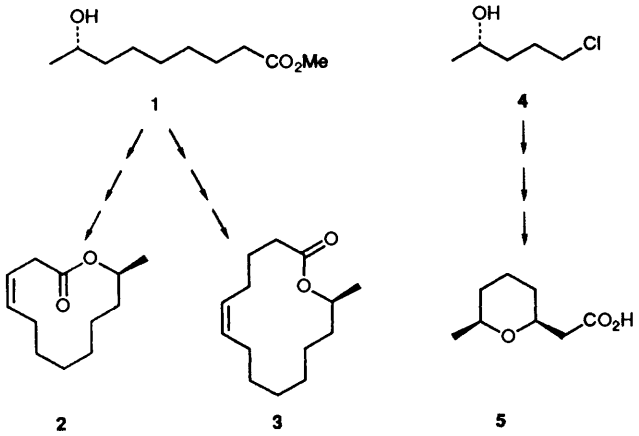
Thermostable Enzymes in Organic Synthesis, Part 6.[a] Total synthesis of (*S*)-(−)-Zearalenone using a TBADH-Generated Trifunctional Chiron

Ehud Keinan,* Subhash C. Sinha and Anjana Sinha-Bagchi
Department of Chemistry, Technion – Israel Institute of Technology, Technion City, Haifa 32000, Israel

Chiral alcohols produced by *Thermoanaerobium brockii* alcohol dehydrogenase (TBADH)-catalysed asymmetric reduction of polyfunctional ketones are useful building blocks for natural products synthesis. In particular, the ability of TBADH to discriminate between two ketones having equal chemical reactivity is demonstrated by enzymatic reduction of dec-9-ene-2,6-dione to produce optically pure (*S*)-2-hydroxydec-9-en-6-one. The total synthesis of (*S*)-(−)-zearalenone with optical purity that exceeds 99.5% has been achieved by using the latter compound as a starting material.

Thermoanaerobium brockii alcohol dehydrogenase (TBADH) is an unusual biocatalyst that effects the reduction of a broad range of aliphatic ketones to the corresponding secondary alcohols with excellent enantioselectivity. In our previous work we have produced a wide variety of chiral mono- and bi-functional secondary alcohols by TBADH-catalysed reduction of the corresponding ketones.[1–3] These bifunctional alcohols were conveniently employed as chiral building blocks (chirons)[4] for total synthesis of natural products containing chiral 'carbinol' (alcohol) centres. This approach is particularly attractive for total synthesis of the naturally occurring macrolides,[5] many of which contain a methyl 'carbinol' moiety, frequently in an *S* configuration. We demonstrated this advantage (Scheme 1) by employing (*S*)-(+)-methyl 8-hydroxynonanoate **1** in the total synthesis of (*S*)-(+)-dodec-3(*Z*)-en-11-olide (ferrulactone II) **2**[6] and (*S*)-(+)-tetradec-5(*Z*)-en-13-olide **3**,[3] which are synergistic aggregation pheromones of two major widespread pests of stored grains: the rusty grain beetle, *Cryptolestes ferrugineus* (Stephens),[7] and the flat grain beetle, *Cryptolestes pusillus* (Schonherr),[8] respectively. Similarly, (*S*)-(+)-5-chloropentan-2-ol **4** was employed in the total synthesis of [(*S*,*S*)-(+)-(*cis*-6-methyltetrahydropyran-2-yl)]acetic acid **5**, a natural constituent of the perfume material civet.[2,9]



Scheme 1

Our success in the total synthesis of chiral pheromone macrolides set the stage for a more complex synthetic challenge, *i.e.* the total synthesis of optically pure(*S*)-(−)-zearalenone **6**. This 14-membered, resorcylic acid macrolide is produced by various fusaria which colonize maise, barley, oats and wheat.[10] Since its isolation from the mycelium of the fungus *Gibberella zeae* (*Fusarium graminearum*) in 1962,[11] this mycotoxin, which exhibits anabolic, estrogenic, and antibacterial activity, has attracted much attention among chemists, biochemists, and veterinarians, as well as pharmaceutical companies.[10] Zearalenone, and its derivatives zearalanone, zearalenol and zearalanol, are potent animal-growth promoters, increasingly used as nontoxic, hormone-like agents that promote growth in cattle and sheep. To date, (*S*)-(−)-zearalenone is commercially extracted from various species of *Fusarium*, followed by appropriate separation and purification procedures.

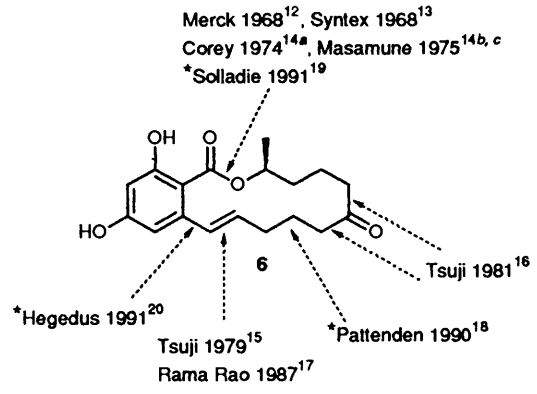


Fig. 1 Ring-closure approaches to zearalenone

We describe here the total synthesis of (*S*)-(−)-zearalenone using a chiral building block that is obtained *via* TBADH-catalysed reduction of a ketone. This highly selective reduction of one carbonyl function in a polyfunctional molecule containing two ketones of equal chemical reactivity represents a unique advantage of enzyme-aided organic synthesis.

Results and Discussion

Retrosynthetic analysis of the zearalenone molecule reduces the synthetic problem into three smaller tasks: (1) preparation of the aromatic portion; (2) preparation of an appropriately functionalized aliphatic chain; (3) attachment of the two fragments to yield the final macrolide structure. Synthesis of the aromatic fragment, an orsellinic acid derivative, is easily achievable by well established procedures. Also, attachment of the aromatic and aliphatic portions and macrocyclization is also well documented. For example, the Merck[12] and Syntex[13] groups have constructed zearalenone by lactonization, a process that has been remarkably improved by Corey[14a] and

[a] For the preceding paper in this series see ref. 4.

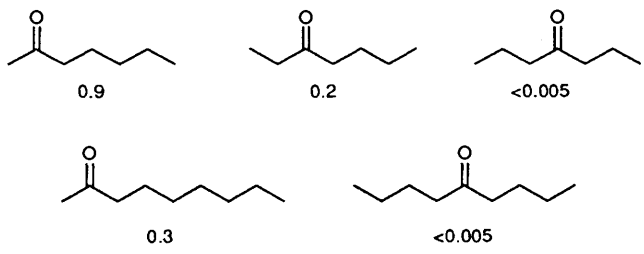


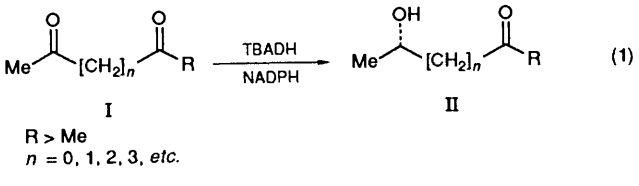
Fig. 2 Relative rates of TBADH-catalysed reduction

Masamune[14b,c] (Fig. 1). Tsuji and co-workers[15,16] as well as Rama Rao[17] have designed intramolecular alkylation methods using stabilized carbanions. Three different approaches to the total synthesis of zearalenone **6** in its naturally occurring, *S*-form have recently appeared in the course of our work (marked with * in Fig. 1). Pattenden and Hitchcock constructed the macrocycle *via* 1,4-addition of an allylic radical to an α,β-unsaturated ketone.[18] Solladie *et al.*[19] obtained the chiral building block from a chiral sulphoxide group using the macrolactonization technique. Hegedus employed (*R*)-propylene oxide as a chiral building block, by using palladium(0)-catalysed coupling of an aryl iodide with a vinylstannane.[20]

We decided to adopt Tsuji's approach,[15] using the orsellinic acid derivative **14**, thereby reducing the synthetic problem to the preparation of an appropriately functionalized, 10-carbon-chain containing an asymmetric alcoholic centre. The most commonly practiced path to such fragments involved chain extension, starting from relatively small, readily available chirons, such as 1,2-epoxypropane (propylene oxide) and an alkyl 3-hydroxybutanoate.[21] Our previous observations of the substrate specificity of TBADH reductions indicated an attractive approach to obtain the desired chiral aliphatic fragment *via* a TBADH-catalysed regio- and enantio-selective reduction of a methyl ketone in a polyfunctional substrate. The main advantage of this strategy is the introduction of the valuable asymmetric centre relatively late in the synthesis.

The basic idea originated from our earlier studies of the relative rates of reduction of methyl, ethyl, propyl and butyl ketones by TBADH.[1a] Representative rate values for several isomeric heptanones and nonanones are given in Fig. 2.

These results, as well as other observations,[2,3] have rasied speculation regarding the structure of the active site of TBADH. Assuming that the reacting carbonyl function is positioned in close proximity to the coenzyme nicotinamide moiety, the two alkyl groups on the carbonyl compound occupy two hydrophobic sites that differ from one another in volume as well as in affinity toward these groups. It appears that the 'small' alkyl site can accommodate groups such as methyl, ethyl, isopropyl and cyclopropyl, but not n-propyl or more bulky substituents. The 'large' alkyl site, however, can accommodate much larger moieties, particularly linear chains.[1a,3] This hypothesis led us to predict that the enzymatic system may well discriminate between ketones of equal chemical reactivity. For example, a linear molecule containing two or more ketones, one of which is a methyl ketone [**I** in equation (1)], is expected to be regioselectively reduced at the latter site to give the corresponding α-methyl-substituted alcohol **II**.



I **II**

R > Me
n = 0, 1, 2, 3, *etc.*

Indeed, our experiments with diketone **9** indicated that (1) this compound is a substrate for TBADH; (2) that it is reduced exclusively at the methyl ketone functionality to produce the corresponding keto alcohol **10**; (3) that the latter compound is obtained with an *S* configuration and in very high optical purity (> 99% ee, see Fig. 3); and (4) that compound **9** is a very reactive substrate, as reflected by its relative rate of TBADH-catalysed reduction (0.45 on the relative scale given in Fig. 2).

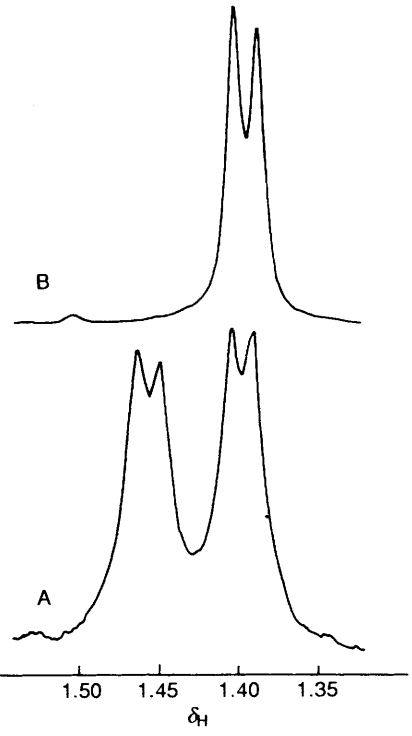
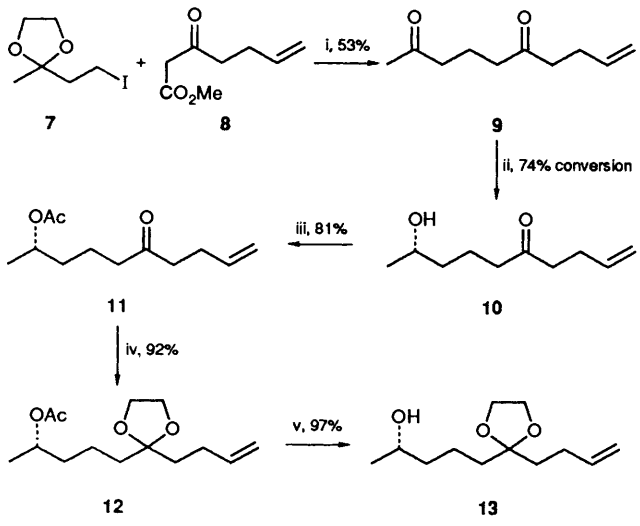


Fig. 3 Determination of optical purity of 9-acetoxydec-1-en-5-one **11** by ^{1}H NMR spectroscopy. A, Partial NMR spectrum of racemic **11** in the presence of 60 mol% $Eu(tfc)_3$ in $CDCl_3$. B, Partial spectrum of optically active **11** under the same conditions.

These observations open attractive opportunities for the preparation of polyfunctional chiral building blocks, such as the aliphatic segment of zearalenone. The synthesis of this fragment (structure **13**) is outlined in Scheme 2. Compound **7** was prepared as described.[22] Although synthesis of compound **8** has already been described by the Syntex group,[13] we found that better results were achieved by using Krapcho's conditions (excess of sodium hydride in benzene).[23] Similarly, we found that compound **9**, which had previously been prepared from methyl vinyl ketone and ethyl 3-oxohept-6-enoate,[13] could be synthesized more efficiently *via* a simpler decarboxylation procedure.[24] Enzymatic reduction of dione **9** to compound **10** was carried out at 40 °C, as was generally described in our previous work.[1-3] Reactions were usually interrupted at 70–80% conversion in order to avoid product racemization *via* reversible oxidation.[1] Although the keto alcohol **10** could be isolated and characterized, we found that it underwent spontaneous cyclization to produce the six-membered cyclic hemiketal.[12] Therefore, the crude compound **10** was acetylated and purified in the form of its acetate **11**. Ketalization of the latter to produce compound **12**, followed by acetate hydrolysis afforded the desired 10-carbon building block **13**.

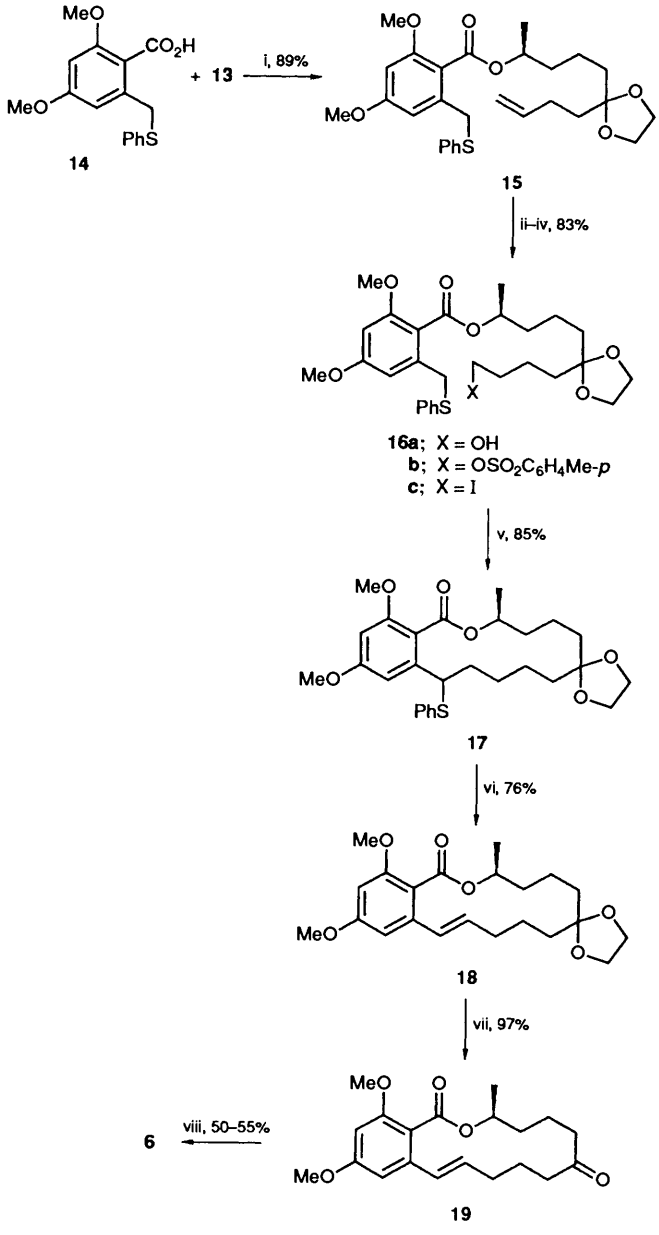
The synthesis of (*S*)-(−)-zearalenone was completed as described in Scheme 3. The orsellinic acid derivative **14** was prepared according to Barton's method,[25] followed by methylation (MeI, K_2CO_3, refluxing acetone, 24 h) and sulphenylation at the benzylic position [lithium diisopropylamide (LDA), (THF), −78 °C, diphenyl disulphide].[26] Conversion of compound **14** into the corresponding acyl chloride, followed by



Scheme 2 Synthesis of the aliphatic portion of zearalenone. *Reagents and conditions:* i, K_2CO_3, acetone–DMF, reflux 24 h; aq. KOH (3%), methanol, reflux, 2 h; aq. HCl (3 mol dm^{-3}), room temp., 1 h; ii, TBADH, $NADP^+$, aq. propan-2-ol, pH 7.9 (phosphate buffer), 40 °C, 48 h; iii, acetic anhydride, pyridine, 60 °C, 24 h; iv, ethylene glycol, PPTS, benzene, reflux; v, aq. KOH (2 mol dm^{-3}), methanol, room temp., 3 h.

reaction with the alcohol **13** in pyridine as described by Tsuji,[15] afforded the ester **15** in less than 50% yield. Significant improvement to 89% yield was achieved with Mukaiyama's method,[27] using equimolar amounts of the alcohol **13** and the free acid **14**. The terminal olefin was converted in high yield into an ω-iodo functionality in a three-step sequence: first, hydroboration of ester **15** with two mol equivalents of 9-borabicyclo[3.3.1]nonane (9-BBN), followed by treatment with hydrogen peroxide[28] to produce the primary alcohol **16a**; second, conversion into the tosate **16b** by using tosyl chloride and triethylamine; and finally, formation of the corresponding iodide **16c** by treatment of the tosate **16b** with sodium iodide and sodium hydrogen carbonate in acetone. Cyclization to give compound **17** was carried out as described by Tsuji.[15a] We found that equivalent results were achieved when using sodium hexamethyldisilazide at 70 °C in place of the potassium derivative at 40 °C. The phenyl sulphide **17** was oxidized by short (10 min) exposure to *m*-chloroperbenzoic acid (MCPBA) and the resultant sulphoxide was thermally eliminated to give olefin **18**. Deketalization with TsOH in acetone–water to give zearalenone dimethyl ether **19**. Demethylation with both boron trichloride and boron tribromide, according to the reported procedure,[12] afforded (*S*)-(−)-zearalenone **6**. This product was found to be identical (by ^1H and ^{13}C NMR, UV, IR, MS, $[\alpha]_D$, melting point, TLC) with an authentic sample purchased from Aldrich Chemical Co. (Cat. # 28,745–8).

Optical purity was determined by optical rotation measurements and, more reliably, by NMR spectroscopy, using the europium chiral shift reagent (+)-tris-{3-[trifluoromethyl(hydroxy)methylene]-camphorato}europium(III) [Eu(tfc)$_3$]. Since satisfactory results could not be obtained with this chiral shift reagent on zearalenone itself, analysis was carried out on zearalenone dimethyl ether **19** (Fig. 4). Optimal separation of the singlet, corresponding to a methoxy group that is ortho to the carboxyl, was achieved with 150 mol% Eu(tfc)$_3$, as shown in Fig. 4A which describes racemic **19**. The same experiment was repeated with our optically active compound **19** (Fig. 4B). A similar experiment that was carried out with an authentic sample of compound **19** [prepared from commercial (S)-(−)-zearalenone and MeI–K_2CO_3 in refluxing acetone for 24 h], which exhibited a partial NMR spectrum identical to that shown in Fig. 4B. Fig. 4C shows the NMR spectrum of a



Scheme 3 Total synthesis of (*S*)-(−)-zearalenone. *Reagents and conditions:* i, 2-Chloro-*N*-methylpyridinium iodide, tributylamine, CH_2Cl_2, reflux, 16 h; ii, 9-BBN, THF, 60 °C, 1 h; aq. NaOH (3 mol dm^{-3}), methanol, H_2O_2, 60 °C, 1 h; iii, triethylamine, TsCl, CH_2Cl_2, 0 °C, 2 h; iv, NaI, $NaHCO_3$, acetone, 40 °C, 24 h; v, $NaN(SiMe_3)_2$, 70 °C, 2 h; vi, MCPBA, CH_2Cl_2, 10 min; toluene, reflux, 1 h; vii, aq. acetone, TsOH, 40 °C, 26 h; viii, BCl_3, BBr_3, CH_2Cl_2, 0 °C, 10 min

mixture of our optically active **19** and the racemic isomer (5%), taken under the same conditions. It may be concluded from these spectra that optical purity of our synthetic zearalenone exceeds 99.5%.

In conclusion, in this paper we have shown once again that chiral alcohols produced by TBADH-catalysed asymmetric reduction of pol functional ketones are useful building blocks for natural produc s syntheses. Of particular interest is the ability of TBADH to discriminate between two ketones having equal chemical reactivity. This property opens attractive opportunit es of obtaining polyfunctional chiral starting materials for organic synthesis. This advantage has been demonstrated by the total synthesis of (*S*)-(−)-zearalenone **6** with optical purity that exceeds 99.5%. The synthesis started with (*S*)-(+)-2-hydroxydec-9-en-6-one **10**, obtained by enzymatic reduction of dec-9-ene-2,6-dione **9**. Attempts at total synthesis of curvularin and

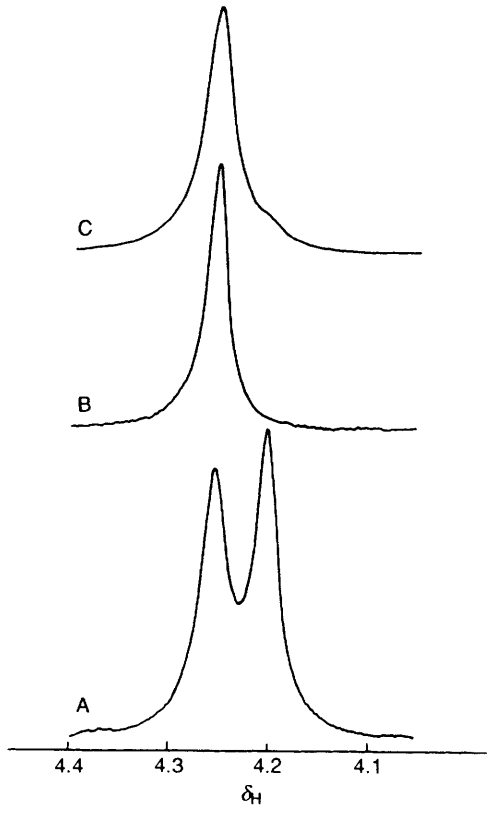


Fig. 4 Determination of optical purity of zearalenone dimethyl ether **19** by ^{1}H NMR. A, Partial NMR spectrum of racemic **19** in the presence of 150 mol% Eu(tfc)$_3$ in $CDCl_3$. B, Partial spectrum of optically active **19** under the same conditions. C, Partial spectrum of optically active **19**, mixed with 5% of the racemic sample.

other naturally occurring macrolides are currently under way in our laboratories.

Experimental

General Methods.—Elemental analyses were carried out at the microanalytical laboratory of the Hebrew University, Jerusalem. IR spectra were measured in chloroform solutions with either a Perkin-Elmer 467 grating spectrometer or an FT infrared Nicolet MX-1 spectrometer, and are given in cm^{-1}. NMR spectra were measured for deuteriochloroform solutions on a Bruker ACE-200 or Bruker AM-400 NMR spectrometers. All chemical shifts are reported in δ-units downfield from Me_4Si, and the *J*-values are given in Hertz. Gas-chromatography mass spectrometry (GCMS) analyses were carried out with a Finnigan ITS40 mass spectrometer attached to Varian 3400 gas chromatograph (equipped with a 0.25 mm × 30 m capillary column packed with DB-5). Mass spectrometry analyses with desorption chemical ionization (CIMS) were performed with isobutane using the same instrumentation. High-resolution mass spectra were determined on a Varian 711 spectrometer. Optical rotations were measured by a JASCO DIP 370 polarimeter, using a one decimeter (1 cm^3) cell. TLC was performed on aluminium sheets precoated with silica gel (Merck, Kieselgel 60, F254, Art. 5549). Column chromatographic separations were performed on silica gel (Merck, Kieselgel 60, 230–400 mesh, Art. 9385) under a pressure of 0.4 atm (flash chromatography). Preparative TLC (PLC) was performed on glass plates precoated with silica gel (Merck, Kieselgel 60 F-254, Art. 5717). Distillations were usually performed with a Buchi kugelrohr apparatus, with the temperatures noted being pot temperatures. THF was dried by distillation over sodium benzophenone ketyl. Methylene dichloride was dried by distillation over phosphorus pentaoxide, dimethylformamide (DMF) by distillation from barium oxide, and dimethyl sulphoxide (DMSO) by distillation over calcium hydride under reduced pressures. Tris-[3-(trifluoromethylhydroxymethylene)-(+)-camphorato]europium(III), Eu(tfc)$_3$, and 9-BBN were purchased from Aldrich.

2-(2-*Iodoethyl*)-2-*methyl*-1,3-*dioxolane* **7**.[22]—Ethyl acetoacetate (43 g, 0.33 mol) was mixed with ethylene glycol (215 g) and toluene-*p*-sulphonic acid (2 g) (PTSA) in benzene (400 cm^3) and the mixture was refluxed for 24 h with continuous removal of water. The mixture was cooled to room temperature, washed with saturated aq. sodium hydrogen carbonate, and dried over anhydrous sodium sulphate. Removal of solvents under reduced pressure afforded ethyl (2-methyl-1,3-dioxolan-2-yl)ethanoate (40 g, 70%), found to be essentially pure by ^{1}H NMR spectroscopy: 4.12 (2 H, q, *J* 7.1), 3.94 (4 H, s), 2.63 (2 H, s), 1.47 (3 H, s) and 1.23 (3 H, t, *J* 7.1).

This crude product (17.4 g, 0.1 mol) was dissolved in dry diethyl ether (30 cm^3) and added dropwise to a cold (0 °C) mixture of lithium aluminium hydride (5.7 g, 0.15 mol) in dry diethyl ether (150 cm^3). The mixture was refluxed for 2 h, cooled to room temperature, quenched with ethyl acetate and then with water, and dried over magnesium sulphate. Removal of solvent under reduced pressure followed by Kugelrohr distillation (90–100 °C/0.1 mmHg) afforded 2-(2-methyl-1,3-dioxolan-2-yl)ethanol (12 g, 91%), found to be pure by ^{1}H NMR spectroscopy: 3.93 (4 H, s), 3.70 (2 H, q, *J* 5.6), 2.88 (1 H, t, *J* 5.6), 1.89 (2 H, t, *J* 5.6 and 1.31 (3 H, s).

The above described alcohol (11.9 g, 0.09 mol) was dissolved in pyridine (70 cm^3), the solution was cooled to 0 °C and mixed with toluene-*p*-sulphonyl chloride (22.33 g, 0.117 mol). The mixture was stirred for 4 h, quenched with ice-water, and extracted with chloroform. The extract was washed successively with aq. copper sulphate and water, and dried over sodium sulphate. Removal of solvent under reduced pressure afforded 2-(2-methyl-1,3-dioxolan-2-yl)ethyl tosate (25.89 g, 99%), found to be pure by ^{1}H NMR spectroscopy: 7.68 (2 H, d, *J* 8.0), 7.25 (2 H, d, *J* 8.0), 4.04 (2 H, t, *J* 7.5), 3.78 (4 H, m), 2.34 (3 H, s), 1.93 (2 H, t, *J* 7.5) and 1.17 (3 H, s).

This tosate (25.8 g, 0.09 mol), sodium iodide (20.25 g, 0.135 mol), and $NaHCO_3$ (11.34 g, 0.135 mol) were mixed in dry acetone (200 cm^3) and heated at 50 °C for 24 h. Solvent was removed under reduced pressure and the residue was worked up with water and chloroform. The organic layer was washed successively with 10% aq. sodium thiosulphate and water, then dried over sodium sulphate, and solvent was removed to produce the iodide **7**[22] (18.9 g, 87%) in the form of an oil. This compound was used without further purification. ^{1}H NMR: 3.91 (4 H, m), 3.14 (2 H, dd, *J* 8.0, 9.0), 2.26 (2 H, dd, *J* 8.0, 9.0) and 1.27 (3 H s).

Methyl 3-*Oxohept*-6-*enoate* **8**.[29]—Synthesis was carried out according to the reported preparation of the corresponding ethyl ester.[13] A solution of hex-5-en-2-one (29.4 g, 0.3 mol) in dry benzene (200 cm^3) was added dropwise during 4 h to a refluxing mixture of dimethyl carbonate (50.6 cm^3, 0.6 mol) and sodium hydride (43.2 g of 50% dispersion in mineral oil, 0.9 mol) in dry benzene (300 cm^3). The reaction mixture was refluxed for an additional 30 min and then cooled to 0 °C. Hydrochloric acid (3 mol dm^{-3}; 300 cm^3, ice cooled) was slowly added to the continuously stirred mixture. The organic layer was separated and the aq. phase was extracted twice with CH_2Cl_2. The combined extract was washed with water to remove traces of acid, then dried over sodium sulphate, and the solvent was removed under reduced pressure. Kugelrohr distillation of the residue (90–100 °C/0.1 mmHg) afforded keto ester **8** (40 g, 85%),

found (by NMR and GCMS) to contain approximately 10% of an isomeric product, methyl 2-acetylpent-4-enoate; ^{1}H NMR: 5.90–5.60 (1 H, m), 4.67 (2 H, dd, *J* 17.0, 9.7), 3.69 (3 H, s), 3.42 (2 H, s), 2.61 (2 H, t, *J* 7.2) and 2.30 (2 H, q, *J* 7.0); MS: 156 (M^+, 7%), 138 (3), 124 (8), 101 (36), 96 (9), 83 (18), 82 (72), 69 (45), 59 (30), 55 (100) and 54 (52); HRMS: (Found: M^+, 156.0797. Calc. for $C_8H_{12}O_3$: M, 156.0808).

Dec-9-ene-2,6-dione **9**.[13]—Compounds **7** (17.7 g, 73 mmol) and **8** (11.4 g, 73 mmol) were mixed with K_2CO_3 (20.18 g, 146 mmol) in acetone (150 cm^3)–DMF (7 cm^3) and the mixture was refluxed for 24 h. Acetone was removed under reduced pressure and the residue was worked up with water and CH_2Cl_2 and purified on a short silica gel column to afford methyl 2-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-3-oxohept-6-enoate (14.0 g, 71%) in the form of an oil. ^{1}H NMR: 5.9–5.6 (1 H, m), 4.97 (2 H, dd, *J* 17.0, 9.7), 3.89 (4 H, br s), 3.66 (3 H, s), 3.48 (1 H, t, *J* 7.9), 2.59 (2 H, q, *J* 7.5), 2.29 (2 H, q, *J* 7.0), 1.92 (2 H, m), 1.60 (2 H, dd, *J* 9.5, 5.2) and 1.27 (3 H, s).

This keto ester (10.4 g, 38.5 mmol) was dissolved in a mixture of aq. KOH (3%; 140 cm^3) and MeOH (115 cm^3) and refluxed for 2 h. Methanol was removed under reduced pressure, the residue was acidified with aq. HCl (3 mol dm^{-3}; 100 cm^3) and the mixture was stirred at room temperature for 1 h. Extraction with CH_2Cl_2, removal of solvent, and Kugelrohr distillation (90–100 °C/0.1 mmHg) afforded dione **9** (4.8 g, 74%) in the form of an oil, ^{1}H NMR: 5.9–5.6 (1 H, m), 4.96 (2 H, dd, *J* 17.0, 9.7), 2.5–2.2 (8 H, m), 2.08 (3 H, s) and 1.79 (2 H, m); CIMS: 169.0 (M^+ + H); IR: 2940, 1710, 1640, 1405, 1365, 1160, 1000 and 910.

Enzymatic Reduction of Dec-9-ene-2,6-dione **9**.—Diketone **9** (3 cm^3), 2.79 g, 16.6 mmol) was added to an aq. solution (300 cm^3) containing TBADH (23 mg, 851 units), $NADP^+$ (30 mg, 0.036 mmol), phosphate buffer (0.05 mol dm^{-3}), propan-2-ol (60 cm^3) and 2-mercaptoethanol (56.2 mg). The mixture was gently stirred at 40 °C for 48 h, then mixed with excess of ammonium sulphate and extracted with CH_2Cl_2 to give a mixture of (*S*)-9-hydroxydec-1-en-5-one **10** and starting material **9**. This crude mixture was mixed with acetic anhydride (15 cm^3) and pyridine (15 cm^3) and stirred at 60 °C for 24 h. The mixture was cooled to 0 °C, methanol (20 cm^3) was added, and solvents were removed under reduced pressure. The residue was worked up with water and CH_2Cl_2 and separated by column chromatography [silica gel; ethyl acetate–hexane (1:19)] to give recovered compound **9** (0.73 g, 26%) and (*S*)-(+)-9-acetoxydec-1-en-5-one **11** (2.1 g, 81% yield as calculated on the basis of consumed starting material **9**) (see supplementary material*); ^{1}H NMR of **10**: 5.95–5.65 (1 H, m), 5.15–4.85 (2 H, m), 3.65 (1 H, q, *J* 6.2), 2.60–2.30 (6 H, m), 1.65–1.40 (4 H, m) and 1.16 (3 H, d, *J* 6.2); ^{1}H NMR of **11**: 5.9–5.6 (1 H, m), 5.00 (1 H, dd, *J* 13.0, 1.2), 4.93 (1 H, d, *J* 6.0), 4.85 (1 H, q, *J* 6.5), 2.55–2.20 (6 H, m), 1.99 (3 H, s), 1.75–1.40 (4 H, m) and 1.17 (3 H, d, *J* 6.5); ^{13}C NMR of **11**: 200.1, 171.0, 136.8, 114.9, 70.1, 41.9, 41.5, 34.9, 27.5, 21.0, 19.6 and 19.1; CIMS: 213.1 (M^+ + H); IR: 2920, 1715, 1640, 1375, 1250, 1200 and 910; $[\alpha]_D$ +12.8° (*c* 4.12, $CHCl_3$); for acetate **11** (Found: C, 67.54; H, 9.45. Calc. $C_{12}H_{20}O_3$: C, 67.89; H, 9.50%).

Determination of Relative Rate of TBADH-catalysed Reduction of **9**.—A solution of heptan-2-one (57 mg, 0.5 mmol) and substrate **9** (84 mg, 0.5 mmol) in aq. phosphate buffer (20 cm^3, 50 mmol dm^{-3}) containing propan-2-ol (4 cm^3), TBADH (1.6 mg, 59 units), $NADP^+$ (2.5 mg, 0.003 mmol) and 2-mercaptoethanol (4 mg) was kept at 40 °C. Progress of the reaction was monitored by withdrawal of samples (1 cm^3), work-up with ammonium sulphate and ethyl acetate, followed by GCMS analyses. Reduction of both substrates was found to proceed linearly within the first 4 hours: heptanone was reduced at a rate of 18% h^{-1} and compound **9** at a rate of 9% h^{-1}. Since the relative rate of reduction of heptan-2-one reduction was found earlier[1] to be 0.9, the rate for compound **9** is 0.45.

Racemic Mixture of 9-Acetoxydec-1-en-5-one **11**.—4-Iodobutan-2-ol[30] was acetylated with acetic anhydride and pyridine to give 2-acetoxy-4-iodobutane in excellent yield. The latter (7.5 g, 31 mmol) was mixed with methyl 3-oxohept-6-enoate **8** (4.85 g, 31 mmol) and potassium carbonate (8.75 g, 62 mmol) in acetone (100 cm^3)–DMF (5 cm^3) and the mixture was refluxed for 24 h. It was then concentrated under reduced pressure and worked up with CH_2Cl_2 and water to give the crude alkylation product methyl 2-(3-acetoxybutyl)-3-oxohept-6-enoate (11 g).

This crude product was mixed with NaCl (5.85 g, 0.1 mol), water (3.6 g, 0.2 mol), and DMSO (50 cm^3), and the mixture was refluxed for 12 h and then worked up with water and diethyl ether. Solvent was removed under reduced pressure and the residue was purified by column chromatography [silica gel; ethyl acetate–hexane (1:19)] to give racemic acetate **11** (3.29 g, 50%). This product was employed as a reference compound in the NMR experiments using Eu chiral shift reagent (see Fig. 3). Racemic compound **11** served as a starting material for the synthesis of racemic zearalenone dimethyl ether **19** using the same procedures described below for the synthesis of the optically active compound.

4-[2-(4-*Acetoxypentyl*)-1,3-*dioxolan*-2-*yl*]*but*-1-*ene* **12**.—Compound **11** (1.6 g, 7.5 mmol) was mixed with ethylene glycol (250 mmol) and pyridinium toluene-*p*-sulphonate (PPTS) (160 mg, 0.75 mmol) in benzene (100 cm^3) and the mixture was refluxed for 24 h with continuous removal of water. The mixture was cooled to room temperature, and washed with saturated aq. $NaHCO_3$. Solvent was removed under reduced pressure and the residue was purified by column chromatography to give ketal **12** (1.74 g, 92% (see supplementary material); $[\alpha]_D$ +12.2° (*c* 2.04, $CHCl_3$); ^{1}H NMR: 5.95–5.65 (1 H, m), 5.05–4.75 (3 H, m), 3.92 (4 H, s), 2.20–1.90 (2 H, m), 1.95 (3 H, s), 1.75–1.30 (8 H, m) and 1.10 (3 H, d, *J* 6.3); ^{13}C NMR: 170.4, 138.3, 114.1, 111.0, 70.6, 64.8, 36.8, 36.1, 35.8, 27.9, 21.1, 19.7 and 19.5; IR: 2940, 2880, 1720, 1640, 1450, 1375, 1255, 1195, 1130, 950 and 910.

5-[2-(*But*-3-*enyl*)-1,3-*dioxolan*-2-*yl*]*pentan*-2-*ol* **13**.—Compound **12** (1.7 g, 6.75 mmol) was dissolved in methanol (10 cm^3) and the solution was treated with aq. KOH (3 mol dm^{-3}; 15 cm^3) for 3 h. Solvent was removed under reduced pressure and the residue was worked up with water and CH_2Cl_2 to give the alcohol **13** (1.40 g, 97%) as an oil (see supplementary material); CIMS: 215.2 (M^+ + H); $[\alpha]_D$ +7.01° (*c* 2.18, CH_2Cl_2); ^{1}H NMR: 5.90–5.65 (1 H, m), 4.96 (2 H, dd, *J* 18.0, 11.1), 3.92 (4 H, s), 3.78 (1 H, br q, *J* 6.2), 2.10 (2 H, br q, *J* 6.8), 1.75–1.25 (8 H, m) and 1.17 (3 H, d, *J* 6.2); ^{13}C NMR: 138.3, 114.1, 111.2, 67.4, 64.7, 39.1, 36.9, 36.0, 27.9, 23.2 and 19.7; IR: 3460, 2930, 2880, 1640, 1450, 1380, 1150, 1075 and 910 (Found: C, 67.6; H, 10.4. Calc. for $C_{12}H_{22}O_3$: C, 67.25; H, 10.34%).

1-*Methyl*-5-*oxonon*-8-*enyl* 2,4-*Dimethoxy*-6-(*phenylthiomethyl*)*benzoate* **15**.—A solution of acid **14**[24,25] (1.07 g, 3.5 mmol), the alcohol **13** (0.753 g, 3.5 mmol), 2-chloro-*N*-methyl pyridinium iodide (1.13 g, 4.2 mmol), and tributylamine (1.56 g, 8.4 mmol) in methylene dichloride (35 cm^3) was refluxed overnight. Solvent was removed under reduced pressure and the residue was passed through a short silica gel bed to afford ester

* *Supplementary material.* ^{1}H and ^{13}C NMR spectra of compounds **11**–**13**, **15**, **16a**–**c**, and **17**–**19** have been deposited at the British Library Document Supply Centre, as Supplementary Publication SUP 56854 (21 pp). See section 4.4 of Instructions for Authors, January issue.

15 (1.56 g, 89%) (see supplementary material); CIMS: 501.2 ($M^+ + H$); $[\alpha]_D$ +5.36° (*c* 1.0, CH_2Cl_2); ^1H NMR: 7.35–7.05 (5 H, m), 6.33 (2 H, s), 5.90–5.65 (1 H, m), 5.14 (1 H, m), 4.94 (2 H, dd, *J* 18.0, 11.0), 4.15 (1 H, d, *J* 13.0), 4.07 (1 H, d, *J* 13.0), 3.89 (4 H, s), 3.77 (3 H, s), 3.67 (3 H, s), 2.36 (1 H, m), 2.06 (2 H, m), 1.70–1.20 (7 H, m) and 1.31 (3 H, d, *J* 6.6); ^{13}C NMR: 167.0, 161.1, 158.4, 138.4, 137.8, 135.5, 130.0, 128.7, 126.3, 114.0, 111.1, 106.0, 97.8, 71.7, 64.8, 55.7, 55.2, 53.8, 37.0, 36.7, 36.2, 36.0, 27.9, 19.9 and 19.6; IR: 2940, 2880, 2840, 1710, 1605, 1585, 1460, 1330, 1280, 1160, 1100 and 910 (Found: C, 66.95; H, 7.15; S, 6.15. Calc. for $C_{28}H_{36}O_6S$: C, 67.17; H, 7.25; S, 6.39%).

4-[2-(4-*Hydroxybutyl*)-1,3-*dioxolan*-2-*yl*]-1-*methylbutyl* 2,4-*Dimethoxy*-6-(*phenylthiomethyl*)*benzoate* **16a**.—9-BBN (12.4 cm^3 of 0.5 mol dm^{-3} solution in THF) was added dropwise at room temperature to a solution of ester **15** (1.55 g, 3.1 mmol) in dry THF (12 cm^3) and the mixture was stirred at 40 °C for 30 min before being cooled to 0 °C, whereupon methanol (2 cm^3) and aq. NaOH (3 mol dm^{-3}; 5.2 cm^3) were added, followed by dropwise addition of hydrogen peroxide (30%; 5.2 cm^3). The mixture was stirred at 60 °C for 1 h, then cooled to room temperature, brine was added, and the organic layer was separated. The aq. phase was extracted with THF, the combined extracts were dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The residue (3.2 g) was separated from cyclooctanediol by column chromatography [silica gel; hexane-ethyl acetate (2:3)] to give the alcohol **16a** (1.55 g, 96%), found to be pure by NMR spectroscopy (see supplementary material); CIMS: 457.2 ($M^+ + H - CH_2CH_2O$); $[\alpha]_D$ +10.1° (*c* 1.4, CH_2Cl_2); ^1H NMR: 7.30–7.05 (5 H, m), 6.28 (2 H, s), 5.08 (1 H, m), 4.06 (1 H, d, *J* 13.9), 4.02 (1 H, d, *J* 13.9), 3.82 (4 H, s), 3.72 (3 H, s), 3.62 (3 H, s), 3.52 (2 H, t, *J* 6.3), 1.70–1.20 (12 H, m) and 1.26 (3 H, d, *J* 6.3); ^{13}C NMR: 166.9 160.8, 158.0, 137.4, 135.6, 129.7, 128.4, 126.1, 116.1, 111.1, 105.8, 97.4, 71.5, 64.5, 61.9, 55.4, 54.9, 42.0, 36.5, 36.3, 35.7, 32.4, 19.6 and 19.3; IR: 3480, 2940, 2880, 2840, 1705, 1605, 1585, 1460, 1330, 1280, 1160, 1080, 940, 910 and 835.

1-*Methyl*-4-{2-[4-(p-*tolylsulphonyloxy*)*butyl*]-1,3-*dioxolan*-2-*yl*}*butyl* 2,4-*Dimethoxy*-6-(*phenylthiomethyl*)*benzoate* **16b**.—A solution of toluene-*p*-sulphonyl chloride (660 mg, 3.6 mmol) in CH_2Cl_2 (10 cm^3) was added to a solution of the alcohol **16a** (1.48 g, 2.8 mmol) in pyridine (3 cm^3)–triethylamine (1 cm^3) at 0 °C and the mixture was stirred at the same temperature for 2 h, before being worked up with ice–water and CH_2Cl_2; solvent was removed and the residue was purified by column chromatography [silica gel; hexane–ethyl acetate (4:1)] to give tosate **16b** (1.77 g, 92%) (see supplementary material); CIMS: 457.1 ($M^+ + H - TsOH - CH_2CH_2O$); $[\alpha]_D$ +4.54° (*c* 1.29, CH_2Cl_2); ^1H NMR: 7.75 (2 H, d, *J* 8.2), 7.35–7.05 (7 H, m), 6.32 (2 H, s), 5.15 (1 H, m), 4.14 (1 H, d, *J* 14.4), 4.06 (1 H, d, *J* 14.4), 3.96 (2 H, t, *J* 6.4), 3.84 (4 H, s), 3.76 (3 H, s), 3.66 (3 H, s), 2.41 (3 H, s), 1.80–1.20 (12 H, m) and 1.30 (3 H, d, *J* 6.4); ^{13}C NMR: 167.2, 161.2, 158.5, 144.6, 136.9, 136.2, 133.3, 130.2, 129.8, 128.8, 127.6, 126.4, 116.7, 111.2, 106.2, 98.0, 71.8, 70.5, 64.9, 55.9, 55.3, 37.0, 36.9, 36.4, 36.1, 29.0, 21.5, 20.0 and 19.7; IR: 2930, 1705, 1605, 1460, 1355, 1300, 1280, 1160, 1098, 935 and 835.

4-[2-(4-*Iodobutyl*)-1,3-*dioxolan*-2-*yl*]-1-*methylbutyl* 2,4-*Dimethoxy*-6-(*phenylthiomethyl*)*benzoate* **16c**.—Compound **16b** (1.73 g, 2.57 mmol) was mixed with NaI (580 mg, 3.86 mmol) and $NaHCO_3$ (0.325 g, 3.86 mmol) in dry acetone (15 cm^3) and the mixture was stirred at 50 °C for 16 h. Acetone was removed under reduced pressure and the residue was worked up with water and CH_2Cl_2. The organic phase was washed successively with aq. sodium thiosulphate and water, and dried over Na_2SO_4. Removal of the solvent under reduced pressure afforded the iodide **16c** (1.52 g, 94%), found to be pure by NMR spectroscopy (see supplementary material); CIMS: (629.1, M + H); $[\alpha]_D$ +5.23° (*c* 2.4, CH_2Cl_2); ^1H NMR: 7.40–7.05 (5 H, m), 6.33 (2 H, s), 5.16 (1 H, m), 4.18 (1 H, d, *J* 13.3), 4.05 (1 H, d, *J* 13.3), 3.88 (4 H, s), 3.78 (3 H, s), 3.67 (3 H, s), 3.13 (2 H, t, *J* 6.9), 1.90–1.35 (12 H, m) and 1.31 (3 H, d, *J* 6.3); ^{13}C NMR: 167.2, 161.1, 158.3, 137.7, 136.0, 130.0, 128.7, 126.4, 116.5, 111.2, 105.9, 97.8, 71.6, 64.8, 55.8, 55.2, 36.8, 36.7, 36.0, 35.8, 33.5, 24.7, 19.9, 19.7 and 6.7; IR: 2970, 2940, 2920, 1705, 1605, 1585, 1460, 1330, 1270 and 1165.

Cyclization of the Iodide **16c** *to Compound* **17**.—A solution of the iodide **16c** (1.5 g, 2.39 mmol) in THF (48 cm^3) was slowly added during 2 h to a hot (70 °C) solution of sodium hexamethyldisilazide [9.6 cm^3 of 1 mol dm^{-3} solution in THF (123 cm^3)]. The mixture was stirred at 70 °C for an additional 30 min, then was cooled to room temperature, and the solvent was removed under reduced pressure. The residue was treated with saturated aq. ammonium chloride and extracted with ethyl acetate. Removal of the solvents, followed by column chromatography [silica gel; hexane–ethyl acetate (85:15)] afforded cyclized compound **17** (1.02 g, 85%), found to be pure by NMR spectroscopy (see supplementary material); CIMS: 501.2 (M + H); $[\alpha]_D$ −14.1° (*c* 1.0, CH_2Cl_2); ^1H NMR: 7.40–7.00 (5 H, m), 6.63 (1 H, d, *J* 2.2), 6.28 (1 H, d, *J* 2.2), 5.30 (1 H, m), 4.46 (1 H, dd, *J* 10.4, 4.9), 3.84 (4 H, s), 3.74 (6 H, s), 2.10–1.05 (14 H, m) and 1.27 (3 H, d, *J* 6.2); ^{13}C NMR: 167.3, 161.2, 157.4, 142.8, 135.1, 130.9, 128.4, 126.4, 117.1, 111.7, 103.5, 97.4, 70.2, 64.1, 55.8, 55.2, 48.4, 36.5, 35.2, 34.6, 34.0, 24.2, 21.1, 20.9 and 20.6; IR: 2940, 2875, 2840, 1705, 1605, 1585, 1480, 1455, 1435, 1420, 1380, 1335, 1320, 1290, 1155, 1135, 1095, 1065, 1045, 950, 910 and 835.

Zearalenone Dimethyl Ether Ethylene Glycol **18**.—A solution of compound **17** (1.0 g, 2 mmol) in CH_2Cl_2 (50 cm^3) was cooled to 0 °C, a solution of 80% MCPBA (431 mg, 2 mmol) in CH_2Cl_2 (20 cm^3) was added dropwise during 5 min, and the mixture was stirred at the same temperature for an additional 15 min before being washed successively with aq. sodium hydrogen carbonate and water, and the solvent was removed under reduced pressure to give the corresponding sulphoxide (1.02 g).

This crude product was dissolved in toluene (20 cm^3) and the solution was refluxed for 1 h, then cooled to room temperature, and the product was purified by column chromatography [silica gel; hexane–ethyl acetate (17:3)] to give the olefin **18**[12,13,15a] (590 mg, 76%), found to be pure by NMR spectroscopy (see supplementary material); ^1H NMR: 6.56 (1 H, d, *J* 1.5), 6.50–6.15 (3 H, m), 5.30–5.10 (1 H, m), 3.87 (4 H, s), 3.78 (3 H, s), 3.76 (3 H, s), 2.50–1.35 (12 H, m) and 1.31 (3 H, d, *J* 6.2); ^{13}C NMR: 166.2, 161.0, 157.4, 136.5, 132.9, 132.8, 126.0, 116.9, 111.7, 100.9, 97.4, 70.7, 64.2, 64.1, 55.9, 55.3, 35.2, 34.8, 33.0, 30.1, 21.1, 20.2 and 19.5; CIMS (391.1, M + H); $[\alpha]_D$ +69.6° (*c*, 0.73, CH_2Cl_2); IR: 2935, 2880, 2840, 1710, 1600, 1580, 1455, 1420, 1375, 1345, 1265, 1160, 1135, 1100, 1075, 1040, 965, 950, 910, 870 and 835.

Zearalenone Dimethyl Ether **19**.—Compound **18** was treated with aq. acetone and PTSA, as reported[15a] to give compound **19**[12,13,15a,18] (505 mg, 97%) (see supplementary material), m.p. 107–109 °C (lit.,[12] 107–110 °C); CIMS (347.1, M + H); $[\alpha]_D$ +50.08° (*c* 1.25, CH_2Cl_2), +25.0° (*c* 0.44, MeOH) [lit.;[12] +25.0° (MeOH)]; ^{13}C NMR: 211.1, 167.3, 161.1, 157.5, 136.5, 133.0, 128.7, 116.1, 101.1, 97.5, 70.9, 55.7, 55.2, 43.8, 37.3, 34.9, 31.0, 21.5, 21.1 and 19.8; IR: 2930, 2840, 1710, 1600, 1575, 1455, 1350, 1265, 1155, 1100, 970, 910 and 835.

Acknowledgements

We thank the United States–Israel Binational Science Foundation and the joint research program of the National

Council for Research and Development, Israel, and the GSF, Germany for their generous support.

References

1 (*a*) E. Keinan, E. K. Hafeli, K. K. Seth and R. Lamed, *J. Am. Chem. Soc.*, 1986, **108**, 162; (*b*) R. Lamed, E. Keinan and J. G. Zeikus, *Enzyme Microb. Technol.*, 1981, **3**, 144.
2 E. Keinan, K. K. Seth and R. Lamed, *J. Am. Chem. Soc.*, 1986, **108**, 3474.
3 E. Keinan, K. K. Seth, R. Lamed, R. Ghirlando and S. P. Singh, *Biocatalysis*, 1990, **3**, 57.
4 S. Hanessian, *Total Synthesis of Natural Products: the 'Chiron' Approach*, Pergamon, Oxford, 1983.
5 S. Masamune, G. S. Bates and J. W. Corcoran, *Angew. Chem., Int. Ed. Engl.*, 1977, **16**, 585; K. C. Nicolaou, *Tetrahedron*, 1977, **33**, 683; T. G. Back, *Tetrahedron*, 1977, **33**, 3041.
6 E. Keinan, S. C. Sinha and S. P. Singh, *Tetrahedron*, 1991, **47**, 4631.
7 J. H. Borden, M. G. Dolinski, L. Chong, V. G. Verigen, H. D. Pierce, Jr., and A. C. Oehlschlager, *Can. Entomol.*, 1979, **111**, 681; J. W. Wong, V. G. Verigin, A. C. Oehlschlager, J. H. Borden, H. D. Pierce, Jr., A. M. Pierce and L. Chong, *J. Chem. Ecol.*, 1983, **9**, 451; A. M. Pierce, H. D. Pierce, Jr., A. C. Oehlschlager and J. H. Borden, *J. Agric. Food Chem.*, 1985, **33**, 848.
8 J. G. Millar, H. D. Pierce, Jr., A. M. Pierce, A. C. Oehlschlager, J. H. Borden and A. V. Barak, *J. Chem. Ecol.*, 1985, **11**, 1053; J. G. Millar, A. C. Oehlschlager and J. W. Wong, *J. Org. Chem.*, 1983, **48**, 4404.
9 E. Keinan, K. K. Seth, M. Sahai and E. Berman, *J. Org. Chem.*, 1986, **51**, 4288.
10 M. T. Shipchandler, *Heterocycles*, 1973, **3**, 471; V. Betina, *Zearalenone and its Derivatives*, in *Mycotoxins. Chemical. Biological and Environmental Aspects*, Elsevier, 1989.
11 M. Stob, R. S. Baldwin, J. Tuite, F. N. Andrews and K. G. Gillette, *Nature*, 1962, **196**, 1318; C. J. Mirocha, C. M. Christensen and G. H. Nelson, *Appl. Microbiol.*, 1967, **15**, 497; W. H. Urry, H. L. Wehrmeister, E. B. Hodge and P. H. Hidy, *Tetrahedron Lett.*, 1966, 3109.
12 D. Taub, N. N. Girotra, R. D. Hoffsommer, C. H. Kuo, H. L. Slates, S. Weber and N. L. Wendler, *Tetrahedron*, 1968, **24**, 2443.
13 I. Vlattas, I. T. Harrison, L. Tökés, J. H. Fried and A. D. Cross, *J. Org. Chem.*, 1968, **33**, 4176.
14 (*a*) E. J. Corey and K. C. Nicolaou, *J. Am. Chem. Soc.*, 1974, **96**, 5614; (*b*) S. Masamune, S. Kamata and W. Schilling, *J. Am. Chem. Soc.*, 1975, **97**, 3515; (*c*) T. Kaito, S. Masamune and T. Toyoda, *J. Org. Chem.*, 1982, **47**, 1612.
15 (*a*) T. Takahashi, K. Kasuga, M. Takahashi and J. Tsuji, *J. Am. Chem. Soc.*, 1979, **101**, 5072; (*b*) T. Takahashi, N. Toshiharu and J. Tsuji, *Chem. Lett.*, 1980, 369.
16 T. Takahashi, H. Ikeda and J. Tsuji, *Tetrahedron Lett.*, 1981, **22**, 1363; T. Takahashi, T. Nagashima, H. Ikeda and J. Tsuji, *Tetrahedron Lett.*, 1982, **23**, 4361.
17 A. V. Rama Rao, M. N. Deshmukh and G. V. M. Sharma, *Tetrahedron*, 1987, **43**, 779.
18 S. A. Hitchcock and G. Pattenden, *Tetrahedron Lett.*, 1990, **31**, 3641.
19 G. Solladie, M. C. Maestro, A. Rubio, C. Pedregal, M. C. Carreno and J. L. G. Ruano, *J. Org. Chem.*, 1991, **56**, 2317.
20 A. Kalivretenos, J. K. Stille and L. S. Hegedus, *J. Org. Chem.*, 1991, **56**, 2883.
21 K. Mori, *Tetrahedron*, 1989, **45**, 3233.
22 H. Ohta, K. Ozaki and G. Tsuchihashi, *Chem. Lett.*, 1978, 2225; B. M. Trost and R. A. Kunz, *J. Am. Chem. Soc.*, 1975, **97**, 7152.
23 A. P. Krapcho, J. Diamanti, C. Cayen and R. Bingham, *Org. Synth.*, 1973, Coll. Vol. 5, 198.
24 K. Mori and H. Watanabe, *Tetrahedron*, 1986, **42**, 295.
25 A. G. M. Barrett, T. M. Morris and D. H. R. Barton, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2272.
26 F. M. Hauser, R. P. Rhee, S. Prasanna, S. M. Weinreb and J. H. Dodd, *Synthesis*, 1980, 72.
27 T. Mukaiyama, M. Usui, E. Shimada and K. Saigo, *Chem. Lett.*, 1975, 1045.
28 G. Zweifel and H. C. Brown, *Org. React.*, 1963, **13**, 1.
29 S. N. Huckin and L. Weiler, *J. Am. Chem. Soc.*, 1974, 96, 1082.
30 H. Gerlach, K. Oertle and A. Thalmann, *Helv. Chim. Acta*, 1976, **59**, 755.

Paper 1/02795F
Received 11*th June* 1991
Accepted 6*th August* 1991