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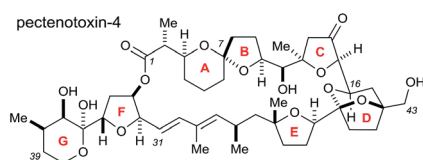
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Introduction

The pectenotoxins (PTXs) are a family of polyether macrolides containing a spiroketal (AB ring), three substituted tetrahydrofurans (C, E and F rings) and 19 or more stereocentres decorating the 40-carbon chain.¹ These intriguing natural products were first isolated in 1985 by Yasumoto and coworkers,² and have been shown to exhibit potent biological activity, including selective cytotoxicity against tumour cell lines.³

The architectural complexity of these highly functionalised macrolactones have garnered significant interest within the synthetic chemistry community,⁴ however only two total syntheses of these molecules have been completed to date: PTX-4 by Evans in 2002 (ref. 5) and PTX-2 by Fujiwara in 2014.⁶



The Donohoe group has made several significant advances towards the total synthesis of PTX-4. We have successfully synthesised the C-1 to C-16 ABC fragment *via* a double osmium catalyzed oxidative cyclisation together with a hydride-shift-initiated spiroketalisation,⁷ as well as preparing the C-21 to C-

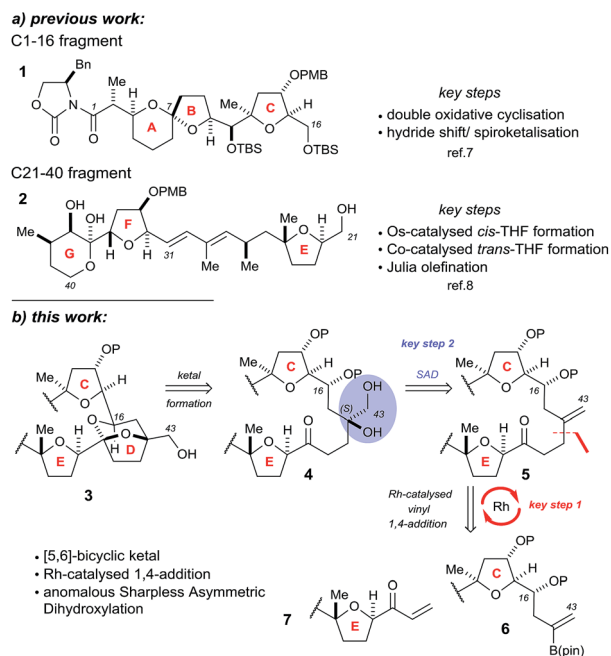
Rhodium-catalysed vinyl 1,4-conjugate addition coupled with Sharpless asymmetric dihydroxylation in the synthesis of the CDE ring fragment of pectenotoxin-4†

Melodie S. W. Richardson,^a Christopher J. Tame,^b Darren L. Poole^b and Timothy J. Donohoe ^{*,a}

Our synthesis of the CDE ring fragment of pectenotoxin-4 utilised two key steps to make the complex bicyclic ketal unit: (i) a rhodium-catalysed vinyl group 1,4-addition as the major C–C bond forming step; (ii) a stereoselective Sharpless Asymmetric Dihydroxylation (SAD) of the resulting 1,1-disubstituted homoallylic alcohol. Subsequent acid-catalysed cyclisation afforded the desired [5,6]-bicyclic ketal of the target molecule. This methodology was shown to be compatible with the desired E ring fragment **35** in order to construct the CDE fragment **37** of pectenotoxin-4.

40 EFG fragment *via* stereodivergent catalytic cobalt and osmium oxidative cyclisations (Scheme 1a).⁸

The major challenge remaining in our synthesis of PTX-4 is uniting these two complex fragments to synthesise the final [5,6]-bicyclic ketal, the D ring. A handful of approaches to this bicyclic structure for PTX-2 (ref. 4o, s, t, x, y, z and 6) and PTX-4



Scheme 1 Previously synthesised fragments and key disconnections proposed in this work for the CDE fragments: (a) previous work; (b) this work.

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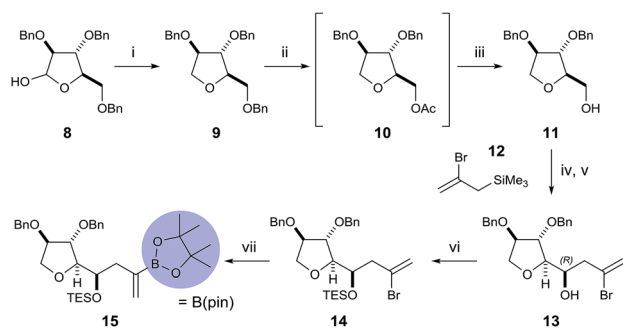


(ref. 4*d*, x and 5) have been published in the literature. Herein, we propose a novel route which proceeds *via* an unusual rhodium-catalysed vinyl 1,4-addition⁹ as the key C–C bond formation step to join the ABC and E ring fragments. It is important to note that this key reaction has the potential to allow complex molecular fragments to be joined under relatively mild conditions and without using a large excess of either, extremely valuable, component. A subsequent stereoselective dihydroxylation–ketalisation sequence should then afford the desired [5,6]-bicyclic ketal structure of the D ring of PTX-4 (Scheme 1*b*). Note here that the sensitive diene containing FG ring fragment will be constructed as it is attached to the E-ring by a Julia reaction, after cyclisation of the D ring, because the 1,3-diene fragment itself would be unlikely to survive the conditions needed for dihydroxylation and/or cyclisation.

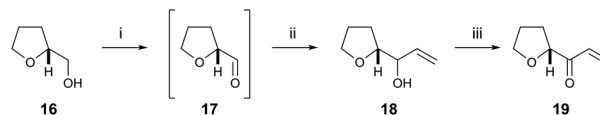
Results and discussion

To begin, we chose to use model C ring boronate **15** as a substitute for the real ABC ring fragment required in the synthesis of PTX-4 (Scheme 2). Starting from commercially available enantiopure furanose **8**, the hemiacetal was reduced to the corresponding THF **9**, and the primary benzyl group removed in two steps, *via* acetate **10**, to reveal **11**.¹⁰ Oxidation of the primary alcohol to the aldehyde followed by a Hosomi–Sakurai reaction¹¹ with bromoallylsilane **12** (ref. 12) afforded the (*R*)-homoallylic alcohol **13** as a single diastereoisomer in 56% yield over two steps. The stereochemistry arises from Felkin–Ahn-controlled addition of the bromoallylsilane **12** and was confirmed *via* Mosher's ester analysis.¹³ Direct conversion of the bromide to the desired boronate was unsuccessful; therefore protection of the secondary alcohol **13** with TESOTf was necessary. Miyaura borylation of TES-protected bromide **14** to the model C ring boronate **15** was then accomplished in 79% yield.¹⁴

Similarly, we started with a less substituted THF ring in place of the desired E ring fragment in our initial studies (Scheme 3). Therefore, (*R*)-tetrahydrofurfuryl alcohol **16** was oxidised to the corresponding aldehyde **17**, and vinyl Grignard reagent was



Scheme 2 Synthesis of the model C ring boronate **15**. Reagents and conditions: (i) Et_3SiH , $\text{BF}_3 \cdot \text{OEt}_2$, MeCN, 95%; (ii) Ac_2O , TFA; (iii) NaOMe, MeOH, 89% over two steps; (iv) DMSO, $\text{SO}_3 \cdot \text{py}$, Et_3N , CH_2Cl_2 , 0 °C; (v) **12**, $\text{BF}_3 \cdot \text{OEt}_2$, CH_2Cl_2 , –78 °C, 56% over two steps; (vi) TESOTf, imidazole, CH_2Cl_2 , 85%; (vii) $\text{B}(\text{pin})_2$, $\text{PdCl}_2(\text{PPh}_3)_2$ (3 mol%), PPh_3 (6 mol%), KOPh, PhMe, 50 °C, 79%.



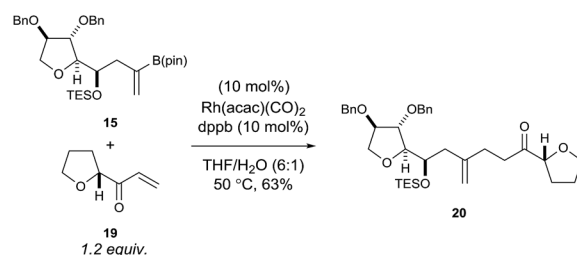
Scheme 3 Synthesis of the model E ring enone **19**. Reagents and conditions: (i) DMSO, $(\text{COCl})_2$, Et_3N , CH_2Cl_2 , –78 °C; (ii) vinyl magnesium bromide, Et_2O , –78 °C, 35% over two steps, 1.15 : 1 dr; (iii) DMP, CH_2Cl_2 , 89%.

added to afford volatile allyl alcohol **18** in 35% yield (1.15 : 1 dr at the hydroxyl centre) over two steps. Oxidation using DMP furnished the model E ring enone **19** in 89% yield.

Using rhodium-catalysed 1,4-addition conditions⁹ on model C ring boronate **15** with **19** was successful and afforded the desired adduct **20** in approximately 40% yield. However, the use of methanol as the solvent formed the methanol 1,4-addition adduct of compound **19** as a by-product, which often co-eluted with the desired products. Pleasingly, we found that replacing methanol with THF as the solvent prevented the formation of this by-product and improved the yield to 63% for the reaction between **15** and **19** (Scheme 4).

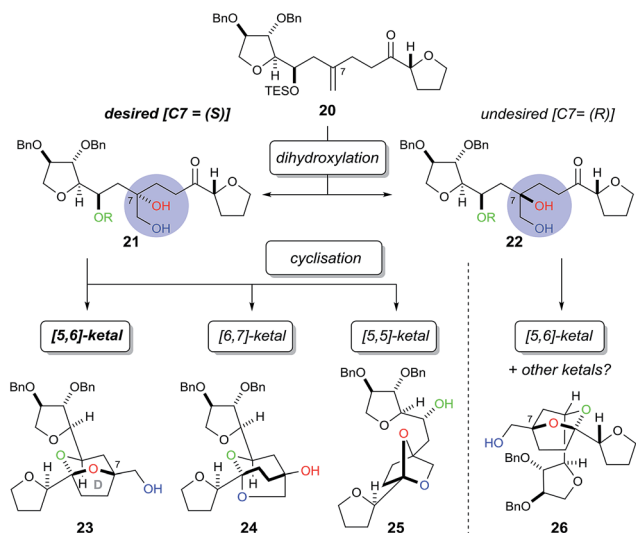
In order to ensure that no epimerisation had taken place adjacent to the ketone carbonyl, we repeated the coupling between **15** and racemic **19** (compound **S6** prepared separately, see ESI† for details). This reaction gave two diastereoisomeric compounds (in an approximately 1 : 1 ratio) and from the ¹³C NMR spectrum of this mixture we could rule out epimerisation in compound **20** formed from enantiopure **19**.

In order to construct the bicyclic acetal D-ring system we next required a facially selective dihydroxylation of the alkene within **20** (to set the stereochemistry at C7, Scheme 5) followed by a ketalisation reaction. Although the stereochemical outcome of dihydroxylation of 1,1-disubstituted alkenes are difficult to predict,¹⁵ we chose to use the Sharpless Asymmetric Dihydroxylation (SAD) to control diol formation. It is worth noting that the original mnemonic proposed by Sharpless for the SAD reaction¹⁶ is often problematic when applied to 1,1-disubstituted alkenes, as first shown by Hale.^{15*a*} In the case of substrate **20**, even if we could achieve near “perfect” facial selectivity for the correct diol **21**, acid-catalysed cyclisation could then result in three possible isomeric bicyclic ketal structures: the desired [5,6]-ketal **23**, [6,7]-ketal **24** and [5,5]-ketal **25** (Scheme 5).



Scheme 4 Rhodium-catalysed 1,4-addition reaction of model C ring boronate **15** with model E ring enone **19**.



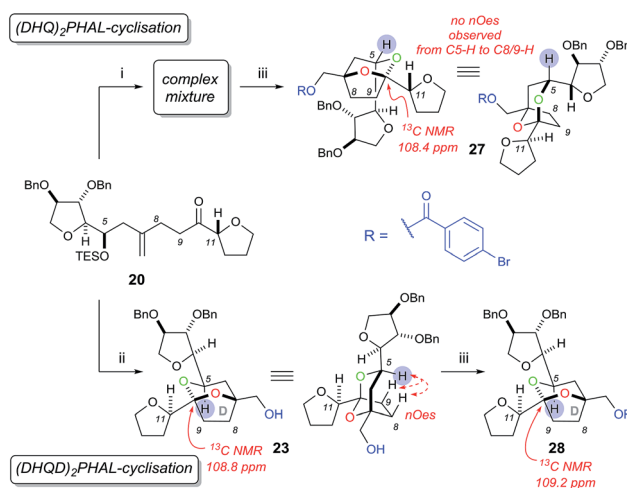


Scheme 5 Possible bicyclic ketal structures arising from diols **21** and **22**.

At first the dihydroxylation of 1,1-disubstituted alkene **20** was attempted using Upjohn conditions¹⁷ to reveal any substrate bias during oxidation, however purification and identification of the desired diol was difficult as a complex mixture of products were obtained, possibly due to TES group migration. It was proposed to cyclise the crude diol using mildly acidic conditions^{5b} while also removing the TES group; however the use of this procedure still produced in a complex mixture.

Undeterred, we chose the Sharpless Asymmetric Dihydroxylation (SAD) conditions to obtain the desired diol stereochemistry. As it is difficult to predict which ligand is required, we used both (DHQ)₂PHAL and (DHQD)₂PHAL separately. According to the mnemonic,¹⁶ we predicted (DHQ)₂PHAL would produce the desired diol. However, using (DHQ)₂PHAL ligand in the dihydroxylation and acid-induced cyclisation sequence produced a mixture of products (Scheme 6). Nevertheless, upon derivatisation of the mixture with 4-bromobenzoic acid we identified [5,6]-bicyclic ketal **27**, with a characteristic ¹³C NMR peak at 108.4 ppm.^{4d} The connectivity, supported by COSY/HSQC/HMBC experiments, was shown to be the [5,6]-ketal over the [6,7] or [5,5] isomers. Moreover, the relative stereochemistry of dihydroxylation could also be assigned as shown, because within the [5,6]-ketal structure we did not observe an nOe enhancement across the ring system (*i.e.* between C-5 to either C-8 or C-9); this would be expected in the desired ketal structure. Looking at the full set of data we concluded that compound **27** contained the [5,6]-bicyclic ketal but with the opposite stereochemistry at C-7 (as set by the initial dihydroxylation).

Interestingly, the use of (DHQD)₂PHAL in the dihydroxylation–cyclisation sequence (oxidation being followed by treatment with acid) also provided one bicyclic ketal diastereoisomer **23** with a ¹³C NMR peak at 108.8 ppm (Scheme 6). Upon detailed NMR (COSY/HSQC/HMBC) analysis, **23** was again confirmed to have the [5,6]-bicyclic ketal connectivity.



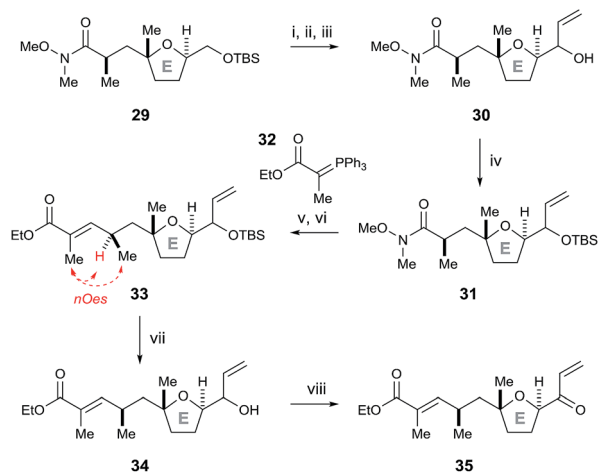
Scheme 6 Sharpless asymmetric dihydroxylation and acid-catalysed cyclisation of **20**. Reagents and conditions: (i) K₂O₈O₂(OH)₄, (DHQ)₂PHAL, K₃Fe(CN)₆, K₂CO₃, MeSO₂NH₂, *t*-BuOH/H₂O (1 : 1), 0 °C then PPTS, CH₂Cl₂/MeOH (1 : 1); (ii) K₂O₈O₂(OH)₄, (DHQD)₂PHAL, K₃Fe(CN)₆, K₂CO₃, MeSO₂NH₂, *t*-BuOH/H₂O (1 : 1), 0 °C then PPTS, CH₂Cl₂/MeOH (1 : 1), 91%; (iii) 4-bromobenzoic acid, DIC, DMAP, CH₂Cl₂, 5% over two steps for **27**, 53% for **28**.

However, this time the molecule did exhibit key nOe enhancements across the bicyclic ring (C-5 to C-8 and C-9), showing it to be the desired [5,6]-bicyclic ketal **23** originating from the correct stereochemistry at C-7. Further derivatisation of **23** with 4-bromobenzoic acid gave compound **28** which was different to the related ketal (**27**) formed from the (DHQ)₂PHAL derived experiments.

We note that other bicyclic ketals ([6,7] and [5,5]) were not isolated in any reaction, however there have been reports that these types of structures may undergo facile degradation upon purification and may not be isolatable.^{4d} Our studies show that in this system it is the (DHQD)₂PHAL ligand that delivers the correct facial selectivity during dihydroxylation, and that acid-catalysed ketalisation then forms the desired [5,6]-ketal system as found in the natural product. The fact that (DHQD)₂PHAL has formed the (*S*)-diol **21** during dihydroxylation is consistent with the reversed stereoselectivity that has been reported during the SAD reaction of 1,1-disubstituted alkenes.^{15a–e,i}

To further test this methodology in the synthesis of pectenotoxin-4, we converted the desired E ring fragment **29** (ref. 8) into the desired enone **35**, with the unsaturated ethyl ester side chain serving as a precursor for a Julia olefination coupling with the FG ring fragment. Therefore, the previously reported E fragment enantiopure **29** (ref. 8) was deprotected with TBAF, before Parikh–Doering oxidation to the aldehyde and vinyl Grignard reagent was added to afford allyl alcohol **30** (Scheme 7). The hydroxyl group was protected with TBSCl, before the Weinreb amide was reduced to the aldehyde with DIBAL-H and a Horner–Wadsworth–Emmons reaction with ylide **32** furnished (*E*)-unsaturated ethyl ester **33** (stereochemistry proven by nOe analysis). Finally, removal of the TBS group





Scheme 7 Synthesis of the E ring enone **35**. Reagents and conditions: (i) TBAF, THF, 0 °C, 96%; (ii) SO₃·py, Et₃N, DMSO, CH₂Cl₂, 0 °C; (iii) vinyl magnesium bromide, Et₂O, 0 °C, 69% over two steps; (iv) TBSCl, imidazole, DMAP, CH₂Cl₂, 88%; (v) DIBAL-H, THF, -78 °C; (vi) **32**, benzene, Δ, 87% over two steps; (vii) TBAF, THF, 78%; (viii) DMP, NaHCO₃, CH₂Cl₂, 90%.

with TBAF followed by oxidation with DMP afforded the E ring enone **35**.

Initial rhodium-catalysed 1,4-addition reaction conditions between model C ring boronate **15** and E ring enone **35** were moderately successful, affording adduct **36** in 30% yield (Scheme 8). Repeating the reaction with a more active catalyst system, [Rh(cod)OH]₂,¹⁸ improved the yield of **36** to 53%. Pleasingly, the dihydroxylation–cyclisation sequence (using (DHQD)₂PHAL ligand) then afforded the desired CDE fragment **37** in 40% yield, as a single compound, with a characteristic ¹³C

NMR peak at 108.0 ppm. Other ligands tested in the osmium catalyzed dihydroxylation of **36**, such as (DHQD)₂PYR and (DHQD)₂AQN, did not improve the yield. It should be noted that the omission of methanesulfonamide and careful monitoring of the reaction progress was required to avoid over-oxidation of the ethyl ester substituted alkene. Moreover, the structure of **37** was confirmed with COSY/HSQC/HMBC NMR experiments to be the desired [5,6]-ketal and the stereochemistry was then assigned by the nOes observed across the bicyclic ring system (C-16 to C-19 and C-20) as was the case for compound **23**. In this case, experiments performed to dihydroxylate and cyclise **36** using the opposite chiral ligand (*i.e.* (DHQ)₂PHAL) only resulted in the formation of a complex mixture of products.

Conclusions

In conclusion, we have developed a novel route to the CDE fragment (C-12 to C-30) of PTX-4. The key C–C bond forming step was a rhodium catalysed 1,4-vinyl group addition to an enone which used a close to equimolar ratio of the two key components. Model studies revealed a reversal of ligand-facial selectivity during the SAD reaction of a 1,1-disubstituted homoallylic alcohol, resulting in the isolation of two different [5,6]-bicyclic ketals depending on the chiral ligand used. This methodology was then extended to incorporate the desired E ring fragment of PTX-4 in the synthesis of a CDE fragment of PTX-4. Further work is ongoing to utilise this methodology and complete the total synthesis of PTX-4.

Conflicts of interest

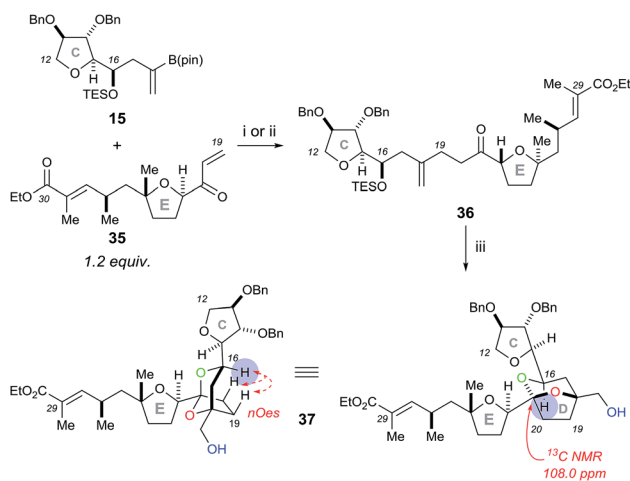
There are no conflicts to declare.

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Scheme 8 Rhodium-catalysed 1,4-addition reaction of the model C ring boronate **15** with E ring enone **35**, followed by the Sharpless asymmetric dihydroxylation and acid-catalysed cyclisation sequence to access the CDE fragment **37**. Reagents and conditions: (i) Rh(acac)(CO)₂ (10 mol%), dppb (10 mol%), THF/H₂O (6 : 1), 50 °C, 30%; (ii) [Rh(cod)OH]₂ (15 mol%), THF/H₂O (6 : 1), 50 °C, 53%; (iii) K₂OsO₂(OH)₄, (DHQD)₂PHAL, K₃Fe(CN)₆, K₂CO₃, *t*-BuOH/H₂O (1 : 1), 0 °C then PPTS, CH₂Cl₂/MeOH (1 : 1), 40%.



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