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A synthetic approach to the phorboxazoles – A strategy for the synthesis of the C1–C19 polyketide fragment

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ABSTRACT

A synthetic approach to the C1–C19 polyketide fragment of the phorboxazoles is disclosed here. While an initial two-directional approach was efficient, it did not proceed in a high enough yield to justify moving forward. A subsequent successful strategy for the generation of the C11–C15 pyrans of both of the phorboxazoles was achieved, and the installation of the C9 stereocenter was able to be demonstrated. Furthermore, an efficient route for the preparation of the C1–C8 fragment with suitable functionality to allow for elaboration into the complete C1–C19 fragment, with the capricious C2–C3 Z-geometry installed, was also achieved.

The phorboxazole family of natural products, including phorbxazoles A (**1**) and B (**2**)[1,2] as well as hemiphorboxazole (**3**),[3] are marine macrolides isolated from an Indian Ocean sponge (*Phorbas* spp.) that have attracted considerable interest for their unique structural features as well as their biological properties (Fig. 1).[4,5] Interestingly, while **1** and **2** possess potent cytostatic properties presumably tied to their ability to interact with cyclin-dependent kinase (CDK) 4,[6] **3** is effectively inactive despite containing the entire macrolide portion of **1**.[3] As part of a broad program aimed at the total synthesis of this family of natural products, we have previously reported our synthetic efforts toward this molecule, specifically our approach to prospective intermediates **4** and **5**.[7,8] We wish to report here our approach to the bis-pyran fragment **6** of the phorboxazoles.

In our initial synthetic approach to this fragment, we envisioned using Schreiber's two-directional synthesis strategy,[9] something that had been applied beautifully by Burke in his total synthesis of **2**.[10] We felt that Smith's anion relay chemistry would be ideal in this regard.[11] Deprotonation of 2-*t*-butyldimethylsilyldithiane (**7**) followed by addition of excess expoxide **8** resulted in the desired Brook rearrangement and double addition to give **9** (Scheme 1). Copper mediated liberation of the ketone proceeded with concomitant deprotection of the silyl ether, and silylation of both of the secondary alcohols was achieved with TIPS triflate followed by reduction of the ketone gave **10** in good overall yield and only 4 steps. With an eye toward using the desymmetrization to effectively set the remaining stereocenter, we liberated the primary alcohols and explored a variety of selective oxidation conditions. Unfortunately, every condition tried returned a complex mixture of products. Despite exploring a myriad of various protecting groups and conditions, our "best" result was from dialdehyde **14**, from which we were able to isolate pyran **15** (phorboxazole numbering designations included for **12** and **15**) in 10% yield. We therefore sought an alternative approach to this fragment.

We felt that any revised pathway should also be sure to address an approach that would allow access to either **1** or **2** from a similar pathway, which we initially felt we would have been able to do from **12**. We recognized that we should be able to use the single stereocenter that would correspond to C11 to set the stereochemistry at what would eventually become C13 of the phorboxazoles depending on the conditions we chose. The only concern, then, would be whether both isomers would give the desired stereocenter at C15. To test this, we generated model systems **16** and **18** (Scheme 2). Iodoetherification of either the 1,3-syn or the 1,3-anti isomers,[12] followed by reductive removal of the iodide, provided good yields of the desired product, which could be confirmed by NMR analysis of the methine protons. With this in hand, we proceeded to take on the real system.

Known ester **20**,[13] readily available in enantiopure form via Noyori reduction of the corresponding β-ketoester, was converted

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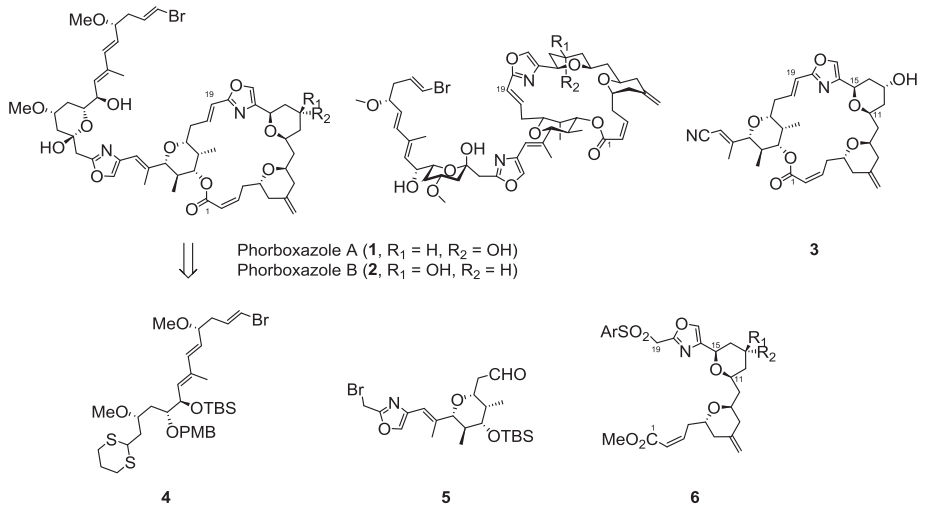
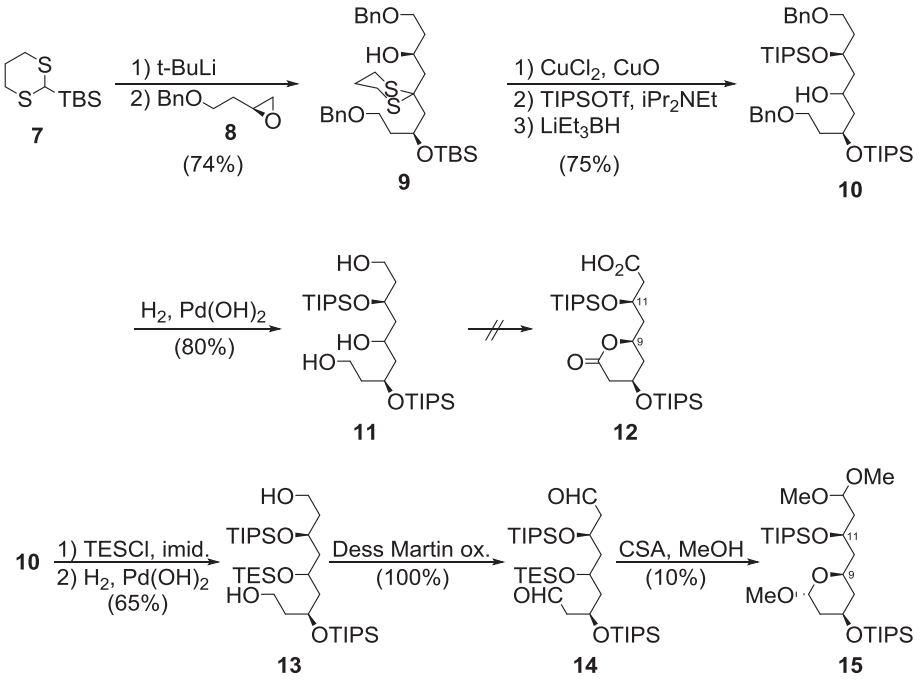
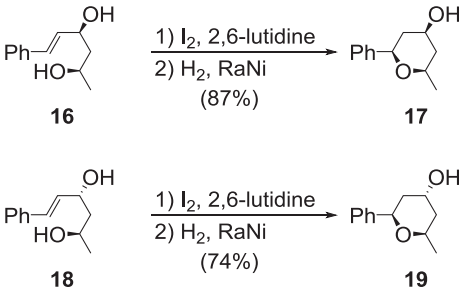


Fig. 1. Structures and retrosynthetic analysis of the phorboxazoles.



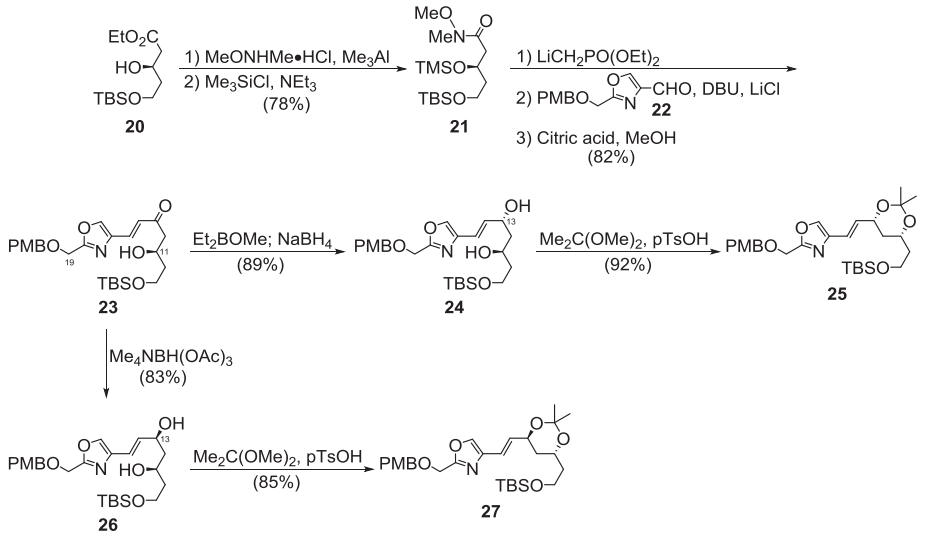
Scheme 1. Two-directional approach to the bis-pyran fragment.



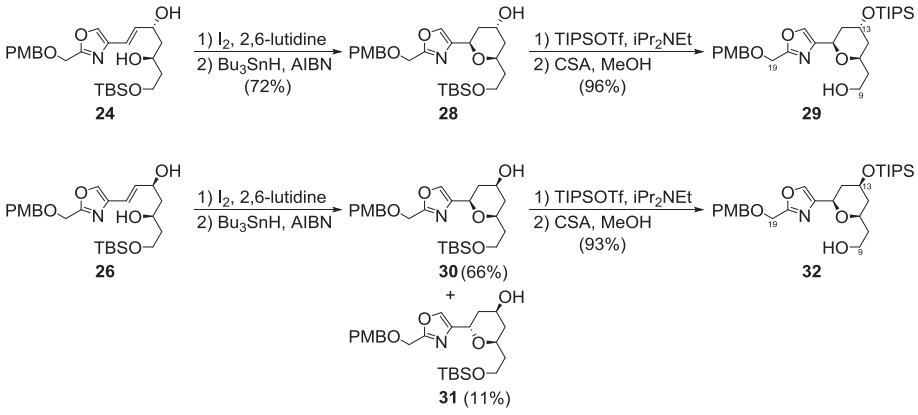
Scheme 2. Iodoetherification approach to the pyran.

into the requisite Weinreb amide and silylated to give **21** (Scheme 3). Following generation of the desired β-ketophosphonate, Horner Wadsworth Emmons olefination with **22**, which we also used for the installation of the exocyclic oxazole in our C20-C32 fragment,[8] provided olefin **23** after liberation of the free secondary alcohol. We were now set to install the C13 stereocenter, and reduction under either directed or Narasaka-Prasad conditions gave the requisite diols (**26** and **24**, respectively).[14,15] To ensure that each of these reductions proceeded as expected, we converted both into their corresponding acetonides using Rychnovsky's protocol and confirmed that each reduction indeed formed the desired products.[16] Iodoetherification proceeded in both cases to give the desired product as the major isomer (Scheme 4), though we did also isolate some of the undesired isomer **31** in the reaction with **26**. Following reductive removal of the iodide, the remaining secondary alcohol could be protected and the primary alcohol liberated under standard conditions.

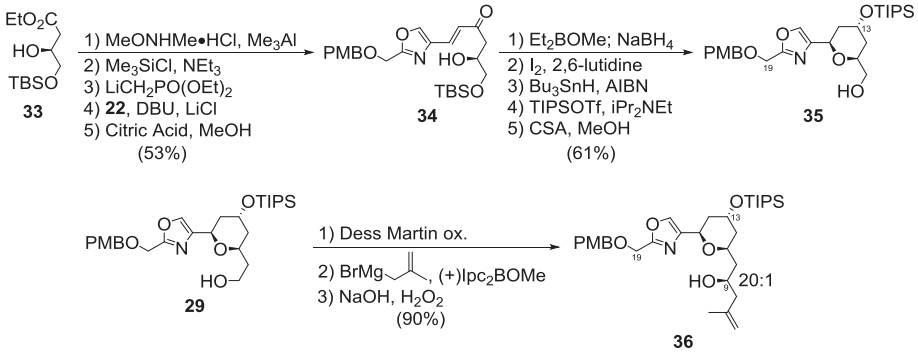
In order to maintain flexibility with respect to our eventual coupling of the two fragments, we also pursued a slightly truncated approach, as outlined with the synthesis of **35** in Scheme 5. How-



Scheme 3. Control of the C13 stereocenter of the phorboxazoles.



Scheme 4. Installation of the pyran via iodoetherification.



Scheme 5. Alternative approach to oxazole pyran scaffold and controlled addition to generate the C9 stereocenter.

ever, with primary alcohols **29** and **32** in hand, we were able to oxidize them to the corresponding aldehydes and show that we could introduce a methallyl nucleophile under the auspices of chiral borane conditions, establishing the C9 center of **36** with excellent stereocontrol (and confirmed via Mosher analysis).[17] This provided confidence that the use of a fully elaborated allyl nucleophile would behave in our real system.

We were fully aware of the difficulties associated with the installation of the *cis*-alkene at C2–C3,[5] so we wanted to have that double bond set at the outset. Malate derived **37** (effectively the protected enantiomer of **33**, Scheme 6)[18] was converted to the Weinreb amide and treated with the lithiated methanol synthon **38**[19] to give ketone **39**, which could be methylenated to provide the latent methallylating agent for our eventual coupling. Following liberation of the diol, in situ epoxidation and addition of a protected propargyl anion led to **40**. The remaining alcohol could be silylated, and the C2-C3 syn geometry created via reduction with Lindlar's catalyst.

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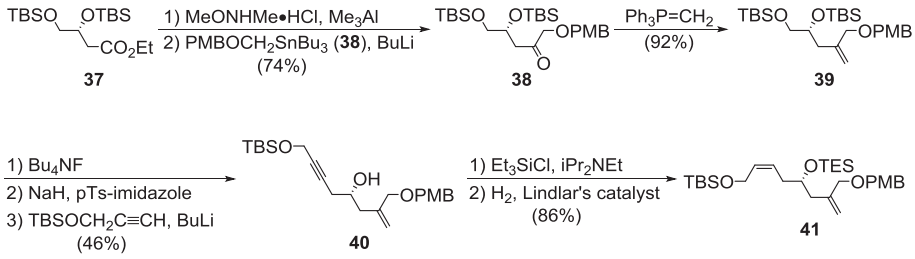

Scheme 6. Synthesis of the C1-C8 fragment.

In summary, we have synthesized two fragments that correspond to the C1–C8 (**41**) and C9–C19 portions of both phorboxazole A and B (**29** and **32**, respectively). We have also established that we can install the eventual C9 stereocenter using an allylated nucleophile. What remains is to achieve the addition of **41** to **29** and **32** with similar control of stereochemistry and to subsequently couple this to the other phorboxazole fragments we have previously disclosed.

Acknowledgements

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