Synthetic studies towards the pectenotoxins: a review

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In this article we provide an overview of synthetic studies towards pectenotoxins (PTXs) that have been reported by several research groups. The difficulties encountered in the synthesis of these series of polyketides are highlighted by the fact that only one total synthesis of PTX4 and PTX8 has been completed to date. The strategies used in the critical bond forming steps and the introduction of key stereogenic centres are compared and contrasted.

1 Introduction

The pectenotoxins (PTXs) are a family of polyether macrolides that were first isolated in 1985 by Yasumoto *et al.* and were often associated with diarrhetic shellfish poisoning (DSP). They were named after the generic name of the Japanese scallop (*Patinopecten yessoensis*) initially used for toxin extraction and they were originally produced by toxic dinoflagellate species of the genera *Dinophysis.*

The first members of the family to be isolated were PTX1-5 (Fig. 1). The relative configuration of PTX1 (**1**) was established by X-ray crystallography[1] however it was not until 1997 that the absolute stereochemistry was determined and revised as a result of NMR studies using chiral amide derivatives of PTX6 (**5**).[2]

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There are currently fourteen members of the family that have been isolated and characterised by comparison of spectroscopic data, with the exception of PTX5 and PTX10 that have not yet been identified.[3]

PTXs comprise a characteristic closed-chain macrolide structure containing a spiroacetal, three substituted tetrahydrofurans and 19 (or 20 in PTX11 and PTX13) stereocentres embedded within a 40-carbon chain (Fig. 1). The main differences between these compounds are the level of oxidation at C43 and the stereochemistry of the spiroacetal system. Naturally occurring PTXs contain a 5,6-spiroacetal ring system with most of them exhibiting an *R* configuration at the C7 spiroacetal centre.

Several research groups reported that only PTX2 was found in *Dinophysis fortii* suggesting that PTX2 is the parent compound and that the other PTXs (*i.e.* PTX1, PTX3 and PTX6) are the products of oxidation of the C-43 methyl group which takes place in the hepatopancreas of the scallop, *P. yessoensis.*[4–6] This conclusion was supported by the fact that PTX2 was detected in

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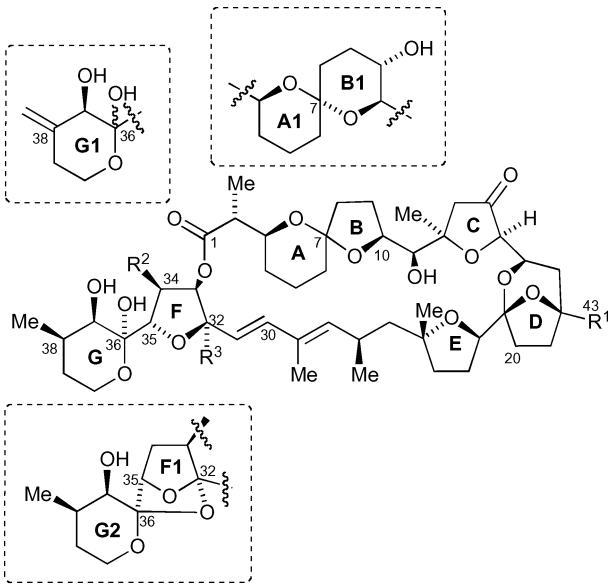
Margaret Brimble was born in Auckland, New Zealand where she was educated and graduated from the University of Auckland with an MSc (1st class) in chemistry. She was then awarded a UK Commonwealth Scholarship to undertake her PhD studies at Southampton University. In 1986 she was appointed as a lecturer at Massey University, NZ. After a brief stint as a visiting Professor at the University of California, Berkeley she moved to the University of Sydney where she was promoted to Reader. In 1999, she returned to New Zealand to take up the Chair in Organic and Medicinal Chemistry at the University of Auckland where her research program continues to focus on the synthesis of spiroacetal containing natural products (especially shellfish toxins), the synthesis of pyranonaphthoquinone antibiotics, the synthesis of alkaloids and peptidomimetics for the treatment of neurodegenerative disorders, and the synthesis of glycopeptides as components for cancer vaccines. She is currently President-Elect of the International Society of Heterocyclic Chemistry.



		R^1	R^2	R^3	C-7	C-36
1	PTX1	CH_2OH	H	H	*R*	α-OH
2	PTX2	CH_3	H	H	*R*	α-OH
3	PTX3	CHO	H	H	*R*	α-OH
4	PTX4	CH_2OH	H	H	*S*	α-OH
5	PTX6	COOH	H	H	*R*	α-OH
6	PTX7	COOH	H	H	*S*	α-OH
7	PTX11	CH_3	OH	H	*R*	α-OH
	Structure	***A1/B1/G***				
8	PTX8	CH_2OH	H	H	*S*	α-OH
9	PTX9	COOH	H	H	*S*	α-OH
	Structure	***A/B/G1***				
10	36*S*-PTX12	CH_3	H	H	*R*	α-OH
11	36*R*-PTX12	CH_3	H	H	*R*	β-OH
12	PTX13	CH_3	H	OH	*R*	α-OH
	Structure	***A/B/G2/F1***				
13	PTX14	CH_3	-	-	*R*	–
	Unidentified					
	PTX5	unidentified				
	PTX10	unidentified				

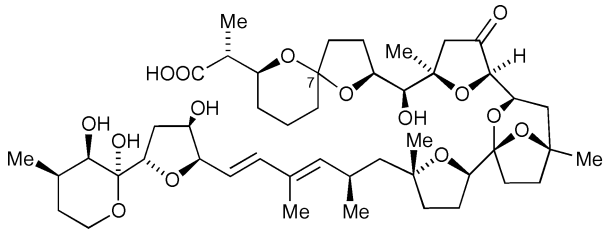
Fig. 1 Structure of the pectenotoxins.

both extracts of *D. fortii* and in extracts of scallop gut, whereas PTX6 could only be detected in the scallop gut and not in the algal extracts.[6]

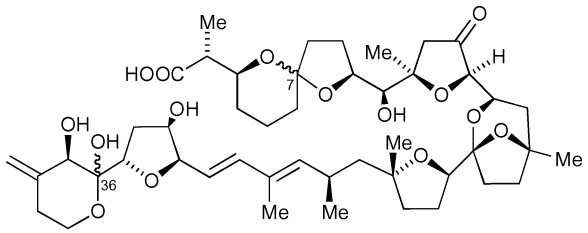
PTX4 (**4**) and PTX7 (**6**) are stereoisomers of PTX1 (**1**) and PTX6 (**5**) respectively, resulting from epimerisation of the spiroacetal centre. This epimerisation is thought to occur in the digestive glands of scallops, presumably by a scallop-derived enzyme as opposed to a random acid-catalysed reaction.[7] It was postulated that this epimerisation was the result of a detoxification process as PTX4 and PTX7 exhibit a lower toxicity compared to their epimers.[5,7] PTX8 (**8**) and PTX9 (**9**), on the other hand, are products arising from chemical transformation of other PTXs and have not been isolated from natural sources.[7] Instead of a 5,6-spiroacetal ring system, they contain a 6,6-spiroacetal ring system with an *S* configuration at the spirocentre, which is thermodynamically more stable due to the maximum stabilisation by the anomeric effect.

Variations in the other ring systems were not known until recently when four additional members of the family were isolated and characterised. PTX11 (**7**),[8] PTX12 (**10** and **11**),[9] PTX13 (**12**),[10,11] and PTX14 (**13**)[11] have the same substituent at C43 and spiroacetal configuration as PTX2 but exhibit variation around the FG ring system. Additional hydroxyl groups at C34 and C32 were observed in PTX11 and PTX13 respectively, while the presence of unsaturation at C38 in PTX12 was observed (Fig. 1). PTX12 also exists as two different isomers depending on the stereochemistry at C36. The most recently isolated PTX14 was identified as the cyclised 32,36-dehydration product of PTX13.

Open-chain analogues of PTXs are also known and have been identified as PTX-seco acid/PTX-SA **14**, **15** and **16** (Fig. 2).[9,12] These seco acids appeared to be less toxic than their parent compounds. For example, PTX2-SA (**14**) did not exhibit cytotoxicity towards KB cells at a dose of 1.8 μg mL, while PTX2 (**2**) was cytotoxic at a dose of 0.05 μg mL, indicating the importance of the macrocyclic structure on the observed toxicity.[12]



PTX2-SA **14** (C7 = *R*)
7-epi-PTX2-SA **15** (C7 = *S*)



PTX12-SA **16** (C7 = *R*/*S*, C36 = *R*/*S*)

Fig. 2 Structure of PTX-seco acids.

In recent years, the classification of PTXs as causative agents for diarrhetic shellfish poisoning has become a subject of debate. Some groups have found a mild diarrhetic effect[13] caused by administration of PTXs but other groups reported no such effect.[14] It was suspected that the earlier reported diarrhetic effect of PTXs may be attributed to the contamination of the sample with okadaic acid[15] or its derivatives, which were often isolated together with the PTXs from dinoflagellate species.

PTXs are hepatotoxic, tumour promoters and cause apoptosis in rat and salmon hepatocytes with PTX2 being the most toxic member of the family.[1,14c,16] Further physiological studies on PTX2 revealed that selective and potent cytotoxicity against several cell lines with differences in the LC_{50} value between sensitive and resistant cell lines of 100-fold or more.[17] PTX2 (**2**) inhibited actin polymerisation in a concentration-dependent manner and formed a 1 : 4 complex with G-actin whereas PTX6 (**5**) caused time- and dose-dependent depolymerisation of F-actin in neuroblastoma cells.[18]

The intriguing complex structure of the PTX family together with their high cytotoxicity has recently prompted several research groups to pursue their synthesis. The presence of a hemiketal (C36), several ketal centres (C7 and C21) together with a ketone α to an ether linkage, render the PTXs susceptible to isomerisation, especially by acids. The presence of a non-anomerically stabilised 6,5-spiroacetal ring system (7*R* configuration) in the majority of cases also provides additional synthetic challenges.

Although the isolation of PTXs was first reported in 1985, it was not until 1997 that the first synthesis of the FG ring fragment of the PTXs was reported by Murai and co-workers.[19] Since then, several other research groups (including ourselves) have also reported their approaches to different fragments of PTXs and only one total synthesis has been reported to date. The objective of this review is to provide an overview of these synthetic studies towards the PTX family in the context of the elegant total synthesis of PTX4 (**4**) and PTX8 (**8**) reported by Evans *et al.*[20]

2 Murai and Fujiwara group's approach to PTX2

In 1997, the Murai and Fujiwara group reported the first synthesis of the FG fragment **17** (Fig. 3), antipoded to that of the natural product PTX2 (**2**).[19] Recently, they have also published the synthesis of the correct enantiomer of this fragment by using similar methodology to that reported earlier and extending it to incorporate the C1–C7 carbon chain thereby affording the left-hand fragment **18** of PTX2 (Fig. 3).[21] The key step in this synthesis involves selective generation of an α-lithiated tetrahydrofuran **23** from the corresponding phenylthioacetal **20** (Scheme 1).[22] Tetrahydrofuran **20**, which contains the correct stereochemistry, was synthesised as a mixture of stereoisomers from alcohol **19**[23] in 5 steps whilst the aldehyde fragment **22** was synthesised from epoxy alcohol **21**[24] in 4 steps (Scheme 1).

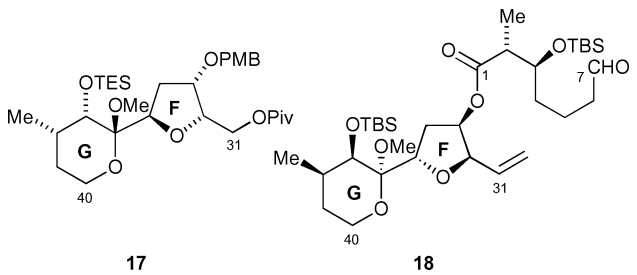
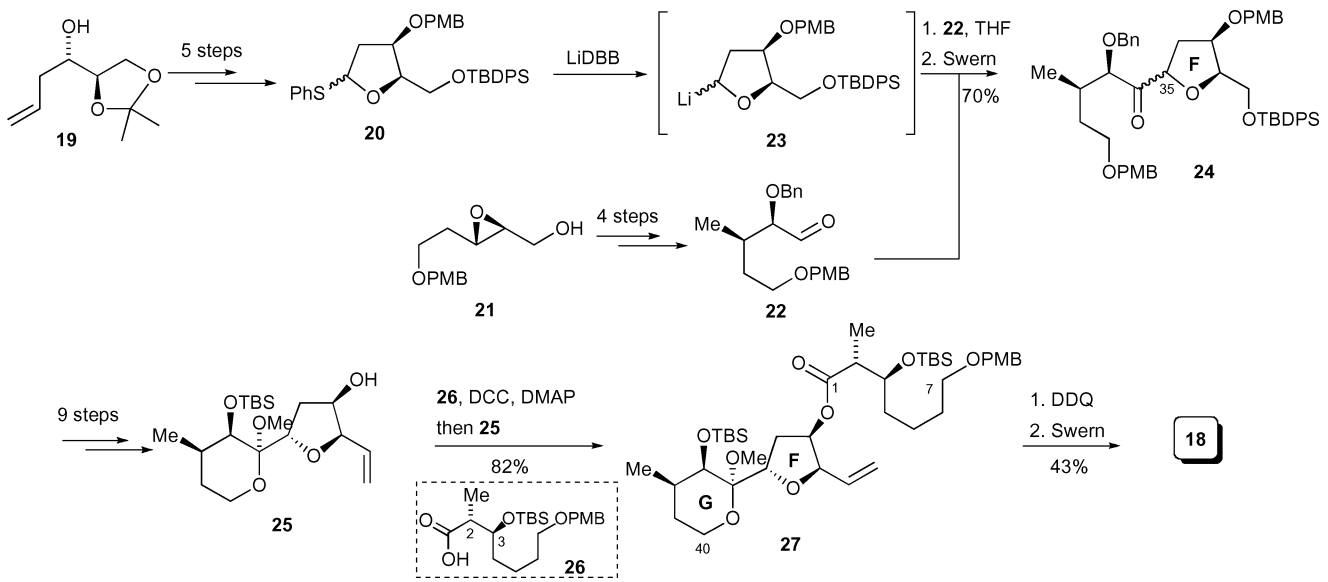


Fig. 3 Murai's synthesis of the FG fragment: **17** (incorrect FG enantiomer fragment) and **18** (correct FG enantiomer fragment).

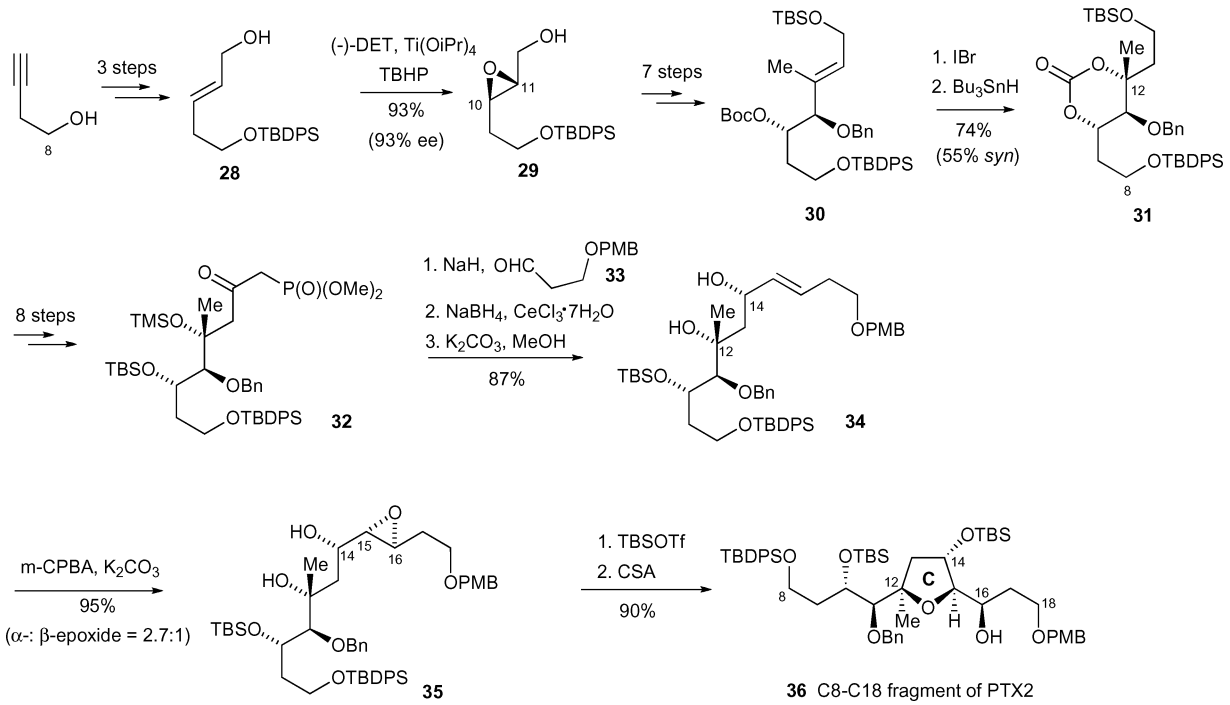
Treatment of phenylthioacetal **20** with lithium di-*tert*-butylbiphenylide at low temperature resulted in the immediate formation of the anion, which upon addition of aldehyde **22** afforded the corresponding coupled product as a mixture of diastereomers. Subsequent Swern oxidation afforded ketone **24** as a 4.2 : 1 mixture of diastereomers at C35 with the desired diastereomer as the major product. After further elaboration (9 steps), alcohol **25** was obtained as a single enantiomer whereupon introduction of the C1–C7 fragment was performed by DCC mediated coupling of acid **26** with alcohol **25**. The C2/C3 chiral centres in acid **26** were installed using an Evans' aldol reaction. Removal of the C7 PMB group in the coupled product **27** and Swern oxidation of the resultant alcohol furnished the left-half FG fragment of PTX2 (**2**).

Murai and Fujiwara's research group also reported an efficient synthesis of the C8–C18 tetrahydrofuran fragment **36** in 2000 (Scheme 2).[25] The main idea behind their synthesis was to introduce all stereogenic centres by utilising proximal chirality and building the chirality from the left side of the molecule.

The initial chiral epoxide building block **29** was prepared by Sharpless asymmetric epoxidation[26] of allylic alcohol **28**. Iodocarbonate cyclisation[27] of the derived trisubstituted olefin **30** set up the third stereogenic centre at C12. Chain homologation *via* Horner–Wadsworth–Emmons reaction of phosphonate **32** with aldehyde **33** followed by Luche reduction[28] of the resultant ketone gave predominantly β-alcohol **34** (at C14), due to the influence of the tertiary hydroxyl group at C12. Subsequent hydroxyl-directed epoxidation of alcohol **34** established the remaining stereogenic



Scheme 1 Synthesis of left-half FG moiety of PTX2 (**2**).



Scheme 2 Murai and Fujiwara's synthesis of C8–C18 THF fragment.

centres with final cyclisation of epoxy alcohol **35** affording the C8–C18 fragment **36**.

3 Micalizio and Roush's approach to PTX2

Soon after Murai published the synthesis of the tetrahydrofuran fragment, Micalizio and Roush[29] also published an alternative approach to this tetrahydrofuran ring with additional D and E rings in place. Their strategy involved a convergent three-component coupling sequence *via* a chelation controlled [3 + 2]-annulation using a chiral γ-allylsilane to construct the 2,5-*trans*-substituted tetrahydrofuran ring. It was recognised from the beginning that this strategy would produce the unnatural stereochemistry at C15 (Fig. 4). However, they postulated that this issue would later be addressed by base-promoted epimerisation making use of the chirality at the adjacent C14 centre.

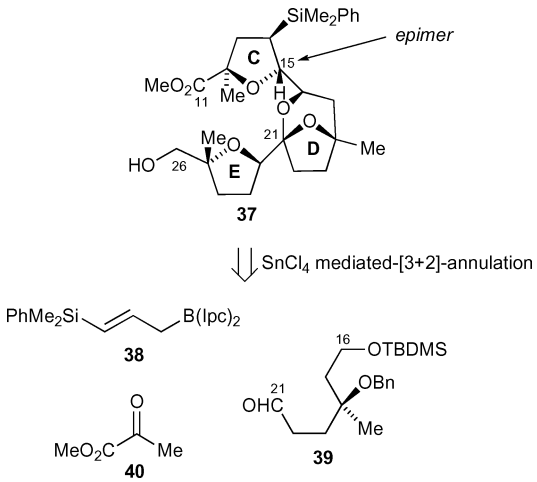


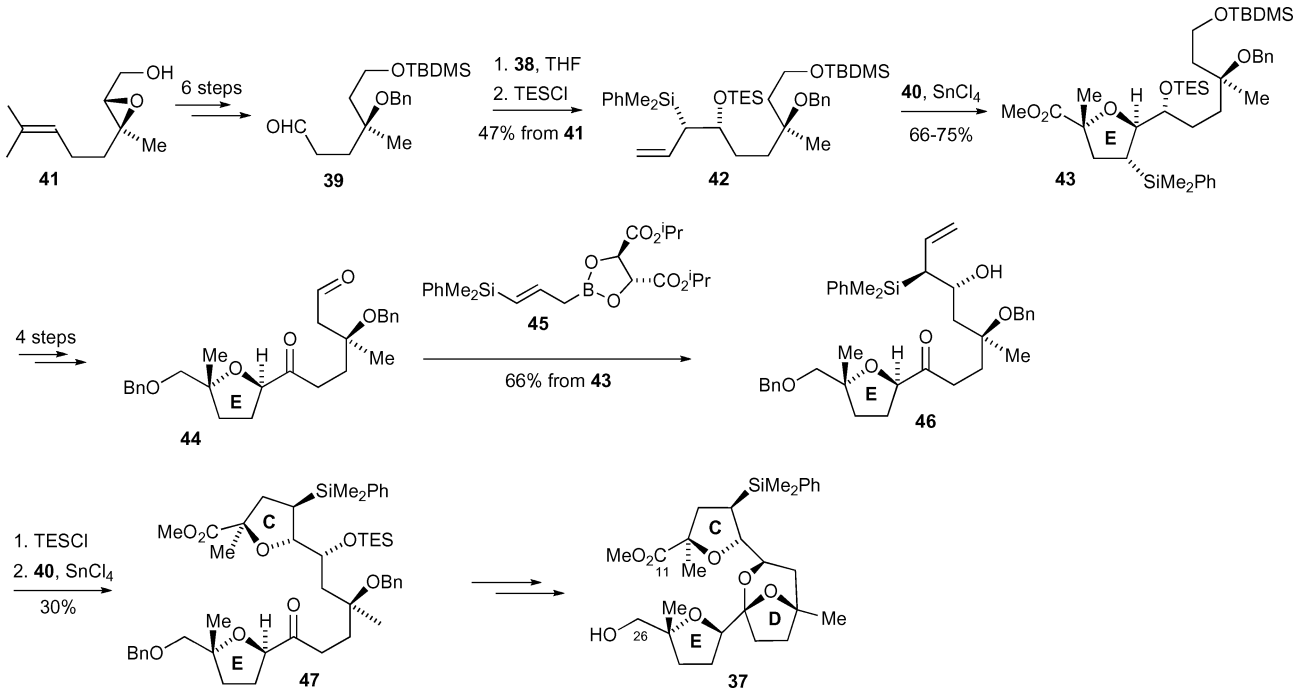
Fig. 4 Micalizio and Roush approach to CDE ring fragment **37**.

With this idea in mind, the construction of the E ring fragment **43** was initially achieved using silylallyl borane **38**, aldehyde **39** and methyl pyruvate **40**. Aldehyde **39** was synthesised in 6 steps from known geraniol epoxide **41**[30] (Scheme 3). Asymmetric silylboration of aldehyde **39** with allylborane **38** provided an inseparable mixture of diastereomeric products favouring the desired *anti*-β-hydroxyallylsilane that was subsequently protected to give silyl ether **42**. The coupling between allylsilane **42** and methyl pyruvate **40** under chelate-controlled $SnCl_4$-promoted [3 + 2]-annulation conditions afforded the desired 2,5-*trans*-substituted E ring **43** in good yield with high stereoselectivity (66–75% yield, >20 : 1 diastereoselectivity).

With this impressive formation of the E ring system, the next strategy was to employ the same annulation methodology to form the C ring system. The required chiral allylsilyl **46** was prepared in high yield and diastereoselectivity by utilising γ-silylallylboronate (*R*,*R*)-**45**[31] which was developed earlier by the same research group. The same $SnCl_4$-promoted coupling conditions were employed affording bis-tetrahydrofuran **47** in 30% yield over two steps. Final deprotection of the silyl ether and benzyl ethers gave a keto diol which spontaneously cyclised to the target CDE ring fragment **37**. Although the yield for the second $SnCl_4$-annulation step was significantly lower and a 2,5-*trans*-substituted tetrahydrofuran C ring was obtained instead of a 2,5-*cis*-substituted tetrahydrofuran, the CDE ring subunit was accessed nevertheless.

4 Paquette's approach to PTX2

In 2002, Paquette and co-workers[32,33] reported their synthetic work directed towards the C29–C40 FG fragment **54** based on



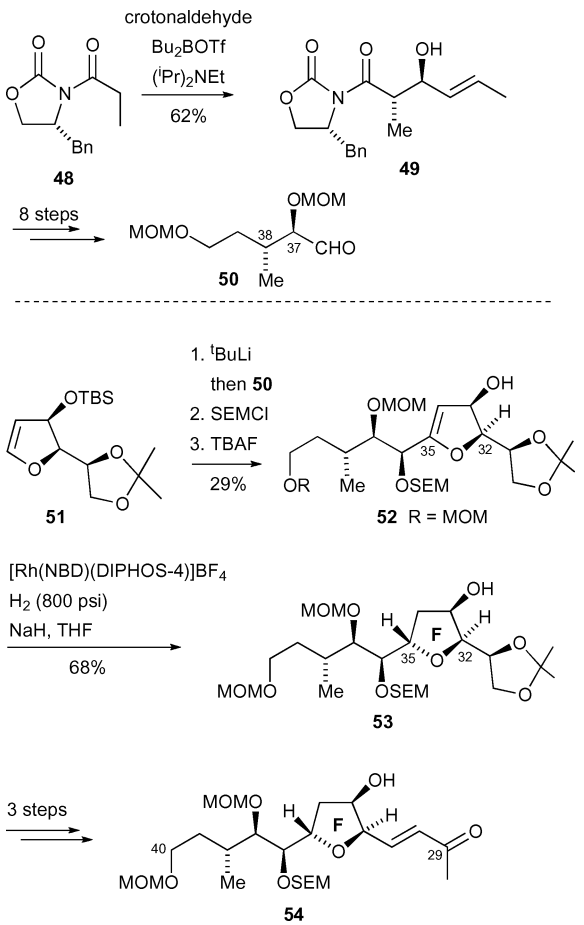
Scheme 3 Synthesis of CDE precursor fragment **37**.

an efficient stereodirected hydrogenation of dihydrofuranol **52** to give a *trans*-substituted tetrahydrofuran ring.

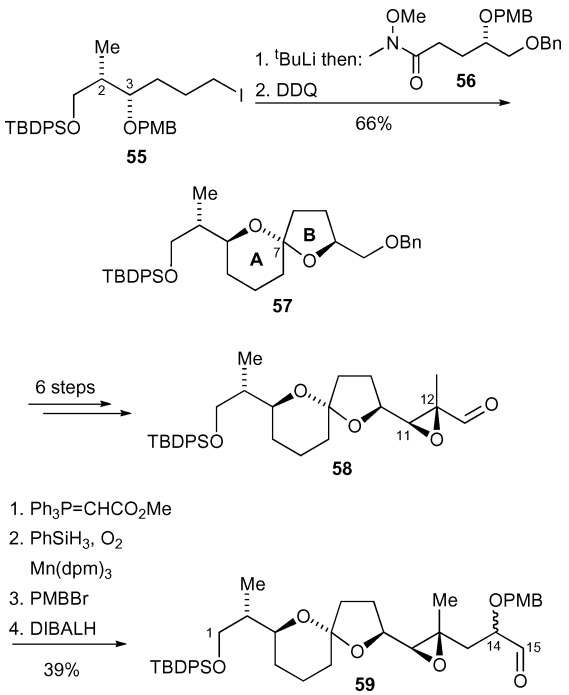
The key fragment **52** was synthesised from reaction of aldehyde **50** with the lithiated **51** (Scheme 4). The stereochemistry at C37 and C38 in aldehyde **50** was established using an Evans' *anti*-aldol reaction whilst dihydrofuran **51** was readily available from D-mannose.[34] Hydroxyl-directed hydrogenation[35] of **52** using the cationic catalyst [Rh(NBD)(DIPHOS-4)BF_4][36] was initially problematic due to competing elimination of water to give the corresponding furan. However, the selective hydrogenation was finally achieved in good yield (68% at 80% conversion) using an ionic complex formed between the sodium salt of **52** and the cationic catalyst above to give the *trans*-substituted tetrahydrofuran **53**. Finally, further carbon extension of **53** in three steps furnished the desired C29–C40 carbon fragment **54** of PTX2 (**2**).

In 2005, Paquette's group also published the synthesis of the right half C1–C26 fragment **67** (Scheme 6), a precursor to the ABCDE fragment in PTX, in continuation of their work towards the total synthesis of PTX2.[37] Their approach was based on the highly convergent synthesis of the C1–C15 AB spiroacetal containing fragment **59** together with C16–C26 sulfone containing fragment **66**. Subsequent union of both these subunits was then effected using a Julia olefination.

The initial synthesis of the C1–C15 building block began by constructing the spiroacetal ring system. Addition of the organolithium derivative of **55** with Weinreb amide **56**, itself derived from L-glutamic acid, followed by the deprotection of the PMB groups afforded spiroacetal **57** in good yield (Scheme 5). The C2/C3 *syn* configuration was established using an Evans' aldol condensation similar to the method used by Murai's group. The stereochemistry at C7 was assumed to be *S* based on the additional stabilisation by the anomeric effect that this configuration possesses. This stereochemistry represents the opposite epimer at C7 compared to the natural PTX2 spiroacetal ring system (C7 = *R* in PTX2).



Scheme 4 Paquette's synthesis of the C29–C40 backbone subunit.



Scheme 5 Synthesis of the C1–C15 fragment **59**.

Further chain extension and introduction of a chiral epoxide (C11/C12) *via* Sharpless epoxidation[38] afforded aldehyde **58**. The final two carbons and the hydroxyl group at C14 were introduced using a Wittig reaction and a Mn^{3+}-catalysed oxidation, respectively.[39]

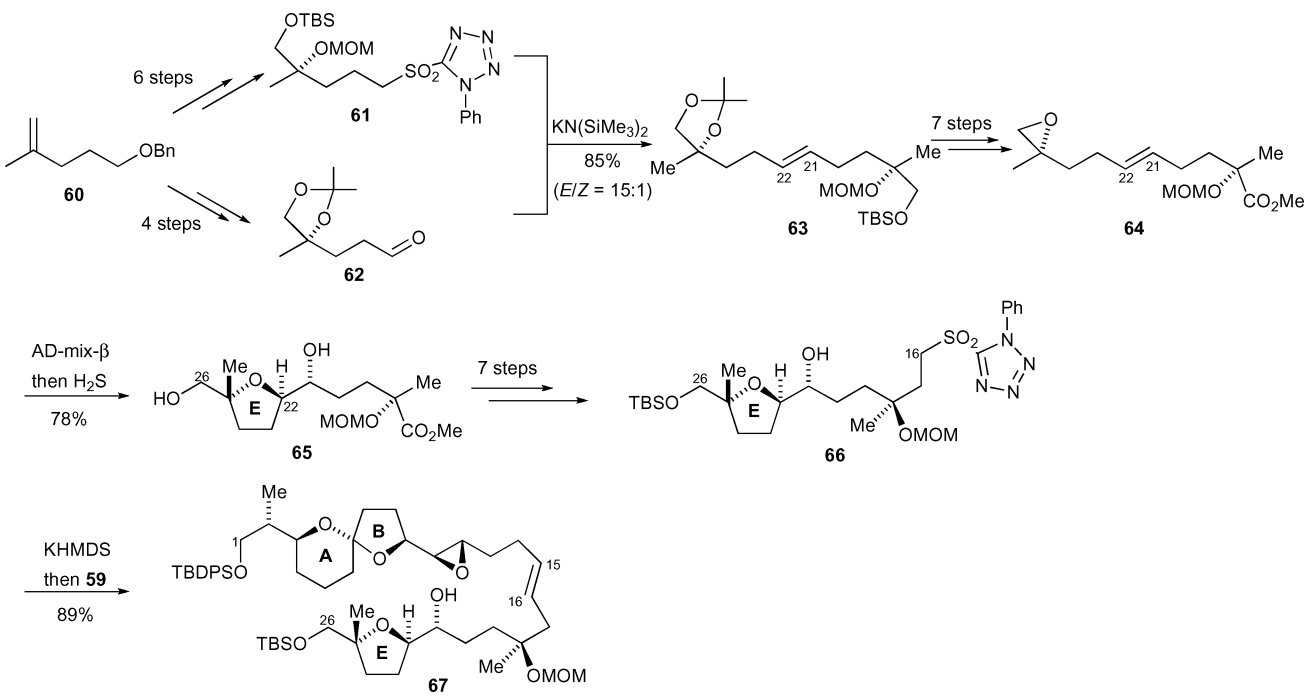
The C16–C26 coupling partner **66** was efficiently constructed from the readily available benzyl ether **60** (Scheme 6). The stereogenic centres in fragments **61** and **62** were constructed *via* Sharpless dihydroxylation[40] and the Julia–Lythgoe coupling of these two fragments was effectively achieved in 85% yield with the isomeric 15 : 1 ratio favouring the *E* isomer. Functional group manipulation of **63** afforded epoxide **64**. The new stereogenic centres at C21/C22 were then introduced *via* asymmetric dihydroxylation using AD-mix-β. Work up of the reaction using hydrogen sulfide promoted acid-catalysed stereoselective cyclisation to give the desired E ring **65** in high yield. Five additional steps then gave the desired phenyltetrazole sulfone **66**, which was then coupled with aldehyde **54** to generate exclusively the C1–C26 containing *E*-olefin **67**.

5 Evans' total synthesis of PTX4 and PTX8

Although a number of synthetic studies towards fragments of the PTXs have been described, only one total synthesis of PTX4 (**4**) and PTX8 (**8**) by Evans and co-workers[20] has been completed to date. PTX4 (**4**) was chosen as the target molecule by this group as the C7 spiroacetal centre in this molecule possesses an *S* configuration and is therefore stabilised by the anomeric effect. Although it was reported that the 7*R*-spiroacetal configuration was more stable in the macrolide framework, the 7*S*-epimer remained the favoured configuration in the acyclic precursors.[12]

Evans' group based their approach for the synthesis of PTX4 (**4**) on the convergent coupling between several complex late-stage intermediates. The retrosynthetic strategy that they employed is illustrated in Fig. 5 wherein the main disconnections across the macrolide C1–O33 bond, the C19–C20 bond and the C30–C31 olefin bond gave rise to three different intermediates, namely ABC fragment **68**, E ring fragment **70** and FG backbone fragment **69**.

The synthesis of fragment **68** began by constructing the required AB spiroacetal ring system. In contrast to Paquette's approach, this group utilised the Wittig reaction between phosphonium salt



Scheme 6 Paquette's synthesis of the C1–C26 left-hand fragment **67**.

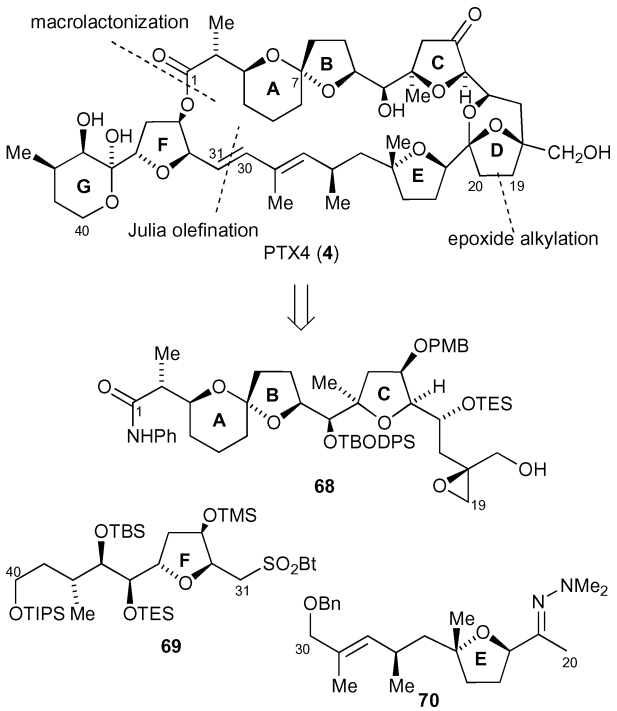


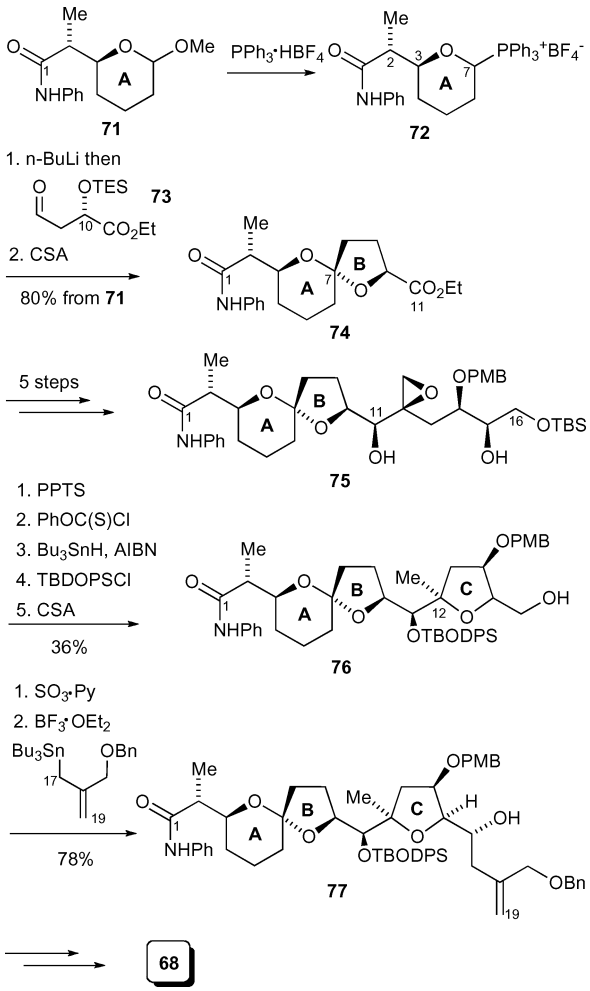
Fig. 5 Evans' retrosynthetic analysis of PTX4 (**4**).

72 and aldehyde **73** to give spiroacetal **74** in high yield with high diastereoselectivity (Scheme 7). Chain elongation and further functional group manipulation including use of an asymmetric epoxidation directed by hydroxyl group at C11[41] allowed access to epoxy alcohol **75** with the stage set for facile formation of the C ring. 5-*exo*-trig cyclisation of **75** followed by deoxygenation under Barton conditions[42] afforded the C ring with the correct oxygenation level at C12. Further elongation to incorporate the C17–C19 chain was achieved with high stereocontrol *via* asymmetric allylation under Felkin control followed by Sharpless epoxidation to furnish[43] the desired C1–C19 fragment **68**.

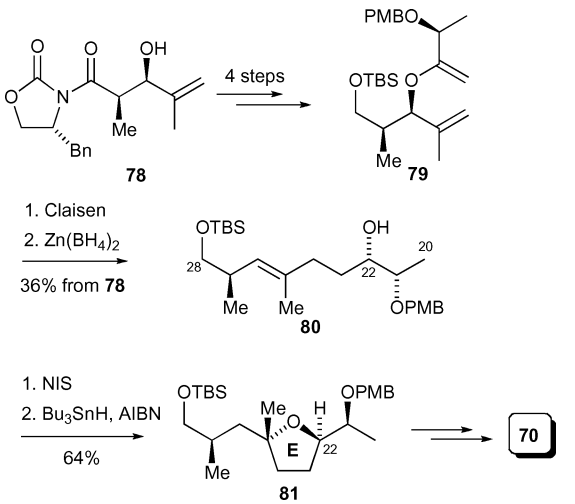
The main approach used to construct the E ring subunit involved iodoetherification of alcohol **80** (Scheme 8). In turn this alcohol, containing the C20–C28 backbone, was prepared efficiently *via* Claisen rearrangement of 1,5-diene **79** followed by chelation controlled reduction of the resultant ketone to set the stereochemistry at C22. Iodoetherification furnished the desired *trans*-substituted E ring with moderate selectivity (dr 72 : 28). Installation of the *N*,*N*-dimethylhydrazone functionality at C21 afforded the required subunit **70** in preparation for union with the ABC subunit **68**.

Evans' approach to the C31–C40 FG subunit **69** was very different from the methods previously described. The key step for assembly of fragment **69** involved union of C31–C35 phosphonium salt **84** with C36–C40 aldehyde **85** (Scheme 9) to form the *Z*-olefin **86** with high stereoselectivity ($Z{:}E = 95 : 5$).

Hydroxyl-directed epoxidation[41] followed by protecting group manipulation afforded epoxide **87**, which contained all the required stereogenic centres for preparation of the FG fragment. Selective deprotection of the benzyl group at C32 and exposure of the resultant alcohol to acidic conditions afforded the corresponding *trans*-substituted F ring which was then further elaborated to benzthiazole **69**, to be used in the subsequent Julia coupling.

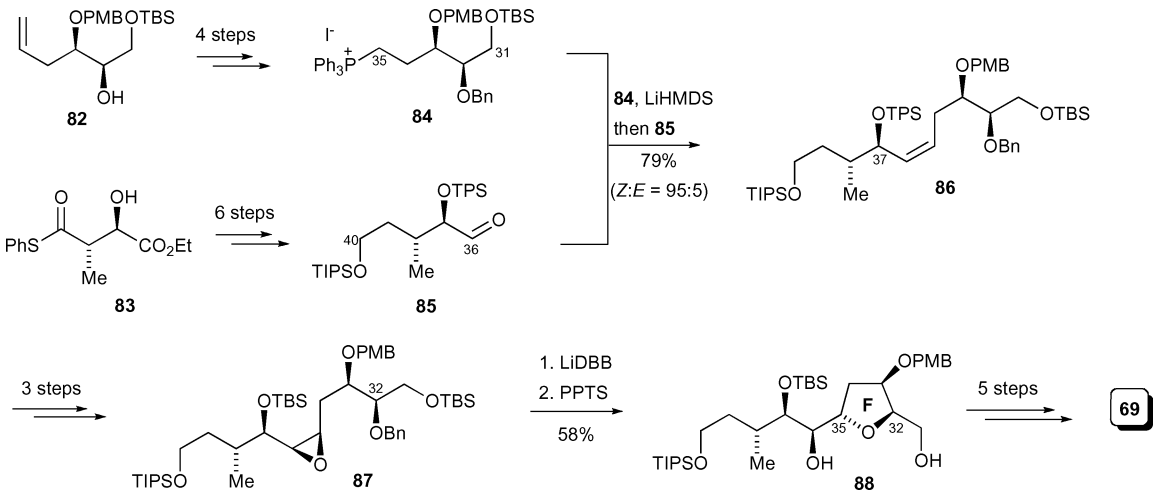


Scheme 7 Synthesis of the C1–C19 subunit of PTX4 (**4**).

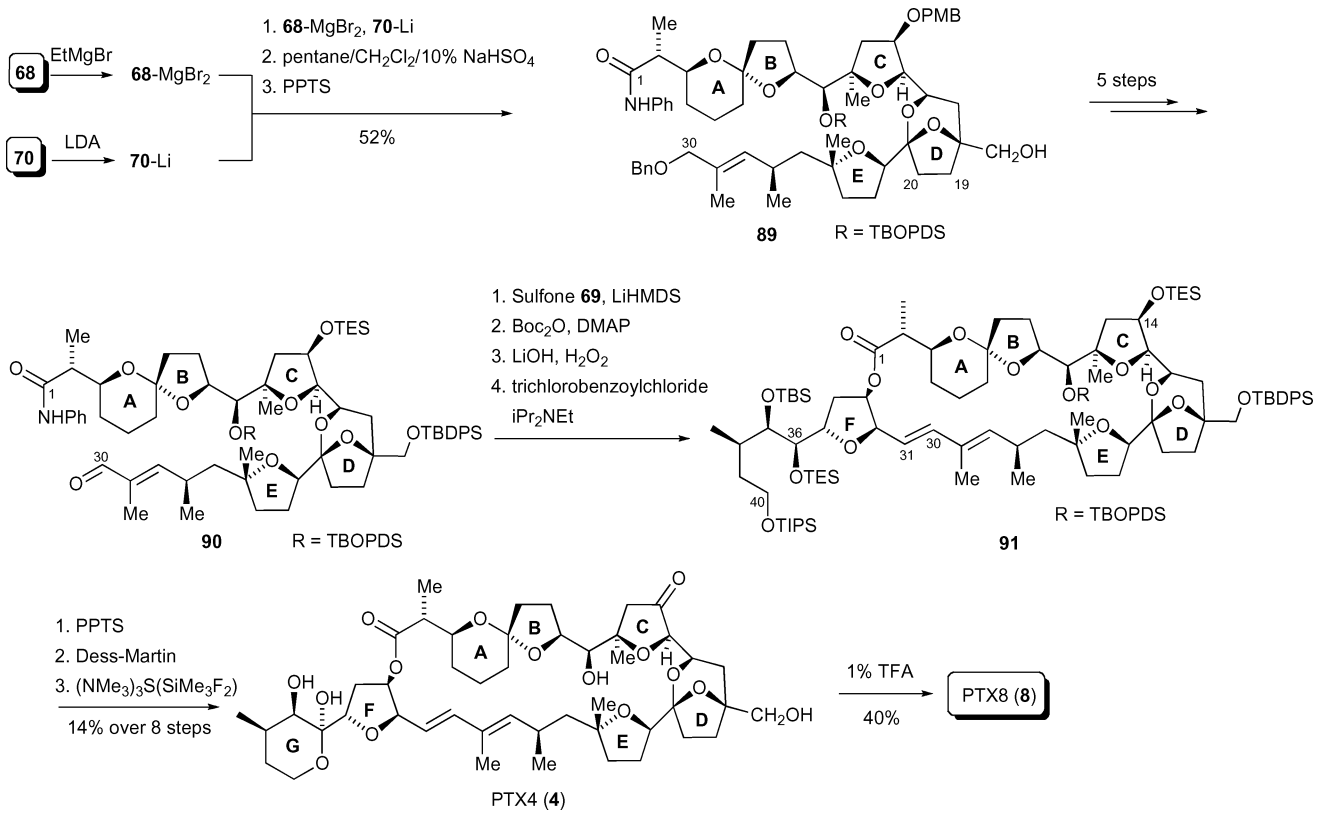


Scheme 8 Synthesis of the E ring subunit **70**.

With all three advanced intermediates **68**, **69** and **70** prepared, completion of the synthesis of PTX4 began by joining ABC fragment **68** with E ring fragment **70**. This key union was achieved by generation of the metalloenamine derived from **70** followed by reaction with the $MgBr_2$-activated epoxide **68** (Scheme 10)



Scheme 9 Synthesis of the C31–C40 subunit **69**.



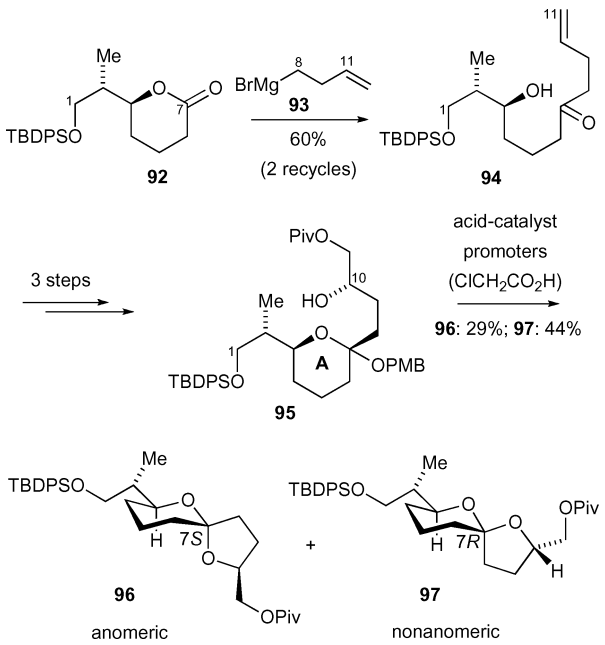
Scheme 10 Completion of the synthesis of PTX4 (**4**) and PTX8 (**8**).

and acidolysis of the derived hydrazinyl lactol afforded ABCDE fragment **89**. Julia coupling of β-alkoxy sulfone **69**[44] with aldehyde **90** and subsequent macrolactonisation under Yamaguchi conditions[45] furnished the C1–C40 carbon backbone of PTX4. Selective deprotection of the TES ethers at C14 and C36 in **91** followed by oxidation of the resultant hydroxyl groups effected construction of the final G ring. Finally, global deprotection afforded PTX4 (**4**) in 36 steps (longest linear sequence) and 0.3% overall yield. PTX8 (**8**) was then obtained from PTX4 (**4**) *via* an isomerisation process using 1% TFA.

6 Pihko's approach to access both spiroacetal anomers

As described earlier, although the natural PTXs exhibit both configurations (*R* and *S*) at the spirocentre, it was known that the 7*R*-epimers were more toxic than the 7*S*-epimers. In spite of this, access to the non-anomerically stabilised 7*R*-spiroacetal had not been addressed until 2004 when Pihko and Aho demonstrated their synthetic approach to prepare both anomers of the PTX spiroacetals.[46]

The key spirocyclisation precursor **95** was prepared in a 70 : 30 diastereomeric ratio (based on the stereogenic centre at C10) *via* Sharpless asymmetric dihydroxylation of the terminal C10/C11 olefin precursor **94**. Both diastereomers were used in the cyclisation studies, however for the purpose of simplification reaction of only the correct 10*S*-isomer **95** is depicted (Scheme 11).



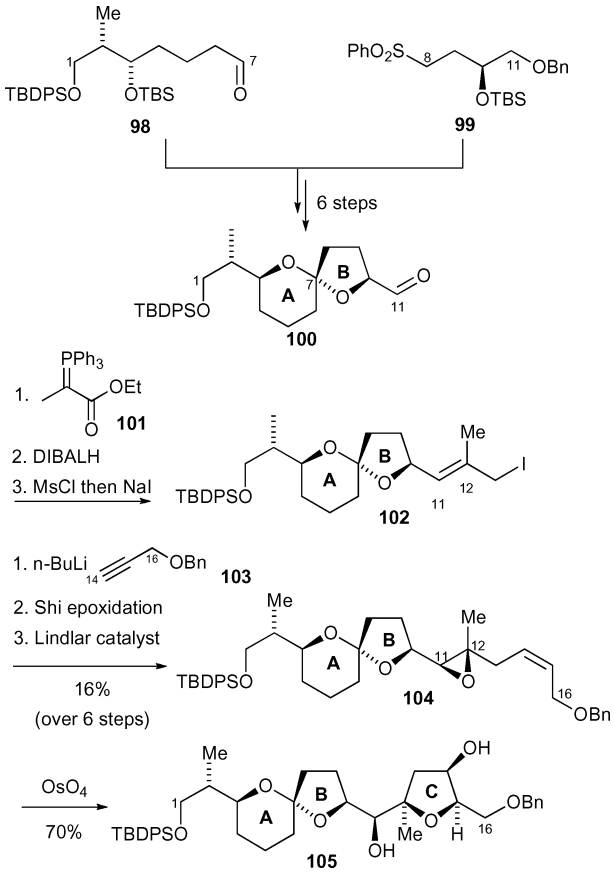
Scheme 11 Access to both anomeric spiroacetals of PTXs.

The key spirocyclisation reaction was performed in the presence of several different acid promoters. The use of a strong acid (*p*-toluenesulfonic acid) resulted mainly in formation of the anomerically stabilised spiroacetal **96** (corresponding to the 7*S*-epimer in natural PTX4 **4** and PTX7 **6**). A few weaker acid promoters were screened and they were found to give progressively larger amounts of the target non-anomeric spiroacetal with chloroacetic acid being found to be the optimal catalyst affording 7*R*-spiroacetal **97** in 44% yield. These studies established a method to obtain both isomers of the spiroacetal portion of PTXs, which could then be used to prepare all members of the PTX family.

7 Brimble's approach to PTX2

Shortly after Paquette and co-workers published their synthesis of the C1–C26 fragment of PTX2 in 2005,[37] we disclosed our approach towards the C1–C16 ABC spiroacetal containing subunit **105**.[47,48] Our strategy hinged on initial formation of the C1–C11 AB spiroacetal fragment **100**. In a similar manner to that observed by Paquette, we also formed the 7*S*-spiroacetal centre as opposed to the required 7*R* in natural PTX2 (Scheme 12). We envisaged that the correct spiroacetal centre could be formed at a later stage after the formation of the macrolide ring.

Incorporation of the remaining C12–C16 carbon chain was achieved *via* Wittig reaction using a stabilised ylide **101** to access *E*-olefin **102** after conversion of the ester to an iodide. Subsequent displacement of allylic iodide **102** with the lithium acetylide derived from **103** followed by Shi epoxidation[49] furnished epoxy olefin **104** with the correct stereochemistry at C11/C12



Scheme 12 Brimble's synthesis of ABC spiroacetal **105**.

(dr 5.5 : 1). Finally substrate controlled dihydroxylation of olefin **104** afforded the corresponding diol which cyclised directly to form the desired C ring thus completing the synthesis of C1–C16 spiroacetal containing ABC fragment **105**.

8 Comparison of the synthetic approaches to subunits of the PTXs

Although several research groups have constructed various subunits of the PTXs, a certain degree of commonality exists in several of the key bond forming steps and for the introduction of several key stereogenic centres. In this part of the article, we have attempted to compare the strategies used for several of the subunits.

8.1 Formation of the ABC spiroacetal containing subunit

8.1.1 Control of spiroacetal stereochemistry and C2/C3 chiral centres. Except for Pihko and Aho, all of the synthetic studies to the AB spiroacetal fragment reported to date used a thermodynamically controlled cyclisation to form the 7*S*-spirocentre thus making use of maximum anomeric stabilisation for formation of the 5,6-spiroacetal (Fig. 6). Another striking similarity was the introduction of the *syn*-stereogenic at C2/C3 by Murai, Paquette and Evans using a boron-mediated aldol reaction. On the other hand, Pihko employed a sequence of Katsuki–Sharpless epoxidation followed by epoxide ring opening using a higher order

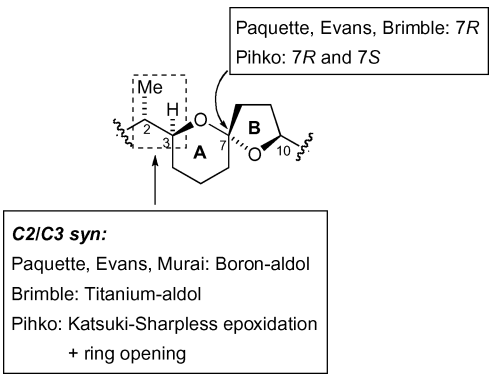


Fig. 6 Comparison of AB spiroacetal formation.

cuprate while we used a Crimmins modified aldol reaction[50] with a titanium enolate.

All of the approaches to the AB spiroacetal subunit relied on disconnection of the C7–C8 bond. The Brimble and Paquette groups assembled the carbon backbone before cyclisation of the hydroxyketone to give the AB spiroacetal. Although the intermediates used to construct this spiroacetal were different (Scheme 5 and 12), interestingly both of these approaches formed identical spiroacetal intermediates (**57** and **100**, Fig. 7). Evans' approach involved initial formation of the A ring system before union with the C8–C11 fragment **73** *via* a Wittig reaction (Scheme 7). Pihko used lactone **92**, which comprised the A ring and extended the side chain using a Grignard reaction (Scheme 11).

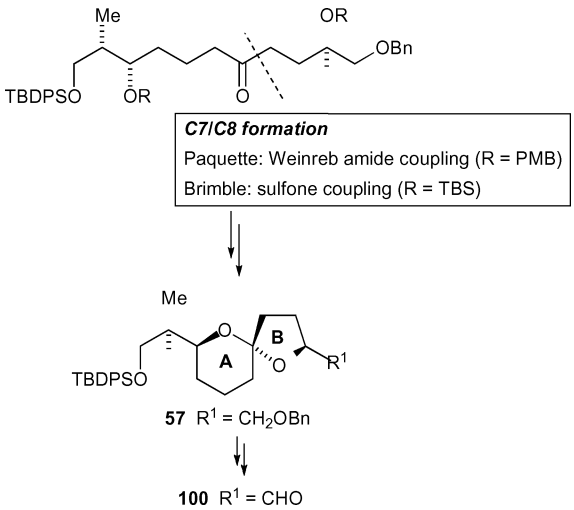


Fig. 7 Identical spiroacetal intermediates accessed by Paquette and Brimble.

8.1.2 Formation of the C-ring *cis*-tetrahydrofuran fragment. A key hydroxy-epoxide cyclisation was used to form the *cis*-tetrahydrofuran C ring by Evans (Scheme 7), Murai (Scheme 2) and Brimble (Scheme 12). Similarly, all the stereogenic centres were correctly established before cyclisation took place. Worthy of note was Roush's approach wherein a [3 + 2]-annulation promoted by $SnCl_4$ was used to form the C ring, notably containing the opposite stereochemistry at C15 (Scheme 3).

8.2 Formation of the E-ring *trans*-tetrahydrofuran subunit

To date, only the Evans, Paquette and Roush research groups have successfully prepared the *trans*-substituted tetrahydrofuran E ring. Each of the three groups used different approaches. Roush used an impressive $SnCl_4$-promoted [3 + 2]-annulation of allylsilane **42** with methylpyruvate affording the desired ring system with high stereoselectivity (Scheme 3).

The Evans group used an iodoetherification of alcohol **80** to construct the *trans*-stereochemistry of the tetrahydrofuran ring (Scheme 8). Paquette's strategy, on the other hand, involved introduction of all the functionality into an acyclic precursor followed by 5-*exo*-trig cyclisation of the epoxy diol derived from olefin **64** (Scheme 6).

8.3 Formation of the FG subunit

The Murai, Paquette and Evans research groups made use of the same disconnection at C35–C36 to construct the FG subunit, however significantly different approaches were adapted to unite the building blocks (Fig. 8). Murai and Fujiwara's research group reacted an α-lithiated tetrahydrofuran (derived from the corresponding phenylthioacetal **20**) with an aldehyde **22** to give the required *trans*-tetrahydrofuran F ring **24** with good stereoselectivity (Scheme 1).

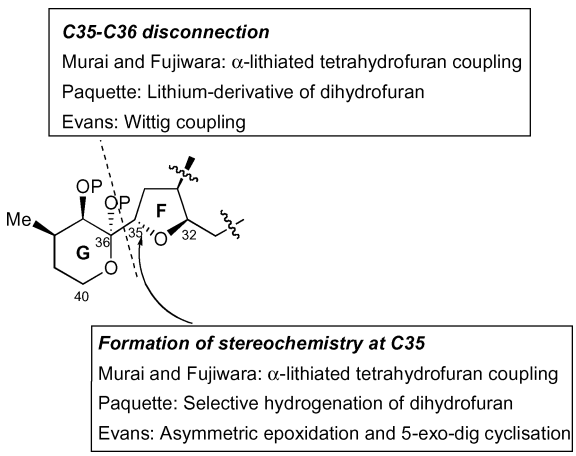


Fig. 8 Comparison of FG ring approaches.

Paquette made use of the union between dihydrofuran **51** with aldehyde **50** followed by a highly selective hydroxyl-directive hydrogenation to set the stereochemistry at C35 (Scheme 4). Evans combined the asymmetric epoxidation of the alcohol derived from **86** and a 5-*exo*-tet cyclisation to establish the desired stereochemistry in the FG subunit **69** (Scheme 9).

9 Conclusions

In summary, six different research groups have contributed significantly to the field of organic synthesis *via* their studies towards the total synthesis of the PTXs. Only one total synthesis of PTX4 (**4**) and PTX8 (**8**) has been reported to date thus reflecting the many synthetic challenges presented by these complex polyketides.

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