

Toward a Total Synthesis of Peloruside A: Enantioselective Preparation of the C8–C19 Region

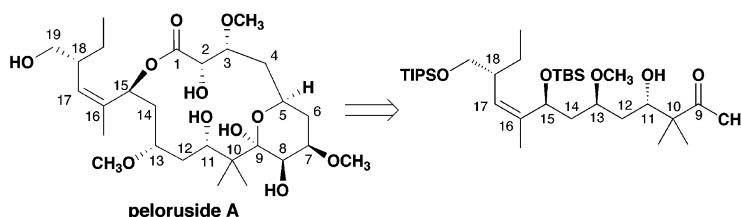
Richard E. Taylor* and Meizhong Jin

Department of Chemistry and Biochemistry and the Walther Cancer Research Center,
University of Notre Dame, 251 Newland Science Hall,
Notre Dame, Indiana 46556-5670

taylor.61@nd.edu

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ABSTRACT



An efficient synthetic sequence toward the C8–C19 region of peloruside A has been developed. The route is highlighted by a selective electrophilic cyclization reaction, a single-step epoxide ring-opening/methylation sequence, and a stereoselective Mukaiyama aldol reaction.

Peloruside A is a cytotoxic macrolide isolated from a New Zealand sponge, *Mycale hentschi*.¹ The structure was originally determined by extensive NMR solution studies. More recently, Miller and co-workers reported a study that established peloruside A as a potent cytotoxic agent with epothilone-like microtubule-stabilizing activity.² This report noted interesting structural similarities between the two biologically related polyketides peloruside A and the epothilones (i.e., contiguous hydroxyl, *gem*-dimethyl, carbonyl; C11–C9 peloruside, C3–C5 epothilone). This proposal implied that the C15-stereogenic center of peloruside A was of opposite configuration to the corresponding center in epothilone. More recently, the absolute stereochemistry of natural peloruside A was unambiguously determined to have the identical C15 stereochemistry as epothilone by the De Brabander group through an elegant total synthesis effort.^{3,4}

Our previous experience with the conformation–activity relationships of epothilone⁵ revealed interesting shape and size similarities to peloruside A, and a comparison is shown

in Figure 1. Although there is no direct experimental evidence, peloruside A and the epothilones may have

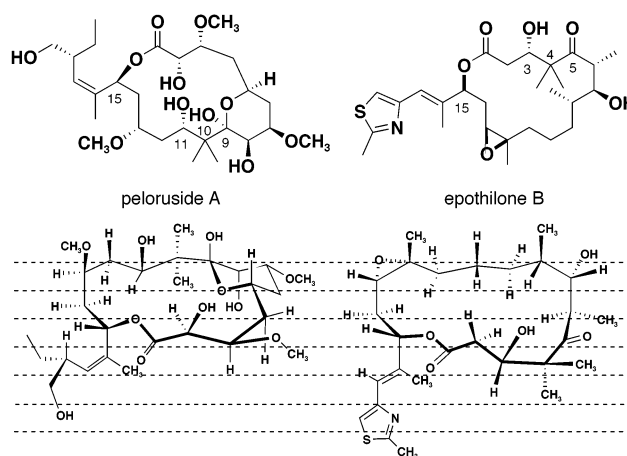


Figure 1. Structural and conformational comparison of peloruside A and epothilone B derived from NMR and computer modeling analysis.

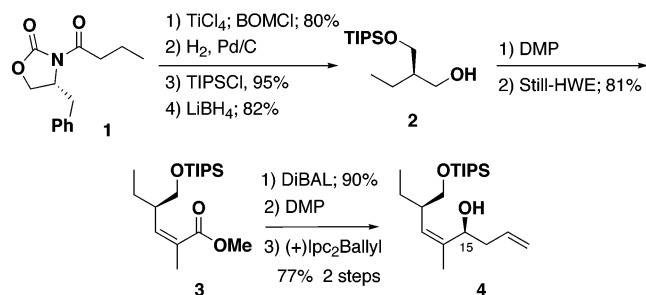
(1) West, L. M.; Northcote, P. T. *J. Org. Chem.* **2000**, 65, 445.

(2) Hood, K. A.; West, L. M.; Rouwe, B.; Northcote, P. T.; Berridge, M. V.; Wakefield, S. J.; Miller, J. H. *Cancer Res.* **2002**, 62, 3356.

overlapping pharmacophores. Toward our interest in the structural and conformational constraints of peloruside's biological activity, we have begun a program where total synthesis is an initial goal. Herein we report our preliminary efforts toward that aim.

The synthesis commenced with readily available oxazolidinone **1** (Scheme 1), which was stereoselectively alkylated

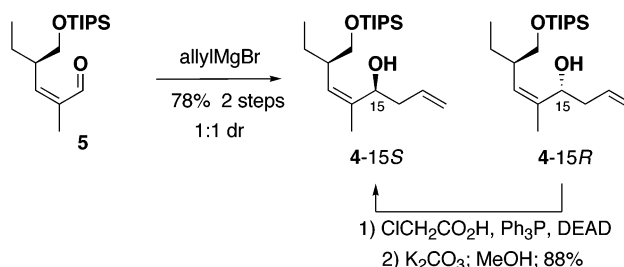
Scheme 1



with BOMCl in the presence of titanium tetrachloride.⁶ After an exchange of protecting groups, the chiral auxiliary was reductively removed with LiBH₄. Oxidation of **2** with Dess–Martin periodinane⁷ followed by a Still–Gennari olefination⁸ provided exclusively the (*Z*)-trisubstituted alkene **3**. Then, a two-step conversion of the methyl ester to the corresponding aldehyde allowed for a Brown asymmetric allylation to set the C15 stereogenic center and provide **4** (dr = 97:3, 77% for two steps).

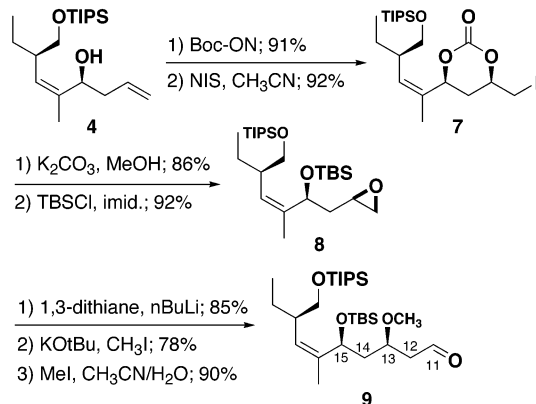
The nonpolar physical properties of alcohol **4** made purification difficult, a common problem with this allylation method due to reaction byproducts. However, a diastereorandom allylation with inexpensive allylmagnesium bromide followed by chromatographic separation and processing of the undesired **4-15R** isomer through Mitsunobu inversion⁹ proved to be a practical alternative for large-scale work. As shown in Scheme 2, simple Grignard allylation proceeded in good yield to provide a 1:1 mixture of diastereomers that were easily separable by column chromatography. The two-step conversion of the undesired isomer proceeded efficiently to provide diastereomerically pure **4-15S**. The 16,17-(*Z*)-olefin geometry was maintained through this sequence as proven by NOE studies (see Supporting Information).

Scheme 2



The next stage of the plan was to build the 1,3-syn relationship between C13 and C15. Iodine-induced carbonate cyclization methodology originally published by Bartlett^{10a} and later improved by Smith^{10b} was first considered, Scheme 3. This is a particularly interesting substrate for this elec-

Scheme 3



trophilic cyclization reaction because of the presence of two potential sites for reactivity. One could envision electrophilic activation of the more electron-rich trisubstituted olefin to provide a five-membered cyclic carbonate¹¹ or the sterically accessible terminal olefin to provide the desired six-membered cyclic carbonate. In fact, treatment of the mixed carbonate with either I₂ or IBr, at low temperature, provided complex mixtures of products. However, the use of *N*-iodosuccinimide proved to be selective for the formation of a single compound, carbonate **7**, in 92% yield. As expected, this material, upon exposure to basic methanol solution and protection, efficiently provided the *syn*-epoxy ether **8**. Generation of the polyacetate *syn*-diol would then be unveiled by epoxide ring opening with an acyl anion synthon.

The lithium anion of dithiane was used to fragment the epoxide and proceeded in 85% yield as shown in Scheme 3. Formation of C13-methyl ether was accomplished with

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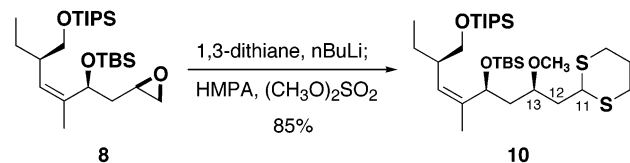
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(10) (a) Bartlett, P. A.; Meadows, J. D.; Brown, E. G.; Morimoto, A.; Jernstedt, K. K. *J. Org. Chem.* **1982**, *47*, 4013. (b) Duan, J. J.-W.; Smith, A. B., III. *J. Org. Chem.* **1993**, *58*, 3703.

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methyl iodide in the presence of KOtBu in 78% yield. This was followed by hydrolysis of the dithiane to provide aldehyde **9**. A more efficient generation of the C13-methyl ether was accomplished by in situ alkylation of the intermediate alkoxide resulting from epoxide ring opening. As shown in Scheme 4, exposure of epoxide **8** to the lithiated

Scheme 4



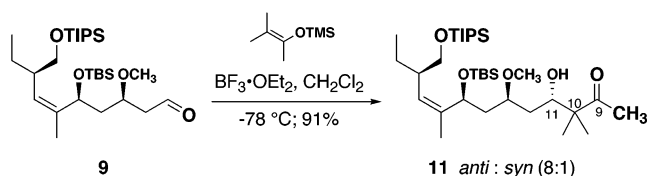
dithiane followed by the addition of an HMPA solution of dimethyl sulfate led to direct isolation of methyl ether **10** in 85% yield.

Mukaiyama aldol¹² reaction of the β -methoxy aldehyde **9** provided methyl ketone **11** in 91% yield as shown in Scheme 5. Mosher ester analysis¹³ of the major isomer, obtained in an 8:1 mixture, proved to have the desired absolute stereochemistry at C11 and thus a 1,3-anti stereochemical relationship between C11 and C13.

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Scheme 5



In summary, we have developed an efficient, enantioselective route to a protected C8–C19 fragment of peloruside A. The route is highlighted by a selective electrophilic cyclization reaction, a single-step epoxide ring-opening/methyl ether formation, and an anti stereoselective Mukaiyama aldol reaction. Conversion of this advanced intermediate to peloruside A and analogues is currently underway in our laboratories, and results along these lines will be reported in due course.

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Supporting Information Available: Full experimental and characterization data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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