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Synthesis of a ring F building block for the ciguatoxins

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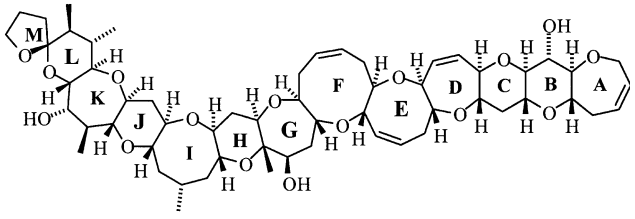
Abstract—The preparation of a new ring F building block for the marine polyether toxins, the ciguatoxins, employing ascorbic acid as a chiral pool starting material, is reported.

1. Introduction

The consumption of fish containing accumulated ciguatoxins (CTXs, e.g. P-CTX-3C **1**; Fig. 1) can lead to disease in humans. This disease, known as ciguatera, is endemic throughout the tropics. As the CTXs are present in very low concentrations (<0.1 ppb) in toxic fish, a very sensitive assay, such as an immunoassay, is required for their detection.[1,2] As part of our program[3] directed towards the synthesis of immunogenic domains of the CTXs, we report herein the details of our preparation of a CTX ring F building block.[4]

The overall strategy at the outset of this work was to develop methods to prepare medium-sized lactones from readily available, enantiomerically pure lactones, such as ascorbic acid **5**. The structure of the ring F lactone building block **2**, the subject of this report, and its retrosynthetic analysis are shown in Scheme 1. We envisaged that this could be achieved from bicyclic **3** after sequential ring opening[5,6] and selective reduction.[7–15] Bicyclic **3**, in turn, could be prepared by nucleophilic allylation and ring closing metathesis (RCM) of **4**.



1 *P-CTX-3C*

Figure 1.

2. Results and discussion

2.1. Preparation of alkene 4

3-Allyl ascorbic acid derivatives have been reported previously. For example, introduction of an allyl group at C3 of ascorbic acid acetonide using a two-step process has been reported by Wimalasena and Mahindaratne.[16] Their method involved the sequence of (i) *O*-allylation (using K_2CO_3 in a DMSO/THF solution) and (ii) thermal rearrangement. Although we found this procedure works quite well, the acetonide group in the product proved to be insufficiently robust to survive subsequent reactions. Thus we employed **6**, the *cyclohexylidene* acetal of ascorbic acid, easily prepared on large scale by adaptation of Tanaka's isoascorbic acid cyclohexylidene acetal preparation. Unfortunately, the aforementioned allylation conditions proved ineffective for **6**. Allylation under neutral conditions proved more satisfactory. Thus, neutralisation of a THF solution of **6** with 1N $NaOH_{(aq)}$ followed by treatment with allyl bromide and stirring for 10 h yielded a mixture of *O*-allylated **7** and *C*-allylated **4a** and **b** (Scheme 2). Claisen rearrangement then gave complete conversion to a 4:1 mixture of the epimeric *C*-allylated furandiones **4a** and **b**.

2.2. Conversion of 4 into bicyclic 3 (R^1=TMS)

As the mixture of **4a** and **b** could not be purified without decomposition, nucleophilic allylation of the ketone was attempted directly on this crude material. Thus allylation using either allyl zinc or Grignard reagents were examined under a variety of conditions. Irrespective of the conditions employed these reactions failed to consume all of the starting material, even with a large excess of allylating reagent. Addition to the corresponding tetramethylsilane (TMS) ether gave far better results. Thus, treatment of **4a** and **b**

Keywords: ciguatoxin; ring expansions; ascorbic acid; oxidation; ring closing metathesis.

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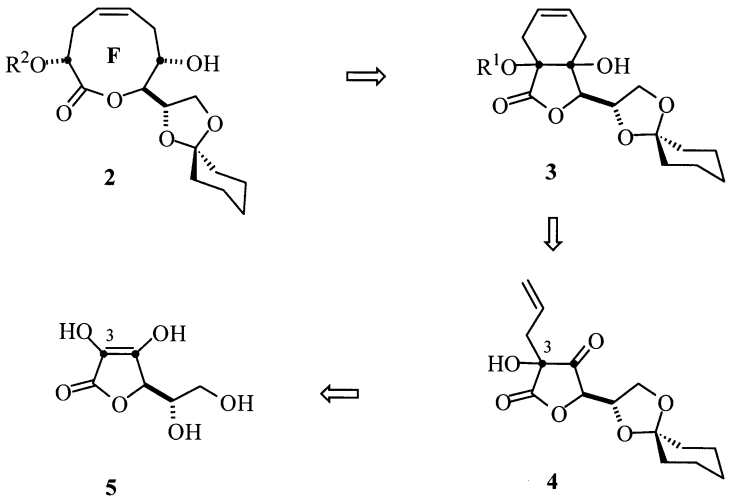
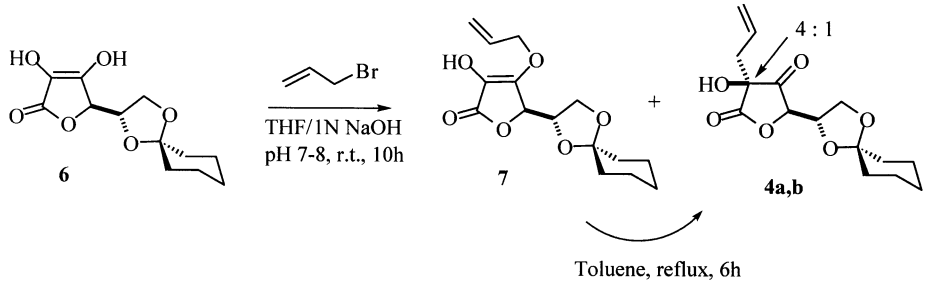
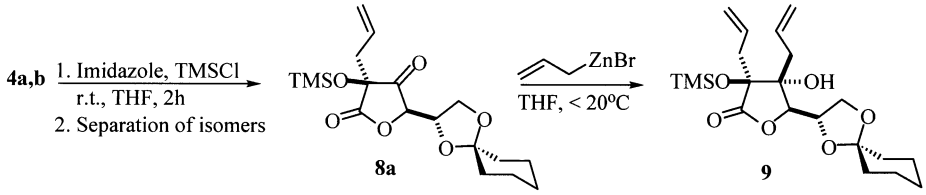


Scheme 1.



Scheme 2.



Scheme 3.

with trimethylsilyl chloride and imidazole in THF at rt for only 2 h gave an excellent yield of TMS ethers **8a** and **b**(Scheme 3) which were easily separated by chromatography.

Allylation under anhydrous conditions using an allyl zinc reagent, however, provided diene **9** in excellent yield (Scheme 3). (Allylation of **8a** using allylmagnesium bromide or $NH_4Cl_{(aq)}$-activated allyl zinc reagents failed to drive the reaction to completion with no selectivity being observed.)

The relative stereochemistry of **9** could not be determined using spectroscopic methods and was ultimately established

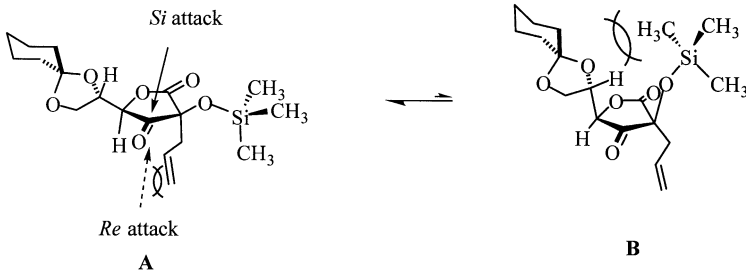
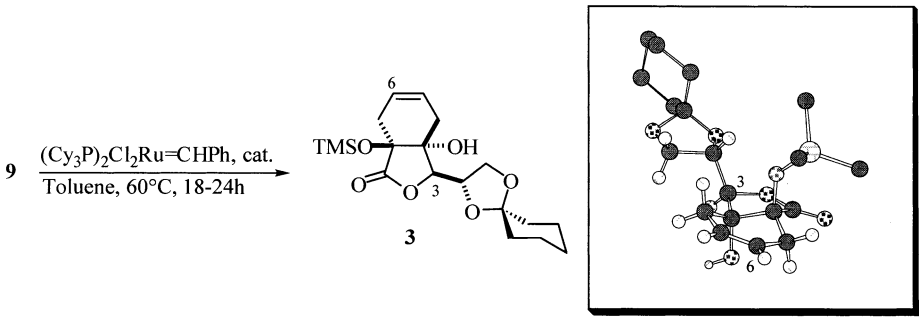


Figure 2.



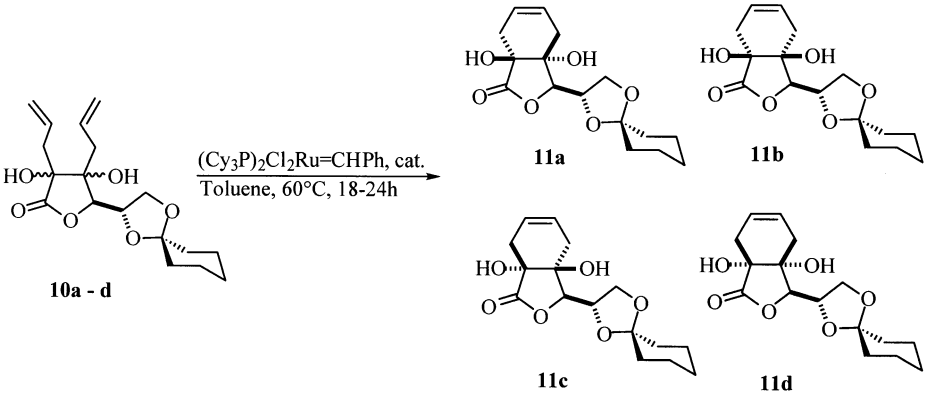
Scheme 4.

by X-ray crystallographic analysis of the crystalline bicyclic product **3** (R^1=TMS) obtained from RCM of **9** (vide infra). Examination of the crystal structure established that allylation had occurred exclusively from the *Si* face of the ketone. Pre-complexation of ketone **8a** with anhydrous $ZnBr_2$, prior to addition of the allylating reagent, yielded identical results. This suggests it is unlikely that side chain or *O*-TMS coordination of the allyl zinc reagent is controlling the selectivity. Variation of the reaction temperature had little effect on the diastereoselectivity with a small amount of starting material being returned at lower temperatures. Conformational analysis of **8a** provides a possible explanation for the diastereoselectivity (Fig. 2). Conformation **A** is most likely favoured as conformation **B** suffers from a serious pseudo-1,3-diaxial interaction and should therefore be significantly higher in energy. Conformation **A** also offers the appropriate (*Si*) face of the ketone with relatively unhindered access.

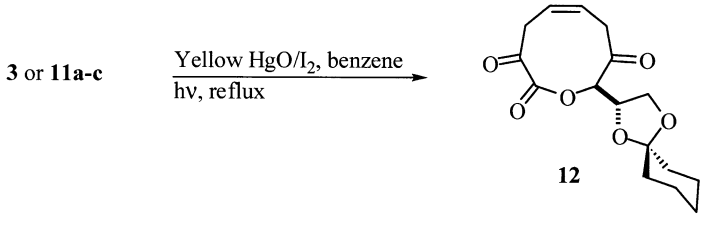
RCM of the diene **9** using Grubbs' catalyst in toluene at 60°C proceeded readily under the described conditions with all of the starting material being consumed. X-Ray crystallography of the product **3** (R^1=TMS, Scheme 1) confirmed the relative stereochemistry at the ring junctions as *trans* (Scheme 4).

RCM studies on the diastereomeric mixtures of dienes **10a–c** obtained from additions to the mixture of ketones **4a** and **b** yielded mixtures from which isobenzofuranones **11a–c** were isolated. These reactions always yielded a small amount of starting material irrespective of reaction times up to 24 h. Extending the reaction time beyond 24 h and/or raising the reaction temperature led to a reduction in yield (Scheme 5).

Purification of the reaction products **11a–d** allowed for their individual stereochemical assignment by direct correlation each of their corresponding to diene precursors **10a–d**. The 3a*S*, 7a*S* isomer **11b** was assigned *cis* relative stereochemistry based on its very rapid (<1 min) cleavage under oxidative conditions ($Pb(OAc)_4$) and based on its proportional representation in the crude mixture. The *trans* assignments of the 3a*R*, 7a*S* isomer **11a** and 3a*S*, 7a*R* isomer **11c** were suggested based on their lack of



Scheme 5.



Scheme 6.

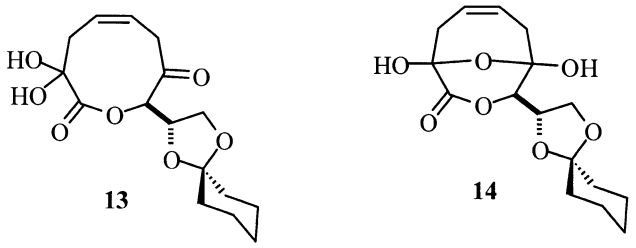


Figure 3.

reactivity towards $Pb(OAc)_4$ and their proportional representation in the crude mixtures. The assignment of isomer **11c** was confirmed directly by X-ray crystallography and isomer **11a** indirectly via chemical transformation of **9**. Negligible amounts of **11d** were present and hence could not be isolated.

2.3. Completion of the synthesis of 2

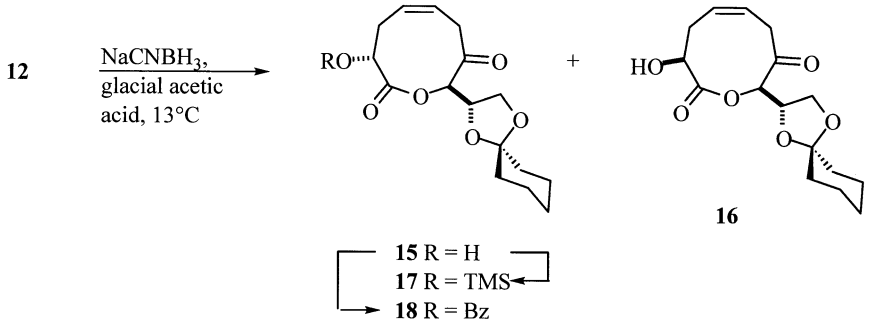
Cleavage of **11b** proceeded at an exceedingly rapid rate with no starting material being detected <1 min after the addition of $Pb(OAc)_4$ at 0°C providing **12** in excellent yield. Cleavage of the *trans* fused bicycles proved somewhat more difficult. Neither isobenzofuranones **11a**,**c** nor the *O*-TMS isobenzofuranone **3** could be cleaved using $Pb(OAc)_4$. Addition of an acid catalyst with the $Pb(OAc)_4$, which has been reported to effect *trans* bicyclic diol cleavages through a non-cyclic mechanism, also failed to yield results.[17] Allowing a mixture of the isobenzofuranone and HgO/I_2[18–20] to reflux whilst being irradiated with a tungsten lamp did induce β-fission of isobenzofuranones **11a**,**c** and *O*-TMS isobenzofuranone **3**. Interestingly both irradiation and heat were required for the reaction to proceed to an appreciable extent. Cleavage using $PhI(OAc)_2/I_2$[21] was successful, however, it was found to be less efficient compared with the HgO/I_2 method (Scheme 6).

Tricarbonyl **12** proved to be very susceptible to hydration producing a variable mixture of **12**, its monohydrate **13** and the bridged hydrate **14** (Fig. 3).

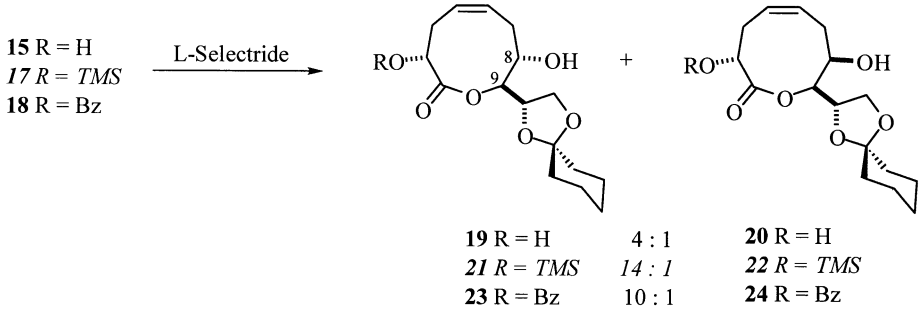
Direct reduction of **12** with $NaBH_4$[6] or triethylborohydride yielded complex mixtures which could not be characterised. Reduction with L-selectride® at approximately −100°C yielded a mixture of the four diastereomers with the desired dihydroxyoxoninone **15** being favoured, albeit in only a 3:2 ratio, over the other isomers. Stepwise reduction of the mixture yielded a more satisfying result with both chemo- and stereoselective reduction of the α-dicarbonyl system being effected in cooled glacial acetic acid with $NaCNBH_3$ as the reducing agent. The selectivity in favour of the desired hydroxyoxonindione **15** over **16** was 95:5 with no concomitant reduction of the isolated ketone carbonyl under these conditions (Scheme 7). Conversion of **15** into benzoate **18** yielded a crystalline derivative whose structure confirmed the relative stereochemistry of **15** as that shown.

Reduction of the isolated ketone using diol **15**, monosilyl ether **17** and monobenzoate **18** was investigated employing L-selectride® as a hydride source (Scheme 8).

As shown the desired diastereomer was favoured in all cases with the *O*-TMS oxonindione **17** yielding a 14:1 ratio in favour of **21** (which is the final target **2**, R^2=TMS, see Scheme 1). Assignment of relative stereochemistry was made based on $J_{8,9}$.[5]



Scheme 7.



Scheme 8.

3. Conclusions

Synthetic equivalents for the target oxoninone **2** have been successfully prepared in nine steps from ascorbic acid cyclohexylidene **6**. Although the initial steps proceed in modest yield this synthesis represents the first preparation of enantiomerically pure oxoninones from ascorbic acid. A key, highly selective oxidative cleavage–reduction sequence from the *O*-TMS isobenzofuranone **3** provided hydroxyoxonindione **15** in 43% overall yield for the two steps.

The methodology described here forms a solid basis on which to build syntheses directed at the preparation of more extended fragments of the central portion of the CTX marine polyether toxins. Investigations towards improving and extending this process are currently underway in our laboratories and will be reported in due course.

4. Experimental

4.1. General methods and materials

Melting points were determined on a Kofler hotstage and are uncorrected. Elemental microanalyses were performed by the Australian Microanalytical Service, National Analytical Laboratories, Melbourne or the University of Otago, Dunedin, New Zealand. Optical rotations were recorded on a Perkin–Elmer Model 141 Polarimeter. Infrared (IR) spectra were recorded on a Perkin–Elmer 1600 Series Fourier Transform spectrophotometer (cm^{-1} scale) and refer to thin films of liquids (neat) or paraffin (Nujol) mulls of solids between NaCl plates. High resolution hydrogen-1 nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 300 MHz on a Bruker DPX-300 spectrometer or 400 MHz on a Bruker Avance DRX 400 spectrometer. The ^{1}H NMR spectral data refer to deuteriochloroform solutions ($CDCl_3$) using residual solvent as internal reference (δ 0.00 ppm). Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 75 MHz on a Bruker APX-300 spectrometer or 100 MHz on a Bruker Avance DRX 400 spectrometer. Mass spectrometry (ESI) was performed using samples in methanol on a Micromass Platform QMS Electrospray mass spectrometer. High-resolution mass spectra (HRMS) for accurate mass determinations were recorded on a Bruker BioApex 47e FTMS fitted with an analytical electrospray source using NaI for accurate mass calibration (accuracy ±3 ppm). Low-resolution mass spectra were recorded on a VG micromass 70/70F or a VG TRIO-1 mass spectrometer with an ion source temperature of 200°C and electron impact energy of 70 eV. X-Ray crystallography was performed on a Nonius Kappa CCD. HPLCs were run on a Waters Alliance 2690 HPLC with a 996 Photodiode array detector using Zorbax RX-SIL normal phase silica (5 micron) columns with dimensions of 4.6×150 mm for analytical work and 9.4×259 mm for semi-preparative with flow rates of 0.3 mL/min and 4.0 mL/min for analytical and semi-preparative respectively. An analytical gradient profile (AGP) of Isopropanol(A)/hexanes(B) was used with gradient of 0–10%A during 0–10mins then hold 10%A 10–29mins. The semi-preparative gradient profile (SGP) was 0–10%A 0–15mins then hold 10%A 15–30mins. Retention times are in minutes.

4.2. Compound data

4.2.1. *C*-Allylated furandiones 4a,b. Sufficient aqueous 1N NaOH (~200 mL) was added to a solution of *O*-cyclohexylidene furanone **6** (51.2 g, 0.2 mol) in THF (460 mL) such that a pH of between 7 and 8 was obtained. Allyl bromide was added dropwise (18.9 mL, 0.22 mol) to this solution and the mixture allowed to stir for 10 h. The solution was extracted with EtOAc (3×300 mL) and the combined extracts washed with brine (200 mL), dried ($MgSO_4$) and the solvent evaporated in vacuo to yield an orange oil (23.5 g). The oil was dissolved in toluene (650 mL) and heated to reflux for 6 h after which time the solvent was removed in vacuo to yield a mixture of the C3 allyl epimers (4–5:1, **4a/4b**) as a dark orange oil (22.5 g). The purity was estimated to be >80% by NMR spectroscopy. This material was used in subsequent reactions without purification. The data presented here are for the mixture. **4a** ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33–1.70 (m, 10H), 2.65 (bd, J=~7.5 Hz, 2H), 4.05 (dd, J=8.7, 7.0 Hz, 1H), 4.17 (dd, J=8.7, 6.9 Hz, 1H), 4.51 (dt, J=6.9, 2.0 Hz, 1H), 4.65 (d, J=2.0 Hz, 1H), 5.20–5.28 (m, 2H), 5.60–5.74 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.8, 23.9, 25.1, 34.8, 34.9, 39.6, 64.4, 71.8, 74.2, 81.5, 111.8, 123.1, 127.4, 172.5, 205.4; HRMS Calcd for $C_{15}H_{20}O_6Na$ ($M+Na^+$): m/z 319.116, Found 319.117. **4b**. Resonance used for diastereomeric ratio determination: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.72 (bd, J=~7 Hz, 2H, H8).

4.2.2. Allylfurandione TMS ether 8a. Imidazole (1.38 g, 20 mmol) and chlorotrimethylsilane (2.5 mL, 20 mmol) were added to crude furandiones **4a**,**b** (2.96 g, 10 mmol) in THF (50 mL) under N_2. The solution was allowed to stir for 2 h after which time it was diluted with Et_2O (50 mL) and poured into water (100 mL). The etherial layer was separated and the aqueous layer extracted with two further portions of Et_2O (25 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed in vacuo to yield an oil which was purified by flash chromatography (10% Et_2O/hexanes) to yield **8a** as a single isomer (1.71 g, 46%). FTIR (neat) 2938s, 1816s, 1771s cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.14 (s, 9H), 1.17–1.87 (m, 10H), 2.56 (d, J=7.6 Hz, 2H), 3.95 (dd, J=8.5, 7.3 Hz, 1H), 4.09 (dd, J=8.5, 6.7 Hz, 1H), 4.46–4.52 (m, 1H), 4.53 (d, J=2.3 Hz, 1H), 5.08–5.18 (m, 2H), 5.57–5.71 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 1.6, 23.6, 24.9, 35.0, 35.1, 42.9, 64.5, 73.1, 76.2, 81.0, 111.2, 121.6, 128.1, 171.9, 205.1; HRMS Calcd for $C_{18}H_{28}O_6Si$ (M^+): m/z 368.166, Found 368.166.

4.2.3. Diallylfuranones 10a–d. *Method 1*. Freshly titrated allyl magnesium chloride (23 mL, 1.1 M, 25.3 mmol) was added to the crude furandione **4a**,**b** (2.96 g, 10 mmol) in THF (100 mL) at −78°C. The mixture was allowed to stir for 4 h after which time the reaction was quenched by the addition of sat. aqueous NH_4Cl (100 mL) and allowed to warm to rt. The product was extracted with EtOAc (3×50 mL), dried ($MgSO_4$) and the solvent evaporated in vacuo to yield an orange coloured oil. Purification by flash chromatography (25% EtOAc/hexanes) yielded the *cis*

diallylated furanone **10b** (430 mg, 13%, R_f 0.6, TLC 40% EtOAc/hexanes) as a pure compound along with a fraction consisting of the *trans* isomers **10a** and **c** along with **4a** (4:1 **10a**/**4a**) and other minor unidentified impurities (360 mg, R_f 0.5, TLC 40% EtOAc/hexanes). This sample was not purified further. *Method 2*. Allyl bromide (8.8 mL, 0.1 mol), sat. aqueous NH_4Cl (100 mL) and Zn (6.57 g, 0.1 mol) were added sequentially to a solution of the crude furandione **4a**,**b** (5.96 g, 20 mmol) in THF (20 mL) which was being vigorously stirred at rt. After a short initiation time a temperature rise from 25 to 50°C was observed with a significant gaseous evolution. The reaction was allowed to stir vigorously for 1 h then diluted with Et_2O (40 mL). After separation of the organic layer the aqueous phase was extracted further with Et_2O (3×40 mL). The combined extracts were dried ($MgSO_4$) and the solvent evaporated in vacuo to yield a pale yellow oil. The crude ^1H NMR spectrum indicated a 2:3:1 ratio of the *cis* diallylated furanone **10b**, *trans* diallylated furanone **10a** and starting material **4a** as determined by integration of the H5 doublets at 4.18, 4.24 and 4.65 ppm, respectively. Two flash chromatography purifications on silica gel (25% EtOAc/hexanes) yielded one fraction consisting of a mixture of *cis* diallylated furanone **10b** and starting material **4a** in a 1:1 ratio and another fraction consisting of the *trans* diallylated furandione **10a** and starting material **4a** (1.31 g, 11:1, **10a**/**4a**). Products from this reaction were not purified further. **10b**. $[\alpha]_D^{29}=+61.8$ (*c* 1.17, $CHCl_3$); FTIR ($CHCl_3$) 3426b, 2935s, 1785s cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24–1.67 (m 10H), 2.29 (dd, *J*=14.3, 8.5 Hz, 1H), 2.42–2.61 (m, 3H), 3.99 (dd, *J*=8.4, 7.7 Hz, 1H), 4.14 (dd, *J*=8.3, 6.8 Hz, 1H), 4.18 (d, *J*=2.0 Hz, 1H), 4.48 (ddd, *J*=7.7, 6.8, 2.0 Hz, 1H), 4.53 (s, 1H), 5.16–5.22 (m, 4H), 5.83–6.03 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.9, 24.0, 24.9, 34.9, 35.3, 37.0, 38.1, 65.5, 73.2, 78.0, 78.3, 79.0, 112.0, 119.7, 119.8, 130.6, 131.4, 175.1; HRMS Calcd for $C_{18}H_{26}O_6Na$ ($M+Na^+$): *m*/*z* 361.163, Found 361.161.

4.2.4. Diallylfuranone TMS ether 9a. *Method 1*. Allyl bromide (0.45 mL, 5.2 mmol), sat. aqueous NH_4Cl (5 mL) and Zn (330 mg, 5.0 mmol) were sequentially added to a vigorously stirred solution of the TMS ether **8a** (368 mg, 1.0 mmol) in THF (1 mL) at rt. The heterogenous mixture was allowed to stir for 1 h then diluted with Et_2O (5 mL) and the organic layer separated. The aqueous layer was extracted further with Et_2O (2×5 mL) and the combined extracts dried ($MgSO_4$). Evaporation of the solvent in vacuo yielded a pale yellow oil. NMR analysis indicated a 1:1 mixture of the starting TMS ether **8a** and **9** whose NMR spectra were identical to those obtained from Method 2. *Method 2*. A crystal of I_2 followed by allyl bromide (2.4 mL, 28 mmol) was added dropwise, with stirring, to zinc powder (3.6 g, 56 mmol) in THF (15 mL) under N_2. The temperature during the addition was maintained below 20°C with the aid of an ice bath once the reaction had been initiated as indicated by the discolouration of the I_2 and accompanied temperature rise. Upon completing the addition the mixture was stirred for a further 10 min and the excess zinc filtered off under N_2. A portion of the allyl zinc reagent (6.1 mL, 3.6 equiv. based on 100% conversion) was subsequently added in one portion to a solution of the *O*-TMS furandione **8a** (1.0 g, 2.7 mmol) in THF (25 mL). A slight temperature rise was observed and after stirring for a further 1 h sat. aqueous NH_4Cl (25 mL) was added. The organic phase was separated and the aqueous phase extracted with Et_2O (3×20 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent evaporated in vacuo to yield a pale yellow oil. Purification by flash chromatography (30% Et_2O/hexanes) yielded the **9** (1.05 g, 94%) as a colourless oil. $[\alpha]_D^{26}=+45.4$ (*c* 1.0, $CHCl_3$); FTIR (neat) 3452b, 3079s, 2948s, 1770s, 1639s cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.22 (s, 9H), 1.24–1.70 (m, 10H), 2.29 (dd, *J*=14.0, 8.3 Hz, 1H), 2.35 (s, 1H), 2.52–2.60 (m, 2H), 2.61–2.69 (m, 1H), 3.93 (dd, *J*=8.5, 7.2 Hz, 1H), 4.10 (dd, *J*=8.4, 6.5 Hz, 1H), 4.15 (d, *J*=6.0 Hz, 1H), 4.34 (ddd, *J*=7.2, 6.5, 6.0 Hz, 1H), 5.13 (m, 4H), 5.82–6.08 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 2.3, 23.9, 24.0, 25.2, 35.2, 35.9, 37.3, 39.3, 65.4, 72.9, 80.5, 82.6, 83.0, 110.6, 119.4, 121.8, 131.9, 132.6, 174.7; HRMS Calcd for $C_{21}H_{34}O_6SiNa$ ($M+Na^+$): *m*/*z* 433.202, Found 433.201; Anal. Calcd for $C_{21}H_{34}O_6Si$: C, 61.4; H, 8.4. Found: C, 61.4; H, 8.4%.

4.2.5. *cis*-Isobenzofuranone 11b. A solution of Grubbs' catalyst (80 mg, 10 mol%) in degassed toluene (0.5 mL) was added at 60°C under Ar to a solution of *cis* diallyl furanone **10b** (136 mg, 0.40 mmol) in degassed toluene (7 mL). The solution was stirred at this temperature for 20 h after which time the solvent was removed in vacuo. The residue was dissolved in ether and passed through a silica plug to remove some of the black tar like material. Collection of the filtrate and evaporation of the solvent yielded a clear, black coloured oil. Flash chromatography of the oil (75% Et_2O/hexanes) yielded starting material **10b** (14 mg) and **11b** (75 mg, 59%) as a white foam. **11b**. $[\alpha]_D^{26}=-47.0$ (*c* 2.2, $CHCl_3$); FTIR ($CHCl_3$) 3444b, 3036w, 2937s, 2861m, 1784s, 1638m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.34–1.69 (m, 10H), 2.38–2.42 (m, 2H), 2.40–2.48 (m, 1H), 2.53–2.62 (m, 1H), 3.74 (bs, 1H), 4.03 (dd, *J*=8.5, 7.4 Hz, 1H), 4.17 (dd, *J*=8.5, 6.8 Hz, 1H), 4.21 (d, *J*=2.3 Hz, 1H), 4.49 (ddd, *J*=7.3, 6.8, 2.3 Hz, 1H), 5.61–5.68 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.8, 24.8, 30.6, 32.9, 34.8, 35.2, 65.4, 72.4, 74.7, 76.1, 78.0, 112.0, 122.5, 123.0, 177.1; HRMS Calcd for $C_{16}H_{22}O_6Na$ ($M+Na^+$): *m*/*z* 333.131, Found 333.129.

4.2.6. *trans*-Isobenzofuranones 11a and c. Grubbs' catalyst (340 mg, 10 mol%) in degassed toluene (5 mL) was added under Ar to a purified mixture of diallylated furanones **10a**–**c** (1.34 g, 4.0 mmol) in degassed toluene (85 mL) at 70°C. The solution was stirred for 24 h at between 60 and 70°C after which time the solvent was evaporated and the black residue purified by flash chromatography using 75% Et_2O/hexanes as the eluant. Two fractions were collected the first of which was a white foam consisted of a 2:1 mixture of the two *trans* isomers **11a** and **c** (182 mg, 15%), respectively, and a second fraction containing a 10:1 mixture of **11b** and **c** (524 mg, 42%), respectively, as a white foam. Pure *trans* isobenzofuranone **11c** was crystallised (Et_2O/hexanes) from the first mixture and its absolute configuration determined by X-ray crystallography. Repurification of the filtrate yielded the *trans*-isobenzofuranone **11a** as a pure compound. **11a**. $[\alpha]_D^{25}=-34.5$ (*c* 1.0, $CHCl_3$); FTIR ($CHCl_3$) 3330b, 3020s, 2939s, 1790s cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.35–1.73 (m, 10H), 2.33 (ddd, *J*=17.0, 5.2, 1.0 Hz, 1H),

2.42–2.55 (m, 3H), 2.75–2.83 (m, 1H), 4.11 (t, J=8.1 Hz, 1H), 4.24 (dd, J=8.2, 6.6 Hz, 1H), 4.30 (ddd, J=8.0, 6.6, 1.0 Hz, 1H), 4.52 (d, J=1.0 Hz, 1H), 5.71–5.77 (m, 1H), 5.85–5.91 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.5, 23.7, 24.6, 29.2, 29.7, 34.5, 35.0, 65.6, 71.8, 71.9, 76.3, 85.2, 112.3, 122.3, 125.0, 175.3; HRMS Calcd for $C_{16}H_{22}O_6Na$ ($M+Na^+$): m/z 333.131, Found 333.132. **11c**. Mp 177–178°C; $[\alpha]_D^{26}$=+81.3 (c 1.5, acetone); FTIR ($CHCl_3$) 3444b, 2924s, 1787s, 1771s cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37–1.78 (m, 10H), 2.25–2.36 (m, 2H), 2.51–2.60 (m, 1H), 2.66 (s, 1H), 2.72–2.80 (m, 1H), 4.08 (dd, J=8.4, 7.4 Hz, 1H), 4.21 (dd, J=8.4, 6.7 Hz, 1H), 4.50 (ddd, J=7.4, 6.7, 2.8 Hz, 1H), 4.55 (s, 1H), 4.69 (d, J=2.8 Hz, 1H), 5.69–5.79 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.9, 23.9, 24.9, 29.0, 30.4, 35.0, 35.3, 65.5, 73.2, 75.2, 76.7, 81.2, 111.7, 122.9, 123.0, 174.9; HRMS Calcd for $C_{16}H_{22}O_6$ (M^+): m/z 310.142, Found 310.141; Anal. Calcd for $C_{16}H_{22}O_6$: C, 61.9; H, 7.2; Found: C, 61.9; H, 7.2%.

4.2.7. Isobenzofuranone TMS ether 3. Grubbs' catalyst (440 mg, 20 mol%) in degassed toluene (10 mL) was added at 60°C to diallylated TMS ether **9** (1.1 g, 2.7 mmol) in degassed toluene (270 mL) under Ar. The solution was heated at between 60 and 70°C for 20 h after which time the solvent was evaporated in vacuo. The residue was dissolved in CH_2Cl_2 and filtered through a silica gel plug. After washing the product was eluted with Et_2O and the solvent evaporated. Trituration of the resultant black solid with portions of hot hexanes, containing a hint of CH_2Cl_2, removed the black colour. Crystallisation (hexanes/CH_2Cl_2) of the pale black solid yielded **3** (630 mg, 61%) as white needles. A second crop of **3** (91 mg, 9%) was obtained by recrystallisation of the mother liquor. Slow recrystallisation (Et_2O/hexanes) yielded crystals suitable for X-ray crystallography. Mp 143°C; $[\alpha]_D^{27}$=+27.7 (c 0.47, $CHCl_3$); FTIR ($CHCl_3$) 3461b, 2943s, 1787s cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.15 (s, 9H), 1.37–1.72 (m, 10H), 2.00 (bs, 1H), 2.07–2.14 (m, 1H), 2.40–2.60 (m, 3H), 3.67 (dd, J=8.3, 6.5 Hz, 1H), 4.08 (dd, J=8.3, 6.5 Hz, 1H), 4.39 (d, J=10.0 Hz, 1H), 4.58 (dt, J=10.0, 6.5 Hz, 1H), 5.65–5.69 (m, 1H), 5.75–5.79, (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 1.3, 23.8, 24.0, 25.1, 29.1, 30.0, 34.7, 36.4, 65.5, 74.6, 74.7, 75.8, 90.5, 110.1, 122.9, 124.3, 174.3; HRMS Calcd for $C_{19}H_{30}O_6SiNa$ ($M+Na^+$): m/z 405.171, Found 405.170; Anal. Calcd for $C_{19}H_{30}O_6Si$: C, 59.7; H, 7.9; Found: C, 59.7; H, 8.0%.

4.2.8. Oxonintrione 12. *Method 1*. Lead tetraacetate (63 mg, 0.14 mmol) was added at 0°C to *cis* isobenzofuranone **11b** (40 mg, 0.13 mmol) in CH_2Cl_2 (1.3 mL). The brown solution was allowed to stir at this temperature for 10 min after which time the reaction was quenched with H_2O (2 mL) and filtered through a plug of Celite®, eluting with CH_2Cl_2. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2×2 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent evaporated in vacuo to yield a pale brown oil (36 mg). ^{1}H NMR analysis of the oil indicated three significant compounds in varying ratios with **12** as the major component with the proposed gem-diol **13** and *bis*-hemiacetals **14** as the minor components. Attempted purification, by flash chromatography, of this product on silica gel resulted in partial decomposition with the recovered material having a different and variable ratio of **12** and the proposed products **13** and **14** along with other unidentified impurities. *Method 2*. Yellow HgO (2.83 g, 13 mmol) was added under Ar to a stirred solution of isobenzofuranone TMS ether **3** (2.0 g, 5.2 mmol) in rigorously deoxygenated benzene (250 mL). The mixture was heated to reflux by irradiation with a white light (275 W). Whilst at reflux a solution of I_2 (3.17 g, 12.5 mmol) in deoxygenated benzene (300 mL) was added over a 1 h period. The reaction was irradiated and reflux maintained until all of the starting material had been consumed as determined by TLC (75% Et_2O/hexanes). Once complete (~8–9 h) the reaction mixture was cooled and filtered through a Celite® plug which was eluted with Et_2O. The filtrate was transferred to a separating funnel and washed sequentially with sat. aqueous $Na_2S_2O_5$ (2×200 mL) and brine (100 mL). The organic layer was dried ($MgSO_4$) and the solvent evaporated in vacuo to yield a pale yellow coloured foam (1.74 g). ^{1}H NMR analysis of this material indicated some residual TMS-I by-product along with three significant compounds in a ratio of 5:1:1 with **12** as the major component as determined by NMR. The other two compounds were assigned as **13** and **14** as described in the lead tetraacetate cleavage above. NMR data for the crude trione **12**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31–1.67 (m, 10H), 2.99 (ddd, J=10.7, 6.3, 1.4 Hz, 1H), 3.18 (dd, J=13.2, 6.2 Hz, 1H), 3.85 (dd, J=8.9, 5.6 Hz, 1H), 4.06–4.14 (m, 2H), 4.12 (dd, J=8.9, 7.0 Hz, 1H), 4.64 (ddd, J=7.0, 5.6, 2.8 Hz, 1H), 5.22 (d, J=2.8 Hz, 1H), 5.63 (dt, J=10.5, 6.2 Hz, 1H), 5.75–5.83 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.8, 23.9, 25.0, 34.4, 35.7, 41.7, 43.0, 64.8, 74.0, 79.1, 111.0, 123.2, 129.0, 160.2, 189.5, 202.5.

4.2.9. Hydroxyoxonindione 15. Sodium cyanoborohydride (190 mg, 2.0 mmol) was added in four portions to a frozen (~13°C) solution of the crude oxonintrione **12** (460 mg, 1.5 mmol, derived via HgO/I_2 method from 675 mg of **3**) in glacial acetic acid (15 mL). After the additions had been made the reaction was allowed to warm to rt over a 20 min period then slowly quenched by addition in portions to a mixture of EtOAc (20 mL) and ice cold, sat. aqueous $NaHCO_3$ (100 mL) in a separating funnel. The $NaHCO_3$ solution was kept cold and saturated during the quenching by the addition of ice and solid $NaHCO_3$. Once all of the acetic acid had been neutralised the organic layer was separated and the aqueous layer extracted with EtOAc (2×20 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed in vacuo to yield an oil. A ^{1}H NMR spectrum of the crude material indicated a 95:5 ratio of hydroxyoxonindione **15** and its C3 epimer **16**. Purification by flash chromatography (25% Et_2O/CH_2Cl_2) yielded a white solid which was crystallised (Et_2O) providing **15** (232 mg, 43% over two steps) as fine needles. Mp 115–117°C; $[\alpha]_D^{26}$=+311.9 (c 1.0, $CHCl_3$); FTIR ($CHCl_3$) 3500b, 3021s, 2937s, 1760s, 1726s cm^{-1}; ^{1}H NMR (300 MHz, [D6] acetone) δ 1.30–1.81 (m, 10H), 2.42 (ddd, J=13.3, 6.3 Hz, 3.2 1H), 2.74 (dd, J=10.8, 6.4 Hz, 1H), 2.99–3.09 (m, 1H), 3.83 (dd, J=8.7, 6.1 Hz, 1H), 3.81–3.90 (m, 1H), 4.12 (dd, J=8.5, 6.9 Hz, 1H), 4.42 (d, J=5.5 Hz, 1H), 4.55 (ddd, J=6.9, 6.1, 3.1 Hz, 1H), 4.70–4.77 (m, 1H), 5.15 (d, J=2.9 Hz, 1H), 5.42 (dt, J=10.7, 6.6 Hz, 1H), 5.83 (dtt, J=10.8, 6.1, 1.3 Hz, 1H); ^{13}C NMR

(75 MHz, [D6] acetone) δ 24.5, 24.7, 25.8, 33.6, 35.6, 36.3, 42.2, 65.4, 71.2, 76.1, 78.3, 111.0, 124.7, 130.2, 173.9, 205.9; HRMS Calcd for $C_{16}H_{22}O_6K$ ($M+K^+$): *m/z* 349.105, Found 349.105. **16**. Resonances used for diastereomeric ratio determination: ^{1}H NMR (300 MHz, [D6] acetone) δ 4.90 (d, *J*=2.3, 1H, H9).

4.2.10. Oxonindione TMS ether 17. Chlorotrimethylsilane (122 μL, 0.96 mmol) and imidazole (82 mg, 1.2 mmol) were added to a stirred solution of hydroxyoxonindione **15** (100 mg, 0.32 mmol) in THF (1.5 mL) at rt under N_2. The reaction was stirred for 12 h after which time it was quenched with sat. aqueous NH_4Cl (5 mL) and extracted with EtOAc (3×5 mL). The combined extracts were dried ($MgSO_4$) and the solvent removed in vacuo to yield a colourless oil. Purification by flash chromatography (15% Et_2O/hexanes) yielded a white solid which was crystallised (Et_2O) to yield **17** (122 mg, 99%) as feathery white needles. Mp 63–64°C; $[\alpha]_D^{26}$=+251.9 (*c* 0.94, $CHCl_3$); FTIR ($CHCl_3$) 2944m, 1771s, 1727s cm^{-1}; ^{1}H NMR (400 MHz, [D6] acetone) δ 0.14 (s, 9H), 1.28–1.75 (m, 10H), 2.36 (ddd, *J*=13.2, 6.1, 3.3 Hz, 1H), 2.71–2.77 (m, 1H), 3.06–3.12 (m, 1H), 3.82 (dd, *J*=8.6, 6.1 Hz, 1H), 3.80–3.87 (m, 1H), 4.11 (dd, *J*=8.6, 6.8 Hz, 1H), 4.53 (ddd, *J*=6.8, 6.1, 3.2 Hz, 1H), 4.85–4.91 (m, 1H), 5.14 (d, *J*=3.1 Hz, 1H), 5.42 (dt, *J*=10.6, 6.6 Hz, 1H), 5.76–5.84 (m, 1H); ^{13}C NMR (100 MHz, [D6] acetone) δ 0.0, 24.5, 24.7, 25.8, 34.6, 35.6, 36.4, 42.3, 65.5, 72.1, 76.1, 78.1, 111.0, 124.6, 130.3, 172.5, 205.8; HRMS Calcd for $C_{19}H_{30}O_6SiNa$ ($M+Na^+$): *m/z* 405.171, Found 405.171.

4.2.11. Oxonindione benzoate 18. Benzoic anhydride (66 mg, 0.29 mmol), triethylamine (40 μL, 0.29 mmol) and a catalytic amount of DMAP were added to hydroxyoxonindione **15** (60 mg, 0.19 mmol) in THF (1 mL) at rt. The solution was stirred at rt for 2 h after which time the reaction was quenched with sat. aqueous NH_4Cl (5 mL) and extracted with Et_2O (3×5 mL). The combined organic extracts were washed with sat. aqueous $NaHCO_3$ (2×5 mL) and the organic layer dried ($MgSO_4$). Evaporation of the solvent in vacuo and recrystallisation (Et_2O/hexanes) yielded **18** (80 mg, 99%) as colourless crystals which were suitable for X-ray crystallography. Mp 168°C; $[\alpha]_D^{25}$=+47.3 (*c* 0.9, $CHCl_3$); FTIR ($CHCl_3$) 3036s, 2936s, 1775s, 1727s cm^{-1}; ^{1}H NMR (300 MHz, [D6] acetone) δ 1.10–1.77 (m, 10H), 2.68–2.76 (m, 1H), 2.76–2.86 (m, 1H), 3.28–3.38 (m, 1H), 3.85–4.01 (m, 1H), 3.89 (dd, *J*=8.7, 6.0 Hz, 1H), 4.16 (dd, *J*=8.7, 6.9 Hz, 1H), 4.59 (ddd, *J*=6.9, 6.0, 3.0 Hz, 1H), 5.21 (d, *J*=3.0 Hz, 1H), 5.56 (dt, *J*=10.7, 6.6 Hz, 1H), 5.78–5.86 (m, 1H), 5.99 (dtt, *J*=10.8, 6.2, 1.3 Hz, 1H), 7.51–7.56 (m, 2H), 7.65–7.68 (m, 1H), 8.07–8.10 (m, 2H); ^{13}C NMR (75 MHz, [D6] acetone) δ 24.5, 24.7, 25.8, 30.2, 35.6, 36.4, 42.2, 65.5, 73.1, 76.1, 78.8, 111.2, 126.0, 129.2, 129.5, 130.4, 130.5, 134.4, 165.9, 169.2, 205.3; HRMS Calcd for $C_{23}H_{26}O_7Na$ ($M+Na^+$): *m/z* 437.158, Found 437.158; Anal. Calcd for $C_{23}H_{26}O_7$: C, 66.7; H, 6.3; Found: C, 66.6; H, 6.2%.

4.2.12. Dihydroxyoxoninone 19. A 1 M solution of L-selectride® (0.12 mL, 0.12 mmol) in THF was added under N_2 to 3-hydroxyoxonindione **15** (15 mg, 48 μmol) in THF (0.5 mL) at −100°C and the temperature was maintained after the addition between −100 and −78°C. These conditions were maintained for 30 min after which time the reaction was quenched with sat. aqueous NH_4Cl (5 mL) and allowed to warm to rt. The resultant mixture was diluted with EtOAc (5 mL) and the organic phase separated. The aqueous phase was extracted further with EtOAc (2×5 mL) and the combined extracts dried ($MgSO_4$). Evaporation of the solvent in vacuo yielded an oil which was subsequently filter through a silica plug (Et_2O) to removed the bulk of the borane. ^{1}H NMR analysis indicated a 4:1 mixture of the two C8 epimers (**19**/**20**). This sample was not purified further. However, the major adduct **19** was obtained diastereomerically pure during the purification of the hydroxyoxoninone TMS ether **21** by preparative HPLC (see below). Desilylation of hydroxyoxoninone TMS ether **21** provided dihydroxyoxoninone **19** when using an hexane/isopropanol HPLC gradient. HPLC (AGP) 20.3; (SGP) 18.6; $[\alpha]_D^{28}$=−91.0 (*c* 1.6, $CHCl_3$); FTIR ($CHCl_3$) 3460b, 3019s, 2941s, 1741s, 1656b cm^{-1}; ^{1}H NMR (300 MHz, [D6] acetone) δ 1.18–1.55 (m, 10H), 2.16–2.23 (m, 1H), 2.25–2.36 (m, 2H), 2.47–2.67 (m, 1H), 3.81 (dd, *J*=8.4, 6.3 Hz, 1H), 4.02 (dd, *J*=8.4, 6.7 Hz, 1H), 4.05–4.09 (m, 1H), 4.10–4.19 (m, 1H), 4.20 (d, *J*=6.2 Hz, 1H), 4.41 (ddd, *J*=6.8, 6.3, 3.7 Hz, 1H), 4.43 (d, *J*=5.7 Hz, 1H), 4.67 (bdd, *J*=∼8.5, 3.4 Hz, 1H,), 5.62–5.66 (m, 1H), 5.67–5.70 (m, 1H); ^{13}C NMR (75 MHz, [D6] acetone) δ 24.5, 24.6, 25.8, 34.6, 35.1, 35.7, 36.4, 65.7, 70.3, 71.2, 75.5, 80.0, 109.9, 126.1, 131.1, 176.3; HRMS Calcd for $C_{16}H_{24}O_6Na$ ($M+Na^+$): *m/z* 335.147, Found 335.146. **20**. Resonances used for diastereomeric ratio determination: ^{1}H NMR (300 MHz, [D6] acetone) δ 4.88 (bdd, J_{9-10}=7.7 Hz, J_{9-8}=3.5 Hz, 1H, H9).

4.2.13. Hydroxyoxoninone TMS ether 21. A 1 M solution of L-selectride® (0.36 mL, 0.36 mmol) in THF was added under N_2 to a solution of oxonindione TMS ether **17** (92 mg, 0.24 mmol) in THF (3 mL) whilst cooling using a pentane/liquid N_2 cooling bath (∼−133°C). The solution was allowed to react for 30 min and was then quenched with sat. aqueous NH_4Cl (5 mL) and allowed to warm to rt. The resultant mixture was diluted with EtOAc (5 mL) and the organic layer separated. The aqueous layer was extracted further with EtOAc (2×5 mL) and the combined organic extracts dried ($MgSO_4$) and the solvent evaporated in vacuo to yield an oil. ^{1}H NMR analysis of the oil indicated the borane by-product was still present along with a 14:1 mixture of **21** and its C8 epimer **22**, respectively. The borane was removed using a silica plug eluting with 20% Et_2O/CH_2Cl_2 which co-eluted the epimers (58 mg, 63%) as a colourless oil. **21**. $[\alpha]_D^{25}$=−52.0 (*c* 1.5, $CHCl_3$); FTIR ($CHCl_3$) 3469b, 2936s, 1755s cm^{-1}; ^{1}H NMR (300 MHz, [D6] acetone) δ 0.11 (s, 9H), 1.28–1.56 (m, 10H), 2.17–2.30 (m, 2H), 2.30–2.43 (m, 1H), 2.43–2.62 (m, 1H), 3.80 (dd, *J*=8.4, 6.2 Hz, 1H), 4.00–4.10 (m, 1H), 4.03 (dd, *J*=8.4, 6.7 Hz, 1H), 4.15–4.27 (m, 1H), 4.41 (ddd, *J*=6.7, 6.1, 3.6 Hz, 1H), 4.69 (bdd, *J*=∼8.7, 3.4 Hz, 1H), 5.56–5.67 (m, 1H), 5.63–5.73 (m, 1H); ^{13}C NMR (75 MHz, [D6] acetone) δ 0.0, 25.6, 25.9, 35.4, 35.5, 35.9, 36.5, 66.0, 71.2, 71.2, 75.5, 79.9, 110.0, 125.7, 131.6, 174.8; HRMS Calcd for $C_{19}H_{32}O_6SiNa$ ($M+Na^+$): *m/z* 407.187, Found 407.187. **22**. Resonances used for diastereomeric ratio determination: ^{1}H NMR (300 MHz, [D6] acetone) δ 4.90 (bdd, J_{9-10}=7.0 Hz, J_{9-8}=5.1, 1H, H9).

4.2.14. Hydroxyoxoninone benzoate 23. A solution of L-selectride® (53 μL, 53 μmol) in THF was added under N_2 to oxonindione benzoate **18** (20 mg, 48 μmol) in THF (2 mL) at between −100 and −90°C. After the addition the temperature was maintained at −90°C for 30 min and the reaction was then quenched with sat. aqueous NH_4Cl (5 mL) and allowed to warm to rt. The mixture was diluted with EtOAc (5 mL) and the organic phase separated. The aqueous phase was extracted with EtOAc (2×5 mL) and the combined organic phases were dried ($MgSO_4$). Evaporation of the solvent in vacuo yielded an oil. ^{1}H NMR analysis of the oil indicated a mixture consisting of the residual borane by-product and a 10:1 mixture of **23** and its C8 epimer **24**, respectively. The mixture was purified using preparative TLC (75% Et_2O/hexanes) collecting the bands at R_f 0.61 and 0.71 which, respectively, were **23** (14.6 mg, 73%) and the C8 epimer **24** contaminated with other unidentified impurities (1.8 mg). **23**. $[\alpha]_D^{24}=-95.9$ (*c* 1.0, $CHCl_3$); FTIR ($CHCl_3$) 3486bs, 2938s, 1759m, 1725s cm^{-1}; ^{1}H NMR (300 MHz, [D6] acetone) δ 1.36–1.42 (m, 2H), 1.52–1.64 (m, 8H), 2.20–2.47 (m, 2H), 2.58–2.68 (m, 1H), 2.79–2.94 (m, 1H), 3.80 (dd, *J*=8.4, 6.9 Hz, 1H), 4.04 (dd, *J*=8.4, 6.7 Hz, 1H), 4.15–4.35 (m, 1H), 4.46 (dt, *J*=6.8, 3.3 Hz, 1H), 4.51 (d, *J*=6.0 Hz, 1H), 4.73 (bdd, *J*=~8.6, 3.4 Hz, 1H), 5.02–5.21 (m, 1H), 5.69–5.85 (m, 1H), 5.76–5.89 (m, 1H), 7.51–7.57 (m, 2H), 7.57–7.70 (m, 1H), 8.06–8.10 (m, 2H); ^{13}C NMR (75 MHz, [D6] acetone) δ 24.6, 25.9, 30.3, 35.3, 36.0, 36.4, 65.7, 71.2, 72.4, 75.4, 79.9, 110.1, 124.9, 129.5, 130.4, 130.6, 132.9, 134.3, 166.1, 171.6; HRMS Calcd for $C_{23}H_{28}O_7Na$ (M+Na): *m/z* 439.173, Found 439.173. **24**. Resonances used for diastereomeric ratio determination: ^{1}H NMR (300 MHz, [D6] acetone) δ 4.88–4.93 (m, 1H, H9).

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 144205, 144206 and 166204. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk). Deposited data may be accessed by the journal and checked as part of the refereeing process. If data are revised prior to publication, a replacement file should be sent to CCDC.

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References

1. Lewis, R. J. *Memoirs of the Queensland Museum* **1994**, *34*, 549–553.
2. Lewis, R. J. *Toxicon* **2001**, *39*, 97–106.
3. Campi, E. M.; Eriksson, L.; Guy, S. T.; Jackson, W. R.; Perlmutter, P. *J. Mol. Catal.* **1998**, *143*, 243–252.
4. Bond, S.; Perlmutter, P. *J. Chem. Soc., Chem. Commun.* **2000**, 567–568.
5. Oishi, T.; Maruyama, M.; Shoji, M.; Maeda, K.; Kumahara, N.; Tanaka, S.; Hirama, M. *Tetrahedron* **1999**, *55*, 7471–7498.
6. Oishi, T.; Shoji, M.; Maeda, K.; Kumahara, N.; Hirama, M. *Synlett* **1996**, 1165–1167.
7. Curtis, N. R.; Holmes, A. B.; Looney, M. G. *Tetrahedron Lett.* **1992**, *33*, 671–674.
8. Curtis, N. R.; Holmes, A. B. *Tetrahedron Lett.* **1992**, *33*, 675–678.
9. Bendall, J. G.; Payne, A. N.; Screen, T. E. O.; Holmes, A. B. *J. Chem. Soc., Chem. Commun.* **1997**, 1067–1068.
10. Carling, R. W.; Clark, J. S.; Holmes, A. B. *J. Chem. Soc., Perkin Trans. 1* **1992**, 83–94.
11. Fujiwara, K.; Awakura, D.; Tsunashima, M.; Nakamura, A.; Honma, T.; Murai, A. *J. Org. Chem.* **1999**, *64*, 2616–2617.
12. Nicolaou, K. C.; Wallace, P. A.; Shi, S.; Ouellette, M. A.; Bunnage, M. E.; Gunzner, J. L.; Agrios, K. A.; Shi, G.; Gärtner, P.; Yang, Z. *Eur. J. Chem.* **1999**, *5*, 618–627.
13. Nicolaou, K. C.; Prasad, C. V. C.; Ogilvie, W. W. *J. Am. Chem. Soc.* **1990**, *112*, 4988–4989.
14. Nicolaou, K. C.; McGarry, D. G.; Somers, P. K.; Kim, B. H.; Ogilvie, W. W.; Yiannikouros, G.; Prasad, C. V. C.; Veale, C. A.; Hark, R. R. *J. Am. Chem. Soc.* **1990**, *112*, 6263–6276.
15. Nicolaou, K. C.; McGarry, D. G.; Somers, P. K.; Veale, C. A.; Furst, G. F. *J. Am. Chem. Soc.* **1987**, *109*, 2504–2506.
16. Wimalasena, K.; Mahindaratne, M. P. D. *J. Org. Chem.* **1994**, *59*, 3427–3432.
17. Bell, R. P.; Rivlin, V. G.; Waters, W. A. *J. Chem. Soc.* **1958**, 1696–1697.
18. Goosen, A.; Laue, H. A. H. *J. Chem. Soc. C* **1969**, 995–997.
19. Goosen, A.; Laue, H. A. H. *J. Chem. Soc. B* **1969**, 383–385.
20. O'Dell, D. E.; Loper, J. T.; Macdonald, T. L. *J. Org. Chem.* **1988**, *53*, 5225–5229.
21. Freire, R.; Marrero, J. J.; Rodríguez, M. S.; Suárez, E. *Tetrahedron Lett.* **1986**, *27*, 383–386.