

Synthetic Studies Toward Pectenotoxin

2. Part II. Synthesis of the CDE and CDEF Ring Systems

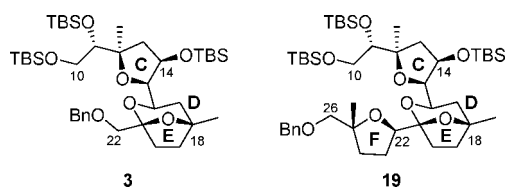
Hannes Helmboldt,[†] Jatta E. Aho,[†] and Petri M. Pihko^{*‡}

Department of Chemistry, Helsinki University of Technology, POB 6100, FI-02015 TKK, Finland, and Department of Chemistry, University of Jyväskylä, POB 35, FI-40014 University of Jyväskylä, Finland

petri.pihko@jyu.fi

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ABSTRACT

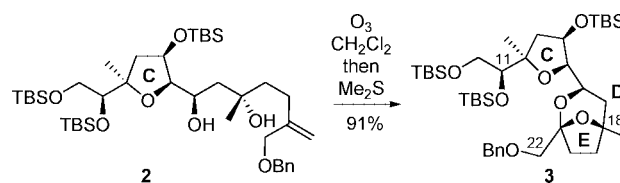


A convergent synthesis of the CDE and CDEF ring systems of pectenotoxin-2 from C and F ring precursors is described.

In the previous communication, we presented a stereocontrolled route to the open-chain C₁₀–C₂₂ fragment of the pectenotoxins (PTXs).¹ Herein, we describe the synthesis of the advanced CDE and CDEF ring systems, strategic intermediates for the total synthesis of PTX2.

Having completed the synthesis of the fully functionalized C₁₀–C₂₂ fragment **2**, all that remained was the ozonolysis of the C₂₁ olefin and subsequent intramolecular ketalization to furnish the CDE ring system. Fortunately, the mild reductive workup conditions of ozonolysis (Me₂S at –78 °C to rt, for 3 h) also triggered the internal ketalization event to afford the desired CDE ring system **3** in 91% yield (Scheme 1).

Scheme 1. Synthesis of the CDE ring system



The stereochemistry of the CDE ring fragment was clearly established by extensive NOE studies and analysis of the relevant coupling constants (Figure 1).

At this juncture, a number of strategic issues remained unanswered. The utility of the methyltitanation–ozonolysis sequence with more synthetically realistic fragments, bearing

(6) The optimization required: (1) Lowering the amount of active osmium in the dihydroxylation mixture. According to ref 5b, terminal olefins react more slowly in the presence of MeSO₂NH₂ if only 0.2 mol % of K₂OsO₄·2H₂O is used. The commercially available AD-mix β contains about 0.4 mol % of catalyst. (2) The reaction was run only to ca. 30% conversion, and the remaining starting material was recycled. (3) Use of transesterification catalyst, 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), to ensure complete lactone formation. See: Schuchardt, U.; Sercheli, R.; Vargas, R. M. *J. Braz. Chem. Soc.* **1998**, *9*, 199–210.

[†] Helsinki University of Technology.

[‡] University of Jyväskylä.

(1) Aho, J. E.; Salomäki, E.; Rissanen, K.; Pihko, P. M. *Org. Lett.* **2008**, *10*, 4179–4182.

(2) (a) Fischer, R.; Hoffmann, W.; Langguth, E.; Siegel, H. *Eur. Pat. Appl.* 1995 4179-4182. (b) Silvestri, M. A.; He, C.; Khoram, A.; Lepore, S. D. *Tetrahedron Lett.* **2006**, *47*, 1625–1626.

(3) Hagen, G.; Mayr, H. *J. Am. Chem. Soc.* **1991**, *113*, 4954–4961.

(4) Kawashima, M.; Fujisawa, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 4051–4055. Other methods of (*E*)-olefin construction, such as Julia–Kocienski olefination, gave remarkably inferior *E:Z* selectivities.

(5) (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.

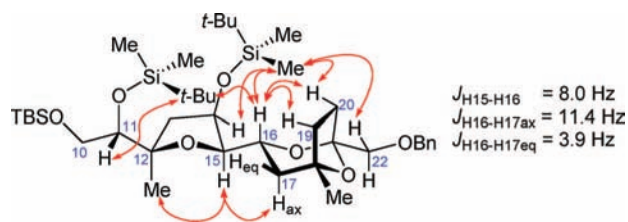
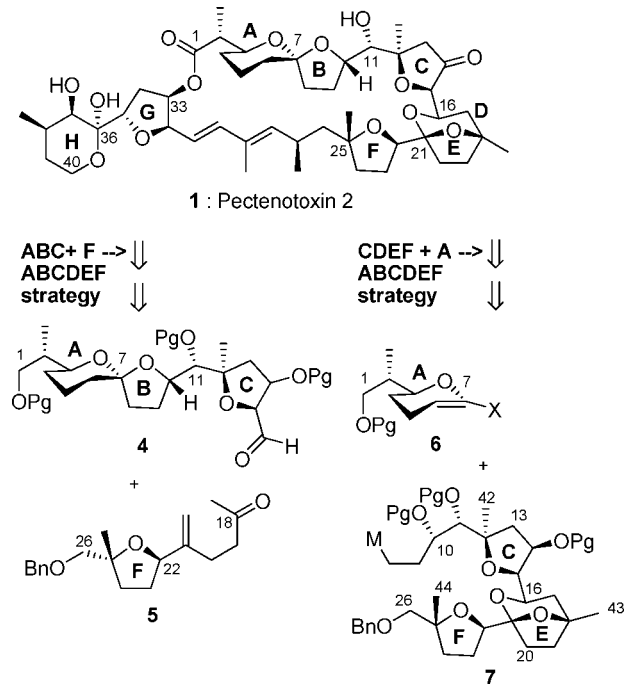


Figure 1. Selected diagnostic NOESY cross-peaks and coupling constants in the CDE ring fragment **3**.

at least the F ring system, remained to be demonstrated. In addition, we have previously addressed the synthesis of the nonanomeric AB ring system of the PTXs, and the compatibility of the DE ring synthesis with this sequence would be highly desirable. Ideally, we would like to include the nonanomeric AB spiroketal unit with the C ring building block (the ABC + F → ABCDEF strategy, Scheme 2). To

Scheme 2. Two Different Strategies for the Construction of the ABCDEF Ring System of PTX2 and Structures of Potential Building Blocks^a

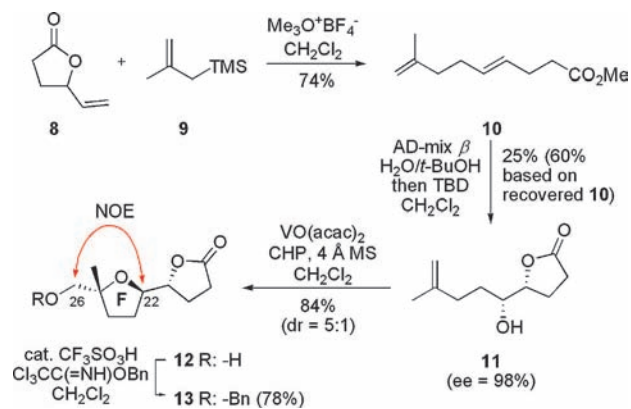


^aPg = protecting group, M = metal, X = leaving group.

test the viability of this strategy, the stability of the nonanomeric AB spiroketal unit to the DE ring ketalization conditions must be tested in a realistic system bearing the F ring.

Synthesis of the F ring building block **5** commenced with ring opening of easily accessible γ -vinyl butyrolactone **8**² with methallylsilane **9**³ in the presence of Meerwein's salt to give diene **10** in good yield as a single isomer (Scheme 3).⁴ In the next step, a regioselective asymmetric dihydroxy-

Scheme 3. Synthesis of the F Ring THF Unit



lation⁵ under carefully optimized reaction conditions⁶ gave access to lactone **11** with useful levels of regioselectivity (4:1) and 98% ee.⁷ Repeated reaction cycles afforded gram quantities of lactone **11**.

The bishomoallylic alcohol **11** was epoxidized using a combination of catalytic VO(acac)₂ and cumene hydroperoxide (CHP).⁸ Under these conditions, the intermediate epoxy alcohol readily cyclized to give the 2,5-*trans* substituted tetrahydrofuran **12** as the major product (dr = 5:1).⁹ The stereochemistry of the product could readily be predicted by the Kishi model.^{8b} The stereochemistry of the product was assigned by key NOE correlations observed in **12** and the benzyl ether¹⁰ derivative **13** (Scheme 3).

Lactone **13** was transformed into the desired ketone **5** in a four-step sequence (Scheme 4): (1) conversion into Weinreb amide **14**, (2) Ley oxidation¹¹ of the secondary alcohol, (3) Wittig olefination of the crude ketone, and (4) treatment of the Weinreb amide with methyl magnesium chloride.

(7) A benzoate derivative was used for ee determination (see Supporting Information).

(8) (a) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136–6137. (b) Nakata, T.; Schmid, G.; Vranesic, B.; Okigawa, M.; Smith-Palmer, T.; Kishi, Y. *J. Am. Chem. Soc.* **1978**, *100*, 2933–2935. (c) Hashimoto, M.; Harigaya, H.; Yanagiya, M.; Shirahama, H. *J. Org. Chem.* **1991**, *56*, 2299–2311. For a recent review, see: (d) Hartung, J.; Greb, M. *J. Organomet. Chem.* **2002**, *661*, 67–84.

(9) The use of CHP instead of TBHP and the presence of molecular sieves greatly improved the reproducibility of this reaction, but no change in the diastereoselectivity was observed.

(10) Iversen, T.; Bundle, D. R. *J. Chem. Soc., Chem. Commun.* **1981**, 1240–1241.

(11) Griffith, W. P.; Ley, S. V.; Whitecombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625–1627.

(12) (a) Ukaji, Y.; Kanda, H.; Yamamoto, K.; Fujisawa, T. *Chem. Lett.* **1990**, 597–600. (b) Ruano, J. L. G.; Tito, A.; Culebras, R. *Tetrahedron* **1996**, *52*, 2177–2186.

(13) The use of excess MeTi(OiPr)₃ gave finally in all cases reproducible results.

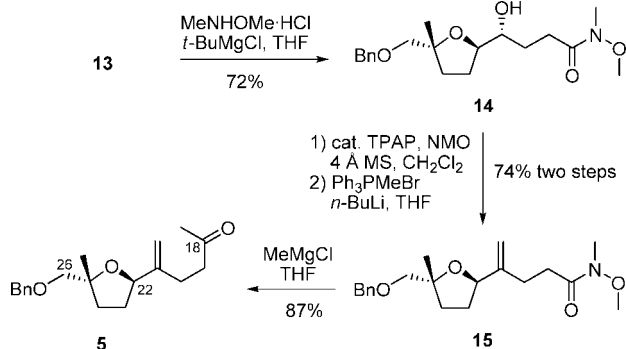
(14) Presumably, the presence of additional chelating groups (benzyl ether, two THF ring units) in **17** interferes with the reaction.

(15) Veysoglu, T.; Mitscher, L. A.; Swayze, J. K. *Synthesis* **1980**, 807–810.

(16) For a review of nonanomeric spiroketals, see: Aho, J. E.; Pihko, P. M.; Rissa, T. K. *Chem. Rev.* **2005**, *105*, 4406–4440.

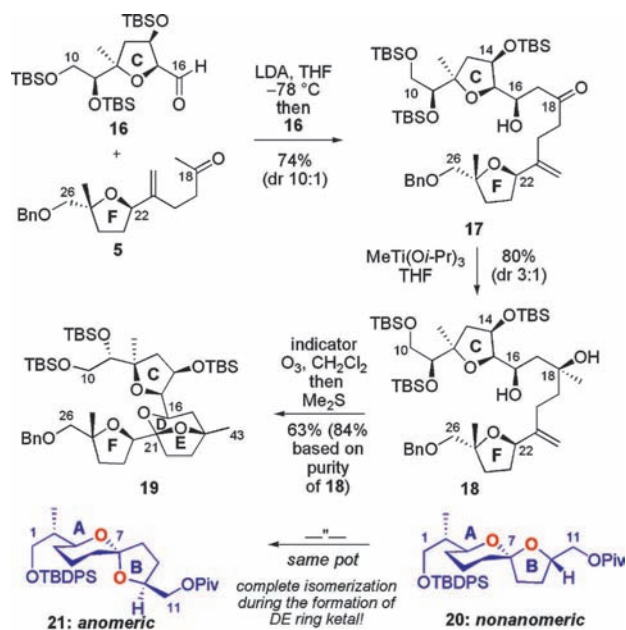
(17) ~50% of the isomerization of **20** to **21** occurred within 5 min (see Supporting Information for details). For the synthesis and characterization of **20** and **21**, see: Pihko, P. M.; Aho, J. E. *Org. Lett.* **2004**, *6*, 3849–3852.

Scheme 4. Synthesis of Ketone **5**

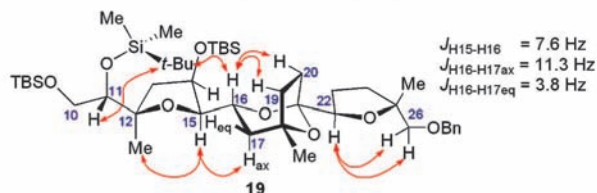


The aldol union of ketone **5** and aldehyde **16**¹ yielded the β -hydroxyketone **17** with excellent selectivity (Scheme 5) and

Scheme 5. Synthesis of the CDEF Ring Fragment of PTX2 and the Key Strategic Experiment



Selected NOESY cross-peaks and coupling constants for **19**



good yield. However, the key hydroxyl-directed methyltitanation¹² of **17** required a considerable amount of experimentation¹³ to obtain a reproducible protocol. The reaction was much more sluggish than with the simpler C₁₀–C₂₂

precursor aldol system.¹ Ultimately, a slightly modified version of the in situ protocol described in previous communication afforded diol **18** reproducibly in good yield and acceptable diastereoselectivity (3:1 dr).¹⁴

In the final step, treatment of diol **18** with ozone in the presence of indicator Sudan Red 7B¹⁵ followed by mild reductive workup furnished ketal **19** in very good yield based on the (*S*)-configuration of C₁₈. The stereochemistry of the CDEF ring system was confirmed by NOESY experiments and also by comparison with the CDE ring system **3**.

As outlined above (Scheme 2), one of the key strategic issues in the total synthesis of PTX2 is the stability of the nonanomeric spiroketal. The lability of nonanomeric spiroketals under acidic conditions is well-known,¹⁶ but we had high hopes that the ozonolysis–ketal cyclization sequence used for the synthesis of the CDE and CDEF ring systems would be mild enough to preserve the AB spiroketal¹⁷ intact. In the event, the ozonolysis/cyclization step was also conducted on a mixture of **19** and a small amount of nonanomeric **20** (see Scheme 5). To our surprise, concomitant with the formation of the DE ring ketal system during the workup stage, the nonanomeric AB ring system **20** underwent *complete isomerization* into the more stable anomeric isomer **21**.¹⁷ Presumably, the acidic side products generated during the ozonolysis step are strong enough to catalyze both ketal formation and spiroketal isomerization. In any case, this result strongly suggests that a more cautious strategy where the formation of the nonanomeric AB ring system takes place *after* the cyclization of the DE ring ketal should be employed in the total synthesis of PTX2.

In summary, we have synthesized advanced C₁₀–C₂₂ (CDE) and C₁₀–C₂₆ (CDEF) intermediates **3** and **19**. These intermediates possess the correct stereochemistry and proper functionalization to allow their use as building blocks for the total synthesis of PTX2. Our synthesis of the CDEF ring system from ketone **5** (7 steps from known **10**, 18% overall yield) and aldehyde **16** (9 steps, 46% overall yield) is highly convergent and has also yielded important insight into the overall strategy required for the total synthesis of this labile natural product. Further studies toward the total synthesis of PTX2 via the A + CDEF strategy are underway.

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

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