ORGANIC LETTERS

2005
Vol. 7, No. 7
1303−1305

# Total Synthesis of (+)-Peloruside A

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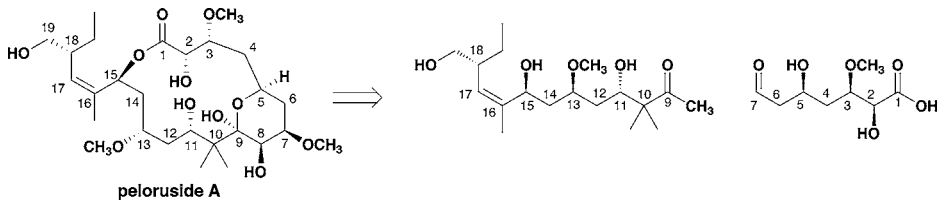
**Received January 13, 2005**

## ABSTRACT




**A total synthesis of (+)-peloruside A has been successfully achieved. The strategy was highlighted by a late stage aldol coupling of two complex fragments followed by an intramolecular hemi-ketal cyclization, a MOM group participated epoxide ring fragmentation reaction, and a highly selective methylation. This convergent route allows access to rationally designed analogues.**

Peloruside A, isolated from a marine sponge, *mycale*, was reported by Northcote in 2000.[1] More recently, Miller and co-workers reported a study that established peloruside A as a potent cytotoxic agent with paclitaxel−like microtubule-stabilizing activity.[2] Peloruside A was shown to induce the formation of multiple asters, micronuclei, microtubule bundles, and rodlike fibers in a similar manner as paclitaxel. In addition, both compounds induce cell-cycle arrest in the G2-M phase and, ultimately, apoptosis.

In 2004, key biological experiments concluded that peloruside A appears not to bind to the taxol binding site on tubulin.[3] In fact, the polyketide laulimalide was able to displace peloruside A, and thus these compounds appear to have related binding sites. Although the early solution NMR studies[1] provided the relative stereochemistry of the compound's 10 stereogenic centers, the absolute stereochemistry remained unknown until recently when the De Brabander group at the UTSW Medical Center reported an elegant total synthesis.[4,5]

As a crucial aspect of a program designed to determine the structural and conformational constraints of peloruside's biological activity, the development of a total synthesis became an initial goal. We hoped to develop a practical and stereoselective route that not only would lead to the natural product but also could provide a variety of rationally designed analogues. We considered a convergent strategy based on an aldol coupling of two complex fragments. Those fragments are a C8−C19 methyl ketone and a C1−C7 aldehyde as shown in Figure 1.

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10.1021/ol050070g CCC: $30.25 
**Published on Web 03/11/2005**

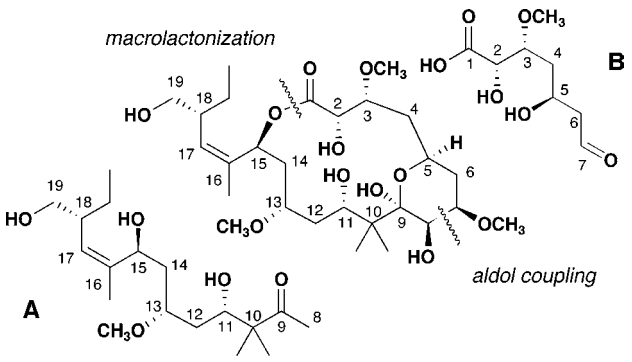
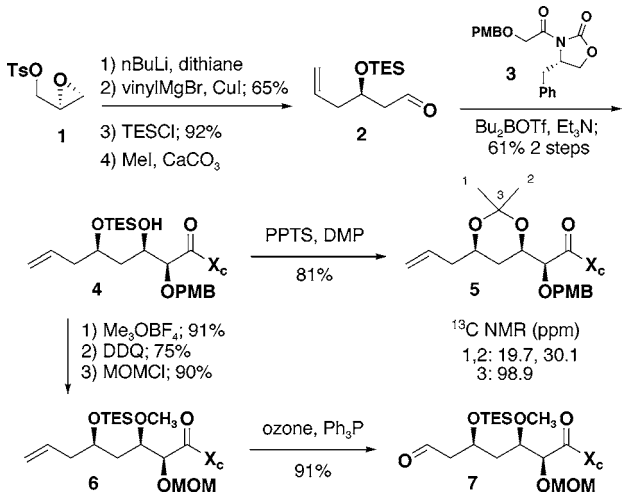



**Figure 1.** Connectivity Analysis for the Synthesis of Peloruside A

We have previously published an efficient route to the ketone fragment A.[6] The route to fragment B is outlined in Scheme 1. Treatment of commercially available (*S*)-glycidyl

**Scheme 1**



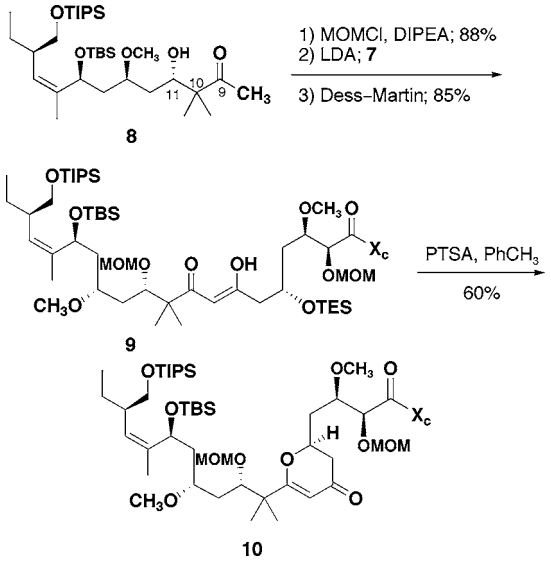

tosylate **1** with lithiated 1,3-dithiane followed by a copper-catalyzed Grignard addition afforded a secondary alcohol.[7] Protection of this hydroxyl group as its triethylsilyl (TES) ether and removal of the 1,3-dithiane provided the aldehyde **2**. The aldehyde was then used directly in the coupling reaction with easily prepared oxazolidinone **3**[8] to provide aldol adduct **4** as a single diastereomer. The relative stereochemistry of the aldol coupling was confirmed by the synthesis of acetonide **5** and NMR analysis.[9]

After the C3-methyl ether was generated from **4**, the PMB ether at C2 was exchanged for a MOM ether. Unfortunately, attempts to use a MOM-protected glycolate enolate in the preceding aldol coupling, failed. After this exchange of protecting groups, the terminal olefin was oxidatively cleaved by ozone to give the C1−C7 fragment B as aldehyde **7**.

When we reported the synthesis of C8−C19 ketone fragment A,[6] the C11 hydroxy group was left unprotected because we envisioned the need to explore different protecting groups at this position for the following crucial aldol coupling reaction. Previous studies in this area[10] had demonstrated that the protecting group at C11 could affect the construction of the highly oxidized pyran unit. After model reaction studies, we decided to protect alcohol **8** as its MOM ether because (1) it does not generate significant steric hindrance (vide infra) and (2) it could be removed in a final global deprotection along with the C2-MOM group and the primary TIPS ether.

With both fragments in hand, we proceeded with the key aldol coupling and the construction of the pyran, Scheme 2.

**Scheme 2**




Ketone **8**, after protection of C11, was treated with LDA, and the resulting enolate was then reacted with aldehyde **7**. The resulting mixture of diastereomeric aldol adducts was subjected to Dess−Martin periodinane oxidation[11] to give *β*-diketone **9**, which existed as an enol tautomer in solution.

The next synthetic hurdle was the removal of the C5-TES group under acidic conditions and the generation of the corresponding pyranone through an intramolecular condensation. Treatment of diketone **9** with catalytic protic acid in toluene at room temperature quickly removed the C5-TES ether; however, the following intramolecular cyclization that would provide pyranone **10** proved to be a very slow reaction. The conversion was <50% even after stirring for 24 h at room temperature. Moreover, the starting material

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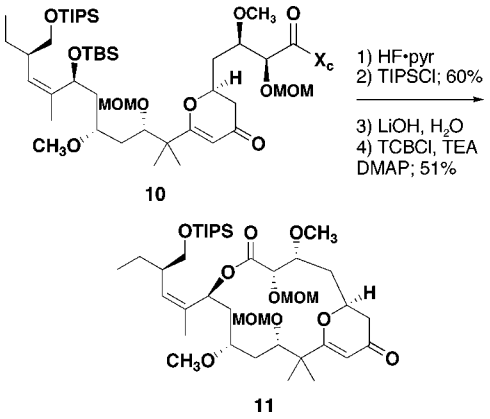
(10) De Brabander, J. K. (UTSW) Personal communication; also see ref 4.
(11) Dess, D. B., Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

and product were both unstable to these conditions, and thus the yield of **10** was low. Fortunately, the conditions reported by De Brabander, in a simpler system, solved the problem.[4] Thus, catalytic quantities of PTSA (*p*-toluenesulfonic acid) in toluene shortened the reaction time to 3 h and provided **10** in 60% yield.

For the next stage, we chose to perform the macrolactonization prior to modification of the pyran region in order to minimize the use of protecting groups, Scheme 3. Thus

**Scheme 3**




pyranone **10** was subjected to excess pyridine/HF complex to remove the silyl protecting groups at C15 and C19. The primary hydroxy of the resulting diol was then selectively reprotected as a triisopropylsilyl ether (TIPS). This compound, upon exposure to aqueous LiOH, provided the corresponding seco-acid, which after activation as a mixed anhydride under Yamaguchi's protocol[12] provided the macrocyclic lactone **11**.

With advanced intermediate lactone **11** in hand, completion of peloruside A required elaboration of the pyran unit and global deprotection. As shown in Scheme 4, ketone **11** was stereoselectively reduced under Luche reduction conditions[13] at low temperature. The resulting unstable allylic alcohol, when treated with mCPBA in methylene chloride, yielded a triol **12** with complete and selective loss of the C11-MOM protecting group. Interestingly, running the reaction in a mixed solvent of methylene chloride/methanol provided a mixture of products retaining the C11-MOM group even with identical workup and purification procedures. Thus, we propose that the selective loss of the C11-

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

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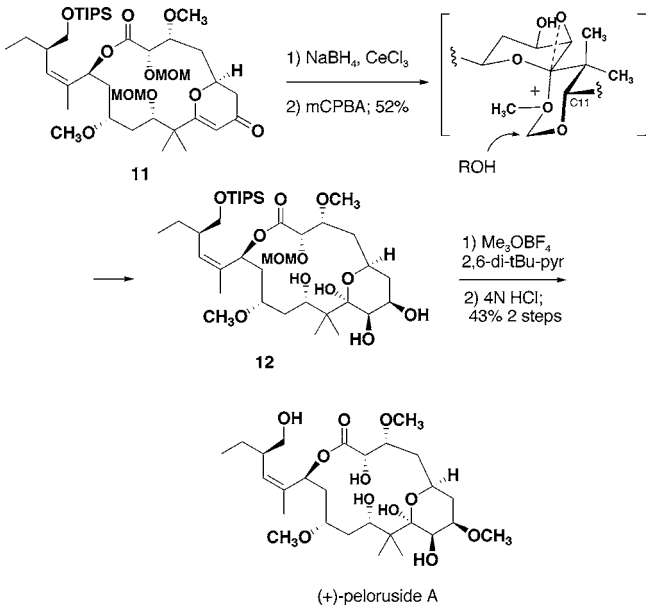
**Scheme 4**




MOM group is a result of an intramolecular glycal epoxide ring fragmentation, through a six-membered transition state, followed by hydrolysis of the intermediate oxo-carbenium ion. Presumably, the resulting methyl glycoside is unstable to the workup.

Completion of the total synthesis was accomplished by a highly selective methylation of less hindered equatorial hydroxyl at C7. Finally, global deprotection provided material spectroscopically and chromatographically consistent with (+)-peloruside A.

In conclusion, we have successfully achieved a total synthesis of (+)-peloruside A. The convergent route is highlighted by an aldol coupling of two complex fragments and an interesting MOM group participated epoxide ring fragmentation. These studies represent our initial contribution to the study of peloruside A. Exploitation of the chemistry for the preparation of rationally designed analogues is currently under investigation in our laboratory.

**Acknowledgment.** Support of this work by the National Cancer Institute and the National Institutes of Health is gratefully acknowledged (CA85499). We sincerely thank Professor Jef De Brabander for a sample of peloruside A and helpful suggestions.

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

OL050070G