Total Synthesis of the Mycotoxin (−)-Zearalenone based on Macrocyclisation using a Cinnamyl Radical Intermediate

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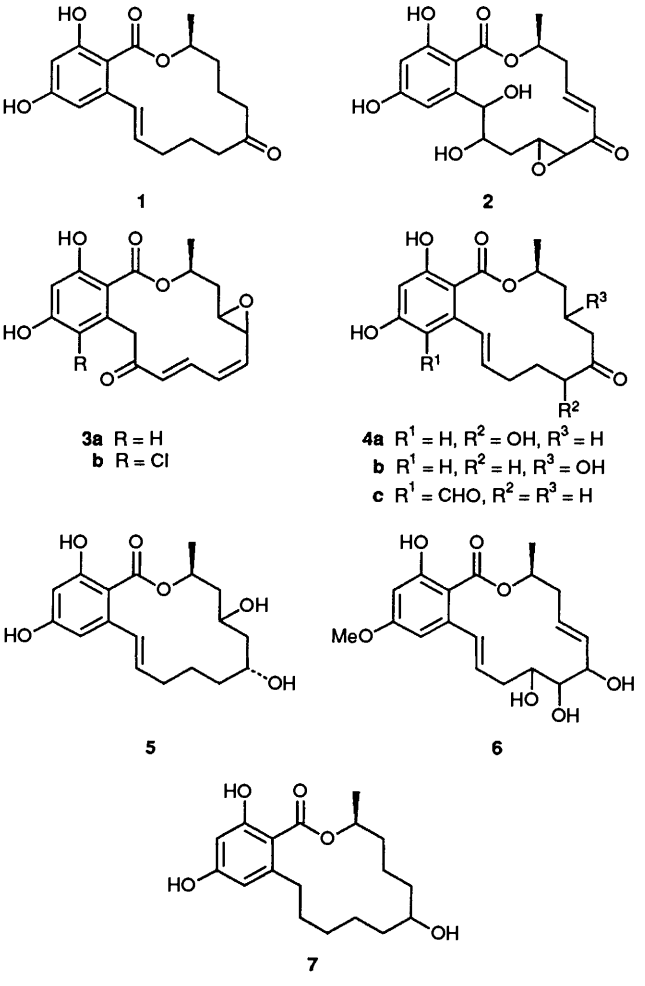
A concise synthesis of optically active (−)-zearalenone, which uses a novel 14-*endo*-*trig* macrocyclisation from a cinnamyl radical intermediate onto an α,β-enone electrophore as a key feature, is described.

The 14-membered macrolide zearalenone **1** is an oestrogenic mycotoxin produced by various fusaria which colonise maize, barley, oats and wheat.[1] Zearalenone was first isolated from the mycelium of the fungus *Gibberella zeae* (*Fusarium graminearum*), and it is now considered as the progenitor of the growing family of biologically important 'resorcylic acid lactones' (RALs), *e.g.* hypothemycin **2**,[2] monorden **3a**[3] and monocillin **3b**,[4] which have since been found in nature. The hormonal activity of zearalenone and related naturally occurring derivatives, *e.g.* **4**–**7**, has been linked to the close spatial similarity of these molecules to oestradiol.[5] Today, zearalenone is produced industrially by fermentation and is used in the manufacture of zearalanol **7** (also called zeranol).[6] Zearalanol is employed as an anabolic cattle-growth stimulant, and the compound has also undergone clinical trials as a potential treatment for menopausal and post menopausal syndrome.[7]

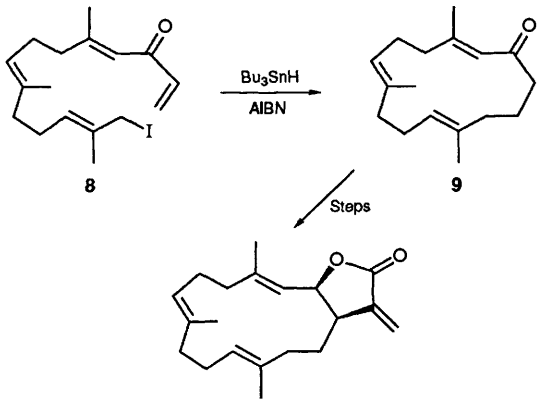
Although a number of syntheses of racemic zearalenone have been published,[8,9] at the outset of our work no total synthesis of natural (*S*)-zearalenone had been described. The first total synthesis of (±)-zearalenone was described by the Merck group in 1968,[8g] and employed a strategy whereby the 14-membered ring was produced by a macrolactonisation protocol. Some time later Tsuji *et al.*[8b–d] described the use of intramolecular alkylation from the anion of a substituted benzyl phenyl sulfide to elaborate the 14-membered ring in zearalenone.

In earlier work we have described the use of allyl carbon centred radical intermediates in macrocyclisation reactions leading to members of the cembranoid family of natural diterpenes, *e.g.* **8** → **9** → **10** (Scheme 1).[10] The presence of a δ-unsaturated ketone residue in the macrolide part of zearalenone **1**, permitted us to build on this earlier work and conceive a new synthetic strategy to zearalenone based on a 14-*endo*-*trig* cyclisation from the cinnamyl radical intermediate **12**, shown in Scheme 2.[11] In this paper we describe the successful outcome of this idea.

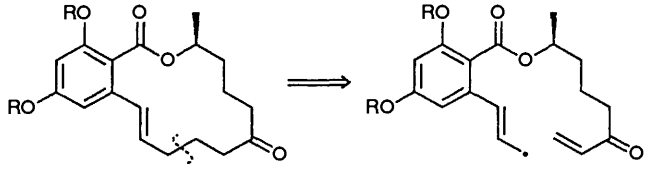
We analysed that the cinnamyl bromide **13b**, derived by direct bromination of the (*E*)-propenyl aromatic **13a**, would function as the most appropriate precursor to the cinnamyl radical intermediate **12** for macrocyclisation to **11** (Scheme 3). A convenient precursor to **13a** would then be the resorcinol derivative **14**, derived from the readily available methyl orsellinate **15**.[12] Thus, deprotonation of the orsellinate derivative **15** using lithium diisopropylamide followed by quenching of the resulting anion with diphenyl disulfide first led to the benzyl phenyl sulfide derivative **16** in 60% yield.[13] Treatment of **16** with potassium hexamethyldisilylamide at −78 °C followed by iodoethane next produced the substituted sulfide **17** in 94% yield, which on oxidation with sodium periodate followed by thermal elimination of phenylsulfenic acid from the resulting sulfoxide gave rise to the *E*-alkene **18** in 86% overall yield. Saponification of the methyl ester **18** using potassium hydroxide in dimethyl sulfoxide (DMSO) then provided the resorcinol derivative **14** as white crystals.



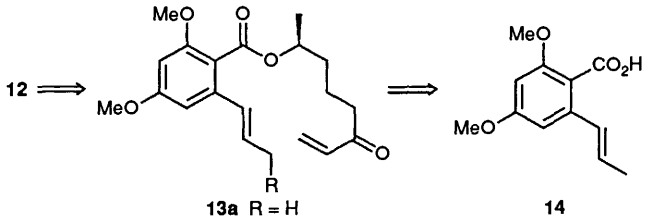
The aim next was to esterify the benzoic acid **14** with the known chiral alcohol derivative **22**[14] derived from natural parasorbic acid **19**[15] leading to the chiral ester **24** containing all but two of the carbon atoms in the radical macrocyclisation precursor **12**. Thus, sequential reduction of (*S*)-(+)-parasorbic acid **19**, using catalytic hydrogenation, to **20**, and lithium aluminium hydride, followed by treatment of the resulting cyclic hemi-acetal **21** with propanedithiol in the presence of boron trifluoride led smoothly to the dithiane alcohol **22** whose optical rotation was in accordance with literature data. When this alcohol **22** was treated with the acid chloride produced from the benzoic acid **14**, the chiral ester **23** was secured in 64% yield. Deprotection of **23** using mercuric chloride and mercuric acetate next provided the corresponding aldehyde **24** which upon treatment with vinylmagnesium bromide led to the allylic alcohol **25**. Oxidation of **25** using manganese dioxide in



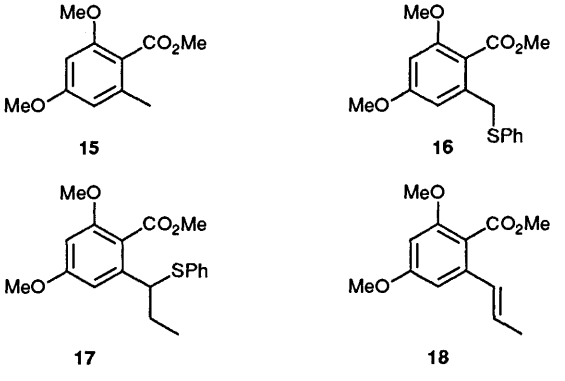
Scheme 1



Scheme 2

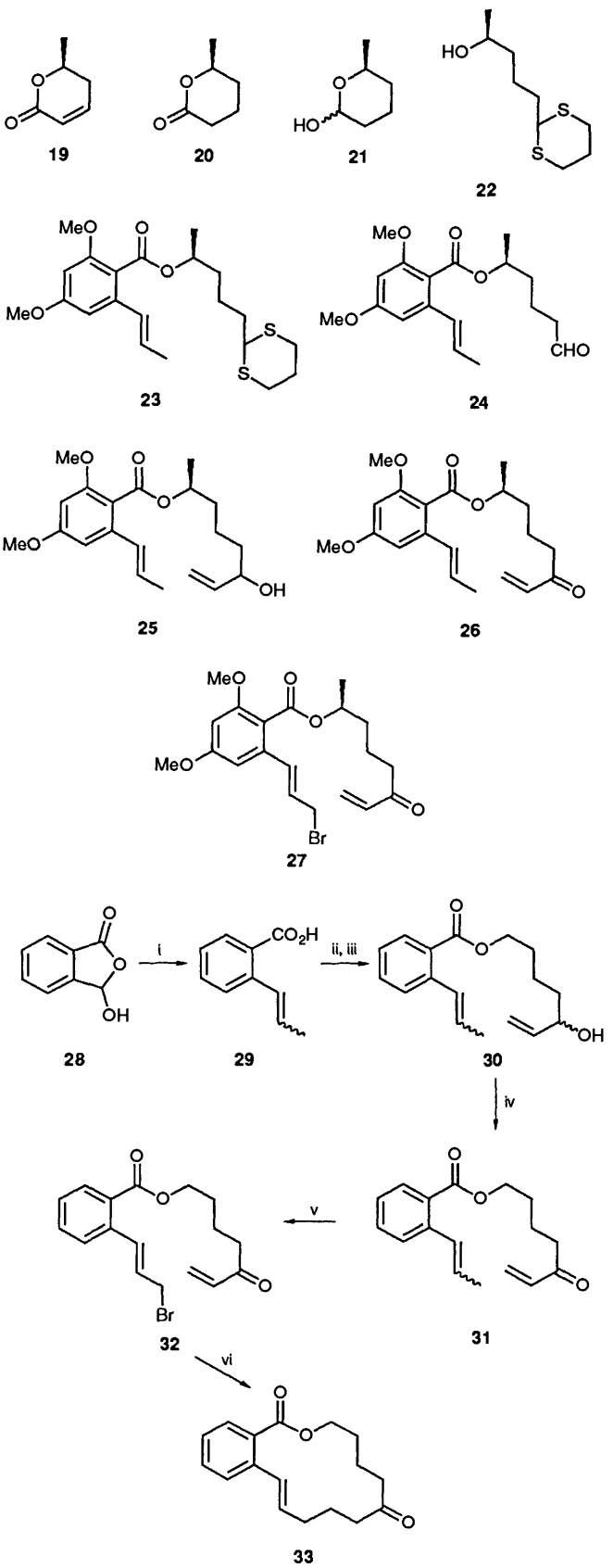


Scheme 3



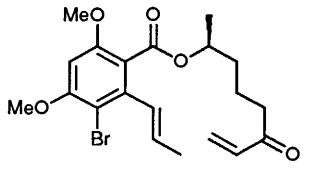
dichloromethane then gave the key enone intermediate **26**, for elaboration to the bromide **27** and hence zearalenone **1**.

In model work we had been able to produce the enone **31** directly analogous to **26**, using a few simple steps starting from the hydroxyphthalide **28** (Scheme 4). When this enone **31** was treated with *N*-bromosuccinimide in the presence of catalytic azoisobutyronitrile (AIBN) in refluxing carbon tetrachloride solution it underwent smooth selective bromination leading exclusively to the *E*-allyl bromide **32** uncontaminated by positional or stereoisomers. Furthermore, when a solution of tributyltin hydride and catalytic AIBN in benzene was added by syringe pump to a solution of the allyl bromide **32** at 80 °C under nitrogen, work-up produced only the (*E*)-keto macrolide **33** resulting from 14-*endo-trig* cyclisation. No products resulting from competitive 12-*endo-trig* (or *exo*) radical cyclisation were detected.



Scheme 4 *Reagents:* i, 2 equiv. $MeSOCH_2Na$, $[Ph_3PCH_3]Br$, THF; ii, $(COCl_2)$, DMF, CH_2Cl_2; iii, $HO(CH_2)_4CH(OH)CH{=}CH_2$; iv, MnO_2, CH_2Cl_2; v, NBS, AIBN, CCl_4; vi, Bu_3SnH, AIBN, PhH

When the conditions used to brominate **31** were translated to the enone intermediate **26** *en route* to zearalenone, only the product **34** resulting from aromatic bromination was obtained initially. However, in the less polar solvent benzene, and using light from a Infraphil UV lamp as initiator, the bromination of the enone **26** with *N*-bromosuccinimide proceeded smoothly producing the (*E*)-cinnamyl bromide **27** in 64% yield.[16] Finally, when the bromide **27** was treated with tributytin hydride, or more conveniently with tris(trimethylsilyl)silane,[17] and AIBN under high dilution in toluene at 85 °C, it underwent clean 14-*endo-trig* cyclisation to (*S*)-(+)-zearalenone dimethyl ether **35** which was produced as a white crystalline solid in 55% yield. Demethylation of the dimethyl ether **35**, using boron tribromide in dichloromethane[8f] at −40 °C, then afforded (*S*)-(−)-zearalenone **1** which was identical in all respects with naturally derived material.



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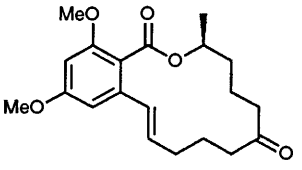

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The synthesis of zearalenone described here constitutes the first total synthesis of zearalenone in its optically active form. Following the publication of our preliminary report of this work[11] two additional syntheses of non-racemic zearalenone were disclosed. In the first of these,[18] the macrocyclic portion in the zearalenone was produced by a conventional macrolactonisation procedure, whereas in the second synthesis[19] an interesting intramolecular palladium-catalysed aryl–vinyl sp^2–sp^2 coupling reaction was employed to close the macrocycle ring.

Experimental

For general experimental details see ref. 10. *J*-Values are in Hz.

Methyl 2,4-*Dimethoxy*-6-[1-(*phenylthio*)*propyl*]*benzoate* **17**.—A solution of methyl 2,4-dimethoxy-6-[(phenylthio)methyl]-benzoate **16** (4.20 g, 13.2 mmol)[13] in anhydrous tetrahydrofuran (THF) (40 cm^3) was added dropwise over 0.5 h to a stirred solution of potassium bis(trimethylsilylamide) (0.5 mol dm^{-3}) in toluene (79.3 cm^3, 37.9 mmol) under nitrogen at −78 °C. The orange solution was stirred at −78 °C for 30 min and then freshly distilled ethyl iodide (2.78 g, 17.8 mmol) was added. The mixture was stirred at −78 °C for 45 min and then quenched with water (120 cm^3) and diethyl ether (150 cm^3). The ether phase was separated, washed with water (50 cm^3) and brine (50 cm^3) and then dried and evaporated to leave a yellow oil. Purification by chromatography on silica using 30% diethyl ether in hexane as eluent gave the *sulfide* (4.30 g, 94%) as a pale yellow liquid; λ_{max}(EtOH)/nm 207 (42 600); ν_{max}(film)/cm^{-1} 2950, 1725, 1600, 1580 and 1160; δ_H 0.92 (t, *J* 7, CH_2CH_3), 1.92 (dq, *J* 7, 7, CH_2CH_3), 3.80 (OMe), 3.82 (OMe), 4.22 (t, *J* 7, ArC*H*SAr), 6.32 (d, *J* 2, ArH), 6.67 (d, *J* 2, ArH) and 7.12–7.45 (m, 5 H, ArH); δ_C 12.2 (q), 30.2 (t), 51.7 (t), 52.0 (d), 55.4 (t), 56.0 (t), 97.6 (d), 103.9 (d), 116.9 (s), 126.9 (d), 128.7 (d), 131.9 (d), 135.3 (s), 142.8 (s), 157.9 (s), 161.8 (s) and 168.3 (s); *m*/*z* 345 (9%, $M^+ - H$) (Found: C, 66.0; H, 6.65%. $C_{19}H_{22}O_4$ requires C, 65.8; H, 6.40%).

Methyl 2,4-*Dimethoxy*-6-(E-*prop*-1-*enyl*)*benzoate* **18**.—A solution of sodium periodate (2.48 g, 11.6 mmol) in water (5 cm^3) was added dropwise over 15 min to an ice-cold solution of the sulfide **17** (4.01 g, 11.6 mmol) in methanol (50 cm^3). The solution was warmed to room temperature and then stirred for 12 h. The white precipitate which formed was filtered off, washed with methanol and the filtrate was then evaporated. The residue was dissolved in diethyl ether (50 cm^3), dried and evaporated to leave a colourless oil which was redissolved in toluene (150 cm^3) and heated under reflux for 2 h. The cooled mixture was evaporated to leave an oil which was purified by chromatography on silica gel using 30% diethyl ether in hexane as eluent to give the *aryl ester* (2.34 g, 86%) as a colourless oil; λ_{max}(EtOH)/nm 223 (24 000); ν_{max}(film)/cm^{-1} 2960, 1720, 1600, 1580 and 1160; δ_H 1.86 (d, *J* 7, =CMe), 3.78 (OMe), 3.82 (OMe), 3.88 (OMe), 6.20 (dq, *J* 16, 7, CH=C*H*Me), 6.33 (d, *J* 2, ArH), 6.38 (d, *J* 16, ArC*H*) and 6.58 (d, *J* 2, ArH); δ_C 18.7 (q), 52.3 (q), 55.4 (q), 56.0 (q), 97.3 (d), 101.5 (d), 115.3 (s), 127.8 (d), 129.2 (d), 138.0 (s), 158.0 (s), 161.4 (s) and 168.7 (s); *m*/*z* 236 (36%, M^+) (Found: C, 65.7; H, 7.0%. $C_{13}H_{16}O_4$ requires C, 66.1; H, 6.8%).

2,4-*Dimethoxy*-6-(E-*prop*-1-*enyl*)*benzoic Acid* **14**.—Aqueous sodium hydroxide (20%; 30 cm^3) was added in one portion to a solution of the ester **18** (1.76 g, 7.46 mmol) in DMSO (100 cm^3) under nitrogen and the mixture was then heated at 120 °C for 3 h. The cooled mixture was acidified with dilute HCl (2 mol dm^{-3}; 100 cm^3) and then extracted with diethyl ether (3 × 50 cm^3). The combined diethyl ether portions were extracted with saturated aqueous $NaHCO_3$ (50 cm^3) and the basic extract was then washed with diethyl ether (50 cm^3), acidified to pH 1 with dilute HCl (2 mol dm^{-3}) and extracted with diethyl ether (2 × 50 cm^3). Evaporation of the dried organic extracts left a white solid which on crystallisation (diethyl ether–hexane) gave the *acid* (1.44 g, 87%) as white crystals, m.p. 85–86 °C; λ_{max}(EtOH)/nm 223 (24 000); ν_{max}($CHCl_3$)/cm^{-1} 3300, 2940, 1720, 1595 and 1570; δ_H 1.89 (dd, *J* 7, 2, =CCH_3), 3.89 (OMe), 3.92 (OMe), 6.17 (dq, *J* 16, 7, CH=C*H*Me), 6.48 (d, *J* 2, ArH), 6.62 (d, *J* 2, ArH) and 6.80 (dd, *J* 16, 2, ArC*H*); δ_C 18.4 (q), 55.1 (q), 56.0 (q), 97.1 (d), 102.8 (d), 128.6 (d), 128.9 (d), 140.4 (s), 158.5 (s), 160.5 (s), 161.7 (s) and 171.0 (s); *m*/*z* 222 (67%, M^+) (Found: C, 64.55; H, 6.4%. $C_{12}H_{14}O_4$ requires C, 64.85; H, 6.35%).

(2S)-5-(*Dithian*-2-*yl*)*pentan*-2-*ol* **22**.—The dithianyl alcohol was prepared using the procedure described by Lichtenthaler *et al.*[14] It showed $[\alpha]_D^{24}$ +6.7 (*c* 1 $CHCl_3$) {lit. $[\alpha]_D^{20}$ +7.0 (*c* 1 $CHCl_3$)}.

(2S)-5-(*Dithian*-2-*yl*)*pentan*-2-*yl* 2,4-*Dimethoxy*-6-(E-*prop*-1-*enyl*)*benzoate* **23**.—Dimethylformamide (1 drop) was added to a solution of the acid **14** (1.24 g, 5.58 mmol) and oxalyl chloride (3.55 g, 28.0 mmol), in anhydrous THF (25 cm^3) under nitrogen. The solution was stirred at room temperature for 2 h and then evaporated to dryness under reduced pressure. The residue was dissolved in anhydrous CH_2Cl_2 (25 cm^3) and pyridine (440 mg, 5.58 mmol) and a solution of the alcohol **22** (1.07 g, 5.20 mmol) in dry CH_2Cl_2 (5 cm^3) was then added dropwise. The resulting solution was stirred at room temperature under nitrogen for 24 h and then washed with water (25 cm^3), dried and evaporated to leave a pale yellow oil. Purification by chromatography on silica with 50% diethyl ether in hexane as eluent gave the *ester* (1.36 g, 64%) as a colourless oil, $[\alpha]_D^{24}$ +17.6 (*c* 1.0, $CHCl_3$); λ_{max}(EtOH)/nm 224 (22 100); ν_{max}(film)/cm^{-1} 2940, 1720, 1600 and 1575; δ_H 1.35 (d, *J* 7, OCHCH_3), 1.35–1.80 (m, 8 H), 1.88 (d, *J* 7, =CCH_3), 2.72–2.96 (m, SCH_2, 4 H), 3.78 (OMe), 3.80 (OMe), 4.02 (t, *J* 7, OCH), 6.20 (dq, *J* 16, 7, =C*H*Me), 6.38 (d, *J* 16, ArC*H*), 6.48 (d, *J* 2, ArH) and 6.58 (d, *J* 2, ArH); δ_C 18.7 (q), 20.1 (q), 22.7 (t), 26.0 (t), 30.4 (t), 35.3 (t), 35.6 (t), 47.4 (d), 55.4 (t), 55.9 (t), 71.6 (d), 97.4 (d), 101.4 (d), 116.1 (s), 127.8 (d), 129.0 (d), 137.6 (s), 157.8 (s), 161.2 (s) and 167.8 (s); *m*/*z* 411 (15%, $M^+ + H$) (Found: C, 61.4; H, 7.55. $C_{21}H_{30}O_4S_2$ requires C, 61.4; H, 7.4%).

(2S)-6-*Oxohexan*-2-*yl* 2,4-*Dimethoxy*-6-(E-*prop*-1-*enyl*)-*benzoate* **24**.—A mixture of the thioacetal **23** (413 mg, 1.00 mmol), mercuric chloride (602 mg, 2.22 mmol) and mercuric oxide (238 mg, 1.10 mmol) in aqueous acetonitrile (10%, 25 cm^3) was heated under reflux for 1 h. The cooled mixture was filtered through Kieselguhr and the filtrate was then washed with aqueous ammonium acetate (10%; 15 cm^3). Evaporation of the dried organic phase left a yellow oil which was purified by chromatography on silica gel using 60% diethyl ether in hexane as eluent to give the *aldehyde* (174 mg, 54%) as a colourless oil; $[\alpha]_D^{24}$ +15.4 (*c* 1.0, $CHCl_3$); λ_{max}(EtOH)/nm 222 (26 500); ν_{max}/cm^{-1} 3940, 1720, 1710, 1600 and 1580; δ_H 1.40 (d, *J* 7, $OCHCH_3$), 1.35–1.80 (m, 4 H), 1.86 (dd, *J* 7, 2, $=CHCH_3$), 2.56 (t, *J* 7, CH_2CHO), 3.77 (OMe), 3.80 (OMe), 5.22 (m, 1 H, CO_2CH), 6.25 (dq, *J* 16, 7, $=CHMe$), 6.36 (d, *J* 2, ArH), 6.42 (dd, *J* 16, 2, ArCH) and 6.58 (d, *J* 2, ArH); δ_C 18.0 (t), 18.5 (q), 20.0 (q), 35.3 (t), 43.4 (t), 55.3 (q), 55.8 (q), 71.1 (d), 97.5 (d), 101.8 (d), 127.9 (d), 129.0 (d), 137.6 (s), 157.9 (s), 161.3 (s), 167.7 (s) and 201.8 (d); *m*/*z* 321 (99%, M + H).

(2S,6RS)-6-*Hydroxyoct*-7-*en*-2-*yl* 2,4-*Dimethoxy*-6-(E-*prop*-1-*enyl*)*benzoate* **25**.—A solution of vinylmagnesium bromide (860 mm^3) in THF (1.0 mol dm^{-3}; 0.86 mmol) was added dropwise over 5 min to a stirred solution of the aldehyde **24** (250 mg, 0.78 mmol) in dry THF (10 cm^3) under nitrogen at −10 °C. The mixture was stirred at −10 °C for 30 min and then quenched with dilute HCl (2 mol dm^{-3}; 5 cm^3), water (10 cm^3) and diethyl ether (25 cm^3). Evaporation of the dried organic layer left an oil which was purified by chromatography on silica gel using 60% diethyl ether in hexane as eluent to yield the *allylic alcohol* (251 mg, 93%) as a colourless oil; λ_{max}(EtOH)/nm 224 (22 200); ν_{max}/cm^{-1} 3500, 2950, 1720, 1600 and 1580; δ_H 1.30 (d, *J* 7, $OCHCH_3$), 1.42–1.80 (m, 6 H), 1.82 (dd, *J* 7, 2, $=CHCH_3$), 3.80 (OMe), 3.82 (OMe), 4.10 (m, 1 H, CHOH), 4.90–5.35 (m, 3 H), 5.70–6.20 (m, 3 H), 6.38 (d, *J* 2, ArH) and 6.50 (d, *J* 2, ArH); δ_C 18.5 (q), 20.1 (q), 21.3 (t), 35.9 (t), 36.9 (t), 55.4 (q), 56.0 (q), 71.7 (d), 72.9 (d), 97.6 (d), 101.9 (d), 114.5 (t), 128.0 (d), 128.9 (d), 137.7 (s), 141.3 (d), 158.0 (s), 161.3 (s) and 167.8 (s) (Found: M^+, 348.1951. *M*, 348.1937).

(2S)-6-*Oxooct*-7-*en*-2-*yl* 2,4-*Dimethoxy*-6-(E-*prop*-1-*enyl*)-*benzoate* **26**.—A mixture of the allylic alcohol **25** (133 mg, 0.38 mmol) and manganese dioxide (1.16 g, 13.3 mmol) in dry CH_2Cl_2 (25 cm^3) was stirred for 24 h under nitrogen at room temperature, and then filtered through Kieselguhr. The filtrate was evaporated to leave a pale yellow oil which was purified by chromatography on silica gel using 40% diethyl ether in hexane as eluent to give the *enone* (91 mg, 69%) as a colourless oil, $[\alpha]_D^{24}$ +27.2 (*c* 1.1, $CHCl_3$); λ_{max}/nm 220 (25 000); ν_{max}/cm^{-1} 2950, 1720, 1680, 1600 and 1580; δ_H 1.32 (d, *J* 7, $OCHCH_3$), 1.42–1.80 (m, 4 H), 1.86 (d, *J* 7, $=CHCH_3$), 2.65 (t, *J* 7, CH_2CO), 3.82 (OMe), 3.85 (OMe), 4.95–5.38 (m, CO_2CH), 5.80 (dd, *J* 10, 4, $CH=CH_2$), 6.20–6.42 (m, 4 H) and 6.56 (d, *J* 2, ArH); δ_C 18.8 (q), 20.1 (q), 20.4 (t), 35.7 (t), 39.5 (t), 55.7 (q), 56.2 (q), 71.6 (d), 97.8 (d), 102.1 (d), 128.1 (t), 128.2 (d), 129.3 (d), 136.9 (d), 138.0 (s), 158.3 (s), 161.6 (s), 168.0 (s) and 201.0 (s); *m*/*z* 347 (10%, M + 1) (Found: C, 68.95; H, 7.8. $C_{20}H_{26}O_5$ requires C, 69.3; H, 7.6%).

Hept-6-*ene*-1,5-*diol*.—A solution of vinylmagnesium bromide (4.4 mmol) in THF (1.0 mol dm^{-3}; 4.4 cm^3) was added dropwise over 10 min to a stirred solution of 2-hydroxypyran (200 mg, 2.0 mmol) in anhydrous THF (25 cm^3) at 0 °C under nitrogen. The mixture was stirred at 0 °C for 0.5 h and then quenched with saturated aq. NH_4Cl (20 cm^3) and EtOAc (25 cm^3). The organic layer was separated and the aqueous layer was then extracted with EtOAc (25 cm^3). The combined organic extracts were dried and then evaporated under reduced pressure to leave a residue which was purified by chromatography on silica using diethyl ether as eluent to give the diol (210 mg, 81%) as a colourless liquid; ν_{max}(film)/cm^{-1} 3340, 2940, 1640, 1420, 990 and 920; δ_H 1.46 (m, 6 H, CH_2), 3.53 (t, *J* 7, CH_2OH), 4.80 (dt, *J* 7, 8, CHOH), 5.12 (dd, *J* 10, 1, $=CH_2$), 5.28 (dd, *J* 16, 1, $=CH_2$) and 5.94 (ddd, *J* 16, 10, 7, $CH=CH_2$); δ_C 22.6 (t), 33.3 (t), 37.7 (t), 62.7 (t), 73.4 (d), 114.3 (t) and 142.4 (d); *m*/*z* 130 (21%, M^+).

2-(*Prop*-1-*enyl*)*benzoic Acid* **29**.—A suspension of sodium hydride (3.60 g, 150 mmol) in dry DMSO (150 cm^3) was heated to 80 °C for 45 min under nitrogen. The resulting solution of dimsyl anion was divided into two 75 cm^3 portions. Ethyltriphenylphosphonium bromide (24.7 g, 67 mmol) was added to one portion and the solution was then stirred at 25 °C for 10 min. 3-Hydroxyphthalide **28** (100 g, 67 mmol) was dissolved in the second portion, and the resulting solution was then added dropwise over 20 min to the stirred solution of the ylide at 0–5 °C (ice bath). The mixture was stirred at 25 °C for 15 h and then quenched with water (150 cm^3) and ether (150 cm^3). The separated aqueous layer was acidified to pH 1 with aq. HCl (2 mol dm^{-3}) and then extracted with dichloromethane (3 × 100 cm^3). The combined organic extracts were washed with 5% aq. citric acid (5 × 50 cm^3), dried and concentrated under reduced pressure. The residue was purified by dry column chromatography on silica G using 25% diethyl ether in hexane then 50% diethyl ether in hexane as eluent to give 2-propenylbenzoic acid (4.86 g, 45%) as a 4:7 mixture of *E* and *Z* isomers in the form of white crystals, m.p. 58–61 °C (Et_2O–pentane); λ_{max}/nm 265 (20 000); ν_{max}/cm^{-1} 3516, 2915, 1701, 1600, 1240 and 766; δ_H 1.75 (dd, *J* 1, 7, Me), 1.94 (dd, *J* 1, 7, Me), 5.86 (dq, *J* 12, 7, $=CHMe$), 6.18 (dq, *J* 16, 7, $=CHMe$), 6.95 (dd, *J* 1, 12, ArCH=), 7.24–7.58 (m, ArH and ArCH=), 8.00 (dd, *J* 1, 7, ArH) and 8.10 (dd, *J* 1, 8, ArH); δ_C 14.3 (q), 18.9 (q), 126.4 (d), 126.6 (d), 126.7 (d), 127.5 (s), 128.0 (d), 129.0 (d), 129.7 (d), 129.8 (d), 131.1 (d), 131.3 (s), 131.5 (d), 132.4 (d), 133.0 (d), 139.7 (s), 140.7 (s), 173.0 (s) and 173.4 (s); *m*/*z* 162 (15%, M^+).

5-*Hydroxyhept*-6-*enyl* 2-(*Prop*-1-*enyl*)*benzoate* **30**.—DMF (1 drop) was added to a stirred solution of the acid **29** (0.37 g, 2.3 mmol) and oxalyl chloride (0.59 g, 4.6 mmol), in anhydrous THF (10 cm^3) under nitrogen. The solution was stirred at room temperature for 2 h and then evaporated to dryness under reduced pressure. The residue was dissolved in anhydrous CH_2Cl_2 (5 cm^3) and the solution was then added dropwise over 0.25 h to a solution of hept-6-ene-1,5-diol (0.30 g, 2.3 mmol) and pyridine (0.20 g, 2.5 mmol) in dry CH_2Cl_2 (10 cm^3). The resulting solution was stirred at room temperature under nitrogen for 24 h, washed with water (25 cm^3), dried and evaporated to leave a pale yellow oil. Purification by chromatography on silica using 50% diethyl ether in pentane as eluent gave the *ester* (0.41 g, 68%) as a 4:7 mixture of *E* and *Z* isomers in the form of a colourless oil; λ_{max}/nm 202 (19 000); ν_{max}(film)/cm^{-1} 3440, 2940, 1710, 1600, 1570 and 1260; δ_H 1.40–2.72 (m, 9 H), 4.15 (m, CHOH), 4.26 (t, *J* 7, 1 H, OCH_2), 4.31 (t, *J* 7, 1 H, OCH_2), 5.15 (d, *J* 10, 1 H, $=CH_2$), 5.33 (d, *J* 16, 1 H, $=CH_2$), 5.81–6.20 (m, 2 H, ArCH=CH and $CH=CH_2$), 6.88 (d, *J* 16, ArCH=CH), 7.10–7.56 (m, 3 H, ArH) and 7.82–8.00 (m, 1 H, ArH); δ_C 14.4 (q), 22.2 (t), 28.9 (t), 36.8 (t), 65.0 (t), 73.1 (d), 114.8 (t), 126.3 (d), 126.6 (d), 126.7 (d), 127.4 (d), 129.0 (d), 130.0 (d), 130.4 (d), 130.6 (d), 131.0 (d), 131.5 (d), 132.0 (d), 138.9 (s), 141.4 (d) and 167.6 (s); *m*/*z* 162 (94%, $M^+ - C_7H_{14}O$) (Found: C, 74.4; H, 8.2. $C_{17}H_{22}O_3$ requires C, 74.5; H, 8.0%).

5-*Oxohept*-6-*enyl* 2-(*Prop*-1-*enyl*)*benzoate* **31**.—A mixture of the allylic alcohol **30** (500 mg, 18.3 mmol) and manganese dioxide (6.36 g, 73.2 mmol) in dry CH_2Cl_2 (50 cm^3) was stirred

under nitrogen at room temperature for 24 h, and then filtered through Kieselguhr. The filtrate was evaporated to leave a pale yellow oil which was purified by chromatography on silica gel using 40% diethyl ether in hexane as eluent to give the *enone* (358 mg, 71%) as a 4:7 mixture of *E* and *Z* isomers in the form of a colourless oil; λ_{max}/nm 202 (19 000); ν_{max}(film)/cm^{-1} 2960, 1710, 1680, 1620, 1400 and 1255; δ_H 1.60–2.00 (m, 7 H), 2.70 (t, *J* 7, CH_2CO), 4.16–4.50 (m, OCH_2), 5.78 (dd, *J* 10, 4, C*H*=CH_2), 6.10–6.50 (m, 3 H, ArCH=C*H* and CH=CH_2) and 6.92–8.00 (m, 5 H, ArH and ArCH=); δ_C 14.1 (q), 18.5 (q), 20.4 (t), 28.2 (t), 38.9 (t), 64.4 (t), 126.0 (d), 126.4 (d), 126.5 (d), 127.1 (d), 127.7 (d), 128.3 (d), 129.7 (d), 130.1 (d), 130.3 (d), 130.7 (d), 131.3 (d), 131.8 (d), 136.4 (t), 138.7 (s), 139.0 (s), 167.3 (s) and 199.9 (s) (Found: C, 75.1; H, 7.6. $C_{17}H_{20}O_3$ requires C, 75.0; H, 7.4%).

5-*Oxohept*-6-*enyl* 2-(E-3-*Bromoprop*-1-*enyl*)*benzoate* **32**.—A mixture of the ester **31** (320 mg, 1.18 mmol), *N*-bromosuccinimide (230 mg, 1.29 mmol) and AIBN (5 mg) in dry, degassed CCl_4 was heated under reflux for 3 h. The cooled mixture was filtered and the filtrate was then evaporated under reduced pressure to leave a yellow oil which was purified by chromatography on silica using 30% diethyl ether in pentane as eluent to give the *bromide* (267 mg, 67%) as a colourless oil; λ_{max}/nm 203 (21 000); ν_{max}(film)/cm^{-1} 2960, 1710, 1580, 1620, 1255 and 750; δ_H 1.70–1.96 (m, 4 H, CH_2), 2.72 (t, *J* 7, CH_2CO), 4.25 (d, *J* 8, CH_2Br), 4.40 (t, *J* 7, CH_2O), 5.88 (dd, *J* 9, 4, C*H*=CH_2), 6.18–6.65 (m, 3 H, CH=CH_2 and ArCH=C*H*) and 7.30–7.75 (m, 5 H, ArH and ArCH); δ_C 20.7 (t), 28.5 (t), 33.2 (t), 39.2 (t), 65.0 (t), 127.8 (d), 128.0 (t), 129.3 (s), 130.7 (d), 132.3 (d), 133.5 (d), 136.8 (d), 137.9 (s), 167.3 (s) and 200.0 (s); *m*/*z* 270 (7%, M^+ − HBr) (Found: C, 58.1; H, 5.8%. $C_{17}H_{19}BrO_3$ requires C, 58.1; H, 5.45%).

(11E)-3,4,5,6,9,10-*Hexahydro*-8H-2-*benzooxacyclotetradecine*-1,7-*dione* **33**.—(i) A solution of tributyltin hydride (157 mg, 0.54 mmol) and AIBN (5 mg) in dry, degassed benzene (10 cm^3) was added over 8 h *via* syringe pump to a solution of the bromide **32** (98 mg, 0.28 mmol) in dry, degassed benzene (100 cm^3) heated under reflux under an atmosphere of nitrogen. The cooled mixture was evaporated under reduced pressure and the residue was then dissolved in diethyl ether. The ether solution was stirred with 20% aq. KF for 24 h, filtered and the organic layer was separated, dried and evaporated to leave a yellow oil. Purification by chromatography on silica using 25% diethyl ether in hexane as eluent gave the *macrolide* (47 mg, 61%) as white needles, m.p. 78–80 °C (pentane); λ_{max}/nm 203 (20 000); ν_{max}($CHCl_3$)/cm^{-1} 2920, 1720, 1600, 1460, 1250 and 1075; δ_H 1.50–2.04 (m, 6 H), 2.10–2.65 (m, 6 H), 4.20–4.50 (m, OCH_2), 5.88 (dt, *J* 16, 7, =C*H*CH_2), 6.88 (d, *J* 16, ArCH), 7.15–7.60 (m, 3 H, ArH), 7.78 (m, 1 H, ArH); δ_C 21.5 (t), 22.7 (t), 27.4 (t), 31.3 (t), 37.1 (t), 43.2 (t), 65.7 (t), 127.0 (d), 127.4 (d), 129.1 (s), 130.9 (d), 131.4 (d), 132.0 (d), 132.3 (d), 138.2 (s), 168.7 (s) and 211.2 (s); *m*/*z* 272 (5%, M^+) (Found: C, 75.1; H, 7.7. $C_{17}H_{20}O_3$ requires C, 75.0; H, 7.4%).

(ii) A solution of tris(trimethylsilyl)silane (130 mg, 0.52 mmol) and AIBN (5 mg) in dry toluene (10 cm^3) was added over 8 h *via* syringe pump to a stirred solution of the bromide **32** (128 mg, 0.37 mmol) in dry, degassed toluene (120 cm^3) at 85 °C under nitrogen. The solution was heated at 85 °C for 2 h and then cooled and evaporated to leave a residue which was purified by chromatography on silica gel using 25% diethyl ether in hexane as eluent to give the *macrolide* (58 mg, 59%) as white needles, m.p. 78–80 °C which showed identical spectroscopic properties to those reported above.

(2S)-6-*Oxooct*-7-*en*-2-*yl* 2,4-*Dimethoxy*-6-[3-*bromoprop*-1-(E)-*enyl*]*benzoate* **27**.—A solution of the enone **26** (100 mg, 0.29 mmol) in dry, degassed benzene (10 cm^3) was photolysed in the presence of *N*-bromosuccinimide (56 mg, 0.32 mmol) using a Phillips Infraphil UV lamp for 1 h under nitrogen. The cooled mixture was evaporated to leave a yellow semi-solid which was purified by chromatography on silica gel using 50% diethyl ether in hexane as eluent to give the *bromide* (77 mg, 64%) as an unstable colourless oil; λ_{max}/nm 202 (24 000); ν_{max}/cm^{-1} 2940, 1715, 1680, 1600 and 1580; δ_H 1.32 (d, *J* 7, $OCHCH_3$), 1.42–1.80 (m, 4 H), 2.65 (t, *J* 7, CH_2CO), 3.78 (OMe), 3.82 (OMe), 4.08 (d, *J* 7, CH_2Br), 4.95–5.38 (m, CO_2CH), 5.80 (dd, *J* 10, 4, C*H*=CH_2), 6.22–6.48 (m, 4 H) and 6.60 (d, *J* 7, ArH); δ_C 19.7 (t), 20.1 (q), 29.7 (t), 35.3 (t), 39.1 (t), 55.5 (q), 55.9 (q), 71.7 (d), 98.7 (d), 101.8 (d), 128.1 (t), 128.3 (d), 128.6 (d), 135.6 (s), 136.5 (d), 157.8 (s), 161.4 (s), 167.5 (s) and 200.4 (s); *m*/*z* 577 (5%, M^+ + matrix).

(11E,3S)-14,16-*Dimethoxy*-3-*methyl*-3,4,5,6,9,10-*hexahydro*-8H-2-*benzooxacyclotetradecine*-1,7-*dione* **35**.—A solution of tris(trimethylsilyl)silane (35 mg, 0.14 mmol) and AIBN (5 mg) in dry toluene (2 cm^3) was added over 8 h *via* a syringe pump to a stirred solution of the bromide **27** (41 mg, 0.10 mmol) in dry, degassed toluene (35 cm^3) at 85 °C under nitrogen. The solution was heated at 85 °C for 2 h and then cooled, and evaporated to leave a residue which was purified by chromatography on silica gel using 50% diethyl ether in hexane as eluent to give the zearalenone (18 mg, 55%) as a white crystalline solid, m.p. 110–111 °C (Et_2O and hexane) (lit.,[8g] m.p. 112–114 °C), $[\alpha]_D^{24}$ +47.8 (*c* 0.5, $CHCl_3$) {lit.,[8g] $[\alpha]_D^{24}$ +49.8 (*c* 1.0, $CHCl_3$)}; λ_{max}/nm 236 (28 400); ν_{max}/cm^{-1} 2930, 1710, 1600 and 1575; δ_H 1.33 (d, *J* 7, $OCHCH_3$), 1.90–2.90 (m, 12 H), 3.79 (OMe), 3.82 (OMe), 5.06–5.46 (m, CO_2CH), 5.90–6.05 (m, =C*H*CH_2), 6.28 (d, *J* 16, ArCH), 6.30 (d, *J* 2, ArH) and 6.55 (d, *J* 2, ArH); δ_C 19.8 (q), 21.1 (t), 21.5 (t), 31.0 (t), 34.9 (t), 38.3 (t), 43.8 (t), 55.2 (q), 55.7 (q), 71.0 (d), 97.5 (d), 101.0 (d), 128.8 (d), 133.0 (d), 136.5 (s), 157.4 (s), 161.1 (s), 167.4 (s) and 211.2 (s) (Found: M^+, 346.1776. *M*, 346.1780).

(11E,3S)-14,16-*Dihydroxy*-3,4,5,6,9,10-*hexahydro*-8H-2-*benzooxacyclotetradecine*-1,7-*dione* **1**.—A solution of boron tribromide (180 mm^3) in CH_2Cl_2 (1.0 mol dm^{-3}; 0.18 mmol) was added dropwise to a stirred solution of zearalenone dimethyl ether (16 mg, 0.05 mmol) in dry CH_2Cl_2 (5 cm^3) under nitrogen maintained at −40 °C. The mixture was stirred at −40 °C for 1 h before pouring onto saturated aqueous $NaHCO_3$ (5 cm^3). The aqueous phase was acidified, and then extracted with CH_2Cl_2 (3 × 10 cm^3). Evaporation of the combined dried organic extracts left a yellow solid which was purified by chromatography on silica gel using 75% diethyl ether in hexane as eluent to give zearalenone (5.3 mg, 36%) as a white crystalline solid, m.p. 164–166 °C (Et_2O–hexane) and mixed m.p. 163–164 °C (lit.,[8g] m.p. 164–166 °C), $[\alpha]_D^{24}$ −191 (*c* 0.5, $CHCl_3$) {lit.,[8g] $[\alpha]_D^{24}$ −191 to −198 (*c* 1.0, $CHCl_3$)}; λ_{max}/nm 236 (29 700); ν_{max}/cm^{-1} 3300, 2920, 1680, 1620 and 1580; δ_H 1.38 (d, *J* 7, $OCHCH_3$), 1.40–2.90 (m, 12 H), 4.95–5.05 (m, CO_2CH), 5.70 (m, =$CHCH_2$), 5.75 (OH), 6.35 (d, *J* 2, ArH), 6.40 (d, *J* 2, ArH), 7.0 (d, *J* 16, ArCH) and 12.10 (OH); δ_C 20.8 (q), 21.0 (t), 22.3 (t), 29.7 (t), 31.0 (t), 32.0 (t), 34.7 (t), 36.6 (t), 42.9 (t), 73.4 (d), 102.4 (d), 108.3 (d), 132.5 (d), 133.1 (d), 144.0 (s), 160.4 (s), 165.5 (s), 171.3 (s) and 211.3 (s) (Found: M^+, 318.1480. *M*, 318.1467).

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