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Enantioselective Total Synthesis of Peloruside A: A Potent Microtubule Stabilizer

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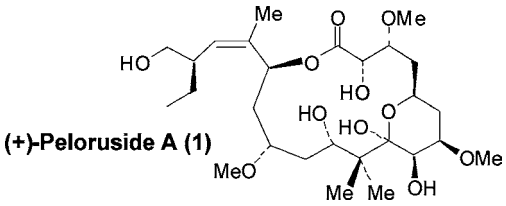
ABSTRACT



(+)-Peloruside A (1)

An enantioselective total synthesis of (+)-peloruside A (1) is described. Peloruside A (1) is a potent microtubule stabilizer with significant clinical potential. The synthesis is convergent and involves the assembly of C1–C10 segment 2 and C11–C24 segment 3 by a novel aldol protocol followed by Yamaguchi macrolactonization of the resulting *seco*-acid, selective methylation of hemi-ketal and removal of the protecting groups to peloruside A.

Peloruside A (**1**), a 16-membered macrolide antitumor agent, was first isolated by West and Northcote from the New Zealand marine sponge, *Mycale hentscheli*.[1] It has shown potent antitumor activity against P388 murine leukemia cells with an IC_{50} value of 10 ng/mL (10 nM). Peloruside A is a microtubule stabilizing agent and arrests cells in the G2-M phase.[2] However, like laulimalide, it binds to the non-taxoid site of tubulin and has shown a synergistic effect with taxol.[3,4] Peloruside A represents a new class of antitumor agents with significant clinical potential. The intriguing structure, very low natural abundance, and clinical potential of peloruside A has attracted an immense synthetic interest. Thus far, De Brabander et al. and subsequently Taylor and co-workers have achieved the total synthesis of peloruside A.[5] Furthermore, a number of synthetic studies of peloruside A subunits have been reported.[6] Herein we report a convergent total synthesis of (+)-peloruside A. The key steps involve efficient assembly of C1−C10 segment and C11−C24 segment by a novel reductive enolization followed by a stereoselective aldol process, an efficient Yamaguchi macrolactonization, *Z*-selective olefination, Sharpless asymmetric dihydroxylation, and Brown's asymmetric allylation reactions.

As shown in Figure 1, our synthetic strategy involves the assembly of fragments **2** and **3** by a stereoselective aldol reaction, followed by a macrolactonization of the corre-

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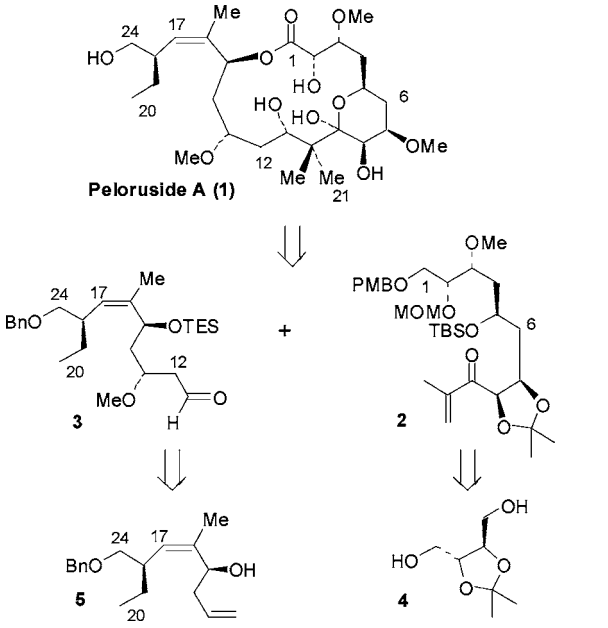
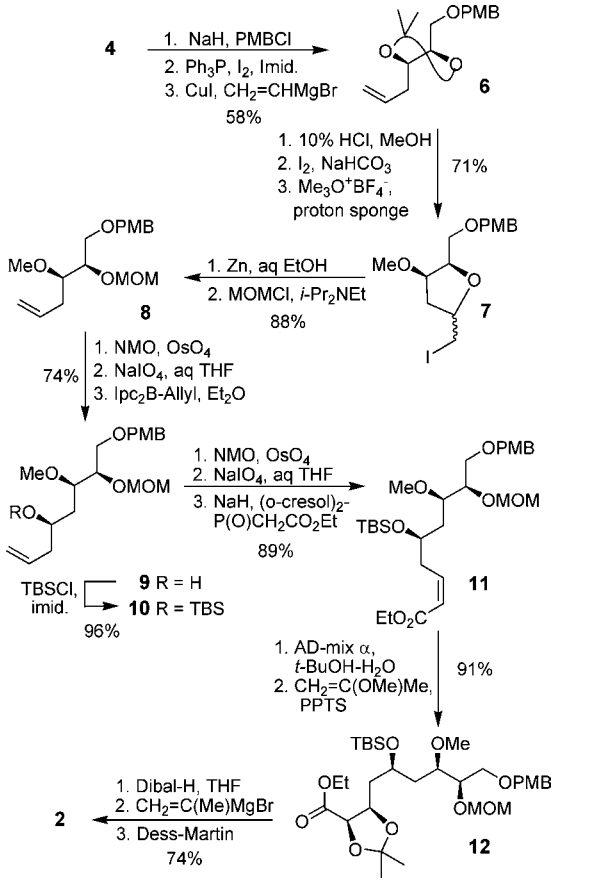


Figure 1. Retrosynthetic analysis of peloruside A.

sponding carboxylic acid at C1 and hydroxyl group at C-15. The presence of *gem*-dimethyl groups at C-10 makes the C7−C11 lactol segment of peloruside A sterically quite hindered. Direct aldol reactions involving a *gem*-dimethyl ketone or aldehyde typically result in poor yields and side reactions. In fact, Zhou and co-workers have carried out the synthesis of the backbone core of peloruside A by an aldol reaction involving isopropyl ketone.[6d] In this context, they have reported numerous difficulties in direct aldol and Mukaiyama aldol reactions. Both published peloruside A syntheses utilized methyl ketone aldol reaction and avoided this problem.[5] We, however, planned to install C-10 *gem*-dimethyl and C-11 hydroxyl groups by a reductive enolization of enone **2** followed by reaction with aldehyde **3**. While this strategy is appealing, there is little to no precedence of this type of aldol reaction in the literature. To install the C7 and C8 hydroxyl groups, we planned to utilize the Sharpless asymmetric dihydroxylation reaction.[7] The C5 stereocenter can be introduced stereoselectively by Brown's asymmetric allylation process.[8] The C2 and C3 chiral centers are derived from the known compound **4**. Aldehyde **3** could be obtained from Brown's asymmetric allylation[8] of the corresponding aldehyde derived from **5**. The corresponding antipode was synthesized by us previously.[6c]

As shown in Scheme 1, the synthesis of C1−C10 segment **2** commenced with the commercially available (−)-2,3-*O*-isopropylidene-D-threitol **4**. It was converted to isopropylidene derivative **6** in a three-step sequence involving (1) mono-benzylation of **4** with sodum hydride and PMBCl in THF, (2) conversion of the alcohol to an iodide with iodine

Scheme 1. Synthesis of Enone **2**



and triphenylphosphine in THF at 0 °C, and (3) reaction of the resulting iodide with vinylmagnesium bromide in the presence of a catalytic amount of CuI in THF at −30 °C. Acid-catalyzed removal of the isopropylidene group followed by iodoetherification with iodine in the presence of sodium bicarbonate in acetonitrile afforded the iodide. The C3 hydroxyl group was methylated with trimethyloxonium tetrafluoroborate and a proton sponge in CH_2Cl_2 to afford **7**.[9] Reductive cleavage of the iodoether with zinc dust and 95% ethanol at 80 °C followed by protection of the alcohol as a MOM ether provided **8**. The terminal olefin was converted to an aldehyde as described by Jin and co-workers.[10] Subsequent asymmetric allylation[8] followed by TBS protection of the resulting alcohol furnished **10**. The terminal olefin was converted to an aldehyde as described above, and a Horner-Emmons olefination of the resulting aldehyde using Ando's protocol[11] furnished the *Z*-olefin **11** selectively (*Z*:*E*, 7:1; 89% in three steps). Sharpless asymmetric dihydroxylation[7] of the pure *Z*-olefin provided the diol in excellent yield (97%) and diastereoselectivity (*dr* 6.3:1 by ^{1}H NMR analysis). Protection of the diol under acidic conditions furnished isopropylidene derivative **12** in good yield (94%). Dibal-H reduction in CH_2Cl_2 at −78 °C yielded

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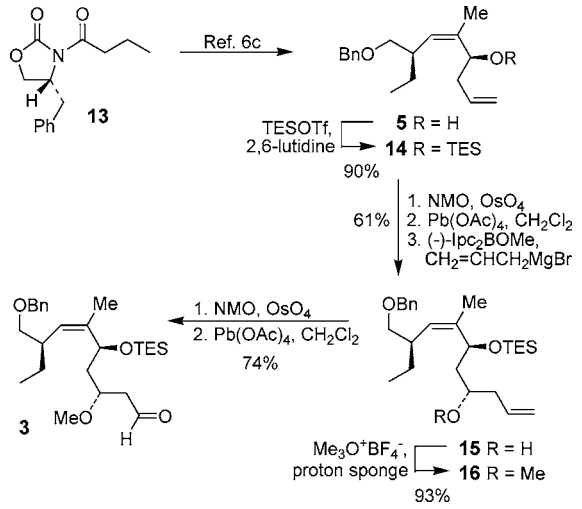
the corresponding aldehyde. Addition of the Grignard reagent followed by Dess−Martin oxidation of the resulting alcohol accomplished the synthesis of the key enone segment **2**.

The synthesis of C11−C24 segment **3** is shown in Scheme 2. Homoallylic alcohol **5** was synthesized utilizing chiral

Scheme 2. Stereoselective Synthesis of Aldehyde **3**

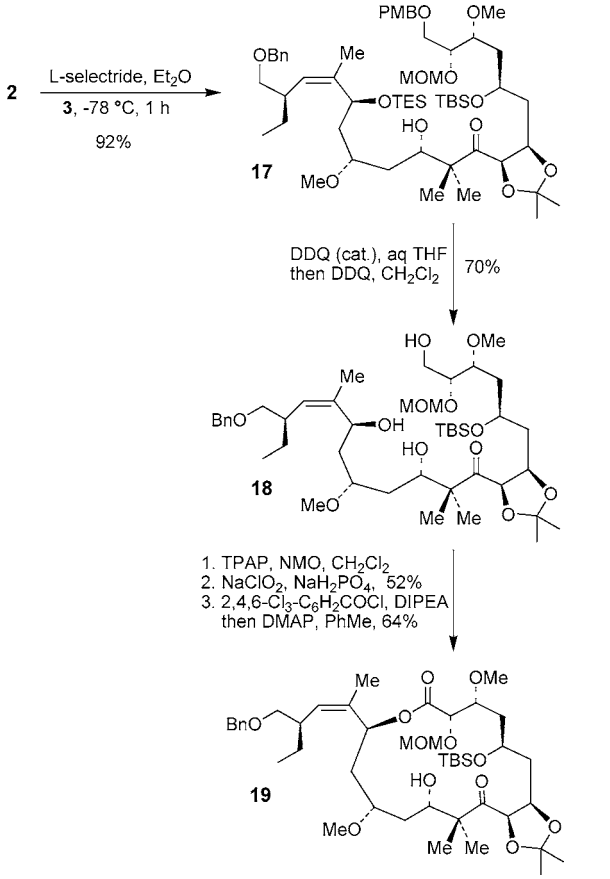


imide **13** as described previously.[6c] The hydroxyl group was protected as a TES ether. Oxidative cleavage of the terminal olefin provided the aldehyde which was exposed to asymmetric allylation[8] to furnish the alcohol **15** diastereoselectively (*dr* 5:1 by ^{1}H NMR analysis). The alcohol was converted to methyl ether **16** as described above, and oxidative cleavage of the resulting olefin provided aldehyde **3** in good yield.

Our subsequent elaboration to aldol coupling reaction and macrolactone synthesis is shown in Scheme 3. With the synthesis of enone **2** and aldehyde **3**, our synthetic strategy calls for the assembly of these segments by reductive enolization of enone **2** followed by aldol addition to aldehyde **3**. Thus, reaction of **2** with 1.1 equiv of L-selectride at −78 °C for 10 min provided the corresponding enolate. Reaction of this enolate with aldehyde **3** at −78 °C for 1 h afforded the aldol product **17** and its diastereomer as a 4:1 mixture in 92% isolated yield. The diastereomers were readily separated by silica gel chromatography. The origin of stereoselectivity as well as the scope and utility of this aldol coupling process is currently under active investigation. This aldol protocol is practical and unprecedented. The efficiency of this process is significantly improved compared to the direct aldol reactions with a related ketone enolate and aldehyde reported by Zhou and co-workers.[6d,12] The TES group of **17** was selectively removed by a reaction with a catalytic amount of DDQ in aqueous THF at 23 °C. Subsequent exposure of the resulting PMB ether to an excess of DDQ in the presence of pH 7 buffer removed the PMB

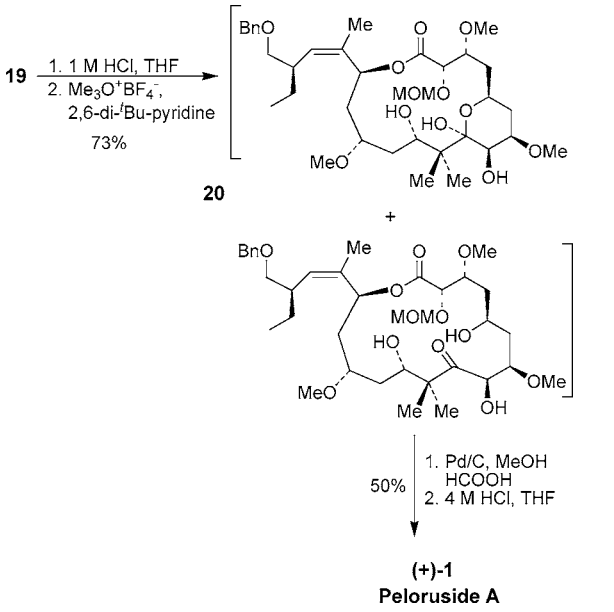
(12) LDA-induced α-dimethyl ketone aldol coupling gave a 29% yield and 40% loss of starting material; see ref 6d.

Scheme 3. Aldol Coupling and Macrolactone Synthesis



group. TPAP oxidation of **18** selectively oxidized the primary alcohol to an aldehyde, which was oxidized with sodium chlorite to the carboxylic acid. The resulting acid was

Scheme 4. Completion of Peloruside A



subjected to Yamaguchi lactonization[13] protocol with 2,4,6-trichlorobenzoyl chloride in the presence of DMAP to provide the corresponding macrolactone **19** in good yield.

Completion of peloruside A is shown in Scheme 4. Macrolactone **19** was converted to synthetic (+)-peloruside A as follows: deprotection of the TBS and isopropylidene groups with 1 M aqueous HCl to provide a mixture of ketone and hemi-ketal. Methylation of the resulting diol with trimethyloxonium tetrafluoroborate in CH_2Cl_2 selectively protected the equatorial hydroxyl group to give methyl ether **20**.[14] Removal of the benzyl group by transfer hydrogenation conditions followed by removal of MOM group by exposure to aqueous 4 N HCl at 23 °C furnished **1**. Spectral data (^{1}H and ^{13}C NMR) of synthetic peloruside A (**1**, $[\alpha]^{23}_D$ +15.1, *c* 0.1, CH_2Cl_2) are identical to those reported for the natural (+)-peloruside A.[1]

In summary, we have achieved an enantioselective synthesis of (+)-peloruside A. The synthesis featured a very effective reductive aldol process and an efficient formation of a 16-membered macrolactone. Other key reactions involved selective methylation, *Z*-selective olefination, Sharpless asymmetric dihydroxylation, and Brown's asymmetric allylation reactions. Structural modification and biological studies are currently in progress.

Acknowledgment. This work was partially supported by the National Institute of Health.

Supporting Information Available: Experimental procedures and ^{1}H and ^{13}C NMR spectra for compounds **1**−**3**, **6**−**12**, **14**−**20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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