Singlet oxygen initiated cascade transformation of a simple difuran into the key ABC-ring motif of the pectenotoxins†‡

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The key ABC-ring motif of the pectenotoxins has been synthesized, starting from a simple and readily accessible difuran precursor, using a complex singlet oxygen-mediated cascade reaction sequence.

As a continuation of our interest in the development of new and efficient synthetic approaches to natural products[1] and important natural products motifs[2] based on implementing cascade reaction sequences including, as the key element, singlet oxygen-mediated photooxygenations,[3] we sought to explore the possibility of synthesising the key ABC-ring system of polyether macrolactones pectenotoxins 2c, 8, 9 and 11c (Fig. 1) using such chemistry.

Since the first isolation of members of the pectenotoxin (PTX) family in 1985 from *Patinopecten yessoensis* scallops, by Yasumoto and his coworkers,[4] more than 20 other structurally related compounds have been isolated from *Dinophysis* dinoflagellates worldwide.[5] PTXs have aroused particular interest because they interact with the actin cytoskeleton at a new and unique site[6] conferring on them potent cytotoxicity against human lung, colon and breast cancer cell lines.[5a,7] Excluding subtle variations in the oxidation state at C_{43} (Fig. 1), PTXs structural diversity originates mainly from differing types and configurations of AB spiroketal subunit that are interconvertible by means of acid equilibration.[5b] Only four PTXs bear a [6,6]-spiroketal, while in the rest a [6,5]-spiroketal is present.

PTX4 and PTX8 were synthesised in 2002 with characteristic eloquence by Evans and coworkers.[8] The ABC-fragment, containing a [6,5]-spiroketal, has been synthesised by the groups of Paquette,[9] Brimble[10] and Pihko[11] using acid catalysed ketalisation of hydroxyketones, or ketals, for the formation of the C_7 spiroketal, as well as a classical 5-*exo* epoxide opening for the construction of the C-ring.[12] More exotic approaches, namely the cyclization of a spirodiepoxide and reductive cyclization of a cyanoacetal for the synthesis of the [6,5] AB-spiroketal, have recently been developed by the groups of Williams[13] and Rychnovsky,[14] respectively.

The main focus of work emanating from our laboratories has been to explore new ways of employing singlet oxygen, a powerful, selective and green oxidant, as a cascade reaction sequence-mediator.[1–3] To this end, we have recently reported

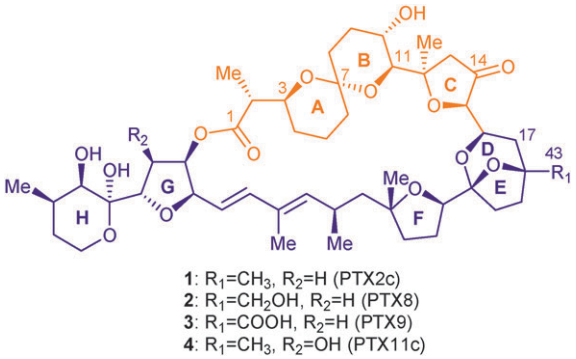
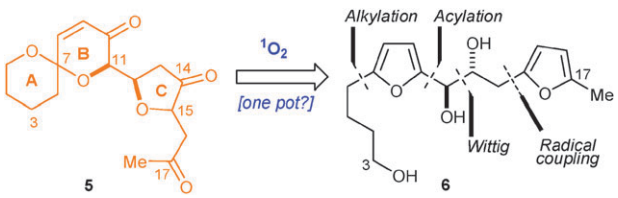


Fig. 1 Structures of PTXs 2c, 8, 9 and 11c.

methods to rapidly synthesise [6,5]- and [6,6]-spiroketals,[2c,d] as well as to make 3-keto-tetrahydrofurans[2e] using singlet oxygen ($^1O_2$) oxidation of an appropriately substituted simple furan precursor. Based on this experience gained designing and implementing these cascade reaction sequences, we thought it might be possible, although definitely ambitious, to combine the methodologies in one super-cascade sequence mediated by $^1O_2$ that would yield the key ABC-ring motif (**5**, Scheme 1) of PTXs 2c, 8, 9 and 11c starting from a relatively simple difuran precursor **6**.

Our investigation began by targeting the cascade reaction sequence precursor, difuran-triol **6**. We hoped to achieve the synthesis of **6** using *syn*-dihydroxylation of a *cis*-olefin, to be prepared by means of a Wittig reaction (Scheme 1). According to precedent,[2c,15] we believed it should be possible to introduce all the requisite substituents at the *ortho* positions of the difuran **6** using known anionic- or radical-based methods at an early stage in the synthetic sequence.

The strategy was implemented, and, in a straightforward manner, free radical coupling of an excess of commercially available sylvan (**7**) with ethyl iodoacetate according to Baciocchi conditions[15] afforded ethyl 2-(furan-2-yl)acetate (**8**, Scheme 2) in 91% yield. Reduction of **8**[15b] with $LiAlH_4$ followed by iodination (I_2, PPh_3, imidazole) gave iodide **9**, which was converted to the corresponding phosphonium salt **10** in 68% overall yield (over 3 steps). Wittig coupling between the phosphonium salt **10** and aldehyde **13** (prepared by *ortho*-formylation of known furan **12**[2c,d] with DMF) afforded



Scheme 1 Retrosynthetic analysis of ABC motif of PTXs.

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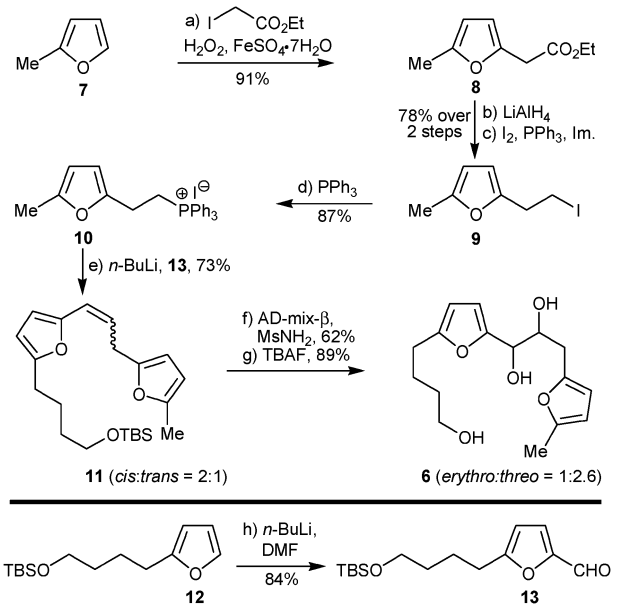
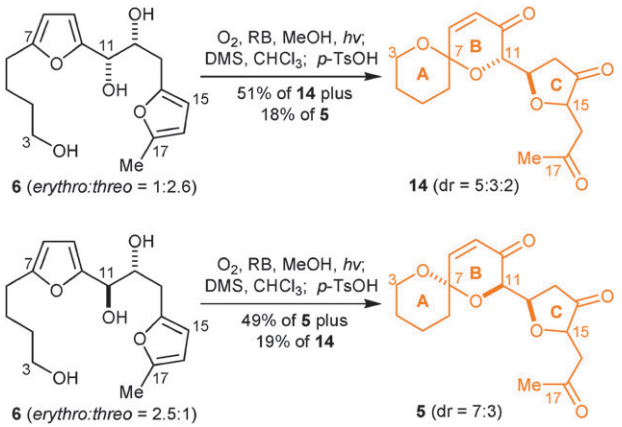
olefin **11**, as a mixture of two geometrical isomers (*cis*:*trans* = 2:1, Scheme 2), in 73% yield. Sharpless asymmetric dihydroxylation (SAD)[16] of olefin **11** (*cis*:*trans* = 2:1) resulted in the unexpected formation of a 1:2.6 mixture of *erythro*/*threo* 1,2-diols[17] in 62% yield, while 20% of the starting material (exclusively *cis*-**11**) was recovered. The unexpected formation of the *threo* diastereoisomer of **6** as the major product of this *syn*-dihydroxylation reaction of an olefin whose major geometrical isomer is *cis* configured, implies a degree of *cis*/*trans* isomerisation during the course of the reaction. The fact that the recovered starting olefin is exclusively *cis* is in agreement with the known faster dihydroxylation of a *trans* olefin *versus* its *cis* isomer. When the recovered *cis*-**11** was resubjected to SAD conditions a 2.5:1 mixture of *erythro*/*threo* 1,2-diols was formed. Finally, TBAF assisted deprotection of the primary alcohol resulted in the formation of the requisite photooxygenation precursor difuran-triol **6** in a total of eight simple synthetic steps.

With difuran-triol **6** in hand, the stage was now set for us to obtain proof of principle for the ambitious singlet oxygen-initiated cascade reaction that we had envisioned as a means of accessing the key ABC-ring motif of the pectenotoxins. A solution of **6** (*erythro*/*threo* = 1:2.6) in MeOH, containing rose bengal as photosensitizer, was irradiated for three minutes with visible spectrum light whilst oxygen was being bubbled gently through it. Very careful replacement of MeOH with either $CHCl_3$ or CH_2Cl_2 followed by treatment for 72 h with an excess of dimethyl sulfide (DMS) and then with *p*-TsOH for 3 h resulted in the remarkable formation of compound **14** (51%, mixture of 3 diastereoisomers in 5:3:2 ratio, Scheme 3) accompanied by a chromatographically separable, less polar, compound **5** (18%, mixture of 2 diastereoisomers in 7:3 ratio). When the same photooxidation conditions were applied to **6** (*erythro*/*threo* = 2.5:1) formation of compound **5** (49%, mixture of 2 diastereoisomers in 7:3 ratio) was accompanied by compound **14** (19%, mixture of 3 diastereoisomers in 5:3:2 ratio). Careful NOE studies undertaken on



Scheme 2 Synthesis of the photooxygenation precursor difuran-triol **6**.

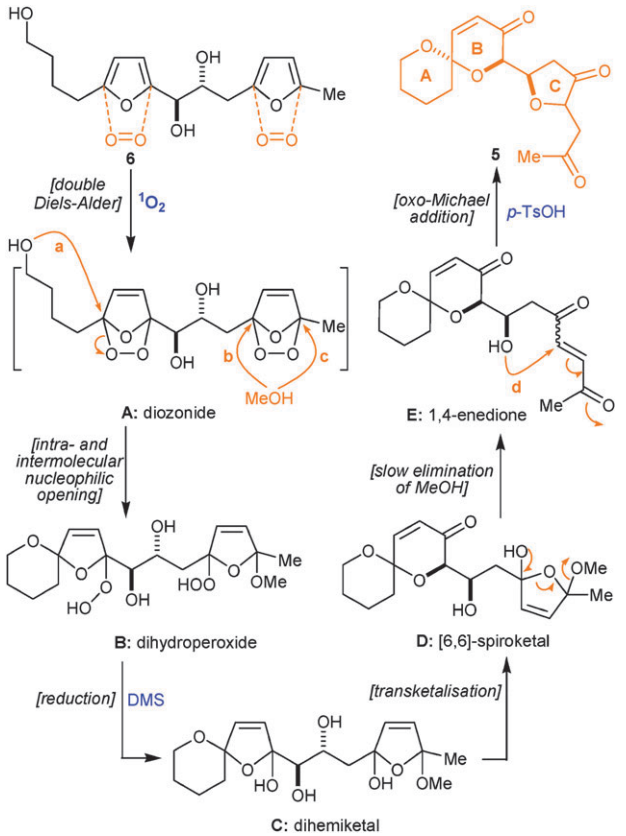


Scheme 3 Singlet oxygen initiated cascade transformation of difuran-triol **6** into the ABC motif of PTXs 2c, 8, 9, and 11c.

the major diastereoisomer of **14** (observation of NOE between H_3 and H_{11}, as well as H_{12} and H_{15}) prove that the relative stereochemistries of C_7 compared to C_{11}, as well as C_{12} compared to C_{15} are correct. Similar NOE studies on **5** (observation of NOE between H_3 and H_{11}) are consistent with the anomeric C_7 spiroketal for both diastereoisomers.[18]

The synthetic strategy for PTXs ABC-ring motif synthesis that had just been successfully implemented, had been predicated on our previous experience in the field[1a–c,g,2c–e] which would also support the following mechanistic rationale (Scheme 4) for the transformation of **6** into **5**. First of all, the formation of dihydroperoxide **B** (Scheme 4) is expected to occur *via* one intra- and one intermolecular nucleophilic opening of fleeting diozonide **A**. For simplicity, only one of the two possible regioisomers (nucleophilic openings **b** and **c**) of dihydroperoxide **B** appears in Scheme 4. Each regioisomer is in turn a mixture of diastereoisomers resulting in a very complicated ^{1}H NMR spectrum for dihydroperoxide **B**. The very careful replacement of MeOH with $CHCl_3$ followed by treatment of the mixture of dihydroperoxides **B** with an excess of dimethyl sulfide (DMS) reduces[1a–c,2c–e] the two hydroperoxy groups of **B**, thus, affording the corresponding dihemiketal **C**. A transketalisation reaction[2d] leads to the transformation of the [6,5]-spiroketal of **C** into the [6,6]-spiroketal **D**. Under the same reaction conditions the remaining hemiketal moiety of intermediate **D** slowly eliminates a molecule of MeOH,[1a–c,2e] thus revealing the 1,4-enedione moiety of intermediate **E**. In the final step of this remarkable cascade sequence, *p*-TsOH catalyses an *oxo*-Michael cyclisation[2e] between the –OH group of **E** and the 1,4-enedione moiety resulting in the formation of the sought after ABC-ring motif of PTXs in the form of compound **5**.

From a practical standpoint, it is very important to note that during the 72 h treatment of the photooxidation mixture with DMS the reaction was continuously monitored by ^{1}H NMR. The fact that the intermediates **B**, **C**, **D** and **E** (Scheme 4) are mixtures of different regio- (not shown) and stereoisomers, and also the fact that some of these intermediates coexist during the course of the reaction, made analysis of the ^{1}H NMR spectra challenging. However, it is very important to undertake this monitoring by ^{1}H NMR because not only does the DMS/DMSO ratio remain unchanged once complete reduction of all the



Scheme 4 A mechanistic explanation.

hydroperoxy groups has been attained, but the amount of MeOH present also becomes static once the opening of the hemiketal to the 1,4-enedione moiety has been achieved, thus the right moment for the addition of the *p*-TsOH is indicated. This final reagent addition initiates a gross simplification of the reaction's TLC profile that has been complex up to this point, as two less polar (compared to preceding intermediates) spots start to dominate.

In summary, we have designed and successfully executed a most ambitious singlet oxygen-driven reaction cascade sequence wherein a simple and readily accessible difuran precursor is transformed to a complex multiringed motif found in the pectenotoxin family of natural products. This sequence perfectly showcases the power singlet oxygen has to mediate intricate cascade reaction sequences and transform simple molecules to complex ones with ease and efficiency.

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18 For detailed NOE studies see supporting information section.