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Total Synthesis of (±)-Strobilurin E

Gunda Bertram, Angela Scherer and Wolfgang Steglich*

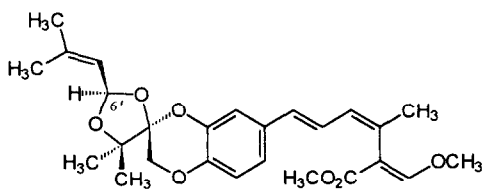
Institut für Organische Chemie der Universität München, Karlstraße 23, D-80333 München, Germany

Wolfgang Weber and Timm Anke

LB Biotechnologie der Universität, Paul-Ehrlich-Straße 23, D-67663 Kaiserslautern, Germany

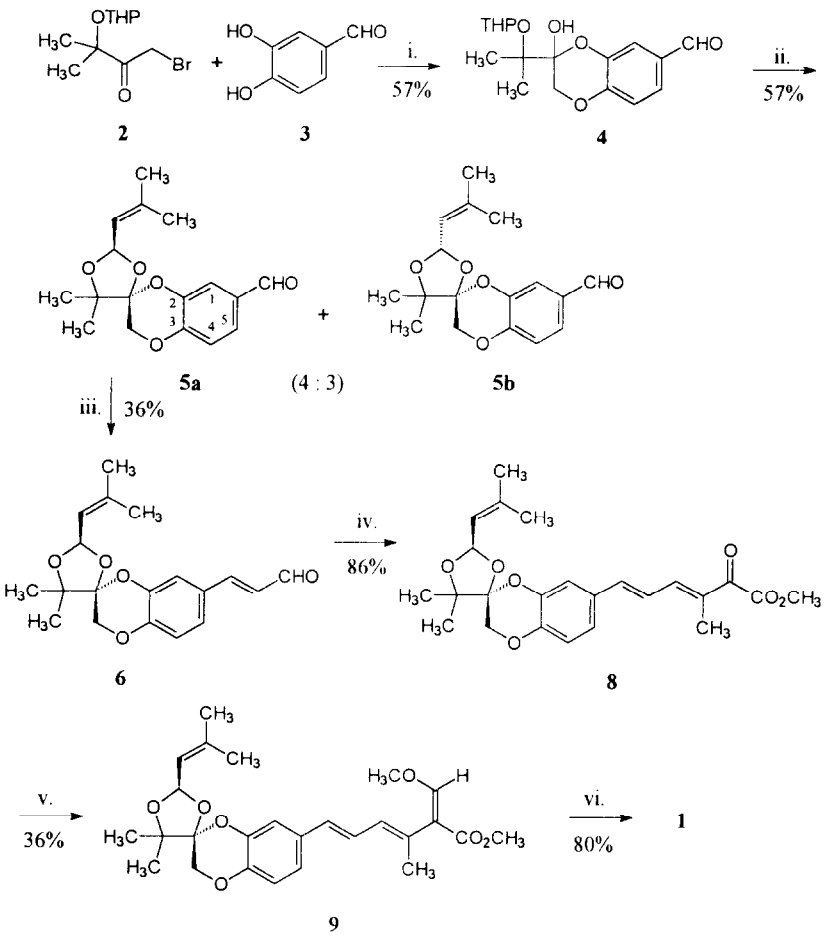
Abstract: The potent antifungal and cytostatic antibiotic strobilurin E (**1**) has been obtained in 6 steps from 3,4-dihydroxybenzaldehyde (**3**) and the bromoketone **2**. The strobilurin side chain was elaborated by three consecutive Wittig reactions and a photochemical double bond isomerisation

Strobilurins are a group of antifungal metabolites from basidiomycetes which served as leads for the development of a novel class of fungicides for crop protection.[1] One of the structurally most complex strobilurins is strobilurin E (**1**)[2,3] which is produced by *Crepidotus fulvotomentosus*. Its structure and relative stereochemistry were established by spectroscopic methods including 2D-NMR and NOE experiments (Fig. 1).[4] Strobilurin E exhibits antifungal and powerful cytostatic activities.[2] In this publication we report the total synthesis of the racemic compound.[5]



1 (relative configuration)

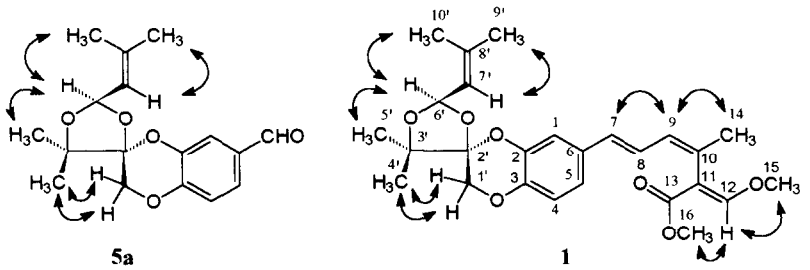
The great sensitivity of the spiroacetal system against traces of acid makes synthetic operations without the use of acid compulsory. We therefore developed a new method for the construction of the strobilurin side chain[6] which relies on three consecutive Wittig reactions. Key building block was the spiroacetal aldehyde **5a** which was easily prepared from bromoketone **2**.[7] The reaction of **2** with 3,4-dihydroxybenzaldehyde (**3**) (Scheme 1) proceeded with complete regioselectivity and afforded the dioxane derivative **4**[3] in 57% yield. Small amounts of a di-substitution product were removed by chromatography. Reaction of **4** with 3-methylbutenal in the presence of pyridinium tosylate (PPTS) afforded spiroacetal **5** as a 4:3-mixture of the diastereomers which was easily separated by chromatography on silica gel. The stereochemistry of the two components **5a**[3] and **5b**[3] was established by NOE experiments (Figure 1) and the attachment of the dioxane



Scheme 1. Reagents and conditions: (i). K_2CO_3, acetone, reflux; slow addition of **2** to excess of **3**. (ii). 3-Methylbutenal, cat. PPTS, benzene, reflux overnight; chromatography on silica gel, hexane/EtOAc (10:1). (iii). Ph_3P=CHCHO, benzene, 30 h, reflux. (iv). $H_3CC(=PPh_3)COCO_2CH_3$ (7), 3 h, 170-175 °C. (v). Ph_3P=$CHOCH_3$, THF, 15 h, r.t., flash chromatography on silica gel, hexane/EtOAc (7:1). (vi). hv (>300 nm), acetone-benzene (10:1), 30 min; HPLC: LiChrosorb Diol Si 60, 7 mm (25 x 0.4 cm), hexane/EtOAc (9:1). Yields relate to chromatographically pure compounds.

ring was determined from the ^{1}H-coupled ^{13}C NMR spectrum. Whereas the signal of C-2 appears as a pair of doublets (^2J- and ^3J-couplings with 1-H and 4-H, respectively) the signal of C-3 is a triplet of triplets. Irradiation at the resonances of 1-H and 5-H or the adjacent methylene protons causes the expected simplifications.

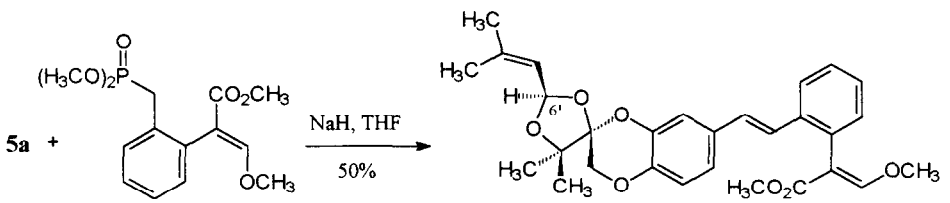
The 'natural' stereoisomer **5a**[3] reacted with formylmethylenetriphenylphosphorane[8] to yield 36% of the (*E*)-enal **6** besides 20% of the homologous (*E,E*)-dienal formed by a repeated chain elongation. Enal **6** was heated with phosphorane **7**[9] without solvent for 3 h at 180 °C. By this procedure the (*E,E*)-α-oxoacid ester **8**[3] was formed in 86% yield under complete stereocontrol. Reaction of **8** with methoxymethylenephosphorane[6a,b] and purification of the product by flash chromatography afforded (9*E*)-strobilurin E (**9**) in 35% yield.



5a **1**

Figure 1. NOE relationships for spiroacetal aldehyde **5a** and strobilurin E (**1**)

Irradiation of **9** in acetone/benzene (10:1) for 1 h with a mercury high pressure lamp with Solidex filter (90% intensity at 300 nm)[6a,10] under HPLC control led to a clean conversion into (±)-strobilurin E (**1**). HPLC separation afforded the antibiotic in 80% yield. It proved to be identical with the natural product by direct HPLC comparison and the agreement of its spectroscopic and biological properties.



10 **11**

Scheme 2

The synthesis was used for the preparation of several modified strobilurin E derivatives,[4] e. g. 6'-epistrobilurin E and the stilbene analogue **11**.[1a,3,11] The latter was synthesised by a Horner-Emmons reaction of spiroaldehyde **5a** with phosphonate **10** (Scheme 2). Like strobilurin E,[2] **11** inhibits the growth of HeLa-S3 cells in concentrations as low as 1 ng/ml. 6'-Epistrobilurin E and the 6'-epimer of stilbene **11** were obtained from aldehyde **5b** and exhibited slightly lower antifungal and cytostatic activities. The simple spiroacetal aldehydes **5a** and **5b** were devoid of any biological activity.

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3. Characterisation of strobilurin E and the synthetic products:
(+)-**1**: Colourless oil, $[\alpha]_D$ +78.5 (c = 2.5, $CHCl_3$); ^1H NMR (400 MHz, MeOH; numbering in Fig. 1): δ 1.32 (s, 5'-CH_3), 1.42 (s, 4'-CH_3), 1.73, 1.78 (each d, J = 0.5 Hz, 9'- and 10'-CH_3, resp.), 1.93 (s, 14-CH_3), 3.73 (s, 16-CH_3), 3.85 (s, 15-CH_3), 4.07, 4.27 (each d, J = 10.5 Hz, 2'- and 1'-H, resp.), 5.23 (d × hept, J = 7.5 + 0.5 Hz, 7'-H), 5.97 (d, J = 7.5 Hz, 6'-H), 6.19 (d, J = 10.5 Hz, 9-H), 6.39 (d, J = 16 Hz, 7-H), 6.47 (dd, J = 16.0 + 10.5 Hz, 8-H), 6.82 (d, J = 8 Hz, 4-H), 6.91 (dd, J = 8.0 + 1.5 Hz, 5-H), 6.93 (d, J = 1.5 Hz, 1-H), 7.53 (s, 12-H); ^{13}C NMR (100.6 MHz, MeOD; numbering in Fig. 1): δ 18.31 (C-9'), 22.05 (C-4'), 23.81 (C-14), 25.14 (C-5'), 25.93 (C-10'), 51.96 (C-16), 62.32 (C-15), 66.88 (C-1'), 83.10 (C-3'), 99.60 (C-6'), 102.56 (C-2'), 111.60 (C-11), 115.67 (C-1), 117.74 (C-4), 121.33 (C-5), 123.14 (C-7'), 126.68 (C-8), 130.99 (C-9), 131.24 (C-7), 131.67 (C-10), 133.56 (C-6), 142.46 (C-8'), 142.86 (C-2), 143.46 (C-3), 160.52 (C-12), 169.60 (C-13); assignments secured by ^1H-^1H, ^1H-^{13}C, and COLOC correlations and NOE experiments (Fig. 1); EI-MS (180 °C): m/z 456.2146 (M^+, 100%), 425 (4), 372 (10), 319 (19), 313 (10), 297 (5), 235 (90), 207 (14), 167 (38), 153 (10), 141 (8), 115 (8), 83 (20), 75 (58), 55 (20), 41 (22). HRMS: Calc'd for $C_{26}H_{32}O_7$: 456.2148. Found: 456.2146.
4: M.p. 86-90 °C; ^1H NMR ($CDCl_3$): δ 1.30-1.95 (m, 12H), 3.45-3.60, 3.90-4.10, 4.20-4.40, 4.95-5.05, 5.70-5.85, 6.90-7.10 (each m, 1H), 7.35-7.50 (m, 2H), 9.81 (s, 1H).
5a: ^1H NMR (C_6D_6): δ 0.94, 1.31 (each s, 3H), 1.32, 1.43 (each d, J = 1 Hz, 3H), 3.40, 3.98 (each d, J = 11 Hz, 1H), 5.35 (d × hept, J = 7 + 1 Hz, 1H), 6.12 (d, J = 7 Hz, 1H); 6.81 (d, J = 8 Hz, 1H), 7.10 (dd, J = 8 + 2 Hz, 1H), 7.51 (d, J = 2 Hz, 1H), 9.60 (s, 1H). Calc'd for $C_{17}H_{20}O_5$: 304.1311. Found: 304.1313.
5b: ^1H NMR (C_6D_6): δ 0.83, 1.26 (each s, 3H), 1.38, 1.41 (each d, J = 1 Hz, 3H), 3.48, 3.86 (each d, J = 11 Hz, 1H), 5.53 (d × hept, J = 7 + 1 Hz, 1H), 5.92 (d, J = 7 Hz, 1H); 6.79 (d, J = 8 Hz, 1H), 7.09 (dd, J = 8 + 2 Hz, 1H), 7.49 (d, J = 2 Hz, 1H), 9.56 (s, 1H). Calc'd for $C_{17}H_{20}O_5$: 304.1311. Found: 304.1313.
6: ^1H NMR ($CDCl_3$): δ 1.33, 1.39 (each s, 3H), 1.71 (d, J = 0.5 Hz, 6H), 4.18, 4.28 (each d, J = 11 Hz, 1H), 5.19 (d × hept, J = 8 + 0.5 Hz, 1H), 6.66 (dd, J = 16 + 7 Hz, 1H), 6.93, 7.23 (each d, J = 8 Hz, 1H), 7.26 (s, 1H), 7.58 (d, J = 16 Hz, 1H), 9.58 (d, J = 7 Hz, 1H). Calc'd for $C_{19}H_{22}O_5$: 330.1467. Found: 330.1467.
8: ^1H NMR ($CDCl_3$): δ 1.32, 1.42 (each s, 3H), 1.72 (d, J = 0.5 Hz, 6H), 2.01, 3.90 (each s, 3H), 4.02, 4.28 (each d, J = 11 Hz, 1H), 5.20 (d × hept, J = 8 + 0.5 Hz, 1H), 5.85 (d, J = 8 Hz, 1H), 6.83-6.91, 6.96-7.04, 7.22-7.26 (each m, 2H); EI-MS (180 °C): m/z 429 (13%), 428 (M^+, 51), 369 (6), 344 (21), 286 (20), 285 (100), 284 (11), 257 (20), 167 (40). Calc'd for $C_{24}H_{28}O_7$: 428.1835. Found: 428.1826.
9: ^1H NMR ($CDCl_3$): δ 1.34, 1.47 (each s, 3H), 1.78, 1.81 (each d, J = 0.5 Hz, 3H), 1.98 (s, 3H), 3.73, 3.89 (each s, 3H), 4.20, 4.31 (each d, J = 11 Hz, 1H), 5.23 (d × hept, J = 8 + 0.5 Hz, 1H), 6.00 (d, J = 8 Hz, 1H), 6.10 (dt, J = 11.5 Hz, 1H), 6.43 (d, J = 15.5 Hz, 1H), 6.87 (d, J = 8 Hz, 1H), 6.99-7.03 (m, 2H), 7.05 (d, J = 15.5 Hz, 1H), 7.08 (d, J = 2 Hz, 1H), 7.43 (s, 1H); EI-MS (180 °C): m/z 458 (4%), 457 (24), 456 (M^+, 94), 340 (19), 319 (18), 257 (18), 235 (100), 167 (45), 75 (35). Calc'd for $C_{26}H_{32}O_7$: 456.2148. Found: 456.2149.
11: ^1H NMR (C_6H_6): δ 1.01, 1.36 (each s, 3H), 1.35, 1.46 (each d, J = 1 Hz, 3H), 2.80, 3.40 (each s, 3H), 3.59, 4.05 (each d, J = 11 Hz, 1H), 5.39 (d × hept, J = 7.5 + 1 Hz, 1H), 6.00 (d, J = 8 Hz, 1H), 6.10 (d, J = 11.5 Hz, 1H), 6.43 (d, J = 15.5 Hz, 1H), 6.87 (d, J = 8 Hz, 1H), 6.99-7.03 (m, 2H), 6.18 (d, J = 7.5 Hz, 1H), 6.90-7.05 (m, 4H), 7.25-7.65 (m, 6H); EI-MS (180 °C): m/z 493 (7%), 492 (M^+, 20), 376 (10), 319 (38), 257 (18), 235 (100), 207 (12), 167 (20), 153 (14). Calc'd for $C_{29}H_{32}O_7$: 492.2148. Found: 492.2159.

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8. Prepared from 1-bromo-3-hydroxy-3-methyl-2-butanone and dihydropyran in CH_2Cl_2 with PPTS (cat.) in 95% yield. The bromoketone was obtained from 2-hydroxy-2-methyl-3-butyne in excellent overall yield according to the procedure of H. Meister, Liebigs Ann. Chem. **724**, 128-136 (1969).

9. Prepared in 50% yield from $(Ph)_3EtP^+Br^-$, diethyl oxalate and NaH in DMSO (25 min, 25 °C).

10. The success of this isomerisation depends on the fact that the twisted π–system of strobilurin E absorbs at a lower wavelength than that of the planar 9*E*-isomer. UV (MeOH): λ_{max} (**1**) = 300-320; λ_{max} (**9**) = 325 nm.

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