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

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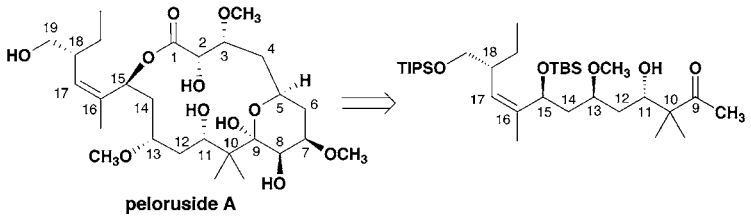
ABSTRACT



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 epothilone[5] 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

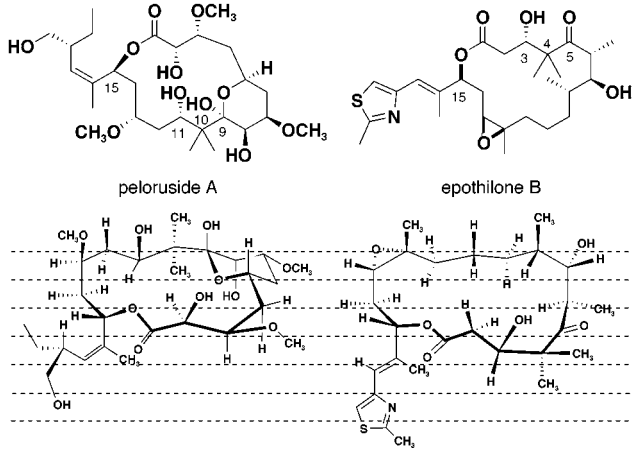


Figure 1. Structural and conformational comparison of peloruside A and epothilone B derived from NMR and computer modeling analysis.

(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.

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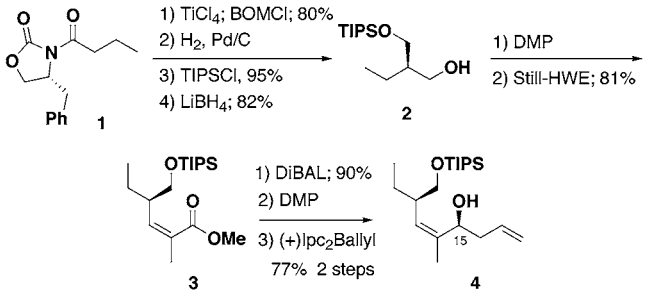
overlapping pharmacophores. Toward our interest in the structural and conformational constraints of peloruside's biological activity, we have begun a program where total synthesis is an initial goal. Herein we report our preliminary efforts toward that aim.

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

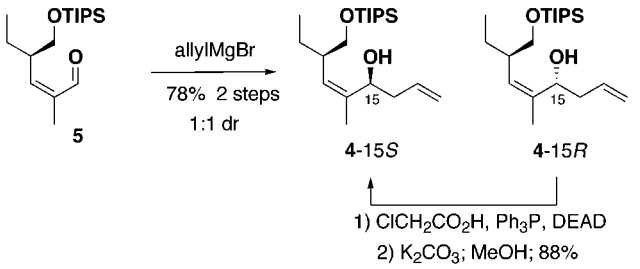
Scheme 1



with BOMCl in the presence of titanium tetrachloride.[6] After an exchange of protecting groups, the chiral auxiliary was reductively removed with $LiBH_4$. Oxidation of **2** with Dess–Martin periodinane[7] followed by a Still–Gennari olefination[8] 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).

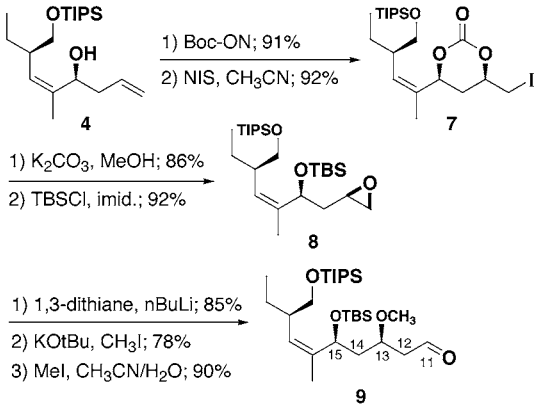
The nonpolar physical properties of alcohol **4** made purification difficult, a common problem with this allylation method due to reaction byproducts. However, a diastereorandom allylation with inexpensive allylmagnesium bromide followed by chromatographic separation and processing of the undesired **4**-15*R* isomer through Mitsunobu inversion[9] 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**-15*S*. 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 carbonate[11] or the sterically accessible terminal olefin to provide the desired six-membered cyclic carbonate. In fact, treatment of the mixed carbonate with either I_2 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

(3) Liao, X.; Wu, Y.; De Brabander, J. K. *Angew. Chem., Int. Ed.* **2003**, *42*, 1648.

(4) For additional synthetic efforts towards peloruside A, see: (a) Paterson, I.; Di Francesco, M. E.; Kuhn, T. *Org. Lett.* **2003**, *5*, 599. (b) Ghosh, A. K.; Kim, J.-H. *Tetrahedron Lett.* **2003**, *44*, 3967. (c) Hoye, T. R.; Hu, M. 38th National Organic Chemistry Symposium, Bloomington, IN, June 8–12, 2003; Abstract A22. (d) Ghosh, A. K.; Kim, J.-H. *Tetrahedron Lett.* **2003**, *44*, 7659.

(5) (a) Yoshimura, F.; Rivkin, A.; Gabarda, A. E.; Chou, T.-C.; Dong, H.; Sukenick, G.; Morel, F. F.; Taylor, R. E.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 2518. (b) Taylor, R. E.; Chen, Y.; Beatty, A.; Myles, D. C.; Zhou, Y. *J. Am. Chem. Soc.* **2003**, *125*, 26. (c) Taylor, R. E.; Zajicek, J. *J. Org. Chem.* **1999**, *64*, 7224.

(6) Ihara, M.; Katsumata, A.; Setsu, F.; Tokunaga, Y.; Fukumoto, K. *J. Org. Chem.* **1996**, *61*, 677.

(7) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

(8) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.

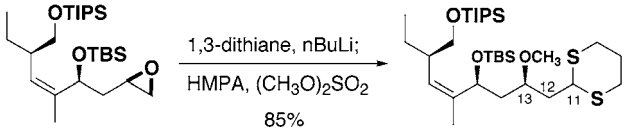
(9) Mitsunobu, O. *Synthesis* **1981**, 1.

(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.

(11) Bongini, A.; Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *J. Org. Chem.* **1982**, *47*, 4626.

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



8 **10**

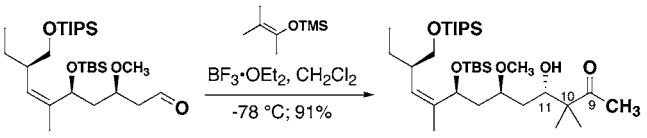
dithiane followed by the addition of an HMPA solution of dimethyl sulfate led to direct isolation of methyl ether **10** in 85% yield.

Mukaiyama aldol[12] reaction of the β-methoxy aldehyde **9** provided methyl ketone **11** in 91% yield as shown in Scheme 5. Mosher ester analysis[13] 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.

(12) (a) Reetz, M. T.; Kesseler, K.; Jung, A. *Tetrahedron Lett.* **1984**, *25*, 729. (b) Trieselmann, T.; Hoffmann, R. W. *Org. Lett.* **2000**, *2*, 1209. (c) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322. (d) Willson, T. M.; Kocrenski, P.; Jarowicki, K.; Isaac, K.; Hitchcock, P. M.; Faller, A.; Campbell, S. F. *Tetrahedron* **1990**, *46*, 1767.

(13) Dale, J. S.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

Scheme 5



9 **11** *anti* : *syn* (8:1)

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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