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FIRST TOTAL SYNTHESIS OF STROBILURIN B

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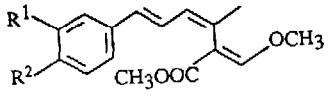
Abstract: A general approach to the synthesis of all known strobilurins - a class of natural products - is outlined with strobilurin B as an example.

Strobilurin A (**1**) was first isolated in 1969 under the name of mucidin by Musilek and co-workers[1] from the fungus *Oudemansiella mucida*. The structure as well as a total synthesis of this compound was disclosed in a patent by the same authors[2]. Independently, Anke, Steglich and co-workers discovered strobilurin A (**1**) and B (**2**) in a culture of *Strobilurinus tenacellus*[3]. The configuration of the double bonds was initially assigned incorrectly (all E) but later corrected in the course of a total synthesis of strobilurin A (**1**)[4]. A stereo-controlled synthesis of both isomers of strobilurin A (**1**)[5] finally confirmed the reassigned E,Z,E-configuration definitively. Since then two further members of the strobilurin family (**3**)[6] and **4**)[7]) as well as the closely related hydroxystrobilurin D[8], oudemansin A[9] and B[10] have also been isolated and described.



	R^1	R^2		R^1	R^2
1	H	H	3		H
2	OCH_3	Cl	4	H	OCH_3

The strong antifungal activity of these compounds and their inhibition of eucariotic respiration has stimulated considerable synthetic interest in this group of compounds. This resulted in three total syntheses of strobilurin A (**1**)[2),4),5)] as well as several ones of oudemansins[11].

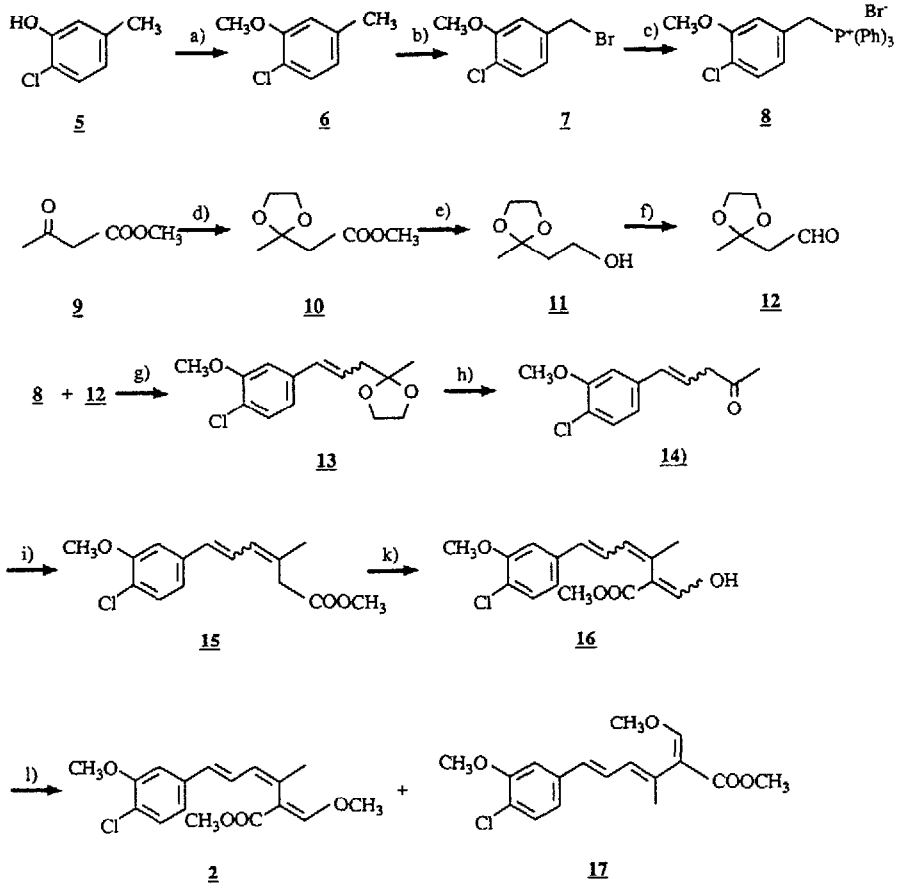
Our original approach to strobilurin B (**2**) was through a reaction sequence analogous to Steglich's original synthesis of strobilurin A (**1**)[4]. However, in contrast to the facile reaction of cinnamic aldehyde itself, 4-chloro-3-methoxycinnamicaldehyde did not react with 2-ketobutyric acid or any other suitable partner in an aldol type condensation under all conditions tried. We assume that the donor effect of the aromatic substituents decreases the reactivity of the aldehyde and may lead to an unfavourable equilibrium in this reaction. Therefore, it was decided to search for an alternative, more general approach to the strobilurins.

Our strategy was based on building up the polyolefinic side chain by consecutive Wittig reactions. This approach is at first glance disadvantageous due to the low degree of stereoselectivity often obtained in these reactions. However, here this fact was welcome, since it provided us with the possibility of comparing the biological activity of the different isomers.

Alkylation of 4-chloro-3-hydroxytoluene (**5**) with dimethylsulfate (-> **6**) followed by radical bromination of the alkyl side chain (-> **7**) and reaction with triphenylphosphine provided the phosphonium salt **8** in 45% yield over 3 steps. The aldehyde **12**, to be used as the first Wittig partner, was synthesized from methyl-3-ketobutyrate **9** by protecting the ketone moiety as its acetal, preferably in an orthoester mediated reaction with ethanediol (-> **10**) followed by a LAH-reduction (-> **11**) and reoxidation to the aldehyde (44% yield over 3 steps). The Wittig reaction between these two building blocks (**7**, **12**) gave a 1:1 mixture of both double-bond isomers (-> **13**) which were hydrolyzed to the free ketone (-> **14**) without prior separation[12]. Treatment with methoxycarbonylmethylenetriphenylphosphorane produced the expected α,ß-unsaturated ester, which rapidly isomerised under the reaction conditions,to bring the double bond into conjugation with the aromatic system(-> **15**)[13]. Deprotonation and formylation in the 2 position was followed by O-methylation of the resulting enols **16**. Column chromatography[14] of the reaction mixture gave 25% (2 steps) of the desired strobilurin B (**2**)[15] (4.5% yield overall), and of 27% of the 3E-isomer **17**[16], together with 4% of a mixture of other double-bond isomers and 10% of unreacted **15**.

All the other known strobilurins (**1**,**3**,**4**), as well as several analogues, were successfully synthesized in an analoguous way.

Structure-activity studies based on *"in vivo"* tests against several phytopathogenic fungi revealed that only the natural E,Z,E-isomers (e.g. **2**) were highly potent fungicides, whereas all the other isomers (e.g. **17**) had no or only marginal fungicidal activity.



a) $(CH_3O)_2SO_2$, DMF, K_2CO_3, RT, quant.; b) NBS, AIBN, CCl_4, reflux, 62%; c) $P(C_6H_5)_3$, toluene, reflux, 73%); d) Ethyleneglycol, $HC(OCH_3)_3$, pTSA, RT, 98%; e) LAH, THF, reflux, 75%; f) Pyridine·SO_3, DMSO, NEt_3, RT, 60%; g) t-BuOK, THF, RT, 72%; h) pTSA, acetone/H_2O, 50°C, 72%; i) Methoxy-carbonylmethylenetriphenylphosphorane, toluene, reflux, 80%; k) $HCOOCH_3$, NaH, RT; l) $(CH_3O)_2SO_2$, K_2CO_3, DMF, RT, 25% **2**, 27% **17**.

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References and Notes

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11) See for example: M.D.Wittman and J.Kallmerten, J.Org.Chem., 52, 4303, (1987) and references cited therein.
12) Separation of the two isomers is possible by flash chromatography on silica gel with 1:1 hexane: dichloromethane as eluent.
13) The disubstituted double bond is of E configuration, whereas the trisubstituted one is present as a 1:1 mixture of the E and Z isomers.
14) Silica gel; hexane: diethyl ether = 3:1 to 1:2
2: Rf 0,25 (1:1 ether/hexane)
17: Rf 0,23 (1:1 ether/hexane)
15) The spectroscopic data of this compound are identical to the literature data[3].
16) The structural assignment of **17** is based on the following spectroscopic data:
^{1}H-NMR (d_6-acetone): H(C-8): 7,26 ppm; H(C-12): 7,38 ppm
^{13}C-NMR (d_6-acetone): C(14) : 17,6 ppm

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