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Synthesis of the pectenotoxin 4 EFG rings

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Cobalt versus osmium: control of both *trans* and *cis* selectivity in construction of the EFG rings of pectenotoxin 4[**]

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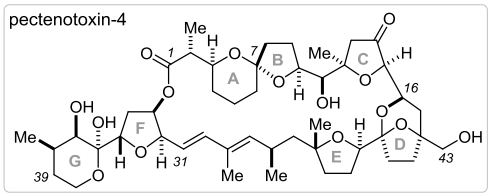
Abstract: Catalytic oxidative cyclisation reactions have been employed for the synthesis of the E and F rings of the complex natural product target pectenotoxin 4. The choice of metal catalyst (cobalt or osmium based) allowed for the formation of THF rings with either trans or cis stereoselectivity. Fragment union using a modified Julia reaction then enabled the synthesis of an advanced synthetic intermediate containing the EF and G rings of the target.

The pectenotoxin (PTX) family of natural products are a series of macrocyclic polyethers which boast intriguing structural complexity and potent biological (eg anti-tumour) activity.[1] The first members of the family, PTXs-1-5, were isolated by Yasumoto and co-workers off the coast of Japan, in 1985.[1] Local folklore had described the occurrence of gastroenteritis following the ingestion of shellfish harvested in late spring to summer. Therefore, Yasumoto and co-workers examined native scallops in the hope that the toxins causing this disease could be identified. It was discovered that the digestive glands of the scallops contained PTXs-1-5 along with the polyether fatty acids dinophysistoxin (DTX)-1 and -3. Since this report, a series of other pectenotoxin natural products (approximately 20) have been isolated. These more recently isolated natural products have structures that are similar to the original PTX compounds, with variation mainly occurring at the spirocyclic acetal centre together with differing oxygenation patterns on the macrocyclic polyether backbone.[2]

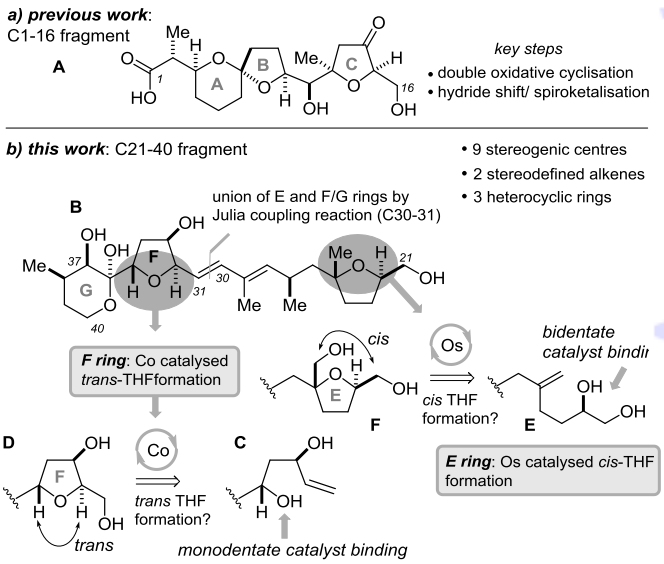


Given their intriguing structure and biological activity it is not surprising that the pectenotoxins have attracted the interest of synthetic organic chemists. Despite the fact that an impressive set of synthetic methods have been focused on preparing these natural products[3] there have only been two successful syntheses of any pectenotoxins to date, by Evans (PTX-4) [4] and Fujiwara (PTX-2).[5]

We were attracted to the pectenotoxins because of the prevalenc of multiply substituted THF rings bearing a range of stereochemica arrangements (compare rings C, E and F). These targets provide challenging test for methodology we have developed which use catalytic osmium to construct THF rings with a high degree c stereochemical control.[6] Indeed, our previous work in this area ha described a short route to the C1-C16 fragment of PTX-4 using a osmium catalysed double oxidative cyclisation in concert with hydride initiated spiroketalisation sequence (Scheme 1a).[7]

With the ABC fragment completed, we now wished to synthesis the EFG portion of this natural product (Fragment **B**, Scheme 1b We envisaged that **B** could be broken into two smaller fragment (the E ring and the FG unit) which could be coupled by a key Juli reaction (Scheme 1b), followed by formation of the hemi-aceta containing G ring as the final step.

Accessing both the E and F THF rings would require tw different oxidative cyclisation approaches. Of particular interest wa the possibility of using either cobalt (2,5-*trans*, F ring)[8] or osmiur (2,5-*cis*, E-ring)[6] catalysis to install the required stereocentres in divergent manner. The two different stereochemical outcomes hav their origins in the way that the alcohol substrate binds to the meta prior to cyclisation. Mono-dentate binding, as exhibited by cobal leads to *trans* stereochemistry (see **C→D**), while bidentate bindin (of a 1,2-diol) to osmium enforces *cis* stereochemistry in the TH product (see **E→F**). We sought to utilise both of these catalyti cyclisations to our advantage in the synthesis of PTX-4.



Scheme 1. *Cis* and *trans* THF cyclisation modes using Os and Co catalysis

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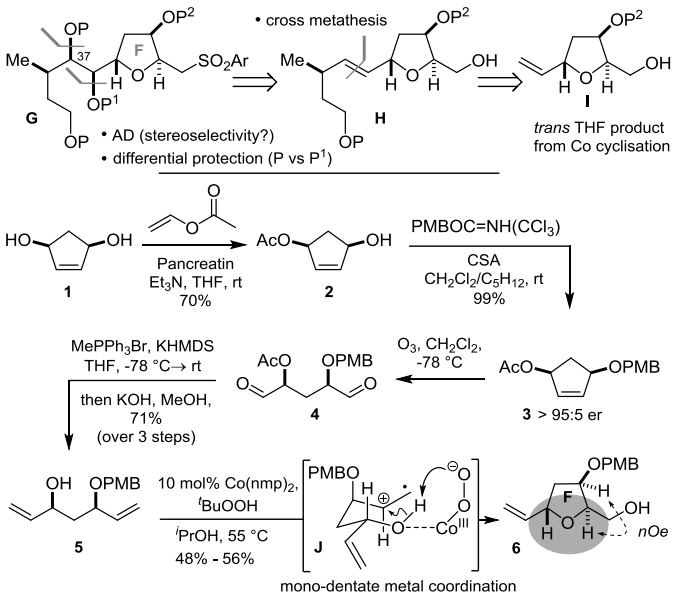
Scheme 2 shows the key sulfone sub-target **G** required for the Julia coupling; the stereochemistry at C37 could be installed by a Sharpless AD reaction on *trans*-alkene **H**, itself derived by cross-metathesis of the cobalt cyclisation product **I**.

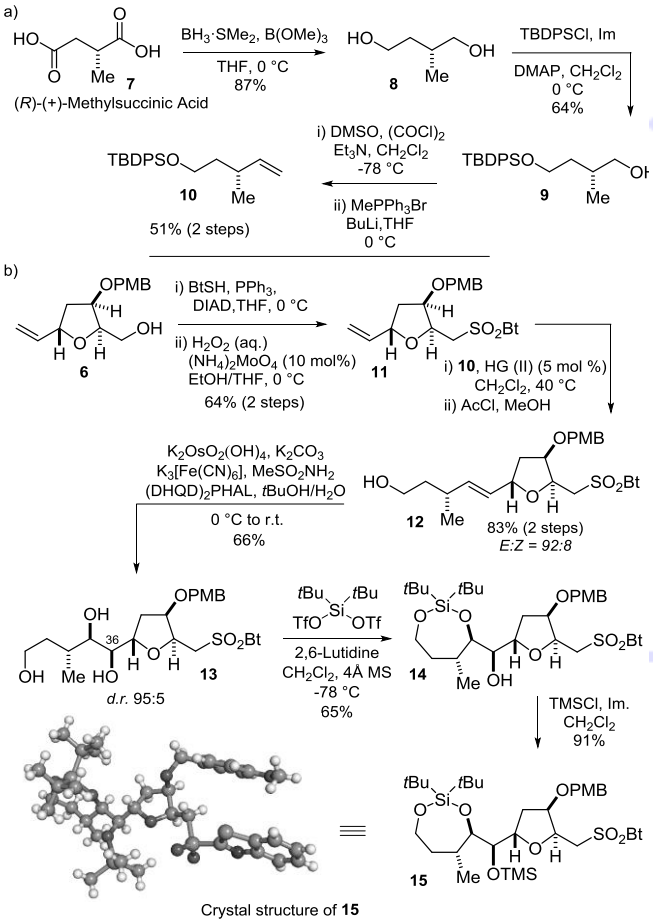
Our synthesis of the pectenotoxin F ring fragment **I** began with commercially available meso diol **1**, which was desymmetrised using Pancreatin catalysis to give a mono-acetate **2** of known absolute configuration (Scheme 2).[9] Protection of the remaining hydroxyl group as a PMB ether was accomplished under acidic conditions to furnish compound **3.** This material was determined to have ≥95:5 enantiomeric ratio by a sequence that involved acetate deprotection and Mosher's ester analysis of the unprotected alcohol. Subsequent ozonolysis of **3** was followed immediately by a double methylenation reaction on the unstable aldehyde **4** under Wittig conditions to produce the cyclisation substrate **5** (after *in situ* acetate deprotection). Finally, the key cobalt catalysed *trans* THF forming reaction transformed **5** into **6** in acceptable yield and as a single (*trans*) diastereoisomer (*via* an intermediate such as **J**), as proven by nOe experiments.



Scheme 2. Formation of the *trans* THF F-ring of PTX-4 by cobalt catalysed cyclisation.

In order to complete construction of the FG ring scaffold, the corresponding cross metathesis coupling partner **10** was prepared from (*R*)-methylsuccinic acid **7** using the four step sequence shown in Scheme 3a.[10] The pivotal step revolved around regioselective protection of the least hindered alcohol group of diol **8** with TBDPSCl, as reported by Lautens. Note that the mixture of regioisomers formed during this step could not be separated until the formation of alkene **10**.

Experimentation showed that it was desirable to transform compound **6** into the (Julia) sulfone coupling partner **11** prior to cross metathesis; this was achieved in a two-step displacement/oxidation process, Scheme 3b. The cross metathesis coupling between **10** (4 equivalents) and **11** then proceeded with Hoveyda Grubbs (II) catalyst in 83% yield,[11] followed by TBDPS deprotection with HCl/MeOH, to give the *E*-alkene **12** (92:8 dr, *J*= 15 Hz). Diastereoselective dihydroxylation of **12** was accomplished with good selectivity (95:5 dr) using the $(DHQD)_2PHAL$ ligand for a Sharpless asymmetric dihydroxylation reaction.[12] Interestingly, selectivity of 95:5 dr for the alternative *syn* diol diastereoisomer could be achieved by using a $(DHQ)_2PHAL$ ligand for the dihydroxylation (structure not shown). Regioselective protection of triol **13** was essential for further manipulation because the hydroxyl group at C-36 must be oxidised selectively later in the synthesis. Pleasingly, reaction of **13** with di-*tert*-butylsilyl ditriflate (DTBSOTf) afforded the cyclic bis-protected compound **14** in 65% yield. Presumably compound **14** is formed after initial reaction of the primary alcohol with the silylditriflate, followed by selective ring closure to form a seven, rather than eight, membered ring. Finally, the C-36 hydroxyl was protected with a labile TMS group in 91% yield to form product **15** as a crystalline solid whose structure was confirmed by Single Crystal X-ray diffraction studies.[13] Pleasingly, this structure proves beyond doubt the *trans* selectivity of the Co-catalysed cyclisation, the sense of diastereoselectivity during dihydroxylation and the regioselectivity of triol **13** protection using the silylditriflate reagent.



Scheme 3. Cross metathesis and asymmetric dihydroxylation *en route* to the pectenotoxin FG ring system: MBT mercaptobenzothiazole.

Next, we embarked on a synthesis of the pectenotoxin E-rin utilising the osmium catalysed oxidative cyclisation to set th desired stereochemistry between the C-22 hydroxymethyl and C-2 methyl groups. Our route began with a regioselective 1,2-protection of the triol derived from reduction of (*R*)-malic acid (**16→17**, Scheme 4). Conversion of the remaining primary alcohol into the iodide was followed by sequential S_N2 displacement by the anion of TMS-acetylene, and silyl deprotection, to furnish compound **18**. A nickel catalysed hydroalumination (followed by an iodination quench) as developed by Hoveyda then allowed for the selective formation of regioisomer **19**,[14] which was coupled to a zinc reagent derived from serine under Negishi conditions to form 1,1-disubstituted alkene **20**.[15] The osmium catalysed THF forming reaction was then attempted under conditions that were acidic enough to deprotect the acetal and so form the chelating 1,2-diol

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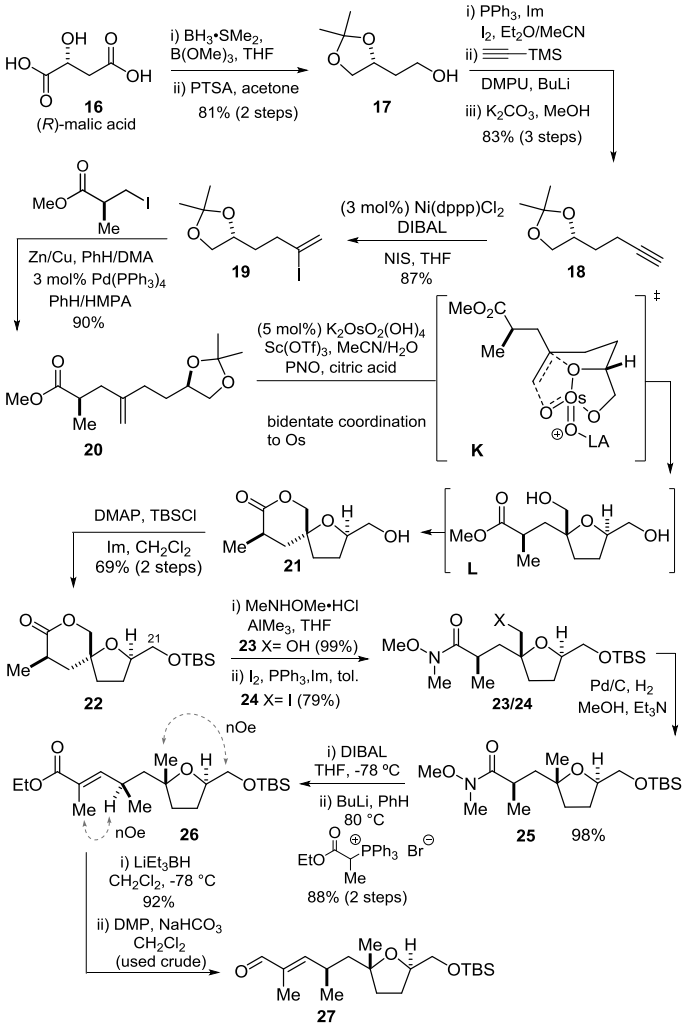
motif *in situ*, this forming the basis for the cyclisation *cis*-stereochemistry. Pyridine N-oxide (PNO) is a particularly effective reoxidant for this transformation because it allows osmium to be shuttled between the (IV) and (VI) oxidation states without forming unwanted Os(VIII).[16] Transition structure **K** provides a plausible explanation for the observed stereochemical outcome of the reaction. Note that the initially formed diol **L** lactonised *in situ* so that the product was **21**, which was isolated as TBS ether **22** in 69% yield over the two steps. The formation of lactone **21** was a planned extension of the oxidative cyclisation that enabled us to form the THF ring and allow selective protection of the hydroxyl groups within **L**, all in one pot.

Opening of the lactone **22** was accomplished by reaction with *N*-methyl-*O*-methyl hydroxylamine and trimethyl aluminium to form **23**, with the Weinreb amide functionality installed for easy access to the corresponding aldehyde later in the synthesis. Reduction of the C-25 hydroxymethyl group was accomplished in two steps: firstly formation of the iodide **24** with iodine and triphenyl phosphine followed by hydrogenolysis using H_2 gas and a palladium catalyst (**25**). Thus, the C-25 hydroxymethyl group derived from the oxidative cyclisation was transformed into the C-25 methyl group with the correct relative stereochemistry. Finally, the Weinreb amide was reduced to an aldehyde and olefinated with a methyl substituted stabilised ylid to form (*E*)-alkene **26**. The ester was reduced and then transformed into aldehyde **27** in preparation for Julia coupling with the previously prepared sulfone **15**. Note that nOe measurements on the ester **26** confirmed both the alkene and THF ring stereochemistry as shown.

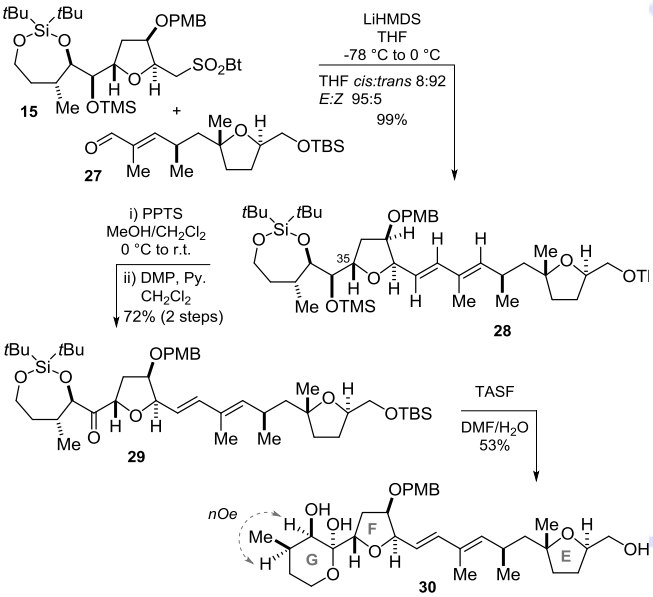


Scheme 4. Osmium catalysed oxidative cyclisation

We were now able to examine the key C-C bond forming reaction to join the two fragments; based on precedent from Evans, we chose a modified Julia coupling to accomplish this step.

A complication with this coupling was the fact that the E-ring was prone to reversible ring opening *via* elimination of the anion derived from sulfone **15**; this led to formation of the coupled alkene product containing an unwanted *cis*-THF ring. This problem had originally been identified by Evans and, by using conditions which involved a lithium anion and low temperatures, Evans' protocol allowed the formation of **28** as a 92:8 mixture of *trans* / *cis* THF diastereoisomers, coupled with selective formation of the *E*-alkene (J= 16 Hz).[4]

The synthesis of the C21-40 fragment **30** was then completed by selective TMS deprotection at C36, followed by oxidation to the ketone **29** using DMP. Finally, TASF promoted deprotection of a silyl protecting groups liberated a triol that spontaneously forme the desired cyclic hemi-acetal EFG system **30** *in situ*.[17]



Scheme 5. Completion of the synthesis of the pectenotoxin-EFG ring system

In conclusion, we have demonstrated the synthetic utility of bot the osmium and cobalt catalysed oxidative cyclisation reactions controlling the relative stereochemistry of the E- and F-rings preser in PTX-4. Both catalytic cyclisations performed well, and afforde very high levels of diastereoselectivity for the desired products. Th two fragments were then combined using a Julia coupling, whic allowed for the synthesis of the C21-40 EFG fragment of the targe PTX-4.

Keywords oxidation · catalysis · pectenotoxin · osmium · cobalt

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[17] We have assumed that the stereochemistry at C36 (hemiacetal) is formed as the thermodynamically more stable stereoisomer with an axial C-36 hydroxyl group; this assumption is based on the behaviour of related systems as reported in the two previous synthesis of the pectenotoxins.[4,5]

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Synthesis of the pectenotoxin 4 EFG rings

Cobalt versus osmium: control of both *trans* and *cis* selectivity in construction of the EFG rings of pectenotoxin 4

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Two types of oxidative cyclisation reaction, utilising either osmium or cobalt catalysis, provide complete control of the relative stereochemistry of THF rings embedded in the complex pectenotoxin-4 ring system. In this manner, rapid access to either *trans* (Co) or *cis* (Os) 2,5-disubstituted THF rings was facilitated. A significant portion of the natural product was then put together using cross metathesis and Julia coupling as the key C-C bond forming protocols.