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Synthesis of the floresolide B hydroquinone lactone core using ring-closing metathesis

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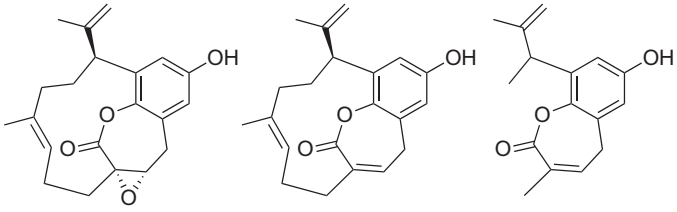
Abstract—The hydroquinone lactone core of the floresolides was synthesized through a ring-closing metathesis (RCM) approach. Optimal RCM efficiency was obtained at *higher* reaction concentration. An unexpected Lewis acid-promoted rearrangement of the hydroquinone and other observations relevant to on-going total synthesis efforts are discussed.

The floresolides[1] are cytotoxic hydroquinone cyclophanes that bear a structural relationship to the longithorone family of prenylated quinones and hydroquinones.[2] The longithorones and the floresolides are both isolated from similar ascidian species found in shallow waters off the Flores Islands, which suggests a possible biogenetic relationship as well. No synthetic approaches to the floresolides have been reported.[3] Our interest in the floresolides as synthetic targets stems from the cyclophane, a motif found within the floresolide tricyclic structure as well as the structure of other natural products under current investigation in our Laboratory.

The major synthetic challenge presented by the floresolides is the *ansa* bridge, which features an isolated, trisubstituted alkene. Isolated, trisubstituted alkenes are often difficult to prepare in a regio- and stereo-specific manner, and when manifest within a cyclophane, the methods available for controlled construction of this functionality are limited considerably. We envision, for the total synthesis, installing this remote alkene before annealing the hydroquinone lactone, as the rigid bicyclic lactone limits the conformational degrees of freedom available to the system. As part of our end game strategy, we aim to effect a ring-closing metathesis[4] to prepare the seven-membered lactone (Fig. 1).

Several potential problems face the proposed olefin metathesis cyclization: (1) Trisubstituted electron-deficient alkenes can be difficult to prepare by ring-closing metathesis. (2) Pendant alkenes such as the isopropenyl group must be inert to metathesis side reactions. (3) Most significantly, the *Z* conformation of esters is on the order of 8.5 kcal/mol lower in energy than the *E* conformation.[5] The *Z*-ester places the chain termini at



floresolide A **(1)** *floresolide B* **(2)** **3**

Figure 1. Floresolides A and B and model lactone **3**.

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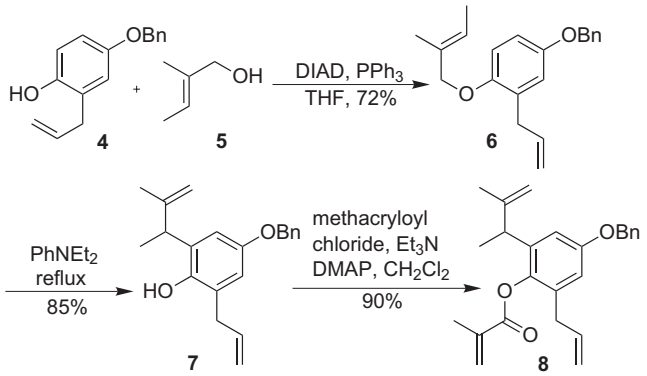
impossibly separated regions of space (vide infra). This unfavorable equilibrium must be overcome for cyclization to occur.[6]

Indeed, despite the ubiquity of olefin metathesis reactions in synthesis, we could find no prior examples of ring-closing metatheses to afford trisubstituted, α,β-unsaturated lactones within either seven-, eight-, or nine-membered rings.[7–9] We are also concerned, considering Fürstner's findings,[7c] about possible olefin migration in the aftermath of cyclization to afford the β,γ-unsaturated lactone.

For the sake of our studies and for instructive purposes relating to future synthetic efforts, we deemed it critical to establish precedent for our cyclization by investigating the synthesis of a model hydroquinone lactone system (**3**). Lactone **3** is essentially a nor-prenyl analog of floresolide B (**2**), in which five carbons of the *ansa* bridge are omitted. The synthesis of **3** described herein addresses the aforementioned concerns, expands the scope of the RCM reaction, and provides key insight for our on-going efforts directed toward the total synthesis of floresolides A and B.



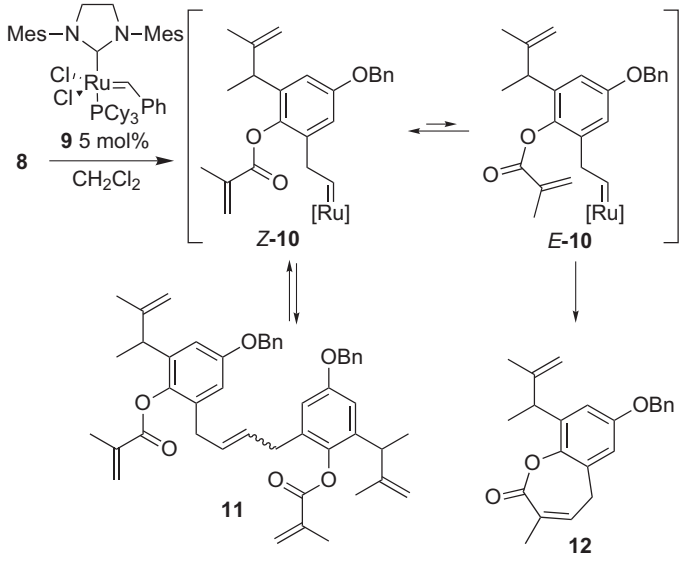
Scheme 1. Synthesis of the cyclization substrate.

Our synthetic sequence began with a Mitsunobu coupling[10] of phenol **4**[11] and (*E*)-2-methyl-2-butenol (**5**).[12] An aromatic Claisen rearrangement[13] of **6** then provided **7**, the 2,6-diallylated phenol. Acylation with methacryloyl chloride afforded **8**, our substrate for the key metathesis cyclization (Scheme 1).

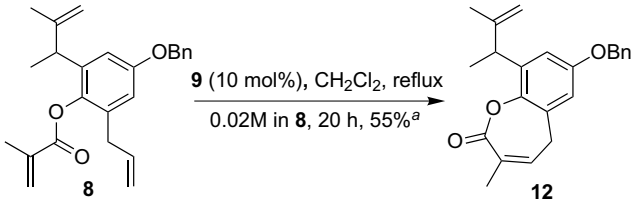
Our initial attempts at cyclization using Grubbs' second-generation catalyst (**9**, 5 mol %)[14] confirmed the expected synthetic hurdles but yielded encouraging results (Scheme 2). We employed high dilution conditions (0.004 mol/L) to thwart expected cross-metathesis pathways. Nonetheless, pseudo-dimer[15] **11** (from cross-metathesis of the allyl moiety) was the major product, along with a low yield (<20%) of the desired lactone (**12**).

Note that the 'third alkene', the terminal disubstituted propenyl moiety, remains intact throughout this process. We hypothesize that acrylate **8** enters the catalytic cycle exclusively by reaction at the terminal, monosubstituted allyl group to generate alkylidene **10**. Cyclization onto the electron-deficient disubstituted acrylate is slow, particularly considering that the acrylate alkene is inaccessible in the (preferred) *Z*-ester conformation (*Z*-**10**, Scheme 2).[5] Therefore, reversible intermolecular cross-coupling occurs even at relatively high dilution. Pseudo-dimer **11** then reenters the catalytic cyclic exclusively via **10**, which in time cyclizes onto the acrylate to afford lactone **12**.[16]

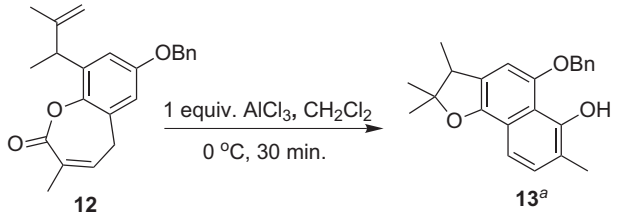
Guided by this hypothesis, we elected to forgo high dilution in favor of a higher catalyst concentration, which we expected would increase the rate at which the system reaches the thermodynamically preferred lactone (**12**). Thus, **8** and **9** (10 mol %) were dissolved in a convenient amount of methylene chloride (0.02 mol/L) and heated at reflux for 20 h to provide lactone **12** as the sole identifiable product, isolated in 55% yield after recrystallization (Scheme 3).[17]



Scheme 2. Initial attempt at olefin metathesis.



Scheme 3. Optimized cyclization conditions: [a]Average yield of **12** following chromatographic purification and recrystallization (three experiments).

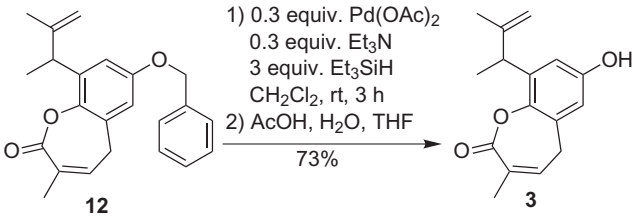


Scheme 4. Lewis acid-promoted rearrangement of **12**.

To complete our study we needed to cleave the benzyl ether[18] and reveal hydroquinone **3**. We looked first at Lewis acids rather than reducing agents out of concern for the pendant alkenes present in **12**. In doing so, we observed an interesting rearrangement (albeit counter to our synthetic goals) exemplified by the aluminum chloride-promoted reaction outlined in Scheme 4. Naphthol **13** was the only detectable product from this experiment.[19]

Birkofer's hydrogenolysis[20] was recently shown to remove benzyl ethers selectively in the presence of other potentially labile functionality.[21] Consistent with prior reports, a black, heterogeneous mixture of **12**, palladium acetate, triethylamine, and triethylsilane gave rise to hydroquinone lactone **3** after workup with acetic acid. Triethylamine is a necessary component for debenzylation; however, it also promotes isomerization of **12** to the β,γ-unsaturated lactone. For best results (in this case), triethylamine must be included in molar ratios equal to or less than that of the palladium catalyst. This carefully optimized protocol affords the floresolide lactone model system (**3**) in 73% yield as the sole isolated product (Scheme 5).

In summary, we prepared a hydroquinone lactone model of floresolides A and B using a ring closing metathesis as the key step. This heretofore unprecedented metathesis formation of a seven-membered methacrylate lactone



Scheme 5. Birkofer hydrogenolysis of benzyl ether **12**.

occurs best by embracing the kinetic detour through cross-metathesis en route to the thermodynamically preferred cyclization product (**12**). We also identified and circumvented the propensity of this system to rearrange to naphthol **13**. Armed with these key insights into the hydroquinone lactone chemistry, we are now constructing the *ansa* bridge to advance material suitable for the total synthesis of the floresolides. Details of our on-going efforts will be reported in due course.

Acknowledgments

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Supplementary data

Experimental procedures and characterization data for all compounds and a proposed mechanism for the transformation **12**→**13**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.09.023.

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