ORGANIC LETTERS

2005
Vol. 7, No. 13
2659−2662

Synthesis of the ABC Fragment of the Pectenotoxins

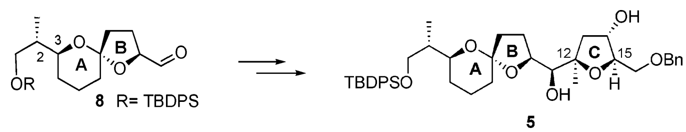
Rosliana Halim, Margaret A. Brimble,* and Jörn Merten

Department of Chemistry, The University of Auckland, 23 Symonds Street, Auckland, New Zealand

m.brimble@auckland.ac.nz

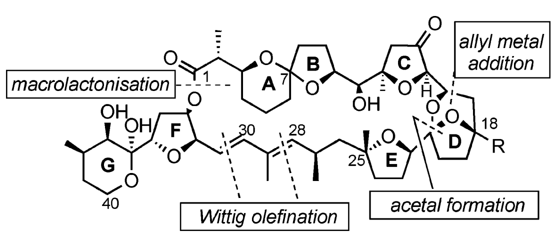
Received April 13, 2005

ABSTRACT



A highly stereocontrolled synthesis of the C1–C16 ABC spiroacetal-containing fragment 5 of PTX7 (4) has been achieved. Appendage of the C ring to the AB fragment involved Wittig reaction of spiroacetal aldehyde 8 with a stabilized ylide 9 followed by displacement of allylic iodide 27 with a lithium acetylide to afford enyne 7. Fructose-derived chiral dioxirane and dihydroxylation were then used to introduce the correct functionality in the tetrahydrofuran C ring.

The pectenotoxins (PTXs) are a family of complex macrolides[1] that were first isolated in 1985 by Yasumoto and co-workers.[1a] PTX2 (**1**) (Figure 1) is produced by the dinoflagellate *Dinophysis fortii* and is the parent compound of this family of toxins.[2] PTX2 (**1**) exhibited selective and potent cytotoxicity against several cancer cell lines at the nanomolar level.[3] PTX2 (**1**) and PTX6 (**3**) have also been shown to interact with the actin cytoskeleton at a unique site,[4] thus providing an important research tool for the study of basic cellular behavior.



1: PTX2 (7*R*, R=Me)
2: PTX4 (7*S*, R=CH_2OH)
3: PTX6 (7*R*, R=COOH)
4: PTX7 (7*S*, R=COOH)

Figure 1. Structure of PTXs and the principal disconnections used for the synthesis of PTXs.

The potent biological activity of these molecules together with their exquisitely complex structure has attracted the attention of several research groups,[5−8] notably Evans et al.[9] who have reported the only total synthesis of PTX4 (**2**) and PTX8 to date. We herein describe our synthesis of the C1−C16 ABC fragment of PTXs (Scheme 1) by appendage of the C ring to an AB spiroacetal unit.

Our approach to the synthesis of PTX7 (**4**) adopts a highly convergent strategy based on the sequential addition of the

(1) (a) Yasumoto, T.; Murata, M.; Oshima, Y.; Sano, G. K.; Matsumoto, J. *Tetrahedron* **1985**, *41*, 1019. (b) Murata, M.; Sano, M.; Iwashita, T.; Naoki, H.; Yasumoto, T. *Agric. Biol. Chem.* **1986**, *50*, 2693. (c) Sasaki, K.; Wright, J. L. C.; Yasumoto, T. *J. Org. Chem.* **1998**, *63*, 2475. (d) Suzuki, T.; Beuzenberg, V.; Mackenzie, L.; Quilliam, M. A. *J. Chromatogr. A* **2003**, *992*, 141. (e) Miles, C. O.; Wilkins, A. L.; Samdal, I. A.; Sandvik, M.; Petersen, D.; Quilliam, M. A.; Naustvoll, L. J.; Rundberget, T.; Torgesen, T.; Hovgaard, P.; Jensen, D. J.; Cooney, J. M. *Chem. Res. Toxicol.* **2004**, *17*, 1423.

(2) Lee, J.-S.; Murata, M.; Yasumoto, T. *Mycotoxins and Phycotoxins*; Elsevier: Tokyo, Japan, 1988; p 337.

(3) Jung, J. H.; Sim, C. J.; Lee, C.-O. *J. Nat. Prod.* **1995**, *58*, 1722.

(4) (a) Spector, I.; Braet, F.; Shochet, N. R.; Bubb, M. R. *Microscop. Res. Technol.* **1999**, *47*, 18. (b) Leira, F.; Cabado, A. G.; Vieytes, M. R.; Roman, Y.; Alfonso, A.; Botana, L. M.; Yasumoto, T.; Malaguti, C.; Rossini, G. P. *Biochem. Pharm.* **2002**, *63*, 1979.

(5) (a) Amano, S.; Fujiwara, K.; Murai, A. *Synlett* **1997**, 1300. (b) Awakura, D.; Fujiwara, K.; Murai, A. *Synlett* **2000**, 1733.

(6) (a) Paquette, L. A.; Peng, X.; Bondar, D. *Org. Lett.* **2002**, *4*, 937. (b) Peng, X.; Bondar, D.; Paquette, L. A. *Tetrahedron* **2004**, *60*, 9589.

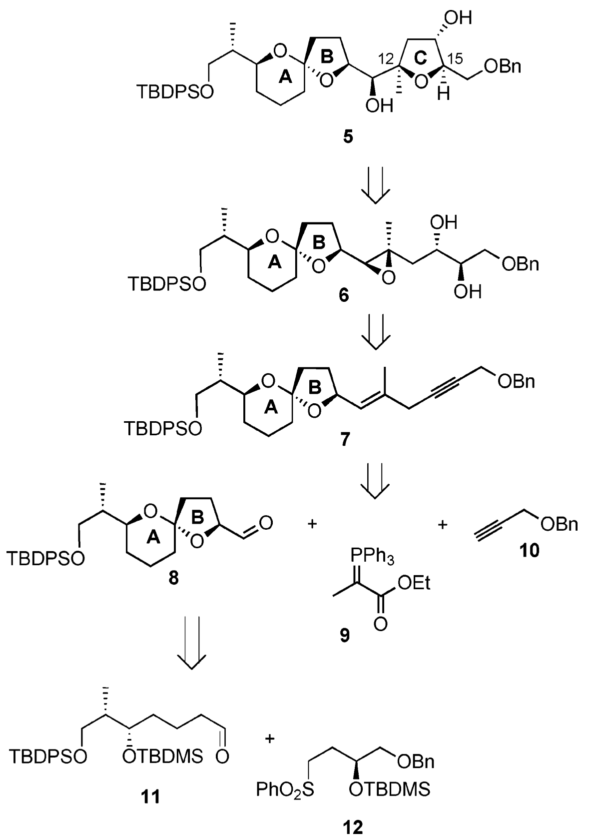
(7) Micalizio, G. C.; Roush, W. R. *Org. Lett.* **2001**, *3*, 1949.

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

(9) (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. Engl.* **2002**, *41*, 4573.

10.1021/ol0507975 CCC: $30.25
Published on Web 06/02/2005

Scheme 1. Retrosynthetic Analysis of ABC Fragment **5**



C, D, and E rings to an initial AB spiroacetal ring system followed by introduction of the FG fragment via Wittig olefination before the final macrolactonization step (Figure 1).

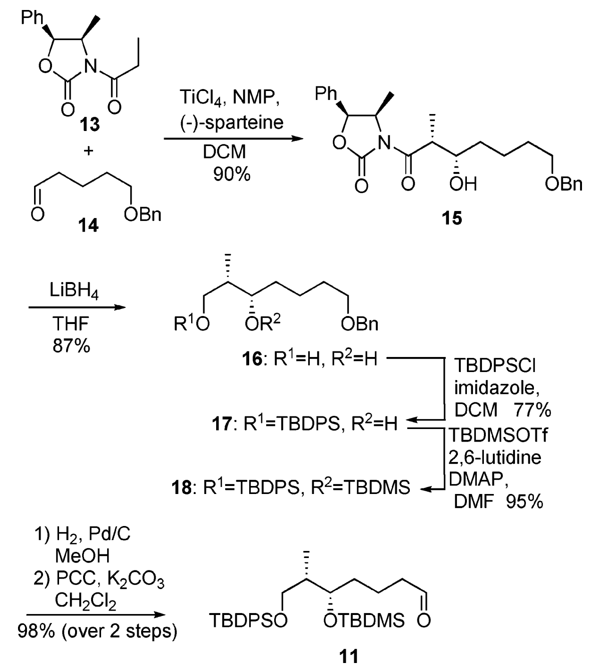
Our retrosynthetic analysis of the key spiroacetal-containing ABC tricyclic fragment **5** is depicted in Scheme 1. The ABC fragment **5** is constructed via a 5-*exo*-tet cyclization of epoxy-diol **6**, in which all the necessary stereogenic centers of the C ring are already installed. Epoxy-diol **6** in turn is obtained from enyne **7** by asymmetric epoxidation followed by semihydrogenation and dihydroxylation. Enyne **7** is prepared from spiroacetal aldehyde **8**, stabilized ylide **9**, and acetylene **10**. Finally, spiroacetal **8** is derived from the union of aldehyde **11** with sulfone **12**.

The synthesis of PTX2 (**1**) requires establishment of the (7*R*)-configuration of the spirocenter. However, the (7*S*)-configuration as present in PTX4 (**2**) and PTX7 (**4**) is stabilized by the anomeric effect and is in fact the thermodynamically favored stereochemistry when the spiroacetal ring is not embedded in the macrocyclic structure. It was therefore planned to obtain the natural (7*R*)-isomer of PTX2 (**1**) at a later stage in the synthesis after assembly of the macrolide ring based on the precedent reported by Sasaki and co-workers[10] for PTX4 (**2**). Our initial attention was therefore directed toward the synthesis of spiroacetal **8** with (7*S*)-configuration as present in PTX7 (**4**).

(10) Sasaki, K.; Wright, J. L. C.; Yasumoto, T. *J. Org. Chem.* **1998**, *63*, 2475.

Aldehyde **11** was prepared starting with a modified[11] Evans aldol reaction between propanoyloxazolidinone **13**[12] and known aldehyde **14**[13] to set up the required syn stereochemistry (Scheme 2). Enolization of **13** with titanium

Scheme 2. Synthesis of C1−C7 Containing Aldehyde **11**



tetrachloride followed by condensation with aldehyde **14** in the presence of (−)-sparteine afforded the syn adduct **15** in 90% yield as a single isomer. Reductive removal of the chiral auxiliary provided diol **16**, the primary alcohol of which was selectively protected as a TBDPS ether **17**. The secondary alcohol was then silylated to give **18**. These steps proceeded smoothly in good yield over three steps. Hydrogenolysis of the benzyl group followed by PCC oxidation of the resulting alcohol afforded the desired aldehyde **11** in 98% yield.

Sulfone **12** was prepared starting from (*R*)-(+)-benzylglycidol **19**[14] (Scheme 3). Treatment of methyl phenyl sulfone with *n*-BuLi in a mixture of THF and hexamethylphosphoramide (HMPA)[15] followed by addition of glycidol **19** effected regioselective ring opening of the epoxide. The resulting alkoxide was then trapped directly with a premixed solution of *tert*-butyldimethylsilyl trifluoromethanesulfonate and 2,6-lutidine in THF to afford the required sulfone **12** in 97% yield.

With sulfone **12** in hand, the next step was to effect its union with aldehyde **11** (Scheme 3). α-Deprotonation of sulfone **12** with *n*-BuLi followed by addition of aldehyde

(11) (a) Crimmins, M. T.; King, B. W.; Tabet, E. A. *J. Am. Chem. Soc.* **1997**, *119*, 7883. (b) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894.

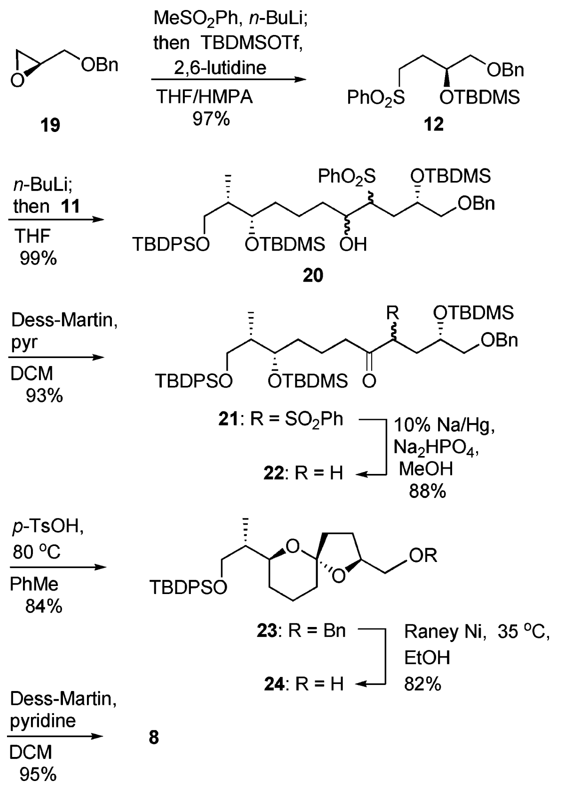
(12) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.

(13) Börjesson, L.; Csöregh, I.; Welch, C. J. *J. Org. Chem.* **1995**, *60*, 2989.

(14) Lai, M.; Oh, E.; Shih, Y.; Liu, H. *J. Org. Chem.* **1992**, *57*, 2471.

(15) Craig, D.; Smith, A. M. *Tetrahedron Lett.* **1990**, *31*, 2631.

Scheme 3. Synthesis of AB Spiroketal Moiety **8**



11 afforded the coupled product as an inseparable mixture of four diastereomers in 99% yield. Oxidation of the resulting alcohols **20** to the corresponding ketones was then effected using Dess−Martin reagent[16] buffered with pyridine. Treatment of the sulfone diastereomers **21** with sodium mercury amalgam in methanol then afforded ketone **22** as a single isomer in 88% yield. Selective deprotection of the TBDMS groups in the presence of the TBDPS group was achieved by heating ketone **22** under reflux with *p*-toluenesulfonic acid in toluene, resulting in clean cyclization of the resultant diol to give the 5,6-spiroacetal **23** as a single isomer in 84% yield. Debenzylation of **23** in the presence of Raney nickel followed by oxidation of the resulting alcohol afforded the desired AB spiroacetal fragment **8** in 78% yield over two steps. The stereochemistry of the spirocenter was determined to be 7*S* on the basis of NOE studies (Figure 2).

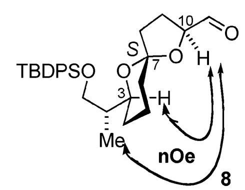
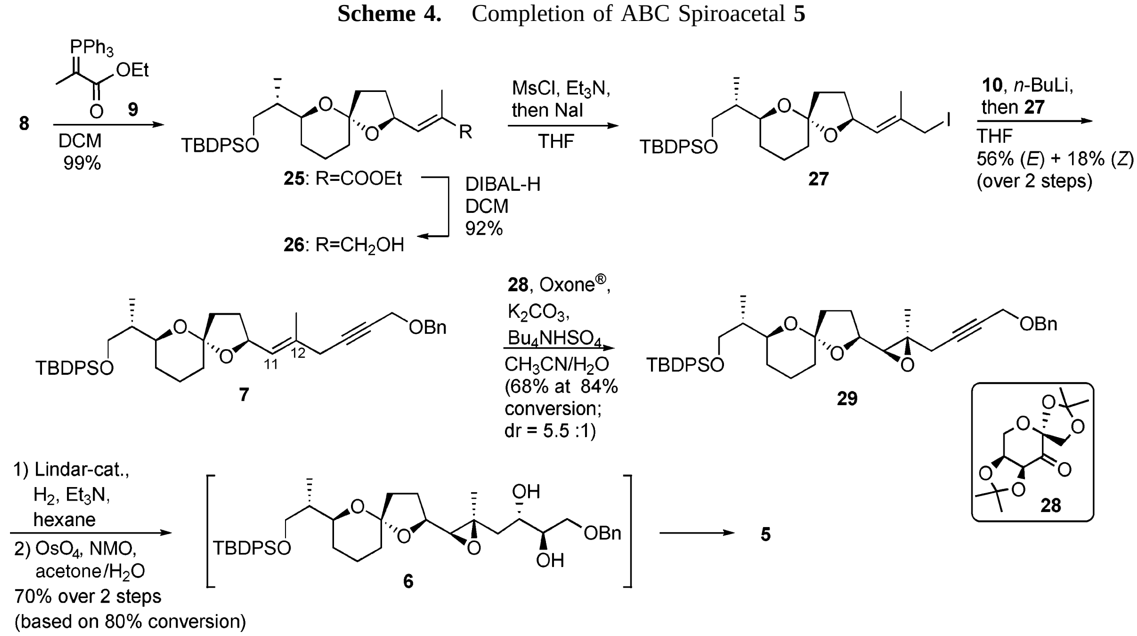


Figure 2. NOE correlations of spiroacetal **8**.

The assembly of the ABC tricyclic ring system **5** commenced with Wittig olefination of spiroacetal aldehyde **8** with ylide **9** (Scheme 4) in CH_2Cl_2 affording the desired (*E*)-olefin **25** (*E*:*Z* = 100:1 by ^{1}H NMR analysis) in quantitative yield. Reduction of ester **25** using diisobutylaluminum hydride (DIBAL-H) afforded allylic alcohol **26** in 91% yield. Conversion of **26** to the iodide **27** in preparation for coupling with acetylene **10**[17] was achieved via the intermediacy of the mesylate. The unstable iodide **27** was directly coupled with the lithium acetylide derived from **10** to afford (*E*)-enyne **7** in 56% yield from alcohol **26**. The undesired (*Z*)-isomer was also obtained in 18% and was easily separated from (*E*)-enyne **7** by flash chromatography.

Scheme 4. Completion of ABC Spiroacetal **5**



Finally having assembled the C1−C16 carbon skeleton **7**, the next step was the stereoselective introduction of the appropriate functionality to the enyne system in order to generate the required epoxy diol **6**, which could then be transformed into the target ABC ring fragment **5**. The C11/C12 stereogenic centers were introduced via asymmetric epoxidation, adopting the method reported by Shi and co-workers[18] using the chiral dioxirane formed from ketone **28** and Oxone (Scheme 4) to afford the desired *syn*-epoxide **29**. Semireduction of the alkyne **29** over Lindlar catalyst followed by dihydroxylation of the resulting (*Z*)-olefin with osmium tetroxide afforded diol **6**, which cyclized directly to form the target ABC spiroacetal fragment **5** in 70% overall yield.

NOE correlations observed for fragment **5** showed a correlation between 12-Me and H-15 (Figure 3), establishing the formation of the desired *cis*-tetrahydrofuran C ring.

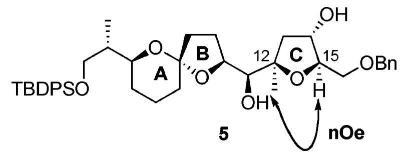


Figure 3. NOE correlation between 12-Me and H-15 in fragment **5**.

In summary, the ABC spiroacetal fragment **5** of PTX7 (**4**) has been synthesized in a highly stereocontrolled manner (19 steps, 5% overall yield from **13**). The key strategy in the synthesis involved generation of the (*E*)-geometry across the C11/C12 bond via Wittig olefination. The (*E*)-alkene was later converted to a *syn*-epoxide using a Shi asymmetric epoxidation. Dihydroxylation generated the C14/C15 diol that immediately cyclized to afford the tricyclic ABC fragment **5** of PTX7 (**4**).

Acknowledgment. M. Brimble acknowledges the award of a James Cook Research Fellowship from the Royal Society of New Zealand.

Supporting Information Available: Experimental details and spectroscopic data for compounds **24**, **26**, **7**, and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0507975

(16) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

(17) Sammelson, R. E.; Millar, R. B.; Kurth, M. J. *J. Org. Chem.* **2000**, *65*, 2225.

(18) Wang, Z.-X.; Tu, T.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224.

(19) (a) Wang, L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7568. (b) Kolb, H. C.; Andersson, P. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1994**, *116*, 1278. (c) This ligand is preferred for AD reactions using 1,2-disubsituted *cis*-olefins.