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SYNTHESIS OF THE HOST-SELECTIVE PLANT TOXINS AF IIa, AF IIc and AKII, EMPLOYING SHARPLESS CHIRAL EPOXIDATION UNDER KINETIC CONTROL

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SUMMARY: Sharpless chiral epoxidation of the ethyl esters of (2E,4E,6Z) -, (2E,4E,6E)- and (2E,4Z,6E)-8-hydroxy-9-methyldeca-2,4,6,9-tetraenoic acid gave predominantly the (8R,9S)-epoxyalcohols. These were converted into the host-specific plant toxins AF IIa, AF IIc and AK II, thereby effecting a total synthesis of these compounds.

In the preceding communication[1] a synthesis of (2E,4E,6Z)-, (2E,4E,6E)- and (2E,4Z,6E)-hydroxytetraene esters (1) - (3) by hydrostannation and Pd^0 coupling was developed. These alcohols now form the basis of our synthesis of the two strawberry-type toxins AF IIa and AF IIc (4 and 5),[2] and the pear type AK II (6),[3] as their ethyl esters. Synthetic development of (1) - (3) demands selective epoxidation forming (S)-chirality at C-9, together with the introduction of (R)-chirality at C-8. In order to effect this we have explored Sharpless' procedure[4] using recently described conditions[5] which permit kinetic resolution as well as stereofacial control. Preliminary epoxidations showed that the 9,10- allylic double bond was substantially more reactive than the 6,7-, as expected.

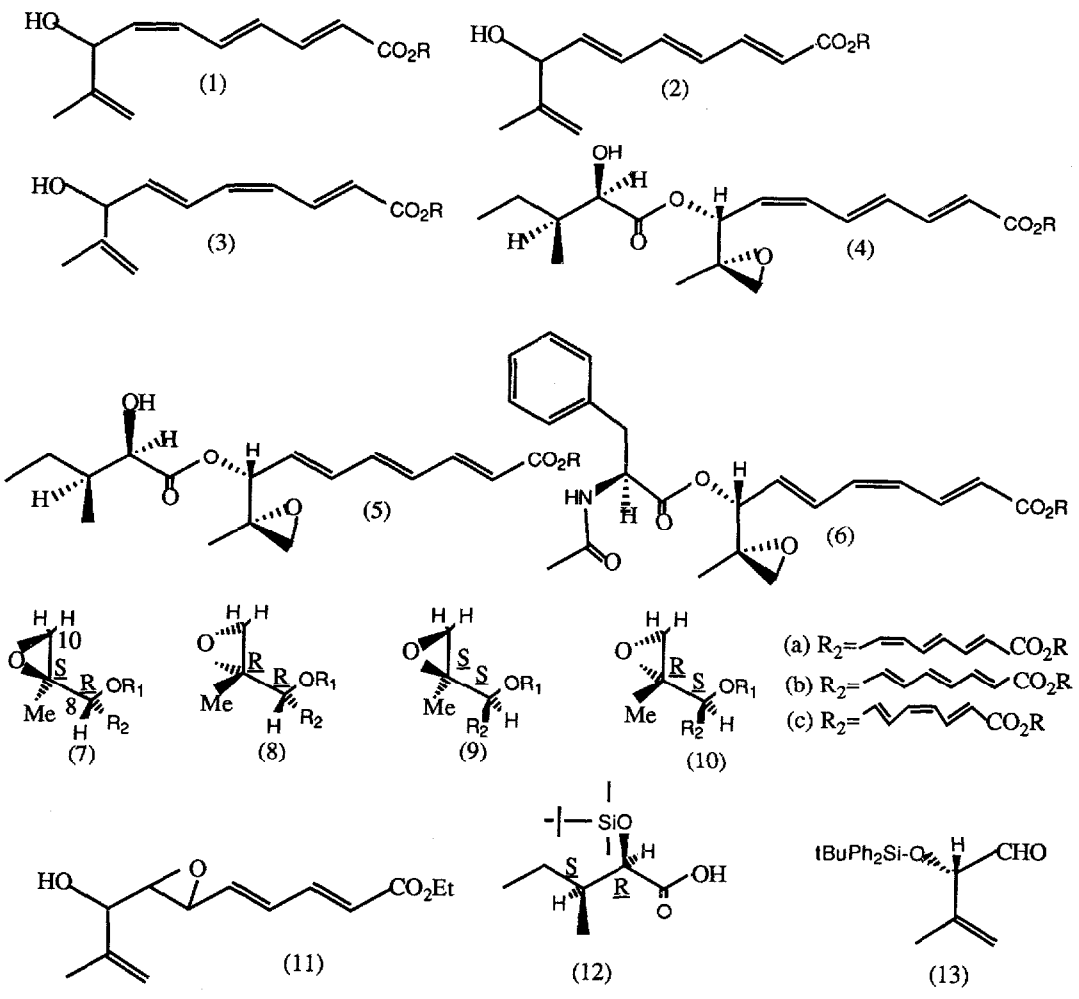
The results of Sharpless epoxidation are shown in Table 1. In the case of the all-trans-tetraene ester (2), the yield was lowered through formation of some unwanted 6,7-epoxide (11):

TABLE 1

Alcohol	Epoxide*	$[\alpha]^{23}$ (EtOH)
(1)	63% (A)	+13.6° (c,0.85)
(2)	58% (B)	+51.1° (c,0.66)
(3)	67% (C)	+72.0° (c,0.85)

*Yield based on 50% conversion

Consideration of literature data[4,5,6,7] indicated that the (D)-(-)-diisopropyl tartrate (DIPT) / $Ti(OPr^i)_4$ / Bu^tOOH system should lead to the (S)-epoxide with the major, rapidly formed, epoxide being the desired (8R,9S) (7), along with small amounts of the enantiofacial isomer (8). The slow-forming epoxide should be (9), though enantiofacial selectivity seems less pronounced in the slow reaction and appreciable amounts of (10) might be formed. Structural examination (i.r., u.v., ^{1}H.n.m.r., ^{13}C.n.m.r. and accurate mass data) confirmed that all three products of Table 1. had retained the correct 9,10-epoxy-



triene structures with triene geometry unaltered. For chiral analysis and for product isolation it was decided to esterify the epoxy-alcohol mixture (C) obtained from (3) with N- acetyl L-phenylalanine, and those, (A) and (B), from (1) and (2), with the silylated acid (12). The latter was synthesised by a procedure outlined by Irie and his colleagues[8] following a sequence that involves diazotisation of isoleucine, replacement by hydroxyl with retention, and then Mitsunobo inversion. The (2R,3S)-silylated acid (12) had $[\alpha]^{23}$ +18.5° (c,1.0, EtOH).Esterification of the product (A) with (12) using DCC and 4-pyrrolidinopyridine[10] followed by chromatography, gave as the major ester the (8R,9S,2'R,3'S)-(7a, R_1 = (12)) (66% 0f the mixture). Its ^{1}H.n.m.r. spectrum [the double doublet form of H-10a and H-10b at ~2.63 and 2.88 is characteristic of the (8R,9S) system] and ^{13}C.n.m.r. spectra indicated >96% purity with the correct (2E,4E,6Z)-geometry. Desilylation (63%) with tetra-n-butylammonium fluoride gave

AF IIa toxin ethyl ester (characterised by u.v., i.r., ^{13}C.n.m.r. and M+),[α]^{23} +153.3^{0} (c,0.78, EtOH), with ^{1}H.n.m.r. data identical with those published for the natural methyl ester,[2] except for ethyl ester resonances.[10] The remainder of the silylated product (34%) consisted of two difficultly separable (hplc) diastereoisomers of (7a, R_1 = (12)), as indicated by n.m.r. spectroscopy. It seems likely that these are the (8R,9R,2'R,3'S)-(8) and (8S,9S,2'R,3'S)-(9) diastereoisomers, the former the minor product of the fast reaction, the latter the major product of the slow reaction; both are spectroscopically differentiated from (7a,R_1 = (12)).

In a similar way, esterification (90%) of protected alcohol B gave on esterification with (12), followed by hplc, a major band (75%) and a minor band (25%) The former, (7b,R_1 = (12)), having the expected spectral and other data, was desilylated (60%) to give the (8R,9S,2'R,3'S,2E,4E,6E)-stereoisomer (5) having ^{1}H.n.m.r. data identical[11] with those given for AF toxin IIc[2] (except for ethyl ester resonances). It was characterised as for the AF IIa compound (above) and had [α]^{23} -4.5^{o} (c, 0.90, EtOH). Again, the smaller band contained two difficultly separable diastereoisomers, thought to be the (8R,9R,2'R,3'S)- and the (8S,9S,2'R,3'S)-.

The third synthesis, that of AK toxin II, had an added complication in that during the esterification of the protected epoxy-alcohol product C, racemisation of the N-acetyl-L- phenylalanine occurred. The ester mixture (75%) furnished, on hplc (silica, elution ethyl acetate (1)/hexane (1)), two pairs of bands, each in the ratio 34 : 16. The two larger bands were spectroscopically very similar and comparison showed that they differed only in ^{1}H resonances around the 2'-centre, especially the 3'-protons (faster running: quartet δ3.11 - 3.15, slower: doublet 3.12, J 6Hz). The slower running band [α]^{23} +52.9^{o} (c, 0.65, EtOH) had ^{1}H n.m.r. data identical, except for ethyl ester resonances, with the data published for AK-toxin II,[12] the structure of which is established by a single crystal X-ray determination as the (8R,9S,2'S,2E,4Z,6E)- diastereoisomer.[3] The faster eluted product is therefore (2'R), [α]^{23} +30.5^{o} (c, 0.45,EtOH); both were characterised as previously. Again the two smaller bands appear to each contain (8c) and (9c) with R_1 in one case N-acetyl-L-phenylalanine and in the other the -D-.

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[10] ^{1}H.n.m.r. data for synthetic (4, R = Et) with data for natural AF IIa toxin methyl ester in parentheses: δ H-2, 5.95d, J15.3Hz (5.95d, J15.6); H-3, 7.36dd, J11.3,15.3Hz (7.37dd, J11.2,15.6); H-4, 6.41dd, J11.3,14.8 Hz (6.40dd,J11.2,15.0); H-5, 6.92dd,J11.7,14.6Hz (6.93dd,J11.6,15.0); H-6, 6.33dd,J11.2,11.2Hz (6.33dd,J10.7,11.6); H-7, 5.52dd,J10.2,10.2Hz (5.52dd,J9.6,10.7); H-8, 5.82d,J10Hz (5.80dJ9.6); H-10A, 2.62d,J4.8Hz (2.62d,J4.6); H-10B, 2.78d,J4.7Hz (2.78d,J4.6); H-11, 1.38s (1.38br.s); H-2', 4.20d,J3.0Hz (4.19dd,J2.7,5.7); H-3',1.83m (1.83m); H-4', 1.37-1.54m (1.36m); H-5', 0.97t,J7.4Hz (0.97t,J7.6); H-6', 0.86d,J6.8Hz (0.87d,J6.9); OH 2.63br.s (2.59d,J5.7).

[11] ^{1}H.n.m.r. data for synthetic (5, R = Et) with data for natural AF IIc toxin methyl ester in parentheses: δ H-2, 5.93d,J15.3 (5.94d,J15.2); H-3, 7.29dd,J11.1,15.2Hz (7.29dd,J 11.2,15.2); H-4, 6.38dd,J11.0,14.7Hz (6.39dd,J11.2,14.4); H-5, 6.43dd, J11.0,15.1Hz (6.43dd,J10.7,14.9); H-6, 6.53dd,J10.6,14.7Hz (6.53dd,J10.7,14.4); H-7, 5.81dd,J7.3,14.8Hz (5.80dd,J7.4,14.8); H-10A, 2.63d,J4.8Hz (2.62d,J4.8); H-10B, 2.79d,J4.8Hz (2.78d,J4.8); H-11, 1.36s (1.36s); H-2', 4.23d,J2.7Hz (4.21dd,J2.8,5.8); H-3', 1.83m (1.83m); H-4', 1.36-1.56m (1.36m); H-5', 0.98t,J7.4Hz (0.97t,J7.5); H-6', 0.85d,J6.9Hz (0.87d,J6.9); OH, 2.64br.s (2.60d,J5.8).

[12] ^{1}H.n.m.r. data for synthetic (6, R = Et) with data for AK II toxin methyl ester in parentheses: δ H-2, 5.95d,J15.2Hz (5.95d,J15.4); H-3, 7.69dd,J15.1,11.5Hz (7,70dd,J15.4,11.5); H-4, 6.20dd,J11.2,11.2Hz (6.20dd,J11.5,11.5); H-5, 6.28dd,J10.9,10.9Hz (6.29dd,J11.5,11.5); H-6, 6.84dd,J15.15,11.2Hz (6.84dd,J15.0,11.5); H-7, 5.69dd,J15.2,7.9Hz (5.70dd,J15.0,7.7); H-8, 5.27d.J7.9Hz (5.27d,J7.7); H-10A, 2.62d,J4.7Hz (2.61d,J4.6); H-10B, 2.75d,J4.75Hz (2.75,J4.6); H-11, 1.31s (1.31s); H-2', 4.91m; H-3', 3.12d,J6.1 (3.12d,J6.2); H-5' and 9', 7.09dd,J7.7,1.6Hz (7.08dd,J7.9,1.6); H-6',7',8', 7.21-7.27m (7.20-7.35m); H-11', 2.01s (2,01s); NH, 5.99br.s (5.92-5.95s)

[13] Irie and his colleagues have recently reported different syntheses of AK II and AF IIc toxins[8] based on (13), obtained by a lengthy (11 stage) degradation of Vitamin C as a chiral source.[14]

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