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Total synthesis of strobilurin B

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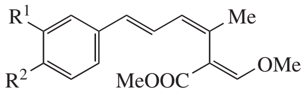
A nine-stage total synthesis of strobilurin B has been carried out with an overall yield of 5.5%. The key step was the stereocontrolled condensation between *N-tert*-butylaldimine and α,β-enal followed by reduction of the formyl group into methyl.

Strobilurin antibiotics are a group of natural compounds[1,2] with unique bioactivity[3] discovered in the last quarter of the 20th century. They can disconnect the respiratory chain in mitochondria and thus display a high fungicide and antimicrobial activity.[4] For the same reason, strobilurins are a useful tool in studies on the biochemistry of cellular respiration.[5]

To date, 15 representatives of this group of compounds are known. All of these are derivatives of methyl (3*Z*,5*E*)-6-aryl-3-methyl-2-methoxymethylidenehexa-3,5-dienoate with general formula **1** differing in aromatic ring substituents.

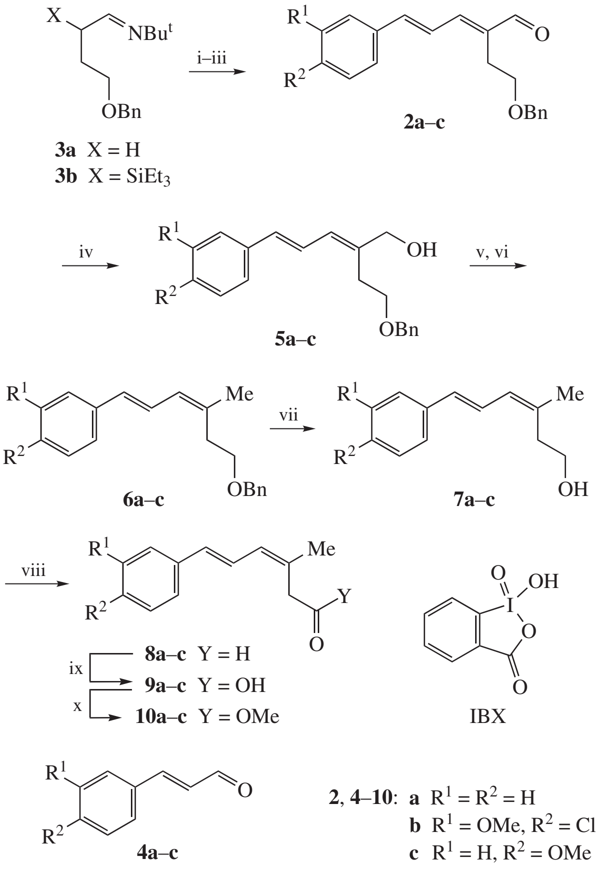


1a $R^1 = R^2 = H$
1b $R^1 = OMe, R^2 = Cl$
1c $R^1 = H, R^2 = OMe$

In the past few years, our team has carried out an original efficient formal synthesis of the simplest strobilurins A (**1a**) and X (**1c**) (Scheme 1).[6] It is based on the thermodynamic preference for the (2*E*,4*E*)-dienals **2a**,**c**, which ensures an over 98% content of this isomer prepared by condensation of deprotonated 4-benzyloxybutanal *tert*-butylimine (**3a**) with (*E*)-cinnamic (**4a**) and (*E*)-4-methoxycinnamic (**4c**) aldehydes.[7] Reagents and conditions were found[6,8] that allowed dienals **2a**,**c** to be converted, *via* the stages of (2*E*,4*E*)-dienols **5a**,**c**, (1*E*,3*Z*)-aryldiene ethers **6a**,**c**, (3*Z*,5*E*)-dienols **7a**,**c**, (3*Z*,5*E*)-dienals **8a**,**c** and (3*Z*,5*E*)-diene acids **9a**,**c**, to (3*Z*,5*E*)-aryldiene esters **10a**,**c**, with high (⩾ 98%) retention at each stage of the aryldiene configuration of conjugated C=C bonds once formed in dienals **2a**,**c**. Inasmuch as conversion of esters **10a**,**c** to strobilurins **1a**,**c**, respectively, has been reported in literature,[9] the syntheses of **10a**,**c** that we completed are equivalent to a formal synthesis of strobilurins A (**1a**) and X (**1c**).

The purpose of this study was to find out whether Scheme 1 could be used to synthesize strobilurin B (**1b**) containing two substituents at the aromatic ring that have opposite effects on the electron system of the conjugated aryldiene moiety of the compounds being studied.

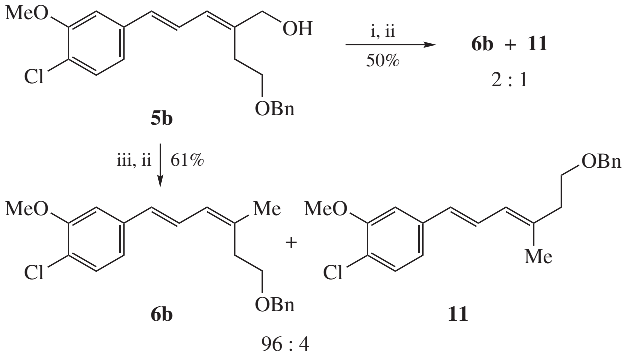
Synthesis of (2*E*,4*E*)-dienal **2b**, the key intermediate in the synthesis of strobilurin B according to Scheme 1, was published recently.[10] It was carried out in 60% yield and with >98% stereochemical purity by the Peterson condensation between deprotonated 4-benzyloxy-2-triethylsilylbutanal *tert*-butylimine **3b** and (*E*)-4-chloro-3-methoxycinnamic aldehyde **4b**.



Scheme 1 *Reagents and conditions*: i, LDA, C_6H_{14}–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, BuLi, C_6H_{14}–HMPA, 0 °C, then TsCl, HMPA, 0 °C, 2.5 h; vi, $LiAlH_4$, THF, room temperature, 4 h; vii, $AlCl_3$–$PhNMe_2$ (3:4), CH_2Cl_2, 0 °C, 1 h; viii, IBX, DMF, room temperature, 1h; ix, $NaClO_2$, DMSO–H_2O, pH 9; x, CH_2N_2, Et_2O, 0 °C.

Dienal **2b** undergoes quantitative and stereospecific reduction to (2*E*,4*E*)-dienol **5b** on treatment with $NaBH_4$ in ethanol. The structure of **5b** was confirmed unambiguously using a combination of physicochemical methods. In particular, the (2*E*,4*E*) configuration of the diene bond system C=C in dienol **5b** follows from the data of ^{1}H NMR NOE spectroscopy. In fact, the ^{1}H NMR spectrum of dienol **5b** shows three signals in the resonance region of protons bound to the C=C conjugated bond system: two doublets at δ 6.29 (J 11.0 Hz) and 6.51 (J 15.5 Hz) ppm and a doublet of doublets at δ 6.94 ppm (J_1 11.0 Hz, J_2 15.5 Hz). In this case, only the proton with the doublet signal at δ 6.29 ppm manifests an NOE (5.4%) with the protons of the CH_2OH group, whereas the proton with a doublet-doublet signal (δ 6.94 ppm) shows an NOE (2.6%) with the protons of the allylic CH_2 group. These data allow us, first, to assign the doublet signal at δ 6.29 ppm to HC(3), and second, to make a conclusion that the C(2)=C(3) bond has an (*E*)-configuration. Accordingly, the second doublet signal at δ 6.51 ppm was assigned to HC(5). Its coupling constant with HC(4) (15.5 Hz) suggests that the C(4)=C(5) bond has an (*E*)-configuration. The high stereochemical purity of dienol **5b** also follows from its ^{1}H NMR spectral data: the spectrum region of δ 0–3.70 ppm showed the only signal [2.67 (t)], which was assigned to =C–C*H*$_2$CH$_2$OBn.

We intended to convert the hydroxymethyl group of dienol **5b** to a methyl group by hydride reduction of the corresponding C(1)-tosylate (without isolation), as it was done for dienols **5a,c** (Scheme 1).[6,8] However, reduction of the tosylation product of dienol **5b** obtained under the same conditions as those used to synthesize individual dienol **5c** tosylate (TsCl, 0 °C, 2 h)[8] (Scheme 2) gave a mixture of the target (1*E*,3*Z*)-aryldiene ether **6b** with its (1*E*,3*E*)-isomer **11** in 2:1 ratio.

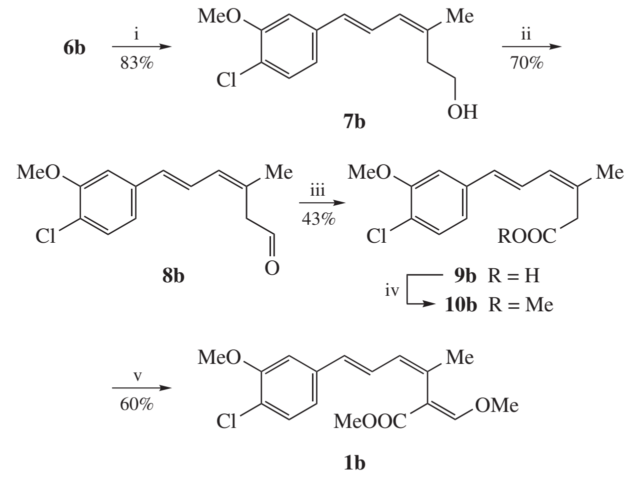


Scheme 2 *Reagents and conditions*: i: BuLi, C_6H_{14}–HMPA, 0 °C, then TsCl, HMPA, 0 °C, 2 h; ii, $LiAlH_4$, THF, 20 °C, 2 h; iii, BuLi, C_6H_{14}–THF, –80 °C, then TsCl, HMPA, –80 °C, 30 min, then heating to –20 °C, 2.5 h.

The evidence for the structure of compounds **6b** and **11** follows, first, from HMRS data: the spectrum of the mixture of these compounds shows a single $(M+Na)^+$ ion. Second, the ^{1}H NMR spectrum of this mixture contains not only signals of diene ether **6b** [2.64 (t, H$_2$C^5), 6.09 (d, HC^3) and 6.40 (d, HC^1)] but also additional signals close to each of them: a triplet at δ 2.45 ppm and two doublets at δ 6.05 and 6.36 ppm, respectively. The integral intensity ratio of each pair of similar signals amounts to 2:1. Third, the ^{13}C NMR spectrum of the mixture of compounds **6b** and **11** in question contains, along with the signal of the MeC^4 group of the major (*E*,*Z*)-isomer (δ 24.48 ppm), also a signal of the MeC^4 group of the (*E*,*E*)-isomer (δ 17.34 ppm).[11]

Clean conversion **5b** → **6b** *via* the preparation of its tosylate succeeded if the temperature of the tosylation stage was decreased. In fact, even at –10 °C the content of the undesired isomer **11** decreased to 20% (^{1}H NMR data). Further lowering the temperature of TsCl addition to –80 °C followed by slow heating of the reaction mixture to –20 °C gave a product of tosylate hydride reduction, which was isolated in 60% yield, namely a mixture of the target diene ether **6b**[†] and its (2*E*,4*E*)-isomer **11** in 96:4 ratio (^{1}H NMR data).

Deprotection of diene ether **6b** (Scheme 3) is the next stage in the synthesis of **1b** along the route considered. Previously,[8] we checked a few methods recommended in the literature for deprotection of benzyl ethers[12–16] and found that anhydrous $AlCl_3$ in the presence of excess $PhNMe_2$[13] is the optimum reagent for our purpose. Debenzylation of ether **6b** at –5 °C using this method gave crystalline (3*Z*,5*E*)-dienol **7b**[‡] in 85% yield (Scheme 3). The total content of stereo- and regioisomers in the product did not exceed 1% (^{1}H NMR data).



Scheme 3 *Reagents and conditions*: i, $AlCl_3$–$PhNMe_2$ (3:4), CH_2Cl_2, –5 °C, 3.5 h; ii, IBX, DMF, room temperature, 1 h; iii, $NaClO_2$, DMSO–H_2O, pH 9, 0 °C, 2.5 h; iv, CH_2N_2, Et_2O, 0 °C; v, NaH, HCOOMe, room temperature, 4.5 h, then $(MeO)_2SO_2$, DMF, K_2CO_3, 14 h.

Conversion of (3*Z*,5*E*)-dienol **7b** to diene acid **9b** was carried out *via* the stage of unstable (3*Z*,5*E*)-dienal **8b**. The latter was obtained in a good yield by oxidation of dienol **7b** with *o*-iodoxybenzoic acid (IBX)[17] in DMF[18] and was then converted without additional purification to (3*Z*,5*E*)-acid **9b**[§] by treatment with $NaClO_2$ in aqueous DMSO at pH 9.[19]

Crystalline acid **9b** containing <2% of the (3*E*,5*E*)-isomer was quantitatively converted to its methyl ester **10b**[¶] on treatment with ethereal CH_2N_2. The structures of dienal **8b**, acid **9b** and methyl ether **10b** were confirmed by HRMS and ^{1}H NMR spectroscopy using NOE, as described above for dienol **5b**. Their stereo- and regiochemical purity exceeds 98% (^{1}H NMR data).

The conversion of diene ester **10b** to strobilurin **1b** was reported[9] without experimental details. We performed this operation (Scheme 3) in 'one pot' by adding NaH (6 mmol, as 80% suspension in mineral oil) to a stirred mixture of ester **10b** (156 mg, 0.56 mmol) and methyl formate (0.5 ml, 8 mmol) at room temperature under argon. After 4 h, the mixture was treated with dimethyl sulfate (Scheme 3). Chromatography of the reaction product on SiO_2 gave strobilurin B in 60% yield. Its overall yield in our nine-stage synthesis was 5.5%. The physicochemical characteristics of the product[††] agree with literature data.[20]

[†] Ether **6b** was isolated in individual state by flash chromatography. ^{1}H NMR (CDCl$_3$) δ: 1.90 (s, 3H, MeC^4), 2.64 (t, 2H, H$_2$C^5, *J* 7.1 Hz), 3.62 (t, 2H, H$_2$C^6, *J* 7.1 Hz), 3.92 (s, 3H, MeO), 4.56 (s, 2H, C*H*$_2$Ph), 6.09 (d, 1H, HC^3, *J* 10.7 Hz), 6.40 (d, 1H, HC^1, *J* 15.4 Hz), 6.92 (s, 1H, Ar), 6.93 (d, 1H, Ar, *J* 7.4 Hz), 7.00 (dd, 1H, HC^2, J_1 10.7 Hz, J_2 15.4 Hz), 7.29–7.40 (m, 6H, Ar).

[‡] Individual dienol **7b**, mp 79–81 °C (hexane–Et$_2$O, 1:2), yield 83%. ^{1}H NMR (CDCl$_3$) δ: 1.64 (t, 1H, OH, *J* 5.8 Hz), 1.89 (s, 3H, MeC^3), 2.57 (t, 2H, H$_2$C^2, *J* 6.6 Hz), 3.77 (dt, 2H, H$_2$C^1, J_1 6.6 Hz, J_2 5.8 Hz), 3.92 (s, 3H, MeO), 6.16 (d, 1H, HC^4, *J* 11.0 Hz), 6.41 (d, 1H, HC^6, *J* 15.4 Hz), 6.91 (s, 1H, Ar), 6.94 (d, 1H, Ar, *J* 8.0 Hz), 6.98 (dd, 1H, HC^5, J_1 11.0 Hz, J_2 15.4 Hz), 7.27 (d, 1H, Ar, *J* 8.0 Hz).

[§] Acid **9b**, yield 30% (with respect to **7b**), mp 124–126 °C. ^{1}H NMR (CDCl$_3$) δ: 1.98 (s, 3H, MeC^3), 3.34 (s, 2H, H$_2$C^2), 3.94 (s, 3H, MeO), 6.21 (d, 1H, HC^4, *J* 11.0 Hz), 6.48 (d, 1H, HC^6, *J* 15.2 Hz), 6.92 (dd, 1H, HC^5, J_1 11.0 Hz, J_2 15.2 Hz), 6.92 (s, 1H, Ar), 6.97 (d, 1H, Ar, *J* 8.2 Hz), 7.28 (d, 1H, Ar, *J* 8.2 Hz).

[¶] Methyl dienoate **10b**. ^{1}H NMR (CDCl$_3$) δ: 1.94 (s, 3H, MeC^3), 3.30 (s, 2H, H$_2$C^2), 3.71, 3.93 (2s, 2×3H, MeO), 6.16 (d, 1H, HC^4, *J* 10.7 Hz), 6.45 (d, 1H, HC^6, *J* 15.4 Hz), 6.91 (s, 1H, Ar), 6.91 (dd, 1H, HC^5, J_1 10.7 Hz, J_2 15.4 Hz), 6.92 (s, 1H, Ar), 6.97 (d, 1H, Ar, *J* 8.2 Hz), 7.28 (d, 1H, Ar, *J* 8.2 Hz).

[††] Strobilurin B **1b**, mp 89–91 °C. ^{1}H NMR (CDCl$_3$) δ: 1.99 (s, 3H, MeC^3), 3.75, 3.86, 3.91 (3s, 3×3H, MeO), 6.26 (d, 1H, HC^4, *J* 10.5 Hz), 6.43 (d, 1H, HC^6, *J* 15.5 Hz), 6.58 (dd, 1H, HC^5, J_1 10.5 Hz, J_2 15.5 Hz), 6.85 (s, 1H, Ar), 6.92 (d, 1H, Ar, *J* 8.0 Hz), 7.26 (d, 1H, Ar, *J* 8.0 Hz), 7.44 (s, 1H, C*H*OMe).

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