Tetrahedron Letters,Vol.30,No.32,pp 4299-4302,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Maxwell Pergamon Macmillan plc

SYNTHESIS OF THE (2E,4Z,6E)-, (2E,4E,6E)- and (2E,4E,6Z)-TETRAENOL STEMS OF THE HOST-SELECTIVE AK AND AF TOXINS BY HYDROMETALLATION

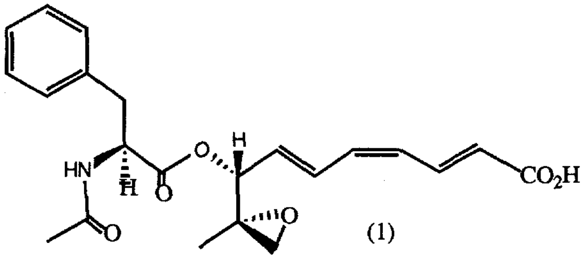
Leslie Crombie, Mark A. Horsham and Sandra R. M. Jarrett.
Department of Chemistry, The University of Nottingham. Nottingham, NG7 2RD.

SUMMARY: Hydrozirconation and hydrostannation, together with Pd^o catalysed coupling, are used to make (2E,4Z,6E)-, (2E,4E,6E)- and (2E,4E,6Z)-tetraenol stems as synthetic intermediates for synthesis of the AK-II, AF-IIc, AF -IIa host-selective plant toxins.

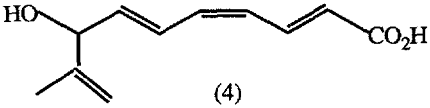
Host-selective toxins produced by fungi can show highly selective toxicity towards cultivar types of the host plant and cause large scale economic damage particularly towards newly introduced cultivars.[1] The structures of the host-selective AK-toxin II (1),[2] produced by Alternaria kikuchiana Tanaka, the cause of black-spot disease in susceptible cultivars of the Japanese pear,[3] as well as AF-toxins IIa (2) and IIc (3)[4] from the specific strawberry pathotype of Alternaria alternata (Fries) Keisler[5] have been elucidated. Our synthetic approach to these structures led to a requirement for the triene structures (4)-(6), and we have approached the problem by hydrometallation techniques.

The acetylenic alcohol (7, R=H)[6] was made in 72% yield by treating methacraldehyde with acetylene magnesium bromide in THF at 0°C and then tertiarybutyldimethylsilylated[7] (89%). The protected alcohol was treated with bis(cyclopentadienyl)zirconium (zirconocene) chloride hydride in dry benzene under argon[8] to give (8a) which, in a model reaction, was coupled with the trans-vinyl bromo-ester (9) in the presence of a Pd^o catalyst[9] made from bis-triphenylphosphine palladium (II) chloride and di-isobutylaluminium hydride in THF to give the protected triene (10a) (56%). However, the latter proved unexpectedly resistant to deprotection by tertiarybutylammonium fluoride in THF[10] and yields were poor, so (7,R=H) was protected by treatment with dihydropyran (77%) and also by ethyl vinyl ether (80%). Some deprotection was observed during hydrozirconylation of both (7a) and (7b) and yields of (10b) and (10c) after Pd^o coupling were modest (42 and 41% respectively). They were however, readily deprotected (>90% yield) under acid conditions.

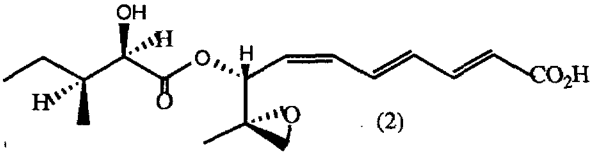
For extension of the coupling to give tetraenes (4) and (6), the (2E,4Z)- and (2E,4E)-esters (13) and (14) were made by Wittig reaction[11] between (11) and (12), the isomers being separated by reversed-phase h.p.l.c. Coupling (Pd^o) of (14) with (8) gave (15) in yields of 25%,14% and 10% for the three protecting groups (a) - (c). Again, although the desired (2E,4Z,6E)-geometry was obtained, coupling of (13) with (8) gave yields of only 25%, 12% and 10% for the three protecting groups (a) - (c). In view of these poor yields, and the unsatisfactory TBDMS deprotection by F$^-$, attention was turned to hydrostannation in which a free hydroxyl is tolerated.



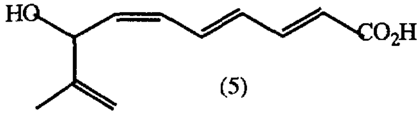
(1)



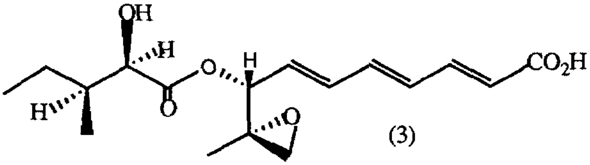
(4)



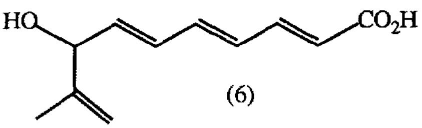
(2)



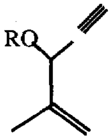
(5)



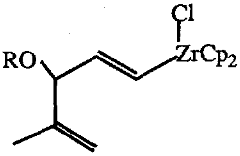
(3)



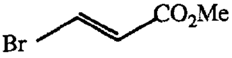
(6)



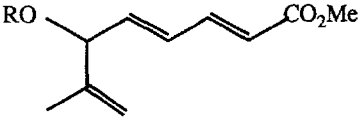
(7)



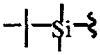
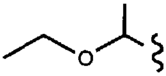
(8)

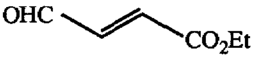


(9)



(10)

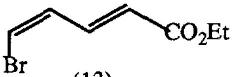
(a) R =  (b) R = Thp (c) R = 



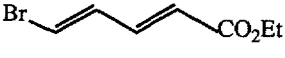
(11)

$Ph_3P{=}CHBr$

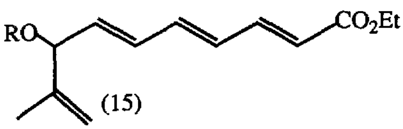
(12)



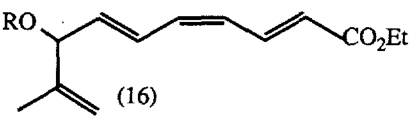
(13)



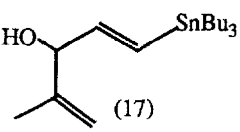
(14)



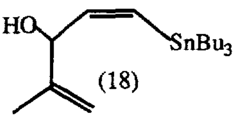
(15)



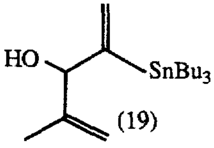
(16)



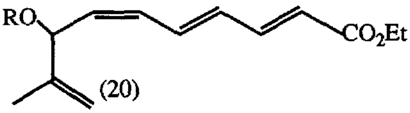
(17)



(18)



(19)



(20)

Hydrostannation of (7, R=H), using 1.3 equiv. of tributyltin hydride in the presence of azobisisobutyronitrile[12] for 2h at 80°C gave (17) (53%), a stable product which could be stored at 20°C for a long period, along with a difficultly separable ~ 1:1 mixture (30%) of (18) and (19). Fortunately the (Z)-isomer (18) could be obtained in 80% yield by an alternative route,[13] treatment of (7, R=H) with 0.5 mol of lithium aluminium hydride in THF followed by treatment with tributyltin triflate at -78°C and work up with ammonia and aqueous methanol. The results of coupling the (E)- stannene (17) with the (2E,4E)- vinyl bromide (14) and its (2E,4Z)- isomer (13) are shown in Table 1, along with the coupling of the (Z)- stannene with (14). Reactions[14] were smooth and highly stereoselective and provide the basis for the synthesis of the AK and AF toxins described in the next communication. Coupling constants for the protons attached to the unsaturated carbons, along with ^{13}C.n.m.r. data, confirm the stereochemical assignments for the tetraene esters (4) - (6).

TABLE 1.

Vinyl tin	Vinyl halide	Catalyst[a]	Product	Yield
(17)	(9)	A	(10, R=H)	81%
(17)	(14)	A	(15, R=H)	72%
		B	(15, R=H)	65%
(17)	(13)	A	(16, R=H)	70%
		B	(16, R=H)	50%
(18)	(14)	A	- - -	0%[b]
		B	(20, R=H)	60%

[a] A = $(Ph_3P)_2PdCl_2$/ DMF; B = $(MeCN)_2PdCl_2$/ DMF.

[b] No reaction after 24h.

REFERENCES

[1] J.M. Daly and H.W. Knoche in 'Advances in Plant Pathology', 1983. 1, 83. Ed. D.S. Ingram and P.H. Williams, Academic Press, London and New York.

[2] T. Nakashima, T. Ueno, H. Fukami, T. Taga, H. Masuda, K. Osaki, H. Otani, K. Kohimoto and S. Nishimura, Agric. Biol. Chem., 1985, 49, 807. T. Nakashima, T. Ueno and H. Fukami, Tetrahedron Lett., 1982, 4469.

[3] H. Otani, K. Kohmoto, S. Nashimura, T. Nakashima, T. Ueno and H. Fukami, Ann. Phytopath. Soc. Japan, 1985, 51, 285.

[4] S. Nakatsuka, K. Ueda, T. Goto, M. Yamamoto, S. Nishimura and K. Kohmoto, Tetrahedron Lett., 1986, 27, 2753.

[5] N. Maekawa, M. Yamamoto, S. Nishimura, K. Kohmoto, M. Kuwada and Y. Watanabe, Ann. Phytopath. Soc. Japan, 1984, 50, 600. M. Yamamoto, S. Nishimura, K. Kohmoto and H. Otani, Ann. Phytopath. Soc. Japan, 1984, 50, 610.

[6] M. Malacria and M. Ronmestant, Tetrahedron, 1977, 33, 2813.

[7] J.M. Aizpura and C. Palomo, Tetrahedron Lett.,1985, 26, 475.

[8] D.W. Hart, T.F. Blackburn and J. Schwartz, J. Am. Chem. Soc., 1975, 97, 679.

[9] N. Okukado, D.F. Van Horn, W.C. Klima and E. Negishi, Tetrahedron Lett., 1978, 1027.

[10] For similar difficulties see E.J. Corey and A. Venkateswarlu, J. Am. Chem. Soc., 1972, 94, 6190.

[11] M. Matsumoto and K. Kuroda, Tetrahedron Lett., 1980, 21, 4021.

[12] Conditions of M.E. Jung and L.A. Light, Tetrahedron Lett., 1982, 23, 3851.

[13] E.J. Corey and T. Eckrich, Tetrahedron Lett., 1984, 25, 2415.

[14] The conditions used were similar to those of J.K. Stille and B.L. Groh, J. Am. Chem. Soc., 1987, 109, 813

(Received in UK 16 June 1989)