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Access to Both Anomers of Pectenotoxin Spiroketals by Kinetic Spiroketalization

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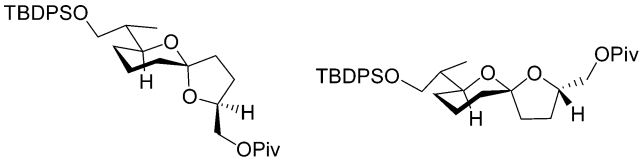
ABSTRACT



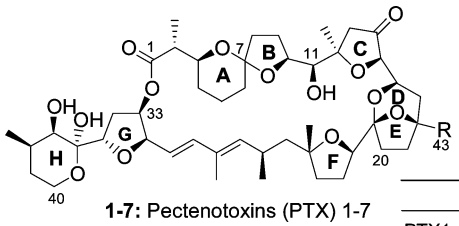
AB spiroketal segment of PTX-4 and PTX-7 Stabilized by anomeric effect Thermodynamic product

AB spiroketal segment of PTX-1–3 and PTX-6 No stabilization from anomeric effect Obtained under kinetic conditions

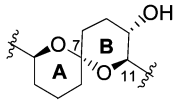
A concise synthesis of both AB ring spiroisomers of the pectenotoxins is described. The nonanomeric AB spiroketal ring system of the pectenotoxins-1, -2, -3, and -6 is formed under very mild, kinetic spiroketalization conditions, along with the anomeric isomer. Only catalytic asymmetric transformations were used as the source of chirality in the synthesis route.

The pectenotoxins (PTX) comprise a family of marine natural products isolated from scallops *Patinopecten yessoensis*. The first members of the family were isolated and characterized by Yasumoto and co-workers in 1985;[1] in subsequent studies, a total of 10 PTX toxin congeners have been found.[2] The compounds have drawn considerable attention as a result of their significant cytotoxicity against a variety of lung, colon, and breast cancer cell lines and their still largely unknown mode of action. PTX-2 and PTX-6 are known to interact with the actin cytoskeleton at a unique site, effecting depolymerization of F-actin.[3]

Structurally, the pectenotoxins share a common carbon skeleton, and the different congeners differ from each other in the C_7 spiro geometry and in the oxidation state of C_{43} (Figure 1). Synthetic efforts toward the pectenotoxins have been reported by the Murai,[4] Roush,[5] and Paquette[6] groups,



1-7: Pectenotoxins (PTX) 1-7



8-10: Pectenotoxins 8-10

	R	C_7
PTX1 :	CH_2OH	*R*
PTX2 :	CH_3	*R*
PTX3 :	CHO	*R*
PTX4 :	CH_2OH	*S*
PTX5 :	unidentified	
PTX6 :	COOH	*R*
PTX7 :	COOH	*S*
PTX8 :	CH_2OH	*S*
PTX9 :	COOH	*S*
PTX10 :	unidentified	

Figure 1. Structures of the pectenotoxins.

(1) Yasumoto, T.; Murata, M.; Oshima, Y.; Sano, M.; Matsumoto, G. K.; Clardy, J. *Tetrahedron* **1985**, *41*, 1019−1025.

(2) (a) Sasaki, K.; Wright, J. L. C.; Yasumoto, T. *J. Org. Chem.* **1998**, *63*, 2475−2480. (b) Daiguji, M.; Satake, M.; James, K. J.; Bishop, A.; Mackenzie, L.; Naoki, H.; Yasumoto, T. *Chem. Lett.* **1998**, *7*, 653−654.

(3) (a) Spector, I.; Braet, F.; Schochet, N. R.; Bubb, M. R. *Microscop. Res. Technol.* **1999**, *47*, 18−37. (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*, 1979−1988.

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culminating in the recent total synthesis of PTX-4 and its conversion to PTX-8 by Evans and co-workers.[7]

The C_7 spiro configuration of PTX-1, PTX-2, PTX-3, and PTX-6, the major and the most cytotoxic toxins of the pectenotoxin family, is *R*, corresponding to a *spiroketal with no anomeric stabilization* (Figure 2). To date, studies

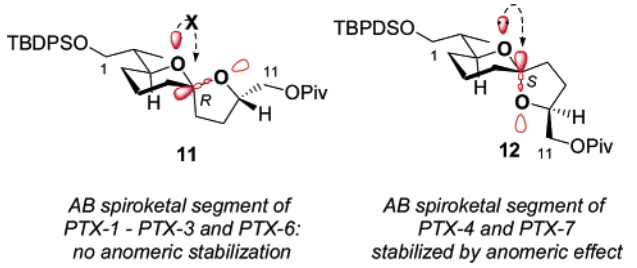
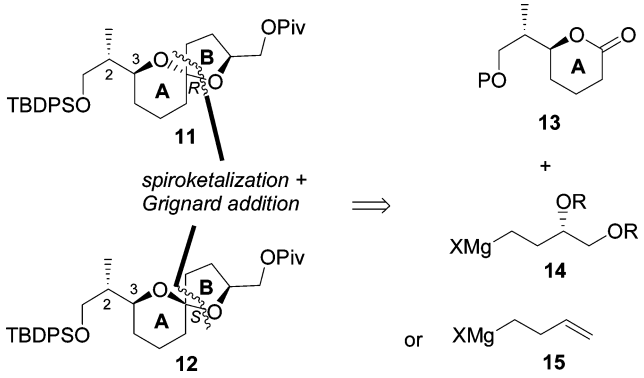


Figure 2. AB spiroketal segments of PTX-1−7.

addressing the synthesis of this structurally challenging subunit have not been reported. Herein, we report an asymmetric synthesis of the C_1-C_{11} AB spiroketal segment of the pectenotoxins that provides access to both spiroketal isomers via a kinetically controlled spiroketalization. Importantly, all stereocenters present in the C_1-C_{11} segment are created by *catalytic* asymmetric transformations.

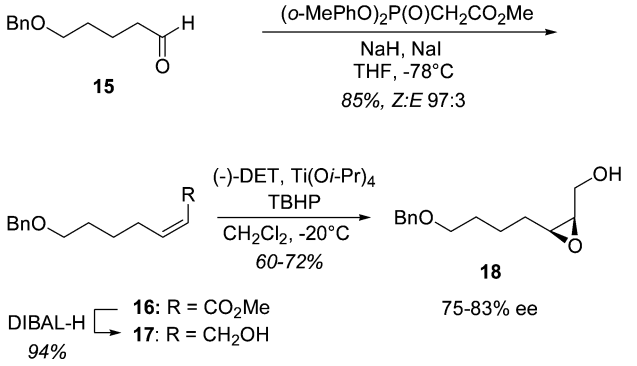
Retrosynthetically, the C_1-C_{11} spiroketal segment could be envisioned to arise from the corresponding A ring building block **13** (Scheme 1) by Grignard addition and asymmetric

Scheme 1. Retrosynthetic Analysis of the AB Ring Segment



dihydroxylation. For setting up the C_2-C_3 syn stereochemistry, we decided to employ a sequence of Katsuki−Sharpless asymmetric epoxidation[8] and regioselective epoxide ring opening with a higher order cuprate. This strategy required a highly stereoselective access to the (*Z*)-allylic alcohol **17** (Scheme 2). In recent studies, we have reported[9] an improved

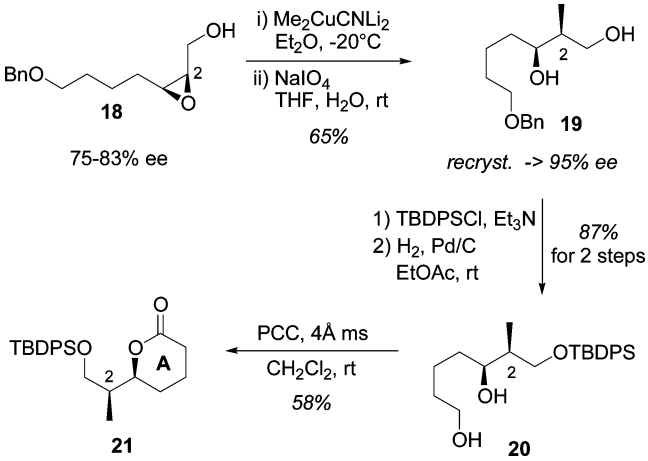
Scheme 2



protocol for (*Z*)-olefination of alkenes using the Ando phosphonate[10] and a combination of NaH/NaI as the base. Starting from the known[11] aldehyde **15** (prepared in two steps and 75% overall yield from 1,5-pentanediol), the Horner−Wadsworth−Emmons olefination using our conditions gave the (*Z*)-enoate **16** in 85% yield and 97:3 *Z*:*E* selectivity (Scheme 2). The remaining (*E*)-isomer was readily removed by flash chromatography. Subsequent DIBAL-H reduction gave the pure (*Z*)-allylic alcohol **17** in 94% yield.

The Katsuki−Sharpless asymmetric epoxidation protocol gave the epoxide **18** in 60−72% yield and 75−83% ee. Ring opening of the cis epoxide with higher order cuprate[12] and subsequent cleavage of the 1,2-diol side product[13] (ca 25%) with $NaIO_4$ gave the crystalline diol **19** (Scheme 3).

Scheme 3



Recrystallization afforded the pure diol in 65% overall yield. The enantiomeric purity of the diol had also improved to

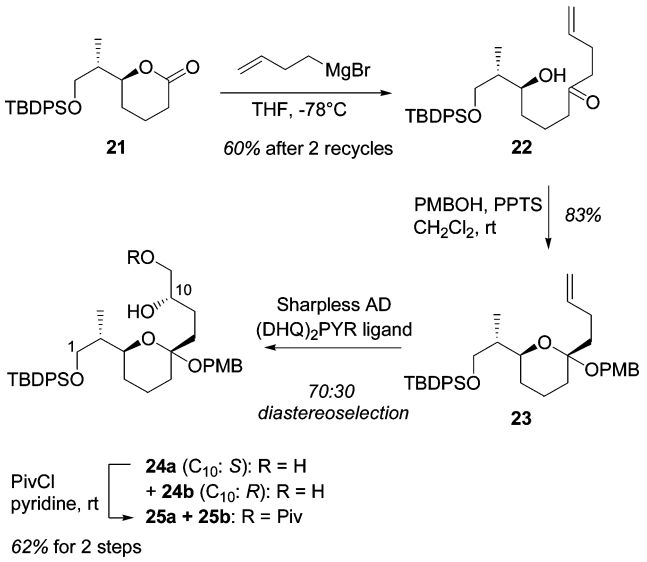
(4) (a) Amano, S.; Fujiwara, K.; Murai, A. *Synlett* **1997**, 1300−1302. (b) Awakura, D.; Fujiwara, K.; Murai, A. *Synlett* **2000**, 1733−1736.
(5) Micalizio, G. C.; Roush, W. R. *Org. Lett.* **2001**, *3*, 1949−1952.
(6) Paquette, L. A.; Peng, X.; Bondar, D. *Org. Lett.* **2002**, *4*, 937−940.
(7) (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.

(8) (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974−5976. (b) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922−1925. (c) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765−5780.

95% ee upon recrystallization.[14] Monosilylation of the diol with TBDPS chloride (98%) and reductive debenzylation (89%) cleanly afforded the diol **20**. Finally, oxidation of **20** with PCC gave the A ring lactone **21** in 58% yield.

Treatment of lactone **21** with 4-butenylmagnesium bromide (Scheme 4) afforded **22** in a total yield of 60% after

Scheme 4



two recycles of the starting material.[15] Acid-catalyzed methanolysis of keto alcohol **22** gave an unstable product that readily decomposed to give a mixture of elimination products. Replacement of MeOH with *i*-BuOH did not improve the stability of the resulting mixed ketal; however, the benzyl and especially the *p*-methoxybenzyl (PMB) ketals were stable enough to be carried over the subsequent steps. The PMB ketal **23** was obtained in 83% yield from **22** by

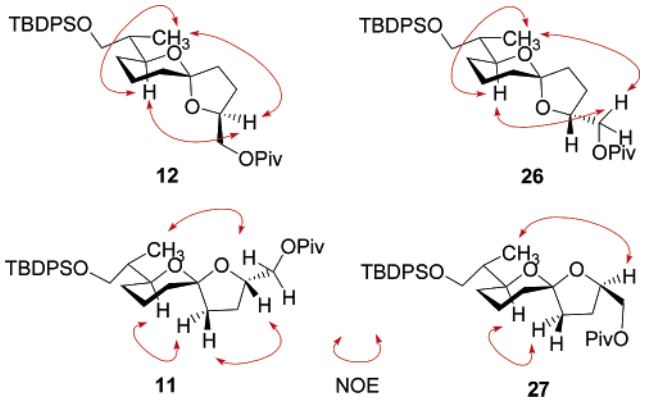


Figure 3. Diagnostic NOESY cross-peaks observed for the spiroketalization products.

treatment with an excess of PMB alcohol and PPTS in CH_2Cl_2.

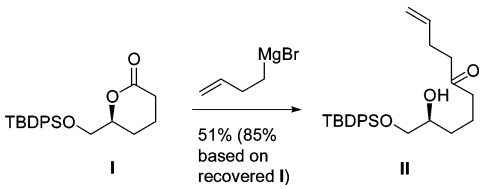
Dihydroxylation of the ketal **23** using the Sharpless ligand $(DHQ)_2PYR$, the ligand typically recommended for dihydroxylation of terminal alkenes,[16] cleanly afforded the diol product in 70:30 diastereoselection. To prevent the formation of the more stable but undesired [6,6]-spiroketal, the crude diol was immediately protected as the monopivalate (PivCl, pyridine), yielding a mixture of **25a** and **25b** in 62% over two steps.

Different acid promoters spanning a pK_a range from <-2 to 5 were screened (Table 1) for the key spiroketalization reaction. The use of a strong acid (*p*-TsOH) led to the rapid formation of a mixture of spiroketals. The less polar products were identified as the two anomerically stabilized spiroketals **12** and **26**; the minor product **26** corresponded to the C_{10} epimer. The more polar product **11** was only observed in the initial stages of the reaction. Further equilibration afforded the spiroketals **12** and **26** almost exclusively (entry 3). Thus, the spiroketal **11** appears to be a *kinetic product*.

The use of weaker acids as promoters afforded progressively larger amounts of the more polar spiroketal isomer **11**. Several diagnostic NOESY cross-peaks clearly identified **11** as the *nonanomeric* spiroketal isomer, with an equatorial C−O bridge (Figure 3).[17] The configurations of the other spiroketal isomers were also assigned by NOESY experiments.

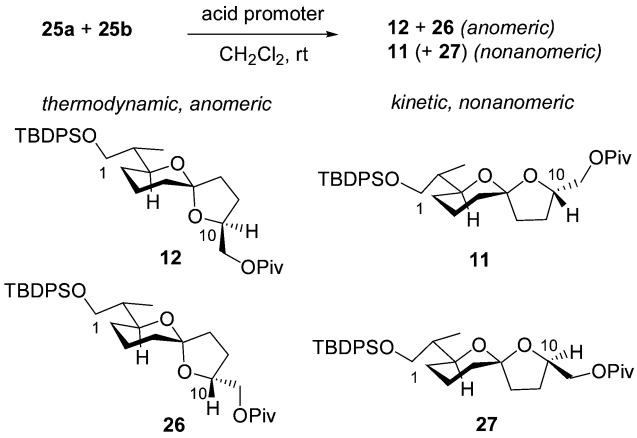
Chloroacetic acid was found to be the optimal acid catalyst for the kinetic spiroketalization, affording the nonanomeric

(9) Pihko, P. M.; Salo, T. M. *Tetrahedron Lett.* **2003**, *44*, 4361−4364.
(10) (a) Ando, K. *Tetrahedron Lett.* **1995**, *36*, 4105−4108. (b) Ando, K. *J. Org. Chem.* **1997**, *63*, 11934-1939. (c) Ando, K. *J. Org. Chem.* **2000**, *65*, 4745−4749.
(11) Börjesson, L.; Csöregh, I.; Welch, C. J. *J. Org. Chem.* **1995**, *60*, 2989−2999. We found the following procedure to be very convenient on large-scale benzylation of 1,5-pentanediol: Kiddle, J. J.; Green, D. L. C.; Thompson, C. M. *Tetrahedron* **1995**, *51*, 2851−2864.
(12) Lipshutz, B. H.; Kozlowski, J. Wilhelm, R. S. *J. Am. Chem. Soc.* **1982**, *104*, 2305−2307.
(13) White and co-workers have employed this very robust protocol in a manner very similar to our study: White, J. D.; Blakemore, P. R.; Green, N. J.; Hauser, E. B.; Holoboski, M. A.; Keown, L. E.; Nylund Kolz, C. S.; Phillips, B. W. *J. Org. Chem.* **2002**, *67*, 7750−7760.
(14) Enantiomeric purity of **19** was determined, after its conversion to **20**, by chiral HPLC (see Supporting Information).
(15) In a model system, we had previously utilized a simpler lactone **I** that readily afforded the desired hydroxy ketone **II** upon treatment with 4-butenylmagnesium bromide in 51% yield (85% based on recovered starting material): Pihko, P. M.; Rissa, T. K. Unpublished work.



(16) (a) Crispino, G. A.; Jeong, K.-S.; Kolb, H. C.; Wang, Z.-M.; Xu, D.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 3785−3786. (b) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483−2547. (c) The use of the corresponding $(DHQ)_2AQN$ ligand (see: Becker, H.; Sharpless. K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 448−451) did not improve the selectivity.
(17) Consistent with our assignment, the ^{13}C NMR chemical shift of the C_7 spiro carbon was also shifted downfield relative to **12** and **26** (109.4 ppm in **11** vs 107.2 in **12** and 107.3 in **26**). For comparative data in the [6,6]-spiroketal series, see: Pothier, N.; Goldstein, S.; Deslongchamps, P. *Helv. Chim. Acta*. **1992**, *75*, 604−620. A similar trend is also seen in the pectenotoxins; see ref 2a).

Table 1. Relative Proportions of the Spiroketal Products with Different Acid Promoters[a]



entry	acid promoter	pK_a H_2O (DMSO)	reaction time	**12** (%)	**26** (%)	**11** (+**27**) (%)
1	PPTS (20 mol %)	5.21 (3.4)	10 min	53	18	29[b]
2	TsOH (20 mol %)	−1.3	10 min	51	21	28
3	TsOH (20 mol %)	−1.3	90 min	70	30	<2
4	**$ClCH_2CO_2H$ (80 mol %)**	**2.86**	**4 h**	**29**	**22**	**49**[c]
5	HCOOH (40 mol %)	3.77	4 h	29	28	43
6	AcOH (200 mol %)[d]	4.76 (12.3)	6 h	34	26	40
7	AcOH (3300 mol %)	4.76 (12.3)	21 h	65	35	<2

[a] For entries 2, 3, 5, and 6, the relative proportions were determined by HPTLC analysis after the reaction had reached >90% conversion. For entries 1, 4, and 7, the ratios represent isolated yields of the products. [b] Including 10% **27**. [c] Including 5% **27**. [d] With 20 or 40 mol % AcOH, the reaction failed to go to completion within 24 h.

spiroketal **11** as the major product in 49% yield.[18] Interestingly, under these conditions, less than 5% of the minor C_{10} epimer **27** was formed. Spiroketal **12** corresponds to the C_1−C_{11} AB spiroketal segment of PTX-4 and PTX-7, and spiroketal **11** corresponds to the identical C_1−C_{11} AB segment present in PTX-1-3 and PTX-6.

The formation of the anomerically nonstabilized spiroketal isomers under kinetic control was first demonstrated by Deslongchamps and co-workers in the [6,6]-spiroketal series.[19] They suggest that the formation of the less stable spiroketal isomers can be conveniently explained by assuming an early transition state for the spirocyclization. Kitching[20] has reported similar observations with [6,6]-spiroketals; however, to the best of our knowledge, ours is the first documented example of a kinetically controlled spiroketalization in the [6,5]-series.

Access to the nonanomeric spiroketal **11** provides, for the first time, a direct avenue to all isomers of the pectenotoxins (PTX-1−3 and PTX-4−6), since the remaining pectenotoxins (PTX-8−10) can readily be obtained by acid-catalyzed isomerization.[21]

In summary, we have developed a novel entry into the AB spiroketal portion of the pectenotoxins. Importantly, as a result of kinetic control in the spiroketalization reaction, our route could be applied to the synthesis of all members of the pectenotoxin family, including the thus far elusive members bearing the nonanomeric spiroketal.

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

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(18) Less strong acids such as acetic, formic, and chloroacetic acid clearly afforded higher yields of the nonanomeric product **11**. It should be noted that the pK_a values in DMSO were much more reliable guides to reactivity than those measured in H_2O, presumably because the spirocyclizations were performed in an aprotic solvent (CH_2Cl_2). Thus, PPTS is effectively a *stronger acid* than any of the carboxylic acids in such a medium.

(19) A late transition state would be expected to suffer from significant stereoelectronic strain during the cyclization, since the TS would then become more and more twist-boat-like. An early TS would suffer only from small bias. For a thorough discussion, including illustrations of the different possible transition states, see ref 17.

(20) Chen, J.; Fletcher, M. T.; Kitching, W. *Tetrahedron: Asymmetry* **1995**, *6*, 967−972.

(21) Acid-catalyzed isomerization of PTX-4 bearing an anomerically stabilized spiroketal afforded a mixture of PTX-8 (79%), PTX-1 (10%), and PTX-4 (11%) (ref 7b). While all isomers of the pectenotoxins might be obtainable through these isomerization reactions, isomerization appears to favor products with anomeric stabilization.