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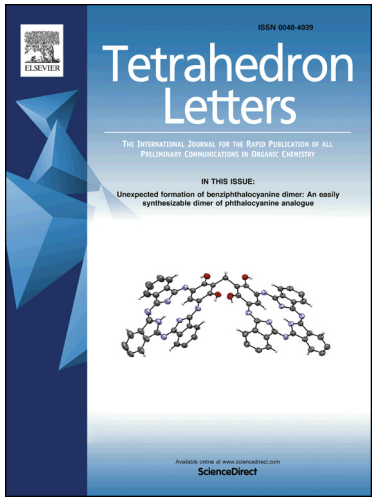

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A Synthetic Approach to the Phorboxazoles – Synthesis of the C20-C32 Central Core

James W. Leahy[a]* and Stephen J. Boyer[b]

[a]Department of Chemistry, University of South Florida, CHE 205, 4202 E. Fowler Avenue, Tampa, FL 33620; Florida Center of Excellence for Drug Discovery and Innovation, University of South Florida, 3720 Spectrum Boulevard, Suite 303, Tampa, FL 33612 and Department of Molecular Medicine, Morsani College of Medicine, University of South Florida, MDC 7, 12901 Bruce B. Downs Boulevard, Tampa, FL 33612. [b]Department of Chemistry, University of California, Berkeley, CA 94720

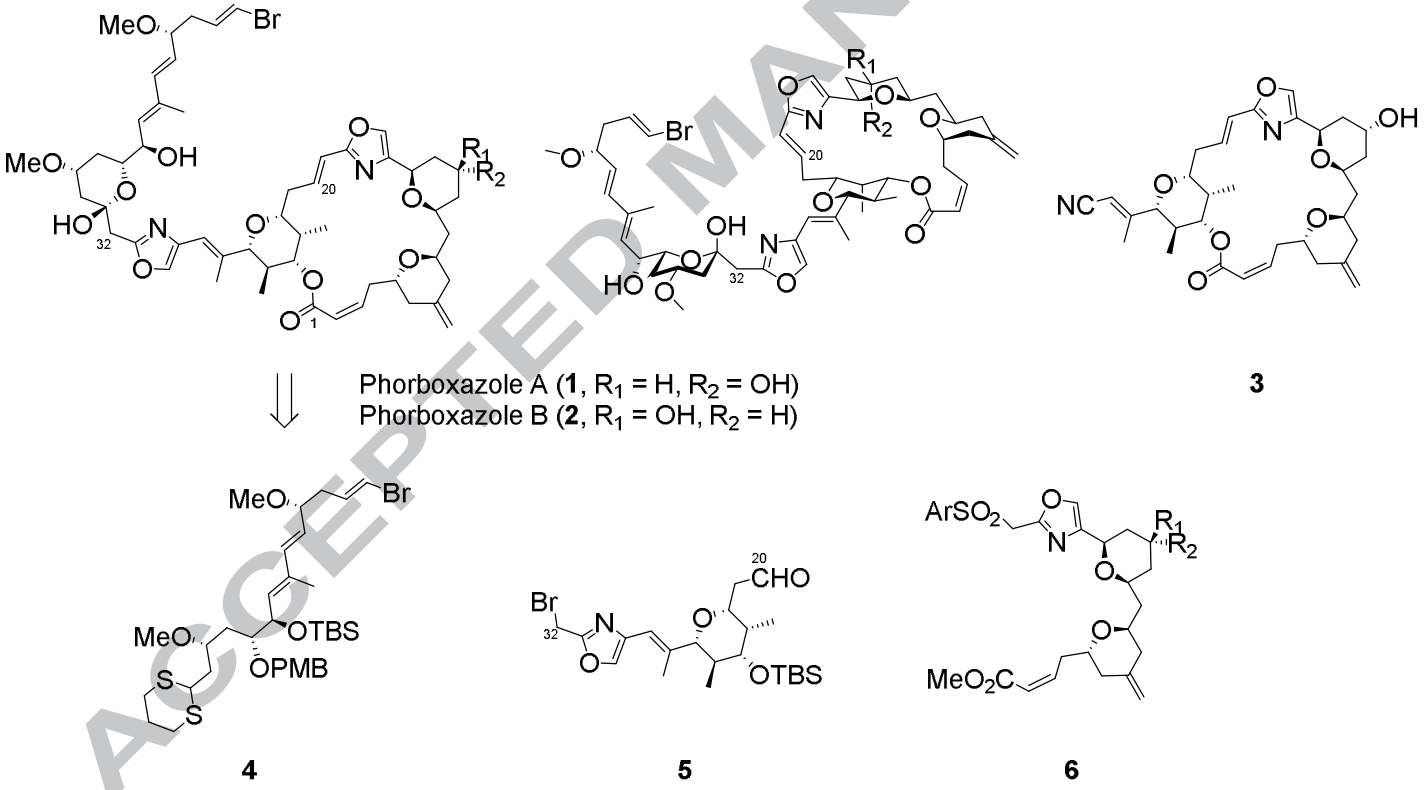
Abstract

An enantiospecific synthesis of the C20-C32 central core of the phorboxazole scaffold, including the non-macrocyclic oxazole is detailed in 17 steps (longest linear sequence) from methacrolein in 7.8% overall yield. All of the stereocenters are communicated from a single Evans aldol reaction, and the final compound is suitably functionalized for further elaboration to the natural products.

Keywords

Phorboxazole; enantiospecific synthesis; oxazole; pentasubstituted pyran

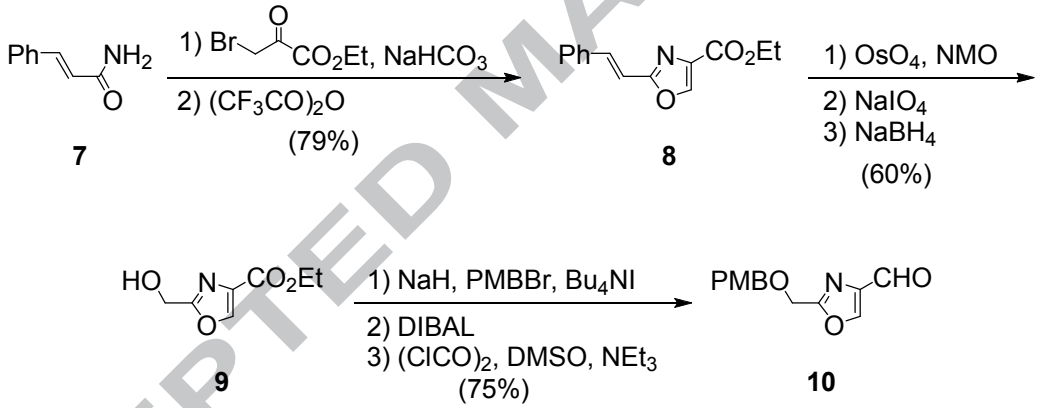
The phorboxazoles (**1** and **2**) and hemiphorboxazole (**3**) are a family of marine macrolides that possess potent cytostatic and antifungal activity.[1, 2] This activity has been ascribed to their ability to regulate cyclin-dependent kinase 4,[3] one of the presumptive targets of Pfizer's breast cancer drug palbociclib.[4] Not surprisingly, the novel architecture and considerable biological activity of these macrolides has attracted significant synthetic interest.[5, 6] Ultimately, that resulted in several completed total syntheses as well as provided synthetic access to a number of novel synthetic analogs and chemical probes. We report here our synthetic approach to the central C20-C32 core of the natural product, including the exocyclic oxazole and the pentasubstituted pyran.



Our retrosynthetic approach to the phorboxazoles was to introduce the exocyclic pyran as a dithiane nucleophile (**4**)[7] to the macrolide appropriately adorned with a bromomethyloxazole. This macrolide would emanate from a Julia olefination at C19/C20 and a C1 esterification, thus

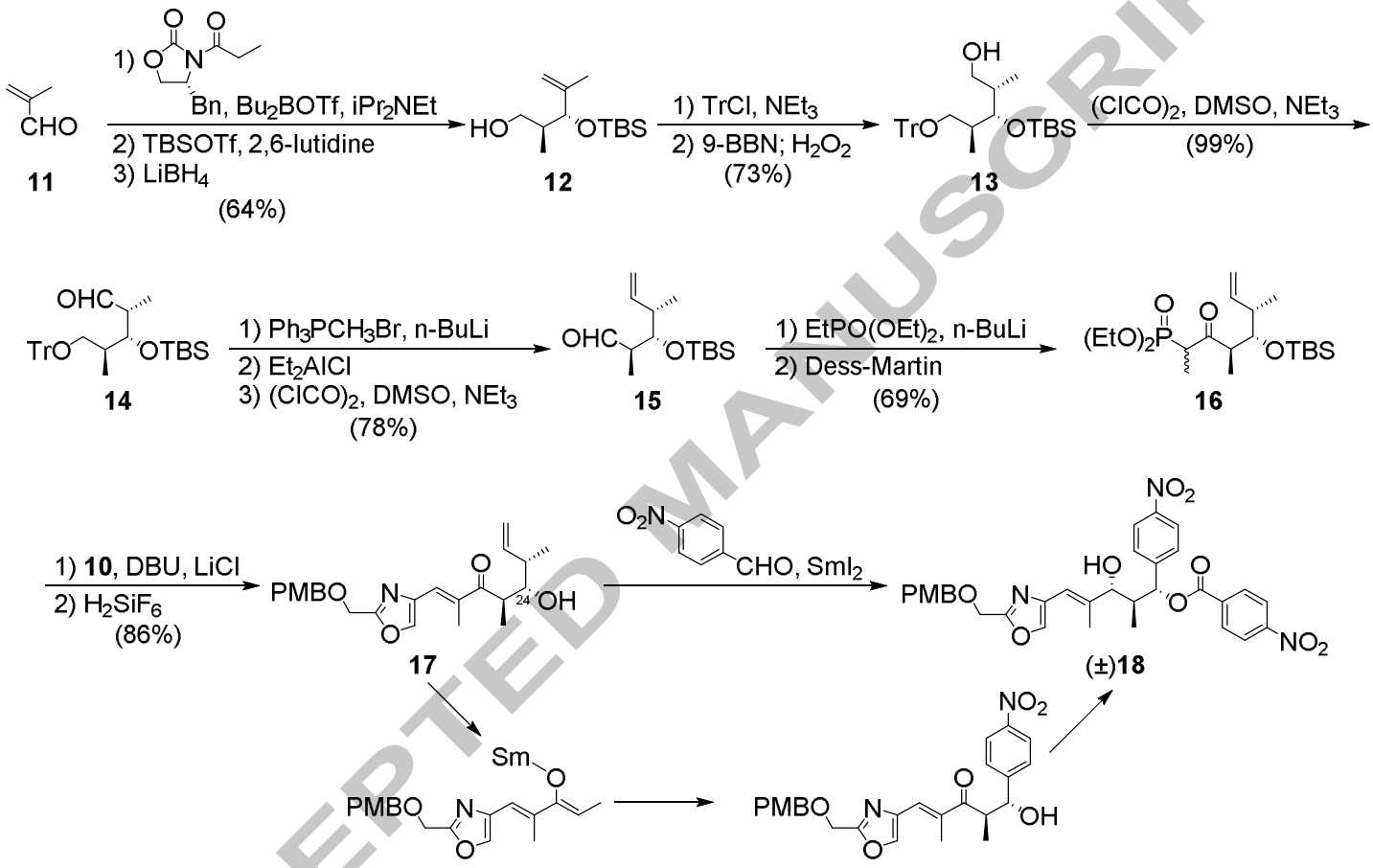
resulting in the two retrons **5** and **6**. We wish to report here our approach to the synthesis of **5**, which resulted in the synthesis of a functional equivalent (**31**, *vide infra*).

While we were confident that our prior synthetic experience on the synthesis oxazole-containing natural products was going to provide a significant advantage as we initiated our approach to **5**,[8, 9] we realized that the methodology developed by Panek for the synthesis of the ulapualides was superior and more practical.[10] Hantzsch cyclization with ethyl bromopyruvate using the readily available and inexpensive **7** gave the crystalline heterocycle **8**, which was oxidatively cleaved and reduced to provide 2-hydroxymethylated adduct **9**. Following protection of the alcohol, the ester was smoothly converted to the corresponding aldehyde (**10**), which was ready to be coupled to the pyran component.



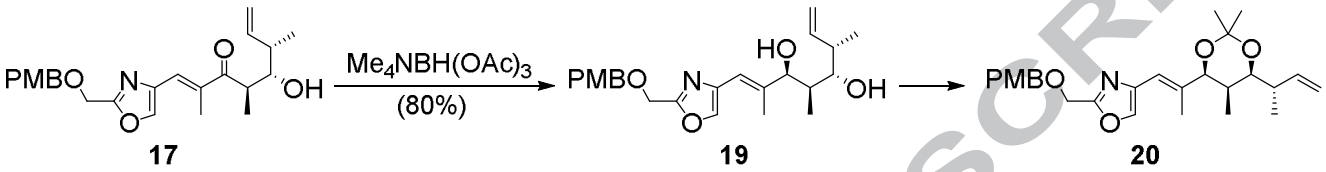
The polypropionate composition of the pyran lent itself to consideration of an Evans aldol approach.[11] Toward this end, aldol addition to methacrolein provided the desired syn product with excellent stereocontrol.[12] Following silylation of the alcohol and reductive removal of the Evans auxiliary, primary alcohol **12** was tritylated to provide the corresponding olefin. Hydroboration with 9-BBN proceeded with complete stereocontrol, yielding the desired stereotriad **13**.[12] The resulting alcohol was oxidized to the aldehyde, and a terminal olefin was installed under Wittig conditions. This was in anticipation of cyclizing the ring using the elegant

carbonylative methodology developed by Semmelhack.[13] Removal of the trityl group and oxidation to the aldehyde allowed for the formation of β-ketophosphonate **16**, which smoothly underwent Horner-Wadsworth-Emmons olefination with **10** to afford the trisubstituted alkene



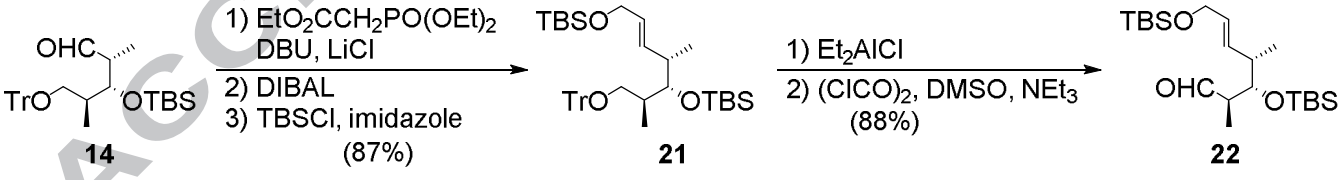
with good stereocontrol (>8:1 E:Z).[14] Secondary alcohol **17** was unmasked with fluorosilicic acid,[15] and the stage was set to use an intramolecular Tishchenko reaction, which would simultaneously set the desired stereocenter at C26 and install an ester at C24.[16] We had done this with an eye toward using an appropriate aldehyde at C1 to form the ester in the natural product, and had even hoped to explore this as a novel macrocyclization strategy. To our surprise, treatment of **17** with p-nitrobenzaldehyde and SmI_2 instead resulted in the generation of racemic

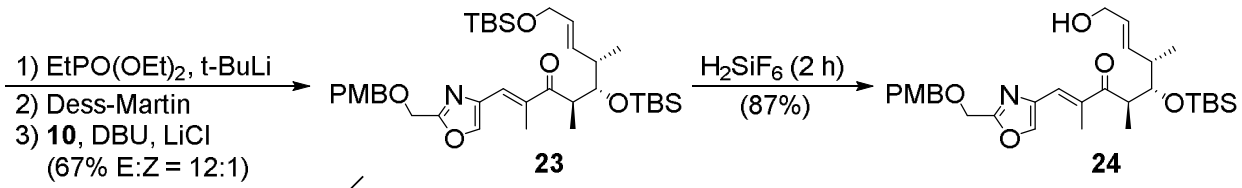
18, which was formed via a retro-aldol of **17** followed by an aldol addition to p-nitrobenzaldehyde and then an intramolecular Tishchenko reduction.[17] Further confounding these efforts was the observation that Evans-Saksena reduction, which typically proceeds with excellent 1,3-anti control,[18] gave us predominantly the unexpected 1,3-syn product **19**

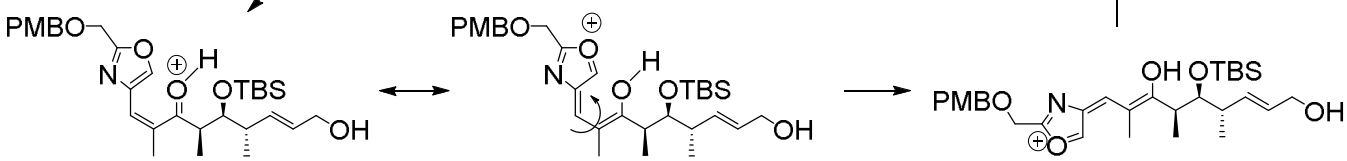


(confirmed via examination of **20** using the Rychnovsky acetonide model).[19] Finally, attempts to cyclize **19** under Pd-carbonylative conditions as a model of our approach to **5** (either as the diol or various analogs with the non-allylic alcohol protected) failed to yield even a trace of the desired product, forcing us to reconsider our cyclization strategy. Toward this end, we recognized a need to prepare a more versatile advanced intermediate.

Aldehyde **14** was extended under Horner-Wadsworth-Emmons conditions, which allowed for the facile generation of **21**. This conversion to the primary allylic silyl ether proved critical, as all attempts to install a β-ketophosphonate in the subsequent steps were incompatible with the initial ester that was formed from **14**. Selective trityl deprotection and Swern oxidation set the

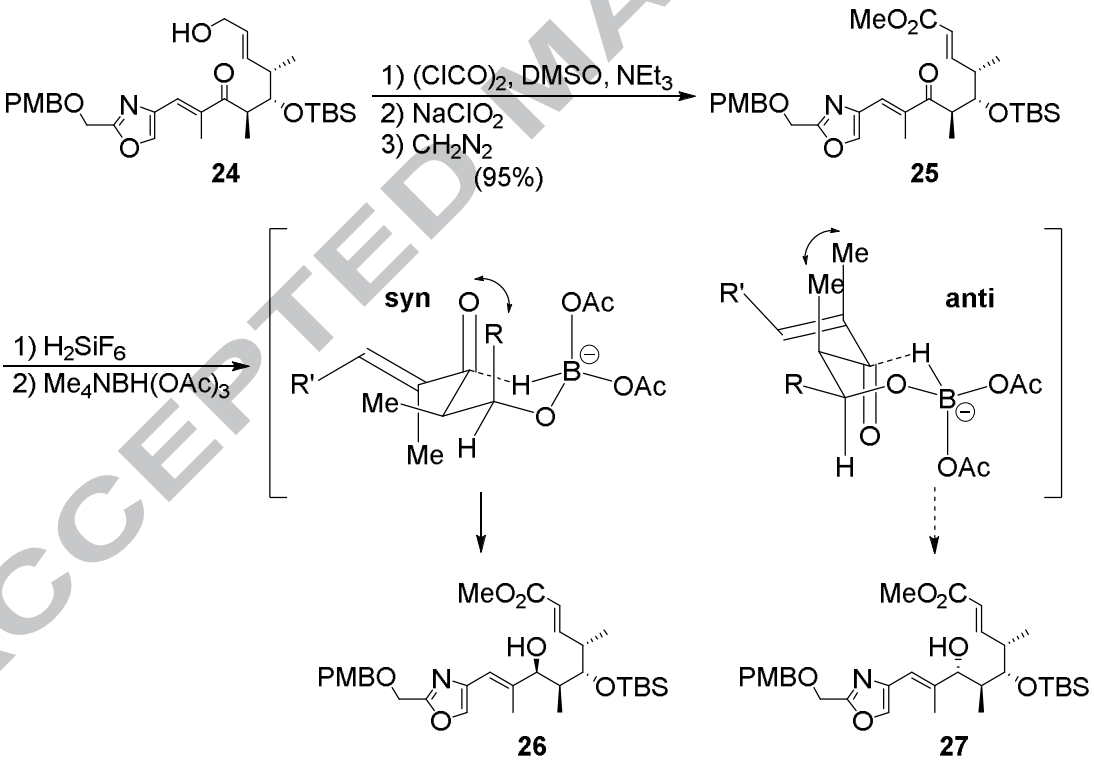






stage for the introduction of the requisite β-ketophosphonate, and installation of the oxazole proceeded as expected (with 12:1 E:Z selectivity). The primary alcohol could then be liberated selectively with fluorosilicic acid over 2 hours. The latter reaction also apparently allowed for the isomerization of the undesired Z-isomer, presumably through protonation of the carbonyl.

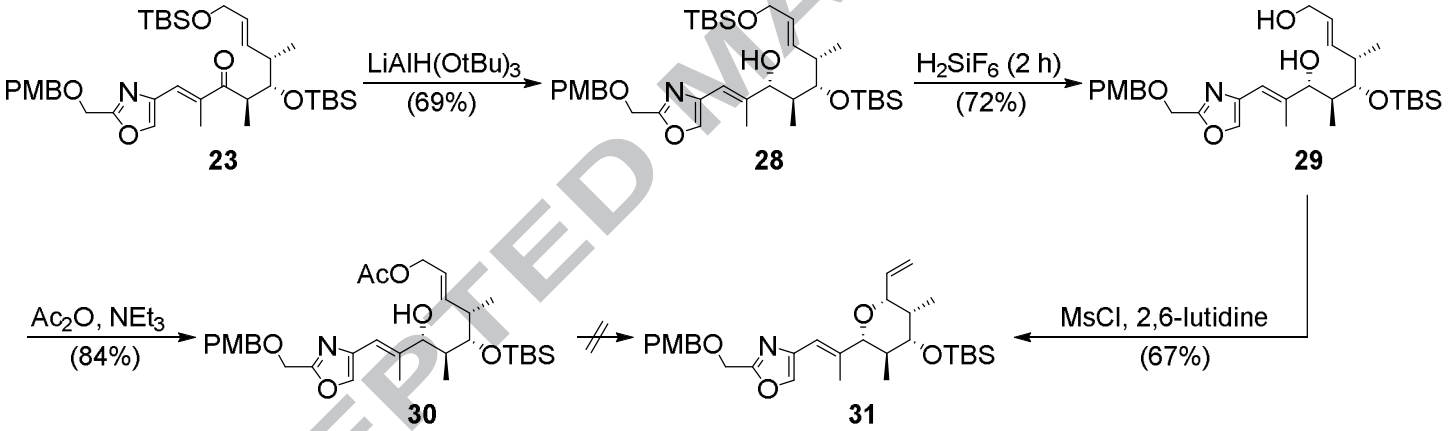
We recognized that Michael cyclization of a substrate such as **27** under equilibrating conditions should greatly favor the desired stereochemistry, so Pinnick oxidation and esterification of **24** yielded **25**.[20] Once again, all attempts to reduce the ketone to give **27** with stereocontrol failed completely. A plausible explanation for this arises from the prospects that intramolecular delivery of the hydride to give the anti-product **27** would, in this case, require an



unfavorable syn-pentane interaction,[21] so the typically disfavored syn product (which forces a pseudodiaxial interaction between the carbonyl and the γ-carbon) proceeds instead. The main

product formed was **26**, which was confirmed using the aforementioned Rychnovsky model.[19] Critically, all of our efforts either resulted in concomitant reduction of the ester or formation of the **26** as the major product.

Our inability to conduct a directed reduction prompted us to consider using the inherent Felkin-Ahn selectivity of the ketone.[22] A number of reducing agents were explored, and ultimately the bulky lithium tri-tert-butoxyaluminum hydride gave us our best results with > 4:1 selectivity. Liberation of the primary alcohol finally revealed cyclization precursor **29**, which we selectively acetylated with an eye toward closing via a Pd-mediated π-allyl process. Once we recognized the futility of this strategy, we were delighted to find that the desired pyran **31** could be formed by simple cyclization with mesyl chloride in the presence of lutidine.



In conclusion, this route provided an enantiospecific synthetic route for the C20-C32 central core of the phorboxazoles where every stereocenter is derived from a single asymmetric Evans aldol addition. The longest linear sequence for this portion of the molecule was 17 steps, and proceeded in 7.8% overall yield. The product obtained in this manner is suitably functionalized on each end to allow for the further elaboration of this material into phorboxazole, and additional efforts in this direction will be reported in due course.

Acknowledgements

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A synthetic approach to the phorboxazoles is disclosed

An enantiospecific synthesis of the C20-C32 exocyclic portion is described

All stereocenters derived from a single chiral auxiliary via an Evans aldol reaction