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An Aldol-Based Synthesis of (+)-Peloruside A, A Potent Microtubule Stabilizing Agent

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Abstract

A convergent synthesis of the marine natural product (+)-peloruside has been reported. This target has been assembled through the successive application of two methyl ketone boron aldol addition reactions to the latent C₇–C₁₁ dialdehyde synthon. This approach afforded a 22-step synthesis of this natural product. The influence of resident stereocenters on aldol reaction diastereoselection has been examined in detail.

Peloruside A (**1**) is a secondary metabolite of a marine sponge (*Mycale* genus) collected from Pelorus Sound, New Zealand. In addition to its structure elucidation, the initial disclosure by Northcote¹ also demonstrated peloruside A to be cytotoxic to P388 murine leukemia cells at nanomolar concentrations. Subsequent investigations² revealed peloruside's anti-proliferation potency is similar to that exhibited by paclitaxel. The first synthesis of **1**, reported by De Brabander, established the absolute stereochemistry of this natural product.³ In the interim, two additional syntheses have been published.^{4,5} The purpose of this communication is to report a convergent approach to this natural product suitable for analogue synthesis.

The deconstruction of **1** relies on the two highlighted aldol disconnections illustrated in Scheme 1. Based on prior art,⁶ we anticipated that the C₃ and C₁₅ stereocenters would favorably influence the stereochemical outcome of these two bond constructions. In the following discussion, the syntheses of subunits **3** and **4** will be described along with their elaboration to (+)-peloruside A (**1**). The synthesis of **5** is included in the Supplementary Information.

The synthesis of C₁–C₆ synthon **3** requires six steps from commercially available (*S*)-4-benzyl-2-oxazolidinone^{7a} and is summarized in Scheme 2. Notably, the illustrated imide-

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Supporting Information Available: Experimental details and analytical data including copies of ¹H and ¹³C NMR spectra for all new compounds (xx pages) (PDF). The synthesis of methyl ketone **5** is also included. This material is available free of charge via the Internet at <http://pubs.acs.org>.

based aldol bond construction establishes the C₂–C₃ syn stereochemistry with excellent diastereoselection.^{7b}

The synthesis of synthon **4**, based on the use of (*S*)-pantolactone, is summarized in Scheme 3. The chelate-controlled borohydride reduction was quite diastereoselective (95:5); however, competing conjugate reduction was noted as a minor side reaction.

Selection of the illustrated C₉ hydroxyl configuration in subunit **4** bears comment. On the basis of previous model studies probing the influence of β-oxygen stereocenters on aldehyde face selectivity,⁸ we concluded that the (*R*)-C₃, (*S*)-C₈ and (*R*)-C₉ stereocenters in fragments **3** and **4** would be mutually reinforcing in this double stereodifferentiating aldol addition. A recent study by Paterson documents the diminished selectivities if the other C₉ epimer is employed in a similar aldol addition.⁹

The aldol union of methyl ketone **3** and aldehyde **4** is summarized in Scheme 4. In developing this reaction, we noted a surprising diastereoselectivity dependence on the particular dialkylboryl enolate employed in the reaction. The desired diastereomer **12-R** was obtained in 81% with 9-BBNOTf (Et₃N, toluene).

Further complexity in this reaction is apparent by varying the C₈ hydroxyl protecting group: when C₈ bears a smaller protecting group (TES) a diminished diastereoselection (10:1) is observed.¹⁰ Finally, the structure of the C₁₁ hydroxyl protecting group was also found to play a role in reaction diastereoselectivity.

The advanced stages of the synthesis are illustrated in Scheme 5. The triacetoxymethylborohydride reduction of **12-R** proceeded with the expected 1,3-anti diastereoselectivity (10:1).¹¹ A selective silylation of the less hindered C₅ hydroxyl group of diol **13a** delivered **13b**.

The aldol union of aldehyde **15** and methyl ketone **5** deserves special mention. As illustrated, this reaction proceeds in good yield and diastereoselectivity (92%, dr=20:1); nevertheless, the success of this reaction critically depends on the nature of the C₉ substituent. For example, the reaction does not proceed if the C₉ carbonyl is reduced and protected. We surmise that it is a simple case of enhanced aldehyde reactivity in **15** due to both reduced steric and enhanced electronic effects.

The chemo- and stereoselective triacetoxymethylborohydride reduction¹¹ of diketone **16a** also raises an interesting challenge. While we anticipated that steric effects would favor a selective anti reduction of the C₁₃ carbonyl, we noted that virtually no C₁₃/C₉ selectivity was obtained for this transformation. A solution to this problem was found in the intramolecular silane reductions reported by Davis.¹² Accordingly, silane **16b** was prepared in anticipation of an intramolecular hydride reduction. The subsequent SnCl₄ promoted intramolecular anti reduction proceeded in the desired sense with 40:1 selectivity (85%). The removal of the C₁₁–C₁₃ disilyloxane protecting group in **17** was followed by a C₁₃–selective methylation of the derived diol to afford **18**. Again, steric effects formed the basis for differentiation of the C₁₁–C₁₃ diol.

In the experiments leading up to the macrocyclization, we anticipated that we might selectively cyclize the diol **19** at C₁₅ since the C₁₁ hydroxyl reactivity was estimated to be lower relative to the C₁₅ hydroxyl group by a comparison of their local steric environments. Toward this end, hydrolysis and subsequent Yamaguchi macrocyclization¹³ of diol **19** proceeded in 66% overall yield to afford the protected peloruside skeleton **20**. It should be noted that the smaller macrolactone corresponding to cyclization of the C₁₁ hydroxyl group was not observed. Subsequent deprotection afforded (+)-peloruside-A whose spectroscopic properties matched that of the natural product.

In conclusion, the synthesis of (+)-peloruside A has been accomplished in 22 steps (longest linear sequence) from commercially available (*S*)-pantolactone. The two pivotal aldol additions provide a straightforward approach to the convergent synthesis of the peloruside A skeleton. Upcoming objectives will focus on analogue synthesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.
(+)-Peloruside A Synthesis Plan

Scheme 2. Synthesis of the C₁₅C₆ Synthon **3**a) **7**, Bu₂BOTf, *i*-Pr₂EtN. b) Me₃OBF₄, proton sponge. c) PPTS, acetone, Δ.

Scheme 3.

Synthesis of the C₇SC₁₁ Synthon **4**

a), BnON(H)CCl₃, TfOH, rt. b) Me₃Al, MeON(H)Me HCl, CH₂Cl₂, 0 C. c) TESCl, Et₃N, DMAP rt. d) Me₂C=CHBr, *t*-BuLi, Et₂O. e) Zn(BH₄)₂, Š30 C. f) TBSCl. g), O₃, PPh₃.

Scheme 4.
The C₆-C₇ Aldol Bond Construction

Scheme 5.**Completion of (+)-Peloruside A Synthesis**

a) $\text{Me}_4\text{N}(\text{OAc})_3\text{BH}$, AcOH, MeCN, S30 C . b) TBSCl, imidazole, rt. c) Me_3OBF_4 , Proton SpongeØ, CH_2Cl_2 , rt. d) $\text{Pd}(\text{OH})_2/\text{C}$, H_2 , EtOAc, rt. e) Dess-Martin, pyridine, CH_2Cl_2 , 0 C. f) 9-BBNOTf, DIPEA, g) $(i\text{Pr})_2\text{SiHCl}$, DMAP, DMF. h) SnCl_4 , S78 C . i) 1:1 TBAF, HOAc, THF, S20 C . j) DDQ. k) H_2O_2 , LiOH. l) $\text{C}_6\text{H}_2\text{Cl}_3\text{COCl}$, DIPEA, THF, rt, then DMAP, toluene, 60°C. m) 1:1 4 N HCl, MeOH, 1 h, 0 C, 2 h at rt.