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STEREOCONTROLLED SYNTHESES OF STROBILURIN A AND ITS (9E)-ISOMER

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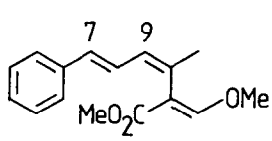
Summary: The (E,Z,E)-configuration (1) of the strobilurins has been confirmed by stereocontrolled synthesis.

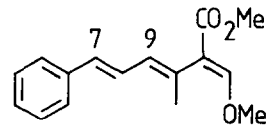
Strobilurin A (1), known also as mucidin,[1] is a fungicidal natural product found in the basidiomycete fungi Oudemansiella mucida[2] and Strobilurus tenacellus.[3] Three additional strobilurins in which the phenyl ring of strobilurin A is substituted, as well as the structurally-related natural products oudemansin A, oudemansin B and myxothiazol, have also been reported.[4]

Strobilurin A was first isolated by Musílek and his co-workers in 1969,[2] its structure being disclosed in a patent filed in 1974.[5] Prior to publication of the patent, the compound was independently isolated from another source but it was incorrectly assigned the (all-E)-configuration (2).[3] A total synthesis compounded this error because it included an ambiguous photo-isomerisation step.[6] More recently, spectroscopic and chemical evidence[7] supports the assignment of the (E,Z,E)-configuration (1) for the natural product.

We now report the first stereocontrolled syntheses of strobilurin A (1) and its (9E)-isomer (2). Comparison of our spectroscopic data with those recorded for the natural product confirms that strobilurin A and, by analogy, the related strobilurins,[4] have the (E,Z,E)-configuration (1).



(1)



(2)

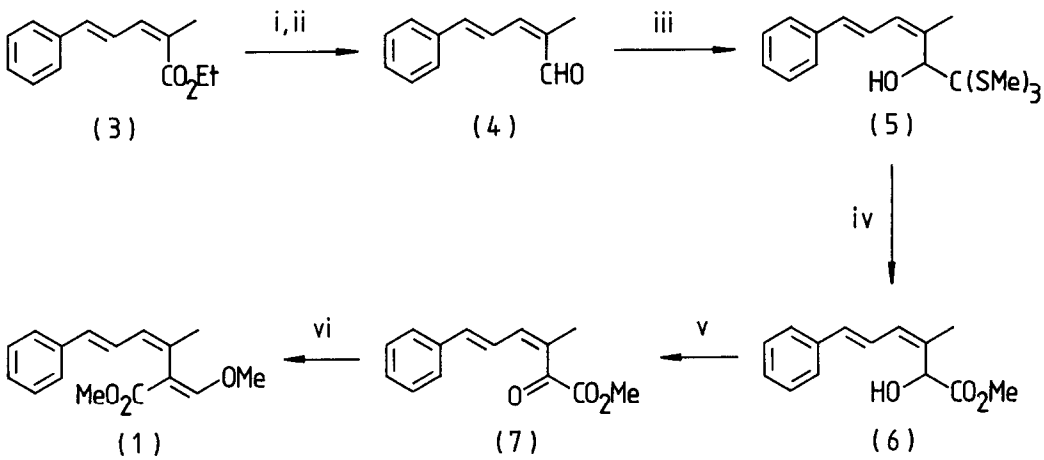
The (Z,E)-dienoate (3)[8] was chosen as starting material for the synthesis of strobilurin A (1). The four geometric isomers of the corresponding methyl ester have been characterised,[9] allowing the configuration of the dienoate (3) to be assigned with certainty. In particular, the chemical shift (δ20.9 p.p.m.) of the vinyl methyl carbon in the ^{13}C-n.m.r. spectrum confirms the (2Z)-configuration.[10]

Reduction of the (Z,E)-dienoate (3) followed by partial oxidation of the resulting allylic alcohol gave the (Z,E)-dienal [(4); 84% over both steps] as a crystalline solid, m.p. 76-77°C. Treatment of the dienal with tris(methylthio)methyl-lithium[11] gave, after aqueous work-up, the (Z,E)-dienol (5), an oil, containing about 10% of the isomeric (E,E)-dienol. Methanolysis[11] then gave the (Z,E)-hydroxyester (6) [42% from the dienal (4)], also an oil, containing about 10% of the isomeric (E,E)-hydroxyester.[12] Oxidation of the (Z,E)-hydroxyester gave the (Z,E)-ketoester (7)[13] and, since this was found to isomerise very readily to the corresponding (E,E)-isomer (9), it was treated immediately with methoxymethylenetriphenylphosphorane[6,7] to give strobilurin A (1) [26% from the hydroxyester (6)] containing about 15% of the corresponding (9E)-isomer (2). Subsequent purification by HPLC[14] gave isomerically-pure strobilurin A (1) as a pale yellow oil, spectroscopic data for which agree very closely with those recorded for the natural product.[3,4] Particularly characteristic features are the main absorption in the UV spectrum (MeOH) at 293nm, the chemical shift ($CDCl_3$) of the vinyl methyl carbon at δ23.7 p.p.m, and the chemical shift ($CDCl_3$) of the olefinic proton on C-8 at δ6.62 p.p.m.

The (9E)-isomer (2) of strobilurin A was prepared from the (E,E)-dienoate (10)[8] *via* the (E,E)-ketoester (9)[13] using the steps described above for the synthesis of strobilurin A. No stereomutation was observed at any stage. Once the geometry of the intermediate ketoester (9) had been established, it was prepared more easily by reaction of the stable ylide (8)[15] with (E)-cinnamaldehyde in refluxing toluene (65% yield). In an alternative approach to the (9E)-isomer (2) of strobilurin A, the (E,E)-dienoate (10) was converted without stereomutation into the homologous (E,E)-dienoate (11).[16] The methoxymethylene unit was then introduced stereospecifically by elimination of methanol from the acetal (12).[17] The (9E)-isomer (2) of strobilurin A prepared by these methods, a cream-coloured solid, m.p. 83-85°C (lit.[7] 75-77°C), was quite distinct from strobilurin A (1). The following spectroscopic features, in particular, differ very significantly from the natural product: the main absorption in the UV spectrum (MeOH) at 304nm, the chemical shift (D_6-acetone) of the vinyl methyl carbon at δ16.9 p.p.m., and the chemical shift ($CDCl_3$) of the olefinic proton on C-8 at δ7.08 p.p.m.

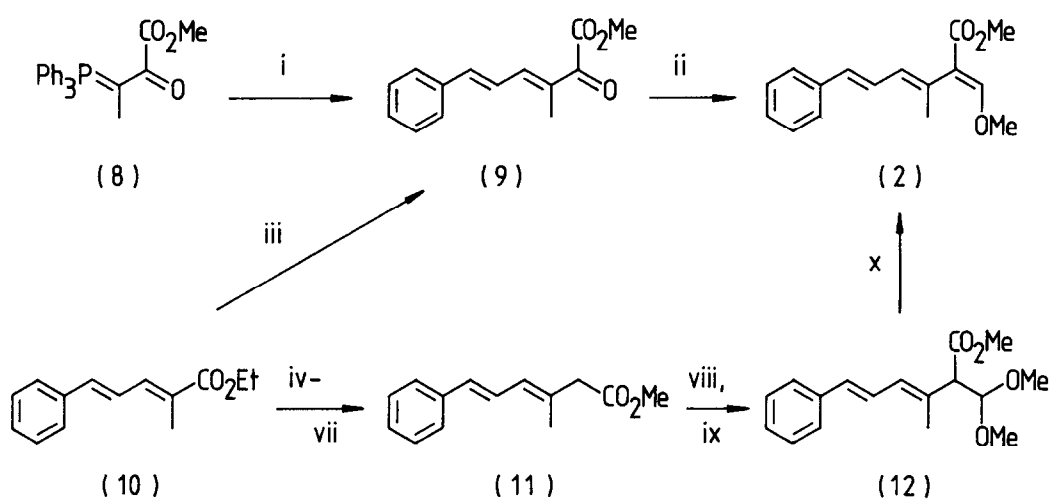
Our synthetic strobilurin A (1) shows activity *in vitro* against a range of plant pathogenic fungi, while its (9E)-isomer (2) is devoid of fungicidal activity.

SCHEME 1



REAGENTS: i, $LiAlH_4$, Et_2O, 0°C, 1h.; ii, MnO_2, CH_2Cl_2, room temp., 3h.; iii, $LiC(SMe)_3$, THF, -70°C; iv, $HgCl_2$, HgO, MeOH : H_2O, 12 : 1, room temp., 15 mins.; v, MnO_2, CH_2Cl_2, room temp., 10 mins., darkness; vi, Ph_3P:CHOMe, Et_2O, room temp., 45 mins., darkness.

SCHEME 2



REAGENTS: i, (E)-Cinnamaldehyde, refluxing PhMe, 16h.; ii, Ph_3P:CHOMe; iii, As Scheme 1; iv, $LiAlH_4$; v, PBr_3, py, Et_2O, 5°C; vi, $LiC(SMe)_3$;[11] vii, $HgCl_2$, HgO, MeOH, H_2O;[11] viii, LDA then Me_3SiCl; ix, $(MeO)_3CH$, $TiCl_4$;[16] x, LDA, THF, -70°C.

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8. Reaction of ethyl pyruvate with the phosphorane derived from (E)-cinnamyltriphenylphosphonium bromide ($Bu^tO^-K^+$, Et_2O, room temperature, 30 mins.) gave a 5 : 4 mixture of the (Z,E)- (3) and (E,E)- (10) isomeric dienoates (72%). Reaction of (E)-cinnamaldehyde with (carbethoxyethylidene)triphenylphosphorane (CH_2Cl_2, room temperature, 2h.) gave a 1 : 10 mixture of the same dienoates (3) and (10) respectively (88%). These dienoates, both oils, were easily separated by chromatography. ^{13}C-n.m.r. ($CDCl_3$) : (E,E)-dienoate (10) : δ 12.9, 14.4, 60.6 p.p.m; (Z,E)-dienoate (3) : δ 14.4, 20.9, 60.3 p.p.m.

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12. (Z,E)-Hydroxyester (6) : ^{1}H-n.m.r. ($CDCl_3$) : δ 5.47 (H.COH, br s), 7.34 (PhCH:CH, dd J 16 and 12Hz) p.p.m. The corresponding protons in the isomeric (E,E)-hydroxyester have chemical shifts of δ 4.69 and 7.08 p.p.m. respectively.

13. (Z,E)-Ketoester (7) : a yellow oil, ^{13}C-n.m.r. ($CDCl_3$) : δ 19.6, 52.5 p.p.m; (E,E)-Ketoester (9) : a pale yellow solid, m.p. 51-52°C (lit.[7] 48-50°C), ^{13}C-n.m.r. ($CDCl_3$) : δ 10.7, 52.5 p.p.m.

14. 40% Diethyl ether in hexane on a Zorbax SIL column.

15. The ylide (8) was prepared (50%) from ethylidenetriphenylphosphorane and dimethyl oxalate in DMSO (compare: M. Le Corre, Bull.Soc.Chim.Fr., 1974, No. 9-10, 1951). M.p. 210°C (decomp.), ^{1}H-n.m.r. ($CDCl_3$) : δ 1.72, (3H, d J 16Hz), 3.80 (3H, s) p.p.m., ^{31}P-n.m.r. ($CDCl_3$, P_4O_6 reference) δ -91.9 p.p.m., IR (nujol) : 1 725 cm^{-1}, MS(EI) : 376 (M^+, 4%), 318 and 317 (24 and 100% respectively, M-CO_2Me).

16. (E,E)-Dienoate (11) : an almost colourless oil, IR (film) : 1 740 cm^{-1}, ^{1}H-n.m.r. ($CDCl_3$) : δ 1.93 (3H, s), 3.11 (2H, s), 3.70 (3H, s), 6.08 (1H, d J 10Hz), 6.47 (1H, d J 15Hz), 6.96 (1H, dd J 15 and 10Hz) p.p.m., ^{13}C-n.m.r. ($CDCl_3$) : δ 17.2, 45.1, 51.8 p.p.m.

17. The dienoate (11) was converted into the acetal (12) using Mukaiyama's method. See, for example, K. Saigo, M. Osaki and T. Mukaiyama, Chem.Letts., 1976, 769.

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