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A Novel Approach to the CDE Ring System of Pectenotoxin-4 Triggered by $VO(acac)_2$-Induced Epoxy-Acetalization

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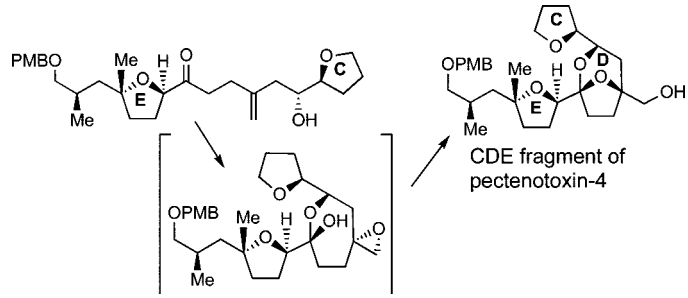
ABSTRACT



A novel approach to the CDE fragment of pectenotoxin-4 is described wherein the bicyclic acetal is constructed via a cascade cyclization induced by $VO(acac)_2$ epoxidation of a homoallylic alcohol.

The pectenotoxins (PTXs) are a family of 20+ polyether macrolactones which were first isolated in 1985 by Yasumoto et al.[1] and named after the Japanese scallop (*Patinopecten yessoensis*) from which they were extracted. These toxins have since been isolated from microalgae and bivalve molluscs located worldwide.[2] PTX-2 is a cytotoxic agent which depolymerizes actin filaments,[3] and an X-ray structure of PTX-2 bound to actin provides valuable insight into the pathway of actin disassembly by the PTX family.[4] PTX-2 also initiates cell death in p-53-deficient tumors, and it has been proposed that PTX-2 results in the depolymerization of actin, followed by the activation of cell death regulating proteins Bim and Bax.[5]

Over the past decade, many groups have been attracted to the synthetic challenge posed by the PTX family. In spite of this, only one total synthesis of PTX-4 and PTX-8 has been reported.[6] The considerable synthetic effort directed toward the various fragments[7] of the PTXs have mainly focused on construction of the spiroacetal ring system,[7a−f] the FG rings,[7g−k] and the substituted tetrahydrofuran C[7l−n] and E[7n,o] rings. The limited methodology reported for assembly of the bicyclic acetal containing CD unit of PTX-2 has focused on intramolecular ketalization of a ketone generated via ozonolysis of an olefin[7q] and intramolecular cyclization of a keto diol,[7p] while Paquette et al.[7k] reported their thwarted attempts to effect construction of the bicyclic D ring via transannular cyclization.

(1) Yasumoto, T.; Murata, M.; Oshima, Y.; Sano, M.; Matsumoto, G. K.; Clardy, J. *Tetrahedron* **1985**, *41*, 1019.

(2) (a) Sasaki, K.; Wright, J. L. C.; Yasumoto, T. *J. Org. Chem.* **1998**, *63*, 2475. (b) Miles, C. O.; Wilkins, A. L.; Hawkes, A. D.; Jensen, D. J.; Selwood, A. I.; Beuzenberg, V.; MacKenzie, A. L.; Cooney, J. M.; Holland, P. T. *Toxicon* **2006**, *48*, 152, and references are cited therein.

(3) (a) Spector, I.; Braet, F.; Schochet, N. R.; Bubb, M. R. *Microsc. Res. Tech.* **1999**, *47*, 18. (b) Leira, F.; Cabadon, A. G.; Vieytes, M. R.; Roman, Y.; Alfonso, A.; Botana, L. M.; Yasumoto, T.; Malaguti, C.; Rossini, G. P. *Biochem. Pharmacol.* **2002**, *63*, 1979. (c) Miles, C. O. *Phycotoxins* **2007**, 159.

(4) Allingham, J. S.; Miles, C. O.; Rayment, I. *J. Mol. Biol.* **2007**, *371*, 959.

(5) Chae, H.-D.; Choi, T.-S.; Kim, B.-M.; Jung, J. H.; Bang, Y.-J.; Shin, D. Y. *Oncogene* **2005**, *24*, 4813.

(6) (a) Evans, D. A.; Rajapakse, H. A.; Stenkamp, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 4569. (b) Evans, D. A.; Rajapakse, H. A.; Chiu, A.; Stenkamp, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 4573.

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Based on the retrosynthetic strategy outlined (Figure 1), our synthetic efforts toward PTX-4 (**1**) have resulted in the

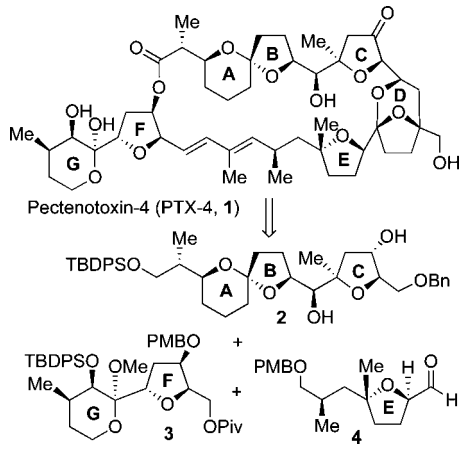


Figure 1. Retrosynthetic analysis of PTX-4 (**1**).

successful synthesis of the ABC rings[7d] **2** and the FG rings[7r] **3** prompting us to next examine methodology for construction of the highly substituted E ring and the bicyclic acetal D rings. We herein report our synthesis of the E ring fragment **4** of PTX-4 (**1**) and subsequent novel $VO(acac)_2$ epoxide induced tandem cyclization of a homoallylic alcohol to install the bicyclic D ring acetal onto the E ring fragment. A simple tetrahydrofuran C ring was used as a model for our ABC tricyclic fragment. The highly functionalized tetracycle **5** is constructed by epoxidation of homoallylic alcohol **6**, which in turn is assembled via the union of E ring aldehyde **4** with sulfone **7** (Figure 2).

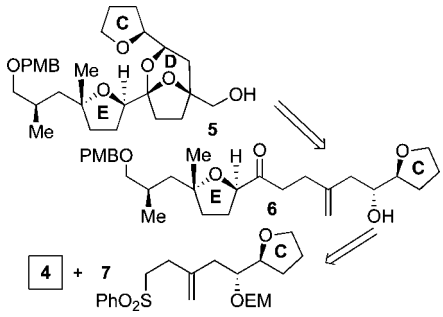
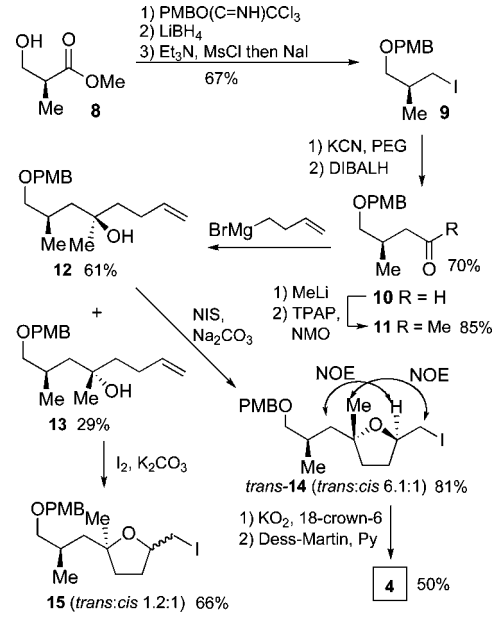


Figure 2. Synthetic strategy for the construction of tetracycle **5**.

Our plans initially focused on the synthesis of the E ring fragment (Scheme 1) using an iodoetherification to construct the *trans*-trisubstituted tetrahydrofuran ring. Thus, our synthesis of E ring aldehyde **4** started from Roche ester **8**, which was then protected, reduced, and substituted via a mesylate to give iodide **9**. Extension of the carbon chain via cyanide displacement and subsequent DIBALH reduction afforded aldehyde **10**. Methylation of **10** followed by oxidation with

Scheme 1. Synthesis of the E Ring Fragment **4**



TPAP and NMO provided methyl ketone **11**. Elongation of the carbon skeleton via addition of a homoallyl Grignard reagent prior to installation of the tertiary methyl group proceeded with low stereoselectivity. Gratifyingly, changing the order of introduction of the two alkyl groups afforded some improvement in that addition of the Grignard reagent derived from 4-bromo-1-butene to methyl ketone **11** favored the desired tertiary alcohol **12** over the undesired alcohol **13** (**12**:**13**; 2.1:1).[8]

Subjecting the major alcohol **12** to iodoetherification[9] readily provided the requisite *trans*-tetrahydrofuran **14** in excellent yield with 6.1:1 *trans*/*cis* selectivity. Interestingly, iodoetherification of the undesired alcohol **13** proceeded indiscriminately, affording both *cis* and *trans* ethers **15** in nearly equal amounts. Confirmation of the relative stereochemistry in *trans*-tetrahydrofuran **14** was achieved using

(7) (a) Pihko, P. M.; Aho, J. E. *Org. Lett.* **2004**, *6*, 3849. (b) Bondar, D.; Liu, J.; Muller, T.; Paquette, L. A. *Org. Lett.* **2005**, *7*, 1813. (c) Halim, R.; Brimble, M. A.; Merten, J. *Org. Lett.* **2005**, *7*, 2659. (d) Halim, R.; Brimble, M. A.; Merten, J. *Org. Biomol. Chem.* **2006**, *4*, 1387. (e) Vellucci, D.; Rychnovsky, S. D. *Org. Lett.* **2007**, *9*, 711. (f) Lotesta, S. D.; Hou, Y.; Williams, L. J. *Org. Lett.* **2007**, *9*, 869. (g) Amano, S.; Fujiwara, K.; Murai, A. *Synlett* **1997**, 1300. (h) Paquette, L. A.; Peng, X.; Bondar, D. *Org. Lett.* **2002**, *4*, 937. (i) Peng, X.; Bondar, D.; Paquette, L. A. *Tetrahedron* **2004**, *60*, 9589. (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. (k) O'Connor, P. D.; Knight, C. K.; Friedrich, D.; Peng, X.; Paquette, L. A. *J. Org. Chem.* **2007**, *72*, 1747. (l) Awakura, D.; Fujiwara, K.; Murai, A. *Synlett* **2000**, 1733. (m) Aho, J. E.; Salomäki, E.; Rissansen, K.; Pihko, P. M. *Org. Lett.* **2008**, *10*, 4179. (n) 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. (o) Kolakowski, R. V.; Williams, L. J. *Tetrahedron Lett.* **2007**, *48*, 4761. (p) Micalizio, G. C.; Roush, W. R. *Org. Lett.* **2001**, *3*, 1949. (q) Helmboldt, H.; Aho, J. E.; Pihko, P. M. *Org. Lett.* **2008**, *10*, 4183. (r) Heapy, A.; Wagner, T. M.; Brimble, M. A. *Synlett* **2007**, 2359.

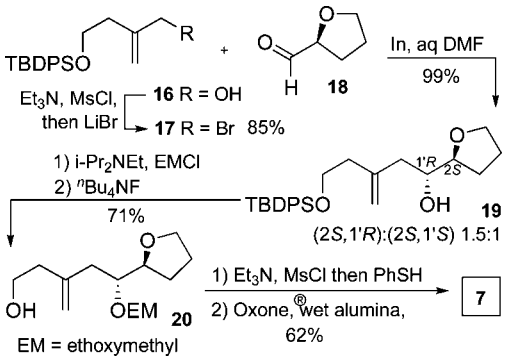
(8) Alcohols **12** and **13** were converted to tetrahydrofuran derivatives, which were then subjected to NOE experiments.

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

NOE analysis (Scheme 1). Finally, employment of potassium superoxide was required to convert the unreactive iodide **14** to an alcohol which then underwent oxidation using Dess−Martin periodinane to afford the unstable aldehyde **4**.

With E ring aldehyde **4** in hand, efforts next turned to the union of **4** with sulfone **7** in which the tetrahydrofuran ring served as a model for the ABC spiroacetal-containing fragment of PTX-4 that we have previously prepared.[7d] Accordingly, addition of allyl metal reagents derived from allylic alcohol **16**[10] (via allyl bromide **17)** to (*S*)-tetrahydrofuran aldehyde **18** was investigated (Scheme 2). (*S*)-Aldehyde

Scheme 2. Synthesis of the Sulfone **7**

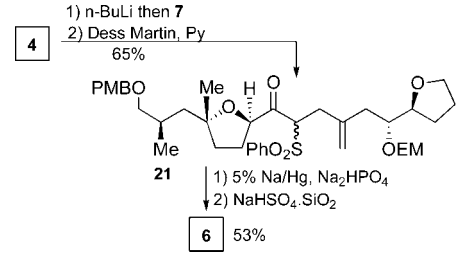


18[11] is prepared via oxidation of the (*S*)-alcohol[12] that is derived from the commercial (*S*)-acid.

Numerous methods to append the allylic fragment to aldehyde **18** were evaluated in an effort to maximize the formation of the desired Felkin−Anh product **19**. Use of organozinc reagents and organolithium reagents met with little success, while Nozaki−Hiyama−Kishi organochromium technology proceeded in moderate yield. After considerable experimentation, the formation of an allylindium species provided the desired homoallylic alcohol **19** in near-quantitative yield with modest selectivity. Fortunately, conversion of alcohol **19** to an ethoxymethyl ether (EM) faciliated separation of the diastereomeric alcohols **20** after removal of the TBDPS group. Alcohol **20** underwent mesylation then treatment with excess triethylamine and thiophenol to afford a phenyl sulfide that was oxidized to sulfone **7** using Oxone and wet alumina. In order to achieve reproducible results, it was imperative that approximately 2 g of wet alumina was used independent of the scale of the reaction. Notably, scaling down the quantity of alumina proportionate to the amount of Oxone used, resulted in the formation of undesired side products (Scheme 2).

Having assembled sulfone **7** and E ring aldehyde **4**, their union proceeded smoothly. Treatment of sulfone **7** with ^{n}BuLi at −78 °C in THF followed by addition of aldehyde **4** afforded an equal mixture of the four diastereomeric hydroxy sulfones in 91% yield that were immediately oxidized with Dess−Martin periodinane to afford a 1:1 mixture of the two diastereomeric keto sulfones **21**. Gratifyingly, careful removal of the phenylsulfonyl group using 5% sodium amalgam at −35 °C and deprotection of the EM group using catalytic $NaHSO_4$•SiO_2 in CH_2Cl_2 proceeded cleanly affording secondary alcohol **6** in 75% yield (Scheme 3).

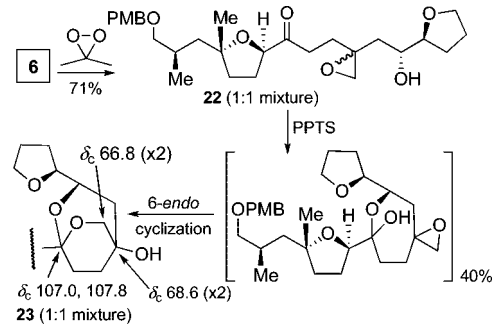
Scheme 3. Union of Sulfone **7** with Aldehyde **4** and Synthesis of Alkene **6**



With the entire carbon backbone for the CDE fragment fully assembled, it was envisaged that epoxidation of alkene **6** would induce facile hemiacetalzation with subsequent attack of the hemiacetal on the epoxide taking place to furnish the desired bicyclic acetal core of the CDE fragment of PTX-4 (**5**). Our aim was to explore the feasibility of the proposed tandem cyclization in the first instance addressing the stereochemical issues associated with the epoxidation step at a later stage.

Epoxidation of alkene **6** using buffered *m*-CPBA led to substantial decomposition whereas use of dimethyldioxirane[13] furnished a 1:1 inseparable mixture of epoxides **22** in 71% yield (Scheme 4). Epoxides **22** were then treated

Scheme 4. Acid-Catalyzed Cyclization of Epoxide **22**



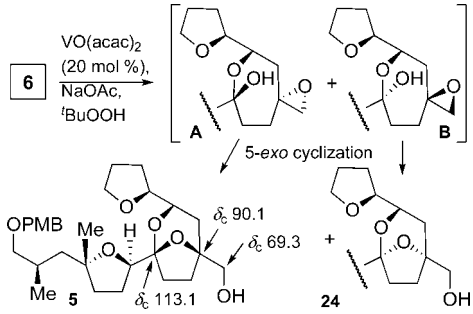
with catalytic pyridinium *p*-toluenesulfonate in MeOH for 20 min. Purification by semipreparative HPLC afforded alcohol **23** as a 1:1 mixture of diastereomers in 40% yield.

(10) Weigand, S.; Bruckner, R. *Synthesis* **1996**, 475.
(11) Belanger, P. C.; Williams, H. W. R. *Can. J. Chem.* **1983**, *61*, 1383.
(12) Alajarin, R.; Alvarezbuilla, J.; Vaquero, J. J.; Sunkel, C.; Decasajuana, M. F.; Statkow, P. R.; Sanzaparicio, J. *Tetrahedron: Asymmetry* **1993**, *4*, 617.
(13) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187.

The ^{13}C NMR spectrum of the purified product revealed a mixture of two diastereomers; however, it was apparent that the cascade type cyclization had not proceeded in the anticipated fashion. Diastereomeric quaternary carbons at δ_C 68.6 ppm suggested nucleophilic attack on the terminal carbon of the epoxide had taken place to furnish quaternary alcohol **23** (Scheme 4).

Attempts to effect installation of the initial epoxide functionality in a diastereoselective fashion met with little success. Epoxidation of alkene **6** using the Shi fructose-derived dioxirane[14] afforded a complex mixture. However, substrate-directed vanadium-catalyzed epoxidation[15] of homoallylic alcohol **6** (Scheme 5) afforded a mixture of two compounds with characteristic quaternary carbons in the ^{13}C spectrum suggesting the presence of the desired cyclized product **5**. Flash chromatography failed to effect clean separation of the mixture hence the crude product mixture was subjected to semipreparative HPLC. The first compound that eluted was a cleavage product with only resonances attributed to the elaborated E ring fragment being observed. It was unclear whether degradation had occurred during the chromatography step or during the epoxidation.

Scheme 5. $VO(acac)_2$-Induced Epoxy-Acetalization of Alkene **6**



NMR analysis of the major fraction revealed the formation of the desired CDE fragment **5** (13% yield after HPLC) as a single isomer (Scheme 5). Notably, a quaternary carbon at δ_C 113.1 ppm and a CH_2OH resonance at δ_C 69.3 ppm established formation of the desired bicyclic acetal. The ^{13}C NMR data were also in agreement with similar data reported for PTX-4.[7]

Irrespective of the level of stereoinduction resulting from the initial substrate-directed epoxidation of alkene **6**, the steric strain experienced in the ensuing cyclization necessitates that only two possible isomers of the CDE fragment namely, **5** and **24**, can be formed proceeding via hemiacetal intermediates **A** and **B** respectively (Scheme 5). Interestingly, 600 MHz NMR analysis of the crude product obtained before semipreparative HPLC indicated the presence of two diastereomeric CDE fragments. One possible explanation is that initial formation of the two CDE fragments **5** and **24** takes place; however, one diastereomer is predisposed to facile degradation upon purification by HPLC.

The completion of the structurally complex CDE fragment **5** of the PTX-4 (1) is reported herein. An efficient synthesis of the 2,5-*trans* E ring fragment **4** together with a facile method to append the model C ring aldehyde **18** to an allylic D ring fragment **17** is also described. Importantly, a tandem cascade cyclization initiated by vanadyl acetylacetonate epoxidation of a homoallylic alcohol furnished a novel method to install the bicyclic acetal motif in the D ring.

Supporting Information Available: Experimental procedures and ^{13}C NMR data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488.
(15) Mihelich, E. D.; Daniels, K.; Eickhoff, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 7690.