Spiro Compounds

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Interplay of Cascade Oxidative Cyclization and Hydride Shifts in the Synthesis of the ABC Spiroketal Ring System of Pectenotoxin-4**

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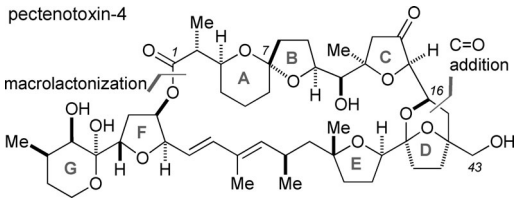
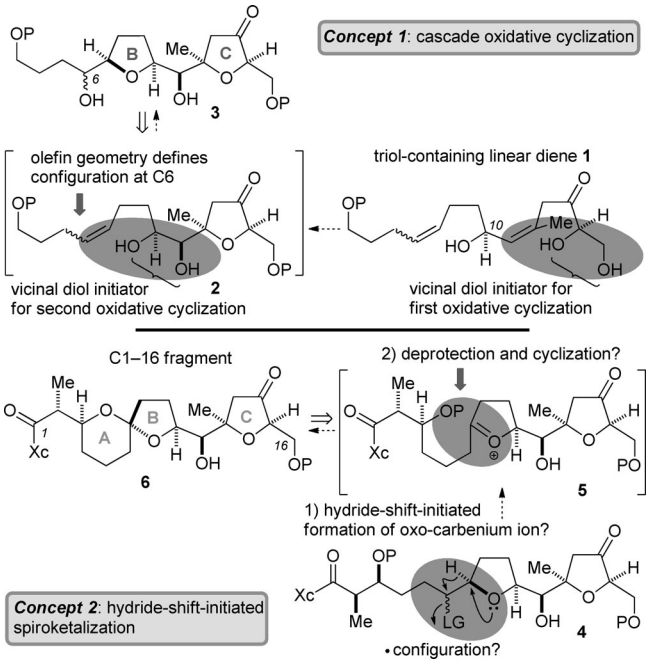
The pectenotoxins (PTXs) are a family of cyclic polyether macrolide toxins first isolated in 1985 by Yasumoto and co-workers from the digestive glands of scallops (*Patinopecten yessoensis*).[1] It has since been discovered that the producers of pectenotoxins are toxic plankton (*Dinophysis* dinoflagellate) found in many coastal areas around the world. To date, more than 20 members have been isolated and characterized, with structural variations commonly involving the configuration of the AB spiroketal (C7) as well as the oxidation state at C43. Recent studies have demonstrated that the pectenotoxins exhibit potent biological activity, including selective cytotoxicity against p53 mutant and p53-deficient tumors.[2]

The exquisite architectural complexity of these 26-membered macrolactones, which consist of either 19 or 20 stereogenic centers embedded within three tetrahydrofuran rings, plus one spiroketal and one bicyclic ketal, poses a synthetic challenge that has attracted considerable attention from many research groups. While significant synthetic endeavors have been directed toward the pectenotoxins,[3] to date only one total synthesis of PTX-4 and PTX-8 has been reported.[4]



In particular we were drawn to the C1–16 fragment of the pectenotoxins, because it contains a pair of THF rings terminating with a spiroketal unit that could be derived from a linear precursor; a synthesis would allow us to develop two concepts that should find general use in organic synthesis. Our first idea was to prepare a triol-containing linear diene, such as **1** (Scheme 1), and carry out an oxidative cyclization[5] in a cascade mode, catalyzed by osmium(VI). In the first instance, we might expect the vicinal diol unit in **1** to chelate to the osmium catalyst and facilitate an oxidative cyclization



Scheme 1. Two new concepts to be developed. LG = leaving group, P = protecting group, Xc = chiral auxiliary.

onto the trisubstituted alkene, thus forming a THF ring (**2**). The stereospecific (*syn*) addition of the two oxygen atoms across the alkene will ensure the correct configuration in the product. We then hoped that the metal chelate formed after cyclization would translocate onto the hydroxy group at C10 and thus enable a second oxidative cyclization onto the pendent C-6,7 alkene, forming **3** in the process. If successful, this method would expand the limits of the catalytic oxidative cyclization and form both THF rings of the target in one pot.

Our second point of interest was the notion of using the exocyclic hydroxy group at C6 to initiate a hydride shift and form an oxo-carbenium ion in situ (see **4**→**5**).[6] If this reaction were successful, we wanted to explore the role of a pendent (protected?) hydroxy group in trapping the cation and forming a spiroketal (**6**).[7] This sequence, which we called hydride-shift-initiated spiroketalization, would be another potentially general piece of methodology for organic synthesis.

Initial results strongly suggested that the success of the hydride shift depended on the relative configuration between the exocyclic hydroxy group (activated as a leaving group) and the ring junction.[8] Moreover, previous experiments with deuterium labeling at the ring junction showed convincingly the intramolecular nature of this hydride shift.[9] The relative

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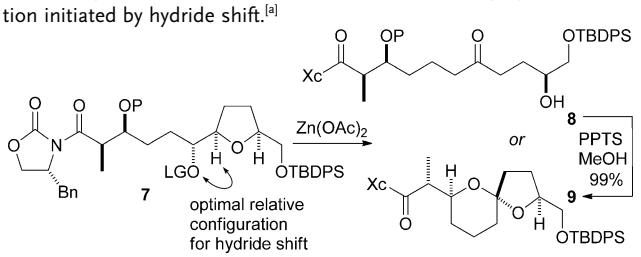
configuration that derives from *syn* oxidative cyclization onto an *E* alkene was found to be optimal for the hydride shift; clearly, this was the arrangement that we focused on.

Our first attempts concentrated on developing the hydride-shift-initiated spiroketalization on a simpler system, so that we could examine the parameters of leaving group, reaction conditions, and protection of the remote oxygen functionality. In particular we wanted to find a protecting group that would not interfere with the hydride shift to form an oxo-carbenium ion, but which could be easily deprotected in order to form a spiroketal (in one-pot?).[10] Moreover, we wanted to examine the viability of different leaving groups on the exocyclic oxygen atom, and their response to solvolysis. Table 1 shows the model system **7** and the various combinations that were tested. The results showed that the general concept worked, and that the biggest factor in deciding the product distribution was the solvent, with aqueous solutions trapping the oxo-carbenium ion followed by ring opening to give ketone **8** (entry 1, compound **8** could be subsequently cyclized under acidic conditions to give spiroketal **9** almost quantitatively). Interestingly, the absence of water and the presence of the polar solvent hexafluoroisopropanol (HFIPA) allowed a one-pot hydride shift, oxygen deprotection, and spiroketalization sequence to occur, forming **9** in 72% yield (entry 2). Further studies showed that both TES and TBS protecting groups gave acceptable yields in the spiroketalization process (entry 3), and that the extra activation imparted by an α-chloromesylate group (Mc)[6] was essential to the success of the reaction (compare with entries 4 and 5). Our conclusion was that we had found the correct balance of protecting-group stability and leaving-group activation in this prototype, and that this new method of spiroketal formation was suitable for application in a more complex setting.

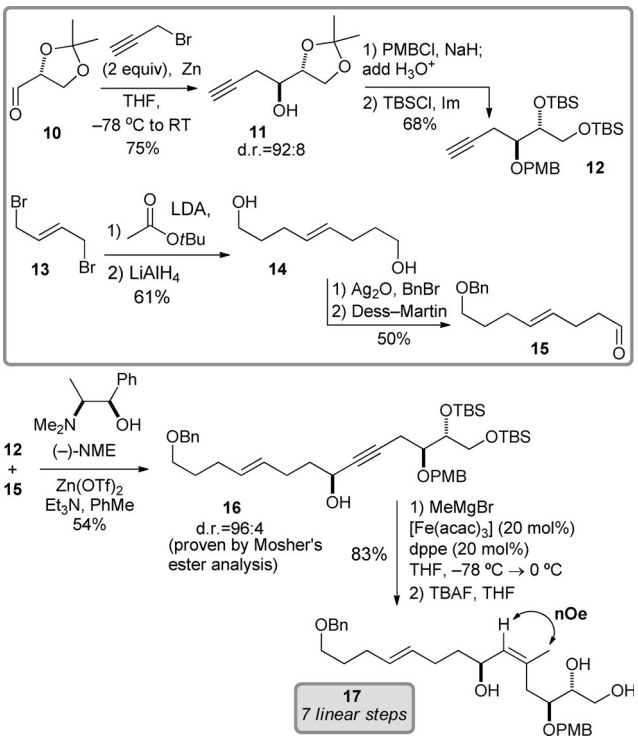
Table 1: Optimization of conditions for one- or two-step spiroketalization initiated by hydride shift.[a]



Entry	OP	LG	Solvent	*T* [°C]	Product	Yield [%]
1	OTES	OMc	DMF (aq)	70–80	**8**	53
2	**OTES**	**OMc**	**HFIPA**	**40**	**9**	**72**
3	**OTBS**	**OMc**	**DMF (aq)**	**70–80**	**8**	**85**
4	OTES	OMs	DMF (aq)	70–80	**8**	35
5	OTBS	OMs	HFIPA	40	**9**	20

[a] Entries in bold highlight optimized reaction conditions. Bn = benzyl, DMF = *N*,*N*-dimethylformamide, HFIPA = hexafluoroisopropanol, Mc = α-chloromesylate, Ms = methanesulfonyl, PPTS = pyridinium *p*-toluenesulfonate, TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl.

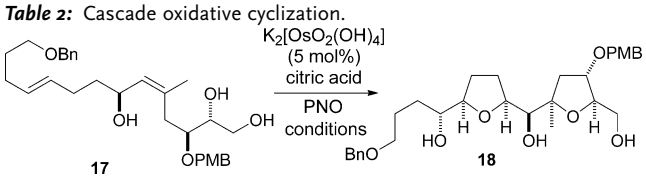
Next, we set about examining the cascade oxidative cyclization and subsequent application of the spiroketalization chemistry to produce the target system. The precursor for oxidative cyclization (**17**) was prepared in seven linear steps (Scheme 2). One of the key steps was the Carreira reaction between alkyne **12** and aldehyde **15**, which proceeded with excellent stereoselectivity (96:4) induced by the chiral ligand (−)-*N*-methylephedrine (NME).[11] In addition, the catalytic regio- and stereoselective methylation of alkyne **16** using conditions recently developed by Zhang and Ready provided the desired trisubstituted alkene **17** with the correct alkene substitution pattern for the oxidative cyclization.[12]



Scheme 2. Formation of the oxidative cyclization substrate using a Carreira reaction, and methylation as described by Zhang and Ready.[12] acac = acetylacetonate, dppe = ethane-l,2-diylbis(diphenylphosphane), LDA = lithium diisopropylamide, NME = *N*-methylephedrine, PMB = *p*-methoxybenzyl, TBAF = tetra-*n*-butylammonium fluoride, Tf = trifluoromethanesulfonyl.

We were now in a position to test the remaining hypothesis underpinning our work, and subjected triol **17** to oxidative cyclization conditions, aiming to produce the bis-THF compound **18** through a double-oxidative-cyclization cascade. The conditions used were those developed as a result of intensive study of the reaction mechanism, and involved the addition of catalytic amounts of potassium osmate ($K_2[OsO_2(OH)_4]$) in an aqueous acetonitrile solution with pyridine-*N*-oxide (PNO) as a re-oxidant and a Lewis acid as promoter (Table 2).[13] Initial studies showed that the addition of a buffer (pH 6.5) to the system was essential in order to prevent acid-promoted decomposition of the starting material. The best set of conditions involved use of $Zn(OTf)_2$ (50 mol%) at 80 °C, giving the desired bis-THF product **18** in 69% yield (entry 3). The double oxidative cyclization, which occurs in a cascade fashion and in this case forms two rings

Table 2: Cascade oxidative cyclization.

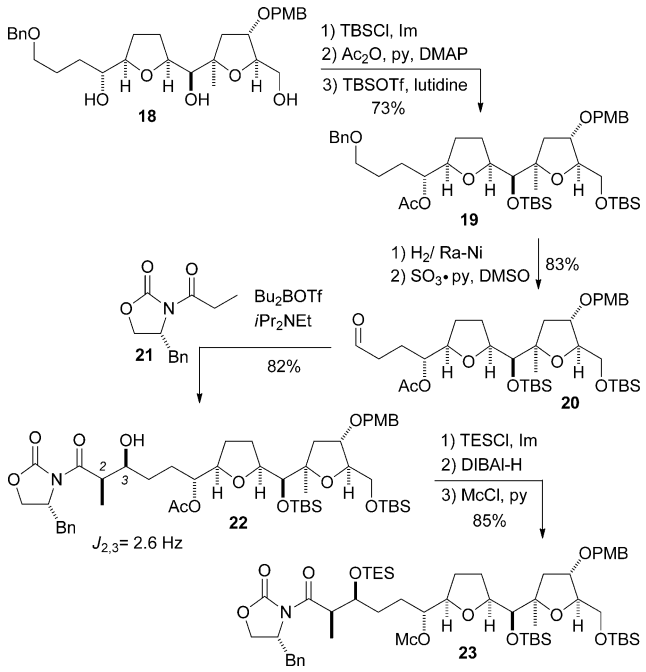


Entry	Lewis acid[a]	*T* [°C]	Solvent	Yield [%]
1	$Zn(OTf)_2$	60	MeCN (aq)	37[b]
2	$Zn(OTf)_2$	60	MeCN (aq)/buffer	33
3	**$Zn(OTf)_2$**	**80**	**MeCN (aq)/buffer**	**69**
4	$Cu(OTf)_2$	80	MeCN (aq)/buffer	55

[a] 50 mol%. [b] Acid-promoted decomposition was also observed. PNO = pyridine-*N*-oxide. Entries in bold highlight optimized reaction conditions.

and four stereogenic centers, is unprecedented and shows the power that this methodology holds for the formation of complex THF-containing products with more than one ring.

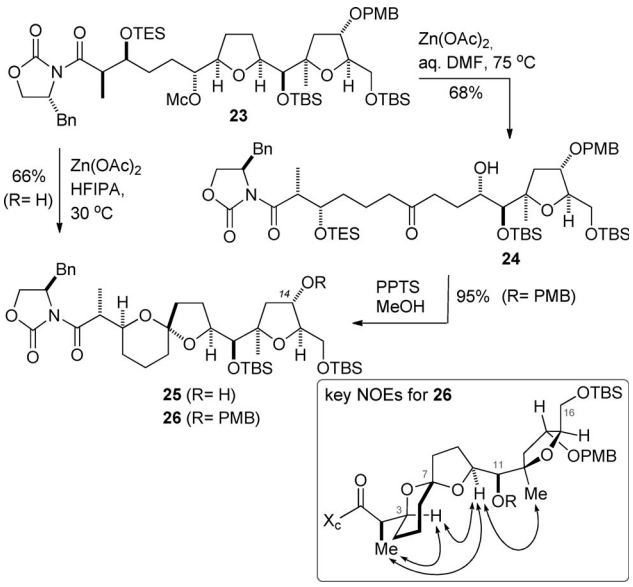
Installation of the aldol-derived side chain involved protecting-group manipulation of product **18**, beginning with protection of the primary hydroxy group (Scheme 3) and followed by regioselective protection of the remaining two hydroxy groups with an acetate (at C6) and then a TBS group (at C11) to give **19**.



Scheme 3. Installation of the spiroketal side chain. DIBAl-H = diisobutylaluminum hydride, DMAP = 4-dimethylaminopyridine, DMSO = dimethyl sulfoxide, py = pyridine.

Next, we examined selective removal of the benzyl group, and discovered that hydrogenolysis of **19** with Raney-Ni catalyst was able to effect this transformation. Subsequent oxidation to the aldehyde (**20**) and Evans aldol reaction with oxazolidinone **21** gave the *syn* adduct **22** as a single diastereoisomer.[14] Finally, and in accordance with the study reported earlier (Table 1), we prepared the spiroketalization precursor **23** by protecting the aldol adduct with a TES group, removing the acetate group, and activating the liberated hydroxy group at C6 as an α-chloromesylate derivative.

To finish our synthesis of the C1–16 fragment of pectenotoxin-4, we investigated the hydride-shift-initiated spiroketalization of **23** under the two sets of conditions that had been previously identified (Scheme 4). Pleasingly, both



Scheme 4. Hydride-shift-initiated spiroketalization.

the one- and two-step reaction sequences worked well and produced the spiroketals **25** and **26** in good yields. Interestingly, the one-pot reaction of **23** in HFIPA effected the removal of the PMB group at C14 to give **25**, while the two-step protocol gave **26** with the PMB group intact (in the natural product, the C14 position bears a ketone, so the formation of **25** may be useful in the context of a total synthesis). The structure of the spiroketal was confirmed by nOe measurements, and these fit very well with the expected, thermodynamically more stable spiroketal as shown.

In conclusion, we have developed two concepts that should find use in organic synthesis, namely a hydride-shift-initiated spiroketalization and a cascade oxidative cyclization that enable the synthesis of bis-THFs. The utility of these methodologies was tested successfully in a synthesis of the C1–16 fragment of the complex and biologically active natural product pectenotoxin-4.

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[1] a) T. Yasumoto, M. Murata, Y. Oshima, M. Sano, G. K. Matsumoto, J. Clardy, *Tetrahedron* **1985**, *41*, 1019–1025; b) K.

Sasaki, J. L. C. Wright, T. Yasumoto, *J. Org. Chem.* **1998**, *63*, 2475 – 2480.

[2] a) H.-D. Chae, T.-S. Choi, B.-M. Kim, J. H. Hung, Y.-J. Bang, D. Y. Shin, *Oncogene* **2005**, *24*, 4813 – 4819; b) D. Y. Shin, G. Y. Kim, N. D. Kim, J. H. Jung, S. K. Kim, H. S. Hang, Y. H. Choi, *Oncol. Rep.* **2008**, *19*, 517 – 526.

[3] For selected references on synthetic approaches to the pectenotoxins, see: a) M. Heapy, T. W. Wagner, M. M. Brimble, *Synlett* **2007**, 2359 – 2362; b) R. Halim, M. A. Brimble, J. Merten, *Org. Lett.* **2005**, *7*, 2659 – 2662; c) R. Halim, M. A. Brimble, J. Merten, *Org. Biomol. Chem.* **2006**, *4*, 1387 – 1399; d) S. Carley, M. A. Brimble, *Org. Lett.* **2009**, *11*, 563 – 566; e) D. Bondar, J. Liu, T. Müller, L. A. Paquette, *Org. Lett.* **2005**, *7*, 1813 – 1816; f) P. D. O'Connor, C. K. Knight, D. Friedrich, X. Peng, L. A. Paquette, *J. Org. Chem.* **2007**, *72*, 1747 – 1754; g) S. D. Lotesta, Y. Hou, L. J. Williams, *Org. Lett.* **2007**, *9*, 869 – 872; h) S. Joyasawal, S. D. Lotesta, N. G. Akhmedov, L. J. Williams, *Org. Lett.* **2010**, *12*, 988 – 991; i) D. Vellucci, S. D. Rychnovsky, *Org. Lett.* **2007**, *9*, 711 – 714; j) J. A. Aho, E. Salomäki, K. Rissanen, P. M. Pihko, *Org. Lett.* **2008**, *10*, 4183 – 4186; k) H. Helmboldt, J. A. Aho, P. M. Pihko, *Org. Lett.* **2008**, *10*, 4179 – 4182; l) J. A. Aho, A. Piisola, K. S. Krishnan, P. M. Pihko, *Eur. J. Org. Chem.* **2011**, 1682 – 1694; m) O. Kubo, D. P. Canterbury, G. C. Micalizio, *Org. Lett.* **2012**, *14*, 5748 – 5751; for a review see n) R. Halim, M. A. Brimble, *Org. Biomol. Chem.* **2006**, *4*, 4048 – 4058.

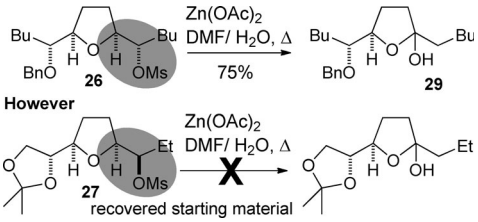
[4] a) D. A. Evans, H. A. Rajapakse, D. Stenkamp, *Angew. Chem.* **2002**, *114*, 4751 – 4755; *Angew. Chem. Int. Ed.* **2002**, *41*, 4569 – 4573; b) D. A. Evans, H. A. Rajapakse, A. Chiu, D. Stenkamp, *Angew. Chem.* **2002**, *114*, 4755 – 4758; *Angew. Chem. Int. Ed.* **2002**, *41*, 4573 – 4576.

[5] For representative examples, see: a) M. de Champdoré, M. Lasalvia, V. Piccialli, *Tetrahedron Lett.* **1998**, *39*, 9781; b) T. J. Donohoe, S. Butterworth, *Angew. Chem.* **2003**, *115*, 978; *Angew. Chem. Int. Ed.* **2003**, *42*, 948; c) D. M. Walba, G. S. Stoudt, *Tetrahedron Lett.* **1982**, *23*, 727 – 730; d) T. J. Donohoe, S. Butterworth, *Angew. Chem.* **2005**, *117*, 4844 – 4846; *Angew. Chem. Int. Ed.* **2005**, *44*, 4766 – 4768; e) H. Cheng, C. B. W. Stark, *Angew. Chem.* **2010**, *122*, 1632 – 1635; *Angew. Chem. Int. Ed.* **2010**, *49*, 1587 – 1590. For a review see: f) V. Piccialli, *Synthesis* **2007**, 2585 – 2607.

[6] a) T. Nakata, S. Nomura, H. Matsukura, *Tetrahedron Lett.* **1996**, *37*, 213 – 216; b) K. Nagasawa, N. Hori, H. Koshino, T. Nakata, *Heterocycles* **1999**, *50*, 919 – 928; c) M. A. Brimble, M. K. Edmonds, *Tetrahedron* **1995**, *51*, 9995 – 10012; d) S. Takahashi, S. Hirota, T. Nakata, *Heterocycles* **2000**, *52*, 1079 – 1082.

[7] See: a) J. E. Aho, P. M. Pihko, T. K. Rissa, *Chem. Rev.* **2005**, *105*, 4406 – 4440; b) M. Wilsdorf, H.-U. Reissig, *Angew. Chem.* **2012**, *124*, 9624 – 9626; *Angew. Chem. Int. Ed.* **2012**, *51*, 9486 – 9488. For a related concept see: S. J. Pastine, D. Sames, *Org. Lett.* **2005**, *7*, 5429, and ref. [6d].

[8] Preliminary results showed that one diastereoisomeric arrangement was superior to the other for initiating a hydride shift. We ascribe the lack of reactivity of **27** to a steric interaction between the ethyl group and the carbon atoms of the THF ring that is present when the C–H bond is aligned antiperiplanar to the OMs group.



[9] T. J. Donohoe, O. Williams, G. H. Churchill, *Angew. Chem.* **2008**, *120*, 2911 – 2913; *Angew. Chem. Int. Ed.* **2008**, *47*, 2869 – 2871.

[10] Studies without a protecting group on the pendant hydroxy group resulted in predominant formation of a bis-THF compound by internal S_N2-like displacement of the leaving group.

[11] D. E. Frantz, R. Fassler, E. M. Carreira, *J. Am. Chem. Soc.* **2000**, *122*, 1806 – 1807.

[12] D. Zhang, J. M. Ready, *J. Am. Chem. Soc.* **2006**, *128*, 15050 – 15051.

[13] a) T. J. Donohoe, K. M. P. Wheelhouse, P. J. Lindsay-Scott, P. A. Glossop, I. A. Nash, J. S. Parker, *Angew. Chem.* **2008**, *120*, 2914 – 2917; *Angew. Chem. Int. Ed.* **2008**, *47*, 2872 – 2875; b) T. J. Donohoe, P. C. M. Winship, D. S. Walter, *J. Org. Chem.* **2009**, *74*, 6394 – 6397.

[14] D. A. Evans, J. Bartroli, T. L. Shih, *J. Am. Chem. Soc.* **1981**, *103*, 2127 – 2129.

