# Synthesis of Model Compounds of Some Biogenetic Precursors of Aflatoxin $B_1$

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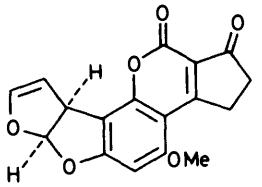
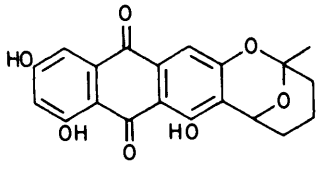
The synthesis of analogues of various natural products occurring during the biosynthesis of the notorious hepatocarcinogen aflatoxin $B_1$ (**1**) is described. These natural products are versiconol (**21**), versiconol acetate (**22**), versicolorin C (**23**), versiconal acetate (**4**), and 4-[2,3-dihydroxy-1-(hydroxymethyl)propyl]-3,8-dihydroxy-1-methoxyxanthone (**24**). The synthesis of an analogue of versiconal (**5**) is also described.

Since its isolation in the early 1960s, the hepatocarcinogenic mycotoxin aflatoxin $B_1$ (**1**) has enjoyed a dominant position in mycotoxin research. This is a result both of the extreme hazard it poses to human and animal health, owing to its frequent natural occurrence, and the ubiquitous nature of its parent fungi, *Aspergillus flavus* and *A. parasiticus*. During the course of this research, particular attention has been devoted to the biogenesis of the metabolite, such that this now represents one of the most highly studied and best understood examples of polyketide fungal biosynthesis.[1,2] Of cardinal interest has been the transformation from averufin (**2**) to versicolorin A (**3**), *via* the pivotal intermediate versiconal acetate (**4**),[3,4] since the dihydrobisfuran system, first evident in the biosynthetic pathway in compound (**3**) is necessary for the acute toxicological effects of aflatoxin $B_1$. Our continuing interest



(**1**)



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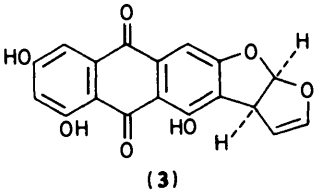
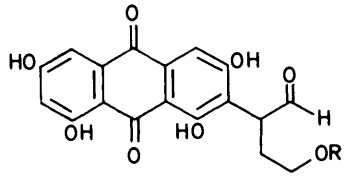
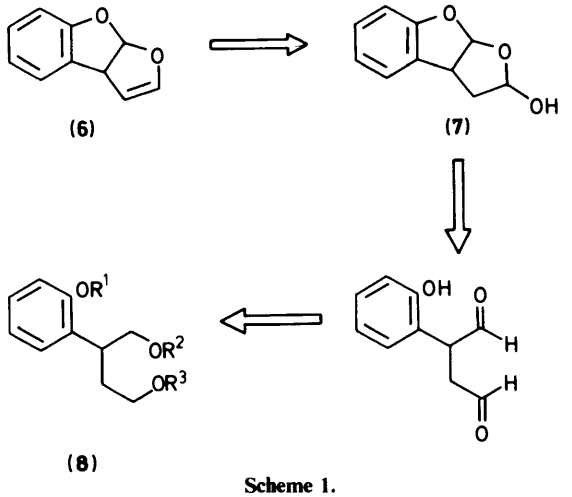


(**3**)



(**4**) R = Ac
(**5**) R = H

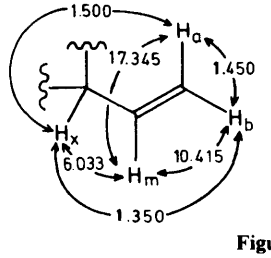


(**6**) (**7**) (**8**)

**Scheme 1.**

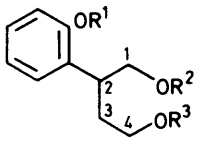
in this problem has led us to develop synthetic methodology to probe further the transformation, and we report herein the preparation of model compounds related to versiconal acetate.

Retrosynthetically (Scheme 1) the dihydrobisfuran system, as represented by structure (**6**), could arise from a suitably protected triol (**8**) as indicated. As manipulation of compound (**8**) should readily produce an analogue of versiconal acetate, and congeners thereof, we set as our first goal the derivative protected as in compound (**9**). Consequently, treatment of but-2-yne-1,4-diol with benzyl chloride in aqueous alkali gave, after purification, 62% of the monobenzylated product, which on reduction with lithium aluminium hydride in tetrahydrofuran (THF), furnishes the olefin (**16**) in 65% yield. Bromination with phosphorus tribromide in diethyl ether gives the bromo derivative (**17**), which was treated immediately with phenol in acetone in the presence of potassium carbonate to yield the diether (**18**) in 76% yield from (**16**). Claisen rearrangement of this material proceeds smoothly to give the phenol (**19**) in 72% yield. The $^1H$ n.m.r. spectrum of this compound confirms the proposed structure, with the protons of the ABMX system resonating as shown in the Figure. The benzylic protons of the

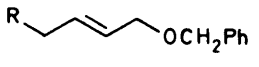



| Proton | $\delta_H$ |
|---|---|
| $H_a$ | 5.131 |
| $H_b$ | 5.233 |
| $H_m$ | 6.153 |
| $H_x$ | 3.821 |

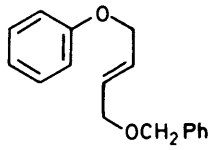
**Figure.**



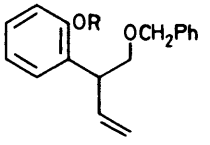
(9) $R^1 = CH_2OMe$, $R^2 = CH_2Ph$, $R^3 = Ac$
(10) $R^1 = CH_2OMe$, $R^2 = CH_2Ph$, $R^3 = H$
(11) $R^1 = R^2 = R^3 = H$
(12) $R^1 = CH_2OMe$, $R^2 = R^3 = H$
(13) $R^1 = R^2 = H$, $R^3 = Ac$
(14) $R^1 = CH_2OMe$, $R^2 = H$, $R^3 = Ac$
(15) $R^1 = H$, $R^2 = R^3 = Ac$



(16) R = OH
(17) R = Br



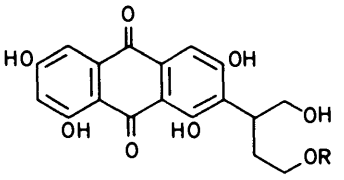
(18)



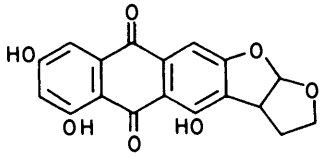
(19) R = H
(20) R = $CH_2OMe$

protecting group appear as an AB quartet ($J$ 11.95 Hz) centred at $\delta_H$ 4.625 and 4.586 respectively, while the remaining aliphatic protons (1-H) resonate at $\delta_H$ 3.932 and 3.836, with a geminal coupling of 8.05 Hz, and vicinal couplings of 2.97 and 6.50 Hz respectively. The $^{13}C$ n.m.r. spectrum of this compound is also entirely in accord with the proposed structure, with the two olefinic carbon atoms resonating at $\delta_C$ 117.53 and 116.32. The three methine carbon resonances appear at $\delta_C$ 74.40, 73.66 (C-2), and 46.06 (C-1). The phenolic carbon atom resonates at $\delta_C$ 154.91, and the nine remaining aromatic resonances appear from $\delta_C$ 136.79—120.34. The phenolic hydroxy group can then be protected as the methoxymethyl derivative (92%) by reaction with chloromethyl methyl ether and sodium hydride in dimethylformamide (DMF), to give compound (**20**). In the $^1H$ n.m.r. spectrum of this compound, the methylene group of the methoxymethyl moiety appears as a singlet at $\delta_H$ 5.197, with the methoxy resonance at $\delta_H$ 3.466. In other respects the spectrum is very similar to that of the phenol (**19**), as is to be expected. Resonances at $\delta$ 94.41 and 55.89 in the $^{13}C$ n.m.r. spectrum of compound (**20**) can be attributed to the newly introduced protecting group, with only minor chemical-shift differences between the remainder of the spectrum and that of compound (**19**), *e.g.* the aromatic, oxygen-bearing carbon atom now resonates at $\delta_C$ 154.67.

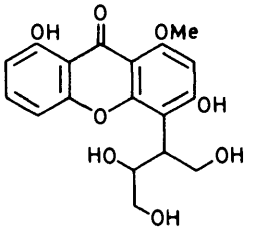
Introduction of the remaining hydroxy group is easily achieved by reaction of compound (**20**) with 9-borabicyclo-[3.3.1]nonane (9-BBN) followed by oxidative work-up to yield compound (**10**) (76%), which can then be acetylated quantitatively to give the desired product (**9**). The $^1H$ n.m.r. data for these two compounds {(**9**) and (**10**)} are given in Table 1, and their $^{13}C$ n.m.r. data in Table 2. The evidence for the proposed structure of compound (**10**) obtained on hydroxylation of compound (**20**) may be summarised by the following n.m.r. spectral differences: $^1H$; the absence of any olefinic resonances in the spectrum of compound (**10**), with the concomitant introduction of two proton signals resonating at



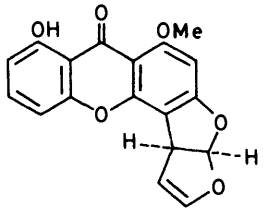
(21) R = H
(22) R = Ac



(23)



(24)



(25)

$\delta_H$ 2.130 and 1.854 (3-$H_2$) and two proton signals resonating from $\delta_H$ 3.637—3.579 (4-$H_2$). (On acetylation these signals shift downfield by *ca.* 0.4 p.p.m.) $^{13}C$; The olefinic carbon resonances ($\delta_C$ 115—118) are not present in the spectrum of compound (**10**). Two additional methylene carbon resonances are present in the aliphatic region at $\delta_C$ 61.12 and 36.02 (C-4 and C-3 respectively), whereas the methine resonance (C-2) at $\delta_C$ 42.76 in olefin (**20**) shifts upfield to $\delta_C$ 35.73 in alcohol (**10**). On acetylation the resonance of C-4 shifts downfield by 2 p.p.m. while that of C-3 shifts upfield by 5 p.p.m.

Having achieved the synthesis of the desired intermediate, routes to analogues of several natural products were now open, *e.g.* versiconol (**21**),[3] versiconol acetate (**22**),[3] versicolorin C (**23**), versiconal acetate (**4**), and 4-[2,3-dihydroxy-1-(hydroxymethyl)propyl]-3,8-dihydroxy-1-methoxyxanthone (**24**),[5] a metabolite related to sterigmatocystin (**25**), produced by *Bipolaris sorokiniana*.

The versiconol analogue (**21**) was readily prepared by hydrogenolysis of compound (**10**) in the presence of 10% palladium–carbon for 8 h to yield triol (**11**) (52%). The $^1H$ and $^{13}C$ n.m.r. chemical shifts of the aliphatic portion of compound (**11**) compared well with the relevant resonances in the natural product (Tables 1 and 2). The only discrepancies of note are the $^1H$ and $^{13}C$ chemical-shift differences for the signals of the atoms in the benzylic position (2-H, C-2). However, as the aromatic portions of the molecules are substantially different, this is to be expected. The close agreement of the remaining

**Table 1.** $^1$H N.m.r. chemical-shift values for selected resonances in compounds (**4**), (**9**)—(**11**), (**13**), (**21**), (**22**), and (**27**)—(**29**)

| | $\delta_H$ | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Atom | (**4**)[3] | (**9**)[a,b] | (**10**)[a,b] | (**11**)[a,c] | (**13**)[a,b] | (**21**)[3] | (**22**)[3] | (**27a**)[a,b] | (**27b**)[a,b] | (**28a**)[a,c] | (**28b**)[a,c] | (**29**)[a,b] |
| 1 a | 6.47 | 3.649 | 3.668— | 3.824 | 3.954 | 3.97 | 3.94 | 5.711 | 5.954 | 5.228 | 5.400 | 6.289 |
| b | | 3.602 | 3.642 | 3.767 | 3.906 | 3.93 | 3.94 | | | | | |
| 2 | 3.36 | 3.570 | 3.534 | 3.240 | 3.090 | 3.72 | 3.75 | 3.237 | 3.426 | 3.513 | 3.419 | 3.600 |
| 3 a | 2.35 | 2.244 | 2.130 | 2.060 | 2.126 | 2.14 | 2.30 | 1.999— | 2.194— | 2.311 | 1.950 | 2.281 |
| b | 2.35 | 2.014 | 1.854 | 1.854 | 2.080 | 2.04 | 2.13 | 1.850 | 2.147 | 1.851 | 1.712 | 2.050 |
| 4 a | 4.34 | 4.035 | 3.637— | 3.559 | 4.071 | 3.53 | 4.03 | 4.143 | 4.278 | 4.014— | 3.333— | 4.049 |
| b | 4.34 | 4.021 | 3.579 | 3.458 | 3.959 | 3.50 | 3.98 | 4.141 | 4.208 | 3.846 | 3.189 | 3.983 |

[a] Recorded on a Bruker WM-500 or a Bruker AM-300 spectrometer. [b] Relative to $CDCl_3$ at $\delta_H$ 7.240. [c] Relative to $(CD_3)_2SO$ at $\delta_H$ 2.490.

**Table 2.** $^{13}$C N.m.r. chemical shifts for selected carbon atoms in compounds (**4**), (**9**)—(**11**), (**13**), (**21**)—(**24**), and (**27**)—(**30**)

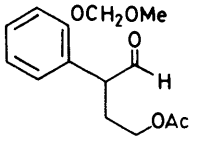
| | $\delta_C$ | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | (**27**)[a,b] | | (**28**)[a,c] | | | (**30**)[a,c] | |
| Carbon atom | (**4**)[3] | (**9**)[a,b] | (**10**)[a,b] | (**11**)[a,c] | (**13**)[a,b] | (**21**)[3] | (**22**)[3] | (**23**) | (**24**)[5] | **a** | **b** | **a** | **b** | (**29**)[a,b] | major | minor |
| 1 | | 55.88 | 56.02 | 66.76 | 67.04 | 63.2 | 62.9 | 112.9 | 62.30 | 105.57 | 101.34 | 102.06 | 96.15 | 109.16 | 61.31 | 62.10 |
| 2 | 43.9 | 35.88 | 35.73 | 40.66 | 41.10 | 34.9 | 35.0 | 43.3 | 42.03 | 46.61 | 42.47 | 45.25 | 43.58 | 46.53 | 44.90 | 44.03 |
| 3 | 27.9 | 30.70 | 36.02 | 35.31 | 29.05 | 32.5 | 27.8 | 30.0 | 72.67 | 31.60 | 26.20 | 30.92 | 26.40 | 33.54 | 70.78 | 73.27 |
| 4 | 61.9 | 63.12 | 61.12 | 61.05 | 62.94 | 60.1 | 62.9 | 66.9 | 66.02 | 61.72 | 63.16 | 65.81 | 65.12 | 67.16 | 64.25 | 64.60 |

[a] Recorded on a Bruker WM-500 or a Bruker AM-300 spectrometer. [b] Relative to $CDCl_3$ at $\delta_C$ 77.00. [c] Relative to $(CD_3)_2SO$ at $\delta_C$ 39.50.

resonances provides strong evidence for the structural assignment of compound (**11**). The ready removal of the methoxymethyl protecting group under hydrogenolysis is surprising but fortuitous. If the reaction time is limited to 20 min the sole isolable product is the protected phenol (**12**).

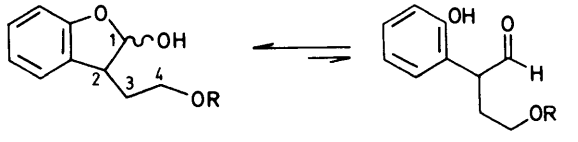
Preparation of diol (**13**), the synthetic analogue of versiconol acetate (**22**), is readily accomplished in two steps from compound (**9**), *via* acidic removal of the methoxymethyl protecting group, followed by hydrogenolysis of the benzyl group. Overall yield for these steps is low (43%), mainly because of appreciable concomitant hydrolysis of the acetate group in the first reaction. If the sequence of steps is reversed, the major product obtained on acid hydrolysis [acetic acid–water–sulphuric acid (1:1:0.002 v/v] of the intermediate (**14**) is the diacetate (**15**). The $^1$H and $^{13}$C n.m.r. data for acetate (**13**) are in good agreement with the corresponding values for versiconol acetate (**22**). There is also a close similarity between the chemical shifts for corresponding atoms in compounds (**11**) and (**13**). Specifically of structural relevance are the expected shifts of the α-(C-4) and the β-carbon (C-3) resonances in the $^{13}$C spectra on acetylation of the primary hydroxy group. The α-shift is downfield and small (0.3 p.p.m.), whereas the β-shift is upfield and large (6.3 p.p.m.). In the $^1$H n.m.r. spectra the resonances of the protons on C-4 are shifted downfield by 0.5 p.p.m. on acetylation.

To accomplish the preparation of the synthetic analogue of versiconal acetate (**4**), it is necessary to retain the phenolic protecting group until the hydroxy group at C-1 has been oxidised to the aldehyde. Consequently, the protected starting material (**9**) was first modified, by hydrogenolysis for 20 min, to the alcohol (**14**), which could then be oxidised with pyridinium chlorochromate (PCC) in dichloromethane to the aldehyde (**26**) in good yield (88%). The presence of a resonance at δ 9.652 in the $^1$H n.m.r. spectrum and a resonance at $\delta_C$ 200.11 in the $^{13}$C n.m.r. spectrum of compound (**26**), provide evidence of the successful oxidation of the primary alcohol in compound (**14**) to the aldehyde. In addition the signals associated with the other protecting groups (methoxymethyl and acetoxy) are still present in the n.m.r. spectra of compound (**26**) in their




(**26**)

characteristic positions, confirming that the hydrogenolysis reaction did not affect the groups other than the benzyl ether moiety. Subsequent acidic deprotection of compound (**26**) afforded the desired analogue (**27**) in 66% yield. In solution this compound exists as a mixture of two major and one minor isomers [equation (1)] in the ratio *ca.* 5:1 for the hemiacetal




(1)

(**a**) 1*R*, 2*R* or 1*S*, 2*S*
(**b**) 1*R*, 2*S* or 1*S*, 2*R*

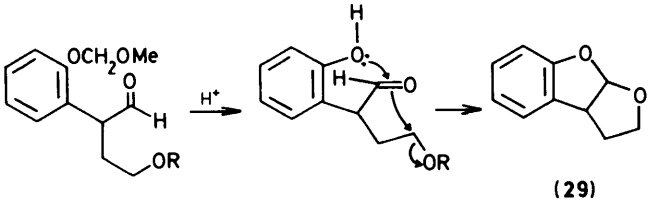
(**c**)

(**27**) R = Ac
(**28**) R = H

forms (**a** and **b**) which are favoured. This phenomenon is similar to that encountered for versiconal acetate (**4**), where 3 isomers are possible.[3] This similarity in the spectroscopic behaviour of the synthetic model and the natural product, coupled with the good agreement observed for the chemical-shift values of corresponding atoms in the two molecules, provides strong evidence for the structural assignment of compound (**27**). In addition to the two major isomers of compound (**27**) present in solution, there is also a small amount of the benzylic aldehyde (**27c**) present, as evidenced in the $^1$H n.m.r. spectrum by a resonance at $\delta_H$ 9.654 and in the $^{13}$C spectrum by a resonance at $\delta_C$ 200.993. For the two forms (**a**) and (**b**) the major epimer shows a 2.18 Hz coupling constant between 1-H and 2-H, whereas in the minor epimer this coupling is 6.26 Hz, which

would suggest that in the major epimer the hydroxy group is pseudoaxial, and in the minor epimer, pseudoequatorial.

As well as compound (**27**), a 15% yield of a further product is formed on acidic deprotection of compound (**26**). This is the analogue (**29**) of versicolorin C (**23**), the formation of which may be rationalised by the mechanism shown in Scheme 2. Final closure to the tetrahydrobisfuran system can occur either with the initial acetoxy function as the leaving group, or *via* hydrolysis and subsequent loss of the hydroxy group. In the $^{13}C$ n.m.r. spectrum of the bisfuran (**29**), the resonance at $\delta_C$ 109.16

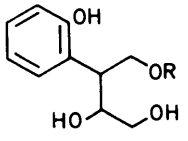



(**29**)

**Scheme 2.**

(C-1) is characteristic of a carbon atom in this environment, bonded to two oxygen atoms. Moreover the $^{13}C$ n.m.r. spectrum shows only three other non-aromatic resonances, all in good agreement with the corresponding resonances in versicolorin C (**23**). Extensive decoupling experiments of signals in the $^1H$ n.m.r. spectrum of the bisfuran (**29**) confirmed the assignments given in Table 1. The resonance at δ 6.289 is characteristic of this proton, and was used as the starting point in the subsequent assignment. On addition of $D_2O$ to the sample, no change was observed in the $^1H$ n.m.r. spectrum of compound (**29**) and this, coupled with the results obtained for the determination of the molecular formula, preclude non-cyclic structural alternatives, thus confirming the structure of compound (**29**).

Recent work on the metabolites of *Bipolaris sorokiniana* has resulted in the isolation of a xanthone (**24**), related structurally to sterigmatocystin (**25**).[5] The analogue (**30**) of this novel xanthone was prepared, and proved useful in the unambiguous structure assignment of the natural product. Thus oxidation of the olefin (**19**) with osmium tetraoxide in pyridine yields a diastereomeric mixture of the two triols (**31**), distinguishable by n.m.r. spectroscopy (2*R*,3*R* or 2*S*,3*S* in the one case, and 2*R*,3*S* or 2*S*,3*R* in the other), in the ratio 2:1, though which diastereoisomeric pair predominates was not determinable. Subsequent hydrogenolysis of this mixture yields (**30**) in the same diastereoisomeric ratio, and an overall yield of 36% from (**19**). An examination of the $^{13}C$ chemical shift values (Table 2) shows that the values for the minor diastereoisomeric pair agree fairly closely with those of the natural product (**24**). This n.m.r. evidence, coupled with the unambiguous nature of the chemical transformations, permits the structural formulation of the products.

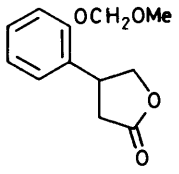



(**30**) R = H

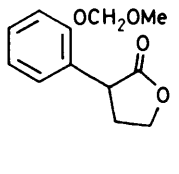
(**31**) R = $CH_2Ph$

Although versiconal (**5**) has not, as yet, been found as a natural product, the analogue (**28**) of this compound was readily prepared (84%) by mild base hydrolysis of its acetate (**27**) for 4 h at room temperature. As was the case for the acetate derivative (**27**), this compound [(**28**)] exists in solution as a mixture of epimers (**28a**) and (**28b**), but now with no trace of the benzylic aldehyde (**28c**). This is most likely due to the necessity of using dimethyl sulphoxide (DMSO) as solvent in the n.m.r. experiments on compound (**28**), as work on derivatives of versiconal acetate (**4**) has shown DMSO to promote the hemiacetal forms over the aldehydic form.[3] As observed for the acetoxy derivatives, the major epimer (**28a**) shows the small coupling constant between 1-H and 2-H (2.26 Hz), whereas for isomer (**28b**) the value of this coupling is 4.37 Hz.

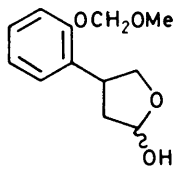
Finally, efforts have been made to prepare the hydroxylated tetrahydrobisfuran derivative (**7**), as it has been shown that this compound may easily be transformed to the analogue (**6**) of aflatoxin $B_1$.[6] Approaches to date have centred around the oxidation of the protected phenol (**12**), but have not as yet borne fruit despite the implementation of numerous reagents. Isolable products include the lactones (**32**) and (**33**) and complex mixtures of the epimeric pairs of lactols (**34**) and (**35**). These experiments and further progress on these oxidation reactions will be reported in due course.



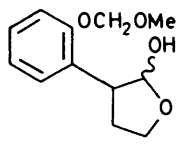

(**32**)




(**33**)




(**34**)




(**35**)

## Experimental

I.r. spectra were measured on a Perkin-Elmer 257 spectrophotometer for solutions in chloroform, and u.v. absorptions on a Unicam SP8-100 spectrophotometer for solutions in methanol. Mass spectra were recorded on a Varian MAT spectrometer. For column chromatography Merck silica gel, particle size 0.063—0.200 mm, was used.

*Diether* (**18**).—A solution of phosphorus tribromide (2.54 g) in diethyl ether (10 ml) was added during 30 min to a stirred solution of the alcohol (**16**)* (5 g) in diethyl ether (40 ml) at −15 °C. After a further 2 h at 0 °C, the reaction mixture was allowed to warm to room temperature, and the solvent was removed under reduced pressure to yield the crude bromo derivative (**17**). This material was treated for 16 h at reflux with a stirred suspension of phenol (3 g) and potassium carbonate (10 g) in acetone (50 ml). Removal of the solvent and purification by chromatography on $SiO_2$ (300 g), with chloroform as eluant, gave the *diether* (**18**) (5.44 g) as an oil, $\lambda_{max.}$ 278 (ε 1 330), 271 (1 700), 264 (1 360), and 224 nm (5 730); $\nu_{max.}$ 2 850, 1 598, 1 585, 1 489, and 1 450 $cm^{-1}$ (Found: $M^+$, 254.1304. $C_{17}H_{18}O_2$ requires *M*, 254.1307).

*Phenol* (**19**).—The diether (**18**) (1 g) was heated at reflux for 30 min. Purification by chromatography on $SiO_2$ (100 g), with ethyl acetate–hexane (1:3 v/v) as eluant, gave the *phenol* (**19**) (716 mg) as a pale yellow oil, $\lambda_{max.}$ 281 (ε 2 350), 275 (2 710), and

* The preparation of this compound was outlined by Y. Kishi in a personal communication to P. S. Steyn.

208 nm (15 210); $\nu_{max.}$ 3 250, 2 855, 1 582, 1 482, and 1 450 $cm^{-1}$ (Found: $M^+$, 254.1307; C, 80.1; H, 7.0%. $C_{17}H_{18}O_2$ requires $M^+$, 254.1307; C, 80.28; H, 7.13%).

*Compound* (**20**).—A solution of the phenol (**19**) (6.5 g) in DMF (30 ml) was added slowly to a stirred suspension of sodium hydride (2.5 g) in DMF (30 ml). After 2 h at room temperature the mixture was treated dropwise with a solution of chloromethyl methyl ether (3.5 ml) in DMF (10 ml), and the mixture was stirred for a further 3 h, and then for 16 h open to the atmosphere in an efficient fume hood. Water (150 ml) was added, the mixture was extracted with chloroform (3 × 50 ml), the combined extracts were dried ($Na_2SO_4$) and filtered, and the solvent was removed. Purification by chromatography on $SiO_2$ (400 g) with ethyl acetate–hexane (1:9 v/v) as eluant gave *compound* (**20**) (7 g) as an oil, $\lambda_{max.}$ 277 (ε 1 430), 270 (1 650), 265 (1 400), and 206 nm (16 805); $\nu_{max.}$ 2 845, 1 700, 1 595, 1 581, 1 480, and 1 446 $cm^{-1}$ [Found: ($M^+ - CH_3OCH_2$), 253.1223. $C_{17}H_{19}O_2$ requires *m/z*, 253. 1227].

*Alcohol* (**10**).—A solution of compound (**20**) (7 g) and BBN (3.05 g) in THF (120 ml) was stirred at reflux under nitrogen for 20 h. Ethanol (16 ml) was added, followed by 6M-aqueous sodium hydroxide (6 ml) and hydrogen peroxide (20%; 11 ml). After 1 h at reflux, the solution was cooled to 20 °C, the solvent was removed below 40 °C, and the residue was partitioned between chloroform and water. The chloroform phase was dried ($Na_2SO_4$) and filtered, and the solvent was removed. Purification by chromatography on $SiO_2$ (450 g) with ethyl acetate–hexane (1:1 v/v) as eluant gave the *alcohol* (**10**) (5.6 g) as a pale yellow oil, $\lambda_{max.}$ 277 (ε 1 410), 270 (1 590), and 209 nm (12 410); $\nu_{max.}$ 3 420, 2 940, 1 601, 1 588, 1 491, and 1 455 $cm^{-1}$ (Found: $M^+$, 316.1674; C, 72.0; H, 7.6%. $C_{19}H_{24}O_4$ requires *M*, 316.1674; C, 72.13; H, 7.65%).

*Acetate* (**9**).—The alcohol (**10**) (1 g), pyridine (6 ml), and acetic anhydride (2 ml) were stirred together at 20 °C for 16 h, poured into water (100 ml), acidified (2M-HCl), and extracted with chloroform (2 × 30 ml). The combined extracts were dried ($Na_2SO_4$) and filtered, and the solvent was removed. Purification by chromatography on $SiO_2$ (70 g) with ethyl acetate–hexane (1:3 v/v) as eluant gave the acetate (**9**) (1.13 g) as an oil, $\lambda_{max.}$ 277 (ε 1 680), 270 (1 910), and 204 nm (17 830); $\nu_{max.}$ 3 000, 1 730, 1 603, 1 587, 1 492, and 1 454 $cm^{-1}$ (Found: $M^+$, 358.1776; C, 70.1; H, 7.3%. $C_{21}H_{26}O_5$ requires *M*, 358.1780; C, 70.37; H, 7.31%).

*Versiconol Analogue* (**11**).—A mixture of the alcohol (**10**) (250 mg) and palladium–carbon (10%; 220 mg) in ethanol (15 ml) was stirred under hydrogen at 23 °C for 8 h. The mixture was filtered and the solvent was removed. Purification by chromatography on $SiO_2$ (25 g) with methanol–chloroform (5:95 v/v) as eluant gave the *versiconol analogue* (**11**) (75 mg) as a gum, $\lambda_{max.}$ 280 (ε 2 410), 275 (2 690), 214 (8 370), and 204 nm (13 320); $\nu_{max.}$ 3 280, 2 940, 1 583, 1 489, and 1 454 $cm^{-1}$ (Found: $M^+$, 182.0937; C, 65.7; H, 7.6%. $C_{10}H_{14}O_3$ requires *M*, 182.0943; C, 65.92; H, 7.74%).

*Diol* (**12**).—The procedure was as above, but the reaction time was limited to 20 min. This gave the *diol* (**12**) (140 mg), $\lambda_{max.}$ 276 nm (ε 1 060), 270 (1 210), and 215 nm (6 510); $\nu_{max.}$ 3 370, 2 920, 1 598, 1 581, 1 489, and 1 450 $cm^{-1}$ (Found: $M^+$, 226.1206. $C_{12}H_{18}O_4$ requires *M*, 226.1205).

*Versiconol Acetate Analogue* (**13**).—A stirred solution of the acetate (**9**) (100 mg), acetic acid (5 ml), water (5 ml), and conc. sulphuric acid (0.01 ml) was heated at 60 °C under nitrogen for 24 h. Water (30 ml) was added, and the solution was extracted with ethyl acetate (3 × 10 ml). The combined extracts were dried ($Na_2SO_4$) and filtered, and the solvent was removed. Purification by chromatography on $SiO_2$ (10 g) with ethyl acetate–hexane (1:1 v/v) as eluant gave the *deprotected phenol* (42 mg) as a pale yellow oil, $\lambda_{max.}$ 280 (ε 2 170), 274 (2 430), and 203 nm (20 020); $\nu_{max.}$ 3 270, 2 910, 1 588, 1 490, and 1 452 $cm^{-1}$ (Found: $M^+$, 314.1518. $C_{19}H_{22}O_4$ requires *M*, 314.1518).

Hydrogenolysis of this compound as described above [Pd–C (10%; 30 mg)] for 3 h, and purification by chromatography on $SiO_2$ (5 g) with methanol–chloroform (5:95 v/v) as eluant, gave the versiconol acetate analogue (**13**) (27 mg) as a pale yellow gum, $\lambda_{max.}$ 280 (ε 1 340), 273 (1 570), and 216 nm (3 810); $\nu_{max.}$ 3 380, 2 970, 1 720, 1 610, 1 596, 1 475, and 1 460 $cm^{-1}$ (Found: $M^+$, 224.1049; C, 64.1; H, 7.1%. $C_{12}H_{16}O_4$ requires *M*, 224.1049; C, 64.27; H, 7.19%).

*Alcohol* (**14**).—Hydrogenolysis of the acetate (**9**) (250 mg) with Pd–C (10%; 200 mg) for 20 min as described above, and subsequent purification by chromatography on $SiO_2$ (25 g) with methanol–chloroform (5:95 v/v) as eluant, gave the alcohol (**14**) (146 mg) as an oil, $\lambda_{max.}$ 276 (ε 1 700), 270 (1 880), 214 (11 150), and 204 nm (13 540); $\nu_{max.}$ 3 460, 2 950, 1 730, 1 600, 1 490, and 1 454 $cm^{-1}$ (Found: $M^+$ 268.1312; C 62.5; H, 7.35%. $C_{14}H_{20}O_5$ requires *M*, 268.1311; C, 62.67; H, 7.51%).

*Aldehyde* (**26**).—A solution of the alcohol (**14**) (70 mg) in dichloromethane (2 ml) was added to a stirred suspension of PCC (84 mg) in dichloromethane (2 ml). After 6 h at 20 °C the solution was filtered and purified by chromatography on $SiO_2$ (10 g) with ethyl acetate–hexane (1:2 v/v) as eluant to give the *aldehyde* (**26**) (61 mg) as an oil, $\lambda_{max.}$ 273 (ε 990), 269 (1 060), 211 (6 090), and 203 nm (6 470); $\nu_{max.}$ 2 890, 1 725, 1 600, 1 585, 1 482, and 1 450 $cm^{-1}$ [Found: ($M^+$ – CHO), 237.1127. $C_{13}H_{17}O_4$ requires *m/z*, 237.1125. Found: C, 63.05; H, 6.8. $C_{14}H_{18}O_5$ requires C, 63.15; H, 6.81%].

*Versiconal Acetate Analogue* (**27**).—Treatment of the aldehyde (**26**) (100 mg) with HOAc–$H_2OH_2SO_4$ as described previously, and purification of the product by chromatography on $SiO_2$ (20 g), with chloroform as eluant, gave firstly the *versicolorin C analogue* (**29**) (9 mg) as an oil, $\lambda_{max.}$ 285 (ε 3 410), 277 (4 170), 215 (7 910), and 204 nm (15 610); $\nu_{max.}$ 2 920, 1 600, 1 480, and 1 465 $cm^{-1}$ (Found: $M^+$, 162.0684; C, 73.9, H, 6.05%. $C_{10}H_{10}O_2$ requires *M*, 162.0681; C, 74.06; H, 6.21%); and then the *versiconal acetate analogue* (**27**) (55 mg) as an oil, $\lambda_{max.}$ 282 (ε 2 300), 276 (2 625), 215 (5 600), and 206 (5 360); $\nu_{max.}$ 2 930, 1 725, 1 597, 1 478, and 1 460 $cm^{-1}$ (Found: $M^+$, 222.0891; C, 65.1; H, 6.5%. $C_{12}H_{14}O_4$ requires *M*, 222.0892; C, 64.85; H, 6.35%).

*Xanthone Analogue* (**30**).—The olefin (**19**) (100 mg) and osmium tetraoxide (100 mg) in pyridine (3 ml) were kept for 24 h at 20 °C. A solution of sodium metabisulphite ($Na_2S_2O_5$) (180 mg) in water (3 ml) was added, and the mixture was stirred for 30 min, then extracted with ethyl acetate (3 × 5 ml; the combined extracts were dried ($Na_2SO_4$), the solvent was removed, and the product was purified by chromatography on $SiO_2$ (25 g) with methanol–chloroform (5:95 v/v) as eluant to give the diastereoisomeric mixture (**31**) (70 mg). Hydrogenolysis of this mixture with Pd–C (10%; 60 mg) for 3 h as described previously, and purification by chromatography on $SiO_2$ (15 g) with methanol–chloroform (1:9 v/v) as eluant, gave the diastereoisomeric mixture (**30**) (25 mg). The mixture was characterised only by its n.m.r. properties (Table 2).

*Versiconal Analogue* (**28**).—A solution of the versiconal acetate analogue (**27**) (25 mg) and potassium hydroxide (10 mg) in methanol was stirred at 20 °C for 4 h. The solvent was

removed below 30 °C, and the product was purified on $SiO_2$ (10 g) with methanol–chloroform (1:9 v/v) as eluant to give the versiconal analogue (**28**) (17 mg) as a pale yellow oil, $\lambda_{max.}$ 326 (ε 810), 277 (2 370), 255 (2 470), and 214 nm (6 170); $\nu_{max.}$ 3 320, 2 920, 1 720, 1 605, 1 480, and 1 450 $cm^{-1}$ [Found: ($M^+ - H_2O$), 162.0680. $C_{10}H_{10}O_2$ requires *m/z* 162.0681. Found: C, 74.0; H, 6.2%; $C_{10}H_{12}O_3$ requires C, 74.06; H, 6.21%].

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