Stereoselective Synthesis of the C(1)–C(11) Fragment of Peloruside A

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ABSTRAC1

A highly stereoselective synthesis of the C(1)–C(11) fragment 4 of peloruside A has been accomplished via a stereoselective double allylboration and an intramolecular epoxide opening to provide the functionally dense C(3)–C(11) segment 14. A glycolate aldol reaction was then employed to introduce the remaining stereocenters at C(2)–C(3).

The cytotoxic marine natural product peloruside A (1, Figure 1),¹ a microtubule-stabilizing agent, represents a recent addition to the important class of natural products that interacts with this validated anticancer chemotherapeutic target.² Peloruside A was first isolated (3 mg/170 g wet sponge) by Northcote and co-workers from marine sponges of the genus Mycale (Carmia) collected in the Pelorus Sound of New Zealand.¹ Determination of its structure and relative stereochemistry indicated that 1 is comprised of a highly oxygenated, 16-membered macrolide ring system that is bridged by a six-membered hemiketal connecting C(5) and C(9). In addition, the natural product contains an unsaturated, branched side chain emanating from C(15). Initial biological characterization demonstrated that 1 exhibits potent cytostatic/cytotoxic activity (IC₅₀ = 3.7-14.9 nM) against a range of cancer cell lines.3 Miller and co-workers have demonstrated that this activity is tied to the ability of peloruside A

to stabilize the formation of microtubules and induce arrest at the G₂-M phase of the cell cycle.⁴ More recent studies have shown that **1** does not bind to the taxoid binding site of β -tublin and maintains acivity against paclitaxel-resistant cell lines.⁵ In addition, peloruside A is more effective at inducing cell death in *ras*-transformed cancer cells than in untransformed cells.⁶ These results highlight the potential utility of peloruside A as a new chemotherapeutic agent.

The significant biological properties of peloruside A coupled with its scarcity in nature and densely functionalized structure have prompted numerous studies directed toward its synthesis. De Brabander and co-workers descibed the first total synthesis of the enantiomer of **1** and thereby confirmed the relative configuration proposed by Northcote and co-workers.⁷ Recently, Taylor and co-workers have also com-

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Figure 1. Retrosynthetic analysis of peloruside A.

pleted a total synthesis of $1.^8$ In addition, many research groups have reported studies directed toward the synthesis of fragments of the peloruside A backbone.⁹ We report herein our synthetic studies culminating in an efficient synthesis of the C(1)–C(11) fragment **4** of peloruside A.

Our retrosynthetic analysis of 1 is outlined in Figure 1. Peloruside A can be simplified into a seco-acid precursor 2 by disconnection of the macrolactone and hemiketal ring systems. We envisioned that 2 could be assembled by using two applications of the double allylboration methodology recently developed in our laboratory.¹⁰ According to this

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analysis, intermediate 2 could be assembled via the formal three-component coupling of aldehydes 3 and 4 with allylborane 7a. Further simplification of intermediate 4 suggests that this fragment could be accessed from aldehydes 5^{11} and 6^{12} via a similar approach.

Our efforts toward the C(1)-C(11) fragment were initiated by the synthesis of the key 1,5-diol intermediate **10** (Scheme 1). Following our previously developed methodology,¹⁰





 $^{\it a}$ Enantiomeric excess values calculated via the Mosher ester method.

treatment of aldehyde 5^{11} with the ^{*I*}Ipc-derived γ -borylsubstituted allylborane **7a** (prepared in situ from the hydroboration of allene 8^{10} with (^{*I*}Ipc)₂BH¹³) followed by introduction of aldehyde 6^{12} provided the desired 1,5-diol (**10**) as a single diastereomer in 77% yield and 85% ee (entry 1).¹⁴ Attempts to improve the enantioselectivity of the first allylation event ($5 \rightarrow 9$) indicated that the enantioselectivity was essentially insensitive to the reaction solvent (entries

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1–3). However, on the basis of the work of Brown and coworkers,¹⁵ we anticipated that the replacement of $({}^{1}\text{Jpc})_{2}\text{B}$ in **7a** with $(2 \cdot {}^{d}\text{Icr})_{2}\text{B}-$ (derived from (+)-2-carene) in **7b** might improve the enantioselectivity of this transformation. Indeed, use of reagent **7b** in the sequence provided diol **10** with excellent enantioselectivity (>95% ee¹⁶) albeit in low yield (36%) due a sluggish reaction between intermediate **9b** and aldehyde **6** (entry 4). Although extended reaction times provided a moderate improvement in the isolated yield of **10** (entry 6), we chose to utilize material obtained by using reagent **7a** for the remainder of the studies described herein.

Selective protection of the C(5)-hydroxyl group of diol **10** with triethylsilyl chloride followed by *m*-CPBA oxidation of the olefin and protection of the C(9)-hydroxyl group as a PMB ether provided epoxide **12** as a 15:1 mixture of diastereomers (Scheme 2). While the stereochemistry of the



epoxide was not determined at this stage, the *threo*configuration shown is consistent with an epoxidation transition state in which A^{1,3} strain in minimized.¹⁷ Although acyclic *trans*-olefins generally react with a low degree of stereoinduction in these transformations, the neighboring quaternary center may play a significant role in influencing the diastereoselectivity of the epoxidation of **11**.

On the basis of the analysis of Gorrichon and co-workers,¹⁸ we anticipated that the proposed *threo*-configuration of



epoxide **12** would lead to a single lactone **13** via a 5-*exo* cyclization upon exposure to ZnCl₂. Gratifyingly, treatment of **12** with anhydrous ZnCl₂ provided lactone **13** in 85% yield. The relative C(5)-C(7) stereochemistry was confirmed via formation of the 1,3-acetonide and ¹³C NMR analysis via the Rychnovsky method.¹⁹ Subsequent methylation of **13** with Meerwein's salt (Me₃OBF₄) provided intermediate **14** in excellent yield. The C(8) stereochemistry was verified by Mosher ester analysis²⁰ of **15**, obtained by reduction of lactone **14** with LiBH₄,²¹ thereby demonstrating that compound **14** contains the correct C(7)-C(8) stereochemistry for peloruside A. The independent verification of the C(7) and C(8) stereochemistry also provides clear evidence that the stereochemistry of epoxide **12** must be as shown.

With the key intermediate **14** in hand, we turned our attention to installation of the remaining C(2)-C(3) stereocenters (Scheme 3). Half-reduction of lactone **14** by treatment with DIBAL-H at -78 °C gave the lactol as a 2:1 mixture of anomers. Treatment of this mixture with an excess of methylidene(triphenyl)phosporane at 65 °C for 16 h followed

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by silvlation of the C(8)-hydroxyl group with triethylsilyl triflate provided compound 16 in excellent yield. Elevated temperatures for olefination of the lactol were required to obtain reasonable reaction rates, presumably due to the influence of the gem-dimethyl group on the lactol \rightarrow δ -hydroxy aldehyde equilibrium. Subsequent reductive removal of the benzyl protecting group of 16 with lithium 4,4'di-tert-butylbiphenyl (LiDBB)²² proceeded cleanly to give alcohol 17. Oxidation of the primary alcohol unit of 17 followed by an asymmetric glycolate aldol reaction²³ with MOM-protected glycolate imide 20²⁴ provided alcohol 19 as a 13:1 mixture of diastereomers, which corresponds to the % ee of the starting aldehyde.²⁵ The stereochemistry at C(3) of **19** was assigned via application of the Rychnovsky method for 1,3-diol configurational assignment.²⁶ O-Methylation of 19 by using Meerwein's salt followed by ozonolysis of the terminal alkene of 21 provided 4, the fully ellaborated C(1)-C(11) fragment of peloruside A.

(25) We presume that the minor aldol product derives from the minor enantiomer of 18 since the % ee of the major diastereomer (determined for compound 21) was >95% by Mosher ester analysis. See Supporting Information for details.

In summary, we have accomplished an efficient and highly stereoselective synthesis of **4** corresponding to the C(1)-C(11) fragment of peloruside A (14 steps, 24% overall yield). Key transformations in the sequence include construction of the C(5)-C(9) 1,5-diol unit via double allylboration with allylboronate **7**, followed by an intramolecular epoxide opening to complete the C(3)-C(11) fragment. The final two stereocenters were simultaneously introduced via an asymmetric glycolate aldol reaction. Continued advancement of these intermediates toward peloruside A (**1**) will be reported in due course.

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Supporting Information Available: Experimental procedure and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0514303

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