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Total Synthesis and Structure Elucidation of (+)-Phorbasin C

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The phorbasins are a class of structurally novel diterpenes isolated from a southern Australian marine sponge (*Phorbas* sp.) that are structurally related to the terrestrial carvotacetone monoterpenes and carvone (Figure 1).[1] Initial isolation of the phorbasins was prompted by an observed growth inhibitory activity of the crude extracts against Gram positive bacteria *Staphylococcus aureus* and *Micrococcus luteus*. More recently, studies have identified that members of this class possess a range of selective cytotoxic properties.[1d] The structures assigned for the phorbasins remain stereochemically incomplete, with the relative stereochemistry of C11 undefined. Recently, the absolute stereochemistry of the family was assigned as depicted, based on an observed positive Cotton effect in the CD spectra of members of the class and application of the helicity rule for conjugated transoid ketones.[1d,2] Here, we describe the first total synthesis and complete structure elucidation of a phorbasin by a pathway that explores the utility of allylic alcohol−alkyne reductive cross-coupling[3] in target-oriented synthesis.

Our plan for the synthesis of phorbasin C is depicted in Figure 2. Due to the stereochemical uncertainty of C11, we aimed to assemble the skeleton by late-stage Suzuki cross-coupling[4] between a suitably functionalized vinyl iodide **1** and each enantiomer of a stereodefined vinylboronic ester **2**.

Anticipating that subtle spectroscopic differences might exist between the diastereomeric products resulting from these Suzuki coupling reactions, this plan would allow for the assignment of the relative stereochemistry of phorbasin C. We then targeted the synthesis of **1** by functionalization of the 1,4-diene **3**, itself being expected to derive from the commercially available diol **4** and TMS-propyne (**5**).[5]

As depicted in Figure 3, protection and diastereoselective dihydroxylation of the chiral diene **4**, followed by Bu_3SnH-mediated dehalogenation furnished the stereodefined diol **6** in 65% yield (dr ≥20:1).[6] Titanium-mediated reductive cross-coupling of this diol with TMS-propyne, via formal metallo-[3,3] rearrangement (**A**), proceeded with exquisite selectivity and furnished the stereodefined 1,4-diene **3**.[3,7] Notably, this reductive cross-coupling process proceeds with allylic transposition, in a suprafacial manner, with high levels of site selectivity (C−C bond formation occurs distal to the TMS substituent of **5**). Interestingly, the initial coupling process affords a new allylic alkoxide (**B**) that has the potential to serve as a substrate for an additional reductive coupling reaction. Fortunately, no product of additional coupling was observed, a selectivity likely due to the steric impediment imposed by the substitution of C6 in intermediate **B**.

Site- and stereoselective directed epoxidation ($VO(acac)_2$, TBHP),[8] followed by oxidation,[9] and Wittig olefination,[10] provided the vinyl epoxide **7** (Figure 4). Palladium-catalyzed substitution

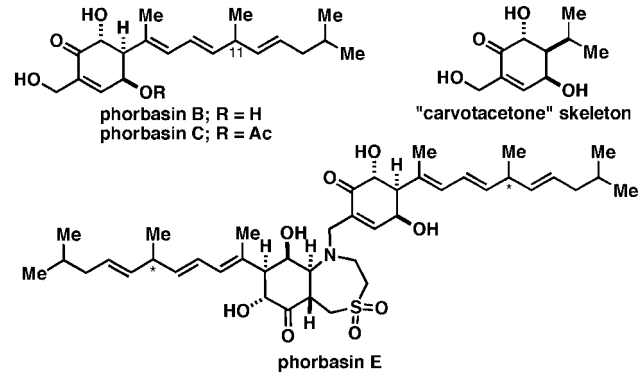

Figure 1. Representative phorbasins and related structures.

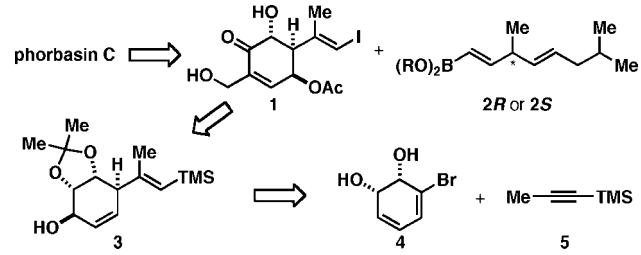

Figure 2. Retrosynthetic strategy for phorbasin C.

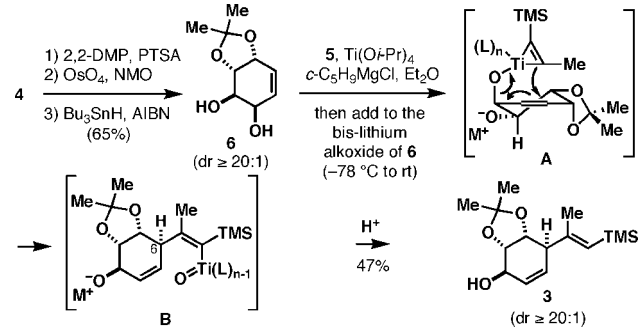

Figure 3. Preparation of stereodefined 1,4-diene **3**.

($Pd(PPh_3)_4$), AcOH, THF)[11] and acylation then delivered the stereodefined carbocycle **8** in 90% yield. Finally, synthesis of the functionalized coupling partner **1** was completed by (1) conversion of the vinylsilane to the corresponding vinyl iodide,[12] (2) removal of the acetonide, (3) selective oxidation to the enone, and (4) site-selective deacylation.[13]

Synthesis of the stereodefined coupling partner **2** followed from conventional functionalization of the known chiral alcohol **10** (Figure 5). Oxidation,[9] followed by a stereoselective Julia-Kocienski olefination[14] provided **12** in 51% yield (*E*:*Z* ≥ 20:1). Removal of the THP ether, followed by oxidation to the aldehyde and Takai olefination[15] delivered the vinyl iodide **13** in 44% yield (*E*:*Z* ≥

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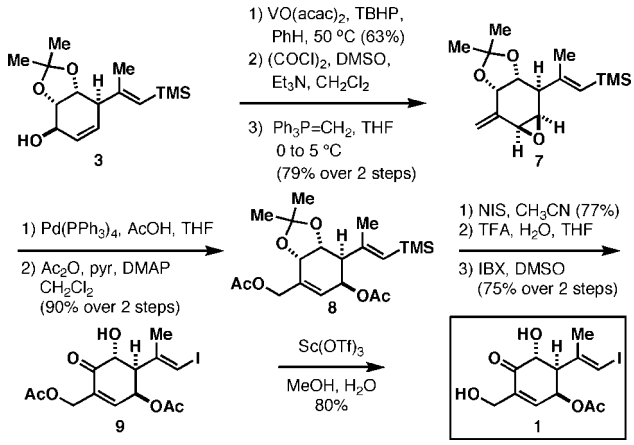

Figure 4. Conversion of **3** to coupling partner **1**.

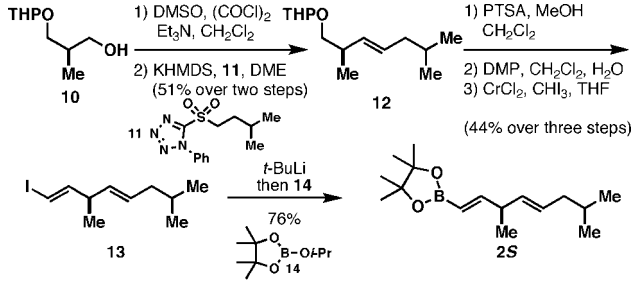

Figure 5. Synthesis of the coupling partners **2*S*** and **2*R***.

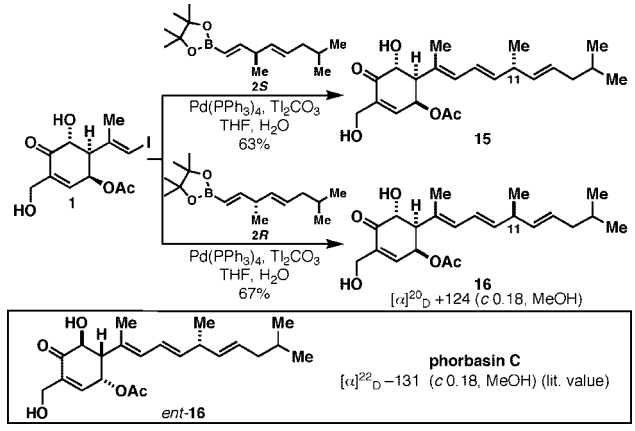

Figure 6. Synthesis and structure elucidation of phorbasin C.

20:1; obtained as a 5:1 mixture with the isomeric 1,3-diene).[5] Finally, conversion to the fully functionalized coupling partner **2*S*** was achieved by lithium halogen exchange and borylation with **14**. Because of the ready availability of *ent*-**10**, this sequence proved equally effective for the preparation of **2*R***.[5]

Suzuki cross-coupling of vinyl iodide **1** with each enantiomer of the vinylboronic ester **2** proceeded uneventfully, delivering the homologated products **15** and **16** in 63% and 67% yield, respectively (Figure 6). While the success of this sequence provided a means to prepare both C(11) epimers of the proposed structure of phorbasin C, the stereochemical assignment of the natural product was not trivial. While, isomers **15** and **16** were virtually indistinguishable by ^{1}H NMR spectroscopy, subtle differences in their ^{13}C spectra were observed. On comparison of these spectra with the natural product, it became clear that diastereomer **16** represents the correct structure of phorbasin C.[5] The absolute stereochemistry of the natural product was then deduced by comparing the optical rotation of **16** ($[\alpha]_D^{20}$ +124 (*c* 0.18, MeOH)) with the value reported for phorbasin C ($[\alpha]_D^{22}$ −131 (*c* 0.18, MeOH)).[1c] On the basis of these grounds, we conclude that the relative and absolute stereochemistry of phorbasin C is that depicted as *ent*-**16** (Figure 6).

In conclusion, our efforts in chemical synthesis have led to the first total synthesis and complete structure elucidation of a phorbasin, a marine-derived class of natural products that possesses selective cytotoxic and antibiotic profiles. The success of this endeavor demonstrates the utility of our site- and stereoselective allylic alcohol−alkyne reductive cross-coupling reaction and further supports the role that organic synthesis plays in the structure elucidation of bioactive natural products.[16]

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

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