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Synthetic Studies Toward Pectenotoxin 2. Part I. Stereocontrolled Access to the $C_{10}-C_{22}$ Fragment

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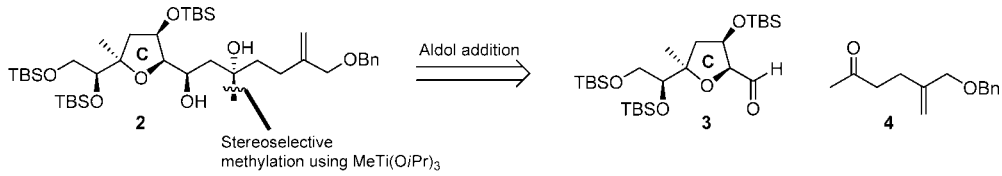
ABSTRACT



A highly stereocontrolled and efficient synthesis for a fully functionalized $C_{10}-C_{22}$ fragment of pectenotoxin 2 is described using a convergent sequence involving a stereoselective methylation of β-hydroxyketone as a key step.

In 1985, the Yasumoto group reported the isolation and characterization of a family of polyether macrolactones, the pectenotoxins (PTXs).[1] The pectenotoxin family has since grown to comprise over 20 structurally related compounds.[2] Originally isolated from scallops (*Patinopecten yessoensis*),[1] the actual producers of PTXs are the *Dinophysis* dinoflagellates, found in coastal areas worldwide.[3] PTXs are cytotoxic compounds that interact with the Actin cytoskeleton.[4] The scarcity of the compounds has hampered further studies into their biological activity and their roles in the marine ecosystems, and as such, access to synthetic PTXs would be immensely helpful.

PTX4 and PTX8 are the only members of the PTX family that have been produced synthetically.[5] The most toxic PTX2

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(5) For total synthesis of PTX4 and PTX8, 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. For other synthetic approaches, see: (c) Amano, S.; Fujiwara, K.; Murai, A. *Synlett* **1997**, 1300–1302. (d) Awakura, D.; Fujiwara, K.; Murai, A. *Synlett* **2000**, 1733–1736. (e) Micalizio, G. C.; Roush, W. R. *Org. Lett.* **2001**, *3*, 1949–1952. (f) Paquette, L. A.; Peng, X.; Bondar, D. *Org. Lett.* **2002**, *4*, 937–940. (g) Peng, X.; Bondar, D.; Paquette, L. A. *Tetrahedron* **2004**, *60*, 9589–9598. (h) Bondar, D.; Liu, J.; Müller, T.; Paquette, L. A. *Org. Lett.* **2005**, *7*, 1813–1816. (i) Halim, R.; Brimble, M. A.; Merten, J. *Org. Lett.* **2005**, *7*, 2659–2662. (j) Fujiwara, K.; Kobayashi, M.; Yamamoto, F.; Aki, Y.; Kawamura, M.; Awakura, D.; Amano, S.; Okano, A.; Murai, A.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2005**, *46*, 5067–5069. (k) Halim, R.; Brimble, M. A.; Merten, J. *Org. Biomol. Chem.* **2006**, *4*, 1387–1399. (l) 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. (m) Kolakowski, R. V.; Williams, L. J. *Tetrahedron Lett.* **2007**, *48*, 4761–4764. (n) O'Connor, P. D.; Knight, C. K.; Friedrich, D.; Peng, X.; Paquette, L. A. *J. Org. Chem.* **2007**, *72*, 1747–1754. (o) Vellucci, D.; Rychnovsky, S. D. *Org. Lett.* **2007**, *9*, 711–714. (p) Lotesta, S. D.; Hou, Y.; Williams, L. J. *Org. Lett.* **2007**, *9*, 869–872.

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has not yet yielded to synthetic efforts, presumably because both PTX2 and PTX1 include a relatively labile nonanomeric spiroketal that readily isomerizes under acidic conditions to more stable isomers. We have already reported the synthesis of the nonanomeric spiroketal unit via kinetic spiroketalization.[6] More recently, the Rychnovsky group has also synthesized the nonanomeric spiroketal of PTX2 using a reductive cyclization approach.[5o]

A successful route to the most interesting PTX congeners, PTX2 and PTX1, must therefore be compatible with the acid-labile nonanomeric spiroketal unit. More specifically, the presence of another ketal group, embedded in the DE ring system in the PTXs, is a cause for concern. In this communication, we present a highly stereocontrolled route to the $C_{10}-C_{22}$ acyclic precursor. The following communication describes the synthesis of the CDE and the CDEF ring systems of PTX2 and also addresses the issue of compatibility of the ketal forming event with the nonanomeric spiroketal unit.

Our approach for the synthesis of the $C_{10}-C_{22}$ fragment, constituting the carbon chain of the CDE ring system, is based on convergent addition of aldehyde **3** and ketone **4** (Figure 1). Among the possible strategies for the construction

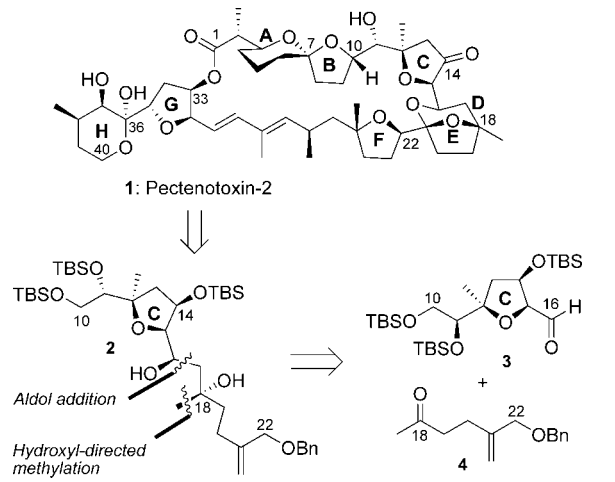


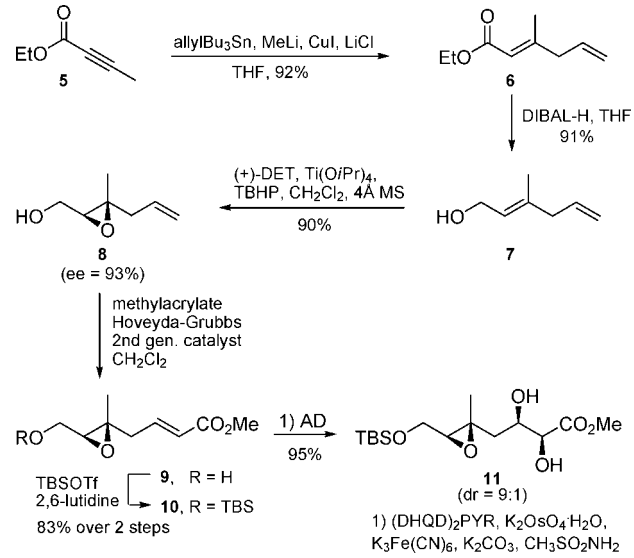
Figure 1. Retrosynthetic analysis of the $C_{10}-C_{22}$ fragment.

of the C_{18} quaternary center, a hydroxyl-directed methylation of the C_{18} ketone with organometallic reagents was selected. A key feature of this strategy was that after a mild ozonolytic cleavage of the C_{21} masking olefin the ketalization to form the DE ring would take place under very mild conditions, without the need to unmask any protecting groups. Potentially, these mild conditions would also tolerate the presence of the nonanomeric AB spiroketal system in more advanced intermediates. Although hydroxyl-directed alkylations have rarely been used in total synthesis, the literature precedents were nevertheless encouraging.[7]

The synthesis began with an addition of allylcopper reagent to commercially available tetrolate **5** to provide the desired

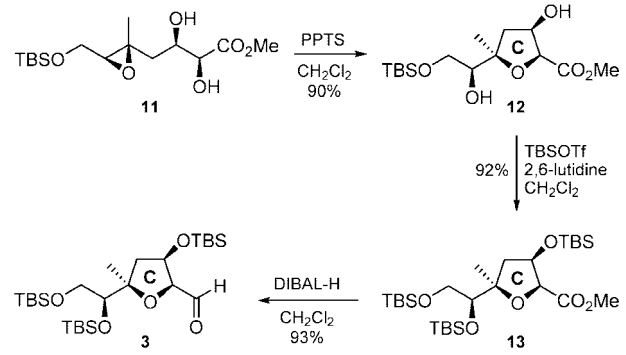
(6) Pihko, P. M.; Aho, J. E. *Org. Lett.* **2004**, *6*, 3849–3852.

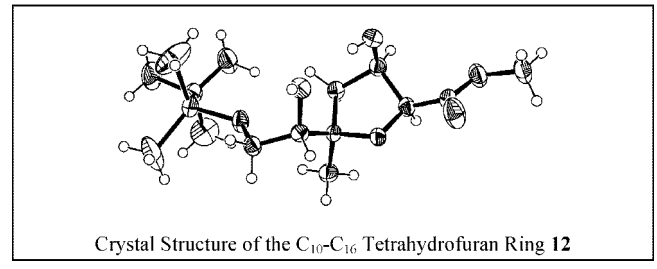
Scheme 1. Synthesis of the $C_{10}-C_{16}$ Fragment



(*E*)-isomer **6** in 92% yield (Scheme 1).[8] Reduction with DIBAL-H afforded allylic alcohol **7** which under Katsuki–Sharpless asymmetric epoxidation conditions furnished

Scheme 2. Synthesis of Aldehyde **3**



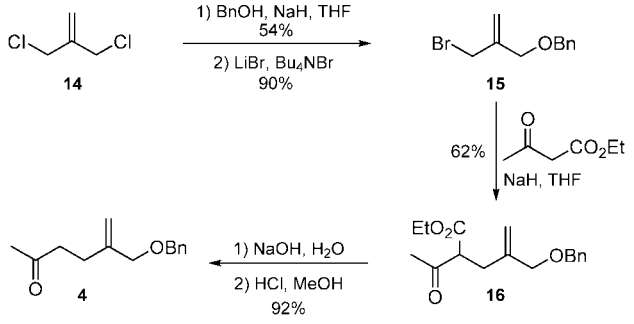

Crystal Structure of the C_{10}-C_{16} Tetrahydrofuran Ring **12**

epoxide **8** in 90% yield and 93% ee. The terminal olefin was reacted with methylacrylate in the presence of Hoveyda–Grubbs second-generation catalyst followed by TBS protection to afford ester **10** in 83% yield over two steps. Asymmetric dihydroxylation with the Sharpless' ligand $(DHQD)_2PYR$ was used to introduce the remaining two stereocenters, giving the desired diol **11** in excellent (95%) yield and 9:1 diastereoselectivity.

Exposure of the diol mixture to catalytic PPTS resulted in cyclization to give the desired tetrahydrofuran ring **12** (Scheme 2). At this stage, the diastereomers could be easily separated by chromatography to give crystalline **12** in 90% yield as a single diastereomer. X-ray crystallographic analysis confirmed the stereochemistry of the product (Scheme 2). Finally, protection of the secondary hydroxyl groups, followed by DIBAL-H reduction, furnished aldehyde **3** in 46% overall yield for 9 steps.[9]

The synthesis of the aldol partner **4** began with commercially available methallyl dichloride **14**, which was selectively monoprotected as benzyl ether (Scheme 3). After

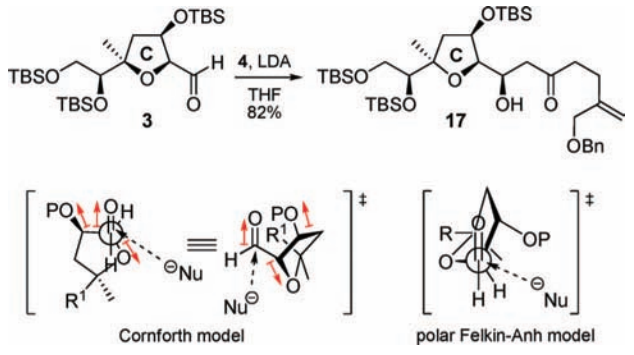
Scheme 3. Synthesis of Ketone **4**



conversion into bromide **15**, monoalkylation of ethyl acetoacetate afforded compound **16** in 62% yield. Finally, ester hydrolysis followed by decarboxylation furnished ketone **4** in 92% yield.

The aldol addition of aldehyde **3** and ketone **4** proceeded nicely to give a single *anti* product **17** in 82% yield (Scheme 4).[10] The *anti* selectivity can be explained by a modified

Scheme 4. Cornforth-Selective Aldol Union of **3** and **4**



Cornforth[11] transition state model, although the polar Felkin−Ahn[12] model also predicts the same stereochemical outcome (Scheme 4). Similar selectivities, albeit with reduced yields, were obtained by using a related enolsilane (TMS/BF_3•OEt_2).[13]

Several different reagents were explored for the methylation of β-hydroxyketone **17** at C_{18}. On the basis of the precedent by Fujisawa,[7a] titanium reagents were considered as prime candidates to achieve the desired *anti* selectivity via internal delivery of the methyl group (Table 1).[14] Pleasingly, our initial experiment at 0.25 mmol scale with MeTi(O*i*Pr)$_3$ gave the desired *anti* diol product **2**[10] in 8:1 diastereoselectivity. However, considerable difficulties were encountered in reproducing this result. Experiments to screen different conditions for this key transformation are summarized in Table 1.[15]

In comparison with methyltitanium reagents, Mg and Zn reagents gave inferior selectivity (entries 2 and 3). Surprisingly, predistilled MeTi(O*i*Pr)$_3$[16] turned out to be very unreactive toward **17**, even with 15 equiv of the reagent (entry 4). Under comparable conditions, more Lewis acidic reagents, $MeTiCl_3$ or MeTi(O*i*Pr)$_2$Cl (entries 5 and 6), did not help, and neither did the use of more reactive Me_2Ti(O*i*Pr)$_2$ or the less-hindered MeTi(OMe)$_3$ (entries 7−9). Addition of excess Ti(O*i*Pr)$_4$[17] did not afford any improvement in selectivity or reproducibility (entry 10). Ultimately, the best *reproducible* selectivities (9:1) and yields (91%) were obtained using an excess of the in situ prepared MeTi(O*i*Pr)$_3$ at −78 °C followed by quick warming to 0 °C (entry 11).

In summary, we have developed an efficient and highly stereocontrolled synthesis for the C_{10}−C_{22} fragment of PTX2 with the correct stereochemistry. The following communica-

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(8) (a) Corey, E. J.; Kim, C. U.; Chen, R. H. K.; Takeda, M. *J. Am. Chem. Soc.* **1972**, *94*, 4395–4396. (b) Lipshutz, B. H.; Ellsworth, E. L.; Dimock, S. H.; Smith, R. A. J. *J. Am. Chem. Soc.* **1990**, *112*, 4404–4410.

(9) The entire synthetic sequence was successfully scaled up to ca. a 20 g scale.

(10) The stereochemistry of the aldol and the methyltitanation steps was established by extensive NOE studies of the CDE and CDEF ring systems. See the following paper in this issue: Helmboldt, H.; Aho, J. E.; Pihko, P. M. *Org. Lett.* **2008**, *10*, 4183−4185.

(11) (a) Cornforth, J. W.; Cornforth, R. H.; Mathew, K. K. *J. Chem. Soc.* **1959**, *11*, 2–127. For excellent discussions and predictions in both cyclic and acyclic systems, see: (b) Evans, D. A.; Cee, V. J.; Siska, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 9433–9441, and refs therein. The high level of diastereoselection observed suggests that the α,β-syn relationship of the oxygen substituents in **3** represents a stereochemically reinforcing case. For a related highly selective aldol bond construction, see: (c) Anderson, O. P.; Barrett, A. G. M.; Edmunds, J. J.; Hachiya, S.-I.; Hendrix, J. A.; Horita, K.; Malecha, J. W.; Parkinson, C. J.; VanSickle, A. *Can. J. Chem.* **2001**, *79*, 1562–1592.

(12) (a) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *9*, 2199–2204. (b) Chérest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, *9*, 2205–2208. (c) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim* **1977**, *1*, 61–70. (d) Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145–162.

(13) See Supporting Information for further details.

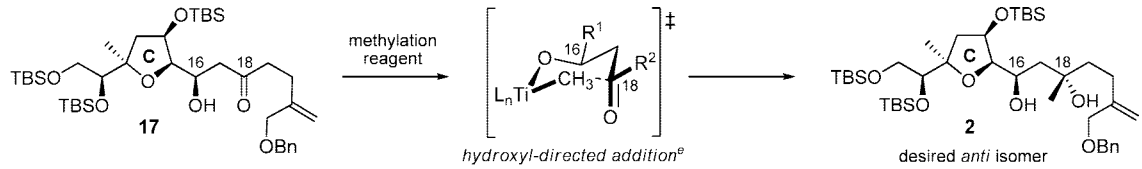
(14) There are two possible modes to achieve 1,3-induction in hydroxyl-directed additions: the nucleophile is delivered either externally (from an external reagent) or internally (directed addition): (a) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560–3578. A chelation-controlled transition state model has also been suggested. (b) Reetz, M. T.; Jung, A. *J. Am. Chem. Soc.* **1983**, *105*, 4833–4835. For a review, see: (c) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191–1223.

(15) For further details, including screens for different solvents and additives, see Supporting Information.

(16) Reetz, M. T.; Westermann, J.; Steinbach, R.; Wenderoth, B.; Peter, R.; Ostarek, R.; Maus, S. *Chem. Ber.* **1985**, *118*, 1421–1440.

(17) Excess Ti(O*i*Pr)$_4$ should facilitate the removal of the product from the metal center and assist in the formation of an active complex: Wu, K.-H.; Gau, H.-M. *Organometallics* **2004**, *23*, 580–588.

Table 1. *anti*-Selective Addition of Methyl Nucleophiles with Different Reagents



entry	methylation reagent[a]	equiv	solvent	temperature [°C]	time [min at −78/0 °C]	dr[b]	conversion[b]
1	$MeTi(OiPr)_3$	5	Et_2O	−78 to0	10/10	8/1 - 2/3	100
2	$MeLi/ZnBr_2$	4	CH_2Cl_2	−78	240	3/2	100
3	MeMgBr	1	Et_2O	−78	15	2/1	100
4	$MeTi(OiPr)_3$[c]	15	Et_2O	−78 to0	10/10	4/1	80
5	$MeTiCl_3$	15	Et_2O	−78 to0	10/10	1/1	20
6	$MeTi(OiPr)_2Cl$	15	Et_2O	−78 to0	10/10	3/1	100
7	$Me_2Ti(OiPr)_2$	15	Et_2O	−78 to0	10/10	6/1	100
8	$Me_2Ti(OMe)_2$	15	Et_2O	−78 to0	10/10	2/1	100
9	$MeTi(OMe)_3$	15	Et_2O	−78 to0	10/10	4/1	100
10	$MeTi(OiPr)_3$[d]	15	Et_2O	−78 to0	10/10	4/1	100
11	**$MeTi(OiPr)_3$**	**15**	**Et_2O**	**−78to0**	**10/10**	**9/1**	**100**

[a] Reagents were prepered in situ. [b] Determined by ^1H NMR from the crude reaction mixture. [c] $MeTi(OiPr)_3$ was distilled prior to use. [d] Excess $Ti(OiPr)_4$ (15 equiv) was used. [e] See ref 14a.

tion describes the use of this strategy for the assembly of the CDE and the CDEF ring systems.

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Supporting Information Available: Experimental procedures, characterization data, and copies of NMR spectra (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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