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

**ARTICLE** *in* JOURNAL OF THE AMERICAN CHEMICAL SOCIETY · MARCH 2009

Impact Factor: 12.11 · DOI: 10.1021/ja900020a · Source: PubMed

J|A|C|S COMMUNICATIONS

Published on Web 02/27/2009

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

David A. Evans,* Dennie S. Welch, Alexander W. H. Speed, George A. Moniz, Andreas Reichelt, and Stephen Ho

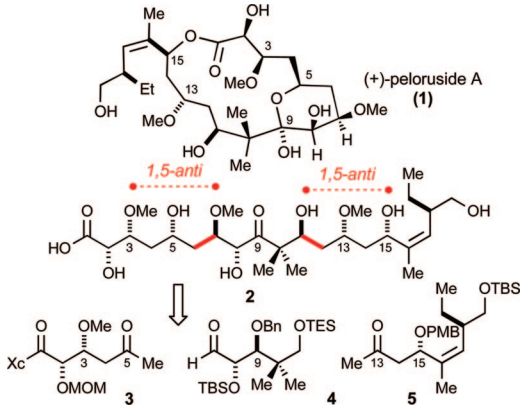
*Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138*

Received January 5, 2009; E-mail: evans@chemistry.harvard.edu

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.

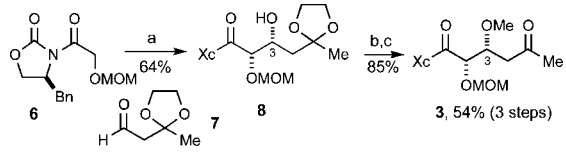
The deconstruction of **1** relies on the two highlighted aldol disconnections illustrated in Scheme 1. Based on prior art,[6] we anticipated that the $C_3$ and $C_{15}$ stereocenters would favorably influence the stereochemical outcome of these two bond constructions. In the following discussion, the 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]

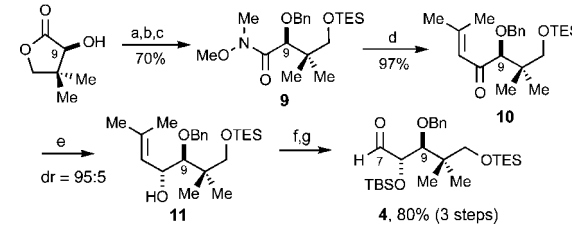



[a] (a) **7**, $Bu_2BOTf$, *i*-$Pr_2EtN$. (b) $Me_3OBF_4$, proton sponge. (c) PPTS, acetone, Δ.

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%) |

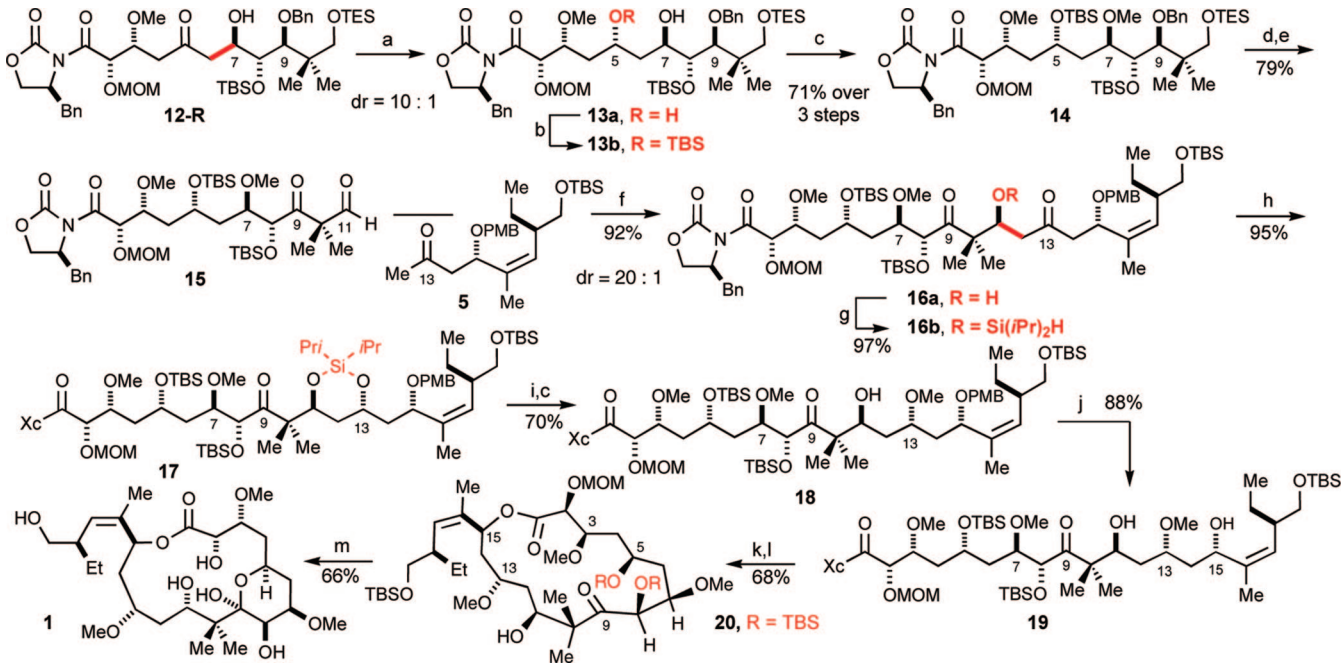
Further complexity in this reaction is apparent by varying the $C_8$ hydroxyl protecting group: when $C_8$ bears a smaller protecting group (TES) a diminished diastereoselection (10:1) is observed. Finally, the structure of the $C_{11}$ hydroxyl protecting group was also found to play a role in reaction 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.

## References

(1) West, L. M.; Northcote, P. T. *J. Org. Chem.* **2000**, *65*, 445–449.
(2) Hood, K. A.; West, L. M.; Rouwé, B.; Northcote, P. T.; Berridge, M. V.; Wakefield, St. J.; Miller, J. H. *Cancer Res.* **2002**, *62*, 3356–3360.
(3) Liao, X.; Wu, Y.; De Brabander, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 1648–1652.
(4) (a) Taylor, R. E.; Jin, M. *Org. Lett.* **2005**, *7*, 1303–1305. (b) Taylor, R. E.; Jin, M. *Org. Lett.* **2003**, *5*, 4959–4961.
(5) Ghosh, A. K.; Xu, X.; Kim, J.-H.; Xu, C.-X. *Org. Lett.* **2008**, *10*, 1001–1004.
(6) (a) Paterson, I.; Gibson, K. R.; Oballa, R. M. *Tetrahedron Lett.* **1996**, *37*, 8585–8588. (b) Evans, D. A.; Coleman, P. J.; Côte, B. *J. Org. Chem.* **1997**, *62*, 788–789. (c) Evans, D. A.; Cote, B.; Coleman, P. J.; Connell, B. T. *J. Am. Chem. Soc.* **2003**, *125*, 10893–10898.
(7) (a) Gage, J. R.; Evans, D. A. *Org. Synth.* **1989**, *68*, 77–82. (b) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129.
(8) Evans, D. A.; Cee, V. J.; Siska, J. *J. Am. Chem. Soc.* **2006**, *128*, 9433–9441.
(9) Paterson, I; Di Francesco, M. E.; Kuhn, T. *Org. Lett.* **2003**, *5*, 599–602.
(10) For an allylation-based approach to the $C_1-C_{11}$ fragment:Owen, R. M.; Roush, W. R. *Org. Lett.* **2005**, *7*, 3941–3944.
(11) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *10*, 3560–3578.
(12) Anwar, S.; Davis, A. P. *Tetrahedron* **1988**, *44*, 3761–3770.
(13) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.

JA900020A