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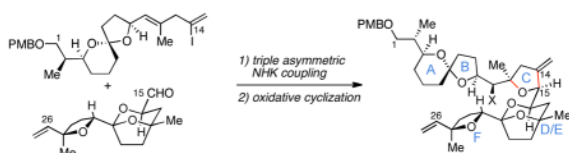
Synthesis of the C1-C26 Hexacyclic Subunit of Pectenotoxin 2

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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 spirroketal-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).^{1–3} Discovered in the digestive glands of the scallop *Patinopecten yessoensis*⁴ and traced back to the dinoflagellates *Dinophysis fortii* and *D. acuminata*,⁵ recent studies have described the isolation of PTX2 from a two-sponge association (*Poecillastra* sp. and *Jaspis* sp.).² 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,⁶ recent studies have determined that PTX2 is selectively cytotoxic to p53-mutant and p53(–) cancers (representing approximately 50% of all human cancers).^{1,7}

While no laboratory synthesis of PTX2 has been reported,⁸ a number of studies directed toward this goal have appeared.⁹ 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 and stereoselective oxidative cyclization via 5-exo ring closure (Figure 1C).

With 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,¹⁰ we targeted construction of the PTX2 CDEF heterocyclic system by double asymmetric NHK coupling¹¹ between aldehyde **4**^{9o} and vinyl iodide **8** (Scheme 1A). Site- and stereoselective

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

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,¹² and subsequent transformation to enyne **15** was realized by sequential homologation with TMS-acetylene and desilylation.¹³ Conversion to the fully functionalized coupling partner **8** was then achieved by a simple three-step sequence: (1) silylation with TBDPSCl, (2) regioselective hydrostannylation,¹⁴ and (3) iodination.

Moving on to explore the basic steps of the annulation process on a model aldehyde, asymmetric NHK coupling¹¹ 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- and stereoselective Sharpless asymmetric epoxidation¹⁵/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).¹⁶

With confidence gained from the successful coupling of **8** with a simple aldehyde, we moved on to study 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.^{9o} 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) in 76% yield (after desilylation: TBAF, THF). Moving on, site-selective Sharpless asymmetric epoxidation and cyclization proved effective for advancing triene **10** to the tetracyclic target **12** in 83% yield.

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**.¹⁷ 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, Bu₄NCl, CH₂Cl₂, pH 8.6 buffer) and Carreira's catalytic asymmetric acetylide addition¹⁸ [propyne, Zn(OTf)₂, (–)-*N*-methylephedrine, Et₃N, 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 (O₃, MeOH, then Me₂S) 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 (Cp₂ZrCl₂, DIBAL, THF, then I₂) and coupling with 2-iodo-allylbromide (*n*-BuLi, *i*-PrMgBr, CuCN•2LiCl).¹⁹

As illustrated in Scheme 5, triple asymmetric²⁰ 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 conditions for selective epoxidation of the C11-C12 trisubstituted alkene of **26**. Standard reaction conditions for Shi epoxidation²¹ 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.

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).²³ 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).²⁴

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- 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.

Supplementary Material

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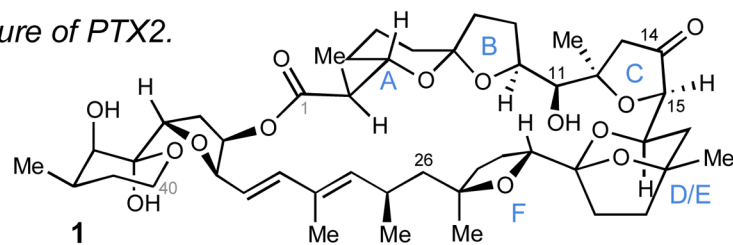
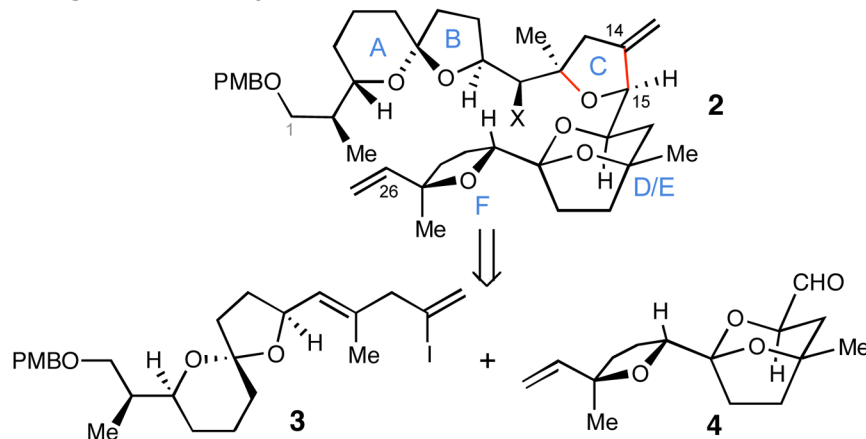
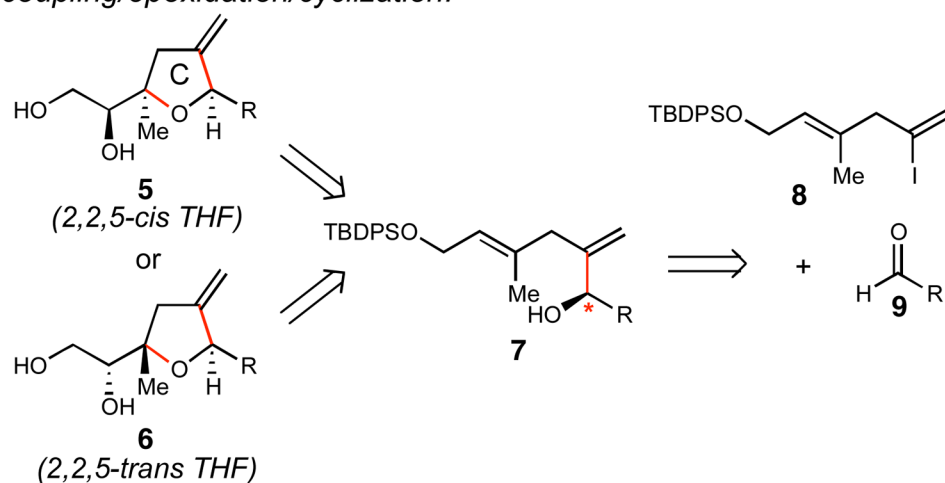
Acknowledgments

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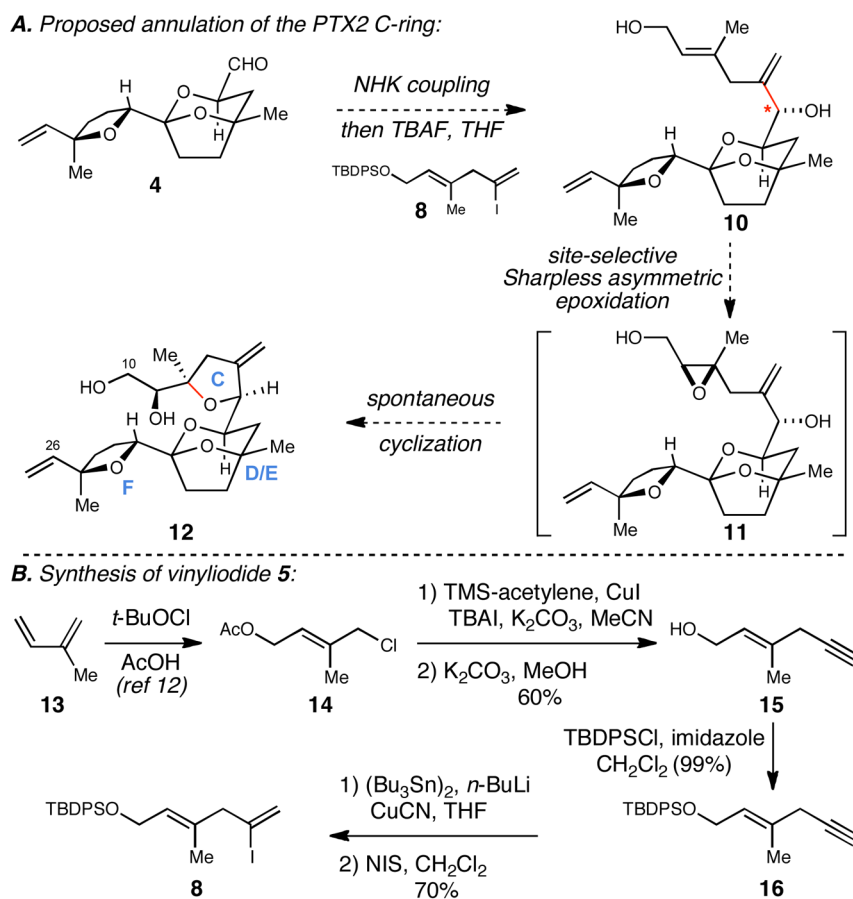
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 24. When the iodoetherification is conducted in acetonitrile, a significant decrease in stereoselection is observed (2,2,5-*cis*:2,2,5-*trans* = 3:1).

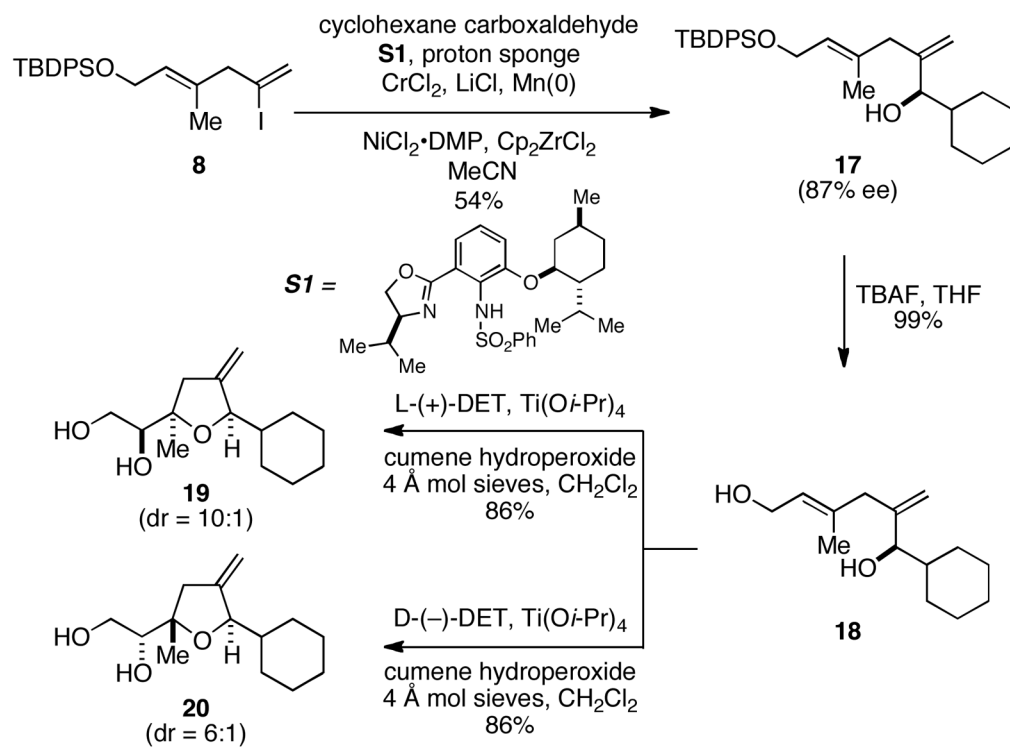
A. Structure of PTX2.**B. Convergent assembly of the C1-C26 subunit of PTX2.****C. C-ring annulation via asymmetric Nozaki-Hiyama-Kishi coupling/epoxidation/cyclization.****Figure 1.**

Introduction.

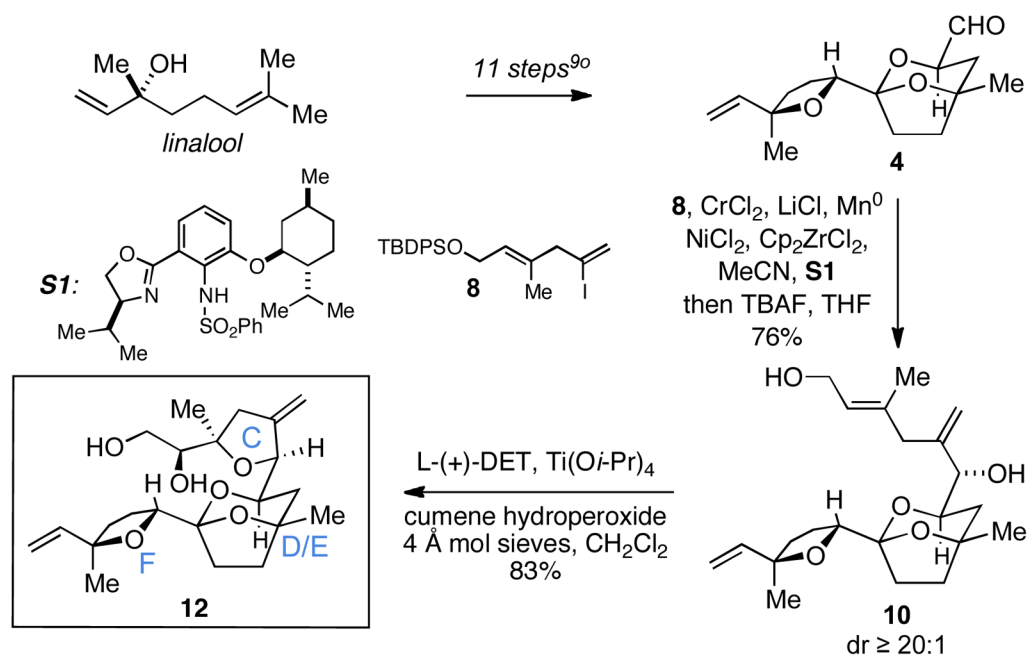
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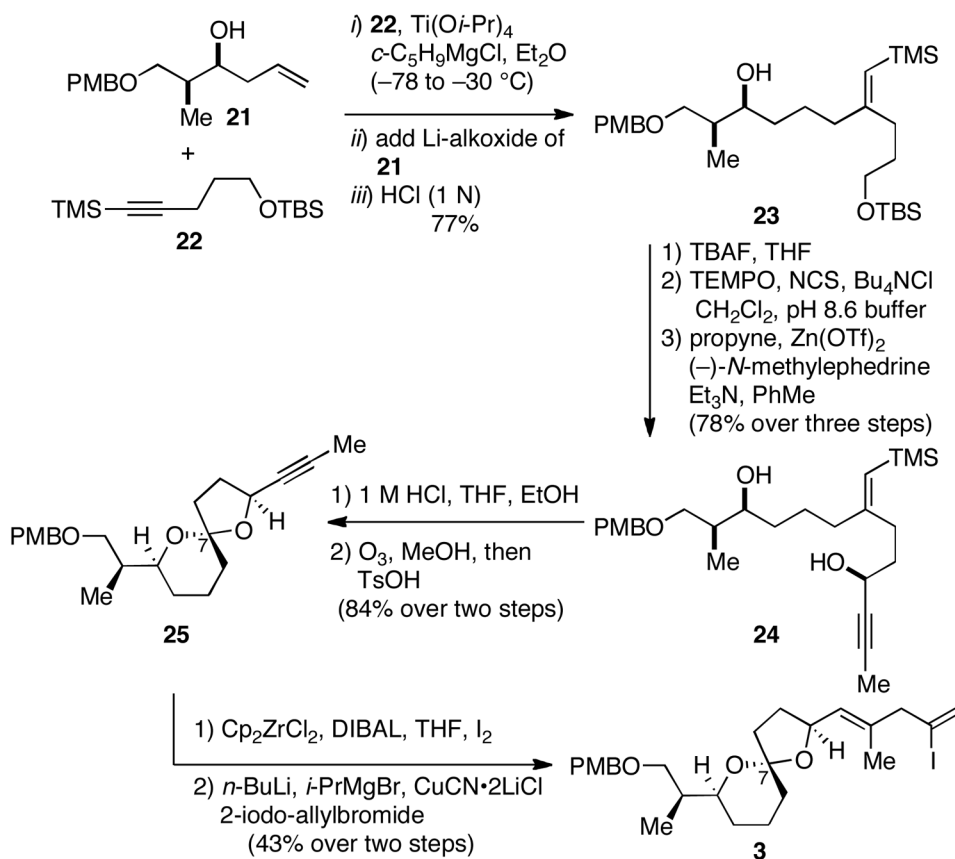
Scheme 1.
C-ring annulation strategy and synthesis of **8**.
A. Proposed annulation of the PTX2 C-ring:
B. Synthesis of vinyl iodide **5**:



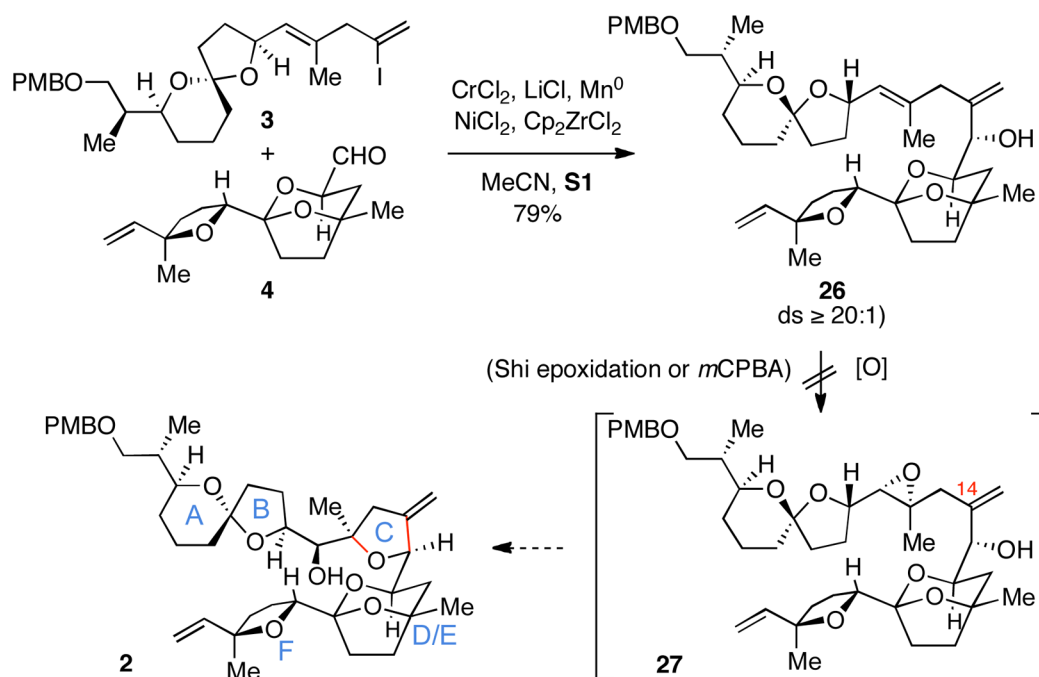
Scheme 2.
 NHK-based annulation for 2,2,5-trisubstituted THFs.



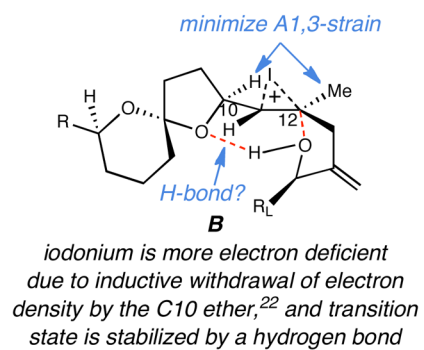
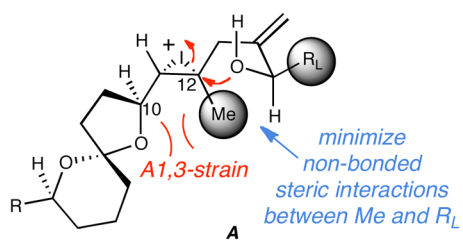
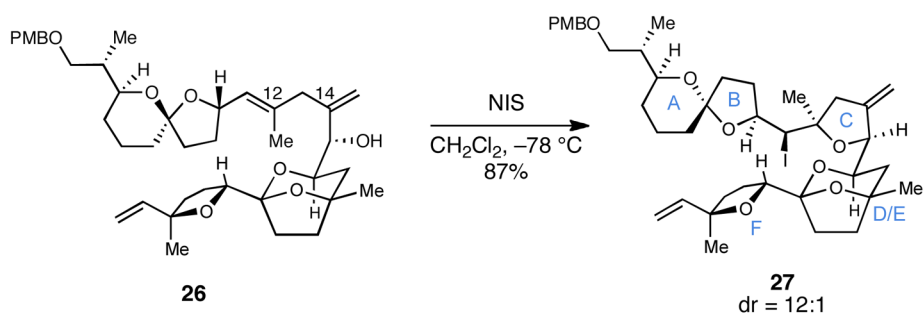
Scheme 3.
Synthesis of a CDEF-containing subunit of PTX2.



Scheme 4.
 Synthesis of the AB spiroketal-containing subunit **3**.



Scheme 5.
NHK coupling between **3** and **4**, and attempted epoxidation/cyclization cascade.



Scheme 6.
Closure of the C-ring via iodoetherification.