Synthesis of the phormidolide A macrocycle supports the proposed configurational reassignment.

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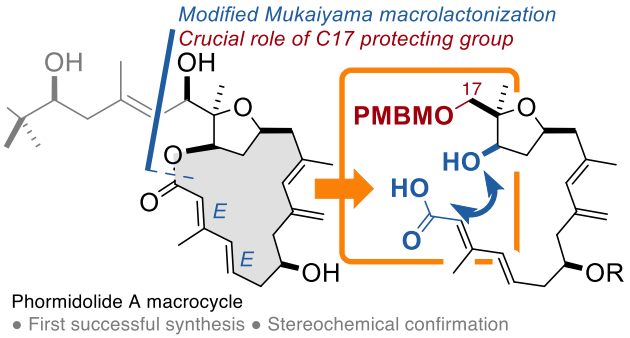
Supporting Information Placeholder



ABSTRACT: We describe the successful synthesis of the phormidolide A macrocycle as a crucial step towards its total synthesis and configurational assignment. Exhaustive exploration of macrocyclization strategies revealed the detrimental effects of a bulky protecting group on the C17 hydroxyl function, leading to the successful use of a C17 *p*-methoxybenzyloxymethyl (PMBM) ether in the macrolactonization reaction. Further elaboration of the macrocycle with a truncated C18-C23 side chain afforded an advanced C1-C23 fragment of phormidolide A. Detailed comparison of spectroscopic data to that of phormidolide A supports the proposed configurational reassignment.

The phormidolides are a group of structurally complex marine natural products that incorporate a tetrahydrofuran (THF)-embedded macrolide linked to a polyhydroxylated side chain terminating in a signature bromomethoxydiene motif.[1–6] Phormidolide A (**1**, originally proposed structure depicted in Figure 1) was isolated from the marine cyanobacteria *Leptolyngbya sp.* by the Gerwick group in 2002. It exhibited brine shrimp toxicity (LC_{50} = 1.5 μM) but was inactive towards various cancer cell lines.[2] A detailed study by the Gerwick group relied on an ACCORD-ADEQUATE NMR pulse sequence to assign the carbon skeletal connectivity of phormidolide A.[2,10] The stereochemistry was assigned by *J*-based configurational analysis and chemical derivatization leading to the proposed structure **1**.[8] Interestingly, its related congeners (phormidolides B-D) demonstrated consistent growth inhibitory activity against a panel of cancer cell lines.[3,6] To date, significant work towards the synthesis of major structural regions in phormidolides B and C has been accomplished by the Álvarez group. In contrast, there has been limited studies targeting phormidolide A itself.

Previously, we reported a synthesis-enabled configurational reassignment of the stereochemistry in the macrocyclic and side chain domains.[9] This work involved spectroscopic comparison between advanced synthetic fragments and that of phormidolide A and its acetonide derivatives. More recently, in collaboration with the Gerwick and Piel groups,[10] we proposed a further reassignment of the remote C7 stereocenter, using a combination of anisotropic NMR spectroscopic studies and computational NMR chemical shift predictions.[5,10] Collectively, this work resulted in the proposed stereostructure **1a** (Figure 1), and the reassignment of eight out of the eleven stereocenters.

To corroborate the proposed configurational reassignment, we aimed to assemble the macrocyclic core (**2**) of phormidolide A and interrogate the veracity of the remote C7 hydroxyl center. We expected that the macrocycle could be accessed through iterative couplings of previously-reported THF fragment **3**[9] with the C1-C4 fragment **4** and C5-C9 fragment **5**[11] using a Horner-Wadsworth-Emmons (HWE) reaction,[12,13] Stille coupling[14–16] and esterification, executed in any order. Herein, we describe the synthesis of a C1-C17 macrocyclic core and outline its elaboration to an advanced C1-C23 fragment *via* the addition of the side chain fragment **6**. Detailed NMR spectroscopic analysis provides firm support for the proposed configurational reassignment, and establishes a strategy that supports ongoing efforts towards the total synthesis of phormidolide A.

The macrocyclic domain of phormidolide features a tetrasubstituted THF ring, a C9-C11 *exo*-diene and an (2*E*,4*E*)-dienoate. Noting that related macrocyclic dienoates often

present synthetic challenges due to their propensity to isomerize,[17–19] we conducted a series of molecular mechanics-based conformational searches for the truncated (2*E*,4*E*)-macrocycle **2** and the three potential stereoisomeric dienoates (see Supporting Information for detailed analysis).[20] This analysis highlighted that the naturally configured (2*E*,4*E*)-dienoate **2** is the *least* stable isomer—*ca.* 6.5 kcal mol^{-1} higher in energy than the (2*Z*,4*E*)-isomer. Thus, from the outset we anticipated challenges with macrocycle formation, as well as the configurational stability of intermediates in the synthesis.

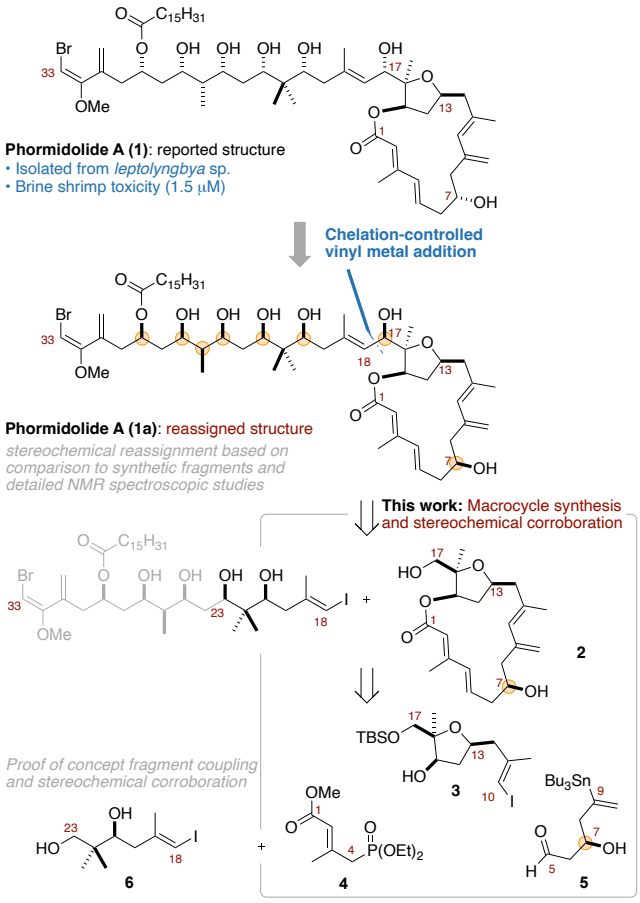
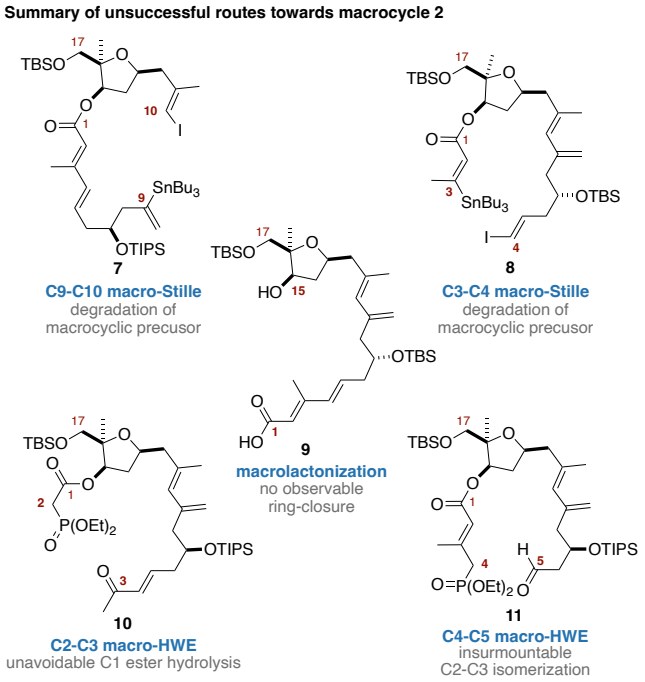


Figure 1. Configurational reassignment of phormidolide A (**1**) to **1a** and retrosynthetic analysis leading back to **2-5** as the target fragments. A proof-of-concept fragment coupling with **6** is also outlined.

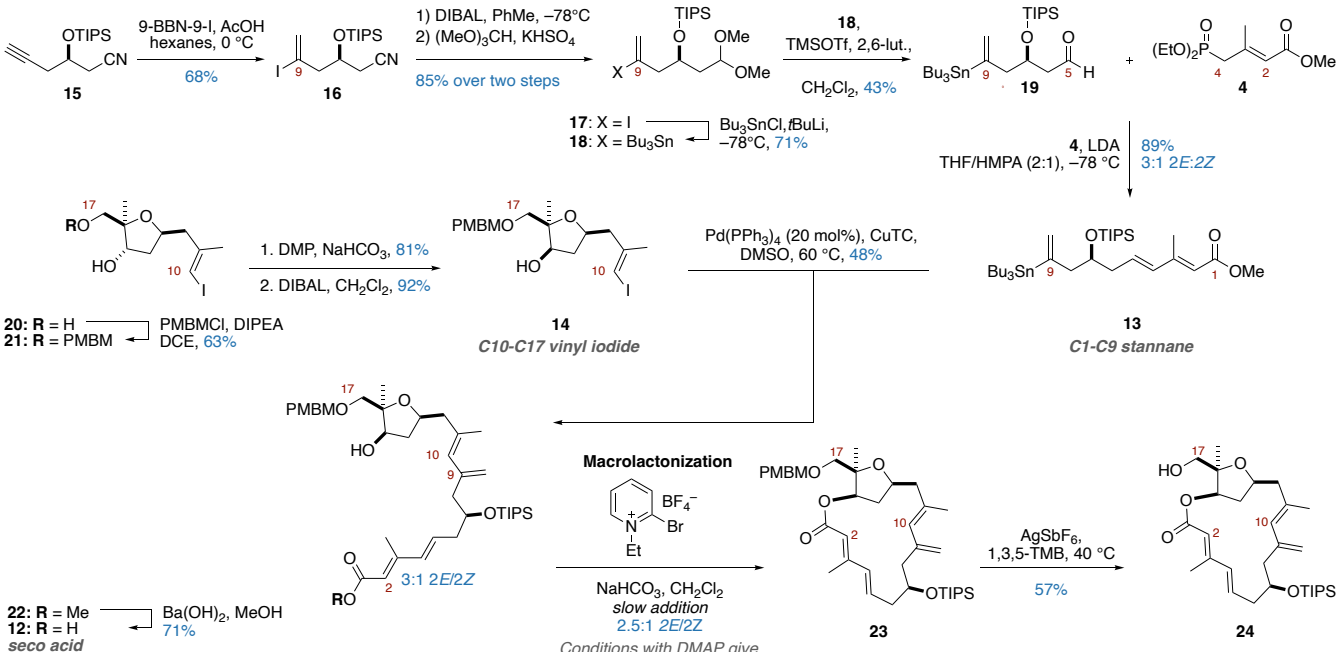
With some trepidation, we evaluated a range of macrocyclization strategies (Scheme 1). To this end, several advanced intermediates **7-11** were prepared, but all failed to deliver the desired (2*E*,4*E*)-macrolactone core. Notably, Stille reactions involving **7** or **8** using Pd(dppf)Cl_2, $Pd_2(dba)_3$, or $Pd(PPh_3)_4$ led only to degradation of the starting material. Activated anhydrides could be formed from seco acid **9** but macrolactonization was not observed. Finally, attempts to form the macrocycle via a HWE reaction using **10** led to C1 ester hydrolysis, while **11** afforded macrocyclization albeit with full isomerization of the C2-olefin. These studies highlighted the synthetic challenge faced in accessing the (2*E*,4*E*)-dienoate, as predicted by our computational modelling. Furthermore, the instability of intermediates required for Pd-catalyzed cross-coupling reactions precluded macrocyclization *via* C3-C4 or C9-C10 bond formation (see Supporting Information for detailed discussion of failed routes).



Scheme 1. Outline of unsuccessful macrocyclization strategies using the Stille substrates **7** and **8**, seco acid **9** and HWE substrates **10** and **11**.

Previous studies have highlighted the critical role played by protecting groups in macrocycle formation involving THF-containing macrolides. For example, during the synthesis of the haterumalides by both Kigoshi and Snider, [21–24] macrolactonization failed when the exocyclic THF-alcohol motif (equivalent to C17 in phormidolide A) was protected with TBS or TBDPS ethers, while the equivalent reaction using a trityl ether proceeded in good yield. We have also shown that using a TBDPS or TBS ether at the equivalent position had a significant impact on macrocyclization in the total synthesis of biselide A (see Supporting Information for discussion).[25] Thus, we speculated that our initial choice of a C17 TBS ether—specifically its steric bulk—may have had a detrimental effect on macrocyclization. Taking these considerations into account, as well as necessary chemical constraints imposed by the synthesis of the macrocycle precursors, two candidate protecting groups—SEM (TMS-ethoxymethyl) and PMBM (*p*-methoxybenzyloxymethyl) ethers—were short-listed. We opted to first assess macrolactonization with a SEM ether at C17, as it offered a variety of mild conditions for its removal.[26,27] This proved to be a synthetic dead-end. While we had some degree of success in the macrolactonization step, the use of a wide range of deprotection conditions (HF, TBAF, HCl, TFA, CSA, CBr_4, or $MgBr_2$)[26–31] led to either no reaction, degradation, or the unwanted removal of the C7-TIPS ether (see Supporting Information for details).

As the SEM protecting group removal was incompatible with our system, we then elected to use a PMBM ether. This protecting group—recently deployed in the total synthesis of the actinoallolides—offered an orthogonal means of oxidative deprotection at C17[32] whilst retaining a similarly smaller steric profile to facilitate the desired macrolactonization.[33] To this end, PMBM-protected C1-C17 seco acid **12** was next targeted. Previous route reconnaissance indicated facile cross-coupling reactivity between a suitably configured C1-C9 stannane and a C10-C17 vinyl iodide. Therefore, a similar strategy was leveraged for the synthesis of PMBM-containing seco acid **12** *via* C1-C9 stannane **13** and C10-C17 vinyl iodide **14** (Scheme 2).



Scheme 2. Preparation of C17-PMBM protected macrocycle **23** and successful deprotection to afford the C1-C17 alcohol **24**. Reactions are conducted at room temperature unless otherwise stated. Abbreviation: CuTC: copper(I) thiophenecarboxylate

Synthesis of the C1-C9 stannane **13** commenced with known alkyne **15.**[34] Iodoborylation with acidic workup[35] afforded vinyl iodide **16**, along with a small amount (15%) of protodeiodinated material (not shown) that was inseparable from **16** by flash column chromatography. This material was then reduced using diisobutyl aluminum hydride (DIBAL) and protected to afford the corresponding acetal **17**. Lithium-iodine exchange followed by treatment with tributyltin chloride gave the vinyl stannane **18**. Acetal deprotection using a silyl triflate/2,6-lutidine system[36,37] afforded aldehyde **19**. The C1-C9 dienoate **13** was prepared *via* HWE coupling of aldehyde **19** and the known phosphonate **4**, which afforded the dienoate as a 3:1 mixture of (2*E*:2*Z*) isomers.[11] Here, the use of HMPA as a co-solvent and low temperatures (–78 °C) were crucial in suppressing isomerization of the (2*E*)-olefin.

Starting from known diol **20**,[9] synthesis of the C10-C17 vinyl iodide **14** commenced with selective protection of the primary alcohol to give the PMBM ether **21**.[38] Subsequent oxidation with Dess-Martin Periodinane (DMP) and DIBAL reduction inverted the C15 configuration to give the C10-C17 vinyl iodide **14**. Coupling of vinyl iodide **14** to the C1-C9 vinyl stannane **13** under modified Stille conditions gave the C1-C17 fragment **22**, and ester hydrolysis afforded the required C1-C17 seco acid **12** as an inseparable 3:1 mixture of (2*E*/2*Z*)-isomers.

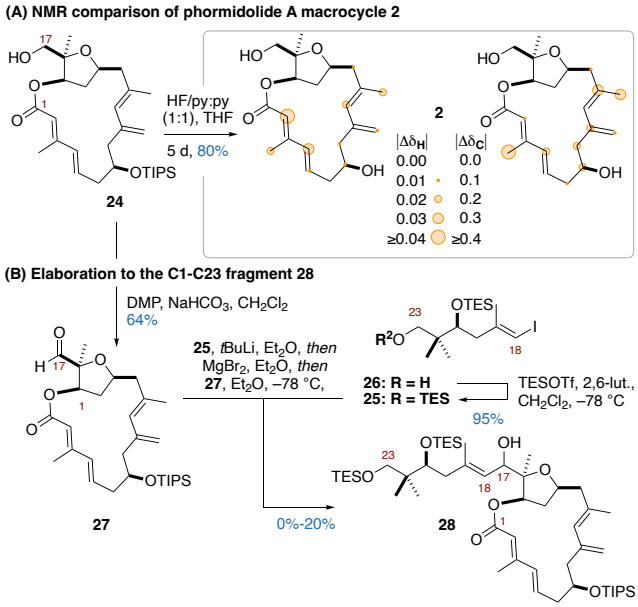
With PMBM-protected seco acid **12** in hand, we next tackled the pivotal macrolactonization step. Early proof-of-concept studies with the analogous C17-SEM-containing seco acid indicated that, while classical DMAP-mediated processes[39] were effective at forging the desired macrolactone, it also resulted in extensive and insurmountable isomerization to predominantly give the undesired (2*Z*)-macrocycle (see the ESI for details).

Despite this outcome, this welcome result contrasted with the analogous C17 TBS-ether **9**, where no macrolactone product was observed, and provided empirical evidence supporting the disproportionate role played by the C17 alcohol protecting group. Control experiments revealed that DMAP was the culprit behind the dienoate isomerization. Based on this observation, we investigated alternative macrolactonization protocols for **12** that did not involve DMAP. This study singularly identified the modified Evans-Mukaiyama reagent (2-bromo-1-methyl pyridinium tetrafluoroborate)[18,40,41] as being most effective, which led to the formation of macrocycle **23** in 37% yield (2*E*:2*Z* = 2.5:1). As this geometric ratio was similar to that obtained after HWE olefination (2*E*/2*Z* = 3:1), these macrolactonization conditions were deemed sufficient to suppress unwanted isomerization. Importantly, we found that the use of a non-nucleophilic tetrafluoroborate counteranion was also vital to suppress olefin isomerization (see Supporting Information for details).[18]

Noting the major by-product in the reaction was the acid anhydride produced from a homocoupling of the seco acid **12**, extensive reaction optimization was next pursued. This revealed the crucial impact of concentration on product yield; we found that improved outcomes were obtained at 0.5 mM with slow addition of the seco acid **12**. After careful chromatography, this optimized procedure reliably afforded macrocycle **23** in a much improved 72% yield as a single geometric isomer. With **23** in hand, we then targeted the removal of the C17 PMBM ether. Unfortunately, standard oxidative (DDQ) conditions used for cleavage led to complete degradation. A screen of deprotection conditions on **23** revealed that $AgSbF_6$ with 1,3,5-trimethoxybenzene (1,3,5-TMB), previously reported for the deprotection of PMB ethers,[42] afforded the C17 alcohol **24** in 57% yield.

With the desired macrocycle **24** in hand, it was now prudent to corroborate our proposed configurational reassignment by comparing ^{1}H and ^{13}C NMR spectroscopic data to that reported from phormidolide A. To this end, the removal of the TIPS ether from the C7 alcohol gave macrocycle **2** (Scheme 3a). A comparison of the ^{1}H NMR spectroscopic data in the C2-C12 region (see Table S1 in Supporting Information for a full comparison of ^{1}H and ^{13}C NMR spectral data) revealed very close chemical shift homology throughout the macrocycle. Aside from H2 (proximal to the side chain absent in **2**), the $\Delta\delta_H$ values were

equal to or less than 0.03 ppm. Of particular note, the $\Delta\delta_H$ values for the protons around C7 were 0.01 ppm or less, supporting our proposed (7*S*) assignment in **1a** together with the remaining configurational assignments throughout the macrocyclic core.



Scheme 3. (A) Deprotection of **24** to afford macrocycle **2** and a highlight of the differences in ^{1}H and ^{13}C NMR chemical shifts between **2** and phormidolide A (1). Differences are represented by different circle radii according to the included legend. (B) Preparation of C1-C23 fragment **28**. Reactions are conducted at room temperature unless otherwise stated.

Next, we sought to investigate the attachment of side chain fragment **25** prepared from known alcohol **26**[9] to provide a potential intermediate for the total synthesis of phormidolide A. Toward this goal, the aldehyde **27** was accessed by oxidation of alcohol **24** (Scheme 3b). A chelation-controlled vinyl metal addition was next conducted using the Grignard reagent derived from iodide **25**. On a small scale (*ca.* 3 mg), conversion to the protected C1-C23 fragment **28** was realized in 68% yield. Unfortunately, and despite considerable effort, this addition reaction proved capricious and irreproducible. Repetition of this reaction on scales ranging from 5 mg to 25 mg gave the addition product **28** in poor yields (<20%), often being undetectable in the crude product mixtures, with most of the material resulting from degradation of the starting aldehyde **27**. Nevertheless, we were able to secure sufficient material for a detailed NMR spectroscopic comparison of the protected C1-C23 fragment **28** with the natural product. Despite the structural differences, we observed close similarities in ^{1}H NMR chemical shift; there is a very close similarity observed for regions around the THF motif and C17-C18 positions (see Supporting Information for details). Together with the data for the synthetic macrocycle **2**, this analysis provides further corroboration for the proposed reassignment of phormidolide A to **1a**.

In conclusion, we have achieved the first synthesis of a truncated macrocycle of phormidolide A. Initial macrocyclization strategies revealed several unanticipated challenges, including degradation, C15 ester hydrolysis, and isomerization of the dienoate. Assessing structural permutations in our open-chain precursors eventually led to the discovery of the key role played by a non-innocent C17 alcohol protecting group. The judicious use of a PMBM ether and the choice of a modified Mukaiyama reagent to suppress unwanted isomerization were critical to facilitate macrolactonization. Furthermore, the chemoselective unmasking of the C17 alcohol allowed for further elaboration. Finally, these results enabled a detailed NMR spectroscopic comparison with phormidolide A. Close correlation between macrocycle **2** and advanced C1-C23 fragment **28** to that reported for the natural product supports the previously proposed configurational reassignment within the macrocyclic domain.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, full characterization data for novel compounds, detailed spectroscopic analysis of **2** and **28**, cartesian coordinates of isomeric macrolactones, summary of failed routes (PDF)

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Author Contributions

G.M., I.P, N.Y.S.L. and R.B. wrote the manuscript. G.M. and N.Y.S.L. performed the experimental studies and all authors were involved in project design.

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