

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

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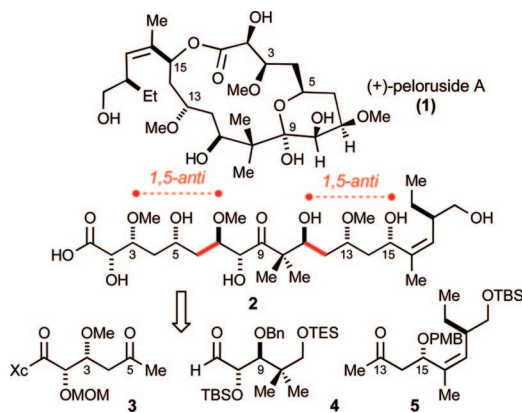
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Peloruside A (**1**) is a secondary metabolite of a marine sponge (*Mycale* genus) collected from Pelorus Sound, New Zealand. In addition to its structure elucidation, the initial disclosure by Northcote<sup>1</sup> also demonstrated peloruside A to be cytotoxic to P388 murine leukemia cells at nanomolar concentrations. Subsequent investigations<sup>2</sup> 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.<sup>3</sup> In the interim, two additional syntheses have been published.<sup>4,5</sup> The purpose of this communication is to report a convergent approach to this natural product suitable for analogue synthesis.

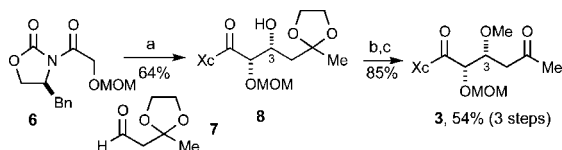
The deconstruction of **1** relies on the two highlighted aldol disconnections illustrated in Scheme 1. Based on prior art,<sup>6</sup> we anticipated that the C<sub>3</sub> and C<sub>15</sub> stereocenters would favorably influence the stereochemical outcome of these two bond constructions. In the following 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<sub>1</sub>–C<sub>6</sub> synthon **3** requires six steps from commercially available (*S*)-4-benzyl-2-oxazolidinone<sup>7a</sup> and is summarized in Scheme 2. Notably, the illustrated imide-based aldol bond construction establishes the C<sub>2</sub>–C<sub>3</sub> syn stereochemistry with excellent diastereoselection.<sup>7b</sup>

### Scheme 2. Synthesis of the C<sub>1</sub>–C<sub>6</sub> Synthon **3**<sup>a</sup>

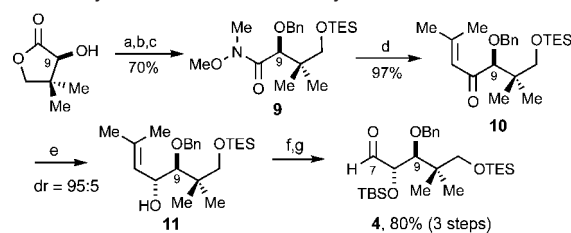


<sup>a</sup> (a) **7**, Bu<sub>2</sub>BOTf, *i*-Pr<sub>2</sub>EtN. (b) Me<sub>3</sub>OBF<sub>4</sub>, proton sponge. (c) PPTS, acetone, Δ.

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<sub>9</sub> 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,<sup>8</sup> we concluded that the (*R*)-C<sub>3</sub>, (*S*)-C<sub>8</sub>, and (*R*)-C<sub>9</sub> 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<sub>9</sub> diastereomer is employed in a related aldol addition.<sup>9</sup>

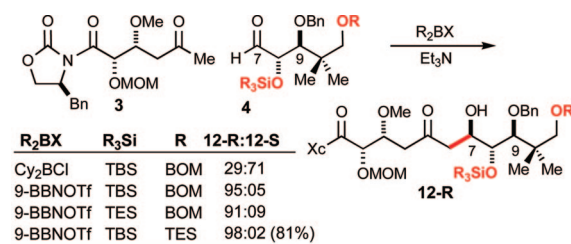
### Scheme 3. Synthesis of the C<sub>7</sub>–C<sub>11</sub> Synthon **4**<sup>a</sup>



<sup>a</sup> (a) BnON(H)CCl<sub>3</sub>, TfOH, rt. (b) Me<sub>3</sub>Al, MeON(H)Me·HCl, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C. (c) TESCl, Et<sub>3</sub>N, DMAP, rt. (d) Me<sub>2</sub>C=CHBr, *t*-BuLi, Et<sub>2</sub>O. (e) Zn(BH<sub>4</sub>)<sub>2</sub>, –30 °C. (f) TBSCl. (g) O<sub>3</sub>, PPh<sub>3</sub>.

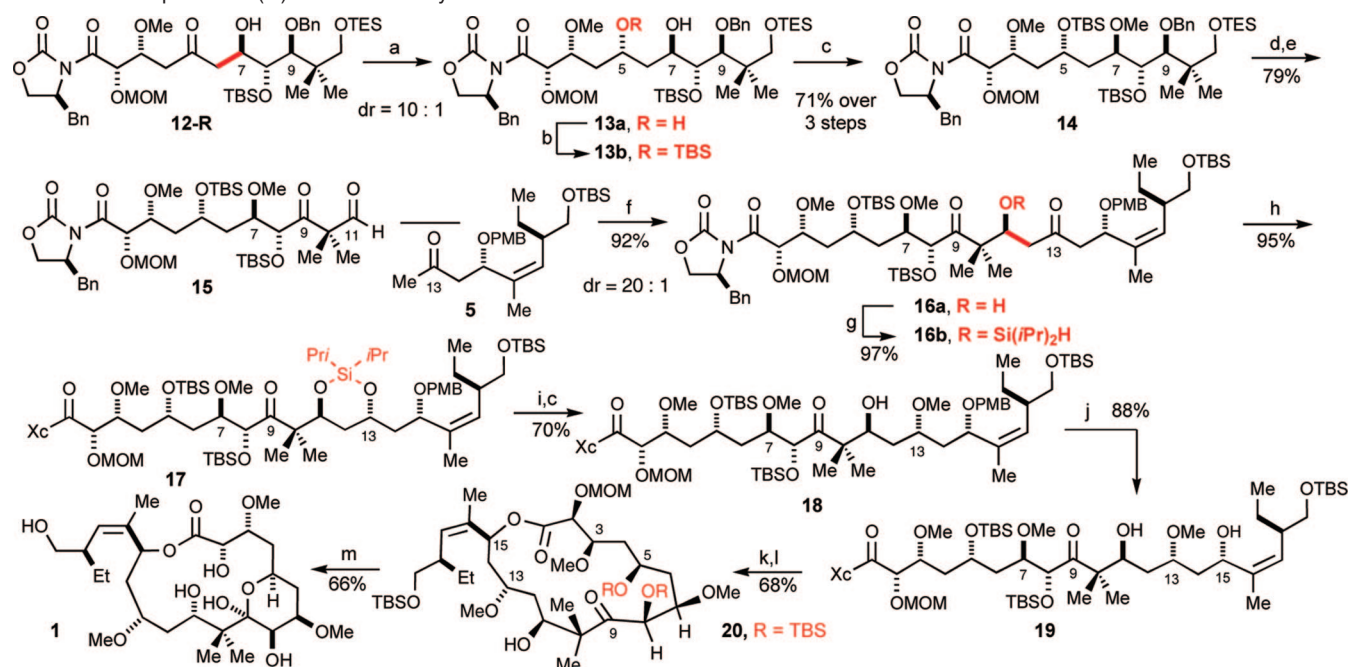
The aldol union of methyl ketone **3** and aldehyde **4** is summarized in Scheme 4.<sup>10</sup> In developing this reaction, we noted a surprising diastereoselectivity dependence on the particular dialkylboranyl enolate employed in the reaction. The desired diastereomer **12-R** was obtained in 81% with 9-BBNOTf (Et<sub>3</sub>N, toluene).

### Scheme 4. C<sub>6</sub>–C<sub>7</sub> Aldol Bond Construction



Further complexity in this reaction is apparent by varying the C<sub>8</sub> hydroxyl protecting group: when C<sub>8</sub> bears a smaller protecting group (TES) a diminished diastereoselection (10:1) is observed. Finally, the structure of the C<sub>11</sub> 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).<sup>11</sup> A selective silylation of the less hindered C<sub>5</sub> hydroxyl group of diol **13a** delivered **13b**.

Scheme 5. Completion of (+)-Peloruside A Synthesis<sup>a</sup>

<sup>a</sup> (a) Me<sub>4</sub>N(OAc)<sub>3</sub>BH, AcOH, MeCN, -30 °C. (b) TBSCl, imidazole, rt. (c) Me<sub>3</sub>OBF<sub>4</sub>, proton sponge, CH<sub>2</sub>Cl<sub>2</sub>, rt. (d) Pd(OH)<sub>2</sub>/C, H<sub>2</sub>, EtOAc, rt. (e) Dess-Martin, pyridine, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C. (f) 9-BBNOTf, DIPEA. (g) (iPr)<sub>2</sub>SiHCl, DMAP, DMF. (h) SnCl<sub>4</sub>, -78 °C. (i) 1:1 TBAF, HOAc, THF, -20 °C. (j) DDQ. (k) H<sub>2</sub>O<sub>2</sub>, LiOH. (l) C<sub>6</sub>H<sub>2</sub>Cl<sub>3</sub>COCl, 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<sub>9</sub> substituent. For example, the reaction does not proceed if the C<sub>9</sub> 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<sup>11</sup> of diketone **16a** also raises an interesting challenge. While we anticipated that steric effects would favor a selective anti reduction of the C<sub>13</sub> carbonyl, we noted that virtually no C<sub>13</sub>/C<sub>9</sub> carbonyl selectivity was obtained for this transformation. A solution to this problem was found in the intramolecular silane reductions reported by Davis.<sup>12</sup> Accordingly, silane **16b** was prepared in anticipation of an intramolecular hydride reduction. The subsequent SnCl<sub>4</sub> promoted intramolecular anti reduction proceeded in the desired sense with 40:1 selectivity (85%). The removal of the C<sub>11</sub>–C<sub>13</sub> disilyloxane protecting group in **17** was followed by a C<sub>13</sub>-selective methylation of the derived diol to afford **18**. Again, steric effects formed the basis for differentiation of the C<sub>11</sub>–C<sub>13</sub> diol.

In the experiments leading up to the macrocyclization, we anticipated that we might selectively cyclize the diol **19** at C<sub>15</sub> since the C<sub>11</sub> hydroxyl reactivity was estimated to be lower relative to the C<sub>15</sub> hydroxyl group by a comparison of their local steric environments. Toward this end, hydrolysis and subsequent Yamaguchi macrocyclization<sup>13</sup> 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<sub>11</sub> 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.

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**Supporting Information Available:** Experimental details and analytical data including copies of <sup>1</sup>H and <sup>13</sup>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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