A Synthetic Approach to the Phorboxazoles – Synthesis of the Exocyclic Fragment

James W. Leahy^{a*} and Linda Joy Brzezinski^b

^aDepartment 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. ^bDepartment of Chemistry, University of California, Berkeley, CA 94720

Abstract

A strategy for the total synthesis of the phorboxazoles, including a synthesis of the exocyclic fragment corresponding to the C33-C41 portion, is reported. The primary objective was to utilize a chelation-controlled addition to an α -alkoxyaldehyde to install the oxygen atom at the C38 position.

Keywords

Phorboxazole; enantiospecific synthesis; chelation-controlled addition to α -alkoxyaldehyde

The phorboxazoles (**1** and **2**) are potent cytostatic and antifungal macrolides that have been isolated from multiple Australian sponge sources.^{1, 2} More recently, hemi-phorboxazole A (**3**) was also isolated,³ and although it contains the full macrolide portion of **1**, it is not biologically

active.⁴ The unique biological activity and structures of the phorboxazoles attracted the attention of the synthetic organic community⁵ even before the structure had been fully elucidated.^{6, 7} These efforts have resulted in a number of groups reporting on their total or partial syntheses which were recently reviewed.^{8, 9} This has prompted us to disclose our own synthetic approach to these natural products.

We envisioned a disconnection of the macrolide about the ester at C1 as well as the C19-C20 olefin, which we felt we could install via a modified Julia coupling, leading to our planned intermediates **5** and **6**, and the approaches to these molecules will be reported in due course. Our plan for the exocyclic fragment **4** was to utilize the C33 hemiketal as an umpolung nucleophile capable of displacing a leaving group at C32.

In our initial work that led to the structural elucidation of the exocyclic portion,⁷ we added nucleophile **8** to the pyran aldehyde **7**, which provided **9** and **10** as a 3:2 mixture of isomers at the position that corresponded to C38. At the time that we conducted this work, we did not yet

know the absolute stereochemistry of the phorboxazoles, which led to these models being prepared antipodal to the stereochemistry of the natural product. They did, however, allow for the determination of the relative stereochemistry between C37 and C38, the latter of which had been unequivocally established via Mosher ester analysis, thus completing the stereochemical assignment for both **1** and **2**. While this was invaluable in allowing us to determine the structure, we were somewhat disappointed to observe that the addition to this aldehyde did not proceed with good chelation control, which would have given us a preponderance of **10**. We therefore sought to modify our synthetic approach so that we would use a more chelation- friendly substituent such as a p-methoxybenzyl ether to enhance the chelation control.¹⁰ It is noteworthy that most of the synthetic approaches to this portion of the phorboxazoles either used an available chiral pool reagent for this position¹¹⁻¹⁸ or set positions C37 and C38 via a Sharpless asymmetric dihydroxylation.¹⁹⁻²³ Notable exceptions were the approaches of Evans,²⁴ Paterson²⁵ and the first generation synthesis of Forsyth,²⁶ all of which were conducted on the closed pyran

ring. While Evans was able to elicit exquisite stereocontrol on the fully elaborated skeleton in the penultimate step of his synthesis, Forsyth and Paterson's addition to a pyran fragment gave predominantly the undesired Felkin-Ahn product.²⁷ This would suggest that the variation in the size of the R substituent impacts this selectivity. We therefore sought to prepare an acyclic precursor that we felt would allow for greater and more predictable stereocontrol upon the formation of the intended C38 stereocenter.

Borane reduction of (*R*)-malic acid gave the corresponding triol,²⁸ which could be selectively protected as dioxane **12**. The remaining primary alcohol was converted into the triisopropylsilyl ether, and DIBAL reduction of the acetal smoothly proceeded at the primary position to give **14**.²⁹ Swern oxidation then provided aldehyde **15**.

With a lack of an α -substituent, we were unlikely to achieve much substrate-derived stereocontrol, and indeed achiral nucleophile addition proceeded to give little to no diastereomeric excess. In our hands, we found that Keck's BINOL-mediated allylation afforded the best yield and diastereomeric ratio, which provided access to **16**.³⁰ Upon methylation of this alcohol, the olefin was converted into an aldehyde via the osmylation/periodate protocol, followed by formation of 1,3-dithiane umpolung **19** using standard conditions. Fluoride-mediated deprotection of the TIPS ether followed by Swern oxidation of the alcohol thus provided aldehyde **21**.

There have been several elegant approaches to the exocyclic triene portion of the phorboxazoles, many of which could be used to add to **21**. However, we wanted to evaluate the selectivity of addition to our substrate, so we prepared **23** from known alcohol **22**.³¹ Metallation

of **23** and addition to **21** ultimately proceeded in quite reasonable yield, and the desired chelation-control product was the major isomer formed. Unfortunately, the level of selectivity was meager at best.

We initially explored simply using the lithiated species derived from **23** via lithium-halogen exchange. The reaction proceeded with modest selectivity (1.6:1) and modest yield (65 %). We explored a series of additives (e.g. LiClO_4 , TiCl_4 , Me_2AlCl , MeAlCl_2 , $\text{BF}_3 \cdot \text{OEt}_2$, SnCl_4 , ZnCl_2) in an effort to improve on these results, though typically these led to incomplete consumption of starting material or decomposition, and without any improvement in the diastereomeric ratio. Our initial concern was that these conditions might have resulted in the epimerization of the C37 stereocenter that might contribute to our limited success, but we were able to independently oxidize both crude **24** and **25** to the same ketone, and neither showed the presence of any diastereomers – thus indicating that epimerization was not likely an issue. Ultimately the best result we obtained was through the auspices of magnesium bromide as Evans had previously observed,²⁴ suggesting that moving away from the pyran does not provide a significant improvement over most of the previous fragment endeavors.

The synthesis of **24** completes a fully elaborated C33-C41 fragment of the phorboxazoles with functionality in place for the further elaboration to the natural products, and the use of a

nucleophile such as Evans' **26** would be expected to give the complete exocyclic fragment.²⁴ In concert with our synthetic approach to the macrocycle, this would provide a route to **1** and **2**.

Additional efforts toward the synthesis of the phorboxazoles will be reported.

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Graphical Abstract