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Total Synthesis of Lehualide B by Allylic Alcohol−Alkyne Reductive Cross-Coupling

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Abstract: The total synthesis of anticancer marine natural product lehualide B is described. Overall, the synthesis proceeds in just eight steps from a simple γ-pyrone, does not require the use of protecting groups, and delivers each nonconjugated trisubstituted alkene with high levels of stereoselection. The challenging C12−C16 bis-trisubstituted 1,4-diene was installed with a complex reductive cross-coupling reaction between a preformed Ti−alkyne complex and a pyrone-containing allylic alcohol.

The lehualides (Figure 1) are a family of pyrone-containing marine natural products recently isolated from an undescribed Hawaiian *Plakortis* sp. that have been shown to possess anticancer properties in a focused evaluation of ovarian (IGROV-ET) and leukemia (K562) cell lines.[1] Interestingly, subtle differences in pyrone substitution apparently lead to dramatic differences in biological properties, as lehualide B (**2**) serves as a nanomolar inhibitor of IGROV-ET cell proliferation, while its isomer lehualide A was not found to have significant growth inhibitory effects in either IGROV-ET or K562 cells. This differential biological profile is interesting, especially in light of the close structural homology between the pyrone ring of lehualide B and the pyridine subunit shared by the piericidins (**3**), potent inhibitors of the mitochondrial electron transport chain protein NADH-ubiquinone reductase (Complex I).[2]

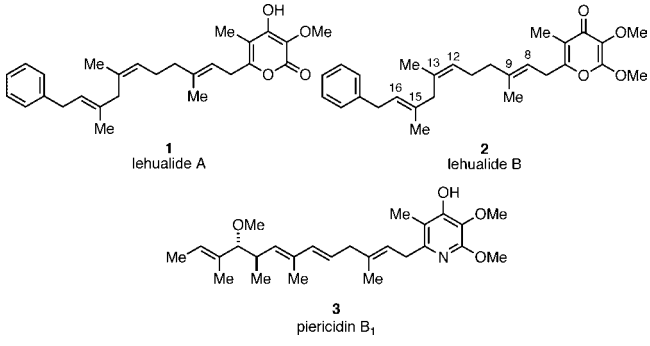

Figure 1. Structure of lehualide A, B, and piericidin B_1.

While lehaulide does not possess a single chiral center, the stereochemistry and substitution of the polyunsaturated tail represent a significant challenge to modern synthetic organic chemistry. Perhaps the most complex stereochemical feature is the C12−C16 skipped diene that is composed of two trisubstituted alkenes of (*E*)- and (*Z*)-stereochemistry. The synthesis of such stereodefined architecture would be difficult with modern synthetic methods based on carbonyl olefination or transition metal-catalyzed cross-coupling. While methods based on carbonyl olefination would inevitably be plagued by challenges associated with the control of stereochemistry in the establishment of the trisubstituted alkenes from ketones and difficulties associated with advancing unstable β,γ-unsaturated systems, transition metal-catalyzed coupling would be similarly complex owing to the multistep nature of synthetic pathways to the required stereodefined coupling partners and the associated problems with regio- and stereocontrol in the reaction of intermediate π-allyl complexes. In addition to these difficulties, each alkene present in the system (from C8−C16) is separated from at least one other unsaturation by a methylene, a structural feature that both decreases stability and further complicates any attempted synthesis. Here, we describe the first total synthesis of any member of the lehualide class of marine natural products, defining a route to lehualide B that installs each trisubstituted alkene with high levels of stereoselectivity and proceeds in just eight steps from a readily available γ-pyrone.

Our plan for the synthesis of lehualide B was centered around a late stage introduction of the C12−C16 bis-trisubstituted skipped diene by a regio- and stereoselective reductive cross-coupling reaction of the fully functionalized coupling partner **5** with alkyne **4** (Figure 2).[3] While we have previously described the merits of

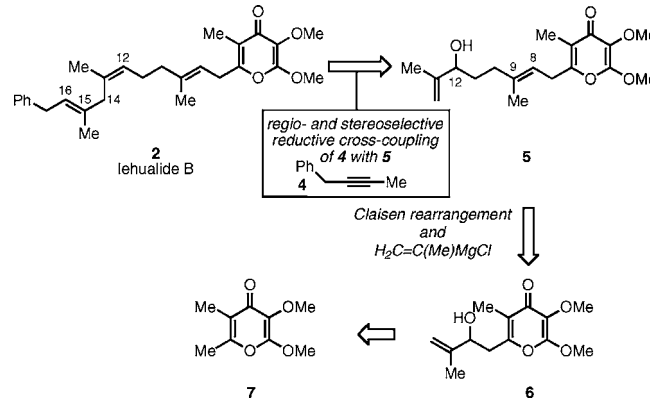

Figure 2. Retrosynthesis of lehualide B.

Ti-mediated reductive cross-coupling of internal alkynes with allylic alcohols as a means of preparing skipped dienes, this planned synthesis of lehualide B presented new challenges to this chemistry that include investigating the compatibility of this process with a potentially sensitive γ-pyrone.[4] Further, this optimistic bond construction called for regioselective functionalization of a relatively simple and sterically unbiased alkyne.[5] Moving on, allylic alcohol **5** was thought to derive from **6**, via stereoselective Claisen rearrangement[6] and addition of 2-propenylmagnesium chloride to the resulting aldehyde. Finally, allylic alcohol **6** was reasoned to be readily available from γ-pyrone **7**.

The synthesis of **7** commenced with β-ketoester **8** (Figure 3). Iodosobenzene diacetate-mediated oxidation in methanol provided the α-methoxy-β-ketoester **9** in 70% yield.[7] Next, formation of the

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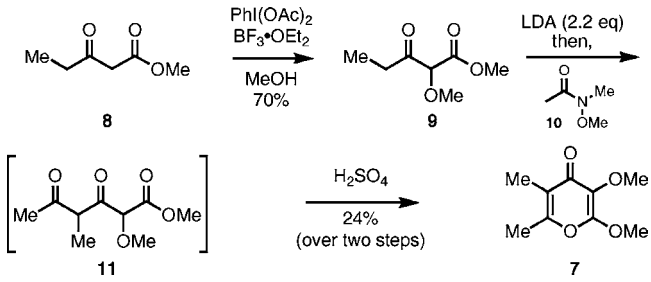

Figure 3. Synthesis of γ-pyrone **7**.

dianion of **9** (LDA, THF), followed by addition of the Weinreb amide **10**, furnished the tricarbonyl **11** as a mixture of isomers. Stirring this tricarbonyl in neat H_2SO_4 for 21 h then resulted in the generation of γ-pyrone **7** in a modest 24% yield (over two steps).

Our successful advance of γ-pyrone **7** to lehualide B is illustrated in Figure 4. Metalation of **7**, followed by addition to the α-phenylseleno aldehyde **12**, provided pyrone **13** in 78% yield. Subsequent oxidation and *syn*-elimination then furnished allylic alcohol **6** in 94% yield. Conversion to the stereodefined γ,δ-unsaturated aldehyde **14** proceeded uneventfully and with the anticipated levels of stereoselectivity typically seen for Claisen rearrangement of related allylic alcohols (90% yield over two steps; $E{:}Z = 10{:}1$).[8] Chemoselective nucleophilic addition of 2-propenylmagnesium bromide then delivered allylic alcohol **5** in 59% yield, suitably functionalized for the planned reductive cross-coupling reaction.

In light of the unexpectedly high reactivity of the pyrone's carbonyl group toward nucleophiles, we opted to access the requisite alkoxide for Ti-mediated reductive cross-coupling by using 2.5 equiv of LiHMDS to simultaneously mask the pyrone as a γ-enolate. As depicted in Figure 5, exposure of the Li-dianion of **5** (**17**), generated by exposure to LiHMDS in THF, to the Ti−alkyne complex **18** (derived from reaction of **4** with $ClTi(O\textit{i}\text{-}Pr)_3$ and $c\text{-}C_5H_9MgCl$) resulted in the formation of coupled products in 50% yield, presumably by a sequence of events that includes (1) rapid and reversible ligand exchange (**17** + **18** ⇌ **19**), (2) intramolecular carbometalation (via **20**), and (3) *syn*-elimination (via **21**).[9] While lehualide B was produced by this C−C bond process, regiochemical control in the functionalization of **4** was poor, leading to the

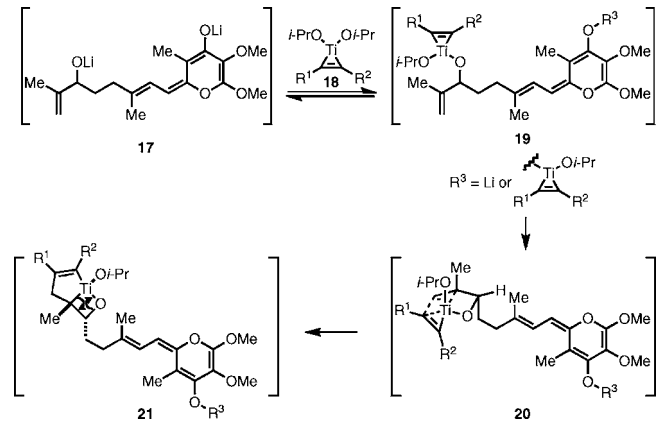

Figure 5. Empirical model for allylic alcohol−alkyne coupling.

formation of a 1.3:1 mixture of isomeric products.[5] To circumvent this problem, we pursued reductive cross-coupling of TMS-propyne (**15**) with allylic alcohol **5**. Preformation of a Ti−alkyne complex of **15** (by exposure to the combination of $ClTi(O\textit{i}\text{-}Pr)_3$ and $c\text{-}C_5H_9MgCl$, −78 to −40 °C) was followed by cannula transfer to a −78 °C solution of the Li-dianion of **5**, followed by slow warming to 0 °C. After aqueous quench of this reaction, we were delighted to find that reductive cross-coupling was successful and furnished the stereodefined vinylsilane **16** in 61% yield ($Z{:}E$ = 7:1; rs ≥ 20:1). Interestingly, no evidence was found for competitive functionalization of the pendant pyrone.

Next, conversion of the stereodefined vinylsilane to the corresponding vinyliodide was straightforward (NIS, $ClCH_2CN$, EtOAc),[10] and subsequent Pd-catalyzed cross-coupling with benzylzinc bromide furnished lehualide B in 63% yield (over two steps).

Overall, we report the first total synthesis of the marine natural product lehualide B. The shortest synthetic pathway proceeds in just six steps from γ-pyrone **7**, yet delivers an inseparable mixture of regioisomeric products. An alternative sequence was established that delivers lehualide B in just eight steps from pyrone **7** and establishes the complex polyunsaturated tail with high levels of stereocontrol. The orthogonality of Claisen rearrangement and Ti-

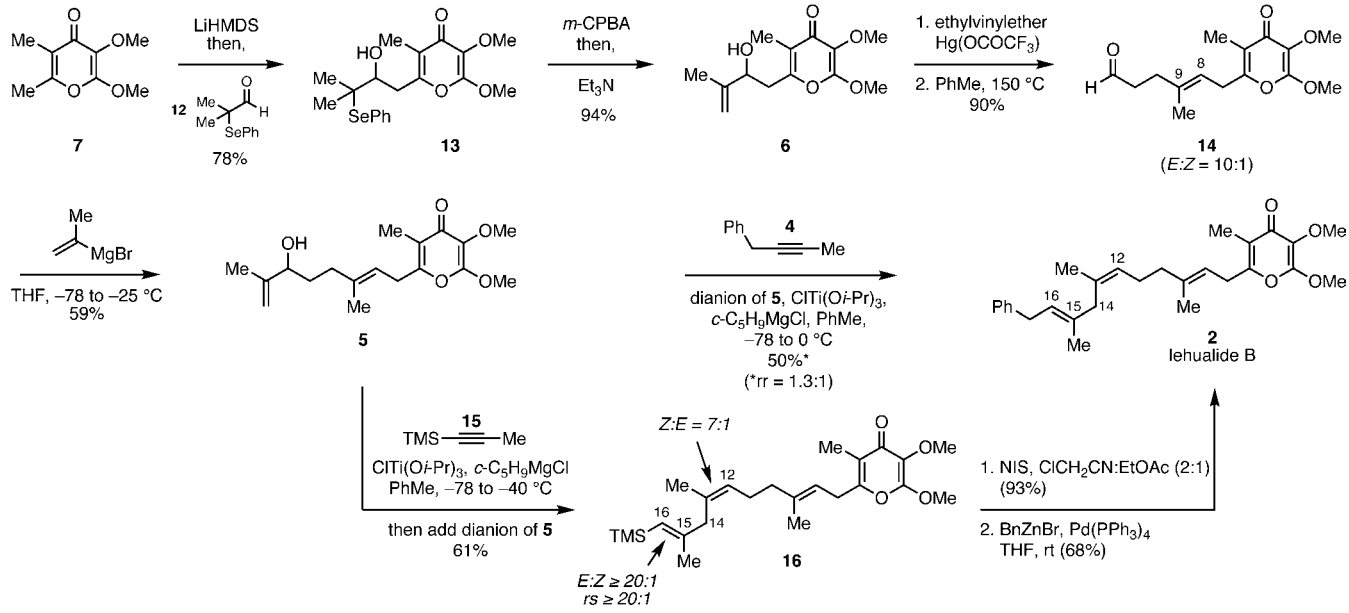

Figure 4. Synthesis of lehualide B.

mediated reductive cross-coupling reaction is notable for the elaboration of the intermediate allylic alcohols **6** and **5**. Finally, the success of the reductive cross-coupling reaction in advancing pyrone **5** speaks to the chemoselectivity possible in this type of bimolecular C−C bond forming process and further supports the role that this and related Ti-mediated convergent coupling reactions can play in complex molecule synthesis.

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Supporting Information Available: Experimental procedures and tabulated spectroscopic data for new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) While our standard reaction conditions for allylic alcohol−alkyne reductive cross-coupling start with preformation of a Ti−alkyne complex (followed by addition of the allylic alkoxide), during the study of this reaction we found that premixing the coupling partners prior to addition of Ti(IV) alkoxide and Grignard reagent provided higher yields of the coupled product.
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