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Rapid Access to Conformational Analogues of (+)-Peloruside A

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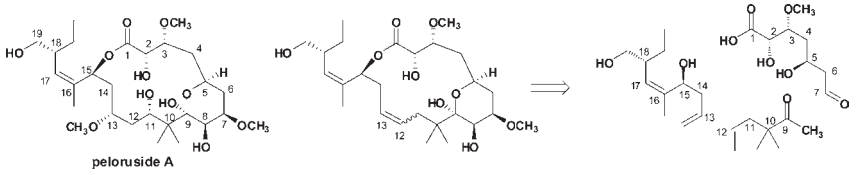
ABSTRACT



An efficient synthetic strategy for rapid access to analogues of peloruside A has been demonstrated. The synthetic route was highlighted by a simple esterification-based fragment coupling and a late stage ring-closing metathesis reaction. This convergent route has provided access to rationally designed analogues inspired by the solution conformational preferences of peloruside A.

Pelorusides A and B, Figure 1, are cytotoxic polyketides isolated from a marine sponge, *Mycale* sp., found off the coast of New Zealand.[1] Peloruside A was found to have paclitaxel-like microtubule stabilizing activity[2] through interaction at the laulimalide binding site.[3] Inspired by both an interesting chemical structure as well as its cancer chemotherapeutic potential, several total syntheses of peloruside A have been reported along with numerous partial efforts.[4,5] In fact, material prepared in our own laboratory enabled experiments that identified a unique binding site on the β-tubulin subunit within microtubules through both H/D-exchange mass spectrometry which was later confirmed by tubulin mutation studies.[6]

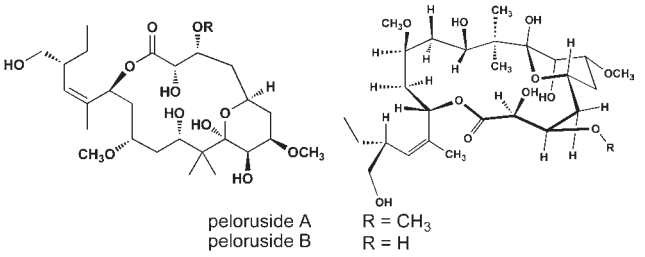


Figure 1. Structure of peloruside A and B.

Despite the availability of both natural and synthetic sources of pelorusides, only a limited set of structure–activity

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relationship studies have been reported.[7] Using a similar approach to our previous investigation of the epothilones,[8] we began with *in silico* and solution conformational studies. Detailed computational modeling experiments complemented by solution NMR studies suggested that flexibility within the C9−C15 region leads to a relatively small set of conformational families.[9] Thus, the solution conformational preferences of peloruside A is largely controlled by the relative rigidity imparted by structural features such as the lactone ester (*s*-trans), the C2,C3-diol monoether (gauche effect), and the C5−C9-dihydropyran (chair conformation). With this information as a guide, we envisioned simplification of the peloruside skeleton by replacement of two stereogenic centers, C11 and C13, housed within the more flexible region, with a set of olefinic isomers, *Z*-**1** and *E*-**2**, Figure 2. The bond trajectories inherent to olefin geometries would restrict *Z*-**1** and *E*-**2** to different conformational families, and their biological activities might offer insight into the tubulin-bound conformation of peloruside A.

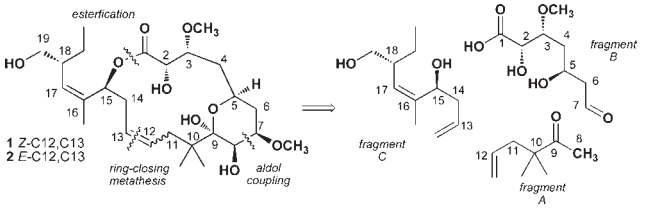

Figure 2. Retrosynthetic analysis of conformational analogues.

To ensure success, our approach to these compounds would rely heavily on our previously developed route to peloruside A.[4a] As highlighted in Figure 2, retrosynthetic simplification of peloruside A conformational analogues *Z*-**1** and *E*-**2** would allow consideration of a late stage ring-closing olefin metathesis to form the C12,C13-alkene from two previously reported fragments, B and C, and simple methyl ketone, fragment A.[10]

Fragment A was readily prepared in two steps as shown in Scheme 1. After generation of lithium enolate of methyl isobutyrate with lithium diisopropylamide and alkylation with allyl bromide, the resulting ester was directly converted to the methyl ketone by the method of Yorifuji.[11] The first of two key fragment coupling reactions proceeded efficiently utilizing an aldol reaction between the lithium enolate of methyl ketone **3** and aldehyde **4** previously prepared in our laboratory.[4b] The resulting mixture of diastereomeric β-hydroxyketones was converted to the β-diketone **5** by oxidation with Dess−Martin periodinane.[12]

(7) Wullschleger, C. W.; Gertsch, J.; Altmann, K.-H. *Org. Lett.* **2010**, *12*, 1120.
(8) Taylor, R. E.; Zajicek, J. *J. Org. Chem.* **1999**, *64*, 7224.
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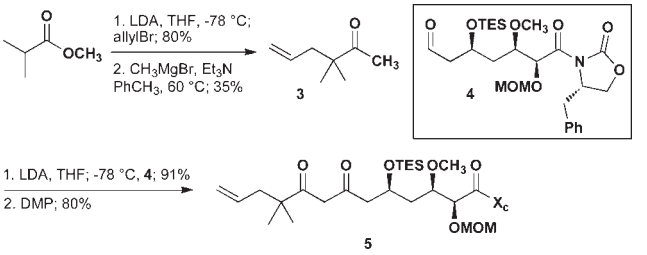
(12) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

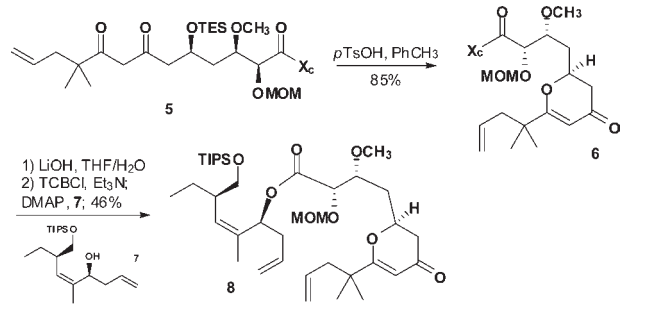
The preparation of this intermediate set the stage for generation of the 4-pyranone and the subsequent fragment couplings necessary for completion of the peloruside skeleton.

Scheme 1. Synthesis of Fragment A and Aldol Coupling To Form Fragment AB



Treatment of diketo-ether **5** with *p*-toluene sulfonic acid in toluene at room temperature readily generated the pyranone **6** through in situ desilylation and dehydrative cyclization, Scheme 2. The chiral auxiliary was then removed by saponification with LiOH. The resulting carboxylic acid was coupled to secondary alcohol **7**,[8] a key intermediate in our previous total synthesis of peloruside A, through the use of a Yamaguchi mixed anhydride, to obtain the ring-closing metathesis (RCM) substrate **8** in 46% yield for two steps.[13]

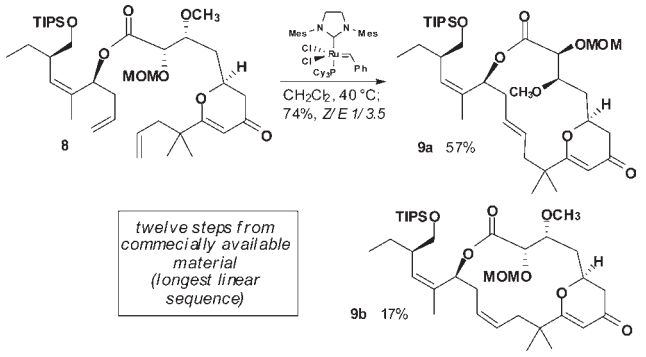
Scheme 2. Creation of the Peloruside Pyran and Yamaguchi Esterification



As highlighted in Scheme 3, diene **8** was then subjected to RCM cyclization with Grubbs' II catalyst to provide the corresponding lactones as a mixture of olefin isomers **9a** and **9b**. The isomeric lactones were separated by column chromatography and obtained in 57% and 17% yield respectively. Unfortunately, spectral overlap within the proton NMR spectra of these intermediates made assignment of olefin geometry difficult at this stage. However, characteristic proton−proton coupling constants for the C12,C13 olefins were easily identified at a later stage. The advanced peloruside intermediates, **9a** and **9b**, represent a valuable platform for analogue design as their preparation was accomplished in just 12 steps from commercial sources.

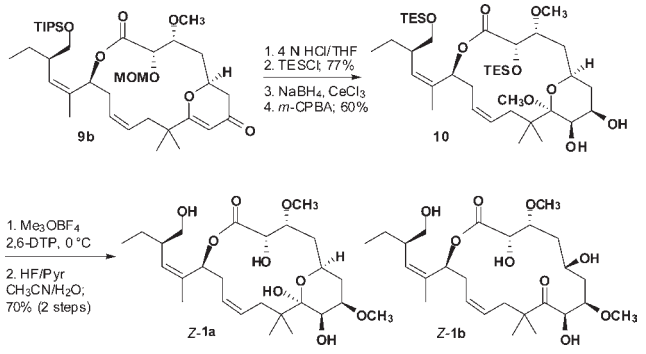
(13) Inanaga, J.; Hirata, K.; Saeki, H.; Kastuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

Scheme 3. Completion of the Peloruside Skeleton via Ring-Closing Metathesis



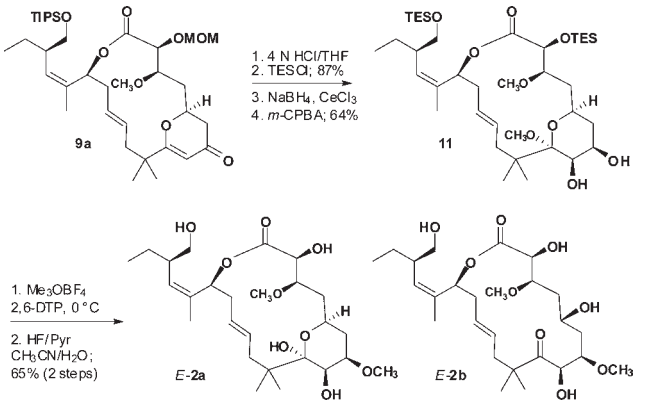
With the peloruside skeleton in hand, completion of the analogue synthesis required elaboration of the pyran through a set of conditions previously developed for the total synthesis of peloruside A, Scheme 4. After some investigation, it was found that early modification of the C2-MOM ether improved later transformations. Thus, selective deprotection of **9b** under aqueous acidic conditions was followed by generation of the corresponding C2, C24-*bis*-triethylsilyl ethers. The enone was then stereoselectively reduced under Luche reduction conditions at −78 °C. The resulting allylic alcohol underwent stereoselective epoxidation with *m*-CPBA in a methylene chloride/methanol mixed solvent to directly provide the methyl pyranoside as diol **10** in 60% yield for two steps. As with peloruside A, methyl ether formation was highly selective for the less hindered equatorial alcohol. However, in the first deviation from observations in the natural system, global deprotection provided a mixture of two compounds, the desired closed pyran **1a** and the open form **1b**. While the isomers can be separated by column chromatography, they equilibrated upon standing to roughly a mixture of equal proportions.

Scheme 4. End Game Functionalization and Preparation of Conformational Analogue *Z*-**1**



Following an identical synthetic protocol outlined in Scheme 5, intermediate **9a** also provided peloruside analogues *E*-**2** as a mixture of open keto-alcohol and closed pyran isomers. While peloruside A prefers the closed pyran isomer, it appears that the inclusion of a C12,C13-olefin generates sufficient additional ring strain such that the open and closed isomers are roughly equal in energy. In addition, these analogues lack a potentially stabilizing intramolecular hydrogen bond array through C9-lactol, C11-hydroxyl, and C13 methoxy group.[14] Moreover, in contrast to the natural system the increased stability of the open form was also accompanied by decreased chemical stability and compounds *Z*-**1** and *E*-**2** were found to degrade within days. The role of the keto-alcohol isomer (open form) in the chemistry and biology of the pelorusides is currently not known.

Scheme 5. End Game Functionalization and Preparation of Conformational Analogue *E*-**2**



In summary, we have utilized conformational analysis to inspire the design of a set of peloruside analogues and a practical synthetic strategy for their preparation. Realization of the route has provided access to conformational analogues of peloruside A in just 18 steps from commercially available material. Unfortunately, the instability of analogues *Z*-**1** and *E*-**2** has thus far complicated the characterization of their conformational preferences as well as their biological evaluation. However, the efficiency of their preparation allows us to consider additional synthetic transformations such as oxidation, reduction, or addition reactions of the C12,C13 olefin increase the stability of the closed pyran and eliminate the observed chemical instability. Results from efforts 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

(14) We thank a reviewer for this suggestion.