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

Robert M. Owen and William R. Roush*,†

Department of Chemistry, University of Michigan, Ann Arbor, Michigan 48109

roush@umich.edu

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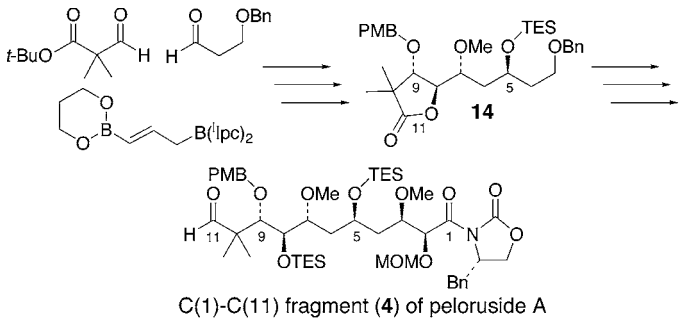
ABSTRACT



C(1)-C(11) fragment (**4**) of peloruside A

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 ($IC_{50} = 3.7-14.9$ 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 G_2-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-

† Address correspondence to this author at: Department of Medicinal Chemistry, Scripps Florida, 5353 Parkside Drive, RF-2, Jupiter, FL 33485.

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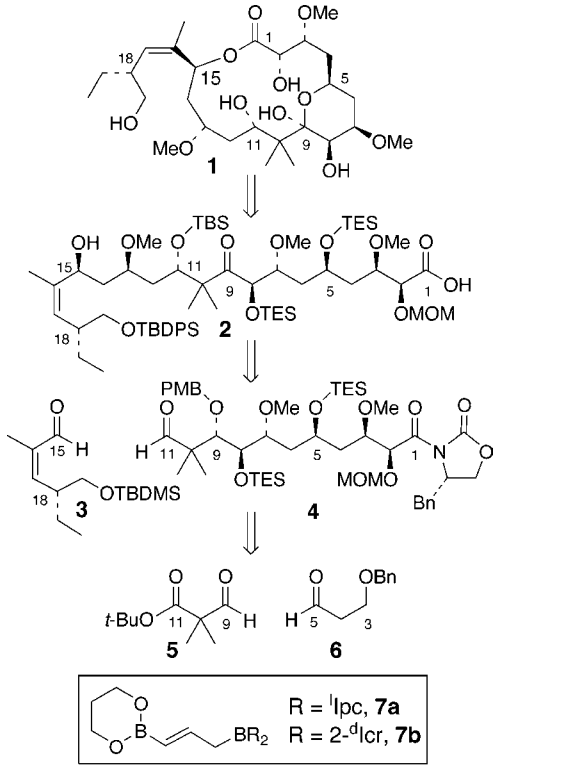


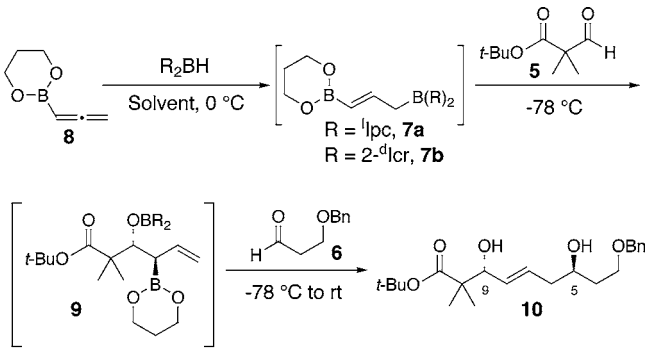
Figure 1. Retrosynthetic analysis of peloruside A.

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.

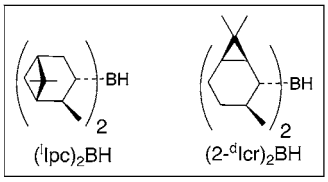
Our retrosynthetic analysis of **1** is outlined in Figure 1. Peloruside A can be simplified into a seco-acid precursor **2** by disconnection of the macrolactone and hemiketal ring systems. We envisioned that **2** could be assembled by using two applications of the double allylboration methodology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

Scheme 1. Optimization of Synthesis of Key 1,5-Diol Fragment **10**



Entry	R_2BH	Solvent	Duration of 2nd allylation	Yield (%ee)[a]
1	$(^{l}Ipc)_2BH$	Et_2O	24 h	77% (85%)
2	$(^{l}Ipc)_2BH$	CH_2Cl_2	24 h	74% (85%)
3	$(^{l}Ipc)_2BH$	toluene	24 h	69% (83%)
4	$(2\text{-}^{d}Icr)BH$	Et_2O	40 h	36% (>95%)
5	$(2\text{-}^{d}Icr)BH$	Et_2O	20 h @ 37 °C	40% (ND)
6	$(2\text{-}^{d}Icr)BH$	Et_2O	96 h	50% (ND)



[a] Enantiomeric excess values calculated via the Mosher ester method.

treatment of aldehyde **5**[11] with the ^{l}Ipc-derived γ-boryl-substituted allylborane **7a** (prepared in situ from the hydroboration of allene **8**[10] with $(^{l}Ipc)_2BH$[13]) 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** → **9**) indicated that the enantioselectivity was essentially insensitive to the reaction solvent (entries

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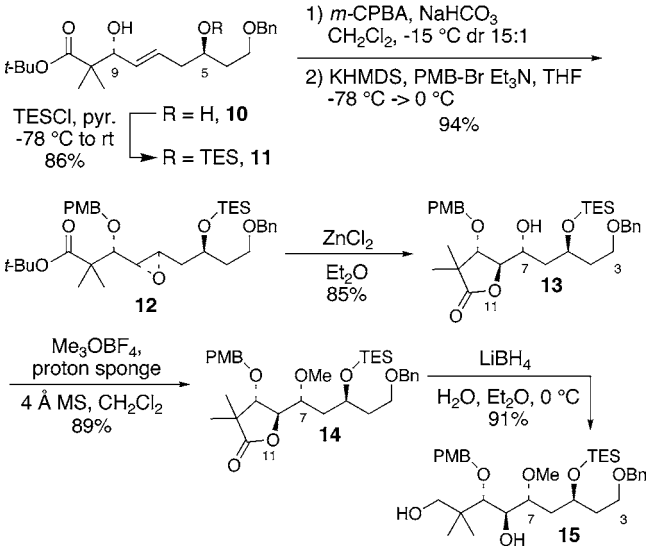
1−3). However, on the basis of the work of Brown and co-workers,[15] we anticipated that the replacement of $(^{l}Ipc)_2B-$ in **7a** with $(2\text{-}^{d}Icr)_2B-$ (derived from (+)-2-carene) in **7b** might improve the enantioselectivity of this transformation. Indeed, use of reagent **7b** in the sequence provided diol **10** with excellent enantioselectivity (>95% ee[16]) 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

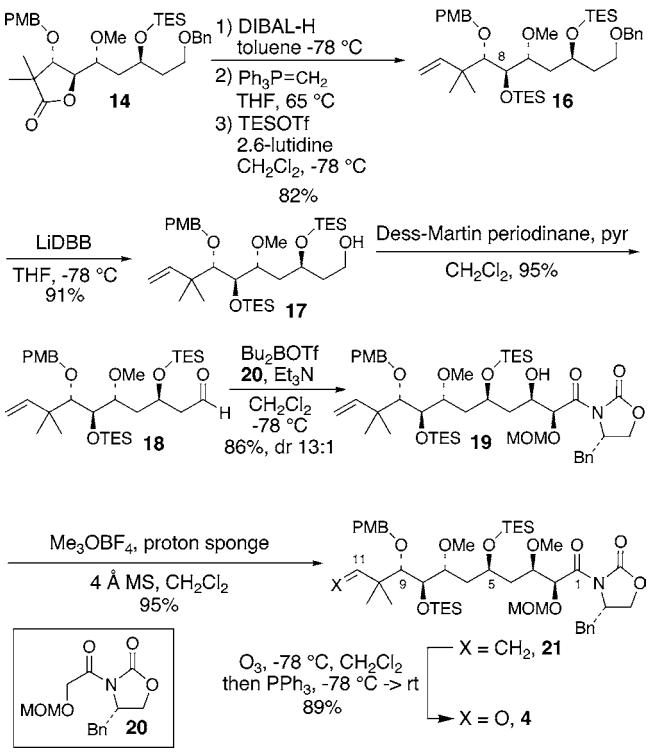
Scheme 2. Synthesis of the C(3)−C(11) Fragment



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

Scheme 3. Completion of C(1)−C(11) Fragment via an Asymmetric Glycolate Aldol Reaction



epoxide **12** would lead to a single lactone **13** via a 5-*exo* cyclization upon exposure to $ZnCl_2$. Gratifyingly, treatment of **12** with anhydrous $ZnCl_2$ provided lactone **13** in 85% yield. The relative C(5)−C(7) stereochemistry was confirmed via formation of the 1,3-acetonide and ^{13}C NMR analysis via the Rychnovsky method.[19] Subsequent methylation of **13** with Meerwein's salt (Me_3OBF_4) provided intermediate **14** in excellent yield. The C(8) stereochemistry was verified by Mosher ester analysis[20] of **15**, obtained by reduction of lactone **14** with $LiBH_4$,[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

(14) Enantioselectivities and absolute stereochemical assignments were determined by ^1H NMR anlaysis of the bis-Mosher ester prepared from the 1,5-diol: Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092. See Supporting Information for details.

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(16) Only a trace (≤2%) of the minor enantiomer could be detected in the ^1H NMR spectra of the bis-Mosher esters.

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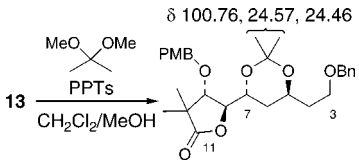

(20) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092. See Supporting Information for details.

(21) See Supporting Information for details.

by silylation 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 → *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 reaction[23] with MOM-protected glycolate imide **20**[24] 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.

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.

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(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.

(26) The relative C(3)−C(5) stereochemistry of **19** was confirmed via the Rychnovsky method. See Supporting Information for details.