

# A Convergent Route to the CDEF-Tetracycle of Pectenotoxin-2

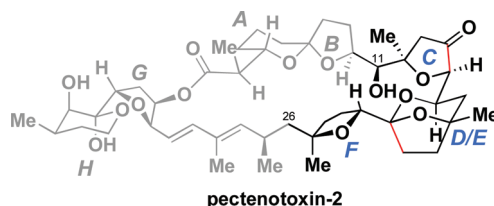
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## ABSTRACT



— = C–C bonds forged in this convergent synthesis of the CDEF tetracycle.

A convergent synthesis of the CDEF-tetracyclic region of pectenotoxin-2 (PTX-2) is described. The synthetic pathway derives from a head-to-tail union of 2 equiv of linalool to establish a stereodefined DEF-tricyclic aldehyde. Subsequent coupling with a “northern” fragment enolate, followed by a tandem Sharpless epoxidation/cyclization, delivers the C10–C26 polycyclic region of the natural product.

Actin is among the most abundant proteins in eukaryotic cells, and its ability to reversibly assemble into long and flexible filaments controls cell shape, movement, cell division, and adherens junctions between cells. The actin network also provides an essential scaffold for critical enzymes and signaling complexes and is necessary for tumor cell migration, invasion, metastasis, and tumor angiogenesis. Marine-derived natural products have defined a rich source of small molecules capable of destabilizing F-actin (i.e., reidispogiolide A, kabiramide C, scytophycin C, swinholide A, aplyronine A, and bistramide).<sup>1</sup> Within this subset, the pectenotoxins represent a particularly novel class, with regard to both their exquisite molecular complexity and their mechanism of action.<sup>2</sup> The most potent of this class, pectenotoxin-2 (PTX-2; Figure 1A), has recently been demonstrated to destabilize F-actin and be selectively cytotoxic to p53 mutant and p53(–) cancers.<sup>3</sup>

(1) (a) Allingham, J. S.; Klenchin, V. A.; Rayment, I. *Cell. Mol. Life Sci.* **2006**, *63*, 2119–2134. (b) Fenteany, G.; Zhu, S. *Curr. Top. Med. Chem.* **2003**, *3*, 593–616.

(2) (a) Yasumoto, T.; Murate, M.; Oshima, Y.; Sano, M.; Matsumoto, G. K.; Clardy, J. *Tetrahedron* **1985**, *41*, 1019–1025. (b) Sasaki, K.; Wright, J. L. C.; Yasumoto, T. *J. Org. Chem.* **1998**, *63*, 2475–2480.

(3) (a) Chae, H.-D.; Choi, T.-S.; Kim, B.-M.; Hung, J. H.; Bang, Y.-J.; Shin, D. Y. *Oncogene* **2005**, *24*, 4813–4819. (b) Shin, D. Y.; Kim, G. Y.; Kim, N. D.; Jung, J. H.; Kim, S. K.; Hang, H. S.; Choi, Y. H. *Oncol. Rep.* **2008**, *19*, 517–526.

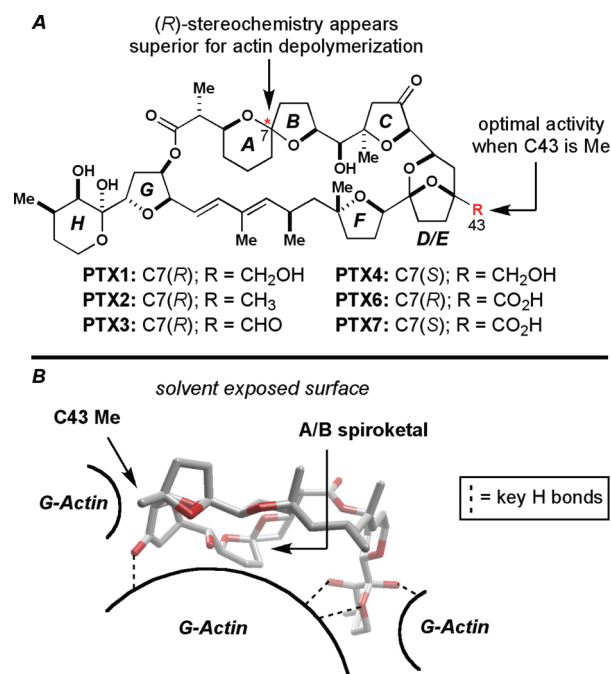


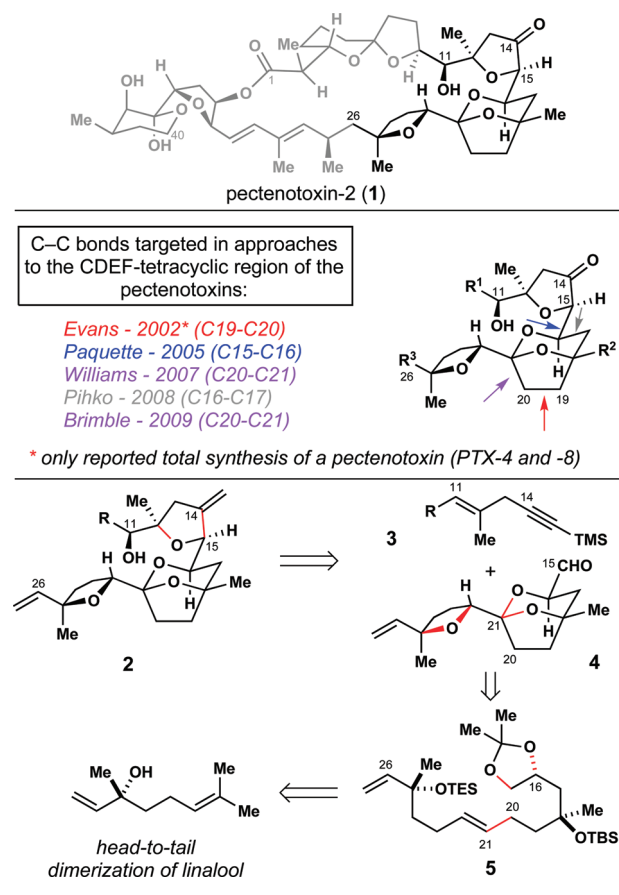
Figure 1. Introduction to the pectenotoxins.

While demonstrating attractive anticancer properties, the development of these marine-derived natural products as potential therapeutics remains in its infancy due primarily to their low natural abundance. Here, we describe our initial foray into the chemistry of PTX-2 that has culminated in a convergent entry to the CDEF tetracyclic heterocycle.

To prioritize our efforts directed toward a chemical synthesis of PTX-2, we began with an analysis of its complex with G-actin (Figure 1B) and the limited structure–activity relationships established for the pectenotoxin family.<sup>4</sup> In short, the C- and H-rings play important roles in binding, while the AB spiroketal appears to serve as a scaffolding element to ensure proper orientation of these subunits. Not surprisingly, this role is significantly affected by the C7 stereochemistry, with the C7(*R*) isomers demonstrating markedly enhanced activities.<sup>5</sup> The oxidation state of C43 also plays an important role in modulating the cytotoxicity of the pectenotoxins; apparently, there exists insufficient molecular features on G-actin to accommodate higher oxidation states at C43.<sup>5</sup> In sum, these structural studies provide insight into the roles that each region of the natural product play in binding to G-actin: The AB-ring system and the 1,3-diene appear to play scaffolding roles to properly orient the CDEF- and GH-subunits for binding. Because of the central role that the CDEF-tetracycle plays and its presence in all known pectenotoxins, our initial chemical studies focused on this subunit.<sup>6,7</sup>

As highlighted in Scheme 1, the CDEF tetracyclic region of PTX-2 (**1**) is quite complex and is composed of stereochemically distinct tetrahydrofurans, a central bridged bicyclic acetal, and three tertiary ethers. To date, a variety of approaches to this system have been reported that embrace chemistry spanning hydrazone alkylation, carbonyl addition, Julia olefination, and aldol chemistry.

**Scheme 1.** Synthetic Strategy for a Model CDEF-Tetracycle



Additionally, a strategy reported by Roush targeted convergent assembly of this subunit via annulation of the C- and F-rings about a central DE-ring precursor.<sup>7a</sup>

We opted to pursue a strategy to tetracycle **2** that was distinct from these previously described approaches, embracing metal-mediated site-selective and stereoselective coupling of a suitably functionalized TMS-alkyne **3** with a tricyclic aldehyde **4**. Overall, reductive cross-coupling followed by stereoselective epoxidation and acid-catalyzed ring closure was targeted as a general convergent annulation strategy for union of a functionalized DEF-tricycle with the “northern” C1–C14 subunit. The requisite coupling partner **4** was then reasoned to be accessible by oxidative functionalization of **5**, itself derived from a head-to-tail dimerization of commercially available linalool in a fashion to forge the C20–C21 bond.

We prepared coupling partners **8** and **10** from linalool by a simple sequence of robust functional group manipulations. As depicted in Scheme 2A, vinyl iodide **8** was generated through the following sequence: (1) TES protection,

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(6) For total syntheses of PTX-4 and PTX-8, see: (a) Evans, D. A.; Rajapakse, H. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4569–4573. (b) Evans, D. A.; Rajapakse, H. A.; Stenkamp, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 4573–4576.

(7) For partial synthesis, and studies toward the syntheses of the pectenotoxins, see: (a) Micalizio, G. C.; Roush, W. R. *Org. Lett.* **2001**, *3*, 1949–1952. (b) Paquette, L. A.; Peng, X.; Bondar, D. *Org. Lett.* **2002**, *4*, 937–940. (c) Pihko, P. M.; Aho, J. E. *Org. Lett.* **2004**, *6*, 3849–3852. (d) Bondar, D.; Liu, J.; Müller, T.; Paquette, L. A. *Org. Lett.* **2005**, *7*, 1813–1816. (e) Halim, R.; Brimble, M. A.; Merten, J. *Org. Lett.* **2005**, *7*, 2659–2662. (f) Vellucci, D.; Rychnovsky, S. D. *Org. Lett.* **2007**, *9*, 711–714. (g) O'Connor, P. D.; Knight, C. K.; Friedrich, D.; Peng, X.; Paquette, L. A. *J. Org. Chem.* **2007**, *72*, 1747–1754. (h) Lotesta, S. D.; Hou, Y.; Williams, L. J. *Org. Lett.* **2007**, *9*, 869–872. (i) Heapy, A. M.; Wagner, T. W.; Brimble, M. M. *Synlett* **2007**, 2359–2362. (j) Fujiwara, K.; Aki, Y.; Yamamoto, F.; Kawamura, M.; Kobayashi, M.; Okano, A.; Awakura, D.; Shiga, S.; Murai, A.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2007**, *48*, 4523–4527. (k) Kolakowski, R. V.; Williams, L. J. *Tetrahedron Lett.* **2007**, *48*, 4761–4764. (l) Aho, J. E.; Salomäki, E.; Rissanen, K.; Pihko, P. M. *Org. Lett.* **2008**, *10*, 4179–4182. (m) Carley, S.; Brimble, M. A. *Org. Lett.* **2009**, *11*, 563–566. (n) Joyasawal, S.; Lotesta, S. D.; Akhmedov, N. G.; Williams, L. J. *Org. Lett.* **2010**, *12*, 988–991.

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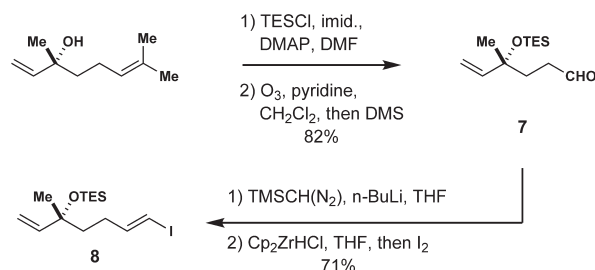
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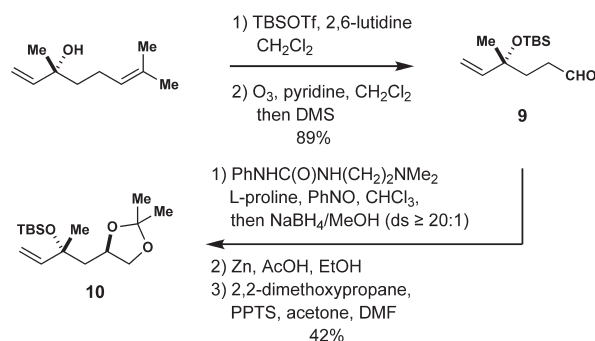
(2) site-selective oxidative cleavage of the trisubstituted alkene,<sup>8</sup> (3) alkynylation,<sup>9</sup> and (4) hydrozirconation/iodination.<sup>10</sup> As illustrated in Scheme 2B, a slightly different sequence of robust reactions was employed to access coupling partner **10**: (1) TBS protection, (2) site-selective oxidative cleavage of the trisubstituted alkene,<sup>8</sup> (3) diastereoselective  $\alpha$ -hydroxylation under the MacMillan/McQuade conditions (dr  $\geq 20:1$ ),<sup>11</sup> (4) reduction, and (5) acetonide formation.

## Scheme 2. Preparation of Linalool-Derived Coupling Partners

### A. Synthesis of a C21-C26 fragment precursor:



### B. Synthesis of a C15-C20 fragment precursor:



As depicted in Scheme 3, the assembly of the tricyclic acetal **4** was accomplished by a simple six-step sequence. First, hydroboration/Suzuki coupling<sup>12</sup> defined a robust means of coupling the linalool derivatives **8** and **10**. After careful purification, Shi epoxidation<sup>13</sup> of **5** provided **11** in 59% yield (dr  $\geq 20:1$ ). Desilylation with TBAF, followed by treatment with HCl in CHCl<sub>3</sub> resulted in cyclization to deliver the stereodefined tetrahydrofuran **12** in 86% yield. Finally, a simple three-step sequence was used to advance this intermediate to the functionalized aldehyde **4**: (1) oxidation to the ketone, (2) acid-promoted desilylation of the tertiary TBS ether with concomitant formation of the bicyclic acetal,<sup>14</sup> and (3) oxidation to the C15 aldehyde.

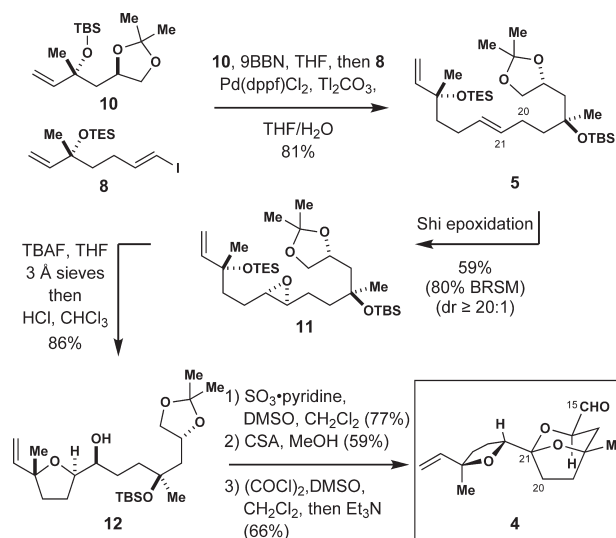
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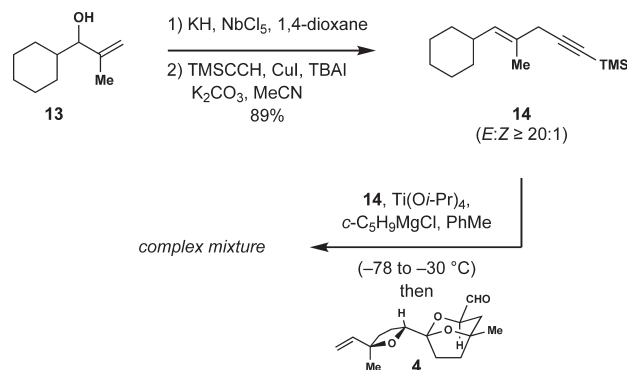
(14) While the yield of this step was moderate (59%), no evidence could be found for the formation of a regioisomeric acetal.

## Scheme 3. Convergent Coupling en Route to a DEF-Tricyclic



With a robust route to the polycyclic acetal **4**, we turned our attention to the synthesis of a suitably functionalized enyne to be employed as a C-ring precursor. As illustrated in Scheme 4, we selected to employ a simple model for the “northern” fragment. Conversion of the readily available allylic alcohol **13** to the stereodefined allylic chloride **14** was possible by a two-step sequence consisting of the nucleophilic addition of 2-propenylmagnesium bromide, followed by NbCl<sub>5</sub>-mediated chlorination (*E:Z*  $\geq 20:1$ ),<sup>15</sup> and coupling with TMS-acetylene (CuI, K<sub>2</sub>CO<sub>3</sub>, TBAI, CH<sub>3</sub>CN).<sup>16</sup>

## Scheme 4. Synthesis of C-Ring Fragment Precursor



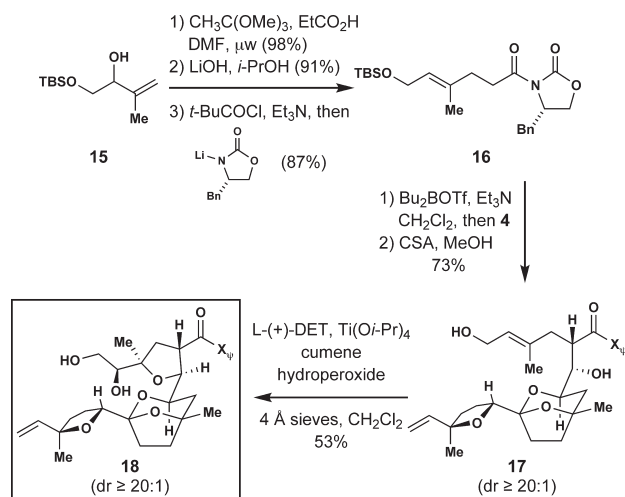
With ample precedent supporting the compatibility of functionalized enynes with Ti-mediated reductive cross-coupling chemistry,<sup>17</sup> fragment assembly was pursued with

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### Scheme 5. Generation of a CDEF-Tetracycle



Sato's regioselective TMS-alkyne–aldehyde reductive cross-coupling reaction.<sup>18</sup> Unfortunately, all attempts to accomplish the Ti-mediated coupling between enyne **14** and aldehyde **4** led to complex product mixtures. While other procedures for reductive cross-coupling of alkynes with aldehydes are well-established,<sup>19</sup> available methods typically do not deliver the regioisomeric product that was required in this PTX-2 synthesis campaign.

In the search for a suitable nucleophile to join a “northern” fragment of PTX-2 with the DEF-tricyclic aldehyde **4**, we turned our attention to well-established aldol chemistry.<sup>20</sup> As

illustrated in Scheme 5, allylic alcohol **15**<sup>21</sup> was converted to the stereodefined imide **16** by a straightforward three-step sequence: (1) Johnson ortho-ester Claisen rearrangement (*E*:*Z* ≥ 20:1), (2) saponification, and (3) imide formation. To our delight, Bu<sub>2</sub>BOTf-mediated stereoselective aldol reaction between **16** and **4** proceeded with high levels of stereoselection (*dr* ≥ 20:1) and delivered, after desilylation (CAS, MeOH), the functionalized diol **17** in 73% yield. Subsequent Sharpless epoxidation<sup>22</sup> led to a metastable intermediate that promptly cyclized *in situ* to furnish the stereodefined C-ring and the fully functionalized CDEF-tetracycle of PTX-2 (**18**) in 53% yield (*dr* ≥ 20:1).

In summary, we have defined a synthetic pathway to the CDEF-tetracycle of pectenotoxin 2-(**1**). The route is highly convergent and delivers the stereochemically dense C10–C26 heterocyclic core by the stepwise construction of two C–C bonds: (1) union of two simple linalool derivatives through forging the C20–C21 bond, and (2) appending the “northern” fragment by C14–C15 bond formation, and oxidative cyclization. Overall, the sequence proceeds in 16 linear steps from linalool (24 total steps) and requires only 11 chromatographic operations. Further, the strategic implication of employing linalool for the entire C15–C26 segment (**4**) that incorporates two stereodefined tertiary ethers is significant and offers a facile means to gain access to this complex segment of the natural product.

**Acknowledgment.** We thank Professor D. Tyler McQuade (Department of Chemistry, Florida State University) for helpful discussions regarding the catalytic asymmetric  $\alpha$ -hydroxylation reaction employed and for a sample of the relevant urea. We also thank Professor Yian Shi (Department of Chemistry, Colorado State University) for helpful discussions.

**Supporting Information Available.** Experimental procedures and tabulated spectroscopic data for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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