Preparation of (2E,4E)-2-(2-benzyloxyethyl)-5-(3-methoxy-4-chlorophenyl)penta-2,4-dienal as a key intermediate in the synthesis of strobilurin B

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Earlier, we have shown that the thermodynamic preference of 2,5-disubstituted 2E,4E-dienals (1) (with respect to their 2Z,4E-isomers (1’)) opens a highly stereoselective approach to the construction of antibiotics of strobilurin series. In fact, starting from dienals 1a,b (Scheme 1), a six-step sequence of stereospecific reactions was developed, which allowed one to obtain aryl-diene esters 2a,b in high yields and stereochemical purity ≥98%. Since the latter are known as synthetic precursors of simplest strobilurins A (3a) and X (3b) and their transformation to 3a,b is described in the literature, the preparation of esters 2a,b formally means the synthesis of the strobilurins named.

In the present work, we describe the synthesis of dienal 1c, a key intermediate in the total synthesis of more complicated strobilurin B (3c). The present work starts a series of studies on the generality of the developed approach to the synthesis of strobilurin antibiotics, as well as the influence of substitution in the aromatic ring on the reactivity and stereochemistry of transformations of arylidene compounds used in the previously mentioned sequence of transformations of dienals 1 to compounds 2 (see Ref. 4).

The choice of strobilurin 3c as the object of study of versatility of the approach developed for the construction of strobilurin antibiotics has been reasoned also by the fact that the synthesis of strobilurin B by one of the methods

Scheme 1

R1 = R2 = H (a); R1 = H, R2 = OMe (b); R1 = OMe, R2 = Cl (c)
described earlier for the synthesis of strobilurin A (3a) failed.

According to the methodology developed for the construction of strobilurins, we planned to obtain dienal 1c by the condensation of benzyloxybutanal N-tert-butylimine (4a)\(^7\) with the earlier undescribed 4-chloro-3-methoxycinnamic aldehyde (5). The latter was synthesized in four steps (Scheme 2) starting from commercially available 6-chloro-m-cresol (6). Its methylation and oxidation of the obtained methoxy derivative 7 with KMnO\(_4\) in aqueous pyridine using the modified by us procedure\(^8\) gave rise to acid 8, which was routinely converted through the step of the corresponding alcohol to the substituted benzaldehyde 9. The transformation of 9 to the cinnamic aldehyde derivative 5 was performed by a two-step Nazarov—Makin method\(^9\) through the preparation of diethyl acetal 10. The compound BF\(_3\)·Et\(_2\)O has proved the optimum catalyst of the first step of this process (the reaction of acetal 10 with ethyl vinyl ether). In this case, ethoxy acetal 11 was obtained in 85% yield (the yield of the undesirable telomer 12, according to the \(^1\)H NMR data, did not exceed 5%). Treatment of ethoxy acetal 11 with the equimolar amount of NaOAc·3H\(_2\)O in AcOH gave enal 5 in total 60% yield in two steps.

The condensation of aldehyde 5 with deprotonated aldime 4a under conditions used earlier in the condensation of 4a with cinnamic and 4-methoxycinnamic aldehydes\(^7\) (Scheme 3, method A), leads, after acidic hydrolysis of the initial reaction product, imine 13, to the target dienal 1c in 40% yield, which contained no more than 2% of its (2Z,4E)-isomer (1c) (\(^1\)H NMR data are given below).

Note that \(^1\)H NMR spectroscopy showed, together with the starting aldehyde 5 and aldehyde 14 formed by hydrolysis of excessive imine 4a, the presence of 4-chloro-3-methoxycinnamic alcohol (15) (~15%, see below) among the other components of the reaction mixture. This allowed us to suggest that aldehyde 5 was involved not only in the condensation with the deprotonated imine 4a, but also in the parallel Cannizzaro reaction.

The efficiency of the condensation failed to be improved either when imine 4a was replaced with its \(N\)-cyclohexyl analog (4b) (Scheme 3, method B) or when the reaction was carried out in the presence of HMPA (Scheme 3, method C). Moreover, in the latter case, the total yield of dienals 1c and 1c was decreased to 27% (however, their ratio remaining the same), whereas the yield of alcohol 15 increased to 30%.

Alcohol 15 has not been described earlier. Its structure unambiguously was confirmed by an alternative synthesis, namely by the reduction of aldehyde 5 with NaBH\(_4\) (98% yield).