 454 nm) strip led to clean reductive cyclization giving rise to the targeted tetrahydropyran **22** in 70% yield with complete 2,6-*cis*-selectivity.

With the THP aglycon **22** in hand, our synthesis investigation entered the final assembly stage, in which attachment of the cinerulose saccharide unit was carried out through stereoselective formation of an α-glycosidic linkage (Scheme 4). After the C5 hydroxyl was unmasked by removal of the benzyl group (20% $Pd(OH)_2/C$, H_2, 91%) from **22**, the resultant alcohol **23** was subjected to a glycosylation with pyranone **7**.[20] Coupling of **23** and **7** by the glycosylation method, making use of a palladium-catalyzed *O*-allylation,[10] furnished **24** in 89% yield as a single anomer. Finally, hydrogenation of the C2′−C3′ alkene in the saccharide generated the fully elaborated C1−C10 fragment **5**.

The spectroscopic signatures of the glyco C1−C10 fragment **5** matched well those of the corresponding sector in madeirolide A. Specifically, a high degree of homology was noted in the ^1H and ^{13}C NMR signals from the C1−C7 as well as the C1′−C6′ regions. In addition, chemical correlation was also conducted by converting methyl ester **22** to thioester **25**, a key intermediate in the related synthesis reported by the Paterson group.[5] All spectroscopic data of thioester **25** corresponded to the reported values in all aspects, indicating the identity of the structure.[21]

The present study has procured a stereoselective and robust synthetic entry to a fully adorned C1−C10 fragment of madeirolide A. Starting from a readily available aldol product, our concise route provides the key intermediate through a series of diastereoselective processes that include Claisen rearrangement, iodolactonization, and radical cyclization, establishing all of the stereocenters along the C1−C10 chain with high stereocontrol. Notably, the 2,6-*cis*-tetrahydropyran and α-cinerulose glycosidic linkage were constructed with complete stereospecificity by taking advantage of the iridium-catalyzed reductive cyclization and palladium-catalyzed glycosylation, respectively. The demonstrated efficiency of visible light photoredox catalysis holds promise for this chemistry in further applications to the synthesis of other THF and THP oxacycle subunits present in the madeirolides. Our campaign for the preparation of the remaining northern fragment, as well as the total synthesis of madeirolide A, is in progress, and the results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00777.

Experimental procedures and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(14) See the Supporting Information for details.

(15) For example, the hydrodeiodination using R_3SiH gave 55% yield. For detailed results of hydrodeiodination under various conditions, see the Supporting Information.

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(18) In this reaction likely involving an ester enolate anion as an intermediate (E1cB mechanism), convergent formation of the (*E*)-acrylate product **21a** from both epimers of acetal **20** is believed to be a consequence of elimination of the primary (C4), in preference to the secondary (C7) alkoxide leaving group via the transition state that minimizes the $A^{1,3}$ strain while leading to a more stable product. For a detailed mechanistic scheme, see the Supporting Information. For a related example, see: Caballero, M.; Garcia-Valverde, M.; Pedrosa, R.; Vicente, M. *Tetrahedron: Asymmetry* **1996**, *7*, 219.

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(21) For the comparison of spectroscopic data and the details of chemical correlation studies, see the Supporting Information.

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