ORGANIC LETTERS

2007
Vol. 9, No. 5
869−872

A Spirodiepoxide-Based Strategy to the A–B Ring System of Pectenotoxin 4

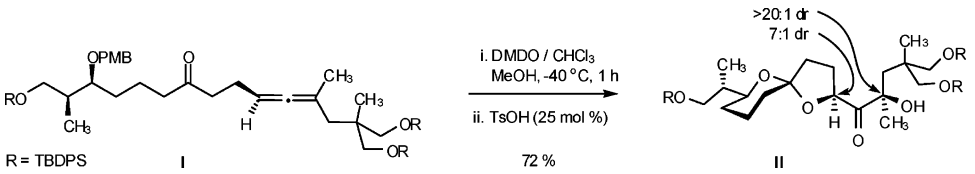
Stephen D. Lotesta, Yongquan Hou, and Lawrence J. Williams*

Department of Chemistry and Chemical Biology, Rutgers, The State University of New Jersey, Piscataway, New Jersey 08854

ljw@rutchem.rutgers.edu

Received December 20, 2006

ABSTRACT



A synthesis of a pectenotoxin 4 C1–C15 segment is reported. Suitable C1–C7 and C8–C15 segments were prepared, coupled, converted to I and the C3-hydroxy variant, and then cyclized. Key findings include the stereoselective conversion of the allene to the corresponding spirodiepoxide, oxidative cleavage of the *p*-methoxybenzyl ether, and cyclization of the spirodiepoxide to spiroketal II.

Here we report studies that culminated in the preparation of a C1−C15 segment of pectenotoxin 4 (PTX-4) using the spirodiepoxide (SDE) functional group. Nucleophilic addition to SDEs gives vicinal triads composed of hydroxyl, ketone, and a syn-substituted substituent (e.g., **6**→**7**, Figure 1B).[1] Although addition of carbon nucleophiles to SDEs would give densely functionalized α-hydroxy ketone motifs related to polyketides (e.g., erythromycin[1,2]), intramolecular addition of oxygen nucleophiles would give highly functionalized cyclic ethers and related ring systems present in a myriad of biomedically relevant substances, including the pectenotoxin class of natural products.[3]

The pectenotoxins (PTXs) have recently been the focus of intense research,[4] and one total synthesis has appeared.[5,6] PTX-4 (Figure 1A) is a 34-membered macrolide that houses seven oxygen-containing ring systems and 19 stereocenters. This target represents a challenging problem to synthesis. In principle, SDEs can provide access to the three tetrahydrofurans of PTX-4 flanked by oxygenated substituents and thereby facilitate the synthesis of this and related targets.

Among the potential strategies for accessing the C1−C15 portion of PTX-4, we were intrigued by the possibility of forming the A−B spiroketal ring system by way of an intramolecular ketone addition to a SDE followed by trapping the oxocarbenium ion with the resident alcohol (**2**→**4**→**7**, Figure 1B). Alternatively, the A−B spiroketal could form by lactol-initiated SDE opening (**2**→**5**→**7**).[7] The stereochemical outcome of each potential pathway notwithstanding, for this study we were aware that isomerization to the more

(1) (a) Katukojvala, S.; Barlett, K. N.; Lotesta, S. D.; Williams, L. J. *J. Am. Chem. Soc*. **2004**, *126*, 15348 and references cited therein. (b) Ghosh, P.; Lotesta, S. D.; Williams, L. J. *J. Am. Chem. Soc*., in press. (c) Lotesta, S. D.; Kiren, S. K.; Sauers, R. R.; Williams, L. J., submitted.

(2) (a) Cane, D. E.; Walsh, C. T.; Khosla, C. *Science* **1998**, *282*, 63. Katz, L. *Chem. Rev*. **1997**, *97*, 2557. (b) Aldridge, D. C.; Turner, W. B. *J. Antibiot.* **1969**, *22*, 170. (c) Achenbach, H.; Muehlenfeld, A.; Fauth, U.; Zaehner, H. *Tetrahedron Lett.* **1985**, *26*, 6167. (d) Kellner, M.; Wolf, G.; Lee, Y. S.; Hansske, F.; Konetschny-Rapp, S.; Pessara, U.; Scheuer, W.; Stockinger, H. *J. Antibiot.* **1993**, *46*, 1334. (e) Rinehart, K. L., Jr.; Martin, P. K.; Coverdale, C. E. *J. Am. Chem. Soc*. **1966**, *88*, 3149.

(3) (a) Friedrich, D.; Paquette, L. *J. Nat. Prod*. **2002**, *65*, 126. (b) Sheu, J.; Wang, G.; Duh, C.; Soong, K. *J. Nat. Prod.* **2003**, *66*, 662. (c) Sakabe, N.; Goto, T.; Hirata, Y. *Tetrahedron* **1977**, *33*, 3077. (d) Badder, A.; Garre, C. *Corresp.−Bl. Schweiz. Aerzte* **1887**, *17*, 385. 1232. (e) Reategui, R. F.; Gloer, J. B.; Campbell, J.; Shearer, C. A. *J. Nat. Prod.* **2005**, *68*, 701. (f) Sasaki, K.; Wright, J. L. C.; Yasumoto, T. *J. Org. Chem.* **1998**, *63*, 2475. (g) Yasumoto, T.; Murata, M.; Oshima, Y.; Sano, M.; Matsumoto, G. K.; Clardy, J. *Tetrahedron* **1985**, *41*, 1019.

(4) For lead references, see: (a) Halim, R.; Brimble, M. A.; Merten, J. *Org. Lett.* **2005**, *7*, 2659. (b) Bondar, D.; Liu, J.; Muller, T.; Paquette, L. A. *Org. Lett.* **2005**, *7*, 1813. (c) Peng, X.; Bondar, D.; Paquette, L. A. *Tetrahedron* **2004**, *60*, 9589. (d) Paquette, L. A.; Peng, X.; Bondar, D. *Org. Lett.* **2002**, *4*, 937. (e) Micalizio, G. C.; Roush, W. R. *Org. Lett.* **2001**, *3*, 1949. (f) Amano, S.; Fujiwara, K.; Murai, A. *Syn. Lett*. **1997**, 1300.

(5) PTX-4: (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.

(6) Natural PTX-4 can be converted into other PTXs (e.g., PTX-8). See: ref 5b and references therein.

(7) Crandall, J. K.; Rambo, E. *Tetrahedron Lett.* **1994**, *35*, 1489.

10.1021/ol063087n CCC: $37.00
Published on Web 02/08/2007

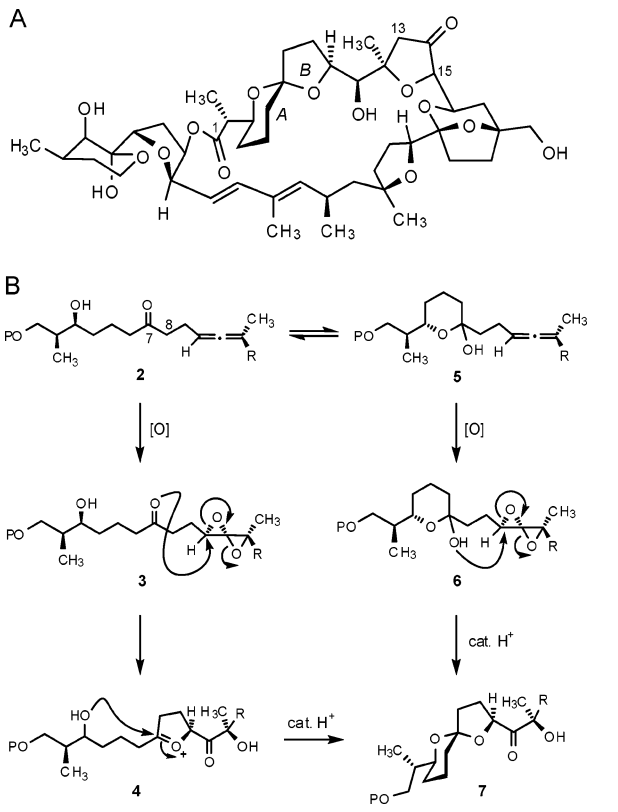


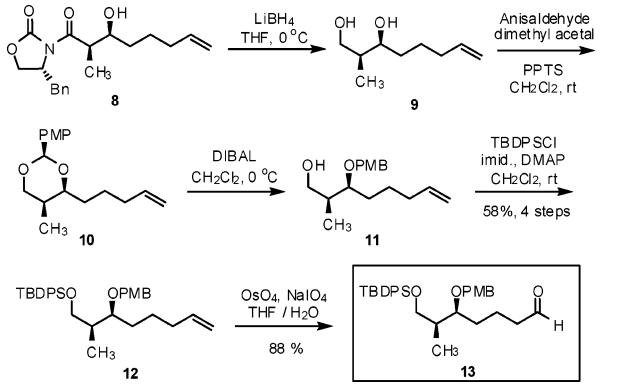
Figure 1. Pectenotoxin 4.

stable spiroketal, which matches the structure of PTX-4, would be readily achieved by the action of Brønsted acid.[5b,8] Although the data presented do not allow one to discern the operative pathway, the preparation of suitable target systems and their oxidative cyclization is summarized in Schemes 1−4.

The C1−C7 fragment was prepared as shown in Scheme 1. Known *syn*-aldol product **8**[9] was reduced with lithium borohydride followed by PMP acetal formation, DIBAL reduction, and then TBDPS protection to afford alkene **12** in 58% yield over four steps. Rigorous purification of **9**−**11** was hampered by the presence of inseparable byproducts. However, **12** was readily purified and obtained in good overall yield (87% average per step). Although ozonolysis of related systems is documented,[10] Lemieux−Johnson[11] oxidation of **12** proved to be superior for this substrate and furnished **13** (88%).

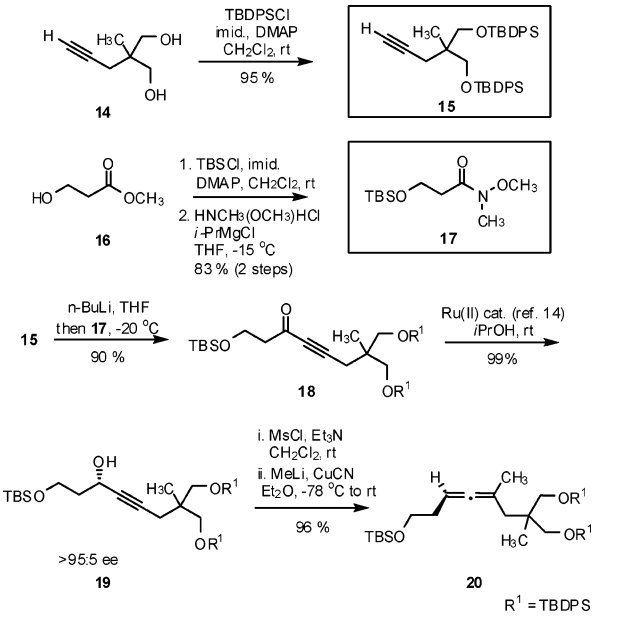
The synthesis of the C8−C15 fragment (**20**, Scheme 2) began with silyl protection of known alkyne diol **14**.[12]

Scheme 1. Synthesis of the C1−C7 Fragment



Weinreb amide **17** was synthesized from commercially available *β*-hydroxy ester **16** by TBS protection and then

Scheme 2. Synthesis of the C8−C15 Fragment



application of the Merck conditions[13] (83%, two steps). Alkynylation of **17** with **15** (90%) gave the expected alkynone, which upon reduction[14] gave the corresponding alkynol **19** (99%, >95:5 ee by Mosher ester analysis).

(8) (a) Pihko, P. M.; Aho, J. E. *Org. Lett.* **2004**, *6*, 3849. (b) Miles, C. O.; Wilkins, A. L.; Munday, R.; Dines, M. H.; Hawkes, A. D.; Briggs, L. R.; Sandvik, M.; Jensen, D. J.; Cooney, J. M.; Holland, P. T.; Quilliam, M. A.; MacKenzie, A. L.; Beuzenberg, V.; Towers, N. R. *Toxicon* **2004**, *43*, 1. See also ref 4a.

(9) **8** was prepared on a multigram scale in two steps from commercially available 5-hexenol according to ref 5a.

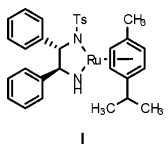
(10) (a) Nakatsuka, M.; Ragan, J. A.; Sammakia, T.; Smith, D. B.; Uehling, D. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 5583. (b) Maurer, K. W.; Armstrong, R. W. *J. Org. Chem.* **1996**, *61*, 3106.

(11) Pappo, R.; Alen, D. S., Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478.

(12) **14** was prepared on a multigram scale following the known two-step procedure. See: Findeis, R. A.; Gade, L. H. *J. Chem. Soc., Dalton Trans.* **2002**, *21*, 3952.

(13) Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U. H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461.

(14) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738. Reaction employed 5 mol % of Ru(II) catalyst **I**.

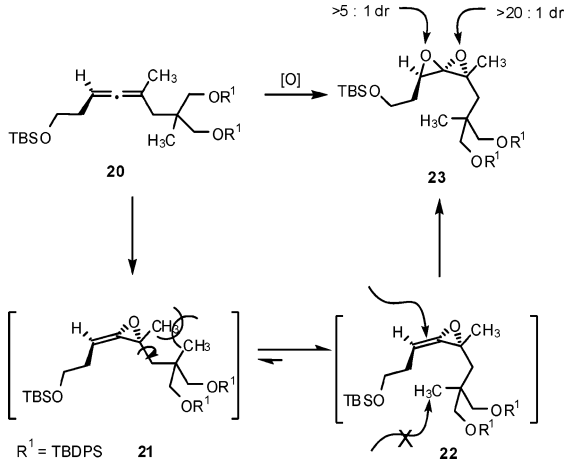


I

Conversion of the propargyl alcohol to the mesylate and then to allene **20** proceeded in excellent yield (96%).

At this stage, we turned our attention to the critical issue of allene oxidation (Scheme 3). For **20**, we expected the first

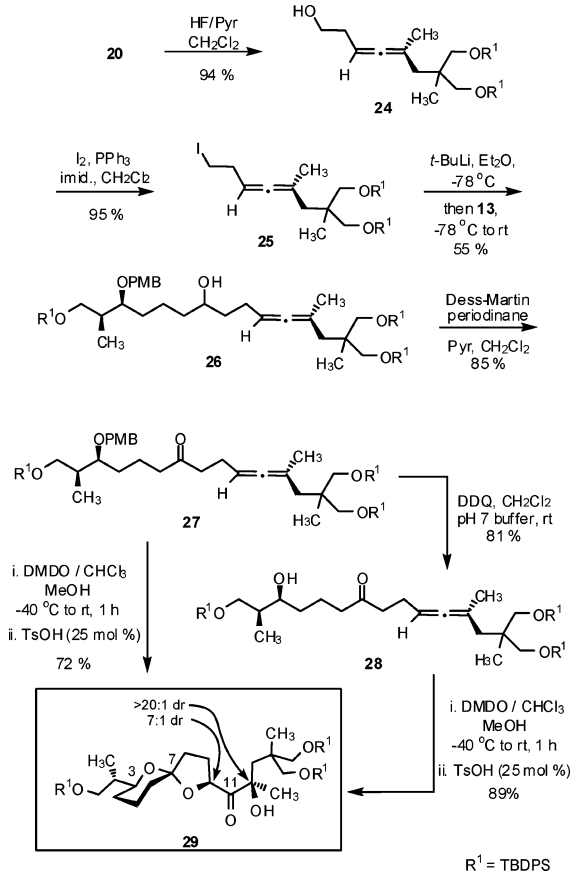
Scheme 3. Stereoselectivity of Allene **20** Oxidation



oxidation to take place on the more highly substituted double bond. The diastereoselectivity of this oxidation was expected to be high for steric reasons (**20**→**21**). The increased reactivity of the allene oxide relative to that of an allene may render the second oxidation less selective than the first. Consequently, we enlisted a bulky substituent at C-14 to control the facial selectivity of allene oxide oxidation.[15] We reasoned that the allene oxide would avoid the destabilizing *syn*-pentane interactions expected in conformers closely related to **21** and would prefer to populate conformers approximated by structure **22**. The oxidant should prefer an approach from the top face of the double bond because the neopentyl group would disfavor attack from the bottom (**22**, see arrows). In the event, exposure of **20** to a solution of dimethyldioxirane (DMDO) in chloroform[16] gave predominantly a single spirodiepoxide to which we assign structure **23** (>5:1[17]).

With routes to fragments **13** and **20** secured and with the supportive evidence that allenes of type **20** would oxidize selectively, we proceeded with the synthesis and study of allene **28** (Scheme 4). The primary TBS group of **20** was removed (→**24**, 94%), and the resultant hydroxyl was converted to iodide **25** (91%).[18] Although anions derived

Scheme 4. Assembly of C1−C15 and Cyclization



from β-allenyl iodides are known to undergo cyclization,[19] their potential addition to aldehydes seemed reasonable on the basis of a recent report by Brummond.[20] Accordingly, lithium halogen exchange of **25** followed by addition of aldehyde **13** under rigorously dry and oxygen-free conditions gave γ-hydroxy allene **26** in 52% yield. Dess−Martin oxidation (85%) and subsequent PMB removal with DDQ (81%) gave **28**.[21]

Upon DMDO oxidation in $CHCl_3$, **28** gave a product mixture that upon careful examination included the desired bicycle as well as isomeric compounds. A separate experiment established that oxidation of **28** followed by addition of water in THF gave predominantly the corresponding diol (not shown). Treatment of the diol with TsOH gave **29** (68%[22]). Upon further evaluation, we arrived at a single-flask procedure for the conversion of **28** to **29**, wherein addition of MeOH to the DMDO oxidation, followed by addition of acid at room temperature, smoothly converted allene **28** to spiroketal **29** (89%, dr 7:1).

(15) Of course, if the general strategy explored here was to be applied in a total synthesis of PTX-4, this group, or its functional equivalent, would have to also serve as a precursor to the keto group at C14 of the natural product.

(16) Gibert, M.; Ferrer, M.; Sanchez-Baeza, F.; Messeguer, A. *Tetrahedron* **1997**, *53*, 8643. See also ref 1b.

(17) (a) The ^{1}H NMR signals for the diastereomeric spirodiepoxides were not baseline resolved. However, the signals that correspond to the erstwhile allenic methyl groups approached baseline resolution. We conservatively estimate spirodiepoxide **23** to be >5:1 dr. (b) The observation of two isomers, instead of the four theoretically possible, is a strong indication that the first oxidation is very highly selective (>20:1). See also refs 1 and: Crandall, J. K.; Batal, D. J.; Sebesta, D. P.; Ling, F. *J. Org. Chem* **1991**, *56*, 1153.

(18) Appel, R. *Angew. Chem., Int. Ed.* **1975**, *14*, 801.

(19) Crandall, J. K.; Ayers, T. A. *J. Org. Chem.* **1992**, *57*, 2993.

(20) Brummond, K. M.; Lu, J. *J. Am. Chem. Soc.* **1999**, *121*, 5087. See also ref 9.

(21) Compound **28** exists as the δ-hydroxy ketone in $CDCl_3$, and no evidence for the lactol isomer was observed. ^{1}H NMR analysis shows a multiplet at 2.5 ppm corresponding to four protons, indicative of two methylenes flanking a ketone. ^{13}C shows no signals in the 100−110 ppm region otherwise expected for a quaternary lactol carbon. Instead, a peak at 210 ppm, indicative of a ketone, is observed.

(22) Two isomers were apparent in a ratio of 7:1.

The product ratio is consistent with our earlier observations for the oxidation of allene **20** to **23**. Thus, the first oxidation at the more substituted double bond of the allene is highly selective (>20:1) and the oxidation of the second bond is, in this case, 7:1.[17b,23] Acid-induced isomerization is known to give the doubly anomeric spiroketal corresponding to **29** in acyclic PTX-type systems.[5b,8] Comparison of key signals in the ^{13}C NMR with the PTXs and similar systems supports this assignment.[24]

Whereas the ability to control allene epoxidation and to predict SDE cyclization has enabled a short synthesis of **29**, our final experiment constitutes an even more direct route to the target. We noted previously the rapid cleavage of PMB ethers in the presence of DMDO, particularly in chloroform.[25] We therefore sought to effect the direct conversion of **27** to **29** and found that treament of **27** under the conditions shown effected its conversion to the targeted spiroketal in 72% yield, which, as before, was obtained as a mixture of two isomers (7:1). Thus, in an excellent overall yield, the following occurred: the PMB group was removed, the allene was selectively converted to a SDE (and thereby two stereocenters were introduced), the SDE was opened to give the C12 tertiary hydroxyl and the C11 carbonyl, and the A−B spiroketal was assembled.

Acknowledgment. Financial support from Merck & Co., Johnson & Johnson (Discovery Award), donors of the American Chemical Society Petroleum Research Fund, and Rutgers, The State University of New Jersey, is gratefully acknowledged. We thank Kaneka America LLC for the generous donation of compound **16**.

Supporting Information Available: Synthetic methods and characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

OL063087N

(23) Trace quantities of a third compound were also observed. The A−B spiroketal shown corresponds to the spiroketal of PTX-4 and related compounds (see refs 5b, 9, and 24) which readily forms selectively under acidic conditions. That the minor isomer is not the diastereomeric A−B spiroketal cannot be ruled out. Hence, we conservatively estimate the selectivity at this center as >10:1.

(24) The ^{13}C chemical shifts of C3 (72.3 ppm) and C7 (107.2 ppm) in **29** correlate well with PTX-4 and other reported PTX spiroketals with this configuration ($\Delta\delta$ = 0.2−1.2 ppm), whereas PTX-1 and related compounds with the alternative spiroketal configuration do not ($\Delta\delta$ = 2.3−3.9 ppm); see refs 3f, 5b, and 8.

(25) For related substituted benzyl cleavage with DMDO, see: (a) Marples, B. A.; Muxworthy, J. P.; Baggaley, K. H. *Synlett* **1992**, 646. (b) Csuk, R.; Dörr, P. *Tetrahedron* **1994**, *50*, 9983.