# The total synthesis of strobilurin B*

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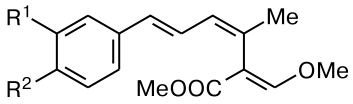
A new regio- and stereocontrolled total synthesis of the antibiotic strobilurin B is performed in nine steps in 5.5% overall yield.

**Key words:** biologically active compounds, strobilurins, stereocontrolled synthesis, dienols, dienals, dienoic acids.

Strobilurins (strobilurin antibiotics) are a group of natural compounds discovered in the last quarter of the XX century[2,3] and exhibiting unique biological activity.[4] By disuniting the mitochondrial respiratory chain, they produce strong fungicidal and antimicrobial effects.[5] For the same reason, strobilurins are used in biochemical investigations of cell respiration.[6]

Fifteen members of this group of compounds are currently known. They are all derivatives of methyl (3*Z*,5*E*)-6-aryl-2-methoxymethylidene-3-methylhexa-3,5-dienoate of the general formula **1** with different substituents in the benzene ring.




**1a—c**

$R^1 = R^2 = H$ (**a**); $R^1 = OMe$, $R^2 = Cl$ (**b**); $R^1 = H$, $R^2 = OMe$ (**c**)

In the last few years, our research team has accomplished the efficient formal syntheses of strobilurins A (**1a**) and X (**1c**) using an original seven-step procedure (Scheme 1).[7] The rationale for this approach is that (2*E*,4*E*)-dienals **2a**,**c** are thermodynamically more favorable. Because of this, condensations of deprotonated *N*-(*tert*-butyl)-4-benzyloxybutanimine (**3A**) with (*E*)-cinnamaldehyde (**4a**) and (*E*)-4-methoxycinnamaldehyde (**4c**) affords the products with high (>98%) contents of this isomer.[8] We have found[7,9] appropriate reagents and conditions for the transformations of dienals **2a**,**c** through such intermediates as (2*E*,4*E*)-dienols **5a**,**c**, (1*E*,3*Z*)-arylhexadienyl ethers **6a**,**c**, (3*Z*,5*E*)-dienols **7a**,**c**, (3*Z*,5*E*)-dienals **8a**,**c**, and (3*Z*,5*E*)-dienoic acids **9a**,**c** into methyl dienoates **10a**,**c**. In each step of this reaction sequence, the yield of the isomer with the desired configuration (as in dienals **2a**,**c**) of the arylalkadiene system of conjugated C=C bonds is >98%. Since the way in which esters **10a**,**c** can be transformed into strobilurins **1a**,**c** is already known,[10] our successful synthesis of compounds **10a**,**c** is equivalent to the formal synthesis of strobilurins A (**1a**) and X (**1c**).

Here we describe the total synthesis of strobilurin B (**1b**) containing two substituents in the aromatic ring that have opposite effects on the electronic system of the conjugated arylhexadiene fragment.

Recently,[11] we have published a procedure for the synthesis of (2*E*,4*E*)-dienal **2b**, the key intermediate in the preparation of strobilurin B. The synthesis involves condensation of α-$Et_3Si$ imine **3B** with 4-chloro-3-methoxycinnamaldehyde (**4b**) (see Scheme 1). The yield of compound **2b** was 60%, stereochemical purity >98%. Dienal **2b** is quantitatively and stereospecifically reduced with $NaBH_4$ in ethanol to (2*E*,4*E*)-dienol **5b**, which was unambiguously identified by physicochemical methods. Specifically, the (2*E*,4*E*)-configuration of the conjugated diene system in dienol **5b** is evident from NOE data for its $^1$H NMR spectrum. In fact, the protons bound to the conjugated system of the C=C bonds are manifested in the $^1$H NMR spectrum of dienol **5b** as three signals: two doublets at δ 6.29 and 6.51 and a doublet of doublets at δ 6.94. However, only the signal at δ 6.29 shows a NOE (5.4%) with the protons of the group $C\underline{H}_2OH$, while the doublet of doublets at δ 6.94 shows a NOE (2.6%) with the protons of the allylic $CH_2$ group. Therefore, the doublet at δ 6.29 can be assigned to HC(3) and the C(2)=C(3) bond can be considered to have a (*E*)-configuration. Accordingly, the other doublet at δ 6.51 was assigned to HC(5). The constant of its coupling with HC(4) (15.5 Hz) suggests the (*E*)-configuration of the C(4)=C(5) bond. The high stereochemical purity of dienol **5b** is also evident from the $^1$H NMR data: the spectral region from δ 0 to 3.70 exhibits, apart from the signal for the OH group, only one signal (t, δ 2.67) assigned to $H_2C(1')$.

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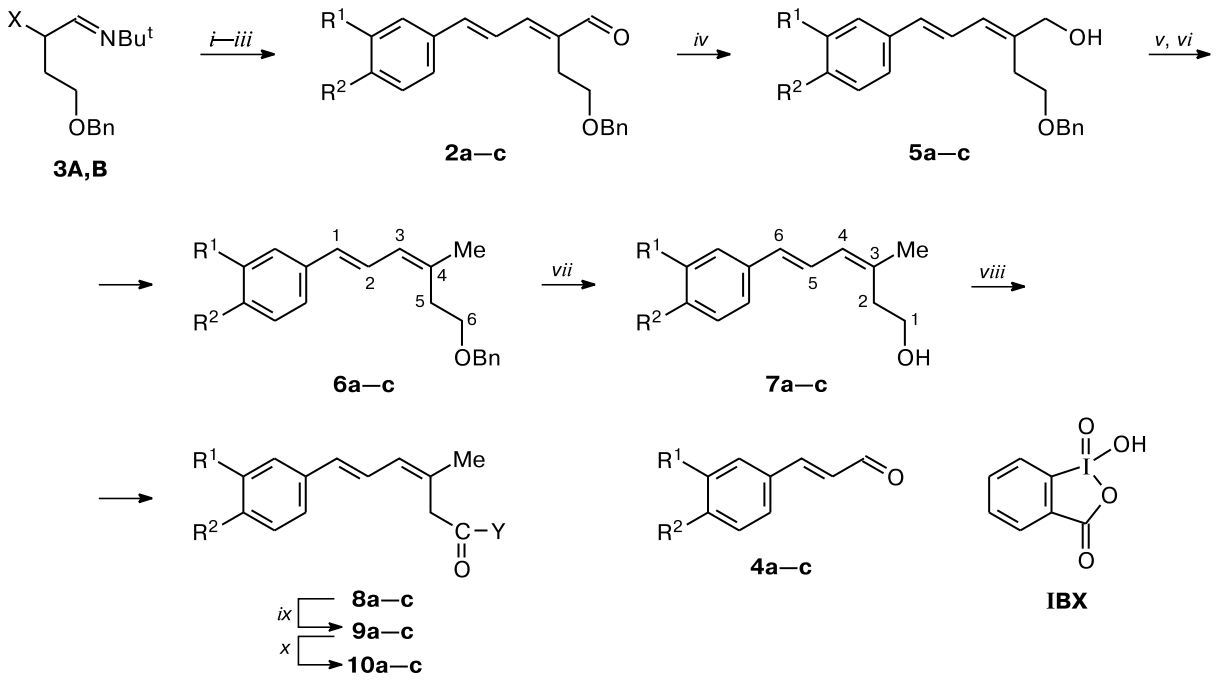
**Scheme 1**




$R^1 = R^2 = H$ (**a**); $R^1$ = OMe, $R^2$ = Cl (**b**); $R^1 = H$, $R^2$ = OMe (**c**)
X = H (**3A**), $SiEt_3$ (**3B**)
Y = H (**8a—c**), OH (**9a—c**), OMe (**10a—c**)

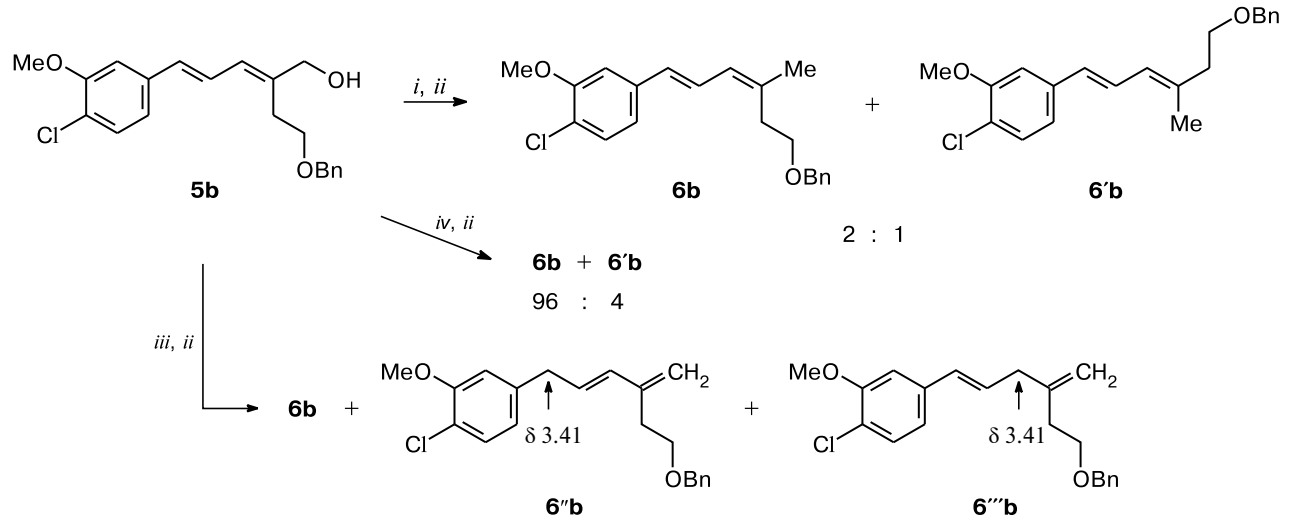
**Reagents and conditions:** *i*. LDA/hexane—THF (1 : 5), 0 °C, 30 min; *ii*. **4a—c**/THF, −80 °C, 1 h, −80 °C→0 °C, 4 h; *iii*. $H_3O^+$; *iv*. $NaBH_4$/EtOH, 3 h; *v*. 1) BuLi/hexane—HMPA, 0 °C, 2) TsCl/HMPA, 0 °C, 2.5 h; *vi*. $LiAlH_4$/THF, 20 °C, 4 h; *vii*. $AlCl_3$—$PhNMe_2$ (3 : 4)/$CH_2Cl_2$, 0 °C, 1 h; *viii*. IBX/DMF, 20 °C, 1 h; *ix*. $NaClO_2$/DMSO—$H_2O$, pH 9; *x*. $CH_2N_2/Et_2O$, 0 °C.

We expected the hydroxymethyl group of dienol **5b** to be transformed into a methyl one by hydride reduction of intermediate *H*-sulfate or tosylate (at the C(1) atom), as it was made with dienols **5a**,**c**.[7] However, treatment of compound **5b** with the complex $Py \cdot SO_3$ followed by *in situ* reduction of the reaction products with $LiAlH_4$ gave a complex mixture of unidentified substances. The reduction of a tosylate obtained from dienol **5b** under the same conditions as in the synthesis of the tosylates of dienols **5a,c** (TsCl, 0 °C, 2 h) afforded a 2 : 1 mixture of the target (1*E*,3*Z*)-arylhexadienyl ether **6b** and its (1*E*,3*E*)-isomer (**6´b**) (Scheme 2).

Structures **6b** and **6´b** were identified by physicochemical methods. For instance, the HRMS of their mixture isolated by column chromatography contains the only ion peak ($[M + Na]^+$). The $^1H$ NMR spectrum of this mixture shows signals for ester **6b** at δ 2.64 (t, $H_2C(5)$), 6.09 (d, HC(3)), and 6.40 (d, HC(1)) as well as additional signals in the proximity of them: a triplet at δ 2.45 and two doublets at δ 6.05 and δ 6.36. The integral intensity ratio of each pair of the closely spaced signals is 2 : 1. In addition, the $^{13}C$ NMR spectrum of the mixture **6b** + **6´b** contains not only a signal for the MeC(4) group of the (*E*,*Z*)-isomer (δ 24.48) but also a less intense signal for the MeC(4) group of the (*E*,*E*)-isomer (δ 17.34).[12]

We attempted to increase the selectivity of tosylation of dienol **5b** by using $Ts_2O$ for this purpose. Unfortunately, the mixture of products isolated by column chromatography after hydride reduction of the tosylates contained not only ether **6b** but also two new compounds other than ether **6´b** (see Scheme 2). Since the HRMS of this mixture exhibits only one peak of the ion $[M + H]^+$ and one peak of the ion $[M + Na]^+$, we assumed that two new products are isomeric to ether **6b** in C=C bond locations. The structures of these products were determined by $^1H$ NMR spectroscopy. Indeed, the spectrum of the mixture shows signals for the major product **6b** as well as two signals of the methylidene group (δ 5.02 and 4.90) with an integral intensity ratio of 7.5 : 1, a signal for the $CH_2$ group between the Ph ring and the C=C bond (d, δ 3.41), and a signal for the $CH_2$ group between two C=C bonds (d, δ 2.95).[13] The integral intensity ratio of the last two signals is also 7.5 : 1. Based on the data obtained, we assigned structure **6˝b** to the product with the higher content in the mixture and structure **6´´´b**, to the product with the lower content. According to $^1H$ NMR data, the ratio of isomers **6b** : **6˝b** : **6´´´b** is 83 : 15 : 2.

**Scheme 2**



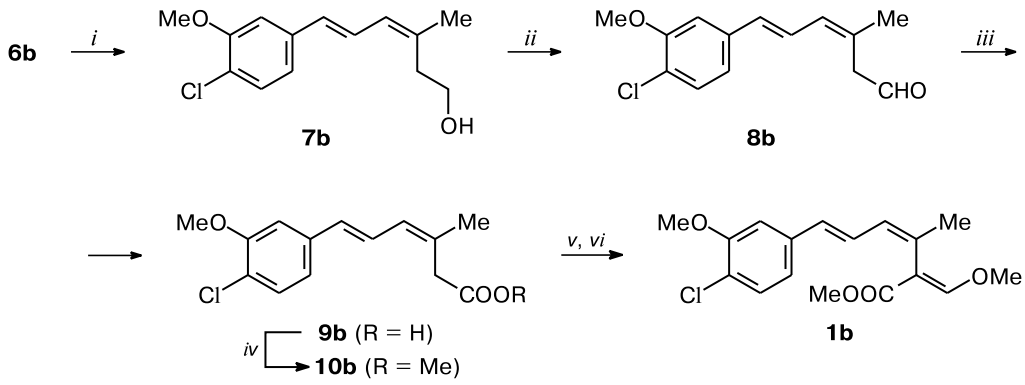

**Reagents and conditions:** *i*. 1) BuLi/hexane—HMPA, 0 °C, 2) TsCl/HMPA, 0 °C, 2 h; *ii*. $LiAlH_4$/THF, 20 °C, 2 h; *iii*. 1) BuLi/hexane, −78 °C, 2) HMPA, 3) $Ts_2O$/THF; warming to −20 °C, exposure time 2.5 h; *iv*. 1) BuLi/hexane—HMPA, −80 °C, 2) TsCl/HMPA, −80 °C, 30 min, 3) warming to −20 °C, 2.5 h.

The configuration of the conjugated C=C bonds in the transformation of dienol **5b** into ether **6b** through a tosylate intermediate was largely retained by lowering the tosylation temperature (see Scheme 2). When dienol **5b** was tosylated with TsCl at −10 °C, the content of (1*E*,3*E*)-isomer **6′b** in the mixture of products obtained by subsequent hydride reduction of the tosylates was decreased to 20% ($^1$H NMR data). When TsCl was added at −80 °C, which was followed by slow warming of the reaction mixture to −20 °C and reduction of the resulting tosylate with $LiAlH_4$ (see Scheme 2), the target ester **6b** was obtained in 60% yield. Isomers **6″b** and **6‴b** were not detected among the reaction products; the content of 1*E*,3*E*-isomer **6′b** was 4% ($^1$H NMR data).

The next step in the synthesis of compound **1b** along the pathway under discussion is debenzylation of ether **6b**. Earlier, by checking several ways recommended[14—19] for deprotection of benzyl ethers, we have found[9] that conjugated arylalkadienyl ethers are debenzylated most conveniently with anhydrous $AlCl_3$ in the presence of $PhNMe_2$.[16] Debenzylation of ether **6b** with this reagent at −5 °C gave crystalline (3*Z*,5*E*)-dienol **7b** in 83% yield (Scheme 3); the content of stereo- and regioisomers in this product did not exceed 1% ($^1$H NMR data).

Dienol **7b** was oxidized into dienoic acid **9b** through the preparation of dienal **8b**, as in similar transformations of dienols **7a,c**.[7] Unstable dienal **8b** was obtained in good yield by oxidation of dienol **7b** with 2-iodoxybenzoic acid

**Scheme 3**




**Reagents and conditions:** *i*. $AlCl_3$ : $PhNMe_2$ (3 : 4)/$CH_2Cl_2$, −5 °C, 3.5 h; *ii*. IBX/DMF, 20 °C, 2 h; *iii*. $NaClO_2$/DMSO—$H_2O$, pH 9, 0 °C, 3 h; *iv*. $CH_2N_2$/$Et_2O$, 0 °C; *v*. HCOOMe, NaH, 20 °C, 4 h; *vi*. $(MeO)_2SO_2$/DMF, 14 h.

(IBX)[20] in DMF[21] and immediately, without purification, transformed into acid **9b** under the action of $NaClO_2$ in aqueous DMSO at pH 9.[22] Crystalline acid **9b** was quantitatively converted into methyl ester **10b** by treatment with an ethereal solution of $CH_2N_2$. The structures of dienal **8b**, acid **9b**, and methyl ester **10b** were proved by physicochemical methods, primarily by HRMS and $^1$H NMR spectroscopy with NOE experiments, as described above for dienol **5b**. Their stereo- and regiochemical purity is >98% ($^1$H NMR data).

A transformation of ester **10b** into strobilurin **1b** has been only sketched earlier. We effected this transformation in "one pot" using a syringe technique, by treating ester **10b** with methyl formate in the presence of NaH and by methylating the resulting enolate with dimethyl sulfate (see Scheme 3). Purification of the crude product by column chromatography on $SiO_2$ gave strobilurin B in 60% yield. Its overall yield in the nine-step synthesis is 5.5%. The physicochemical characteristics of compound **1b** agree with the literature data.[23]

## Experimental

UV spectra were recorded on a U-1900 spectrophotometer in ethanol. IR spectra were recorded on a Specord M-80 spectrometer in thin films or in $CHCl_3$ (for alcohols only). $^1$H and $^{13}$C NMR spectra were recorded on a Bruker AC-200 spectrometer in $CDCl_3$ with reference to its signals (δ 7.27 and 77.0, respectively). The signals for the vinylic protons in the $^1$H NMR spectra were assigned using a NOE experiment. The signals of isomers in the $^{13}$C NMR spectra were assigned using spectral patterns simulated with the MestReNova program (version 6.0.2) (Mestrelab research S.I., www.mestrelab.com, 2009) and $^{13}$C NMR data for related compounds. High-resolution mass spectra (HRMS) were measured on a micrOTOF II instrument (Bruker Daltonics). The details of the HRMS experiments: electrospray ionization (ESI), scan range from *m/z* 50 to *m/z* 3000, positive ion mode (capillary voltage 4500 V); solutions of samples in acetonitrile were infused into the mass spectrometer through a syringe at a rate of 3 μL min$^{-1}$; interface temperature 180 °C, nitrogen as a nebulizing gas (4.0 L min$^{-1}$). Melting points were determined on a Kofler hot stage and are given uncorrected. For column chromatography, Silica gel 60 (0.04—0.06 mm (Fluka) was used. Solvents were purified as follows: diethyl ether and THF were kept over KOH, distilled first over Na and then over $LiAlH_4$, refluxed with sodium benzophenone ketyl until a stable blue coloration was produced, and distilled directly to a reaction vessel. Hexane was distilled over Na; *tert*-butyl methyl ether (TBME), DMF, DMSO, and HMPA were purified by distillation. A solution of LDA was prepared immediately in a reaction vessel from equivalent amounts of diisopropylamine and a 1.3—1.5 *M* solution of BuLi in hexane. Experiments involving NaH, BuLi, and LDA were carried out under argon in glassware previously kept at 160 °C for 12 h and cooled in a stream of argon. "Standard workup" of organic extracts included neutralization, drying with $Na_2SO_4$, and concentration *in vacuo* on a rotary evaporator. Dienal **2b** (see Ref. 11) and IBX (see Ref. 21) were synthesized as described earlier.

**(2*E*,4*E*)-2-(2-Benzyloxyethyl)-5-(4-chloro-3-methoxyphenyl)penta-2,4-dien-1-ol (5b)** was obtained by reduction of dienal **2b** (1.07 g, 3 mmol) with $NaBH_4$ in ethanol at room temperature for 3 h. Yield ~100%, yellow oily substance (decomp. upon heating). HRMS, found *m/z* 381.1231. $C_{21}H_{24}O_3$. Calculated $[M + Na]^+$ = 381.1228. UV ($\lambda_{max}$/nm (ε)): 226 (11 460), 292 (17 200), 302 (17 560), 316 (14 330). IR, ν/cm$^{-1}$: 3607, 3427, 3066, 3018, 2960, 2942, 2866, 1589, 1572, 1491, 1463, 1455, 1411, 1363, 1295, 1253, 1223, 1177, 1092, 1064, 1030, 1008, 963, 909, 863, 805, 782, 752, 699, 668. $^1$H NMR, δ: 2.67 (t, 2 H, $H_2C(1')$, *J* = 6.2 Hz); 2.67 (w.s, 1 H, OH); 3.65 (t, 2 H, $H_2C(2')$, *J* = 6.2 Hz); 3.91 (s, 3 H, MeO); 4.15 (s, 2 H, C$\underline{H}_2$OH); 4.54 (s, 2 H, C$\underline{H}_2$Ph); 6.29 (d, 1 H, HC(3), *J* = 11.0 Hz); 6.51 (d, 1 H, HC(5), *J* = 15.5 Hz); 6.90 (d, 1 H, Ar, *J* = 1.4 Hz); 6.94 (dd, 1 H, HC(4), $J_1$ = 11.0 Hz, $J_2$ = 15.5 Hz); 6.96 (dd, 1 H, Ar, $J_1$ = 8.3 Hz, $J_2$ = 1.4 Hz); 7.20—7.40 (m, 6 H, Ar). $^{13}$C NMR, δ: 29.90 (C(1′)); 56.14 (MeO); 67.90 (C(1)); 69.67 (C(2′)); 73.32 (C$\underline{H}_2$Ph); 110.05 (Ar); 119.33 (Ar); 121.66 (Ar); 124.86 (C(4)); 127.66, 127.80 (Ar); 128.47 (C(3)); 130.22 (Ar); 132.36 (C(5)); 137.46, 137.70, 140.22 (C(2), Ar)); 155.08 (C$\underline{O}$Me).

**(1*E*,3*Z*)-6-Benzyloxy-1-(4-chloro-3-methoxyphenyl)-4-methylhexa-1,3-diene (6b).** ***A.*** A 1.8 *M* solution of BuLi (0.8 mL, 1.44 mmol) in hexane and a solution of TsCl (0.26 g, 1.36 mmol) in HMPA (1 mL) were successively added at −5 °C to a vigorously stirred solution of dienol **5b** (0.36 g, 1 mmol) in a mixture of THF (8 mL) and HMPA (1 mL). The reaction mixture was stirred at 0 to −2 °C for 2.5 h and cooled to −15 °C. Then a solution of $LiAlH_4$ (5 mmol) in THF (4.1 mL) was added dropwise. The resulting mixture was slowly warmed to ~20 °C, stirred at this temperature for 3.5 h, and again cooled to −10 °C. Water (1 mL), 15% aqueous NaOH (1 mL), and again water (3 mL) were successively added dropwise. The precipitate that formed was filtered off and thoroughly washed with TBME. Standard workup of the filtrate gave an oily mixture (0.4 g) containing ethers **6b** and **6′b** in a ratio of 2 : 1 ($^1$H NMR data).

***B.*** A 1.8 *M* solution of BuLi (1.1 mL, 2 mmol) in hexane, HMPA (2 mL), and a solution of $Ts_2O$ (0.65 g, 2 mmol) in THF (5 mL) were successively added at −78 °C to a vigorously stirred solution of dienol **5b** (0.4 g, 1.1 mmol) in THF (15 mL). The reaction mixture was warmed to −20 °C and stirred at this temperature for 2.5 h. Then a solution of $LiAlH_4$ (9.4 mmol) in THF (8 mL) was added dropwise at the same temperature. The reaction mixture was slowly warmed to ~20 °C, stirred at this temperature for 3 h, and subjected to the workup described under ***A***. The resulting mixture (0.4 g) contained ethers **6b**, **6″b**, and **6‴b** in a ratio of 83 : 15 : 2 ($^1$H NMR data).

***C.*** A solution of BuLi (7.7 mmol) in hexane (5.1 mL) and a solution of TsCl (1.47 g, 7.7 mmol) in HMPA (6.5 mL) were successively added at −80 °C to a vigorously stirred solution of dienol **5b** (2.2 g, 6 mmol) in THF (70 mL). The reaction mixture was warmed to −20 °C and stirred at this temperature for 2.5 h. Then a 1.2 *M* solution of $LiAlH_4$ (25 mL, 30 mmol) in THF was added at the same temperature. The reaction mixture was warmed to room temperature, stirred for 3.5 h, again cooled to −10 °C, and subjected to the workup described under ***A***. The ratio of ethers **6b** and **6′b** in the resulting oily mixture (2.1 g) was ~96 : 4 ($^1$H NMR data). Flash chromatography of this mixture on $SiO_2$ with benzene as an eluent gave individual ether **6b** (1.3 g, 61%) (decomp. upon heating). HRMS: found *m/z* 365.1266. $C_{21}H_{23}O_2Cl$. Calculated $[M + Na]^+$ = 365.1279. UV ($\lambda_{max}$/nm (ε)): 226 (16 100), 294 (27 000), 302 (28 800), 314 (25 000). IR,

ν/cm$^{-1}$: 3028, 2935, 2854, 1633, 1585, 1570, 1486, 1450, 1405, 1360, 1294, 1249, 1192, 1174, 1096, 1060, 1027, 961, 880, 865, 805, 739, 697. $^1$H NMR, δ: 1.90 (s, 3 H, MeC(4)); 2.64 (t, 2 H, $H_2$C(5), $J$ = 7.1 Hz); 3.62 (t, 2 H, $H_2$C(6), $J$ = 7.1 Hz); 3.92 (s, 3 H, MeO); 4.56 (s, 2 H, C$\underline{H}_2$Ph); 6.09 (d, 1 H, HC(3), $J$ = 10.7 Hz); 6.40 (d, 1 H, HC(1), $J$ = 15.4 Hz); 6.92 (s, 1 H, Ar); 6.93 (d, 1 H, Ar, $J$ = 7.4 Hz); 7.00 (dd, 1 H, HC(2), $J_1$ = 10.7 Hz, $J_2$ = 15.4 Hz); 7.29—7.40 (m, 6 H, Ar). $^{13}$C NMR, δ: 24.48 (MeC(4)); 33.22 (C(5)); 56.11 (MeO); 68.86 (C(6)); 70.03 (C$\underline{H}_2$Ph); 109.74 (Ar); 119.24 (Ar); 121.06 (Ar); 125.98 (C(2)); 127.25 (C(3)); 127.52, 127.56 (Ar); 128.36 (Ar); 129.54 (C(1)); 130.12 (Ar); 137.61, 138.03, 138.38 (C(4), Ar), 155.05 (C$\underline{O}$Me).

**(3*Z*,5*E*)-6-(4-Chloro-3-methoxyphenyl)-3-methylhexa-3,5-dien-1-ol (7b).** *N*,*N*-Dimethylaniline (2.2 mL, 16.8 mmol) and anhydrous $AlCl_3$ (1.5 g, 11.2 mmol) were successively added at −15 °C to a vigorously stirred solution of benzyl ether **6b** (1.28 g, 3.7 mmol) in $CH_2Cl_2$ (35 mL). The reaction mixture was warmed to −5 °C and stirred for 3.5 h. Then dilute (1 : 10) HCl (25 mL) was added dropwise. After 10 min, the resulting immiscible layers were separated. Organic material from the aqueous layer was extracted with $CH_2Cl_2$ (3×20 mL). The combined organic extracts were subjected to the standard workup. The residue (1.2 g) containing the target dienol **7b** was chromatographed on $SiO_2$ (50 g) with gradient elution from hexane to hexane—ethyl acetate (0→70%). The yield of dienol **7b** was 0.77 g (83%), m.p. 79—81 °C (from hexane—diethyl ether (1 : 2)); the sample is free of the (*E*,*E*)-isomer. Found (%): C, 66.39; H, 6.92; Cl, 14.12. $C_{14}H_{17}ClO_2$. Calculated (%): C, 66.53; H, 6.78; Cl, 14.03. HRMS: found *m*/*z* 253.0984. $C_{14}H_{17}Cl_2O_2$. Calculated $[M + H]^+$ = = 253.0990. UV ($\lambda_{max}$/nm, (ε)): 228 (12 380), 294 (23 250), 305 (30 330), 320 (22 240). IR, ν/cm$^{-1}$: 3620, 3448, 3019, 2966, 2932, 2884, 1640, 1588, 1572, 1489, 1464, 1448, 1411, 1295, 1253, 1208, 1179, 1064, 1031, 962, 803, 789, 774, 745, 731, 669. $^1$H NMR, δ: 1.64 (t, 1 H, OH, $J$ = 5.8 Hz); 1.89 (s, 3 H, MeC(3)); 2.57 (t, 2 H, $H_2$C(2), $J$ = 6.6 Hz); 3.77 (dt, 2 H, $H_2$C(1), $J_1$ = 6.6 Hz, $J_2$ = 5.8 Hz); 3.92 (s, 3 H, MeO); 6.16 (d, 1 H, HC(4), $J$ = 11.0 Hz); 6.41 (d, 1 H, HC(6), $J$ = 15.4 Hz); 6.91 (s, 1 H, Ar); 6.94 (d, 1 H, Ar, $J$ = 8.0 Hz); 6.98 (dd, 1 H, HC(5), $J_1$ = 11.0 Hz, $J_2$ = 15.4 Hz); 7.27 (d, 1 H, Ar, $J$ = 8.0 Hz). $^{13}$C NMR, δ: 24.06 (M$\underline{e}$C(3)); 35.83 (C(2)); 56.14 (MeO); 60.81 (C(1)); 109.73 (Ar); 119.30, 121.20 (Ar); 125.52 (C(5)); 128.40 (C(4)); 130.16 (C(6), Ar); 136.68, 137.80 (C(3), Ar); 155.02 (C$\underline{O}$Me).

**(3*Z*,5*E*)-6-(4-Chloro-3-methoxyphenyl)-3-methylhexa-3,5-dienal (8b).** 2-Iodoxybenzoic acid (1.07 g, 3.82 mmol) was added in one portion at ~20 °C (Ar) in the dark to a stirred solution of dienol **7b** (640 mg, 2.54 mmol) in DMF (20 mL). The reaction mixture was stirred for 2 h (monitoring by TLC). Then TBME (75 mL) was added, and the mixture was filtered through a short column with $SiO_2$ (12 g). The adsorbent was washed with TBME (100 mL). The combined filtrates were subjected to the standard workup. The residue was dried *in vacuo* (1 Torr) at ~20 °C to a constant weight. The yield of dienal **8b** was 445 mg (70%), light yellow thin oil, $R_f$ 0.55 (TBME—hexane (1 : 1)). The content of the (*E*,*E*)-isomer in the sample does not exceed 2% ($^1$H NMR data). Dienal **8b** decomposes when heated. $^1$H NMR, δ: 1.94 (s, 3 H, MeC(3)); 3.37 (d, 2 H, $H_2$C(2), $J$ = 2.10 Hz); 3.93 (s, 3 H, MeO); 6.28 (d, 1 H, HC(4), $J$ = 11.1 Hz); 6.48 (d, 1 H, HC(6), $J$ = 15.2 Hz); 6.84 (dd, 1 H, HC(5), $J_1$ = 11.1 Hz, $J_2$ = 15.2 Hz); 6.92 (s, 1 H, Ar); 6.94 (d, 1 H, Ar, $J$ = 7.2 Hz); 7.29 (d, 1 H, Ar, $J$ = 7.2 Hz); 9.65 (t, 1 H, HC(1), $J$ = 2.10 Hz).

**(3*Z*,5*E*)-6-(4-Chloro-3-methoxyphenyl)-3-methylhexa-3,5-dienoic acid (9b).** Dimethyl sulfoxide (14 mL) and a solution of $NaH_2PO_4 \cdot 2H_2O$ (1.09 g, 7 mmol) in water (8.8 mL) were successively added to a solution of freshly prepared dienal **8b** (625 mg, 2.5 mmol) in THF (17 mL). The mixture was cooled to 0 °C. A solution of $NaClO_2$ (413 mg, 4.56 mmol) in water (8.8 mL) was added dropwise, and the reaction mixture was stirred in the dark at 0 °C for 3 h. Then TBME (100 mL) was added, and the resulting immiscible layers were separated. A salt product from the organic layer was extracted with 10% NaOH (2×50 mL). The combined basic extracts were acidified at 0 °C with dilute (1 : 3) HCl to pH 2. Organic materials were extracted with TBME (3×50 mL). Standard workup of the combined extracts gave acid **9b** (286 mg, 43%), m.p. 124—126 °C. The content of the (*E*,*E*)-isomer in the sample is <3% ($^1$H NMR data). HRMS: found *m*/*z* 267.0778, 289.0605. $C_{14}H_{15}ClO_3$. Calculated $[M + H]^+$ = 267.0782, $[M + Na]^+$ = 289.0602. UV ($\lambda_{max}$/nm (ε)): 228 (12 300), 294 (32 500), 305 (36 800), 320 (30 400). IR, ν/cm$^{-1}$: 3021, 2970, 2918, 2855, 1708, 1588, 1572, 1490, 1464, 1411, 1295, 1224, 1065, 1031, 962, 803, 726, 673, 623. $^1$H NMR, δ: 1.98 (s, 3 H, MeC(3)); 3.34 (s, 2 H, $H_2$C(2)); 3.94 (s, 3 H, MeO); 6.21 (d, 1 H, HC(4), $J$ = 11.0 Hz); 6.48 (d, 1 H, HC(6), $J$ = 15.2 Hz); 6.92 (dd, 1 H, HC(5), $J_1$ = 11.0 Hz, $J_2$ = 15.2 Hz); 6.92 (s, 1 H, Ar); 6.97 (d, 1 H, Ar, $J$ = 8.2 Hz); 7.28 (d, 1 H, Ar, $J$ = 8.2 Hz). $^{13}$C NMR, δ: 24.67 (M$\underline{e}$C(3)); 38.00 (C(2)); 56.19 (MeO); 109.95, 119.47, 121.65 (Ar); 124.95 (C(5)); 129.29 (C(3)); 130.28 (Ar); 131.42, 131.49 (C(4), C(6)); 137.56 (Ar); 155.14 (C$\underline{O}$Me), 177.21 (C(1)).

**Methyl (3*Z*,5*E*)-6-(4-chloro-3-methoxyphenyl)-3-methylhexa-3,5-dienoate (10b)** was obtained by treatment of acid **9b** (200 mg, 0.75 mmol) with a solution of $CH_2N_2$ in diethyl ether at 0 °C according to a standard procedure. Yield ~100%, stereochemical purity >98%, m.p. 78—79 °C (hexane—diethyl ether (1 : 1)). HRMS: found *m*/*z* 281.0941, 303.0754. $C_{15}H_{17}ClO_3$. Calculated $[M + H]^+$ = 281.0939, $[M + Na]^+$ = 303.0758. UV ($\lambda_{max}$/nm (ε)): 223 (16 500), 293 (29 600), 302 (30 900), 314 (26 100). IR, ν/cm$^{-1}$: 3414, 3062, 3036, 2968, 2930, 2902, 2845, 1714, 1590, 1572, 1492, 1484, 1464, 1438, 1415, 1366, 1332, 1303, 1289, 1255, 1230, 1202, 1179, 1165, 1065, 1034, 997, 967, 880, 853, 798, 689, 622, 573. $^1$H NMR, δ: 1.94 (s, 3 H, MeC(3)); 3.30 (s, 2 H, $H_2$C(2)); 3.71, 3.93 (both s, 3 H each, MeO); 6.16 (d, 1 H, HC(4), $J$ = 10.7 Hz); 6.45 (d, 1 H, HC(6), $J$ = 15.4 Hz); 6.91 (dd, 1 H, HC(5), $J_1$ = 10.7 Hz, $J_2$ = 15.4 Hz); 6.92 (s, 1 H, Ar); 6.97 (d, 1 H, Ar, $J$ = 8.2 Hz); 7.28 (d, 1 H, Ar, $J$ = 8.2 Hz). $^{13}$C NMR, δ: 24.57 (M$\underline{e}$C(3)); 38.07 (C(2)); 52.02 (CO$_2$M$\underline{e}$); 56.11 (MeO); 109.84, 119.31, 121.42 (Ar); 125.12 (C(5)); 128.73 (Ar); 130.18 (C(4)); 131.03 (C(6)), 132.19 C(3)); 137.61 (Ar); 155.02 (C$\underline{O}$Me), 177.30 (C(1)).

**Methyl (2*E*,3*Z*,5*E*)-6-(4-chloro-3-methoxyphenyl)-2-methoxymethylidene-3-methylhexa-3,5-dienoate (1b, strobilurin B).** A 80% suspension of NaH (180 mg, 6 mmol) in mineral oil was added (Ar) in one portion at room temperature to a stirred mixture of methyl dienoate **10b** (156 mg, 0.56 mmol) and methyl formate (0.5 mL, 8 mmol). The reaction mixture was stirred for 4 h, whereupon DMF (0.5 mL) and dimethyl sulfate (0.56 mL, 5.6 mmol) were added. The resulting solution was stirred for 14 h and then diluted with water. The product was extracted with diethyl ether (2×10 mL). The combined extracts were successively washed with a saturated solution of $NH_4Cl$, 4% aqueous ammonia, and brine, dried with $Na_2SO_4$, and concentrated *in vacuo*. The residue (0.25 g) was chromatographed on $SiO_2$ (15 g) with gradient elution from hexane to hexane—ethyl acetate (0→30%). The yield of the target compound **1b** was 108 mg (60%), light yellow crystals, m.p. 89—90 °C (*cf.* Ref. 23: m.p.

92—93 °C). $^1$H NMR, δ: 1.99 (s, 3 H, MeC(3)); 3.75, 3.86, 3.91 (all s, 3 H each, MeO); 6.26 (d, 1 H, HC(4), $J$ = 10.5 Hz); 6.43 (d, 1 H, HC(6), $J$ = 15.5 Hz); 6.58 (dd, 1 H, HC(5), $J_1$ = 10.5 Hz, $J_2$ = 15.5 Hz); 6.85 (s, 1 H, Ar); 6.92 (d, 1 H, Ar, $J$ = 8.0 Hz); 7.26 (d, 1 H, Ar, $J$ = 8.0 Hz); 7.44 (s, 1 H, CHOMe). The spectrum completely agrees with the literature data.[23]

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