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Spirodiepoxide Strategy to the C Ring of Pectenotoxin 4: Synthesis of the C1−C19 Sector

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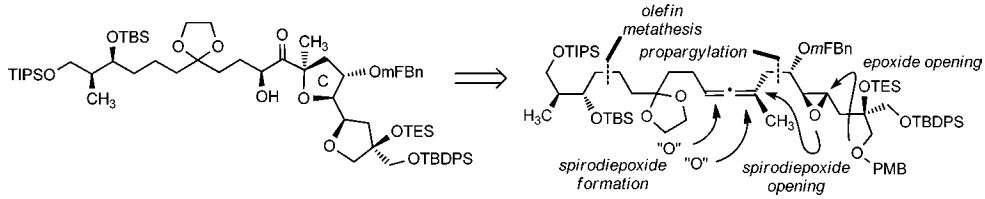
ABSTRACT



The synthesis of a C1−C19 precursor to pectenotoxin 4 is presented. The strategy employed the functionalized allene shown. Key features include: olefin metathesis of two simple fragments to prepare the left portion of the allene-precursor, diastereoselective propargylation of an epoxy aldehyde to form the right portion, use of the DMDO-stable *m*-fluorobenzyl ether, and an allene spirodiepoxidation/C-ring formation cascade.

Here we report a short convergent route to a functionalized fragment (C1−C19) of pectenotoxin 4 that relies upon the use of spirodiepoxides[1] to install the C-ring and functionalized C10−C12 functionality. The pectenotoxins (PTX) represent a significant challenge to chemical synthesis.[2] For example, pectenotoxin 4 (**1**) embodies a 34-membered macrolide, 19 stereocenters, a spiroketal (AB), bicyclic ketal (D) and hemiketal (G), and 3 functionalized tetrahydrofuran rings (C, E, and F). One total synthesis of a pectenotoxin has been achieved to date.[2c,d] Several new methods and strategies have been developed through focused studies on these targets.[3]

One set of related strategies is to fashion the AB spiroketal and then the C-ring via a C10−C12 spirodiepoxide or to

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form these rings in the reverse order,[1a] the difference being that C10−C12 allenes of opposite configuration must be used. For example, double epoxidation of an allene of type **3** would set into motion a spontaneous cascade of bond-breaking and forming events to give the fully substituted C ring system (Figure 1B). In this study we set out to scout

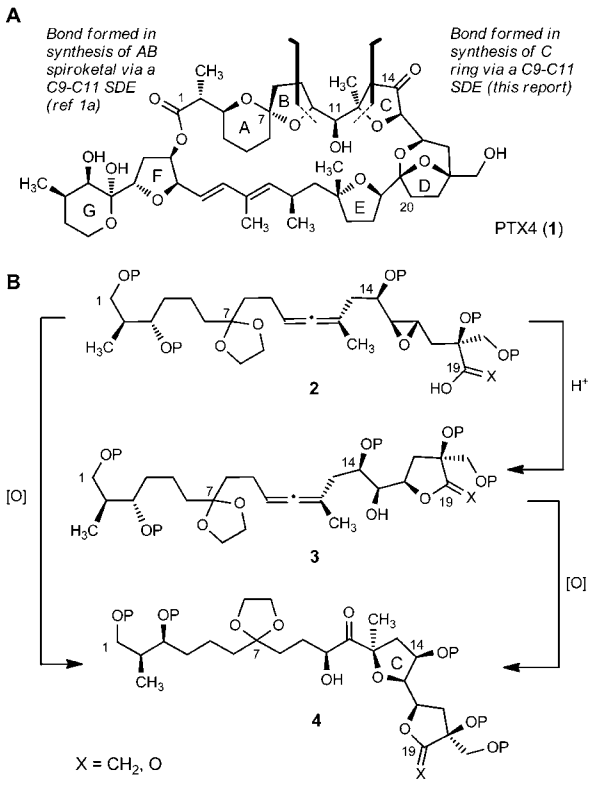
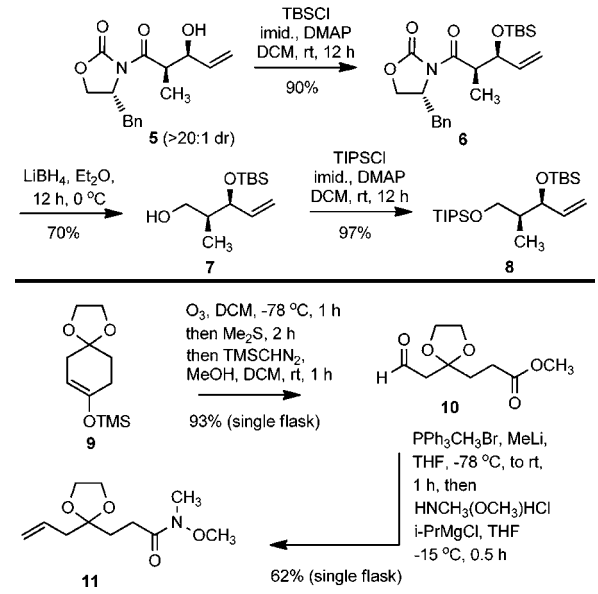


Figure 1. C1−C19: Focus on a C9−C11 Spirodiepoxide.

this possibility,[4] including an expanded cascade sequence to directly convert allenes of type **2**, to oxacycles of type **4** upon epoxidation. As with our earlier work, this strategy takes advantage of copper-mediated stereospecific allene assembly.[1] Thus, we prepared **33**, a specific target of type **4**. Alkenes **8** and **11** were prepared and joined to give the C1−C10 fragment (Schemes 1 and 2); the C11−C19 fragment **26** was also fashioned (Scheme 3). The C1−C10 and C11−C19 fragments were then fused to give the full C1−C19 sector which was evaluated for ring formation (Scheme 4).

The precursors to the C1−C10 fragment were prepared as shown in Scheme 1. Known syn aldol[5] product **5** was converted to the TBS ether (90%) and then reduced with $LiBH_4$ to give **7** (70%). The resultant primary alcohol was also masked (→**8**, 97%). The coupling partner for **8**, amide **11**, was synthesized from silyl enol ether **9** obtained from the corresponding commercially available cyclohexanone ketal (not shown).[6] Ozonolysis[7] and subsequent methylation of the newly formed acid using $TMSCHN_2$[8] in the presence of methanol furnished ester aldehyde **10** in a single flask from **9** (93%). A single flask procedure for the direct

Scheme 1. C1−C10 Precursor Synthesis

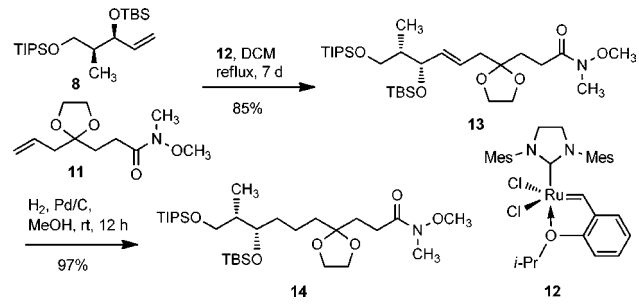


conversion of **10** to amide **11** was also realized. Methylenation of **10** followed by amide formation[9] gave **11** in 62% overall yield. This procedure avoids isolation of the volatile methylenation product.

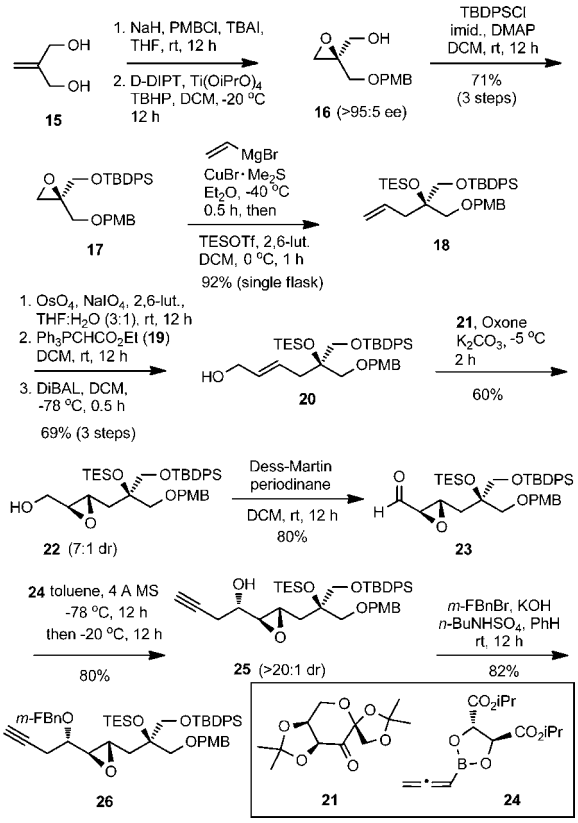
Union of the C1−C10 precursors **8** and **11** was accomplished with catalyst **12**[10] in refluxing DCM (→**13**, 85% yield, single isomer, geometry not assigned, Scheme 2). The use of bulk DCM[11] proved superior to benzene and gave substantially less homodimerization of **11**. Only after treatment of **13** under conditions designed to remove trace ruthenium was hydrogenation efficient (→**14**, 97%).[12] The longest linear sequence to the C1−C10 sector required 6 steps from commercial materials.

The strategy to prepare the C11−C19 fragment was guided, in part, by the desire to evaluate the compatibility of asymmetric propargylation with epoxy aldehydes of type **23** (Scheme 3). The synthesis began with conversion of commercially available diol **15** to mono-PMB ether, subsequent asymmetric epoxidation (**16**, >95:5 ee),[13] and then silyl ether formation (**17**, 71% over three steps). Addition of the higher order vinyl cuprate generated from the vinyl Grignard

Scheme 2. C1−C10 Fragment Synthesis



Scheme 3. C11−C19 Fragment Synthesis



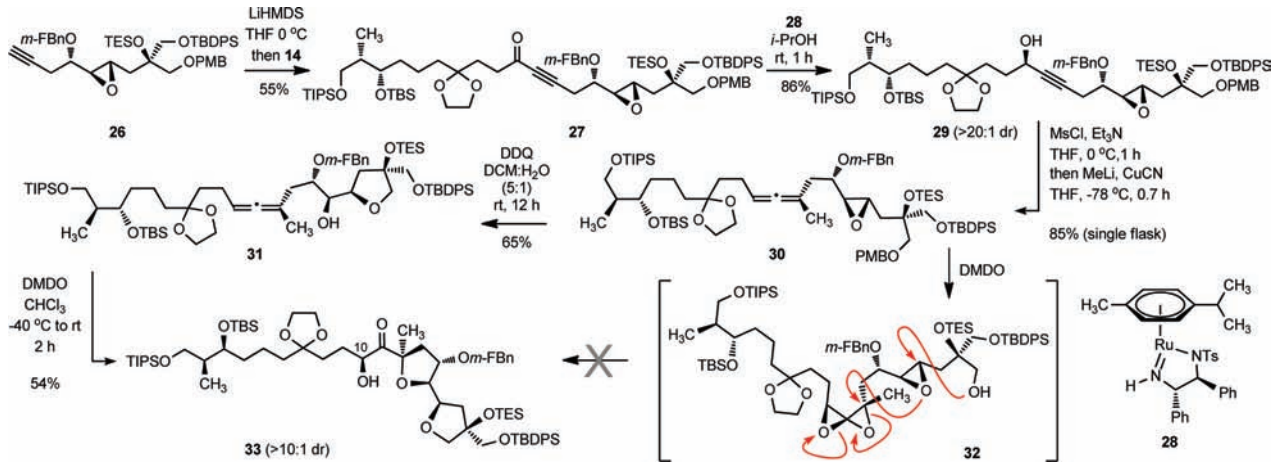
and CuBr•Me_2S effected epoxide opening; immediate exposure of the crude reaction mixture to silylation conditions gave terminal olefin **18** in excellent yield (92% from **17**). Compound **18** was molded into **20** via a three step sequence (69% yield) wherein the alkene was transformed into the aldehyde, which was homologated with **19**, and then reduced to the alcohol. Shi epoxidation proved to be slow (→**22**, 60%) but selective.[14] This method was more efficient than Sharpless epoxidation, which was accompanied by PMB cleavage and subsequent epoxide ring-opening (not shown), as well as formation of the diastereomeric epoxide. Dess-Martin oxidation of **22** furnished the epoxy aldehyde **23** (80%).

Yamamoto propargylation[15] effected conversion of **23** to alkynol **25** in good yield and stereoselectivity (80%, >20:1 dr). Although we did not assign the configuration of this center at this stage, based on NMR analysis of **33** (vide infra) the stereochemistry is as drawn. This under-utilized method is both simple and efficient. The procedure required allenyl boronic acid and D-DIPT for in situ preparation of the chiral allenyl boronate (**24**) and proved compatible with the epoxide, silyl, and PMB protecting groups of **23**. For reasons described below, the hydroxyl group was masked as the *m*-fluorobenzyl ether (*m*-FBn) to give the C11−C19 subunit. The route to **26** required 11 steps from commercial materials.

One of our key strategic interrogatives pertained to the possible union of fragments **14** and **26**. Although there is do direct precedent, we were optimistic that the acetylide derived from **26** could be formed with minimal damage to the epoxide and used in a subsequent nucleophilic acyl substitution reaction.[16] Alkynylide addition to Weinreb amides is slow in comparison to additions to ketones and aldehydes and often requires temperatures near 0 °C. Nevertheless, **26** was smoothly converted to the corresponding epoxy acetylide at 0 °C, and addition of amide **14** to the reaction mixture afforded epoxy alkynone **27** in 55% yield.[17] The epoxide functionality posed no serious complicating factor for alkynylation of the Weinreb amide or the subsequent steps up to the final sequence. Hence, Noyori reduction[18] (86%, >20:1 dr) was followed by mesylation and then copper-mediated allene formation **30** (85%). Although mild oxidations were found to remove the PMB group and thereby afford the corresponding epoxy alcohol (not shown), treatment of **30** with DDQ effected cleavage of the PMB group and spontaneous epoxide opening to furnish **31** (65%).

It is remarkable that spirodiepoxides behave well in complex structural contexts—more so even than in unfunctionalized settings. We were anxious, therefore, to evaluate the spirodiepoxides derived from **30** and **31**. Our expectation

Scheme 4. C1−C19 Sector Synthesis



was that allene oxidation would proceed along standard lines and the major spirodiepoxide stereochemistry would correspond to that shown for **32**. Thus, the first oxygen would be delivered to the more substituted π-bond, since this should be the most nucleophilic portion of the allene. Approach would be highly selective and occur from the most accessible face. The second epoxidation would likely be less selective but would also be governed by sterics.[1g]

PMB ethers are cleaved rapidly in the presence of DMDO in chloroform.[1a] However, we found *m*-FBn ethers to be stable to these conditions. Consequently, we masked the C14 hydroxyl with this group and aimed to convert **30** to **33** directly (c.f. **2** → **4**, Figure 1). The extended cascade would include in situ PMB cleavage as part of the transformation from **30** → **31** → **33**. There is an ill-defined distinction between functionality able to open spirodiepoxides and that which cannot.[1] Considerations along this line identified a provocative possibility: the epoxide might open the spirodiepoxide prior to, or in a concerted manner with, epoxide opening by the hydroxyl group, as shown for **30** → **32** → **33**. Treatment of **30** with excess DMDO under a variety of conditions effected cleavage of the PMB group. formation of the spirodiepoxide (assign as **32**), and other products, but not **33**. The stepwise approach, however, was successful, as exposure of allene **31** to DMDO smoothly furnished **33** as a single isomer (54%).[19] The C10 epimer, the expected minor stereoisomer of this reaction, was not evident. Minor related compounds that appear to be nonstereoisomeric side products were observed by 500 MHz ^{1}H NMR spectroscopy in $CDCl_3$.[20] This transformation illustrates the facility of the spirodiepoxide logic: oxidation converts the axial chirality of the allene into three centers of chirality[21] and also, in this case, sets into motion subsequent conversion to the α-tetrahydrofuranyl-α′-hydroxy ketone.

This report establishes a concise route to the C1−C19 sector of pectenotoxin 4. From commercial reagents, the longest linear sequence to **33** is 16 steps. Aside from establishing stereoselective inroads to the natural product, several notable advances were realized, these include the: (a) highly stereoselective propargylation of an epoxy aldehyde (→**26**), (b) alkynylation of amides with epoxy alkynylides (→**27**), (c) demonstration that the *m*-FBn ether is a robust functional group stable to allene epoxidation conditions (cf. **31** → **33**), and (d) late-stage conversion of an allene to an elaborated tetrahydrofuran via the spirodiepoxide (→**33**). The insights these data provide will be used in further studies toward this target and should be generalizable to other targets as well.

Acknowledgment. Financial support from the NIH (GM-078145) is gratefully acknowledged.

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

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(16) Hoffmann-Roder, A.; Krause, N. *Helv. Chim. Acta* **2002**, *85*, 3176. This report did not include nucleophilic acyl substitution, e.g. addition to amide derivatives; however, it appears to be the only work on alkynylide additions to carbonyl derivatives with epoxides in tow.

(17) The *m*-FBn appears to have compromized this yield. A TBS analogue of **26** (instead of *m*-FB) under the conditions shown formed the acetylide and added to the TIPS analogue of amide **14** (instead of TBS) and gave the corresponding epoxy alkynone in 95% yield.

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(19) A detailed stereochemical analysis (1D and 2D NMR) of **33** is provided in the Supporting Information.

(20) Studies on these minor constutuents are ongoing.

(21) The central carbon of this spirodiepoxide is stereogenic.