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Stereoselective synthesis of key intermediates for the preparation of strobilurins

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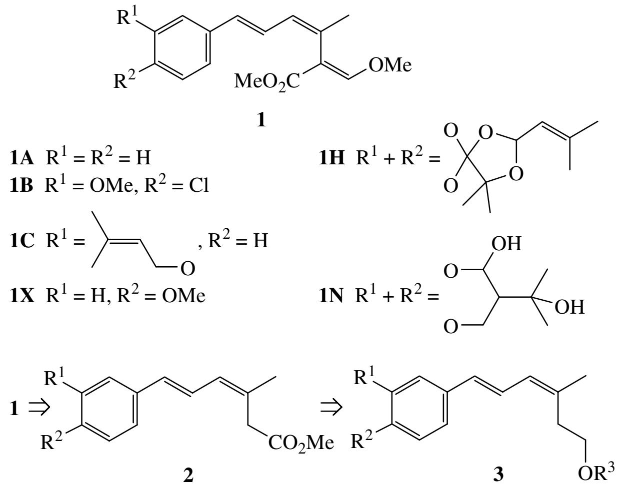
The highly stereoselective synthesis of benzyl and *tert*-butyldimethylsilyl ethers of 3-methyl-6-arylhexa-3(*Z*),5(*E*)-dienols, which are key intermediates in the syntheses of strobilurins A and X, has been developed.

Strobilurins **1** are antifungal antibiotics. About 20 representatives of these compounds have been isolated and characterised; they differ in the nature of the substituents at the aromatic ring. The examples of the simplest strobilurins A (**1A**), B (**1B**) and X (**1X**) and more complicated strobilurins C (**1C**), H (**1H**) and N (**1N**) are shown in Scheme 1.

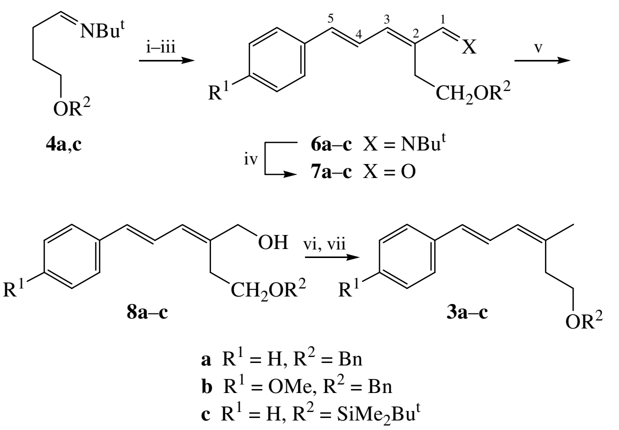


Scheme 1

The known methods for synthesising compounds **1** are non-stereoselective and require a laborious separation of the isomers.[1–3] This paper deals with the development of a highly stereoselective method for building the aryldiene skeleton of strobilurins. As appears from the retrosynthetic analysis (see Scheme 1), ethers **3a** and **3b**, which are precursors of the simplest strobilurins A (**1A**) and X (**1X**), respectively, are convenient objects for this purpose.

To attain our goal, we used the methodology that is akin to that previously developed for a highly stereoselective synthesis of a (*Z*)-trisubstituted C=C bond[4,5] and subsequently used to synthesise low-molecular bioregulators of the polyprenols–dolichols series,[6,7] their modified analogues,[8] and insect pheromones.[9,10]

According to this approach, the synthesis of compound **3a** (Scheme 2) starts with the cross-condensation of LDA-deprotonated 4-benzyloxybutanal *tert*-butylimine **4a** with (*E*)-cinnamic aldehyde **5a** to give rather stable imine **6a** in a good yield. Compound **6a** converts into dienal **7a**[†] only upon prolonged refluxing in aqueous acetone in the presence of catalytic amounts of H_2SO_4. The condensation of compound **4a** with (*E*)-4-methoxycinnamic aldehyde **5b** occurs in a similar way *via* imine **6b** to give dienal **7b**.[†]



Scheme 2 *Reagents and conditions*: i, LDA/Et_2O, 0 °C, 40 min; ii, **5a** or **5b**/Et_2O, –78 °C, 30 min, followed by heating to room temperature, 4 h; iii: 3% HCl, 20 min; iv, H_2SO_4 (cat.)/Me_2CO–H_2O (4:1), reflux, 5 h; v, $NaBH_4$/EtOH, room temperature; vi, Py SO_3/THF, 0 °C, 3 h; vii, $LiAlH_4$, 0 °C, 30 min, then room temperature, 20 h.

Note that condensations of aldimines with α,β-unsaturated aldehydes have not been reported so far.

The stereochemistry of crystalline dienals **7a**,**b** isolated in 80–85% total yields was established by NMR spectroscopy. For example, C–H correlation and COSY methods provided δ and J parameters for the H atoms in the diene system of compound **7b** [δ 6.98 (d, J 15 Hz), 7.05 (d, J 10 Hz), 7.20 (dd, J_1 10 Hz, J_2 15 Hz)]. Of the two doublet signals shown above, only the second signal with δ 7.05 shows NOE (~10%) with H(C^1), which allows us to assign this signal to H(C^3) and conclude that the C^2=C^3 bond has the (*E*) configuration. This conclusion is confirmed by the presence of a signal with δ 9.5 in the ^{1}H NMR spectrum of compound **7b** and a signal with δ ~ 194 in its ^{13}C NMR spectrum; these signals are typical of the CHO group in (*E*)-enals. On the other hand, there are no signals typical of the CHO group in (*Z*)-enals (δ 10 in ^{1}H NMR spectra and δ 191–192 in ^{13}C NMR spectra).[11,12]

The second doublet signal in the ^{1}H NMR spectra of dienal **7b** (δ 6.98) was assigned to H(C^5). Its coupling constant with H(C^4) (15 Hz) suggests the (*E*) configuration of the C^4=C^5 bond. The stereochemistry of compound **7a** was determined in a similar way; the stereoselectivity of the synthesis was almost 100%.

[†] The structures of all new compounds were confirmed by elemental analysis and physico-chemical methods (UV, IR, ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry).

The complete preservation of the diene system configuration in the reduction of compounds **7a**,**b** to diene alcohols **8a**,**b**[†] (the yield is near 100%, Scheme 2) also follows from NMR spectral data for the latter.[‡] Note that the ^{1}H NMR spectra of these dienols contain a single signal of the CH_2OH group with δ 4.15 and the ^{13}C NMR spectra contain a single signal of this group with δ 69.2, which is also characteristic of (*E*)-enols.[12] Similar proof was found for the preservation of the diene system configuration in the reduction of compounds **8a**,**b** *via* the corresponding sulfonic esters (Scheme 2) to target dienes **3a**,**b**.[†,‡] Note that the ^{13}C NMR spectra of the latter contain a single signal of the Me group (δ 24.5), which is also characteristic of internal (*Z*)-methylolefins.[12] No signals are observed in higher field (δ 15–19) where (*E*)-methylolefins usually resonate.[12]

The conversion of dienes **3a**,**b** into esters of type **2** (Scheme 1), which can be smoothly transformed by a known method[2] into the corresponding strobilurins, requires the preliminary protection removal from the hydroxyl group. This operation can be problematic in the case of Bn protection. Therefore, we also synthesised diene **3c** containing an acid-labile *tert*-butyldimethylsilyl group by the sequence of reactions shown in Scheme 2, starting from (*E*)-cinnamic aldehyde **5a** and imine **4c**. Their cross-condensation under the conditions described above after treatment of the reaction mixture with aqueous $(COOH)_2$ gave dienal **7c** in 65% yield;[†] the 2(*E*),4(*E*)-configuration of **7c** was confirmed in the same way as for dienals **7a**,**b**.

The retention of the diene system configuration in the reduction of compound **7c** to **8c**[†] and then to **3c**[†] (the total yield is 52%) was also confirmed as described for compounds **8a**,**b** and **3a**,**b**, respectively.

Thus, the condensation of (*E*)-α,β-unsaturated aldehydes with aldimines occurs with high stereoselectivity; the subsequent reduction of the resulting 2(*E*),4(*E*)-dienals *via* corresponding dienic alcohols and their sulfo esters gives trisubstituted (*Z*,*E*)-dienes **3** with the complete preservation of the diene system configuration.

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[‡] The assignment of signals and determination of the configuration of the system of diene bonds were carried out similarly to that of compound **7b**.