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The vitamin C route to the ciguatoxins: enantioselective synthesis of a ring F building block

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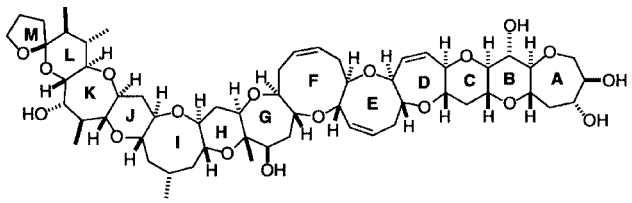
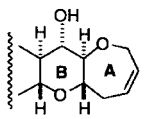
A ten-step enantioselective synthesis of an F ring lactone for CTX antibody assay development, employing vitamin C as a starting material, is described.

Ciguatera, a disease caused by consumption of ciguateric fish (*i.e.* those fish which have accumulated ciguatoxins (CTXs) in their flesh as a result of ingesting *Gambierdiscus toxicus*, a benthic dinoflagellate which synthesizes these toxins) is endemic throughout the tropics.[1] Consequently there is a need to develop a simple assay for the presence of these toxins in fish. Because of the very low concentrations (<0.1 ppb) of ciguatoxins in fish such an assay will need to be highly sensitive, such as an immunoassay.[2] Hence as part of a program[3] directed towards the synthesis of immunogenic domains of the CTXs, we report here, the enantioselective synthesis of a ring F building block.[4]

From a synthetic point of view, the ciguatoxins constitute one of the most synthetically challenging classes of naturally occurring marine toxins.[5] Each of these toxins consists of thirteen contiguous, fused cyclic ethers ranging in size from five to nine members. The structures of two potential targets, the Pacific ciguatoxins 2,3-dihydroxy-P-CTX-3C **1a**[6] and P-CTX-3C **1b**[7] are shown in Fig. 1.



1a 2*R*,3*R*-Dihydroxy-P-CTX-3C



1b P-CTX-3C

Fig. 1 The structures of two Pacific ciguatoxins: P-CTX-3C and 2,3-dihydroxy-P-CTX-3C.

We envisaged the ring F target to be of general structure **4** (Fig. 2). This nine-membered lactone has the correct relative and absolute stereochemistry in place as well as a reactive lactone carbonyl. Related oxoninones have been shown to be valuable intermediates in natural product synthesis.[8–10] In principle **4** should be accessible from vitamin C **2** *via* bicyclic lactone **3** (Fig. 2). Indeed an intermediate bicyclic *ether*, similar to **3**, has recently been reported by Hirama's group to be a very useful intermediate in CTX synthesis.[11]

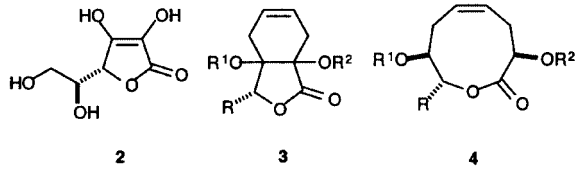
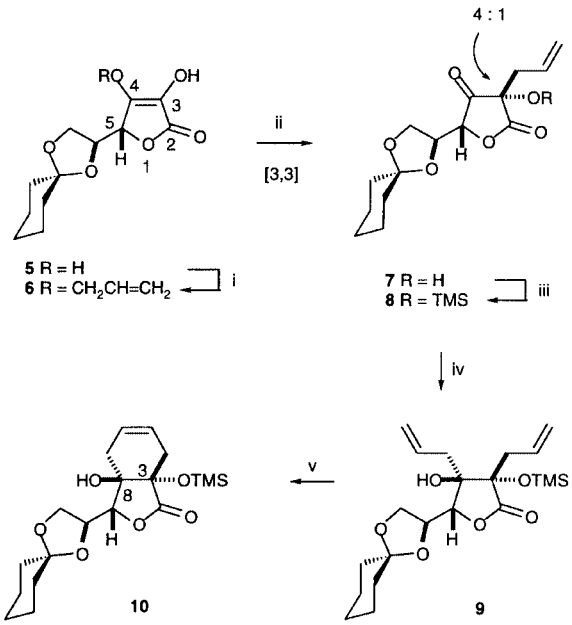


Fig. 2 The structures of vitamin C **2** and two key synthetic targets.

The synthesis of **4** is shown in the Schemes and begins with the cyclohexylidene acetal **5** of vitamin C (Scheme 1). (The corresponding acetonide[12] was employed initially, however it proved to be insufficiently robust in subsequent transformations). Selective *O*-allylation of the C4 hydroxyl of **5** in preference of the hydroxyl at C3, using potassium carbonate/THF–DMSO/allyl bromide, has been reported for vitamin C acetonide.[12] Unfortunately under these conditions we were not able to obtain **6** sufficiently pure for further reactions. Selective C4 *O*-allylation of **5** was ultimately achieved by treatment with allyl bromide in aqueous THF maintaining neutral to slightly alkaline pH. The corresponding *C*-allyl derivative **7** was obtained as a 4 : 1 mixture of diastereomers by heating a toluene solution of **6** at reflux for 6 h. Next it was necessary to generate a diene from **7** which could be closed under ring closing metathesis conditions. Addition of a variety of allyl nucleophiles to **7** gave mixtures of diastereomers which proved very difficult to purify. After considerable experimentation it was found that addition of allylzinc bromide to the *O*-trimethylsilyl derivative **8** (obtainable as a single diastereomer, after purification, by silylation of crude **7**) gave pure diene **9** in excellent yield and complete diastereoselectivity. The preference for attack from the *Si*-face at C4 is probably due to a combination of steric hindrance from the C3 allyl group and coordination to the oxygens at C3 and/or those contained in the side chain acetal. Although the stereochemistry at C3 and C4 is lost later it



Scheme 1 *Reagents and conditions*: i, K_2CO_3, allyl bromide, DMSO–THF, r.t., 6 h or allyl bromide, 1 M NaOH–THF pH 7–8, r.t., 24 h; ii, toluene, reflux, 6 h; iii, TMSCl, imidazole, THF, r.t., 2 h, 20% as a single isomer from **5**; iv, allylzinc bromide, THF, r.t., 30 min, 94%; v, RuCHPh(P-$Cy_3)_2Cl_2$, toluene, 60–70 °C, 24 h, 69%.

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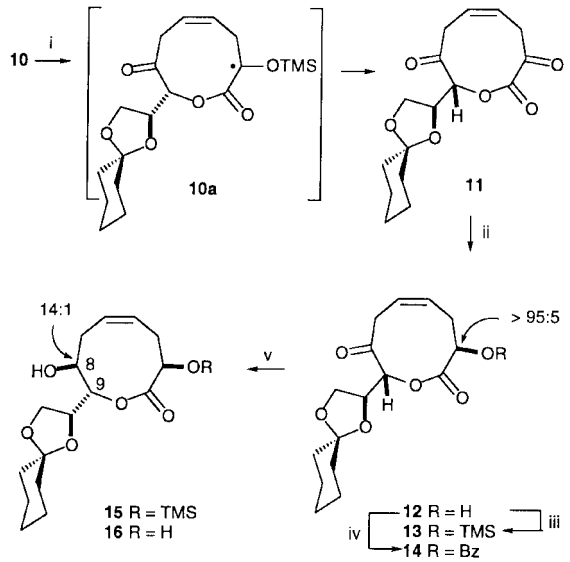

Scheme 2 *Reagents and conditions*: i, HgO, I_2, benzene, *hν*, reflux, 8 h; ii, $NaCNBH_3$, AcOH, *ca.* 13 °C, 20 min, 43% from **10**; iii, TMSCl, imidazole, THF, r.t., 12 h, 99%; iv, $(PhCO)_2O$, Et_3N, DMAP, THF, r.t., 2 h, 99%; v, 1 M LiB[CHMe(Et)]$_3$H, THF, *ca.* −130 °C, 30 min, 73%.

proved operationally more practicable to handle a single stereoisomer through the next sequence of reactions. Thus ring closing metathesis[13] of **9** gave bicyclic lactone **10** in excellent yield. This crystalline product was subjected to single crystal X-ray analysis and the relative stereochemistry of the new stereogenic centres at C3 and C8 was confirmed to be as shown.

Oxidative ring opening of **10**, following adaptations of the conditions of O'Dell *et al.*[14] and Ito *et al.*[15] yielded oxonintrione **11** in good yield (Scheme 2). We assumed that an intermediate such as **10a** would be generated under these conditions. Such intermediates have been proposed before for the oxidative cleavage of silyl ethers.[15] With the nine-membered lactone in hand it remained to reduce the two ketone carbonyls. We found that this was best achieved in a stepwise manner. Thus treatment with sodium cyanoborohydride regio- and stereo-selectively reduced **11** to alcohol **12**. The (*R*)-stereochemistry of the new centre was confirmed by single crystal X-ray analysis of the corresponding benzoate (**14**, R = benzoyl in Scheme 2 and Fig. 3).

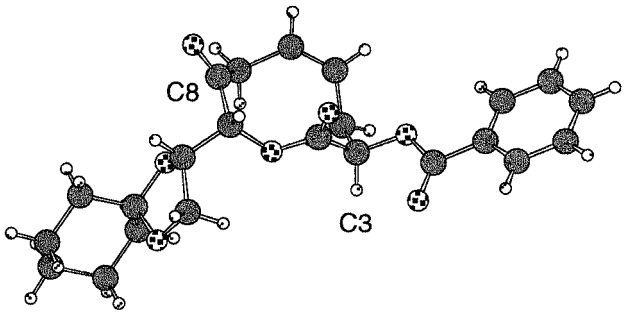

Fig. 3 Single crystals of $C_{23}H_{26}O_7$ **14** were recrystallised from diethyl ether–hexanes, mounted in inert oil and transferred to the cold gas stream of the diffractometer. *Crystal data*: $C_{23}H_{26}O_7$, M = 414.44, monoclinic, space group $P2_1$ (no. 4), a = 10.1336(2), b = 9.5207(2), c = 11.1957(2) Å, β = 104.750(1)°, U = 1044.55(4) Å^3, T = 123 K, Z = 2, μ(Mo-K) = 0.097 mm^{-1}, 14784 reflections measured, 4923 unique (R_{int} = 0.023) which were used in all calculations. The final $wR(F^2)$ was 0.074 (all data), and flack parameter χ = 0.1(6). CCDC 182/1556. See http://www.rsc.org/suppdata/cc/a9/a910163m/ for crystallograpic files in .cif format.

Treatment of **13** with L-selectride {LiB[CHMe(Et)]$_3$H} at −78 °C gave **15** as a 6:1 mixture of diastereomers. Lowering the reaction temperature to *ca.* −130 °C improved the selectivity to 14:1 in favour of the desired isomer. Reduction of **11** with 2 equivalents of L-selectride at *ca.* −130 °C resulted in a mixture of products consisting of 60% **16** and a 1:1:1 mixture of the other three possible diastereomers. The relative stereochemistry of **15** was established by examination of the coupling between H8 and H9 ($J_{8,9}$ 8.7 Hz). For closely related nine-membered cyclic ethers, typical coupling constants are J_{trans} 8.5 Hz, J_{cis} 2.2 Hz.[11] The reasons for the remarkably high diastereoselectivity in the first reduction remain unclear as initial molecular mechanics modelling failed to reveal a low-energy conformation likely to lead to the observed stereochemistry at C3. However, the source of the selectivity in the second reduction appears to be a folded conformation for **13** similar to that shown in Fig. 3 for crystalline **14**. If this conformation is maintained in solution then attack at the *Si* face of the ketone is clearly favoured, generating the observed sterochemistry at C8.

In conclusion, we have demonstrated the usefulness of vitamin C as an enantiomerically pure starting material for the synthesis of oxonins. Key steps included (i) a ring closing metathesis/oxidative cleavage sequence to form the nine-membered ring and (ii) a sequence of two highly diastereoselective reductions. Compounds such as oxonin **15** represent valuable intermediates for the synthesis of F-ring containing CTX domains as well as other naturally occurring oxonins such as obtusenyne and other nine-membered cyclic ethers of marine origin.[16]

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