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Diastereoselective Synthesis of the Pectenotoxin 2 Non-Anomeric AB Spiroacetal

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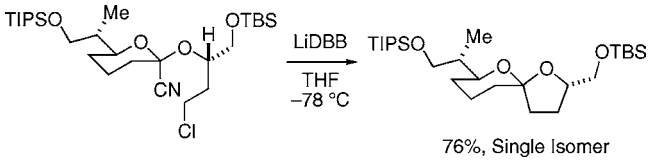
ABSTRACT



76%, Single Isomer

The reductive cyclization reaction of a cyanoacetal has been used to prepare the pectenotoxin 2 (PTX-2) AB spiroacetal with high diastereoselectively for the first time. The strategy is convergent and makes use of the axial-selective reductive lithiation of 2-cyano tetrahydropyran rings to introduce the spiroacetal center with the desired non-anomeric selectivity.

The pectenotoxins are a family of polyether macrolide natural products originally isolated from the scallop *Patinopecten yessoensis* as causative agents for diarrhetic shellfish poisoning.[1] The dinoflagellate *Dinophysis fortii* was found to produce pectenotoxin 2 (PTX-2, Figure 1).[2] PTX-2 is considered the progenitor of PTX-1, PTX-3, and PTX-6, which would be produced upon metabolism by the scallop. PTX-2 exhibits nanomolar cytotoxicity against breast, colon, and lung cancer cell lines.[3] PTX-2 and PTX-6 interact with the actin skeleton at a unique site, effecting depolymerization of F-actin.[4] Actin damage is believed to be responsible for triggering apoptosis in p53-deficient tumor cells by PTX-2.[5] The scarcity, structural complexity, and potent biological activity have made the pectenotoxins priority targets for synthetic chemists.

Evans completed the first and only syntheses of pectenotoxin macrolides, PTX-4 and PTX-8, in 2002.[6] Many other research groups have described approaches to fragments of pectenotoxin, including Murai,[7] Roush,[8] Brimble,[9] and Paquette.[10] Of particular relevance to the current report, Pihko reported the synthesis of the AB spiroacetal segment of PTX-2 by a kinetic cyclization.[11] We now describe a diastereoselective route to the non-anomeric PTX-2 AB spiroacetal.

Control of configuration of the AB spiroacetal of the pectenotoxins is a daunting challenge. The more stable AB spiroacetal with the 7*S* configuration, found in PTX-4 and

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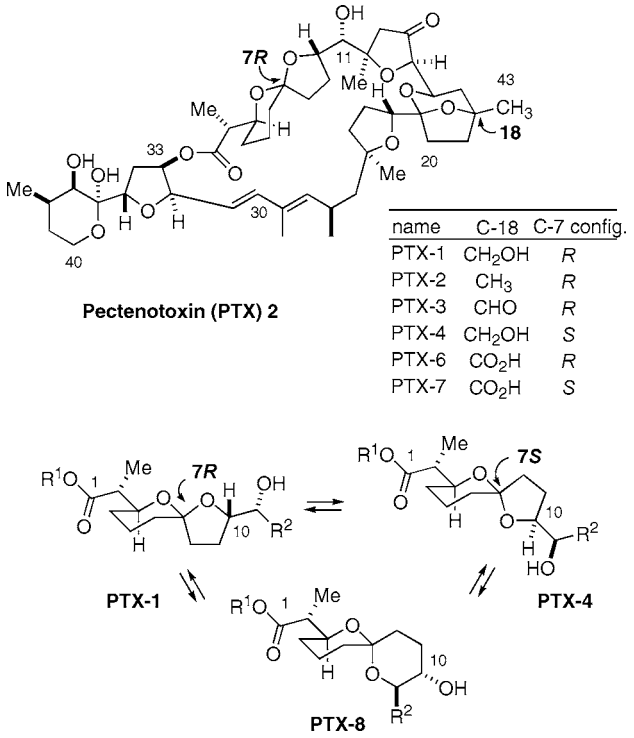


Figure 1. Structures of selected pectenotoxins.

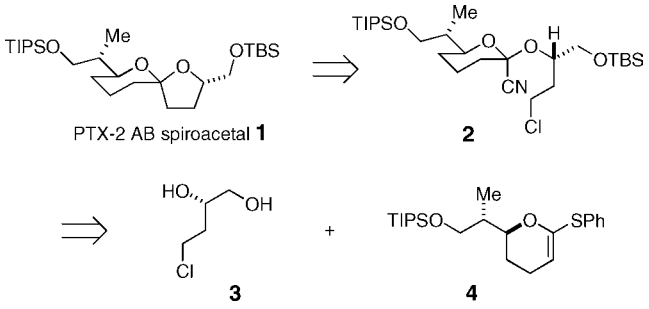
PTX-7, has two anomeric interactions. The less stable AB spiroacetal with the 7*R* configuration has only one anomeric interaction and is found in PTX-1, PTX-2, PTX-3, and PTX-6 (Figure 1). The most active of the pectenotoxins, PTX-2 and PTX-6, both have the non-anomeric 7*R* configuration. Because of constraints in the macrocyclic ring, both spiroacetals epimers in pectenotoxin structure have similar stabilities. With the exception of Pihko's approach, all of the routes to the pectenotoxins described to date rely on a late stage equilibration of the spiroacetal or have not addressed the issue.

Evans reported the equilibration of synthetic PTX-4 to PTX-8 (a [5,5]-spiroacetal that may be an isolation artifact) and 11% of PTX-1, the spiroacetal epimer. This experiment stands in contrast to Sasaki's equilibration of natural PTX-1, which returned 29% of PTX-1 along with PTX-4. Presumably one or the other of these mixtures did not reach equilibrium. If Evans' equilibration study represents a true equilibrium, then the prognosis for a late-stage equilibration leading to the 7*R* pectenotoxins is poor.

Our approach to the pectenotoxin non-anomeric AB spiroacetal is designed around a reductive lithiation and cyclization of 2-cyanotetrahydropyrans. This strategy has been used to prepare non-anomeric [5,4]- and [5,5]-spiroacetals with excellent selectivity[12] and was recently applied to the synthesis of the core of spirofungin B.[13] Tan recently described a complementary epoxide cyclization strategy for the preparation of non-anomeric [5,5]-spiroacetals.[14] The occurrence and synthesis of non-anomeric spiroacetals has recently been reviewed.[15]

The synthetic strategy is outlined in Scheme 1. The non-anomeric AB spiroacetal **1** will be prepared by reductive

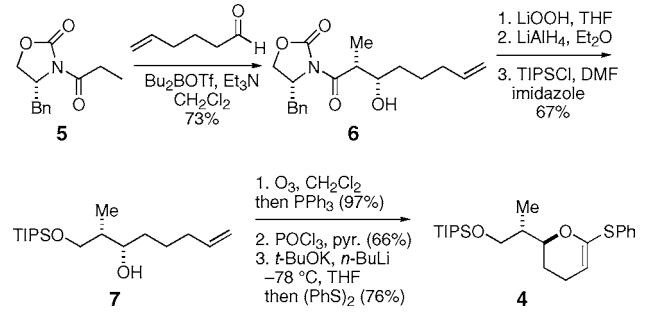
Scheme 1. Retrosynthetic Disconnection of the PTX-2 Non-Anomeric Spiroacetal



lithiation of the 2-cyano tetrahydropyran **2**. Reductive lithiation will generate the axial alkyllithium reagent, which will then cyclize with retention of configuration onto the primary alkyl chloride. The cyano acetal **2** can be further disconnected into the diol **3** and the dihydropyran **4**. The two stereocenters in dihydropyran **4** will arise from an Evans' aldol adduct. Late stage coupling of the diol **3** and dihydropyran **4** makes the strategy convergent.

Synthesis of the dihydropyran **4** is outlined in Scheme 2. Reaction of the boron enolate from **5** with 5-hexenal gave

Scheme 2. Synthesis of the Dihydropyran **4**



the aldol adduct **6** in 73% yield with a 97:3 dr.[6a] Hydrolysis and reduction with LAH produced the expected diol in 70% yield. Selective protection with TIPSCl led to the secondary alcohol **7**. Ozonolysis of **7** generated the lactol as a 1.5:1

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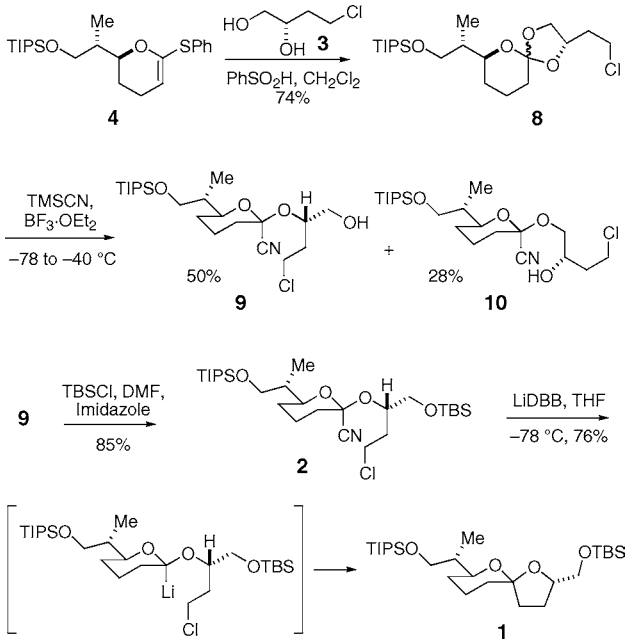
mixture of diastereomers. Dehydration of the lactol with $POCl_3$ in hot pyridine produced the unsubstituted dihydropyran.[16] Introduction of the 2-thiophenyl substituent required optimization. Initial experiments using *t*-BuLi gave modest yields, accompanied by recovered enol ether. Schlosser's base led to better results. Deprotonation at −78 °C in THF, followed by addition of diphenyl disulfide, gave the 2-thiophenyl dihydropyran **4**. The mixture was contaminated with diphenyl disulfide, which was not easily separated by chromatography. Addition of methyllithium to the crude reaction mixture converted it to thioanisole and thiophenol, which were removed under high vacuum. Purification of the product gave 76% of 2-thiophenyl dihydropyran **4** and 16% of the unreacted starting material. Compound **4** was prepared in 7 steps and 24% overall yield.

The synthesis was completed as shown in Scheme 3. Diol **3** was prepared by the previously described procedure from

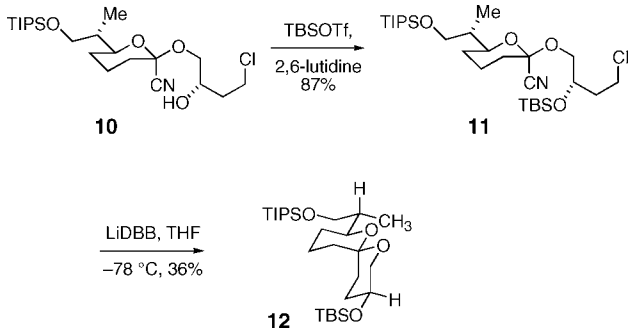
Scheme 3. Synthesis of the Pectenotoxin 2 AB Spiroacetal **1**



commercially available material.[17] Preparation of the orthoester **8** required that both the dihydropyran **4** and the diol be scrupulously dried over 4 Å molecular sieves. Treatment with benzenesulfinic acid gave the orthoester in 74% yield as a 1:1 mixture of diastereomers. In previous cases we have observed primary selective cleavage of orthoesters with TMSCN and $BF_3{\cdot}OEt_2$,[18] but in this case two regioisomers were produced with the preferred regioisomer **9** formed in 50% yield.[19] The secondary orthoester oxygen in compound **8** is relatively unhindered compared with most previous cases, which may account for the low selectivity in the orthoester cleavage. This lack of selectivity may account for minor cyanoacetal isomers observed but not characterized in previous cases.[12,13] After silyl protection, the reductive cyclization reaction was carried out by slow addition of freshly prepared LiDBB in THF at −78 °C. The non-anomeric spiroacetal **1** was isolated in 76% yield as a single diastereomer.

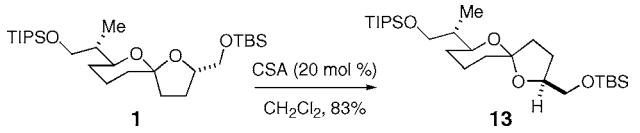
The other regioisomer **10** was not silylated efficiently with TBSCl and imidazole, but it could be silylated with TBSOTf (Scheme 4). Reductive cyclization led to the expected [5,5] non-anomeric spiroacetal **12** in modest, unoptimized yield.

Scheme 4. Cyclization of the Minor Cyanoacetal Isomer



That compound **1** has the non-anomeric configuration at the spiroacetal was confirmed by the characteristic 108.0 ppm ^{13}C NMR peak for the [4,5]-spiroacetal center. Treatment of compound **1** with CSA in CH_2Cl_2 (Scheme 5) led to

Scheme 5. Equilibration of the Pectenotoxin 2 AB Spiroacetal **1**



complete isomerization to the more stable anomeric spiroacetal with a ^{13}C NMR peak at 106.9 ppm. These chemical shifts are consistent with those observed for the pectenotoxin spiroacetals.[20]

The non-anomeric AB spiroacetal of pectenotoxin 2 was prepared by a reductive cyclization strategy. This route is the first highly diastereoselective approach to the less stable spiroacetal in the pectenotoxins and lays the ground work for a diastereoselective approach to the more active pectenotoxin natural products.

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(17) Diol **3** was prepared as described for the enantiomer in ref 12. Commercially available (*S*)-2-(2,2-dimethyl-[1,3]dioxolan-4-yl)-ethanol was treated with MsCl and LiCl in DMF, followed by hydrolysis with Dowex and methanol.

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(19) We first observed this lack of regioselectivity in another case. The structures of **9** and **10** were demonstrated by oxidation to an aldehyde and a ketone, respectively. See Supporting Information for details.

(20) Non-anomeric PTX-1 and PTX-6 show the acetal carbon at 107.5 ppm. Anomeric PTX-4 has the acetal carbon shifted to 106.3 ppm.

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Supporting Information Available: Preparation and characterization of the described compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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