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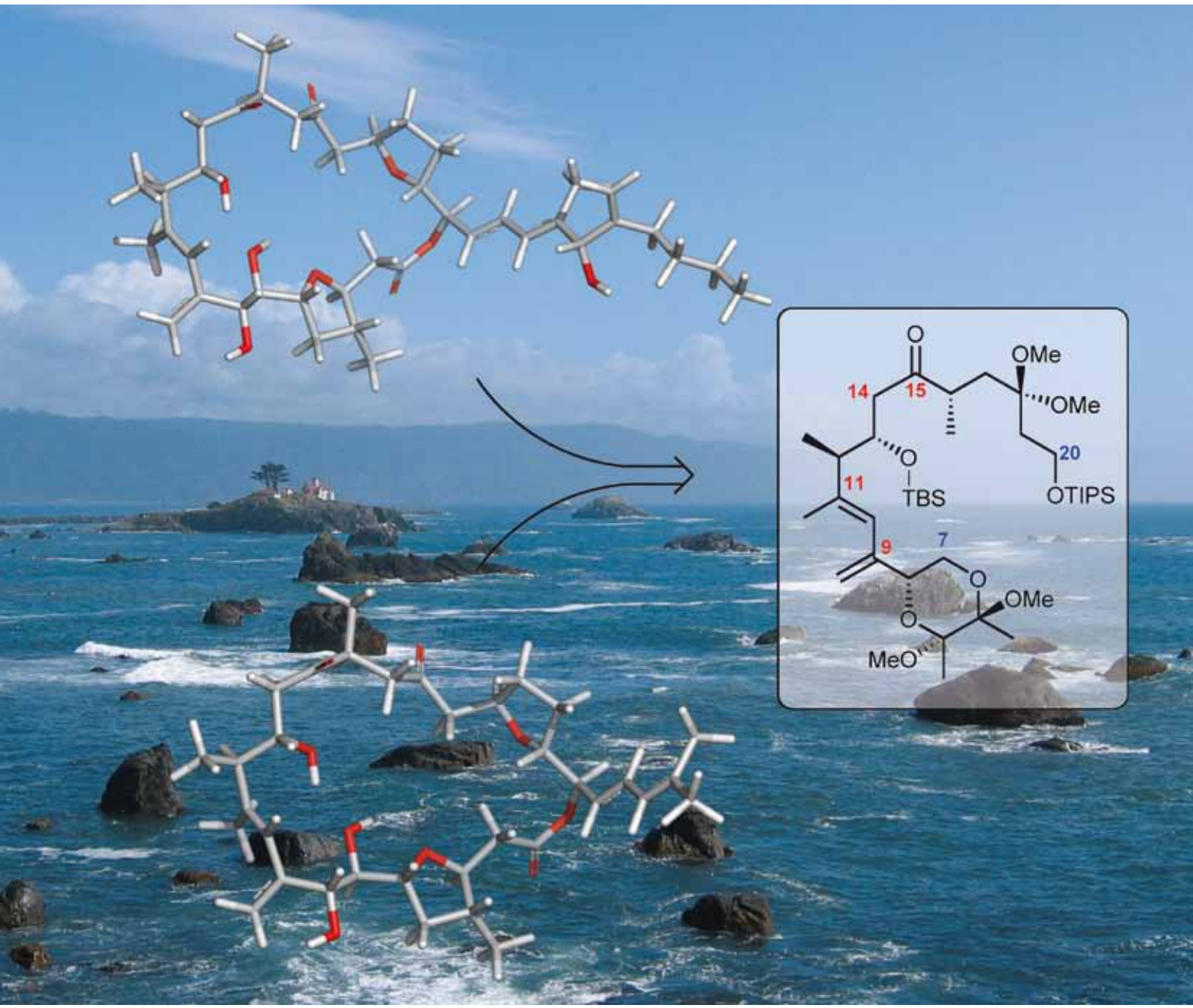

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Efficient synthesis of the C_7-C_{20} subunit of amphidinolides C and F†

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Synthesis of the C_7-C_{20} subunit of amphidinolides C and F has been accomplished utilizing a Me_3Al-mediated ring opening of a vinyl iodide/allylic epoxide to establish the $C_{12,13}$ *anti* stereochemistry, an organolithium coupling/olefination sequence to construct the C_9-C_{11} diene moiety and a sulfone alkylation/hydroxylation strategy to join the C_7-C_{14} and C_{15}-C_{20} fragments.

The amphidinolide natural products have generated considerable attention since their initial discovery in the 1980's by Kobayashi and co-workers.[1] Two of the most complicated members of this family are amphidinolides C (**1**) and F (**2**) (Scheme 1).[2] While most of the amphidinolides have attracted sizable synthetic interest from numerous researchers, macrolides **1** and **2** have been significantly underexplored and remain unconquered synthetic targets.[3] We were drawn particularly to amphidinolide C (**1**) as it is one of the most potent members of this natural product family against a range of cancer cell lines.[2] Additionally, the macrocyclic core of both **1** and **2** possesses significant synthetic challenges: (a) 11 stereogenic centers, (b) two separate substituted THF rings, (c) the sensitive C_{15},C_{18}-diketone moiety and (d) the C_9-C_{11} highly substituted diene. Herein, we detail a unified synthesis of the entire C_7-C_{20} western portion of amphidinolides C and F.

Our retrosynthetic strategy for macrolides **1** and **2** is shown in Scheme 1. The three main disconnections are at the $C_{25,26}$ alkene sidearm, the C-O bond of the macrolactone and the $C_{14,15}$ bond. The C_{25}-C_{26} alkene should be accessible *via* a Julia-Kocienski olefination—thereby allowing access to both natural products **1** and **2** through a common intermediate. The C-O linkage of the macrolactone could be constructed *via* standard Yamaguchi-type cyclization.[4,5] The most difficult of these three dissection points is the C_{14}-C_{15} bond. The proposed route requires a challenging alkylation of an α-branched halide[6] followed by hydroxylation of the resultant sulfone coupled product with *in situ* decomposition to the corresponding ketone.[7] While these types of oxidative desulfurizations have been known for some time, this transformation has found only limited application in complex molecule synthesis.[8,9] Any strategy must also take care to avoid furan formation between the C_{15} and C_{18} carbonyl motifs. Finally, the C_9-C_{11} diene moiety should be accessible *via* an organolithium addition of vinyl iodide **6** to Weinreb amide **7** followed by methylenation.

The C_9-C_{11} diene motif is worthy of additional comment. These types of highly substituted dienes have proven challenging to construct. One illustration of this point is the fact that no method for preparing the C_9-C_{11} diene in amphidinolides C and F has been reported. A structurally related diene is present in amphidinolides B, G and H. While these compounds have attracted significantly more synthetic attention,[10–12] proportionally limited success has been achieved for accessing the key diene motif—likely due to the challenging nature of the metal-mediated cross coupling reaction (*e.g.* Suzuki or Stille reaction) commonly envisioned to form dienes.[12,13] While both Fürstner and Nelson have separately disclosed the ability to construct highly substituted dienes *via* Suzuki couplings, it is important to note that these conditions require extremely high catalyst loadings (up to 70 mol% Pd).[11m,12,14] Consequently, our group has invested considerable effort to develop alternate pathways for constructing these types of structures.[10]

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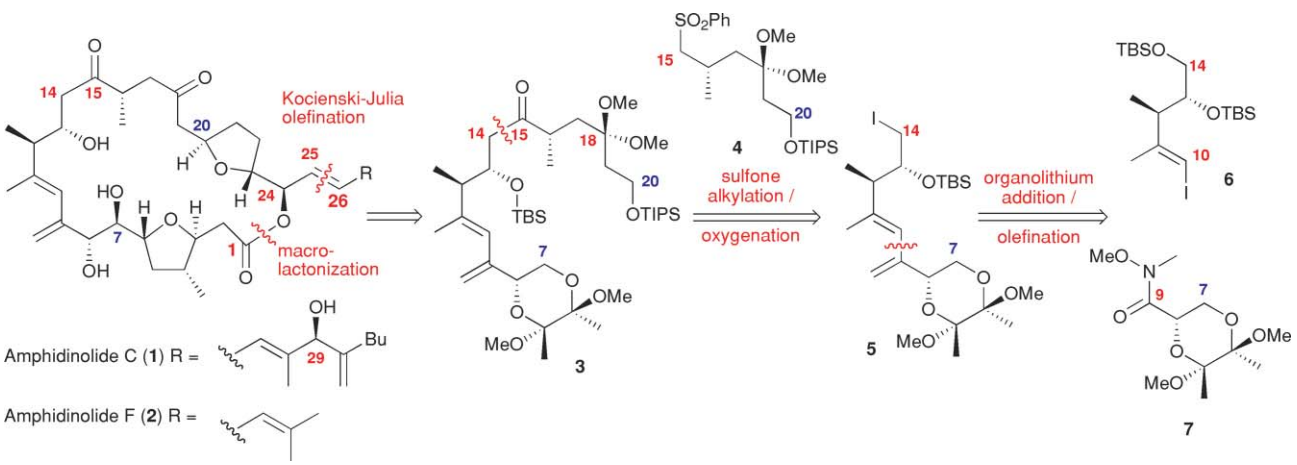
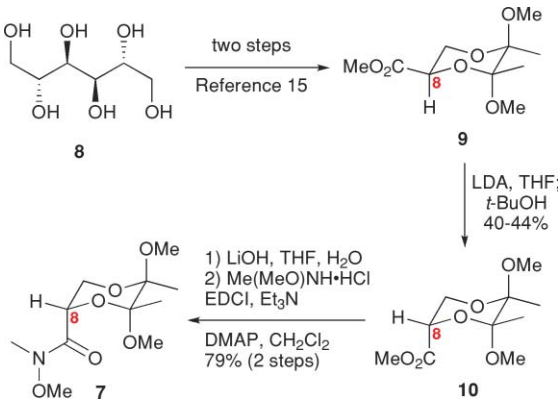
† Electronic supplementary information (ESI) available: Complete experimental procedures are provided, including ^1H and ^{13}C spectra, of all new compounds. See DOI: 10.1039/b916744g



Scheme 1 Retrosynthesis of amphidinolides C and F.

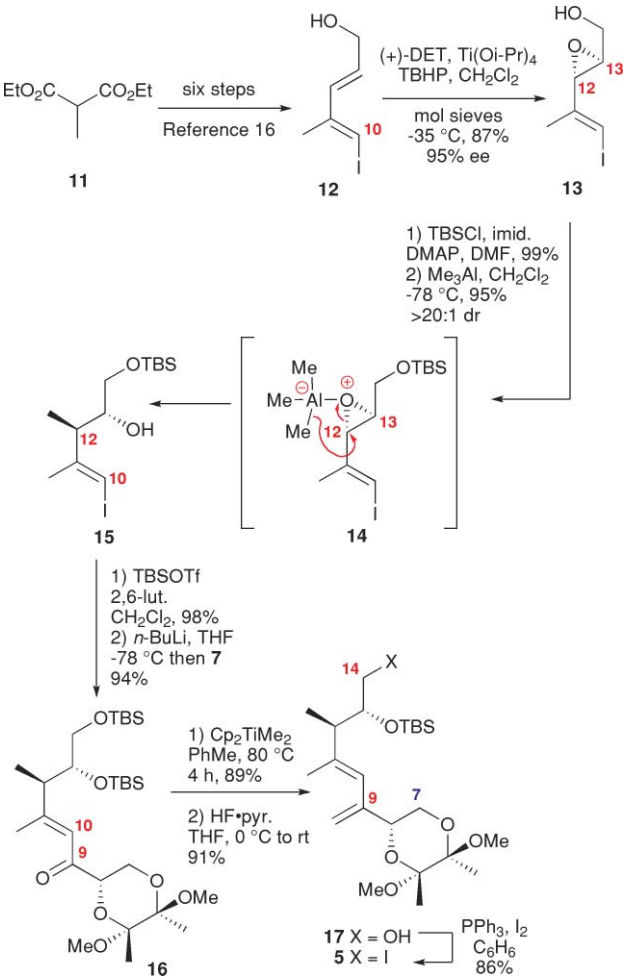
The synthesis of the Weinreb amide subunit is shown in Scheme 2. Amide **7** was readily accessible from the known Ley ester **10**, which in turn was constructed from D-mannitol (**8**).[15] Ley has shown that these diacetal derivatives of glyceraldehyde are significantly more robust than traditional acetonide analogues. We did find that the order of addition (LDA was added to the ester **9**) for the key epimerization of equatorial ester **9** into axial ester **10** was critical to the success of the experiment—use of the alternate order of addition led to a significant reduction in yield (<20%).



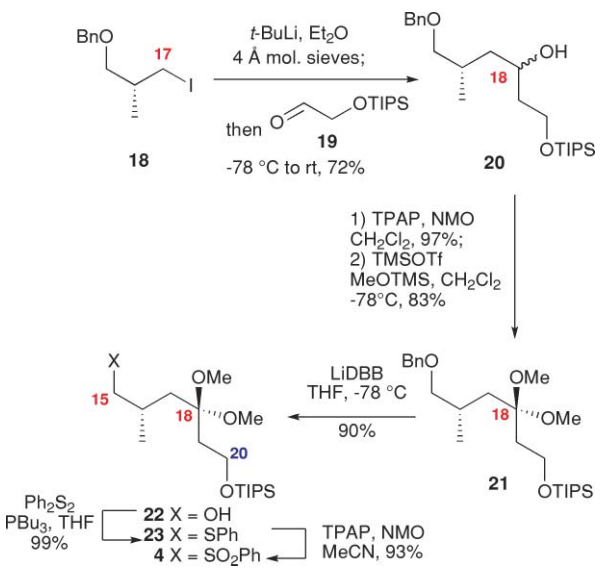
Scheme 2 Synthesis of the Weinreb amide.

Synthesis of the C_7-C_{14} subunit is shown in Scheme 3. The vinyl iodide **12** was available from diester **11** through a known procedure.[16] After Sharpless epoxidation to cleanly provide the epoxide **13**,[17] the first major challenge in this sequence was selective opening of the epoxide at C_{12} with inversion by a methyl nucleophile. Despite the wealth of research on the reactivity of allylic electrophiles, surprisingly few examples of this type of transformation have been reported.[18] Furthermore, no reported examples of accomplishing this transformation on an allylic vinyl iodide have been disclosed. After some experimentation, we were pleased to find that Me_3Al-mediated epoxide ring opening[19] at C_{12} cleanly provided product **15** in good diastereoselectivity (>20:1 dr) at −78 °C. The temperature proved to be critical to the success of this transformation. If the epoxide opening was conducted at −50 °C, significant erosion in the C_{12} stereochemistry was observed (3.5:1 dr).[20] The absolute stereochemistry of **15** was established by degradation to a known compound and by matching the optical rotation data.[21] With the key vinyl halide **15** in hand, silylation followed by halogen-metal exchange and addition to the Weinreb amide **7** cleanly generated the enone **16**. Methylenation of ketone **16** using the Petasis reagent generated the diene. Alternate methylenation conditions (*e.g.* Wittig, Lombardo's reagent) were unsuccessful. Finally, selective desilylation at C_{14} OTBS ether followed by conversion to the iodide generated the key coupling subunit **5**.

The synthesis of the sulfone subunit **4** is detailed in Scheme 4. Starting from the known iodide **18**,[22] halogen/metal exchange followed by addition of the aldehyde **19**[23] generated the alcohol **20** as an inconsequential mixture of isomers at C_{18}. TPAP oxidation[24] of the C_{18} alcohol followed by Noyori ketalization[25] generated the dimethyl ketal **21**. Careful debenzylation with Freeman's LiDBB reagent[26] followed by sulfide formation provided compound **23**. Finally, sulfide oxidation using TPAP[27] provided the C_{15}-C_{20} subunit **4**.

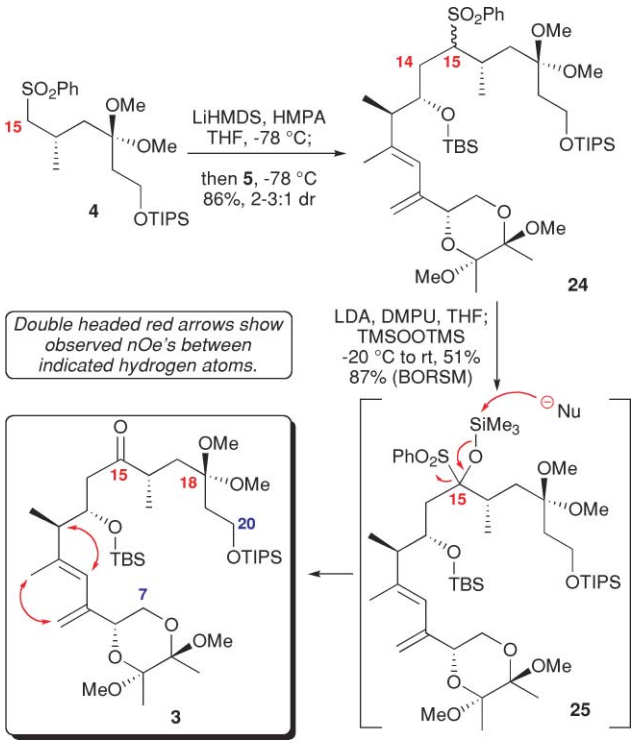


Scheme 3 Synthesis of the C_7-C_{14} subunit



Scheme 4 Synthesis of the C_{15}-C_{20} subunit

With the subunits in hand, efforts turned towards the critical coupling sequence (Scheme 5). Treatment of sulfone **4** with LiHMDS followed by the addition of iodide **5** smoothly provided the $C_{14,15}$ coupled material.[6] Next, treatment of sulfone **24** under



Scheme 5 Completion of the C_7-C_{20} fragment of amphidinolides C and F.

our previously developed hydroxylation conditions[28] (NaHMDS, TMSOOTMS, THF) led to no reaction. Fortunately, modification of the base to LDA led to clean formation of the ketone **3** *via* the presumed intermediate **25**. Key to these reactions is the relative stability of silyloxy sulfone **25** to decomposition to the ketone **3**. This two-step sequence (sulfone alkylation/oxidation) circumvents any problematic furan formation (between C_{15} and C_{18}) and can be viewed as a viable alternative to traditional dithiane chemistry.[29]

In conclusion, synthesis of the C_7-C_{20} fragment of amphidinolides C and F has been disclosed. A diastereoselective ring opening of vinyl iodide/allylic epoxide provided access to the *anti*-stereochemistry. An efficient Weinreb amide coupling/methylenation sequence was used to access the key C_9-C_{11} diene motif. Sulfone alkylation was used to join the C_7-C_{14} and C_{15}-C_{20} subunits. Finally, a hydroxylation/desulfurization process incorporated the C_{15} ketone. Further application towards the synthesis of amphidinolides will be reported in due course.

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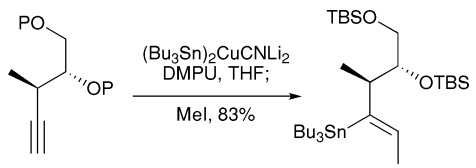

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