J|A|C|S COMMUNICATIONS

Published on Web 02/27/2009

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

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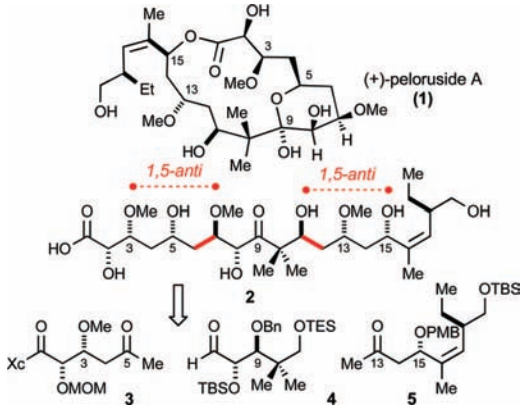
Peloruside A (**1**) is a secondary metabolite of a marine sponge (*Mycale* genus) collected from Pelorus Sound, New Zealand. In addition to its structure elucidation, the initial disclosure by Northcote[1] also demonstrated peloruside A to be cytotoxic to P388 murine leukemia cells at nanomolar concentrations. Subsequent investigations[2] revealed peloruside's antiproliferation 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.

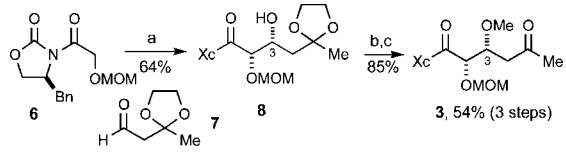
The deconstruction of **1** relies on the two highlighted aldol disconnections illustrated in Scheme 1. Based on prior art,[6] we anticipated that the C_3 and C_{15} stereocenters would favorably influence the stereochemical outcome of these two bond constructions. In the following discussion, the syntheses of subunits **3** and **4** will be described along with their elaboration to (+)-peloruside A (**1**). The synthesis of **5** is included in the Supporting Information.

Scheme 1. (+)-Peloruside A Synthesis



The synthesis of C_1-C_6 synthon **3** requires six steps from commercially available (*S*)-4-benzyl-2-oxazolidinone[7a] and is summarized in Scheme 2. Notably, the illustrated imide-based aldol bond construction establishes the C_2-C_3 syn stereochemistry with excellent diastereselection.[7b]

Scheme 2. Synthesis of the C_1-C_6 Synthon **3**[a]

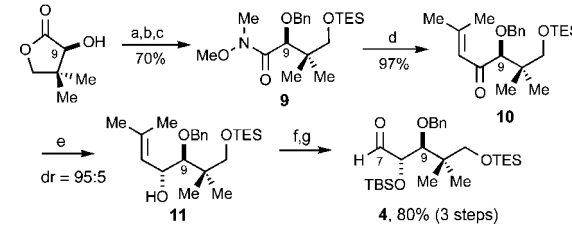


[a] (a) **7**, Bu_2BOTf, *i*-Pr_2EtN. (b) Me_3OBF_4, proton sponge. (c) PPTS, acetone, Δ.

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 C_9 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*)-C_3, (*S*)-C_8, and (*R*)-C_9 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 for this construction when the C_9 diastereomer is employed in a related aldol addition.[9]

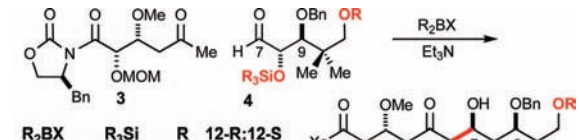
Scheme 3. Synthesis of the C_7-C_{11} Synthon **4**[a]



[a] (a) $BnON(H)CCl_3$, TfOH, rt. (b) Me_3Al, $MeON(H)Me\cdot HCl$, CH_2Cl_2, 0 °C. (c) TESCl, Et_3N, DMAP, rt. (d) $Me_2C{=}CHBr$, *t*-BuLi, Et_2O. (e) $Zn(BH_4)_2$, −30 °C. (f) TBSCl. (g) O_3, PPh_3.

The aldol union of methyl ketone **3** and aldehyde **4** is summarized in Scheme 4.[10] 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 (Et_3N, toluene).

Scheme 4. C_6-C_7 Aldol Bond Construction



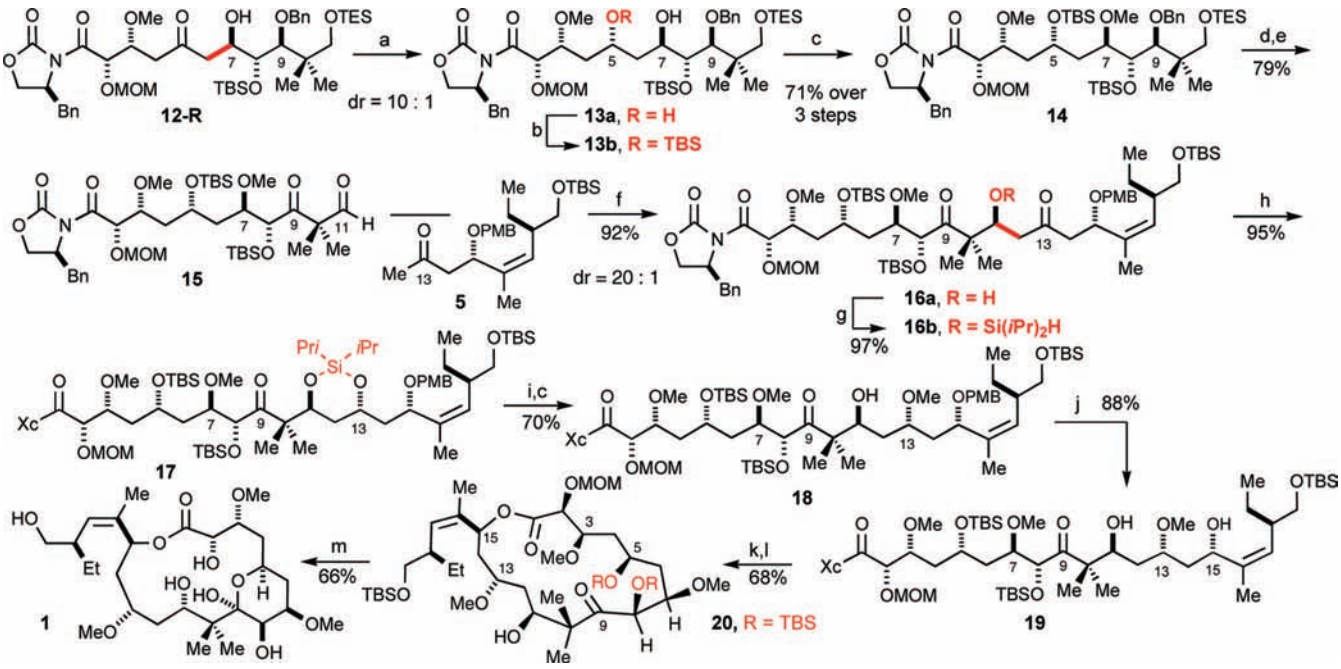
R_2BX	R_3Si	R	12-R:12-S
Cy_2BCl	TBS	BOM	29:71
9-BBNOTf	TBS	BOM	95:05
9-BBNOTf	TES	BOM	91:09
9-BBNOTf	TBS	TES	98:02 (81%)

Further complexity in this reaction is apparent by varying the C_8 hydroxyl protecting group: when C_8 bears a smaller protecting group (TES) a diminished diastereoselection (10:1) is observed. Finally, the structure of the C_{11} 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 triacetoxyborohydride reduction of **12**-R proceeded with the expected 1,3-anti diastereoselectivity (10:1).[11] A selective silylation of the less hindered C_5 hydroxyl group of diol **13a** delivered **13b**.

10.1021/ja900020a CCC: $40.75

Scheme 5. Completion of (+)-Peloruside A Synthesis[a]



[a] (a) $Me_4N(OAc)_3BH$, AcOH, MeCN, −30 °C. (b) TBSCl, imidazole, rt. (c) Me_3OBF_4, proton sponge, CH_2Cl_2, rt. (d) $Pd(OH)_2/C$, H_2, EtOAc, rt. (e) Dess-Martin, pyridine, CH_2Cl_2, 0 °C. (f) 9-BBNOTf, DIPEA. (g) $(iPr)_2SiHCl$, DMAP, DMF. (h) $SnCl_4$, −78 °C. (i) 1:1 TBAF, HOAc, THF, −20 °C. (j) DDQ. (k) H_2O_2, LiOH. (l) $C_6H_2Cl_3COCl$, DIPEA, THF, rt, then DMAP, toluene, 60 °C. (m) 1:1 4 N HCl, MeOH, 1 h, 0 °C, 2 h at rt.

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 C_9 substituent. For example, the reaction does not proceed if the C_9 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 triacetoxyborohydride reduction[11] of diketone **16a** also raises an interesting challenge. While we anticipated that steric effects would favor a selective anti reduction of the C_{13} carbonyl, we noted that virtually no C_{13}/C_9 carbonyl 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 $SnCl_4$ promoted intramolecular anti reduction proceeded in the desired sense with 40:1 selectivity (85%). The removal of the $C_{11}-C_{13}$ disilyloxane protecting group in **17** was followed by a C_{13}-selective methylation of the derived diol to afford **18**. Again, steric effects formed the basis for differentiation of the $C_{11}-C_{13}$ diol.

In the experiments leading up to the macrocyclization, we anticipated that we might selectively cyclize the diol **19** at C_{15} since the C_{11} hydroxyl reactivity was estimated to be lower relative to the C_{15} hydroxyl group by a comparison of their local steric environments. Toward this end, hydrolysis and subsequent Yamaguchi macrocyclization[13] of diol **19** proceeded in 68% overall yield to afford the protected peloruside skeleton **20**. It should be noted that the smaller macrolactone corresponding to cyclization of the C_{11} hydroxyl group was not observed. Subsequent deprotection afforded (+)-peloruside-A whose spectroscopic properties matched those 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 be devoted to analogue synthesis.

Acknowledgment. Support has been provided by the NSF (CHE-0608664) and NIH (5R01-GM081546-01). Support from Merck, Amgen, NSERC of Canada (A.W.H.S.), and the E. Schering Foundation are also gratefully acknowledged. We thank Prof. De Brabander for a sample of (−)-**1**.

Supporting Information Available: Experimental details and analytical data including copies of ^1H and ^{13}C NMR spectra for all new compounds and synthesis of methyl ketone **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA900020A