

# Synthesis of the C1–C26 Hexacyclic Subunit of Pectenotoxin 2

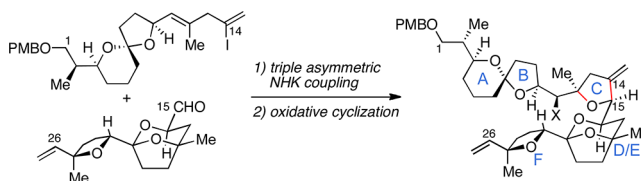
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## ABSTRACT



Synthesis of the C1–C26 hexacyclic subunit of pectenotoxin-2 (PTX-2) is described that features a stereoselective annulation to generate the C-ring by triple asymmetric Nozaki–Hiyama–Kishi coupling followed by oxidative cyclization. Preparation of the C1–C14 AB spiroketal-containing subunit employs a recently developed metallacycle-mediated reductive cross-coupling between a TMS-alkyne and a terminal alkene.

Pectenotoxin-2 (PTX2) is a rare marine-derived polyether natural product that displays rather profound anticancer properties (Figure 1A).<sup>1–3</sup> Discovered in the digestive glands of the scallop *Patinopecten yessoensis*<sup>4</sup> and traced back to the dinoflagellates *Dinophysis fortii* and *D. acuminata*,<sup>5</sup> recent studies have described the isolation of PTX2 from a two-sponge association (*Poecillastra* sp. and *Jaspis* sp.).<sup>2</sup> Initial biological evaluation of PTX2 established its substantial cytotoxic profile, with later studies concluding that this natural product is a unique actin depolymerizing agent. Binding to a site on G-actin that is distinct from other known marine toxins,<sup>6</sup> recent studies have determined that PTX2 is selectively cytotoxic to p53 mutant and p53(–) cancers (representing approximately 50% of all human cancers).<sup>1,7</sup>

While no laboratory synthesis of PTX2 has been reported,<sup>8</sup> a number of studies directed toward this goal have appeared.<sup>9</sup> Here, we describe an efficient assembly of the C1–C26 ABCDEF hexacyclic subunit of PTX2 (**2**) by convergent union of the functionalized vinyl iodide **3** with the tricyclic acetal-containing aldehyde **4** (Figure 1B). While these pursuits have led to the generation of a substantial subunit of pectenotoxin-2 (**2**), they have also defined an approach to stereodefined 2,2,5-trisubstituted THFs based on double or triple asymmetric Nozaki–Hiyama–Kishi (NHK) coupling (**8** + **9** → **7**) and site

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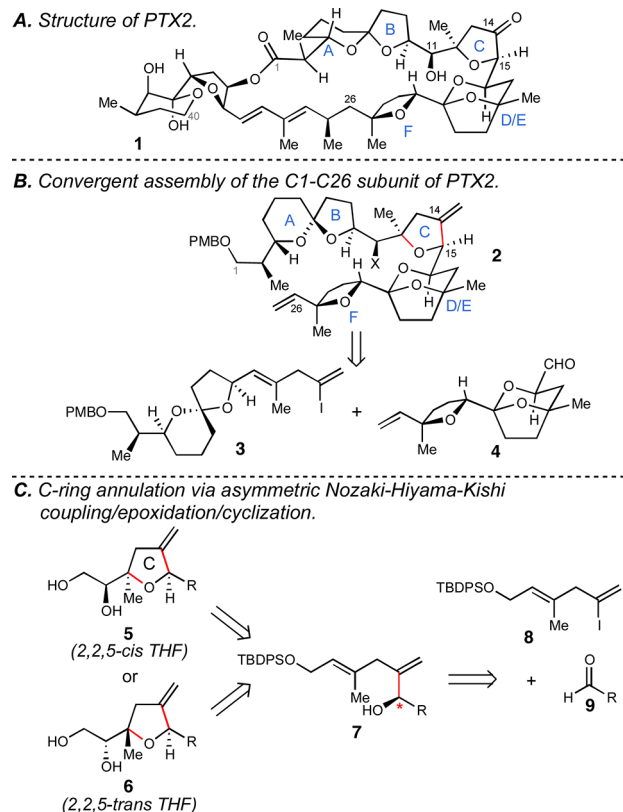
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and stereoselective oxidative cyclization via 5-exo ring closure (Figure 1C).

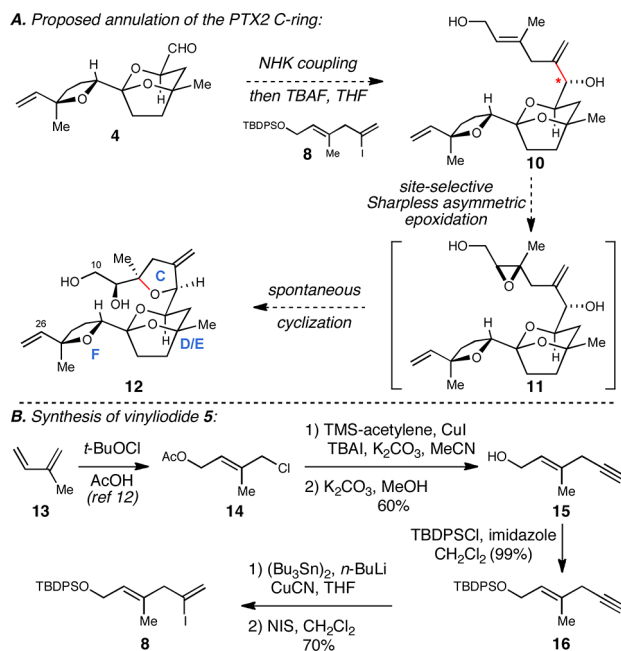


**Figure 1.** Introduction.

With the initial focus on a more modest target than **2**, and deriving inspiration from Professor Kishi's approach to the synthesis of heterocyclic motifs present in the halichondrins,<sup>10</sup> we targeted construction of the PTX2 CDEF heterocyclic system by double asymmetric NHK coupling<sup>11</sup> between aldehyde **4**<sup>9a</sup> and vinyl iodide **8** (Scheme 1A). Site-selective and stereoselective epoxidation of the diol product (**10** → **11**) followed by 5-exo ring closure (**11** → **12**) was then envisioned as a means to establish the complex C10–C26 tetracycle of PTX2.

As illustrated in Scheme 1B, vinyl iodide **8** was prepared by a simple six-step sequence from isoprene. First, conversion to the stereodefined vinylchloride **14** was accomplished by exposure to *t*-BuOCl in AcOH,<sup>12</sup> and subsequent transformation to enyne **15** was realized by sequential homologation with TMS-acetylene and desilylation.<sup>13</sup> Conversion to the fully functionalized coupling partner **8** was then achieved by a simple three-step sequence:

## Scheme 1. C-Ring Annulation Strategy and Synthesis of **8**



(1) silylation with TBDPSCl, (2) regioselective hydrostannylation,<sup>14</sup> and (3) iodination.

Next, to explore the basic steps of the annulation process on a model aldehyde, asymmetric NHK coupling<sup>11</sup> with cyclohexane carboxaldehyde delivered allylic alcohol **17** in 54% yield with 87% ee (Scheme 2). Subsequent desilylation with TBAF provided diol **18** in 99% isolated yield, an intermediate that proved to be an ideal substrate for site-selective and stereoselective Sharpless asymmetric epoxidation<sup>15</sup>/ring closure. Exposure of **18** to reaction conditions for asymmetric epoxidation with (+)-diethyltartrate delivered the 2,2,5-*cis* trisubstituted THF **19** in 86% yield (dr = 10:1) by tandem asymmetric epoxidation/5-exo ring closure. While unrelated to the synthetic challenge associated with the C-ring of PTX2, use of (–)-diethyltartrate in this reaction process resulted in formation of the 2,2,5-*trans* trisubstituted product **20** in 86% yield (dr = 6:1).<sup>16</sup>

With confidence gained from the successful coupling of **8** with a simple aldehyde, we next studied the utility of this sequence for synthesis of the C10–C26 tetracyclic fragment of PTX2 **12**. As illustrated in Scheme 3, aldehyde **4** was prepared as previously described from linalool by an 11-step sequence.<sup>9a</sup> While single asymmetric NHK coupling between aldehyde **4** and vinyl iodide **8** proceeded without appreciable stereoselection (ds = 1.5:1), a double asymmetric variant of this process delivered the allylic alcohol **10** with exquisite levels of selectivity (dr ≥ 20:1)

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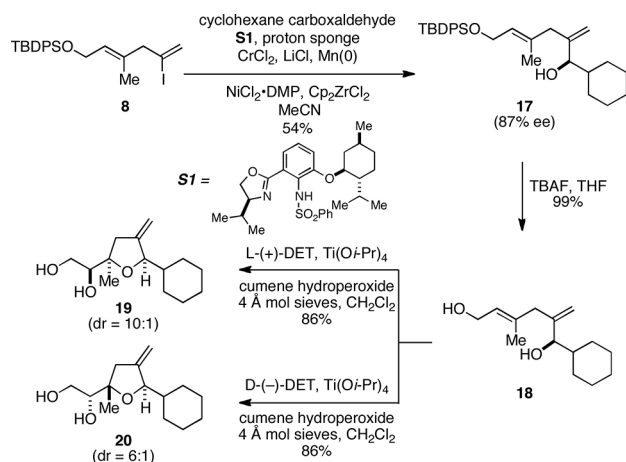
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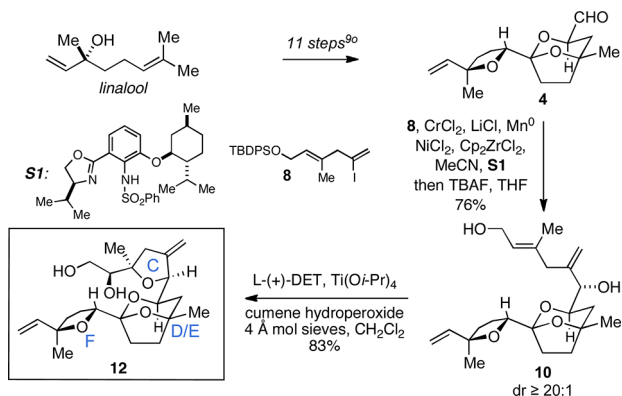
(16) Unfortunately, all attempts to employ an epoxide-containing vinyl iodide in the NHK coupling delivered a complex mixture of products.

**Scheme 2.** NHK-Based Annulation for 2,2,5-Trisubstituted THFs



in 76% yield (after desilylation: TBAF, THF). Also, site-selective Sharpless asymmetric epoxidation and cyclization proved effective for advancing triene **10** to the tetracyclic target **12** in 83% yield.

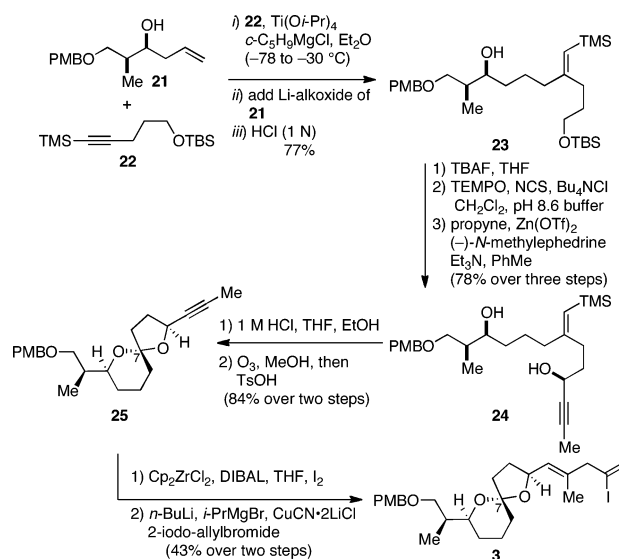
**Scheme 3.** Synthesis of a CDEF-Containing Subunit of PTX2



With a sound foundation of preliminary data that supported the utility of NHK coupling for establishment of the functionalized C-ring of the pectenotoxins, we then targeted synthesis of the fully functionalized C1–C26 subunit of PTX2. As illustrated in Scheme 4, synthesis of the AB spiroketal-containing subunit began with reductive cross-coupling between the stereodefined homoallylic alcohol **21** and TMS-alkyne **22**.<sup>17</sup> This Ti-mediated, hydroxyl-directed coupling process proceeded in 77% yield and delivered **23** as a single regio- and stereoisomer. Next, TBS deprotection (TBAF, THF) was followed by selective oxidation of the primary alcohol to the aldehyde (TEMPO, NCS, Bu<sub>4</sub>NCl, CH<sub>2</sub>Cl<sub>2</sub>, pH 8.6 buffer) and propyne, Zn(OTf)<sub>2</sub>, Et<sub>3</sub>N, PhMe (78% over three steps) to deliver **24**. Finally, conversion to vinyl iodide **3** was accomplished by regioselective hydrozirconation–iodination (Cp<sub>2</sub>ZrCl<sub>2</sub>, DIBAL, THF, then I<sub>2</sub>) and coupling with 2-iodo-allylbromide (*n*-BuLi, *i*-PrMgBr, CuCN·2LiCl) and 2-iodo-allylbromide (*n*-BuLi, *i*-PrMgBr, CuCN·2LiCl).<sup>19</sup>

and Carreira's asymmetric acetylide addition<sup>18</sup> [propyne, Zn(OTf)<sub>2</sub>, (–)-*N*-methylephedrine, Et<sub>3</sub>N, PhMe] to deliver the propargylic alcohol product **24** in 78% yield (dr ≥ 20:1). Protodesilylation of the vinylsilane (1 M HCl, THF, EtOH), oxidative cleavage of the alkene (O<sub>3</sub>, MeOH, then Me<sub>2</sub>S), and acid-promoted dehydration then delivered the AB spiroketal-containing subunit **25** as a mixture of C7-spiroketal isomers (dr = 14:1) in 84% yield. As expected, this spirocyclization provided the product containing the incorrect C7 stereochemistry for PTX2, a structural feature that we plan to address in late stage acid-mediated equilibration once the fully functionalized macrocycle is in place. Finally, conversion to vinyl iodide **3** was accomplished by regioselective hydrozirconation–iodination (Cp<sub>2</sub>ZrCl<sub>2</sub>, DIBAL, THF, then I<sub>2</sub>) and coupling with 2-iodo-allylbromide (*n*-BuLi, *i*-PrMgBr, CuCN·2LiCl).<sup>19</sup>

**Scheme 4.** Synthesis of the AB Spiroketal-Containing Subunit **3**



As illustrated in Scheme 5, triple asymmetric<sup>20</sup> NHK coupling between vinyl iodide **3** and aldehyde **4** delivered the allylic alcohol product **26** in 79% yield (ds ≥ 20:1; Scheme 5). While we were delighted that this coupling proceeded with outstanding levels of stereochemical control and good yield, we were unable to identify reaction

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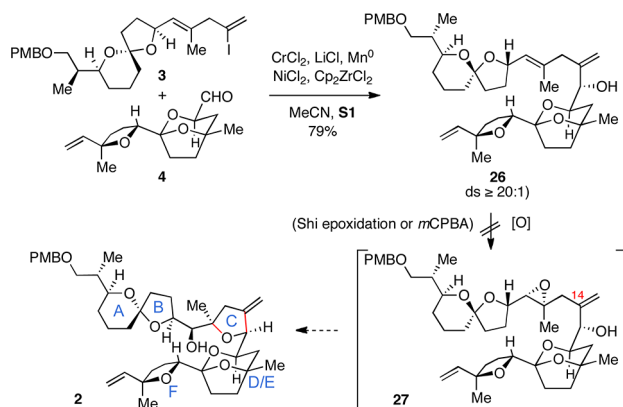
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conditions for selective epoxidation of the C11–C12 trisubstituted alkene of **26**. Standard reaction conditions for Shi epoxidation<sup>21</sup> led to initial partial oxidation of the C14 1,1-disubstituted alkene, while prolonged exposure to the reaction conditions for this oxidation process was insufficient to oxidize both the C14 1,1-disubstituted and the C11–C12 trisubstituted alkene. In an attempt to advance substrate **10** to the desired product, *m*CPBA was also investigated as a potential oxidant but was similarly ineffective for accomplishing the desired epoxidation/cyclization sequence.

**Scheme 5.** NHK Coupling between **3** and **4**, and Attempted Epoxidation/Cyclization Cascade



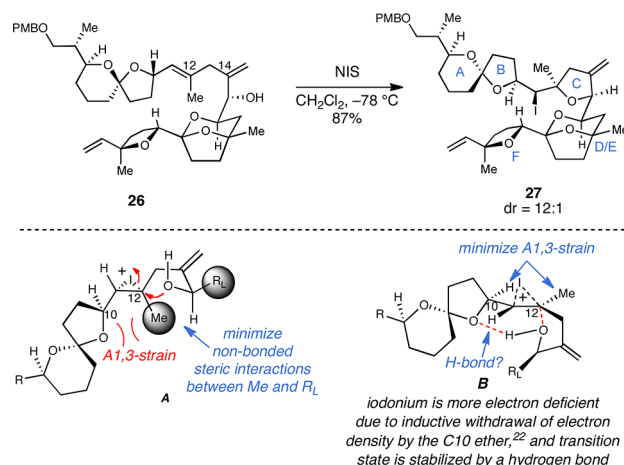
In an attempt to overcome the unexpected difficulty in site-selective oxidation of the triene **26**, we turned our attention to a substrate-controlled iodoetherification reaction to establish the 2,2,5-*cis* trisubstituted THF C-ring of PTX2. To our delight, treatment with *N*-iodosuccinimide in dichloromethane led to efficient cyclization of the C15 hydroxy group onto the trisubstituted alkene to deliver the polycyclic product containing the desired 2,2,5-*cis* trisubstituted THF **27** in 87% yield (*dr* = 12:1; Scheme 6). Stereochemical control in this process is quite interesting, as early studies of a related cyclization by Rychnovsky and Bartlett documented the preference of such ring-forming reactions to deliver 2,2,5-*trans* trisubstituted THFs with outstanding stereocontrol (*ds* = 20:1).<sup>23</sup> While further study is required to understand the sense of stereoselection observed here, the transition state model **A** (Scheme 6) does not adequately support the selectivity observed in the conversion of **26** to **27**. We propose that stereochemical control in this reaction is a result of an organized transition state that features minimization of A1,3 strain and stabilization by an intramolecular hydrogen bond (see **B** in Scheme 6).<sup>24</sup>

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**Scheme 6.** Closure of the C-Ring via Iodoetherification



In conclusion, we report a synthesis of the C1–C26 hexacyclic subunit of PTX2 that proceeds by convergent establishment of the C-ring through sequential Nozaki–Hiyama–Kishi coupling and oxidative cyclization. Our model studies have confirmed that this general strategy is quite effective for generating either 2,2,5-*cis* or 2,2,5-*trans* trisubstituted tetrahydrofurans when employing substrates that are amenable to site-selective and stereoselective Sharpless epoxidation. This annulative process was initially employed to prepare the C10–C26 subunit of PTX2 (**12**) but proved problematic when challenged with a more complex coupling partner containing the C1–C14 northern hemisphere of PTX2 (**3**). In efforts to circumvent the unanticipated low reactivity of the C11–C12 trisubstituted alkene of **26** toward standard conditions for stereoselective epoxidation, we turned to iodoetherification as an alternative means of ring closure. The stereochemical control that we achieved in the conversion of **26** to the ABCDEF subunit of PTX2 **27** is unique among iodoetherification reactions and may speak to the role that hydrogen bonding can play in dictating the stereochemical course of these cyclization reactions. Whether or not intermediate **27** will serve as a useful intermediate in efforts to prepare PTX2 is the subject of ongoing studies.

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**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>.

The authors declare no competing financial interest.