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Synthesis of the C1−C26 Hexacyclic Subunit of Pectenotoxin 2

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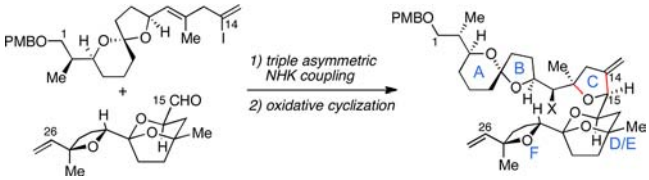
ABSTRACT



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 spriroketal-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 vinyliodide **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

(1) Chae, H.; Choi, T.; Kim, B.; Jung, J.; Bang, Y.; Shin, D. Y. *Oncogene* **2005**, *24*, 4813–4819.
(2) Jung, J. H.; Sim, C. J.; Lee, C. *J. Nat. Prod.* **1995**, *58*, 1722–1726.
(3) Spector, I.; Braet, F.; Shochet, n. R.; Bubb, M. R. *Microsc. Res. Tech.* **1999**, *47*, 18–37.
(4) (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. (c) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897–1909.
(5) (a) Yasumoto, T.; Oshima, Y.; Sugawara, W.; Fukuyo, Y.; Oguri, H.; Igarashi, T.; Fujita, N. *Bull. Jpn. Soc. Sci. Fish.* **1980**, *46*, 1405–1411. (b) Lee, J.; Igarashi, T.; Fraga, S.; Dahl, E.; Hovgaard, P.; Yasumoto, T. *J. Appl. Phycol.* **1989**, *1*, 147–152. (c) Draisci, R.; Lucentini, L.; Giannetti, L.; Boria, P.; Poletti, R. *Toxicon* **1996**, *34*, 923–935.
(6) Allingham, J. S.; Miles, C. O.; Rayment, I. *J. Mol. Bio.* **2007**, *371*, 959–970.
(7) Chae, H. D.; Kim, B. M.; Yun, U. J.; Shin, D. Y. *Oncogene* **2008**, *27*, 4115–4121.
(8) For total syntheses of pectenotoxin-4 and -8, see: (a) Evans, D. A.; Rajapakse, H. A.; Stenkamp, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 4569–4573. (b) Evans, D. A.; Rajapakse, H. A.; Chiu, A.; Stenkamp, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 4573–4576.
(9) 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. (o) Canterbury, D. P.; Micalizio, G. C. *Org. Lett.* **2011**, *13*, 2384–2387.

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

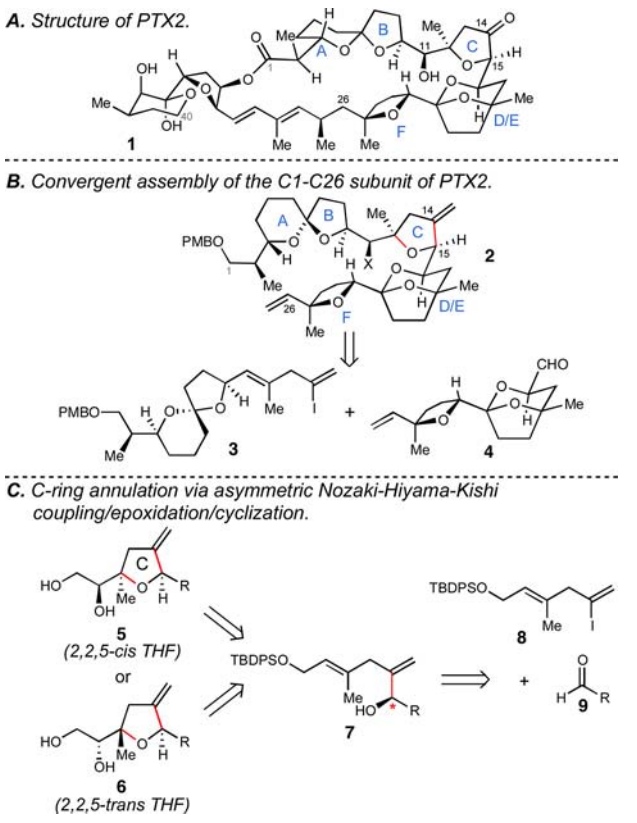
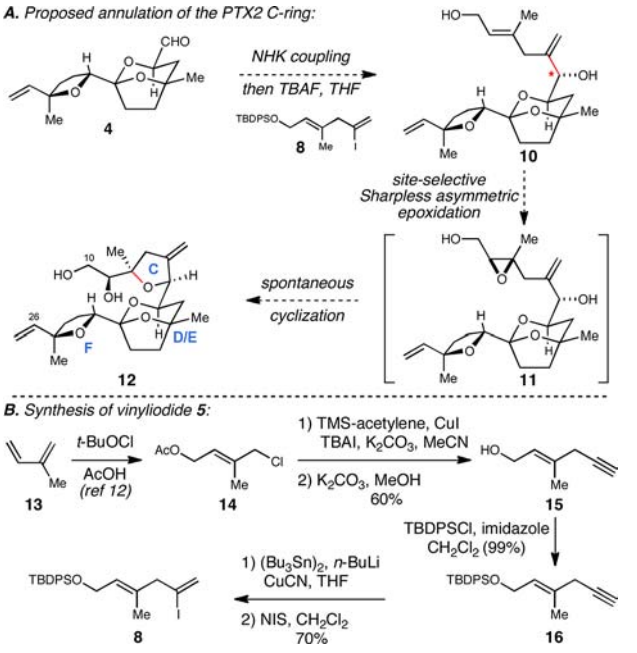


Figure 1. Introduction.

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,[10] we targeted construction of the PTX2 CDEF heterocyclic system by double asymmetric NHK coupling[11] between aldehyde **4**[9o] and vinyliodide **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,[12] and subsequent tranformation 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:

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



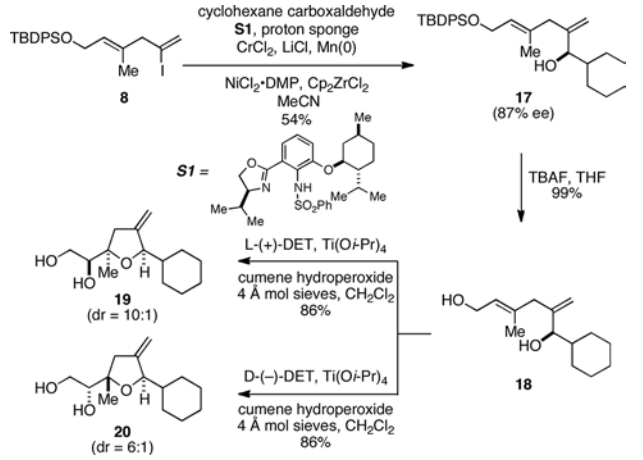
(1) silylation with TBDPSCl, (2) regioselective hydrostannylation,[14] and (3) iodination.

Next, to explore the basic steps of the annulation process on a model aldehyde, asymmetric NHK coupling[11] 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[15]/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 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.[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)

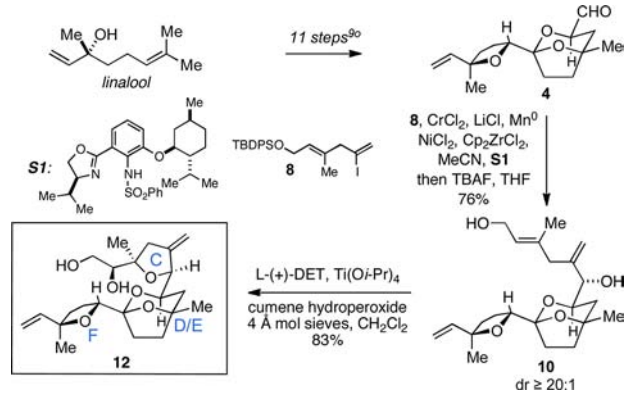
(10) Choi, H.; Demeke, D.; Kang, F.; Kishi, Y.; Nakajima, K.; Nowak, P.; Wan, Z.; Xie, C. *Pure Appl. Chem.* **2003**, *75*, 1–17.
(11) Guo, H.; Dong, C.; Kim, D.; Urabe, D.; Wang, J.; Kim, J. T.; Liu, X.; Sasaki, T.; Kishi, Y. *J. Am. Chem. Soc.* **2009**, *131*, 15387–15393.
(12) Bravo, F.; McDonald, F. E.; Neiwert, W. A.; Do, B.; Hardcastle, K. I. *Org. Lett.* **2003**, *5*, 2123–2126.
(13) Davies, K. A.; Abel, R. C.; Wulff, J. E. *J. Org. Chem.* **2009**, *74*, 3997–4000.
(14) Fuwa, H.; Nakajima, M.; Shi, J.; Takeda, Y.; Saito, T.; Sasaki, M. *Org. Lett.* **2011**, *13*, 1106–1109.
(15) Katsuki, T.; Martin, V. S. *Org. React.* **1996**, *48*, 1–299.
(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



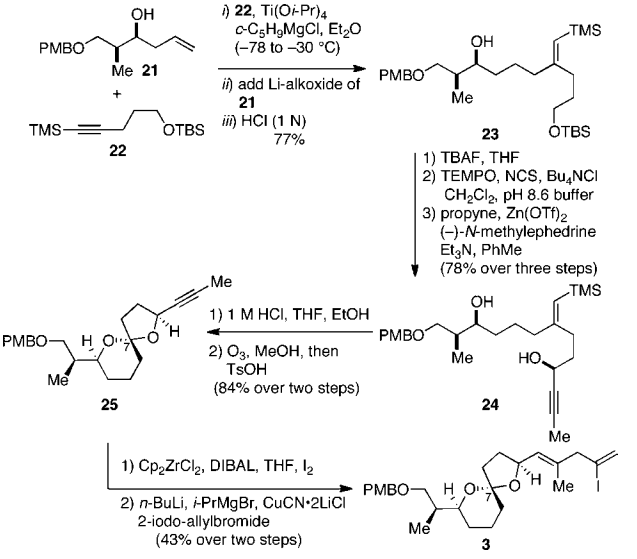
in 76% yield (after desilylation: TBAF, THF). Also, site-selective Sharpless asymmetric epoxidation and cyclization proved effective for advancing triene **10** to the tetracyclic target **12** in 83% yield.

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 spriroketal-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, Bu_4NCl, CH_2Cl_2, pH 8.6 buffer) and Carreira's asymmetric acetylide addition[18] [propyne, $Zn(OTf)_2$, (−)-*N*-methylephedrine, Et_3N, 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_3, MeOH, then Me_2S), 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 vinyliodide **3** was accomplished by regioselective hydrozirconation–iodination (Cp_2ZrCl_2, DIBAL, THF, then I_2) and coupling with 2-iodo-allylbromide (*n*-BuLi, *i*-PrMgBr, CuCN•2LiCl).[19]

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



As illustratred in Scheme 5, triple asymmetric[20] 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

(17) (a) Reichard, H. A.; Micalizio, G. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 1440–1443. (b) Canterbury, D. P.; Micalizio, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 7602–7604. (c) Reichard, H. A.; Micalizio, G. C. *Chem. Sci.* **2011**, *2*, 573–589.

(18) (a) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806–1807. (b) Sasaki, H.; Boyall, D.; Carreira, E. M. *Helv. Chim. Acta* **2001**, *84*, 964–971. (c) Boyall, D.; Frantz, D. E.; Carreira, E. M. *Org. Lett.* **2002**, *4*, 2605–2606.

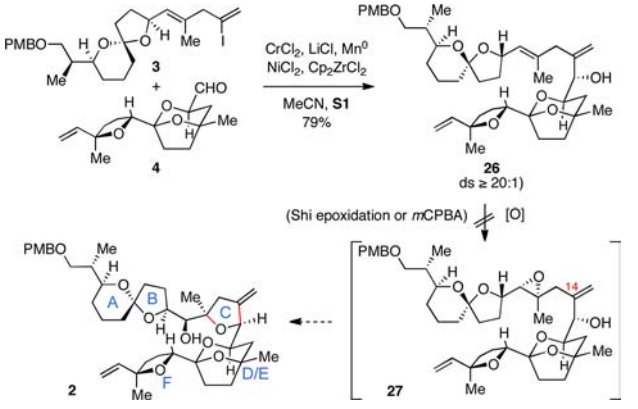
(19) For a review of synthetic applications of organochlorozirconocene complexes, see: (a) Wipf, P.; Jahn, H. *Tetrahderon* **1996**, *52*, 12853–12910. For the preparation of 2-iodo-allylbromide, see: (b) Kurosu, M.; Lin, M.; Kishi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 12248–12249. For a similar process for allylation of a vinyliodide, see: (c) Kitagawa, K.; Inoue, A.; Shinokubo, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 2481–2483.

(20) Duplantier, A. J.; Nantz, M. H.; Roberts, J. C.; Short, R. P.; Somfai, P.; Masamune, S. *Tetrahedron Lett.* **1989**, *30*, 7357–7360.

(21) (a) Wang, Z.; Tu, Y.; Frohn, M.; Zhang, J.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224–11235. (b) Wong, O. A.; Shi, Y. *Chem. Rev.* **2008**, *108*, 3958–3987. (c) Diffendal, J. M.; Danheiser, R. L. *Org. Synth.* 2009, *Coll. Vol. 11*, 183–188.

conditions for selective epoxidation of the C11−C12 trisubstituted alkene of **26**. Standard reaction conditions for Shi epoxidation[21] 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



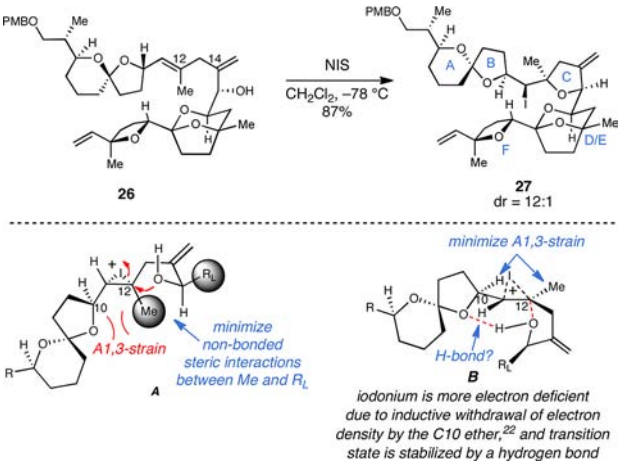
In an attempt to overcome the unexpected difficulty in site-selective oxidation of the triene **26**, we turned our attention to a substrate-controlled iodoetherification reaction to establish the 2,2,5-*cis* trisubstituted THF C-ring of PTX2. To our delight, treatment with *N*-iodosuccinimide in dichloromethane 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).[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]

(22) Houk, K. N.; Moses, S. R.; Wu, Y.; Rondan, N. G.; Jäger, V.; Schohe, R.; Fronczek, F. R. *J. Am. Chem. Soc.* **1984**, *106*, 3880–3882.

(23) Rychnovsky, S. D.; Bartlett, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 3963–3964.

(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).

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.