Organic LETTERS

Letter

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Total Synthesis of Sandresolide B and Amphilectolide

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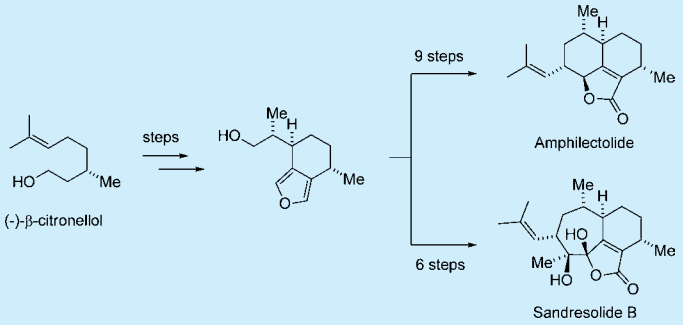
Supporting Information



ABSTRACT: The total synthesis of the diterpenoids sandresolide B and amphilectolide from a common furan building block is presented. Key steps include palladium-mediated carbonylation, lanthanide catalyzed ring closure, Myers alkylation, intramolecular Friedel–Crafts acylation, photooxygenation, and a Kornblum–DeLaMare rearrangement.

The Caribbean octocoral *Pseudopterogorgia elisabethae* is a chemically prolific species that has attracted the interest of natural product chemists for years.[1] Since the 1980s, when the Fenical group first isolated natural products from this family, over 40 marine metabolites have been isolated from *Pseudopterogorgia elisabethae*. Many of these natural products have been collected, isolated, and structurally elucidated by the Rodríguez group, and they feature a broad spectrum of biological activity against inflammation, tuberculosis, cancer, and antiplasmodial activity.[1]

Our synthetic interest in compounds from the *Pseudopterogorgia elisabethae* family arises from the recognition that, although structurally diverse, these natural products also share structural patterns that could be accessed through a common building block. From the outset, our prior experience with furans and their oxidized variants guided our focus toward amphilectolide, the sandresolides, and the caribenols (Figure 1).[2] Interestingly, **1**–**6** were all obtained from deep-sea expeditions near San Andrés island, Colombia, by Rodríguez and co-workers. Amphilectolide, **1**, was structurally elucidated in 2000,[3] and sandresolides A and B, **2** and **3**, were first reported in 1999.[4] Sandresolide C, **4**, a diastereomer of sandresolide B, **3**, with respect to the hydroxyl and acetal stereochemistry, was disclosed in 2009.[5] These compounds also bear a structural resemblance to the caribenols **5** and **6**, reported in 2007.[6] Amphilectolide, **1**, sandresolide C, **4**, and caribenols A and B, **5** and **6**, are active against *Mycobacterium tuberculosis* $H_{37}R_V$ (41%, 15%, 61%, and 94% growth inhibition at 6.25 μg/mL, respectively).[5] Sandresolide C, **4**, also shows an IC_{50} of 18 μg/mL against the *Plasmodium falciparum* W2 (chloroquine-resistant) strain. Curiously, an evaluation of sandresolides A and B, **2** and **3**, has not been reported. It is possible that material limitations have hampered full biological evaluation of sandresolides A and B, **2** and **3**, enhancing their value as synthetic targets.

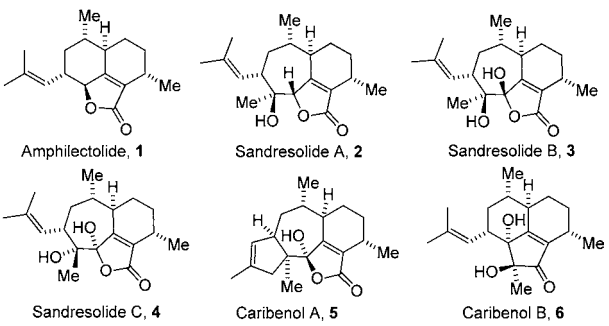


Figure 1. Selected diterpenoids from *Pseudopterogorgia elisabethae*.

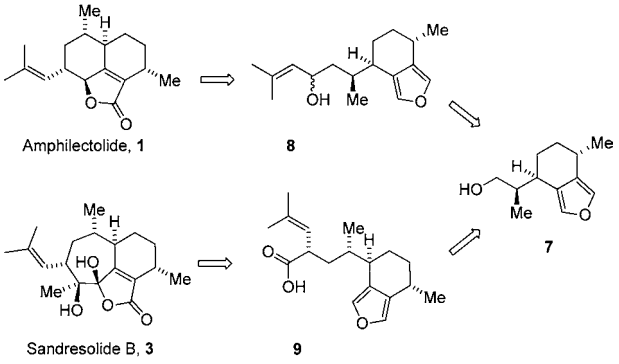
To date, the only total synthesis reported within this collection of natural products is the total synthesis of caribenol A, **5**, by the Yang group.[7] We report herein the first total synthesis of amphilectolide, **1**, and sandresolide B, **3**.

Retrosynthetically, we envisioned that all natural products in Figure 1 could be accessed from a common furan **7**. In the case of amphilectolide, **1**, this could be done via allylic alcohol **8**, whereas in the case of sandresolide B, **3**, this could be achieved via carboxylic acid **9** (Scheme 1). The nucleophilic furan moiety in **8** and **9** would be used to close the six- or seven-membered ring in **1** and **3** via allylic alkylation or Friedel–Crafts acylation, respectively. In the final steps of the syntheses, the butenolide

Received: November 1, 2013
Published: December 5, 2013

dx.doi.org/10.1021/ol403156r | *Org. Lett.* 2014, 16, 166–169

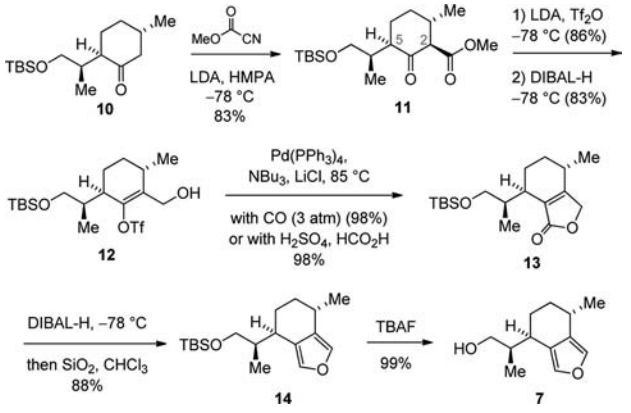
Scheme 1. Retrosynthetic Analysis of Amphilectolide, 1, and Sandresolide B, 3



or hydroxybutenolide would be oxidatively elaborated from the furan.

Our access to furan building block **7** relies on a general strategy developed by Molander to anneal furan rings to ketones.[8] The synthesis commences with the preparation of ketone **10**, available in eight steps from (−)-β-citronellol (Scheme 2).[9] Ketone **10** was homologated with Mander's

Scheme 2. Preparation of Key Furan Building Block 7

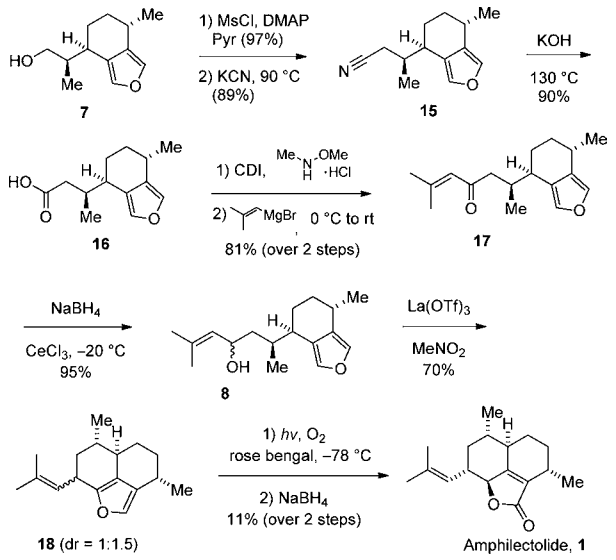


reagent to provide **11**,[10] the relative stereochemistry of which was established by NOE correlations. Conversion of **11** into the corresponding enol triflate required a low temperature and a strong base, and reduction of the resulting ester provided carbonylation precursor **12**.

Initial experiments were guided by known butenolide-producing couplings on simpler substrates. All known protocols at the time proceeded using catalytic amounts of palladium and carbon monoxide (CO) at ambient pressure. In our case, no reaction was observed under these conditions, presumably due to steric constraints. Therefore we employed conditions using CO at elevated pressures (3−5 bar) to achieve a 98% yield of desired butenolide **13**. Even under these conditions, complete conversion required 48 hours of heating at reflux in acetonitrile. Subsequently, this key step was met with even further improvement using CO generated *in situ*.[11] To our delight, the conversion also proceeded in 98% yield and could now take place without the use of a toxic gas canister. Completion of furan building block **7** involved the reduction of butenolide **13**, followed by mild dehydration and cleavage of the TBS protecting group.

With gram quantities of **7** in hand, we proceeded to synthesize amphilectolide, **1** (Scheme 3). Mesylation of furan **7**

Scheme 3. Total Synthesis of Amphilectolide, 1



was followed by homologation with potassium cyanide to furnish nitrile **15**. While direct addition of 2-methyl-2-propenylmagnesium bromide provided enone **17** in 20% yield, we ultimately took a three-step approach involving saponification and conversion to the corresponding Weinreb amide, followed by Grignard addition to furnish unstable enone **17**. Immediate reduction of **17** was carried out under Luche conditions to afford allylic alcohol **8**, a suitable precursor for ring closure.

After gaining access to the allylic alcohol **8**, ring closure was investigated under a variety of protic and Lewis acidic conditions. Lanthanum(III) triflate[12] provided the best yields, although the diastereoselectivity was poor, as it was in all reaction conditions screened. The lanthanum(III) triflate mediated ring closure was verified to proceed via an SN_1 mechanism. When the two diastereomers of precursor **8** were separated and either was subjected to the Lewis acid, the same 1:1.5 ratio of diastereomers of **18** resulted. Unfortunately, the two diastereomers of **18** could not be separated and individually characterized.

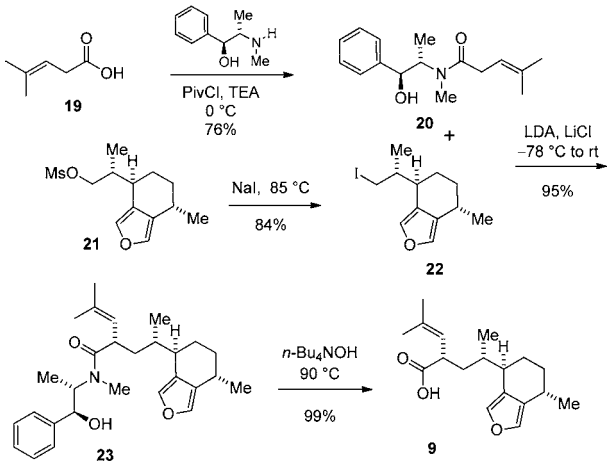
The final steps for amphilectolide, **1**, consisted of a challenging furan oxidation, followed by reduction, to provide the butenolide moiety of **1**. We screened conditions, including the use of peracids,[13] magnesium bis(monoperoxyphthalate) hexahydrate,[14] and photooxygenation using Rose Bengal as a sensitizer.[15] For the latter, rapid consumption of starting material was observed to provide a number of unstable products. Therefore, we explored a variety of reductive, acidic, and basic workup conditions to encourage the collapse of the presumed intermediate endoperoxides. After many failed attempts, the total synthesis of amphilectolide, **1**, was completed via photooxygenation of a diastereomeric mixture of **18** in the presence of Hünig's base, followed by immediate reduction with sodium borohydride. This procedure provided a complex mixture of products, from which amphilectolide, **1**, could be isolated in low yield. All spectra of synthetic amphilectolide, **1**, were in accordance with the reported natural product.[3]

dx.doi.org/10.1021/ol403156r | *Org. Lett.* 2014, 16, 166−169

Building on our experiences gained during the synthesis of amphilectolide, **1**, we then proceeded to synthesize sandresolide B, **3**, in a shorter sequence and with better yields. To this end, we employed a Myers asymmetric alkylation, which is known to be effective in sterically encumbered systems.[16]

In anticipation of the Myers alkylation, we prepared (+)-pseudoephedrine derivative **20** via known acid **19** (Scheme 4).[17] Double deprotonation of **20** provided a highly

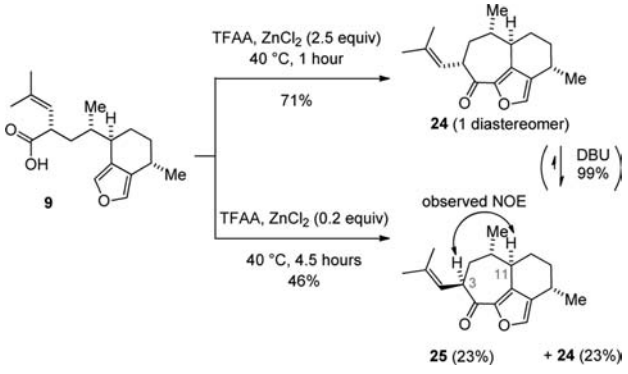
Scheme 4. Myers Alkylation to Access Ring-Closure Precursor 9



nucleophilic enolate, and lithium chloride was added to both accelerate the reaction and suppress *O*-alkylation.[18] Addition of iodide **22**, prepared via a Finkelstein reaction from mesylate **21**, allowed for the preparation of amide **23** in 95% yield and as a single diastereomer. This compound could be saponified to acid **9** using tetrabutylammonium hydroxide at high temperature.[18]

With key acid **9** in hand, we proceeded to install the seven-membered ring of the sandresolides using an intramolecular Friedel–Crafts acylation (Scheme 5). Ring closure was

Scheme 5. Ring Closure and NOE Correlations To Characterize 25



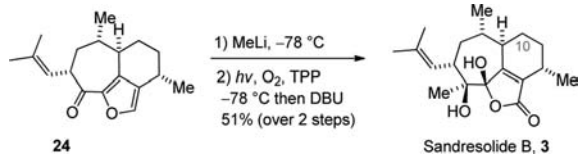
investigated using various activation methods with Lewis and Brønsted acids. The only conditions that provided desired product **24** entailed activation of the acid with trifluoroacetic anhydride followed by gentle heating with zinc chloride. Short reaction times and stoichiometric zinc chloride were key to this ring closure; after 1 hour, epimerization of the stereocenter next to the carbonyl group produced **25**.

We pursued a few avenues to establish the relative stereochemistry of diastereomers **24** and **25**. NOESY measurements were taken on the separable diastereomers, and **25** held the key correlation to establish the structure: protons at C(3) and C(11) showed correlations at δ 3.44 and δ 2.45 respectively.

We also established that **25** is the thermodynamically more stable product: treatment of either diastereomer with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) effected clean conversion to **25**. This finding was confirmed through a conformational search using Macromodel (10 000 step Monte Carlo search, solvent-free OPLS algorithm),[19] which indicated that the undesired diastereomer **25** was thermodynamically more stable by 6.7 kcal/mol. The above findings explain why short reaction times are critical to obtain a diastereomerically clean ring closure: our desired product **24** is the kinetic product.

Completion of sandresolide B, **3**, required a stereoselective addition of a methyl organometallic reagent to the carbonyl of **24**, followed by furan oxidation to form the hydroxybutenolide moiety (Scheme 6). The addition of methyl magnesium

Scheme 6. Completion of Sandresolide B, 3



bromide proceeded smoothly to form the corresponding unstable benzylic tertiary alcohol. We originally hoped to obtain both diastereomers, since one could lead to sandresolide B, **3**, and the other to sandresolide C, **4**. Interestingly, substrate control led to the predominant formation of the precursor of sandresolide B, **3**, which was immediately subjected to photooxygenation. The photooxygenation conditions used in amphilectolide, **1**, did not allow for the clean and reliable formation of sandresolide B, **3**. Optimization led to tetraphenylporphyrine as a photosensitizer,[20] running the reaction without methanol (previously used to solubilize Rose Bengal) to avoid the potential formation of alkoxybutenolides,[15] and using DBU to collapse the *endo* peroxide via a Kornblum–DeLaMare rearrangement.[21] Of the bases screened for this rearrangement, only DBU allowed for the efficient formation of sandresolide B, **3**. These highly optimized conditions provided sandresolide B, **3**, from **24** in 51% yield over two steps.

The proton NMR data of sandresolide B, **3**, were in accordance with the literature except for the axial proton at C(10), which was reported to have the same chemical shift as the equatorial proton in the isolation paper.[4] Our suspicions of a misassignment arose because the axial and equatorial protons are consistently found with different shifts of approximately δ 1.3 and δ 2.0 respectively for all compounds in this project, as well as in the reported spectra of amphilectolide, **1**, and sandresolide C, **4**. The HSQC of sandresolide B, **3**, shows a correlation between the carbon at δ 28.2 and protons at δ 1.27 and δ 2.00 while the reported HMBC correlates the carbon at δ 28.2 with two protons at δ 2.00.[4] Correspondence with the isolationist, Abimael D. Rodríguez, served to confirm the minor misassignment in the isolation paper, verifying that our spectral data for sandresolide B, **3**, matched those of the isolated natural product.

dx.doi.org/10.1021/ol403156r | *Org. Lett.* 2014, 16, 166–169

In summary, we have developed a scaleable route to a valuable furan building block, **7**, which has been used for the first total syntheses of amphilectolide, **1**, and sandresolide B, **3**. Key steps include palladium-mediated carbonylative butenolide formations, a Myers alkylation, a lanthanum(III) triflate-catalyzed ring closure, an intramolecular Friedel–Crafts acylation, photooxygenations, and a Kornblum–DeLaMare rearrangement. The use of our key furan building block **7** in the synthesis of a number of other diterpenoids isolated from *Pseudopterogorgia elisabethae*, such as caribenols A and B, **5** and **6**, is under active investigation in our laboratories and will be reported in due course.[6]

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, spectroscopic and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Deutsche Forschungsgemeinschaft (SFB 749) for financial support. The authors would like to acknowledge Dr. Eddie Myers (LMU, München) for helpful discussions.

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