Syntheses of the Ethyl Esters of the Plant Host-Selective (H-S) Toxins (AF-IIa, AF-IIc and AK-II) Produced by Pathotypes of *Alternaria alternata*

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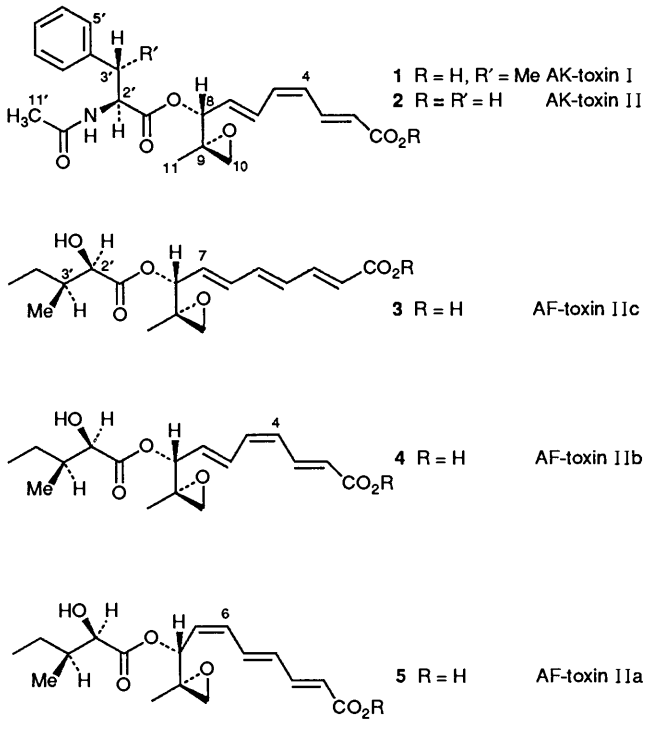
Total syntheses of the ethyl esters of the host-selective (H-S) toxins produced by *Alternaria alternata* (strawberry-type pathogen), AF-IIa and AF-IIc, and by the Japanese pear-type AK-II are reported. The initial synthetic objectives, the 2*E*,4*E*,6*E*, 2*E*,4*Z*,6*E* and 2*E*,4*E*,6*Z* stereoisomers of ethyl 8-hydroxy-9-methyldeca-2,4,6,9-tetraenoate, were attained by the use of acetylene hydrometallation and Pd^0-mediated vinyl halide coupling: for this purpose tin chemistry was superior to the use of zirconium compounds. The tetraene-hydroxy esters were epoxidised selectively at the 9,10-double bond by the Sharpless procedure under conditions of kinetic control (50% reaction), which it was predicted would lead to products of predominantly (8*R*,9*S*)-stereochemistry. Esterification of the epoxides produced from the 2*E*,4*E*,6*E* and 2*E*,4*E*,6*Z* hydroxy esters with synthetic (2*R*,3*S*)-2-(t-butyldimethylsiloxy)-3-methylpentanoic acid, followed by HPLC separation, gave as the major products, stereoisomers which, after deprotection, were characterised as the ethyl esters AF-toxin IIc and AF-toxin IIa. The stereochemical nature of the minor products in the epoxidations is considered. For the synthesis of the AK-II toxin as its ethyl ester, similar esterification with *N*-acetyl-L-phenylalanine was carried out, except that racemisation of the amino acid centre ensued. This led to two major products which were separated and identified as (8*R*,9*S*,2′*S*)- and (8*R*,9*S*,2′*R*)-stereoisomers, the former being identical with the ester of AK-II toxin.

Host-selective (H-S) toxins, produced by the germinating spores of certain fungi, are differentiated from general plant toxins by their high selectivity of action, and by their being the actual initiators of a particular plant disease.[1] There is a complete correspondence between disease susceptibility and toxin selectivity in the host plant and it is possible to turn a morphologically identical, but benign, fungal strain into a virulent pathogen merely by providing it with external H-S toxin. The H-S toxin is produced by a fungus pathogenic only to its hosts, the fungus being completely innocuous to non-hosts which may be very closely related cultivars of the same plant. The apparent single gene control makes these systems of particular interest in molecular biology. In agriculture, the activities of H-S toxins (which are of diverse chemical type) have been disastrous, as in the ruinous episode of 'Victoria blight' in the Victoria strain of oat cultivars during the period around 1946. This was caused by *Helminthosporium victoriae* producing HV-toxin.[1] A similar economic disaster was the devastation of the TMS corn (maize) lines by *Helminthosporium maydis* race T in 1970–1971 (T-toxin).[1]

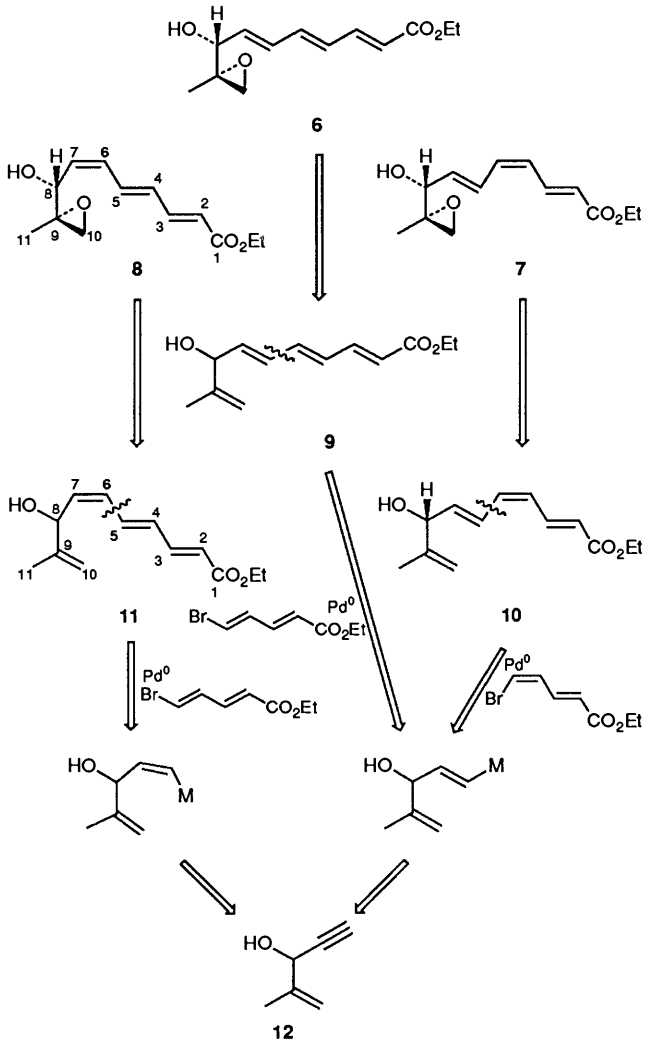
The synthetic work described in this paper relates to the H-S toxin which causes the black-spot disease of Japanese pear, and which is produced by the fungus *Alternaria kikuchiani* Tanaka (later renamed *Alternaria alternata*, Japanese pear pathotype).[2,3] It affects only Nijisseiki cultivars (*Pyrus serotina* Rehder *var.* culta cv. Nijisseiki) and not other cultivars (*e.g.*, *P. serotina* Rehd. *var.* culta cv. Chojuro): originally recognised by Tanaka, it was the first H-S toxin to be described.[4] The chemical nature of the toxins was not known until much later when AK-toxin I (**1**; R = H, R′ = Me) (effective at 5×10^{-9} mol dm^{-3}) and AK-toxin II (**2**; R = R′ = H) (effective at 10^{-7} mol dm^{-3}) were isolated from bulk cultures of the fungus.[5,6] An X-ray single-crystal structure of AK-toxin I [(8*R*,9*S*)-8-(2′*S*,3′*S*)-2′-acetamido-3′-phenylbutyryloxy-9,10-epoxy-9-methyldeca-2*E*,4*Z*,6*E*-trienoic acid] is available.[5] The action of the toxins is to induce rapid loss of potassium ions from the host cell and to produce microscopically visual effects—cell-wall invagination and damage and veinal necrosis.[6] When added to avirulent *A. alternaria* spores, the toxin enables them to invade susceptible plant tissue in exactly the same way as do virulent spores.



Around 1975, a new black-spot disease of strawberry appeared in Japan after the introduction of a newly bred cultivar, Morioka-16. It was again caused by *A. alternaria*, but this time by a strawberry pathotype which was also pathogenic to Japanese pear cultivars of the Nijisseiki type.[7] From a large volume of fungal culture medium it was possible to isolate three groups of toxin. One of these, AF-II, was separated into three toxins, AF-IIa, -IIb and -IIc (proportions 9:1:1); these

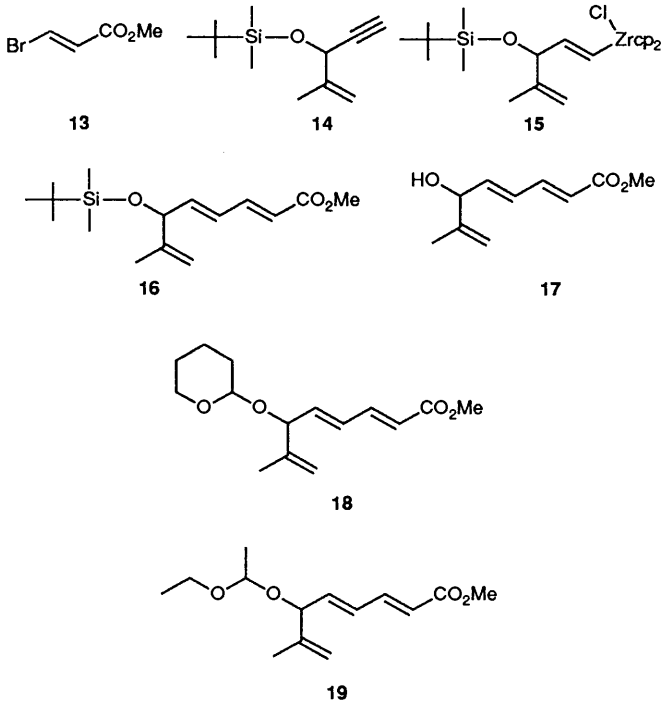
have been identified as compounds **5**; R = H, **4**; R = H and **3**; R = H, respectively.[8,9] These are the 2*E*,4*E*,6*Z*, 2*E*,4*Z*,6*E* and 2*E*,4*E*,6*E* stereoisomers of (8*R*,9*S*)-9,10-epoxy-8-[(2′*R*,3′*S*)-2′-hydroxy-3′-methylpentanoyloxy]-9-methyldecatrienoic acid.*

Our synthetic objectives in the present work were AK-toxin II, AF-toxin IIa and AF-toxin IIc, as their ethyl esters, and Scheme 1 outlines the retrosynthetic plan after disconnection of the acid portion. Primary targets thus become the bisallylic tetraene esters **9**, **10** and **11**, and it was decided to approach them by hydrometallation/palladium(0) chemistry.[10]

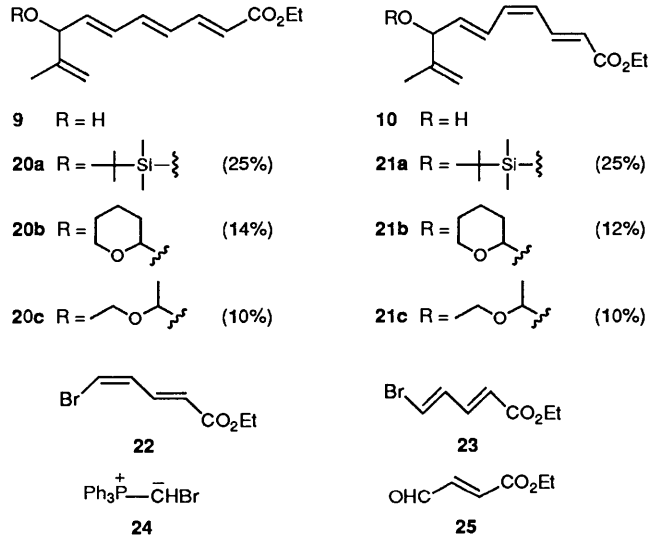


Scheme 1 Retrosynthetic plan for the alcohol fragments

The propargylic alcohol **12**[11] was made in 72% yield, and its hydrozirconation was studied using methyl (*E*)-3-bromopropenoate **13**[12] as a model coupling partner. Hydrozirconation had earlier been used very successfully in our laboratory in connection with the synthesis of geometrically homogeneous polyene isobutylamides, a group of natural insecticides.[13] As expected, hydrozirconation using 2.2 mol equiv. of biscyclopentadienylzirconium chloride hydride [$cp_2Zr(H)Cl$] was unsuccessful because of the free hydroxy group. It was therefore protected as the t-butyldimethylsilyl (TBDMS) ether **14**, formed in 89% yield.[14] Hydrozirconation[15] was now effected smoothly with 1.1 mol equiv. of $cp_2Zr(H)Cl$ in dry benzene and the product **15** was coupled directly with methyl (*E*)-3-bromopropenoate under Pd^0 catalysis.[16] The required *E*,*E*-isomer was obtained pure (56%), its stereochemistry being verified by NMR spectroscopy: there was no evidence that zirconylation had occurred at the terminal olefin of compound **14**. Unfortunately, deprotection of the hydroxy grouping of ester **16** was surprisingly refractory; treatment with 1.0 mol equiv. of tetrabutylammonium fluoride at 23 °C gave only traces of the expected hydroxy ester **17** and no recovered starting material.[17] Other protecting groups were therefore examined.

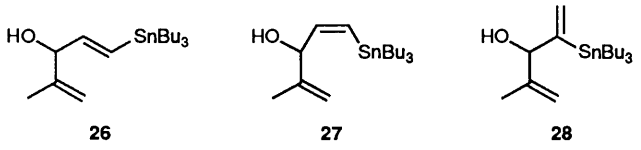


2-Methylpent-1-en-4-yn-3-ol **12** was converted into its tetrahydropyranyl derivative (77%),[18] and into its 1-ethoxyethyl derivative.[19] Each was subjected to hydrozirconation as before, and the resulting vinylzirconocenes were coupled with bromo ester **13** in the presence of Pd^0 catalyst to give the products **18** (42%) and **19** (41%), some premature deprotection being noted. The former was deprotected using pyridinium toluene-p-sulphonate (PPTS), the latter with 0.5 mol dm^{-3} hydrochloric acid in tetrahydrofuran (THF) giving the desired bisallylic alcohol in yields of 90 and 93%, respectively.

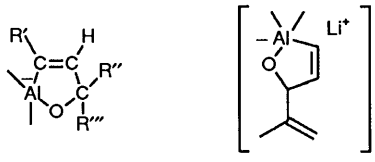


* *Added in proof.* AF-I and AF-III toxins have *E*/*Z* patterns similar to AF-II toxins but with the 2′-hydroxy esterified with 2,3-dihydroxy-3-methylbutyric acid and 2-hydroxy-3-methylbutyric acid respectively.[8b]

For the tetraene esters **10** and **9**, a supply of ethyl 5-bromopenta-2*E*,4*Z*-dienoate **22** and its -2*E*,4*E*-stereoisomer **23** was required. These were obtained by means of a Wittig reaction[20] between the ylide generated from bromomethyl(triphenyl)-phosphonium bromide **24**[21] and potassium-t-butoxide in THF at −78 °C and ethyl 3-formylpropenoate **25**.[22] The Wittig product, formed in 40% yield, proved to be a 60:40 mixture in favour of the 2*E*,4*Z*-stereoisomer, and this, and the 2*E*,4*E*-stereoisomer, were separated by preparative reversed-phase high performance liquid chromatography (HPLC). The 2*E*,4*Z*-stereoisomer can be readily identified by a coupling constant of 15 Hz between 2-H and 3-H and one of 7.3 Hz between 4-H and 5-H.



26 **27** **28**



29 **30**

Pd^0-Catalysed coupling between the hydrozirconated TBDMS ether **15** and the 2*E*,4*Z* and 2*E*,4*E* stereoisomers **22** and **23** each gave the desired protected tetraenes **21a** and **20a** in 25% yield. The tetrahydropyranyl-protected analogue similarly gave compounds **21b** and **20b** in yields of 12 and 14%, respectively. No yield improvement was shown when the ethoxyethyl protecting group was employed, as compounds **21c** and **20c** were formed in yields of only 10%. Attempts at deprotection were also disappointing. Treatment of t-butyldimethylsilyl derivatives **20a** and **21a** variously with tetrabutylammonium fluoride, aq. HF, and boron trifluoride–diethyl ether in chloroform all failed to give the desired alcohols. Similarly, treatment of compounds **20b**, **21b**, **20c** and **21c** with mildly acidic reagents produced complex mixtures of products. Unsatisfactory yields in the coupling, and the difficulties in deprotection, thus made a move away from the use of zirconocenes imperative. Our attention was turned to hydrostannation.

Hydrostannation of alkynols in the presence of azoisobutyronitrile (AIBN) has been achieved without difficulty[23,24] and effort in the literature has been directed to establishing conditions which would favour production of the two stereoisomers:[25,26] it is accepted that under radical conditions the (*Z*)-β-adduct is kinetically favoured and this, on isomerisation, gives the (*E*)-β-adduct. Modelling our conditions on those of Jung and Light,[23] 2-methylpent-1-en-4-yn-3-ol **12** was treated neat with 1.3 mol equiv. of tributyltin hydride in the presence of catalytic amount of AIBN and heated under nitrogen for 2 h at 80 °C. Column chromatography gave a pure sample of the desired pure (*E*)-vinylstannane **26** (53%), together with a 1:1 mixture of the (*Z*)-vinylstannane **27** and the α-adduct **28** in a yield of 30%. Since separation of the mixture proved difficult another method was used for the pure (*Z*)-stereoisomer.

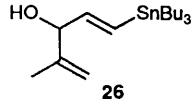
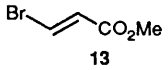
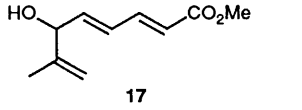
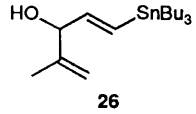
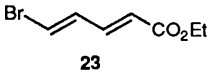
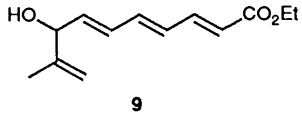
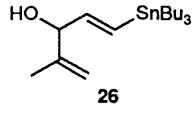
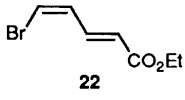
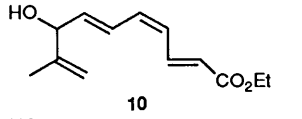
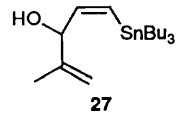
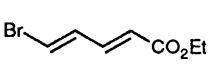
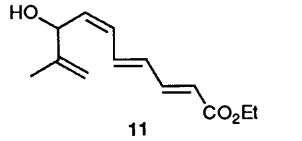
Corey and Echrich[27] have shown that alk-1-yn-3-ols can be hydroaluminated with the formation of a cyclic alkenylaluminate **29**:[28] transmetallation using the electrophilic tributyltin triflate (trifluoromethanesulphonate) then leads to the (*Z*)-vinylstannane in a stereospecific manner. Applied to 2-methylpent-1-en-4-yn-3-ol **12**, treatment with lithium aluminium hydride (0.5 mol) in tetrahydrofuran (THF) for 23 h at 0–5 °C gave a suspension of what is presumed to be compound **30**. After cooling to −78 °C, the mixture was treated with a solution of tributyltin triflate (0.2 mol) in diethyl ether and stirred for 4.5 h. Quenching with ammonia gas followed by aq. methanol gave the (*Z*)-vinylstannane **27**, which was purified chromatographically (>98% pure as judged by ^{1}H NMR spectroscopy) (80% yield).

The stannanes obtained not only withstood chromatography, but could be stored at room temperature for prolonged periods.

We were now in a position to examine the palladium-catalysed coupling of the *E* and *Z* vinylstannanes with the 2*E*,4*E* and 2*E*,4*Z* bromo esters **23** and **22**, and we adopted the procedures described by Stille and Groh.[29] It was observed in

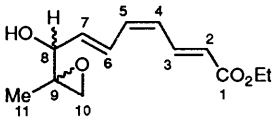
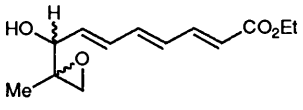
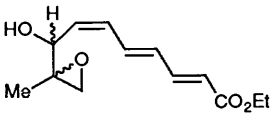
Table 1 Palladium-catalysed stannene–vinyl halide couplings, forming conjugated systems

$$RX + R'SnBu_3 \xrightarrow[DMF,\ room\ temp.]{Pd^0} R\text{-}R' + XSnBu_3$$

	Vinyltin	Vinyl halide	Catalyst[a]	Coupled product	Yield (%)
1	 **26**	 **13**	A	 **17**	81
2	 **26**	 **23**	A B	 **9**	72 65
3	 **26**	 **22**	A B	 **10**	70 50
4	 **27**	 **23**	A B	 **11**	No reaction 60

[a] A $Pd(Ph_3P)_2Cl_2$. B $(MeCN)_2PdCl_2$.

Table 2 Products from a Sharpless epoxidation under kinetic control. (Yields are based on 50% conversion.)

Bisallylic alcohol	Epoxy alcohol	Yield (%)	$[\alpha]_D^{23}$(EtOH)
10		67	+72.0° (*c* 0.54)
9		58	+51.1° (*c* 0.66)
11		63	+13.6° (*c* 0.85)

this work that the use of bisacetonitriledichloropalladium in the weakly co-ordinating solvent dimethylformamide (DMF) produced the most active catalyst and gave high yields of coupled products often spontaneously at room temperature. Bis(triphenylphosphine)dichloropalladium in DMF, though somewhat less active, also gave good yields at ambient temperature. The results of couplings using both of these catalysts are shown in Table 1.

Both $(Ph_3P)_2PdCl_2$ and $(MeCN)_2PdCl_2$[30,31] were effective catalysts for the all-*E*-tetraene ester **9** and the 2*E*,4*Z*,6*E*-ester **10**, though higher yields were obtained with $(Ph_3P)_2PdCl_2$. In the case of the 2*E*,4*E*,6*Z*-tetraenoate **11** the phosphine catalyst failed to effect coupling even after 24 h, though the more active $(MeCN)_2PdCl_2$ effected the transformation in 60% yield. Chromatography of the 2*E*,4*E*,6*Z*-tetraenoate on alumina caused it to stereoisomerise to the crystalline all-*E* compound **9**, m.p. 56–57 °C, but the use of silica gave the desired pure isomer. The stereochemistry and purity of the three tetraenes was validated from their ^1H and ^{13}C NMR spectra (see Experimental section).

Preliminary experiments using the model triene ester **17** showed that epoxidation of the vinyl olefin proceeded strongly preferentially, relative to the conjugated diene system. With this in mind, our strategy was to insert the epoxide into our three synthetic tetraenes using the high enantiofacial selectivity of the Sharpless epoxidation system,[32–36] whilst at the same time taking advantage of the attainable kinetic resolution shown by the later work of the Sharpless group. Whilst no exact parallel was found in the literature, sufficient guidance was present to suggest that the route shown in Scheme 2 might be followed.[35–39] Use of diisopropyl D-(−)-tartrate [(−)-DIPT] in the system and termination of the reaction after only 50% completion would be expected to afford the 8*R*,9*S*-epoxy alcohol as the major product from the fast reaction. Apart from minor amounts of the 8*R*,9*R*-impurity, it was thought that there might be contaminating products from the slow reaction, particularly the 8*S*,9*S*-product. The enantiofacial selectivity for the slow reaction is less than that for the fast, so there might be additional 8*S*,9*R* contamination.

Our standard epoxidation procedure was modelled on the recently modified procedure of Sharpless and his colleagues.[35] A solution of the bisallylic alcohol and 15 mol% of (−)-DIPT was treated at room temperature with activated, powdered 3 Å molecular sieve (30% weight based on the allylic alcohol). The mixture was stirred under argon and cooled to −20 °C, at which point 10 mol% of titanium(IV) isopropoxide was added. The mixture was stirred at −20 °C for 30 min to age the catalyst and was then treated with t-butyl hydroperoxide in 'isooctane' (2,2,4-trimethylpentane) (6 molar, dried with freshly activated 3 Å molecular sieve for 30 min prior to addition). The reaction was monitored by HPLC and quenched with an aq. iron(II) sulphate–citric acid mixture after *ca.* 50% conversion. This required 5–20 h. Extractive isolation with diethyl ether, followed by dry column chromatography, furnished optically active 9,10-epoxy-8-hydroxy-9-methyltrienoate as well as unchanged bisallylic alcohol and any minor products from possible side-reactions. Table 2 gives the optical rotations of the 9,10-epoxy alcohols thus prepared.

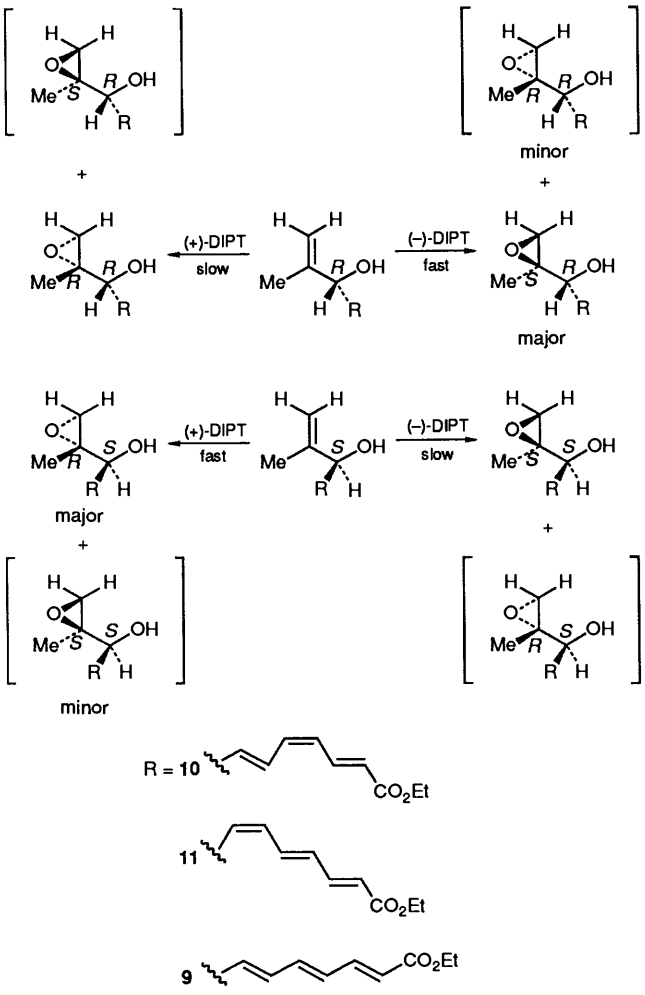
Spectral data (IR, UV, ^1H and ^{13}C NMR and MS) confirmed the structures of the 9,10-epoxydecatrienes and showed that the respective geometries of the conjugated trienes remained intact. Although unequivocal assignment of diastereoisomeric purities could not be made at this stage, the ^1H NMR spectra all showed a pair of doublets between δ 2.6–3.0 (*J* 4.6–4.7 Hz) which is believed to be diagnostic for the 8*R*,9*S*/8*S*,9*R* configuration in such epoxy alcohols, the AB-signals being due to the geminal protons of the epoxide moiety.[40,41]

It seemed possible that yields of epoxide might have been diminished by subsequent titanium tetraisopropoxide-induced opening of the epoxide **31** to give diol **32** but such products were not isolated in sufficient quantity for their characterisation. However, particularly in the case of the all-*E*-tetraene bisallylic alcohol **9**, another competitive process was observed leading to the isomeric epoxide **33**. Although characterised, the stereochemistry of the latter product was not further investigated.

The diastereoisomeric purity in our epoxy alcohol products, which were not easily separable by HPLC, might have been investigated by esterification with Mosher's ester, HPLC on chiral phases, and other methods, but it was decided instead to esterify directly with the optically active acid **34**. This should allow direct separation of the natural diastereoisomers of the AF-toxins (in protected form) and the acid **34** was therefore synthesized using essentially the method outlined by Irie and co-workers.[9,40]

L-Isoleucine **35** was diazotised and converted into the acetoxy derivative **36** (61%) with retention of configuration. The acid was then protected as its benzyl ester and the 2-acetoxy group was preferentially hydrolysed to give benzyl (2*S*,3*S*)-2-hydroxy-3-methylpentanoate **37**. Inversion of configuration was carried out by Mitsunobu esterification.[42] Stirring of the mixture overnight with triphenylphosphine, diethyl azodicarboxylate (DEAD), and formic acid gave benzyl (2*R*,3*S*)-2-formyloxy-3-methylpentanoate **38** which was deformylated in 97% yield. t-Butyldimethylsilylation was achieved in the standard manner, and, finally, hydrogenolysis with palladium on carbon in ethyl acetate gave (2*R*,3*S*)-2-(t-butyldimethylsiloxy)-3-methylpentanoic acid **34** (90%); $[\alpha]_D^{23}$ +18.5° (*c* 1.0, MeOH).

Esterification of the epoxy alcohol mixtures formed by the Sharpless procedure from the 2*E*,4*E*,6*E* and 2*E*,4*E*,6*Z* esters **9** and **11**, using the protected chiral acid **34**, dicyclohexylcarbodiimide (DCC) and 4-pyrrolidinopyridine,[43,44] gave 2′*R*,3′*S* esters in 90 and 85% yields, respectively. The latter were now examined by HPLC and were found to be binary mixtures in the ratio 75:25 and 66:34, respectively, which were carefully separated by HPLC on silica, eluting with ethyl acetate–hexane (1:5). Examination by 400 MHz ^1H NMR and ^{13}C NMR spectroscopy confirmed that the major products were in each



Scheme 2 Expected outcomes of Sharpless epoxidation (under kinetic control) of the tetraene alcohols **9**, **10** and **11**

Table 3 Comparison of ^{1}H NMR data for synthetic **3**; R = Et with natural AF-toxin IIc, methyl ester

	Synthetic **3**; R = Et		Natural AF-toxin IIc, methyl ester[8,9]	
	δ[a]	*J*/Hz	δ[b]	*J*/Hz
2-H	5.93d	15.3	5.94d	15.2
3-H	7.29dd	11.1, 15.3	7.29dd	11.2, 15.2
4-H	6.38dd	11.1, 14.7	6.39dd	11.2, 14.4
5-H	6.43dd	11.0, 15.1	6.43dd	10.7, 14.9
6-H	6.53dd	10.6, 14.7	6.53dd	10.7, 14.4
7-H	5.81dd	7.3, 14.8	5.80dd	7.4, 14.9
8-H	5.36d	7.4	5.34d	7.4
10-H[a]	2.63d	4.8	2.62d	4.8
10-H[b]	2.79d	4.8	2.78d	4.8
11-H	1.36s		1.36s	
2′-H	4.23d[c]	2.7	4.21dd	2.8, 5.8
3′-H	1.83m		1.83m	
4′-H	1.36, 1.56 m		1.36m	
5′-H	0.98t	7.4	0.97t	7.5
6′-H	0.85d	6.9	0.87d	6.9
OH	2.64br s		2.60d	5.8

[a] 400 MHz ($CDCl_3$). [b] 500 MHz ($CDCl_3$). [c] OH Coupling not seen.

case enantiomerically pure (>96% ee) **39** and **40**, the nature of the enantiomers being identified through conversion into the natural products (below). This bears out the predictions relating to the Sharpless reaction stereoselectivity discussed above. In

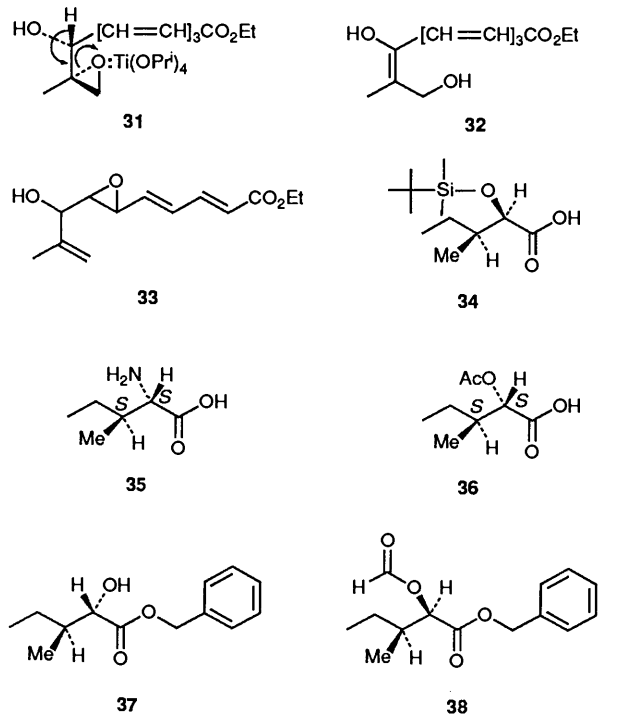


Table 4 Comparison of ^{1}H NMR data for synthetic **5**; R = Et with natural AF-toxin IIa methyl ester

	Synthetic **5**; R = Et		Natural AF-toxin IIa, methyl ester[8]	
	δ[a]	*J*/Hz	δ[b]	*J*/Hz
2-H	5.95d	15.3	5.95d	15.6
3-H	7.36dd	11.3, 15.3	7.37dd	11.2, 15.6
4-H	6.41dd	11.3, 14.8	6.40dd	11.2, 15.0
5-H	6.92dd	11.7, 14.6	6.93dd	11.6, 15.0
6-H	6.33dd	11.2, 11.2	6.33dd	10.7, 11.6
7-H	5.52dd	10.2, 10.2	5.52dd	9.6, 10.7
8-H	5.82d	10.0	5.80d	9.6
10-H[a]	2.62d	4.8	2.62d	4.6
10-H[b]	2.78d	4.7	2.78d	4.6
11-H	1.38s		1.38br s	
2′-H	4.20d[c]	3.0	4.19dd	2.7, 5.7
3′-H	1.83m		1.83m	
4′-H	1.37, 1.54 m		1.36m	
5′-H	0.97t	7.4	0.97t	7.6
6′-H	0.86d	6.8	0.87d	6.9
OH	2.63br s		2.59d	5.7

[a] 400 MHz ($CDCl_3$). [b] 500 MHz ($CDCl_3$). [c] OH Coupling not seen.

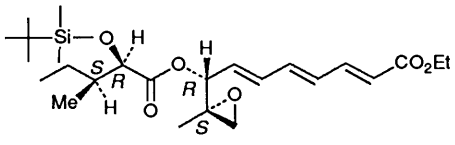
the ^{1}H NMR spectra the geminal protons 10-H[a] and 10-H[b], as in the parent epoxy alcohols, gave rise to a pair of doublets at δ *ca.* 2.63 and 2.80 (*J* 4.8 Hz),[40,41] as is observed for the natural AF-II and AK toxins. The two doublets and five double doublets between δ 5.25–7.38, with their characteristic coupling constants, indicate that, as in their alcohol precursors, the respective geometries of the triene chain remain intact. The ^{13}C NMR spectra affirmed the isomeric homogeneity of compounds **39** and **40**.

The minor components were each seen, by careful NMR study, to be a mixture of two compounds. In view of the known lack of diastereofacial selectivity in the epoxidation of the slow reacting enantiomer of the racemic secondary alcohol, it seems possible that these minor components each comprise mainly two diastereoisomeric esters, one bearing the 8*S*,9*S*, *i.e.* **41** and **42**, and the other either the 8*S*,9*R* or the 8*R*,9*R* configuration, though no detailed examination has been made.

Table 5 ^{13}C NMR data for synthetic esters of AF-toxin IIc **3**; R = Et and IIa **5**; R = Et

	Synthetic **3**; R = Et	Synthetic **5**; R = Et
	δ[a]	δ[a]
C-1	166.9	166.7
C-2	122.6	123.0
C-3	143.6[b]	143.5[b]
C-4	129.9[c]	127.0[c]
C-5	138.3[b]	133.9[b]
C-6	132.2[c]	133.6[c]
C-7	134.5[c]	133.6[c]
C-8	77.4	72.3
C-9	56.5	56.6
C-10	51.9	51.4
C-11	17.6	17.8
C-1′	174.5	174.5
C-2′	73.1	73.0
C-3′	38.6	38.5
C-4′	26.1	26.1
C-5′	12.0	11.9
C-6′	14.3	14.3

[a] 100.62 MHz ($CDCl_3$). [b,c] Assignments may be interchanged.



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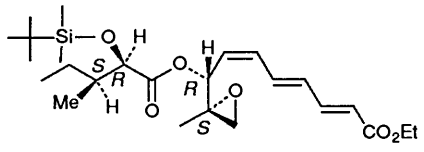

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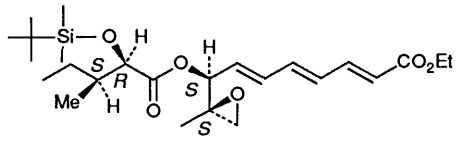

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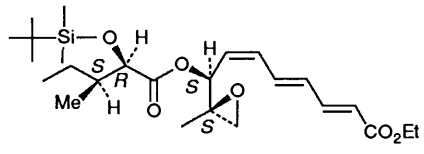

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Desilylation of the major isomers **39** and **40** using tetrabutylammonium fluoride proceeded smoothly to give the ethyl esters of AF-toxins IIa and IIc, compounds **3**; R = Et and **5**; R = Et, respectively, in 60 and 63% yield. Mass measurement, IR and UV data were in keeping with their chemical structures, and their ^1H NMR data are given in Tables 3 and 4 where comparison is made with published data for the methyl esters of the natural compounds.[8] There is excellent agreement between these two bodies of data, and, along with the ^{13}C NMR spectra presented in Table 5, they confirm the identity of our products as the ethyl esters of AF-toxins IIc and IIa.

Similar esterification of the ethyl ester 9,10-epoxy-8-hydroxy-9-methyldeca-2*E*,4*Z*,6*E*-trienoate, as obtained from the Sharpless procedure, with *N*-acetyl-L-phenylalanine under DCC activation, proceeded in 75% yield but this time HPLC indicated four components rather than the two obtained above. The proportions were 34:34:16:16 and it seemed that the doubling of each band was probably due to complete racemisation of the *N*-acetyl-L-phenylalanine, the racemic form of the latter being optically resolved by the optically active epoxy alcohol. Careful HPLC separation gave the two major components (designated compounds **A** and **B**) pure for examination. Optical rotations differed considerably, but IR and UV spectra were almost indistinguishable. The ^1H NMR spectra of the two diastereoisomers gave clear confirmation of their relationship, the spectra being very similar except that there were clear differences at the 3′-H_2 signal: compound **A** showed an AB quartet between δ 3.11–3.15, whilst for compound **B** there was a doublet at δ 3.12 (*J* 6.1 Hz).

Comparison of our ^1H NMR data for stereoisomer **B**

Table 6 Comparison of ^1H NMR data for synthetic **43** with AK-toxin II methyl ester

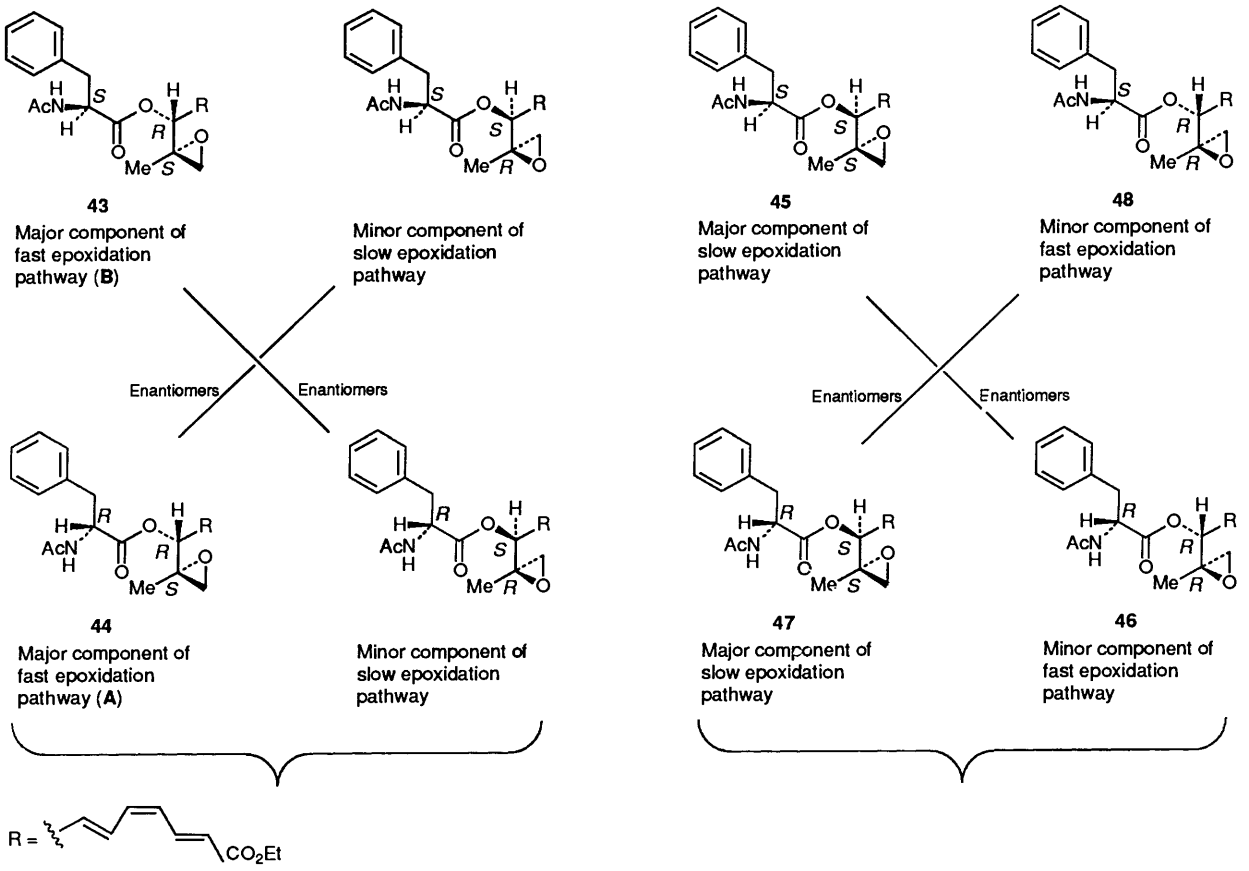
	Synthetic **43**		AK-toxin II, methyl ester[9]	
	δ[a]	*J*/Hz	δ[b]	*J*/Hz
2-H	5.95d	15.2	5.95d	15.4
3-H	7.69dd	15.1, 11.4	7.70dd	15.4, 11.5
4-H	6.20dd	11.2, 11.2	6.20dd	11.5, 11.5
5-H	6.28dd	10.9, 10.9	6.29dd	11.5, 11.5
6-H	6.84dd	15.1, 11.2	6.84dd	15.0, 11.5
7-H	5.69dd	15.2, 7.9	5.70dd	15.0, 7.7
8-H	5.27d	7.9	5.27d	7.7
10-H[A]	2.62d	4.7	2.61d	4.6
10-H[B]	2.75d	4.7	2.75d	4.6
11-H	1.31s		1.31s	
2′-H	4.91m			
3′-H	3.12d	6.1	3.12d	6.2
5′-H	7.09dd	7.1, 1.6	7.08dd	7.9, 1.6
6′-H, 7′-H, 8′-H	7.21–7.27 m		7.20–7.35	
9′-H	7.09dd	7.7, 1.6	7.08dd	7.9, 1.6
11′-H	2.01s		2.01s	
NH	5.99br s		~5.92br s	

[a] 400 MHz ($CDCl_3$). [b] 500 MHz ($CDCl_3$).

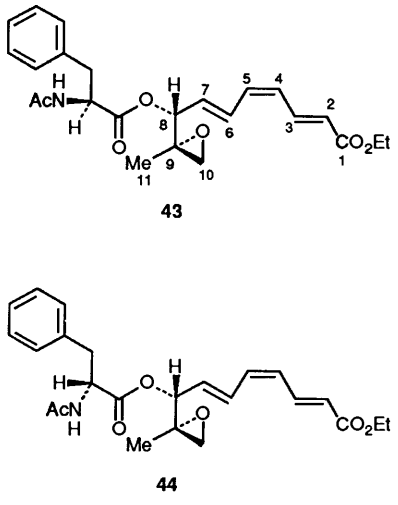
Table 7 ^1H NMR data for the minor epoxidation stereoisomers, possibly **45**/**46** and **47**/**48**, but not individually assigned

	Minor product **C**		Minor product **D**	
	δ[a]	*J*/Hz	δ[a]	*J*/Hz
2-H	5.94d	15.4	5.93d	15.4
3-H	7.31dd	15.2, 11.0	7.25–7.31m	
4-H	6.33dd	11.0, 8.7	6.35dd	10.8, 4.6
5-H	6.37dd	11.0, 8.3	6.40dd	10.8, 4.6
6-H	6.52dd	14.9, 10.6	6.51dd	14.8, 10.7
7-H	5.70dd	15.3, 7.8	5.78dd	15.3, 6.9
8-H	5.22d	7.7	5.20d	7.3
10-H[a]	2.61d	4.7	2.59d	4.9
10-H[b]	2.74d	4.6	2.73d	4.9
11-H	1.31s		1.25s	
2′-H	4.91m		4.93m	
3′-H	3.12d	6.0	3.12–3.13m	
5′-H	7.08dd	4.8, 1.7	7.16dd	8.1, 1.6
6′-H, 7′-H, 8′-H	7.21–7.26m		7.25–7.32m	
9′-H	7.09dd	4.8, 1.7	7.16dd	8.1, 1.6
11′-H	2.00s		1.98s	
NH	5.91br s		5.88br s	

[a] 400 MHz ($CDCl_3$).



Scheme 3 Esterification of the Sharpless kinetic epoxidation products with *N*-acetylphenylalanine involving racemisation: stereochemical relations



(compound **43**) with that reported in the literature for the methyl ester of a sample of AK-toxin II (compound **2**; R = Me, R′ = H), identical with that from natural material,[9] showed excellent agreement (Table 6), whereas stereoisomer **A** (compound **44**) was clearly distinguishable. It will be noted from Scheme 3 that in each case, because of the racemisation of the amino acid component, there could be enantiomeric contamination from the minor component of the slower epoxidation pathway. Though expected to be small, it would result in a diminished optical rotation value: unfortunately the necessary comparative data for the natural ethyl ester are not available. The problem does not of course arise for the AF-toxins.

The two minor components from the esterification possibly contain mainly the pair of enantiomers **45** and **46** and the pair of enantiomers **47** and **48**, not necessarily in equal amounts. They give rise to ^{1}H NMR spectra (Table 7) differing substantially from those of the two major compounds **43** and **44** with regard to the resonances of the proton group 3-, 4-, 5-, 6- and 8-H. Whilst the *E,Z,E* geometry of the triene chain is affirmed by the

Table 8 ^{13}C NMR data for the minor epoxidation stereoisomers, possibly **45**/**46** and **47**/**48**, but not individually assigned

	Minor product C δ[a]	Minor product D δ[a]
C-1	166.9	166.9
C-2	122.5	122.4
C-3	143.5[b]	143.6[b]
C-4	127.2[c]	127.2[c]
C-5	138.3[b]	138.4[b]
C-6	129.8[c]	130.0[c]
C-7	134.9[b]	134.0[b]
C-8	76.7	76.5
C-9	56.5	56.5
C-10	52.3	52.1
C-11	17.3	17.3
C-1′	170.7	170.7
C-2′	53.1	53.2
C-3′	37.9	38.0
C-4′	135.5	135.5
C-5′	129.4	129.3
C-6′	128.6	128.6
C-7′	132.2[c]	132.1[c]
C-8′	128.6	128.7
C-9′	129.4	129.3
C-10′	169.6	169.6
C-11′	23.1	23.1

[a] 100.62 MHz ($CDCl_3$). [b,c] Assignments may be interchanged.

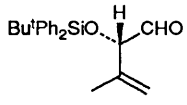
Table 9 ^{13}C NMR data for synthetic AK-toxin II ethyl ester **43** and its 2′-epimer **44**

	Compound **43** δ[a]	Compound **44** δ[a]
C-1	166.8	166.8
C-2	123.4	123.2
C-3	138.2[b]	138.3[b]
C-4	127.3[c]	127.2[c]
C-5	135.0[b]	135.0[b]
C-6	128.8[c]	128.7[c]
C-7	130.2[b]	130.5[b]
C-8	77.1	76.8
C-9	56.5	56.6
C-10	52.3	52.1
C-11	17.4	17.4
C-1′	170.8	170.7
C-2′	53.3	53.3
C-3′	38.0	38.0
C-4′	135.6	135.7
C-5′	129.5	129.4
C-6′	128.7	128.7
C-7′	130.1[c]	129.8[c]
C-8′	128.7	128.7
C-9′	129.5	129.4
C-10′	169.7	169.7
C-11′	23.2	23.1

[a] 100.62 MHz ($CDCl_3$). [b,c] Assignments may be interchanged.

sequence of coupling constants, the 3-H and 6-H double doublets are shielded relative to their counterparts in compounds **43** and **44**, whereas the 4-H and 5-H signals are correspondingly deshielded. As Table 8 shows, the ^{13}C chemical shifts for the two diastereoisomeric pairs clearly differ from those for compounds **43** and **44** in Table 9.

Prior to our preliminary communications on this synthesis, Irie *et al.*[9] reported a different type of synthesis of AK-II and AF-IIc toxins as methyl esters, involving the aldehyde **49** as the



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key intermediate. This was obtained by an eleven-stage degradation of vitamin C as the chiral source.[41] Further elaboration involved Wittig-type chemistry. Since the appearance of our preliminary communications a third synthesis of AK-II toxin has appeared.[45] Shibuya and colleagues used D-fructose as the chiral source, together with Wittig olefination. Our approach is thus quite different in type from these two syntheses. Very recently a synthesis of the chiral epoxy alcohol intermediate **6**, as its methyl ester, has been reported.[46]

Experimental

NMR spectra were recorded using a Bruker WP 80SY (^1H, 80.13 MHz; ^{13}C, 20.15 MHz), a Bruker WM 250 (^1H, 250.13 MHz; ^{13}C, 62.89 MHz), a Bruker AM 400 (^1H, 400.13; ^{13}C, 100.62 MHz) and a Jeol FX 90Q (^1H, 89.9 MHz; ^{13}C 22.5 MHz). *J* Values are in Hz.

Ethyl (E)-3-*Formylpropenoate* **25**.—Selenium dioxide (29 g), ethyl crotonate (44 g, 0.39 mmol) and 1,4-dioxane (150 cm^3) were heated at reflux for 2 h. The mixture was filtered hot, through glass wool, then Celite, to remove selenium. 1,4-Dioxane was removed by distillation at 130 mmHg. The residue was filtered again through Celite, then distilled, to give ethyl (*E*)-3-formylpropenoate (11.24 g, 23%) as a yellow liquid, b.p. 77–80 °C at 14 mmHg (lit.,[22] 75–75.5 °C at 14 mmHg) (Found: M^+, 128.0488. Calc. for $C_6H_8O_3$: M, 128.0473); ν_{max}(neat)/cm^{-1} 3040, 2820, 2720, 1720 and 1690; δ_H(90 MHz; $CDCl_3$) 1.35 (3 H, t, *J* 7.2, CH_2*Me*), 4.30 (2 H, q, *J* 7.2, C*H*$_2$Me), 6.76 (1 H, d, *J* 15.0, C=C*H*CO_2Et), 7.13 (1 H, dd, *J* 7.0 and 15.0, HOCC*H*=C) and 9.90 (1 H, d, *J* 7.0, *H*OCCH=C).

Bromomethyl(triphenyl)phosphonium Bromide.—Triphenylphosphine (30 g, 0.11 mol), methylene dibromide (44 g, 0.23 mol) and toluene (200 cm^3) were heated at reflux for 24 h. The crystals were recrystallised from ethanol–ethyl acetate to give bromomethyl(triphenyl)phosphonium bromide (26.82 g, 55%), m.p. 236–240 °C (lit.,[21] 240–241 °C).

Ethyl 5-*Bromopenta*-2E,4Z-*dienoate* **22** *and Ethyl* 5-*Bromopenta*-2E,4E-*dienoate* **23**.—A suspension of bromomethyl(triphenyl)phosphonium bromide (23.54 g, 0.054 mol) in THF (80 cm^3) was cooled to −78 °C under nitrogen. Potassium t-butoxide (6.05 g, 0.54 mol) was added and a yellow suspension of the ylide was formed immediately. The mixture was stirred (30 min) after which a solution of ethyl 3-formylpropenoate (6.0 g, 0.47 mol) in THF (5 cm^3) was added. After a further 30 min at this temperature, the mixture was allowed to warm to room temperature and was then stirred for 2 h. The mixture was filtered over Celite. The filtrate was concentrated and chromatographed on silica Woelm (dry column) with diethyl ether–hexane (1:4) as eluent. Further purification by kugelrohr distillation gave ethyl 5-bromopenta-2*E*,4*E*/*Z*-dienoate as a pale yellow oil (3.7 g, 40%) (Found: C, 41.35; H, 4.6%; M^+, 203.9794. Calc. for $C_7H_9O_2{}^{79}Br$: C, 41.00; H, 4.42%; M, 203.9786).

The two isomers were separated by reverse-phase preparative HPLC with methanol–water (1:1) as eluent. Each component was 'salted out' of the methanol–water fractions into methylenedichloride, and the solutions were dried over anhydrous magnesium sulphate and concentrated. *Ethyl* 5-*bromopenta*-2E,4Z-*dienoate* **22** was the major component (60%); ν_{max}(neat)/cm^{-1} 3081, 1711, 1631 and 1572; λ_{max}(EtOH)/nm 268 (ε/dm^3 mol^{-1} cm^{-1} 24 500); δ_H(250 MHz; $CDCl_3$) 1.32 (3 H, t, *J* 7.2, *Me*CH_2), 4.24 (2 H, q, *J* 7.1, MeC*H*$_2$), 6.08 (1 H, d, *J* 15.6, 2-H), 6.59 (1 H, d, *J* 7.3, 5-H), 6.78 (1 H, dd, *J* 10.7 and 7.3, 4-H) and 7.59 (1 H, dd, *J* 15.6 and 10.7, 3-H); δ_C(22.5 MHz; $CDCl_3$) 14.3 (C-2′), 60.6 (C-1′), 116.3 (C-5), 125.4 (C-2), 130.7 (C-4), 138.7 (C-3) and 166.4 (C-1).

Ethyl 5-*bromopenta*-2E,4E-*dienoate* **23** was similarly obtained as the minor component (40%); ν_{max}(neat)/cm^{-1} 3061, 1711, 1631 and 1577; λ_{max}(EtOH)/nm 265 (ε/dm^3 mol^{-1} cm^{-1} 31 000); δ_H(250 MHz; $CDCl_3$) 1.30 (3 H, t, *J* 7.1, CH_2*Me*), 4.21 (2 H, q, *J* 7.1, C*H*$_2$Me), 5.93 (1 H, d, *J* 15.3, 2-H), 6.75–6.90 (2 H, m, 4- and 5-H) and 7.17 (1 H, dd, *J* 15.4 and 9.4, 3-H); δ_C(22.5 MHz; $CDCl_3$) 14.3 (C-2′), 60.6 (C-1′), 117.5 (C-5), 122.4 (C-2), 135.4 (C-4), 140.9 (C-3) and 166.4 (C-1).

2-*Methylpent*-1-*en*-4-*yn*-3-*ol* **12**.—Ethynylmagnesium bromide was prepared by addition of a solution of ethylmagnesium bromide [obtained from magnesium (7.2 g, 0.25 g-atom) and ethyl bromide (32.7 g, 0.20 mol)] in dry THF (150 cm^3) to a solution of acetylene in dry THF (200 cm^3). The product was cooled in an ice-bath and a solution of methacrylaldehyde (14 g, 0.20 mol) in THF (35 cm^3) was added dropwise. The mixture was stirred overnight and then poured into cooled, saturated aq. ammonium chloride (600 cm^3). Two phases separated and the aq. layer was extracted with diethyl ether (4 × 125 cm^3). The organic extracts and mother liquor were combined and dried over anhydrous magnesium sulphate. Solvents were removed and the residue was distilled at reduced pressure to give 2-methylpent-1-en-4-yn-3-ol (13.9 g, 72%), b.p. 62 °C at 20 mmHg (lit.,[11] 38 °C at 0.1 mmHg) (Found: C, 74.7;

H, 8.2%; M^+, 96.0564. Calc. for C_6H_8O: C, 74.97; H, 8.39%; M, 96.0577); ν_{max}(neat)/cm^{-1} 3040, 2820, 2720, 1720 and 1690; δ_H(90 MHz; $CDCl_3$) 1.90 (3 H, s, Me), 2.57 (1 H, d, *J* 2.0, C≡CH), 2.75 (1 H, br s, OH), 4.84 (1 H, s, HOC*H*), 5.0 (1 H, s, C=CH) and 5.25 (1 H, s, C=CH).

2-Methyl-3-(tetrahydropyran-2-yloxy)pent-1-en-4-yne.—A solution of 2-methylpent-1-en-4-yn-3-ol (1.0 g, 10.04 mol), dihydropyran (1.31 g, 15.6 mmol, 1.5 mol equiv.), and PPTS (0.26 g, 1.04 mmol, 0.1 mol equiv.) in dry methylenedichloride (40 cm^3) was stirred at room temperature for 4 h. Work-up and distillation gave 2-methyl-3-(tetrahydropyran-2-yloxy)pent-1-en-4-yne (1.55 g, 83%), b.p. 88 °C at 8 mmHg; ν_{max}(neat)/cm^{-1} 3291, 3091, 2121w and 1651; δ_H(90 MHz; $CDCl_3$) 1.65 (6 H, m, $OCH_2[CH_2]_3CHO$), 1.85 (3 H, s, MeC=C), 2.45 (1 H, t, *J* 2.0, C≡CH), 3.35–4.05 (2 H, m, CH_2O) and 4.50–5.25 (4 H, m, 2 × OCH and C=CH_2).

3-(1-Ethoxyethoxy)-2-methylpent-1-en-4-yne.—A solution of 2-methylpent-1-en-4-yn-3-ol (1.0 g, 10.4 mmol) and a catalytic amount of toluene-*p*-sulphonic acid (PTSA) in dry diethyl ether (40 cm^3) was treated with ethyl vinyl ether (1.12 g, 1.5 mol equiv.) and stirred (12 h). Work-up and distillation gave 3-(1-ethoxyethoxy)-2-methylpent-1-en-4-yne (1.50 g, 85%), b.p. 48–49 °C at 5 mmHg; ν_{max}(neat)/cm^{-1} 3300, 3080, 2120w and 1655; δ_H(90 MHz; $CDCl_3$) 1.21 (3 H, t, *J* 7.1, *Me*CH_2), 1.35 (3 H, d, *J* 6.0, *Me*CH), 1.88 (3 H, s, MeC=C), 2.50 (1 H, d, *J* 2.0, C≡CH), 3.65 (2 H, m, O*CH*$_2$Me) and 4.75–5.35 (4 H, m, 2 × OCH and C=CH_2).

3-(t-Butyldimethylsiloxy)-2-methylpent-1-en-4-yne **14**.—To a solution of TBDMSCl (7.85 g, 50.0 mmol) and 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) in dry methylenedichloride was added 2-methylpent-1-en-4-yn-3-ol **12** (5.0 g, 50.0 mmol). The mixture was stirred at room temperature overnight under nitrogen. The solution was washed successively with hydrochloric acid (0.1 mol dm^{-3}) followed by saturated aq. sodium hydrogencarbonate and distilled to give 3-(t-butyldimethylsiloxy)-2-methylpent-1-en-4-yne (9.35 g, 89%), b.p. 98 °C at 26 mmHg; ν_{max}(neat)/cm^{-1} 3300, 3090, 2140 and 1650; δ_H 0.30 (6 H, d Me_2Si), 1.10 (9 H, s, Bu^{t}Si), 2.0 (3 H, s, MeC=C), 2.5 (1 H, d, *J* 2.0, C≡CH), 4.90 (1 H, s, OCH), 5.0 (1 H, s, C=CH) and 5.28 (1 H, s, C=CH).

General Procedure for the Hydrozirconation–Palladium(0) Coupling Reaction between Derivatives of 2-Methylpent-1-en-4-yn-3-ol **12** *and a Vinyl or Dienyl Halide*.—To a solution of the propargylic substrate in dry benzene (distilled from sodium/benzophenone ketyl) was added biscyclopentadienylzirconium chloride hydride (1.1 mol equiv.) and the mixture was stirred in the dark under argon for 4 h. Meanwhile, a suspension of bis(triphenylphosphine)palladium dichloride (14 mol% by wt) in dry THF was cooled to 0 °C and treated with diisobutylaluminium hydride (DIBAL) (28 mol%), resulting in a blackish red suspension. An orange solution of the vinylzirconocene was added to the suspension of the catalyst under argon *via* needle transfer and this was followed by the addition of a solution of the vinyl or dienyl halide in THF. The reddish brown reaction mixture was stirred at room temperature overnight and then concentrated under reduced pressure. Chromatography of the residue on silica furnished the coupled product.

Methyl 6-(1′-Ethoxyethoxy)-7-methylocta-2E,4E,7-trienoate **19**.—3-(Ethoxyethoxy)-2-methylpent-1-en-4-yne (0.40 g, 2.22 mmol) underwent hydrozirconation and palladium(0) coupling with methyl (*E*)-3-bromopropenoate **13** (0.37 g, 2.22 mmol) as above. Chromatographic isolation, and elution with diethyl ether–hexane (1:2), gave *methyl 6-(1′-ethoxyethoxy)-7-methylocta-2E,4E,7-trienoate* **19** (0.24 g, 40%) as a pale yellow oil [Found: *m/z*, 182.1203 ($M^+ - C_4H_8O$). $C_{14}H_{22}O_4$ requires M, 254.1518; M − C_4H_8O, 182.0943]; ν_{max}(neat)/cm^{-1} 3080, 1720, 1650 and 1620; δ_H(90 MHz; $CDCl_3$) 1.17 (3 H, t, *J* 7.0, *Me*CH_2O), 1.39 (3 H, d, *J* 7.2, *Me*CHO), 1.66 (3 H, distorted d, CMe), 3.50 (2 H, m, OMe) 3.74 (3 H, s, OMe), 4.61–5.02 (4 H, m, MeC=CH_2, 2 × OCH), 5.90 (1 H, d, *J* 15.3, 2-H), 5.81–6.41 (2 H, m, 4- and 5-H) and 7.30 (1 H, dd, *J* 15.2 and 10.5, 3-H).

Ethyl 8-(1′-Ethoxyethoxy)-9-methyldeca-2E,4Z,6E,9-tetraenoate **21c**.—3-(Ethoxyethoxy)-2-methylpent-1-en-4-yne (0.23 g, 1.51 mmol) underwent hydrozirconation and palladium(0) coupling with ethyl 5-bromopenta-2E,4Z-dienoate **22** (0.31 g, 1.51 mmol) according to the general procedure. Chromatographic isolation with diethyl ether–hexane (1:1) as eluent gave *ethyl 8-(1′-ethoxyethoxy)-9-methyldeca-2E,4Z,6E,9-tetraenoate* **21c** (0.045 g, 10%) as a yellow oil [Found: *m/z*, 222.1011 ($M^+ - C_4H_8O$). $C_{17}H_{26}O_4$ requires M, 294.1831; M − C_4H_8O, 222.1256]; ν_{max}(neat)/cm^{-1} 3084, 1720, 1650 and 1620; δ_H(250 MHz; $CDCl_3$) (diastereoisomers) 1.20 (3 H, t, *J* 7.05, *Me*CH_2O), 1.33 (6 H, m, *Me*CH and *Me*CH_2OCO), 1.67 and 1.74 (2 × 3/2 H, s, MeC=C), 3.42–3.69 (2 H, m, MeCH_2OCH), 4.23 (2 H, q, *J* 7.0, MeCH_2OCO), 4.57 and 4.66 (2 × 1/2 H, d, *J* 7.0 and 5.7, 8-H), 4.75 (1 H, m, MeC*H*), 4.90 and 4.97 (2 × 1/2 H, s, MeC=C*H*), 5.04 (1 H, s, MeC=C*H*), 5.80 (1 H, dd, *J* 15.1 and 7.0, 7-H), 5.91 (1 H, d, *J* 15.2, 2-H), 6.10 (1 H, dd, *J* 11.1 and 11.6, 4-H), 6.32 (1 H, dd, *J* 11.3 and 11.4, 5-H), 6.82 (1 H, dd, *J* 15.1 and 11.4, 6-H) and 7.75 (1 H, dd, *J* 15 3 and 11.9, 3-H).

Ethyl 8(1′-Ethoxyethoxy)-9-methyldeca-2E,4E,6E,9-tetraenoate **20c**.—3-(Ethoxyethoxy)-2-methylpent-1-en-4-yne (0.23 g, 1.51 mmol) underwent hydrozirconation and palladium(0) coupling with ethyl 5-bromopenta-2*E*,4*E*-dienoate **23** (0.31 g, 1.51 mmol) according to the general procedure. Chromatographic isolation with diethyl ether–hexane (1:1) as eluent gave *ethyl 8-(1′-ethoxyethoxy)-9-methyldeca-2E,4E,6E,9-tetraenoate* (0.043 g, 10%) as a yellow oil [Found: *m/z*, 222.1618 ($M^+ - C_4H_8O$]. $C_{17}H_{26}O_4$ requires M, 294.1831; $M^+ - C_4H_8O$, 222.1256]; ν_{max}(neat)/cm^{-1} 3084, 1722, 1650 and 1620; δ_H(250 MHz; $CDCl_3$) (diastereoisomers) 1.18 (3 H, t, *J* 7.0, *Me*CH_2O), 1.31 (6 H, m, *Me*CH and *Me*CH_2OCO), 1.66 and 1.73 (2 × 3/2 H, s, MeC=C), 3.41–3.68 (2 H, m, MeCH_2OCH), 4.20 (2 H, q, *J* 7.5, MeCH_2OCO), 4.54 and 4.63 (2 × 1/2 H, d, *J* 6.9 and 5.9, 8-H), 4.72 (1 H, m, MeC*H*), 4.89 and 4.96 (2 × 1/2 H, s, MeC=C*H*), 5.02 (1 H, s, MeC=C*H*), 5.81 (1 H, dd, *J* 15.4 and 7.0, 7-H), 5.88 (1 H, d, *J* 15.2, 2-H), 6.32 (1 H, dd, *J* 14.7 and 11.1, 4-H), 6.38 (1 H, dd, *J* 14.8 and 11.3, 5-H), 6.56 (1 H, dd, *J* 15.0 and 11.1, 6-H) and 7.30 (1 H, dd, *J* 15.3 and 11.0, 3-H).

Methyl (E)-3-*Bromopropenoate* **13**.—A solution of (*E*)-3-bromopropenoic acid (4.8 g, 32 mmol) in diethyl ether (100 cm^3) was treated at 0 °C with an ethereal solution of diazomethane [prepared from *N*-methylnitrosourea (10 g) and 40% aq. potassium hydroxide (30 cm^3)]. Work-up gave methyl (*E*)-3-bromopropenoate (4.03 g, 77%), b.p. 45–50 °C at 9 mmHg (lit.,[12] 48–50 °C at 10 mmHg); ν_{max}(neat)/cm^{-1} 3081, 1726 and 1610; δ_H(90 MHz; $CDCl_3$) 3.83 (3 H, s, Me), 6.63 (1 H, d, *J* 15.0, C=C*H*CO_2Me) and 7.71 (1 H, d, *J* 15.0, BrCH=C).

2-Methyl-5-(tributylstannyl)penta-1,4E-dien-3-ol **26**.—2-Methylpent-1-en-4-yn-3-ol **12** (1.2 g, 12.5 mmol) was treated with tributyltin hydride (4.36 cm^3, 16.3 mmol, 1.3 mol equiv.) and a catalytic amount of AIBN (100 mg). The mixture was heated to 78–80 °C and stirred under nitrogen for 2 h, after which period TLC indicated that the reaction was complete. Dry column chromatography of the crude mixture on silica Woelm, and elution with diethyl ether–hexane (1:9), furnished *2-methyl-5-(tributylstannyl)penta-1,4E-dien-3-ol* **26** as an oil

(2.5 g, 53%) [Found: C, 56.1; H, 9.5%; *m/z*, 331.1000 (100%) ($M^+ - C_4H_9$). $C_{18}H_{36}O^{120}Sn$ requires C, 55.84; H, 9.31%; M, 388.1787; $M^+ - C_4H_9$, 331.1083]; ν_{max}(neat)/cm^{-1} 3340, 3080, 1645 and 1595; δ_H(250 MHz; $CDCl_3$) 0.89 {9 H, t, *J* 7.3, ($Me[CH_2]_3)_3Sn$}, 0.89 [6 H, m, ($MeCH_2CH_2CH_2)_3Sn$], 1.31 [6 H, m, ($MeCH_2CH_2CH_2)_3Sn$], 1.49 [6 H, m, ($MeCH_2CH_2CH_2)_3Sn$], 1.71 (3 H, s, Me), 1.78 (1 H, br s, OH), 4.53 (1 H, t, *J* 4.5, OCH), 4.88 (1 H, s, MeC=C*H*), 5.04 (1 H, s, MeC=C*H*), 5.97 (1 H, dd, *J* 19.1 and 5.4, C*H*=CHSn) and 6.24 (1 H, d, *J* 19.1, SnC*H*=CH); δ_C(62.89 MHz; $CDCl_3$) 9.5 (C-3′), 13.7 (4-C′), 18.1 (C-6), 27.3 (C-2′), 29.1 (C-1′), 79.2 (C-3), 110.8 (C-5), 129.0 (C-2), 146.3 (C-4) and 148.4 (C-1).

2-Methyl-5-(tributylstannyl)penta-1,4Z-dien-3-ol **27**.—2-Methylpent-1-en-4-yn-3-ol **12** (2.0 g, 20.8 mmol) was added to cooled (0 °C) lithium aluminium hydride (0.41 g, 10 mmol) in dry THF (75 cm^3). The mixture was stirred at 0 °C for 30 min and then was allowed to warm to room temperature and stirred for 23 h. The resultant slurry was cooled to −78 °C and a solution of tributyltin triflate (1.82 g, 4.2 mmol) in dry diethyl ether (10 cm^3) was added slowly. After 4.5 h at −78 °C, the reaction mixture was quenched with ammonia gas and treated sequentially with (i) methanol (8–10 cm^3, added slowly), (ii) saturated aq. (pH 8) ammonium chloride in aq. ammonia (5–10 cm^3) and (iii) hexane (10 cm^3). The mixture was filtered through Celite and extracted with further portions of hexane. The combined hexane solutions were dried (anhydrous magnesium sulphate), and concentrated under reduced pressure to give a yellow oil. Dry column chromatography on silica, and elution with diethyl ether–hexane (1:9), gave *2-methyl-5-(tributylstannyl)penta-1,4Z-dien-3-ol* **27** as a liquid (1.28 g, 80%) (Found: C, 56.3; H, 9.6. $C_{18}H_{36}OSn$ requires C, 55.84; H, 9.31%); ν_{max}(neat)/cm^{-1} 3426, 3076, 1646 and 1601; δ_H(250 MHz; $CDCl_3$) 0.89 {9 H, t, *J* 7.3, ($Me[CH_2]_3)_3Sn$}, 0.93 [6 H, m, ($MeCH_2CH_2CH_2)_3Sn$], 1.31 [6 H, m, ($MeCH_2CH_2CH_2)_3Sn$], 1.49 [6 H, m, ($MeCH_2CH_2CH_2)_3Sn$], 1.59 (1 H, d, *J* 3.4, OH), 1.75 (3 H, s, Me), 4.37 (1 H, dd, *J* 7.0, 3.2, HOC*H*), 4.87 (1 H, s, MeC=C*H*), 5.04 (1 H, s, MeC=C*H*), 6.09 (1 H, d, *J* 12.7, SnCH=C) and 6.49 (1 H, dd, *J* 12.8 and 7.1, SnCH=C*H*); δ_C(62.89 MHz; $CDCl_3$) 11.2 (C-3′), 13.7 (C-4′), 18.6 (C-6), 27.4 (C-2′), 29.2 (C-1′), 78.8 (C-3), 111.0 (C-5), 132.3 (C-2), 146.5 (C-4) and 147.6 (C-1).

Methyl 6-Hydroxy-7-methylocta-2E,4E,7-trienoate **17**.—(*a*) Methyl (*E*)-3-bromopropenoate **13** (0.41 g, 2.49 mmol) was added to a suspension of 2-methyl-5-(tributylstannyl)penta-1,4E-dien-3-ol **26** (0.96 g, 2.45 mmol) and bis(triphenylphosphine)palladium dichloride (0.27 g, 16 mol% by wt) in dry DMF (freshly distilled and stored over type 4 Å molecular sieves). The mixture was stirred under nitrogen for 5 h, diluted with diethyl ether, and washed with saturated aq. sodium fluoride to remove tributyltin as the insoluble fluoride. The ethereal solution was dried over anhydrous magnesium sulphate, then concentrated under reduced pressure. Chromatography of the residue on alumina (dry column) and elution with diethyl ether–hexane (1:2) gave *methyl 6-hydroxy-7-methylocta-2E,4E,7-trienoate* **17** as an oil (0.37 g, 81%) [Found: M^+, 182.0964 (1.67%). $C_{10}H_{14}O_3$ requires M, 182.0943]; ν_{max}(neat)/cm^{-1} 3440, 3080, 1720, 1710, 1700, 1640, 1615 and 1440; λ_{max}(EtOH)/nm 260 (ε/dm^3 mol^{-1} cm^{-1} 40 500); δ_H(250 MHz; $CDCl_3$) 1.72 (3 H, s, *Me*C=CH), 2.40 (1 H, br s, OH), 3.75 (3 H, s, OMe), 4.69 (1 H, d, *J* 5.2, 6-H), 4.91 (1 H, s, 8-H), 4.92 (1 H, s, 8-H), 5.91 (1 H, d, *J* 15.6, 2-H), 6.10 (1 H, dd, *J* 15.3 and 5.8, 5-H), 6.43 (1 H, dd, *J* 14.9 and 11.3, 4-H) and 7.29 (1 H, dd, *J* 15.4 and 11.1, 3-H); δ_C(22.5 MHz; $CDCl_3$) 18.0 (C-9), 51.6 (C-1′), 75.7 (C-6), 112.1 (C-8), 121.4 (C-2), 128.2 (C-4), 142.8 (C-3), 144.0 (C-5), 145.7 (C-7) and 167.4 (C-1).

(*b*) Methyl 6-(1′-ethoxyethoxy)-7-methylocta-2*E*,4*E*,7-trienoate **19** (0.30 g, 1.27 mmol) was treated with 0.5 mol dm^{-3} aq. hydrochloric acid in THF (5 cm^3), and the mixture was stirred for 1.5 h at room temperature. Chromatography on silica Woelm (dry column), and elution with diethyl ether–hexane (1:3), gave compound **17** as an oil (0.21 g, 93%).

Ethyl 8-Hydroxy-9-methyldeca-2E,4Z,6E,9-tetraenoate **10**.—Ethyl 5-bromopenta-2*E*,4*Z*-dienoate **22** (0.40 g, 1.95 mmol) was added to a suspension of 2-methyl-5-(tributylstannyl)penta-1,4*E*-dien-3-ol **26** (0.83 g, 2.41 mmol, 1.1 mol equiv.) and bis(triphenylphosphine)palladium dichloride (0.23 g, 16 mol% by wt) in dry DMF (25 cm^3) and the mixture was stirred (16 h). Work-up (Et_2O), washing (saturated aq. sodium fluoride) and chromatography [alumina (dry column); diethyl ether–hexane (1:1)] gave *ethyl 8-hydroxy-9-methyldeca-2E,4Z,6E,9-tetraenoate* (0.30 g, 70%) [Found: C, 69.9; H, 8.3%; M^+, 222.1245 (5.06%). $C_{13}H_{18}O_3$ requires C, 70.24; H, 8.16%; M, 222.1256]; ν_{max}(neat)/cm^{-1} 3461, 3101, 1711, 1691 and 1621; λ_{max}(EtOH)/nm 300 (ε/dm^3 mol^{-1} cm^{-1} 32 200); δ_H(400 MHz; $CDCl_3$) 1.31 (3 H, t, *J* 7.1, CH_2Me), 1.74 (3 H, s, Me), 2.12 (1 H, br s, OH), 4.22 (2 H, q, *J* 7.1, CH_2Me), 4.70 (1 H, d, *J* 6.2, 8-H), 4.91 (1 H, s, 10-H), 5.06 (1 H, s, 10-H), 5.89 (1 H, dd, *J* 15.1 and 6.3, 7-H), 5.90 (1 H, d, *J* 15.2, 2-H), 6.11 (1 H, dd, *J* 11.3 and 11.3, 4-H), 6.32 (1 H, dd, *J* 11.0 and 11.0, 5-H), 6.88 (1 H, dd, *J* 15.1 and 11.5, 6-H) and 7.76 (1 H, dd, *J* 15.2 and 12.0, 3-H); δ_C(100.62 MHz; $CDCl_3$) 14.32 (C-2′), 18.1 (C-11), 60.5 (C-1′), 76.0 (C-8), 111.7 (C-10), 122.1 (C-2), 125.5, 126.9 and 136.2 (C-4, -6 and -7), 138.7 and 138.9 (C-3 and -5), 145.9 (C-9) and 167.1 (C-1).

Ethyl 8-Hydroxy-9-methyldeca-2E,4E,6E,9-tetraenoate **9**.—Ethyl 5-bromopenta-2*E*,4*E*-dienoate **23** (0.40 g, 1.95 mmol) was added to a suspension of 2-methyl-5-(tributylstannyl)penta-1,4*E*-dien-3-ol **26** (0.83 g, 2.14 mmol, 1.1 mol equiv.) and bis(triphenylphosphine)palladium dichloride (0.23 g, 16 mol% by wt) in dry DMF (25 cm^3). The mixture was stirred under nitrogen for 16 h, diluted with diethyl ether, and washed with saturated aq. sodium fluoride. The ethereal solution was dried and evaporated. Chromatography on alumina (dry column), and elution with diethyl ether–hexane (1:1), furnished *ethyl 8-hydroxy-9-methyldeca-2E,4E,6E,9-tetraenoate* **9** as a solid (0.31 g, 72%), m.p. 56–58 °C [Found: C, 69.95; H, 8.2%; M^+, 222.1260 (7.37%). $C_{13}H_{18}O_3$ requires C, 70.24; H, 8.16%; M, 222.1256]; ν_{max}(neat)/cm^{-1} 3391, 3076, 1695, 1611 and 1591; λ_{max}(EtOH)/nm 298; δ_H(400 MHz; $CDCl_3$) 1.30 (3 H, t, *J* 7.1, $MeCH_2$), 1.73 (3 H, s, Me), 2.06 (1 H, d, *J* 3.7, OH), 4.20 (2 H, q, *J* 7.1, $MeCH_2$), 4.66 (1 H, t, *J* 4.5, 8-H), 4.90 (1 H, s, 10-H), 5.05 (1 H, s, 10-H), 5.89 (1 H, d, *J* 15.3, 2-H), 5.90 (1 H, dd, *J* 15.1 and 6.2, 7-H), 6.32 (1 H, dd, *J* 15.0 and 11.2, 4-H), 6.38 (1 H, dd, *J* 15.2 and 10.8, 5-H), 6.56 (1 H, dd, *J* 15.0 and 10.8, 6-H) and 7.30 (1 H, dd, *J* 15.3 and 11.2, 3-H); δ_C(100.62 MHz; $CDCl_3$) 14.3 (C-2′), 18.1 (C-11), 60.4 (C-1′), 76.0 (C-8), 111.7 (C-10), 121.3 (C-2), 130.0, 130.3 and 138.4 (C-4, -6 and -7), 139.7 and 144.2 (C-3 and -5), 145.9 (C-9) and 167.1 (C-1).

Ethyl 8-Hydroxy-9-methyldeca-2E,4E,6Z,9-tetraenoate **11**.—Ethyl 5-bromopenta-2*E*,4*E*-dienoate **23** (0.40 g, 1.95 mmol) was added to a suspension of 2-methyl-5-(tributylstannyl)penta-1,4*Z*-dien-3-ol **27** (0.83 g, 2.14 mmol, 1.1 mol equiv.) and bis(acetonitrile)palladium dichloride (0.032 g, 8 mol% by wt) in dry DMF (20 cm^3). The mixture was stirred under nitrogen for 6 h, diluted with diethyl ether, and washed with saturated aq. sodium fluoride. The ethereal solution was dried over anhydrous magnesium sulphate and concentrated under reduced pressure. Chromatography on silica (dry column), and elution with diethyl ether–hexane (1:1), gave *ethyl 8-hydroxy-9-methyldeca-2E,4E,6Z,9-tetraenoate* **11** as a yellow oil (0.26 g, 60%) [Found: C, 69.9; H, 8.3%; M^+, 222.1266 (8.0%). $C_{13}H_{18}O_3$ requires C, 70.24; H, 8.16%; M, 222.1256]; ν_{max}(neat)/cm^{-1} 3402, 3062, 1702,

1617 and 1577; λ_{max}(EtOH)/nm 299 (ε/dm^3 mol^{-1} cm^{-1} 33 600); δ_H(400 MHz; $CDCl_3$) 1.30 (3 H, t, *J* 7.2, *Me*CH_2), 1.74 (3 H, s, Me), 2.22 (1 H, br s, OH), 4.21 (2 H, t, *J* 7.2, MeCH_2), 4.90 (1 H, s, 10-H), 5.03 (1 H, d, *J* 8.6, 8-H), 5.09 (1 H, s, 10-H), 5.61 (1 H, dd, *J* 9.3 and 10.2, 7-H), 5.91 (1 H, d, *J* 15.3, 2-H), 6.20 (1 H, dd, *J* 11.4 and 11.4, 6-H), 6.35 (1 H, dd, *J* 14.8 and 11.4, 4-H), 6.91 (1 H, dd, *J* 14.6 and 11.9, 5-H) and 7.33 (1 H, dd, *J* 15.3 and 11.3, 3-H); δ_C(100.62 MHz; $CDCl_3$) 14.3 (C-2′), 18.4 (C-11), 60.5 (C-1′), 71.8 (C-8), 111.1 (C-10), 121.9 (C-2), 129.5, 131.9 and 134.9 (C-4, -6 and -7) 135.8 and 144.0 (C-3 and -5), 146.1 (C-9) and 167.0 (C-1).

General Procedure for Sharpless Epoxidation and Kinetic Resolution of the Secondary Bisallylic Alcohols.—To a room temperature solution of the bisallylic alcohol (1.0 mol equiv.) and (−)-DIPT (0.15 mol equiv.) in dry methylene dichloride (0.13–0.25 mol dm^{-3} in substrate) were added powdered, activated 3 Å molecular sieves (20–30% wt based on the bisallylic alcohol). The stirred mixture, maintained under argon, was cooled to −20 °C (solid CO_2–acetone), treated with titanium(IV) isopropoxide (0.1 mol equiv.), and stirred for 30 min at this temperature. The reaction mixture was then treated with a solution of t-butylhydroperoxide in 'isooctane' (0.6 mol equiv. of a 2.38 mol dm^{-3} solution, dried with freshly activated 3 Å pellets for 30 min prior to addition). The reaction mixture was stirred at −20 ± 5 °C and monitored by HPLC. After ~50% conversion, the reaction was quenched by the addition of aq. iron(II) sulphate (33%)–citric acid (11%) and the vigorously stirred mixture was allowed to warm up to room temperature until two phases separated. The aq. layer was extracted at least three times with diethyl ether, then the organic layers were combined and dried over anhydrous magnesium sulphate. The solution was concentrated under reduced pressure and the crude product was chromatographed on silica Woelm (dry column) with diethyl ether–hexane (1:1) as eluent.

Ethyl(8R,9S)-9,10-*Epoxy*-8-*hydroxy*-9-*methyldeca*-2E,4Z,6E-*trienoate* **7** *from Compound* **10**.—Asymmetric epoxidation of ethyl 8-hydroxy-9-methyldeca-2*E*,4*Z*,6*E*,9-tetraenoate **10** (0.29 g, 1.32 mmol) was carried out according to the general procedure, using titanium(IV) isopropoxide (37.4 mg, 0.1 mol equiv.), (−)-DIPT (46.14 mg, 0.15 mol equiv.), activated powdered 3 Å sieves (88 mg), and t-butyl hydroperoxide (0.33 cm^3 of a 2.38 mol dm^{-3} solution in 'isooctane'; 0.6 mol equiv.). After 20 h (48% conversion), work-up and chromatography furnished ethyl 9,10-epoxy-8-hydroxy-9-methyldeca-2*E*,4*Z*,6*E*-trienoate (0.10 g, 67%, based on 48% conversion) as a mixture of diastereoisomers, 67% in *ethyl* (8R,9S)-9,10-*epoxy*-8-*hydroxy*-9-*methyldeca*-2E,4Z,6E-*trienoate* **7**; $[\alpha]_D^{23}$ +72.0° (*c* 0.54, EtOH) [Found: M$^+$, 238.1216 (2.0%). $C_{13}H_{18}O_4$ requires M, 238.1205]; ν_{max}(neat)/nm 3460, 1740i, 1710 and 1620; λ_{max}(EtOH)/nm 298; δ_H(400 MHz; $CDCl_3$) 1.31 (3 H, t, *J* 7.1, *Me*CH_2), 1.37 (3 H, s, *Me*$COCH_2$), 2.00 (1 H, br s, OH), 2.64 (1 H, d, *J* 4.7, 10-H), 2.92 (1 H, d, *J* 4.7, 10-H), 4.23 (2 H, q, *J* 7.2, MeCH_2), 4.49 (1 H, d, *J* 6.6, 8-H), 5.86 (1 H, dd, *J* 15.2 and 6.7, 7-H), 5.92 (1 H, d, *J* 15.2, 2-H), 6.13 (1 H, dd, *J* 11.3 and 11.3, 4-H), 6.33 (1 H, dd, *J* 11.0 and 11.0, 5-H) and 6.95 (1 H, dd, *J* 15.1 and 11.5, 6-H) 7.75 (1 H, q, *J* 15.0, 11.5, 3-H); δ_C(100.62 MHz; $CDCl_3$) 14.3 (C-2′), 18.0 (C-11), 50.4 (C-10), 58.8 (C-9), 60.5 (C-1′), 70.4 (C-8), 122.4 (C-2), 127.3 and 127.4 (C-4 and -6), 135.5, 135.9 and 138.7 (C-3, -5 and -7) and 167.1 (C-1).

Ethyl(8R,9S)-9,10-*Epoxy*-8-*hydroxy*-9-*methyldeca*-2E,4E,6E-*trienoate from Compound* **9**.—Asymmetric epoxidation of ethyl 8-hydroxy-9-methyldeca-2*E*,4*E*,6*E*,9-tetraenoate **9** (0.40 g, 1.8 mmol) was carried out according to the general procedure, using titanium(IV) isopropoxide (0.103 g, 0.20 mol equiv.), (−)-DIPT (0.133 g, 0.3 mol equiv.), powdered, activated 3 Å sieves (0.12 g) and t-butyl hydroperoxide (0.47 cm^3 of a 2.38 mol dm^{-3} solution in 'isooctane'; 0.6 mol equiv.). After 5 h (50% conversion), work-up and column chromatography furnished ethyl 9,10-epoxy-8-hydroxy-9-methyldeca-2*E*,4*E*,6*E*-trienoate (0.124 g, 58% based on 50% conversion) as a mixture of diastereoisomers, 75% in *ethyl* (8R,9S)-9,10-*epoxy*-8-*hydroxy*-9-*methyldeca*-2E,4E,6E-*trienoate;* $[\alpha]_D^{23}$ +51.1° (*c* 0.66, EtOH) [Found: M$^+$, 238.1206 (3.9%). $C_{13}H_{18}O_4$ requires M, 238.1205]; ν_{max}(neat)/cm^{-1} 3440, 1740, 1710 and 1620; λ_{max}(EtOH)/nm 297 (ε/dm^3 mol^{-1} cm^{-1} 42 900); δ_H(400 MHz; $CDCl_3$) 1.30 (3 H, t, *J* 7.1, *Me*CH_2), 1.36 (3 H, s, MeC–O), 2.55 (1 H, br s, OH), 2.63 (1 H, d, *J* 4.7, 10-H^a), 2.91 (1 H, d, *J* 4.6, 10-H^b), 4.20 (2 H, q, *J* 7.2, MeCH_2, overlapping with 1 H, d, 8-H), 5.86 (1 H, dd, *J* 15.1 and 6.9, 7-H), 5.90 (1 H, d, *J* 15.9, 2-H), 6.34 (1 H, dd, *J* 14.5 and 11.3, 4-H), 6.45 (1 H, dd, *J* 14.9 and 10.9, 5-H), 6.56 (1 H, dd, *J* 14.7 and 10.9, 6-H) and 7.30 (1 H, dd, *J* 15.3 and 11.3, 3-H); δ_C(100.62 MHz; $CDCl_3$) 14.4 (C-2′), 18.1 (C-11), 50.3 (C-10), 58.9 (C-9), 60.5 (C-1′), 72.7 (C-8), 121.8 (C-2), 131.0 and 132.0 (C-4 and -6), 135.1, 139.3 and 144.0 (C-3, -5 and -7) and 167.1 (C-1).

Ethyl(8R,9S)-9,10-*Epoxy*-8-*hydroxy*-9-*methyldeca*-2E,4E,6Z-*trienoate from Compound* **11**.—Asymmetric epoxidation of ethyl 8-hydroxy-9-methyldeca-2*E*,4*E*,6*Z*,9-tetraenoate **11** (0.232 g, 1.05 mmol) was carried out according to the general procedure, using titanium(IV) isopropoxide (29.6 mg, 0.1 mol equiv.), (−)-DIPT (36.6 mg, 0.15 mol equiv.), powdered, activated 3 Å molecular sieves (70 mg), and t-butyl hydroperoxide (0.26 cm^3 of a 2.38 mol dm^{-3} solution in 'isooctane'; 0.6 mol equiv.). After 20 h (50% conversion), work-up and column chromatography furnished ethyl 8-hydroxy-9-methyl-9,10-epoxydeca-2*E*,4*E*,6*Z*-trienoate (0.078 g, 63%, based on 50% conversion) as a mixture of diastereoisomers, 67% in *ethyl* (8R,9S)-9,10-*epoxy*-8-*hydroxy*-9-*methyldeca*-2E,4E,6Z-*trienoate;* $[\alpha]_D^{23}$ +13.6° (*c* 0.85, EtOH) [Found: *m*/*z*, 220.1069 (3.29%) (M$^+$ − H_2O). $C_{13}H_{18}O_4$ requires M, 238.1205; (M − H_2O), 220.1099]; ν_{max}(neat)/cm^{-1} 3440, 1710, 1620 and 1560; λ_{max}(EtOH)/nm 298 (ε/dm^3 mol^{-1} cm^{-1} 41 800); δ_H(400 MHz; $CDCl_3$) 1.31 (3 H, t, *J* 7.1, *Me*CH_2), 1.34 (3 H, s, *Me*C–O), 2.45 (1 H, br s, OH), 2.63 (1 H, d, *J* 4.7, 10-H^a), 2.96 (1 H, d, *J* 4.7, 10-H^b), 4.22 (2 H, q, *J* 7.1, MeCH_2), 4.65 (1 H, d, *J* 8.9, HOC*H*), 5.53 (1 H, dd, *J* 9.9 and 9.9, 7-H), 5.94 (1 H, d, *J* 15.3, 2-H), 6.31 (1 H, dd, *J* 11.3 and 11.3, 6-H), 6.40 (1 H, dd, *J* 14.8 and 11.4, 4-H), 6.90 (1 H, dd, *J* 14.7 and 11.8, 5-H) and 7.34 (1 H, dd, *J* 15.3 and 11.3, 3-H); δ_C(100.62 MHz; $CDCl_3$) 13.3 (C-2′), 17.0 (C-11), 49.0 (C-10), 57.9 (C-9), 59.4 (C-1′), 67.1 (C-8), 121.3 (C-2), 130.9 and 131.4 (C-4 and -6), 131.6, 133.6 and 142.8 (C-3, - 5 and -7) and 165.8 (C-1).

Ethyl (8R,9S)-8-[(2′S)-2′-*Acetylamido*-3′-*phenylpropionyl*-*oxy*]-9,10-*epoxy*-9-*methyldeca*-2E,4Z,6E-*trienoate* (*AK-Toxin II Ester*) **43** *and Ethyl* (8R,9S)-8-[(2′R)-2′-*Acetylamido*-3′-*phenyl*-*propionyloxy*]-9,10-*epoxy*-9-*methyldeca*-2E,4Z,6E-*trienoate* **44**.—A solution of *N*-acetyl-L-phenylalanine (0.052 g, 0.25 mmol), ethyl 9,10-epoxy-8-hydroxy-9-methyldeca-2*E*,4*Z*,6*E*-trienoate [a diastereoisomeric mixture *ca.* 67% in ethyl (8*R*,9*S*)-9,10-epoxy-8-hydroxy-9-methyldeca-2*E*,4*Z*,6*E*-trienoate] (0.055 g, 0.25 mmol) and 4-pyrrolidinopyridine (4.0 mg, 0.1 mol equiv.) in dry methylene dichloride was treated with DCC (0.056 g, 0.275 mmol) and the mixture was stirred at room temperature for 24 h. The reaction mixture was then diluted with diethyl ether and dicyclohexylurea was filtered off. The filtrate was washed sequentially with water, 5% acetic acid, and water, dried over anhydrous magnesium sulphate and evaporated under reduced pressure to give the crude ester. Dry column chromatography on silica, with benzene–ethyl acetate (1:1) as eluent, gave a cream coloured semi-solid, a mixture of diastereoisomeric esters (0.08 g, 75%). Preparative HPLC, with ethyl acetate–hexane (1:1) as eluent, furnished the C-2′ epimers

resulting from racemisation of *N*-acetyl-L-phenylalanine as the major components. *Ethyl* (8R,9S)-8-[(2′R)-2′-*acetylamido*-3′-*phenylpropionyloxy*]-9,10-*epoxy*-9-*methyldeca*-2E,4Z,6E-*trienoate* (**A**) **44** was eluted first; $[\alpha]_D^{23}$ +30.5° (*c* 0.45, EtOH) [Found: M^+, 427.1982 (7.0%). $C_{24}H_{29}NO_6$ requires M, 427.1995]; $\nu_{max}(CHCl_3)/cm^{-1}$ 3330, 3060, 1740, 1710, 1655, 1621 and 1540; λ_{max}(EtOH)/nm 295 (ε/dm³ mol⁻¹ cm⁻¹ 34 000); δ_H(400 MHz; $CDCl_3$) 1.31 (3 H, t, *J* 7.1, *Me*CH_2), 1.26 (3 H, s, MeC–O), 1.98 (3 H, s, *Me*CONH), 2.59 (1 H, d, *J* 4.8, 10-H[a]), 2.74 (1 H, d, *J* 4.8, 10-H[b]), 3.11–3.15 [2 H, m, ArCH_2 (AB)], 4.23 (2 H, q, *J* 7.1, CH_2Me), 4.92 (1 H, m, $ArCH_2CH$NH), 5.25 (1 H, d, *J* 7.5, 8-H), 5.74 (1 H, dd, *J* 15.1 and 7.2, 7-H), 5.93 (1 H, d, *J* 15.0, 2-H), 6.17 (1 H, dd, *J* 11.3 and 11.1, 4-H), 6.27 (1 H, dd, *J* 11.0 and 11.2, 5-H), 6.88 (1 H, dd, *J* 15.1 and 11.3, 6-H), 7.18 (2 H, dd, *J* 8.2 and 1.6, 5′- and 9′-H), 7.28 (3 H, m, 6′-, 7′- and 8′-H) and 7.70 (1 H, dd, *J* 15.1 and 11.7, 3-H). For ^{13}C NMR data see Table 9.

Ethyl (8R,9S)-8-[(2′S)-2′-*acetylamido*-3′-*phenylpropionyloxy*]-9,10-*epoxy*-9-*methyldeca*-2E,4Z,6E-*trienoate* (**B**) **43** was obtained as the second major fraction; $[\alpha]_D^{23}$ +52.86° (*c* 0.65, EtOH) [Found: C, 67.7; H, 7.0; N, 3.2%; *m/z*, 238.1257 (2.2%) ($M^+ - C_{11}H_{11}NO_2$). $C_{24}H_{29}NO_6$ requires C, 67.45; H, 6.79; N, 3.28%; M, 427.1995; ($M - C_{11}H_{11}NO_2$) 238.1280]; $\nu_{max}(CHCl_3)/cm^{-1}$ 3326, 3066, 1736, 1711, 1656, 1621 and 1540; λ_{max}(EtOH)/cm⁻¹ 295 (ε/dm³ mol⁻¹ cm⁻¹ 34 000); for ^1H NMR data see Table 6. For ^{13}C NMR data see Table 9.

(2S,3S)-2-*Acetoxy*-3-*methylpentanoic Acid* **36**.—A solution of L-isoleucine (20 g, 0.15 mol) in glacial acetic acid (200 cm³) was cooled and treated slowly with ice-cold sodium nitrite [200 cm³ of a 45% (w/v) aq. solution]. After the evolution of nitrogen, the clear solution was evaporated under reduced pressure and the residue was partitioned between ethyl acetate and water. The organic phase was washed, dried (anhydrous magnesium sulphate), and evaporated under reduced pressure to give (2*S*,3*S*)-2-acetoxy-3-methylpentanoic acid as a tan coloured oil (16.2 g, 61%). No further purification of this oil was carried out. It had $[\alpha]_D^{23}$ −9.1° (*c* 1.08, EtOH) [Found: *m/z*, 129.0897 (39%) ($M^+ - CO_2H$). Calc. for $C_8H_{14}O_4$: M, 174.0892; ($M - CO_2H$), 129.0916]; ν_{max}(neat)/cm⁻¹ 3400–3100br, 1740, 1650 and 1470; δ_H(90 MHz; $CDCl_3$) 0.95 (3 H, t, *J* 7.0, *Me*CH_2), 1.00 (3 H, d, *J* 7.0, *Me*CH), 1.44 (3 H, m, MeC*H*, MeCH_2), 2.17 (3 H, s, AcO), 5.0 (1 H, d, *J* 5.0, *H*COC) and 8.60 (1 H, br s, CO_2H).

Benzyl (2S,3S)-2-*Acetoxy*-3-*methylpentanoate*.—DCC (17.7 g, 86.1 mmol) was added to a cooled (ice-bath) solution of (2*S*,3*S*)-2-acetoxy-3-methylpentanoic acid (15 g, 86.1 mmol) and 4-pyrrolidinopyridine (0.64 g, 4.5 mmol) in benzyl alcohol (46.55 g, 5 mol equiv.). The mixture was stirred at room temperature for 16 h, then diluted with ethyl acetate, and dicyclohexylurea was filtered off. The filtrate was washed sequentially with water, 5% acetic acid, and water. The ethyl acetate solution was dried, and concentrated under reduced pressure to give a pale yellow liquid. Excess of benzyl alcohol was distilled off at reduced pressure (1.0 mmHg) and the residue was chromatographed on silica (dry column) to give benzyl (2*S*,3*S*)-2-acetoxy-3-methylpentanoate (11.5 g, 50%); ν_{max}(neat)/cm⁻¹ 3080, 3040, 1750, 1550 and 1460; δ_H(90 MHz; $CDCl_3$) 0.90 (3 H, t, *J* 8.0, *Me*CH_2), 0.95 (3 H, d, *J* 7.0, *Me*CH), 1.35 (3 H, m, MeCH_2CH), 2.17 (3 H, s, AcO), 5.0 (1 H, d, *J* 5.0, HCOC), 5.20 (2 H, s, ArCH_2) and 7.40 (5 H, s, ArH).

Benzyl (2S,3S)-2-*Hydroxy*-3-*methylpentanoate* **37**.—A mixture of benzyl (2*S*,3*S*)-2-acetoxy-3-methylpentanoate (9.20 g, 34.8 mmol), lithium carbonate (3.86 g, 1.5 mol equiv.), methanol (590 cm³), and water (80 cm³) was stirred at room temperature and monitored by TLC for debenzylation. After 10 h, the reaction mixture was diluted with brine and extracted with diethyl ether. The extract was dried and concentrated, and chromatography on silica (dry column), with diethyl ether–hexane (1:3) as eluent, furnished benzyl (2*S*,3*S*)-2-hydroxy-3-methylpentanoate as an oil (3.42 g, 44%); $[\alpha]_D^{23}$ −15.1° (*c* 1.0, EtOH) {lit.,[40] $[\alpha]_D^{23}$ −11.8° (*c* 1.0, EtOH)}; ν_{max}(neat)/cm⁻¹ 3490, 3080, 3040, 1730, 1500 and 1460; δ_H(90 MHz; $CDCl_3$) 0.90 (3 H, t, *J* 8.0, *Me*CH_2), 1.00 (3 H, d, *J* 7.0, *Me*CH), 1.30 (3 H, m, MeC*H*, MeCH_2), 2.72 (1 H, br s, OH), 4.10 (1 H, d, *J* 2.4, *H*COH), 5.20 (2 H, s, ArCH_2) and 7.34 (5 H, s, ArH).

Benzyl (2R,3S)-2-*Formyloxy*-3-*methylpentanoate* **38**.—To a solution of DEAD (1.89 g, 10.86 mmol) and formic acid (0.50 g, 10.86 mmol) in diethyl ether (25 cm³) was added dropwise an ethereal solution (25 cm³) of triphenylphosphine (2.86 g, 10.86 mmol) and benzyl (2*S*,3*S*)-2-hydroxy-3-methylpentanoate **37** (1.62 g, 7.27 mmol). A precipitate of triphenylphosphine oxide and diethyl hydrazinedicarboxylate was formed and the mixture was stirred overnight. The precipitate was filtered off, and the filtrate was concentrated, and then chromatographed on silica (dry column), with diethyl ether–hexane (1:2) as eluent, to give benzyl (2R,3S)-2-formyloxy-3-methylpentanoate **38** (1.59 g, 87%); $[\alpha]_D^{23}$ +39.6° (*c* 1.0, $CHCl_3$) {lit.,[9] $[\alpha]_D^{23}$ +23.3° (*c* 1.2, $CHCl_3$)}; ν_{max}(neat)/cm⁻¹ 3055, 3040, 2880, 1755, 1730, 1500 and 1460; δ_H(90 MHz; $CDCl_3$) 0.82 (3 H, t, *J* 7.0, *Me*CH_2), 0.85 (3 H, d, *J* 7.0, *Me*CH), 1.30 (2 H, m, MeCH_2), 1.95 (1 H, m, MeC*H*), 5.20 (1 H, d, *H*COCO, overlapping with 2 H, s, ArCH_2), 7.40 (5 H, s, ArH) and 8.19 (1 H, s, OOCH).

Benzyl (2R,3S)-2-*Hydroxy*-3-*methylpentanoate*.—A solution of benzyl (2*R*,3*S*)-2-formyloxy-3-methylpentanoate (1.60 g, 6.39 mmol) in methanol (50 cm³), to which 10 drops of 33% aq. ammonia had been added, was stirred at room temperature for 10 min. Extraction and chromatography on silica (dry column) with diethyl ether–hexane (1:3) as eluent furnished benzyl (2*R*,3*S*)-2-hydroxy-3-methylpentanoate as an oil (1.36 g, 96%); $[\alpha]_D^{23}$ +6.0° (*c* 1.1, EtOH) {lit.,[9] $[\alpha]_D^{23}$ +9° (*c* 1.1, EtOH)}; ν_{max}(neat)/cm⁻¹ 3490, 3080, 3040, 1730, 1500 and 1460; δ_H(90 MHz; $CDCl_3$) 0.86 (3 H, d, *J* 7.0, *Me*CH), 0.96 (3 H, t, *J* 7.0, *Me*CH_2), 1.36 (2 H, m, MeCH_2), 1.86 (1 H, m, MeC*H*), 2.79 (1 H, br s, OH), 4.15 (1 H, d, *J* 2.4, HCO), 5.20 (2 H, s, ArCH_2) and 7.30 (5 H, s, ArH).

Benzyl (2R,3S)-2-(*t-Butyldimethylsiloxy*)-3-*methylpentanoate*.—A solution of benzyl (2*R*,3*S*)-2-hydroxy-3-methylpentanoate (1.35 g, 6.05 mmol), and TBDMSCl (1.095 g, 7.26 mmol, 1.2 mol equiv.) in dry DMF (3 cm³) was stirred at room temperature for 16 h. After work-up with diethyl ether, the product was chromatographed on silica (dry column) and eluted with diethyl ether–hexane (1:20). Benzyl (2*R*,3*S*)-2-(t-butyldimethylsiloxy)-3-methylpentanoate was thus obtained as an oil (1.79 g, 91%); ν_{max}(neat)/cm⁻¹ 3080, 3040, 1755, 1730, 1500 and 1475; δ_H(90 MHz; $CDCl_3$) 0.00 (6 H, s, Me_2Si), 0.85 (3 H, d, *J* 7.0 Hz, *Me*CH), 0.95 (3 H, t, *Me*CH_2, overlapping with 9 H, s, Me_3CSi), 1.35 (2 H, m, MeCH_2), 1.80 (1 H, m, MeC*H*), 4.23 (1 H, d, *J* 4.0, HCOSi), 5.25 (2 H, s, ArCH_2) and 7.47 (5 H, s, ArH).

(2R,3S)-2-(*t-Butyldimethylsiloxy*)-3-*methylpentanoic Acid* **34**.—A solution of benzyl (2*R*,3*S*)-2-(t-butyldimethysiloxy)-3-methylpentanoate (1.73 g, 5.14 mmol) in ethyl acetate (37 cm³) was stirred under hydrogen in the presence of 10% palladium on carbon (0.35 g) until hydrogenolysis was complete (TLC). The catalyst was filtered off on a bed of Celite, and the filtrate was evaporated under reduced pressure to give (2*R*,3*S*)-2-(t-butyldimethylsiloxy)-3-methylpentanoic acid **34** as an oil (1.14 g, 90%); $[\alpha]_D^{23}$ +18.5° (*c* 1.06, EtOH) {lit.,[9] $[\alpha]_D^{22}$ +18.5° (*c* 1, EtOH)} [Found: *m/z*, 201.1670 (12.5%) ($M^+ - CO_2H$). Calc. for $C_{12}H_{26}O_3Si$: M, 246.1651; ($M - CO_2H$), 201.1674]; ν_{max}(neat)/cm⁻¹ 3300–3020br, 1730 and 1460; δ_H(250 MHz; $CDCl_3$) 0.095 (6 H, s, Me_2Si), 0.90 (3 H, d, *J* 7.1, *Me*CH), 0.93 (3

H, t, MeCH_2, overlapping with 9 H, s, Me_3CSi), 1.26 (1 H, m, MeCH_2CH), 1.46 (1 H, m, MeCH_2CH), 1.83 (1 H, m, MeCH), 4.19 (1 H, d, J 2.9, HCOSi) and 8.50 (1 H, br s, CO_2H); δ_C(62.85 MHz; $CDCl_3$) −4.9 (SiMe), 12.0 (C-5), 13.7 (C-6), 18.3 (SiCMe_3), 25.8 (SiCMe_3), 26.0 (C-4), 39.7 (C-3), 75.1 (C-2) and 177.8 (C-1).

Ethyl (8R,9S)-8-[(2′R,3′S)-2′-(*t-Butyldimethylsiloxy*)-3′-*methylpentanoyloxy*]-9,10-*epoxy*-9-*methyldeca*-2E,4E,6Z-*trienoate* **40**.—A solution of ethyl 9,10-epoxy-8-hydroxy-9-methyldeca-2*E*,4*E*,6*Z*-trienoate [a diastereoisomeric mixture, 67% in ethyl (8*R*,9*S*)-9,10-epoxy-8-hydroxy-9-methyldeca-2*E*,4*E*,6*Z*-trienoate] (0.058 g, 0.24 mmol), (2*R*,3*S*)-2-(t-butyldimethylsilyloxy)-3-methylpentanoic acid **34** (0.30 g, 1.2 mmol, 5 mol equiv.) and 4-pyrrolidinopyridine (4.3 mg, 0.1 mol equiv.) in methylene dichloride (1.5 cm^3) was treated with DCC (0.25 g, 1.2 mmol, 5 mol equiv.) and the mixture was stirred at room temperature for 24 h. The reaction mixture was then diluted with diethyl ether and dicylohexylurea was filtered off. After being washed sequentially with water, 5% acetic acid, and water, the filtrate was dried over anhydrous magnesium sulphate and evaporated under reduced pressure. Dry column chromatography of the residue on silica Woelm, and elution with diethyl ether–hexane (1:3), gave the ester **40** (0.10 g, 85%). Further purification by HPLC with diethyl ether–hexane (1:5) as eluent, furnished *ethyl* 8-(8R,9S)-[(2′,R,3′S)-(2′-(*t-butyldimethylsiloxy*)-3′-*methylpentanoyloxy*]-9,10-*epoxy*-9-*methyldeca*-2E,4E,6Z-*trienoate* **40** as an oil [Found: *m/z*, 467 (M + H^+ FAB). $C_{25}H_{42}O_6Si$ requires M, 466.2751]; ν_{max}(neat)/cm^{-1} 1750, 1710 and 1620; λ_{max}(EtOH)/nm 294 (ε/dm^3 mol^{-1} cm^{-1} 28 700); δ_H(400 MHz; $CDCl_3$) 0.05 (6 H, s, $SiMe_2$), 0.90 (3 H, d, J 6.8, *Me*CH), 0.93 (9 H, s, $SiCMe_3$), 0.94 (3 H, t, J 7.5, *Me*CH_2CH), 1.28 (1 H, m, MeC*H*HCH), 1.33 (3 H, t, J 7.2, *Me*CH_2O), 1.39 (3 H, s, MeCOC), 1.50 (1 H, m, MeCH*H*CH), 1.83 (1 H, m, MeC*H*), 2.63 (1 H, d, J 4.8, 10-H^a), 2.80 (1 H, d, J 4.8, 10-H^b), 4.15 (1 H, d, J 3.6, HCOSi), 4.24 (2 H, q, J 7.1, MeCH_2O), 5.56 (1 H, dd, J 10.0 and 10.0, 7-H), 5.75 (1 H, d, J 9.2, 8-H), 5.94 (1 H, d, J 15.3, 2-H), 6.33 (1 H, dd, J 11.2 and 11.2, 6-H), 6.43 (1 H, dd, J 14.8 and 11.3, 4-H), 6.96 (1 H, dd, J 14.8 and 11.6, 5-H) and 7.38 (1 H, dd, J 15.3 and 11.3, 3-H); δ_C(100.62 MHz; $CDCl_3$) −4.7 (SiMe), 12.0 (C-5′), 13.6 (C-2″), 14.4 (C-6′), 17.8 (C-11), 18.4 (SiCMe_3) 25.8 (SiCMe_3), 26.1 (C-4′), 39.7 (C-3′), 52.1 (C-10), 56.9 (C-9), 60.5 (C-1″), 71.6 (C-8), 75.0 (C-2′), 122.8 (C-2), 127.9 and 133.2 (C-4, -6 and -7), 134.6 and 143.80 (C-3 and -5), 166.8 (C-1) and 172.7 (C-1′).

Ethyl (8R,9S)-8-[(2′R,3′S)-2′-(*t-butyldimethylsiloxy*)-3′-*methylpentanoyloxy*]-9,10-*epoxy*-9-*methyldeca*-2E,4E,6E-*trienoate* **39**.—A solution of ethyl 9,10-epoxy-8-hydroxy-9-methyldeca-2*E*,4*E*,6*E*-trienoate [a diastereoisomeric mixture, 75% in ethyl (8*R*,9*S*)-9,10-epoxy-8-hydroxy-9-methyldeca-2*E*,4*E*,6*E*-trienoate] (0.082 g, 0.34 mmol), (2*R*,3*S*)-2-(t-butyldimethylsiloxy)-3-methylpentanoic acid **34** (0.42 g, 1.7 mmol, 5 mol equiv.), and 4-pyrrolidinopyridine (6.1 mg, 0.1 mol equiv.) in methylene dichloride (2 cm^3) was treated with DCC (0.35 g, 1.7 mmol, 5 equiv.) and the mixture was stirred at room temperature for 24 h. The reaction mixture was then diluted with diethyl ether and dicylohexylurea was filtered off. The filtrate was washed successively with water, 5% acetic acid, and water, dried ($MgSO_4$), and chromatographed on silica (dry column) with diethyl ether–hexane (1:3) as eluent to give the ester **39** (0.15 g, 90%). Further purification by HPLC, diethyl ether–hexane (1:5) as eluent, furnished *ethyl* (8R,9S)-8[(2′R,3′S)-2′-(*t-butyldimethylsiloxy*)-3′-*methylpentanoyloxy*]-9,10-*epoxy*-9-*methyldeca*-2*E*,4*E*,6*E*-*trienoate* **39** as an oil [Found: *m/z* 467 (M$^+$H, FAB). $C_{25}H_{42}O_6Si$ requires M, 466.2751]; ν_{max}(neat)/cm^{-1} 1750, 1710 and 1622; λ_{max}(EtOH)/nm 293; δ_H(400 MHz; $CDCl_3$) 0.04 (6 H, s, $SiMe_2$), 0.88 (3 H, d, J 6.7, *Me*CH), 0.91 (9 H, s, $SiCMe_3$), 0.93 (3 H, t, J 6.8, *Me*CH_2), 1.28 (1 H, m, MeC*H*CH), 1.30 (3 H, t, J 7.1, *Me*CH_2O), 1.34 (3 H, s, MeCOC), 1.50 (1 H, m, MeCH*H*), 1.83 (1 H, m, MeC*H*), 2.62 (1 H, d, J 4.8, 10-H^a), 2.79 (1 H, d, J 4.9, 10-H^b), 4.16 (1 H, d, J 3.6, HCOSi), 4.21 (2 H, q, J 7.1, MeCH_2O), 5.25 (1 H, d, J 7.1, 8-H), 5.82 (1 H, dd, J 15.0 and 7.0, 7-H), 5.92 (1 H, d, J 15.3, 2-H), 6.35 (1 H, dd, J 14.8 and 11.3, 4-H), 6.42 (1 H, dd, J 15.4 and 11.2, 5-H), 6.54 (1 H, dd, J 14.7 and 10.7, 6-H) and 7.29 (1 H, dd, J 15.3 and 11.2, 3-H); δ_C(100.62 MHz; $CDCl_3$) −4.7 (SiMe), 12.0 (C-5′), 13.7 (C-2″), 14.4 (C-6′), 17.4 (C-11), 18.3 (SiCMe_3), 25.8 (SiCMe_3), 26.1 (C-4′), 39.7 (C-3′), 52.5 (C-10), 56.7 (C-9), 60.5 (C-1″), 75.0 (C-2′), 75.9 (C-8), 122.2 (C-2), 130.8, 131.7 and 133.8 (C-4, -6 and -7), 138.7 and 143.8 (C-3 and -5), 167.0 (C-1) and 172.6 (C-1′).

Ethyl (8R,9S)-9,10-*Epoxy*-8-[(2′R,3′S)-2′-*hydroxy*-3′-*methylpentanoyloxy*]-9-*methyldeca*-2E,4E,6Z-*trienoate*, *AF-Toxin IIa*, *Ethyl Ester* **5**; R = Et.—A solution of ethyl (8*R*,9*S*)-8-[(2′*R*,3′*S*)-2′-(t-butyldimethylsiloxy)-3′-methylpentanoyloxy]-9,10-epoxy-9-methyldeca-2*E*,4*E*,6*Z*-trienoate (34.5 mg, 0.074 mmol) in THF (2 cm^3) was treated with tetrabutylammonium fluoride (74 mm^3 of a 1 mol dm^{-3} solution in THF; 1 mol equiv.). The solution was stirred at room temperature for 20 min, then was evaporated to dryness under reduced pressure. The residue was taken up in diethyl ether and the solution washed (water) and dried ($MgSO_4$). Dry column chromatography of the residue on silica with diethyl ether–hexane (1:1) as eluent furnished *ethyl* (8R,9S)-9,10-*epoxy*-8-[(2′R,3′S)-2′-*hydroxy*-3′-*methylpentanoyloxy*]-9-*methyldeca*-2E,4E,6Z-*trienoate* **5**; R = Et as an oil (16.4 mg, 63%); $[\alpha]_D^{23}$ +153° (*c* 0.78, EtOH) [Found: M$^+$, 352.1814 (0.72%). $C_{19}H_{28}O_6$ requires M, 352.1886]; ν_{max}(neat)/cm^{-1} 3500, 1730, 1710 and 1620; λ_{max}(EtOH)/nm 293 (ε/dm^3 mol^{-1} cm^{-1} 37 500). For ^{1}H NMR data see Table 4. For ^{13}C NMR data see Table 5.

Ethyl (8R,9S)-9,10-*Epoxy*-8-[(2′R,3′S)-2′-*hydroxy*-3′-*methylpentanoyloxy*]-9-*methyldeca*-2E,4E,6E-*trienoate*, *AF-Toxin IIc Ethyl Ester* **3**; R = Et.—A solution of ethyl (8*R*,9*S*)-8-[(2′*R*,3′*S*)-2′-(t-butyldimethylsiloxy-3′-methylpentanoyloxy]-9,10-epoxy-9-methyldeca-2*E*,4*E*,6*E*-trienoate (42.0 mg, 0.091 mmol) in THF (3 cm^3) was treated with tetrabutylammonium fluoride (91 mm^3 of a 1 mol dm^{-3} solution; 1 mol equiv.) and the mixture was stirred at room temperature for 20 min. The product, after evaporation and washing, was chromatographed on silica (dry column) to give *ethyl* (8R,9S)-9,10-*epoxy*-8-[(2′R,3′S)-2′-*hydroxy*-3′-*methylpentanoyloxy*]-9-*methyldeca*-2E,4E,6E-*trienoate* **3**; R = Et as an oil (19.2 mg, 60%); $[\alpha]_D^{23}$ −4.4° (*c* 0.90, EtOH) [Found: M$^+$, 352.1900 (0.98%). $C_{19}H_{28}O_6$ requires M, 352.1886]; ν_{max}(neat)/cm^{-1} 3479, 1729, 1709 and 1619; λ_{max}(EtOH)/nm 292 (ε/dm^3 mol^{-1} cm^{-1} 54 000). For ^{1}H NMR data see Table 3. For ^{13}C NMR data see Table 5.

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