Preparation of (2*E*,4*E*)-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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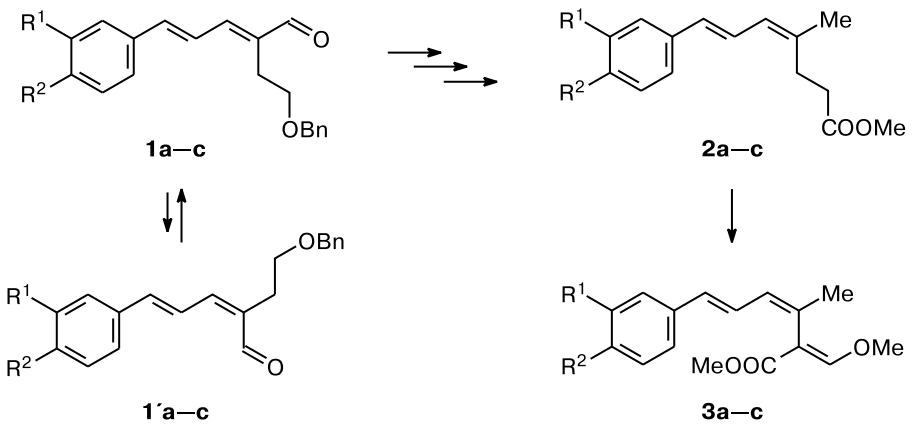
(2*E*,4*E*)-2-(2-Benzyloxyethyl)-5-(4-chloro-3-methoxyphenyl)penta-2,4-dienal was obtained by the condensation of 4-benzyloxybutanal *N*-*tert*-butylimine with 4-chloro-3-methoxycinnamic aldehyde with ≥98% configurational purity and 40% yield. When 4-benzyloxy-2-triethylsilylbutanal imine was used, a 7 : 3 mixture of the target (2*E*,4*E*)-dienal with its (2*Z*,4*E*)-isomer was obtained in 60% yield; the latter quantitatively isomerized to the thermodynamically preferable target (2*E*,4*E*)-dienal.

Key words: strobilurins, aldol condensation, stereocontrolled synthesis, aldimines, arylenals, dienals.

Earlier, we have shown[1] that the thermodynamic preference of 2,5-disubstituted 2*E*,4*E*-dienals (**1**) (with respect to their 2*Z*,4*E*-isomers (**1´**)) opens a highly stereoselective approach to the construction of antibiotics of strobilurin series.[2,3] In fact, starting from dienals **1a**,**b** (Scheme 1), a six-step sequence of stereospecific reactions was developed, which allowed one to obtain aryldiene esters **2a**,**b**[4] 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,[5] 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 aryldiene 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



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

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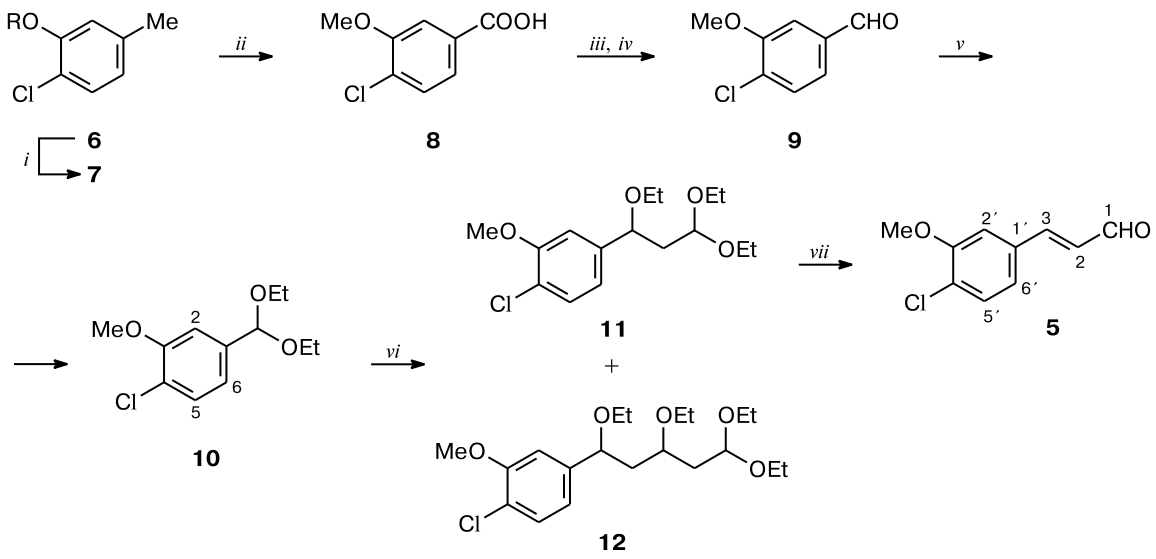
Scheme 2



R = H (**6**), Me (**7**)

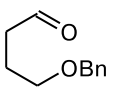
Reagents and conditions: *i*. $(MeO)_2SO_2$/acetone; *ii*. $KMnO_4/H_2O$—Py, 50 °C, 8 h; *iii*. $LiAlH_4$/THF; *iv*. PCC/CH_2Cl_2; *v*. $CH(OEt)_3$/EtOH, $HClO_4$; *vi*. $CH_2{=}CHOC_2H_5/Et_2O$, $BF_3 \cdot Et_2O$; *vii*. NaOAc · 3 H_2O/AcOH, 90 °C.

described earlier for the synthesis of strobilurin A (**3a**) failed[6].

According to the methodology developed for the construction of strobilurins, we planed 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 $BF_3 \cdot Et_2O$ 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 · $3H_2O$ in AcOH gave enal **5** in total 60% yield in two steps.

The condensation of aldehyde **5** with deprotonated aldimine **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 (2*Z*,4*E*)-isomer (**1′c**) (^{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.



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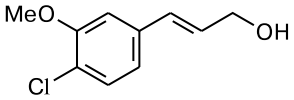

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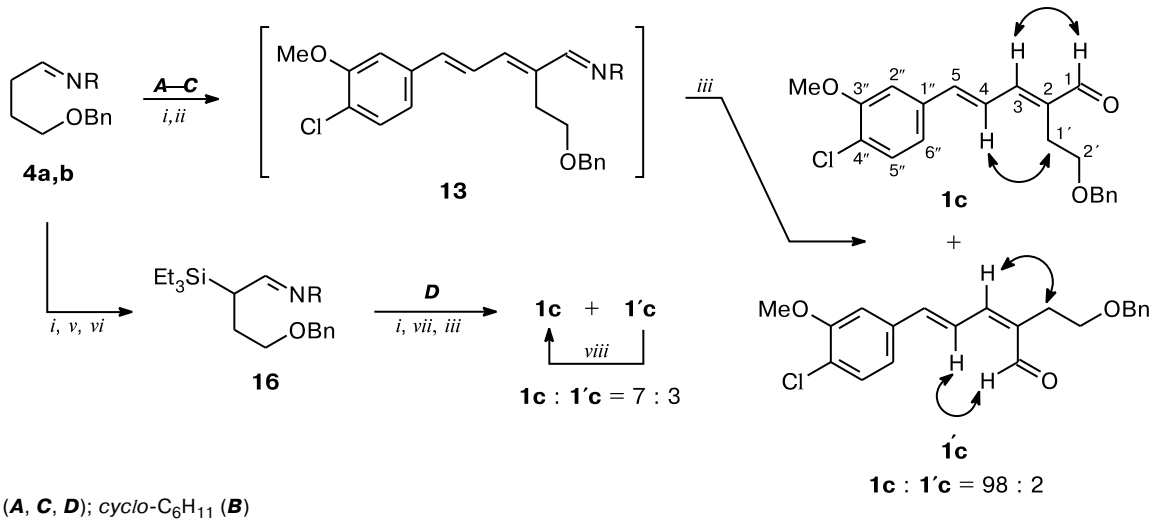
The efficiency of the condensation failed to be improved either when imine **4a** was replaced with its *N*-cyclohexyl analog (**4b**) (Scheme 3, method ***B***) or when the reaction was carried out in the presence of HMPA (Scheme 3, method ***C***). Moreover, in the latter case, the total yield of dienals **1c** and **1′c** 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 unambiguosly was confirmed by an alternative synthesis, namely by the reduction of aldehyde **5** with $NaBH_4$ (98% yield).

Scheme 3



R = Bu^t (***A***, ***C***, ***D***); *cyclo*-C_6H_{11} (***B***)

Methods: ***A***, ***B***: *i—iii*; ***C***: *i*, *iv*, *ii*, *iii*; ***D***: *i*, *vii*, *viii*.

Reagents and conditions:

i: LDA/THF—C_6H_{14}, −15 °C, −15 °C→0 °C, 0 °C, 40 min;
ii. **5**/THF, −80 °C, 1 ч, −80 °C→0 °C, 3.5 h;
iii. H_3O^+;
iv. HMPA, −80 °C, 30 min;
v. Et_3SiCl, −80 °C, 30 min,−80 °C→0°C, 4 h;
vi. H_2O;
vii. **5**, −80 °C, 1.5 h, −80 °C→ −20 °C, 2.5 h;
viii. $CHCl_3$, 100 °C (sealed tube), 1 h.

The Peterson condensation of aldehyde **5** with Et_3Si derivative (**16**) of aldimine **4a** obtained by the silylation of the latter turned out to be more efficient (Scheme 3, method ***D***). In this case, after acidic hydrolysis of the initial reaction products, a mixture of stereoisomeric dienals **1c** and **1′c** was obtained in ~70% yield in the ratio 7 : 3, whereas the content of alcohol **15** did not exceed 2%.

Isomeric dienals **1c** and **1′c** were isolated in the individual states by chromatography in 60% total yield, their structures were unambiguosly confirmed by a combination of physicochemical methods, primarily, by high resolution mass spectrometry (HRMS) and ^{1}H NMR spectroscopy using the NOE procedure. Thus, two one-proton doublet signals at δ 6.95 and 7.09 were found in the region for the resonance of the olefin protons in the ^{1}H NMR spectrum of dienal **1c**, as well as a one-proton doublet of doublets signal at δ 7.31. In this case, the proton with the signal at δ 7.09 showed the NOE (33.9%) with the proton of the formyl group, whereas the proton with the doublet of doublets signal gave the NOE (5%) with the protons of the allyl CH_2 group. These data allow us to, first, assign the doublet at δ 7.09 to HC(3), and, second, make a conclusion on the (*E*)-configuration of the C(2)=C(3) bond. The second doublet signal in the ^{1}H NMR spectrum of dienal **1c** (δ 6.95) was assigned, respectively, to HC(5). Its spin-spin coupling constant with HC(4) (16.2 Hz) indicates the *E*-configuration of the C(4)=C(5) bond. The structure of 2*Z*,4*E*-dienal **1′c** was confirmed similarly. The presence of the NOE (14%) between the proton with the doublet of doublets signal at δ 7.70 in the ^{1}H NMR spectrum of dienal **1′c** and the proton of the formyl group indicate the *Z*-configuration of the C(2)=C(3) bond, which also is confirmed by the presence of the NOE (7.5%) between the proton with the doublet signal at δ 7.12 and the protons of the allyl CH_2 group.

Heating of the solution of 2*Z*,4*E*-dienal **1′c** in chloroform in a sealed tube (100 °C, 1 h) virtually quantitatively gives the target 2*E*,4*E*-isomer (**1c**). It is interesting to note that these conditions are much milder than those required for the transformation of aliphatic *Z*-enals to their *E*-isomers.[10]

In conclusion, the work performed resulted in the preparation of 2*E*,4*E*-dienal **1c** in 60% yield and configurational purity ≥98%, which contain an aryldiene system of the C=C bond in the configuration necessary for the construction of strobilurin B.

Experimental

UV spectra were recorded on a U-1900 Spectrophotometer instrument in ethanol solution, IR spectra were recorded on a Specord M-80 spectrometer for neat samples or (for alcohols) in $CHCl_3$ solution. ^{1}H and ^{13}C NMR spectra of solutions in $CDCl_3$ were recorded on a Bruker AC-200 spectrometer relative to the signals of the solvent (δ 7.27 and 77.0, respectively). The signals for the vinyl protons in the ^{1}H NMR spectra were as-

signed based on the NOE-experiment. The signals in the ^{13}C NMR spectra of isomeric compounds **1c** and **1´c** were assigned with allowance for the calculated spectra obtained using the MestReNova 6.0.2 program (Mestrelab research S.I., www.mestrelab.com, 2009) and the spectral data for the relative compounds.[11] The numeration of atoms for some compounds in Schemes 2 and 3 is given so that to make convenient description of their NMR spectra and not always corresponds to the IUPAC nomenclature requirements. High resolution mass spectra (HRMS) were measured on a micrOTOF II (Bruker Daltonics) instrument using electrospray ionization (ESI), the scanning range from *m/z* 50 to 3000, positive ions (capillary voltage 4500 V). The samples were injected using a syringe. The solvent acetonitrile, the solution flow speed 3 μm min^{-1}. The interface temperature 180 °C, the sprayer gas nitrogen (4.0 L min^{-1}). Melting points were measured on a Kofler heating stage and were not corrected. Column chromatography was performed on Silicagel 60 (0.04—0.06 mm, Fluka). The solvents were purified using the following methods: diethyl ether and THF were kept over KOH, with subsequent distillation over Na and $LiAlH_4$, then, they were refluxed with Na-ketyl benzophenone until a blue color was persistent and distilled directly into the reaction vessel; hexane was distilled over Na; $MeOBu^t$ was purified by distillation. A solution of LDA was prepared directly in the reactor from equivalent amount of diisopropylamine and 1.3—1.5 *M* hexane solution of BuLi. Experiments with the use of BuLi and LDA were carried out under argon, using a glassware which was dried at 160 °C during 12 h and cooled in the flow of argon. The standard treatment of the organic extracts included their neutralization, drying with Na_2SO_4, and concentration *in vacuo* on a rotary evaporator. The reactants $NaBH_4$, $HC(OEt)_3$, and 6-chloro-*m*-cresol (Fluka) were used without additional purification.

4-Chloro-3-methoxybenzaldehyde (9) was obtained (see Scheme 2) as described earlier[8] as colorless crystals with m.p. 53—54 °C. It was shown that transformation of compound **7** to acid **8** at 50 °C reached completion within 8 h, rather than within 24 h as it was reported in the work.[8] Physicochemical characteristics of compounds **7**—**9** correspond to the literature data.[8]

4-Chloro-3-methoxybenzaldehyde diethyl acetal (10). A 60% solution of $HClO_4$ (0.3 mL) was added to a solution of aldehyde **9** (10.5 g, 61.6 mmol) and ethyl orthoformate (11 g, 74.3 mmol) in anhydrous ethanol (100 mL) (Ar) with stirring, the reaction mixture was stirred for 5.5 h at room temperature, followed by addition of a 10% solution of NaOH in MeOH (2.5 mL), ethanol was evaporated *in vacuo* after 15 min. The residue was dissolved in $MeOBu^t$ (100 mL) and after standard treatment an oily liquid (14.6 g) was obtained, which was fractionally distilled *in vacuo* to obtain acetal **10** (12.6 g, 84%), b.p. 106—110 °C (1 Torr). Found (%): C, 58.94; H, 7.15; Cl, 14.50. $C_{12}H_{17}ClO_3$. Calculated (%): C, 58.90; H, 7.00; Cl, 14.49. HRMS, *m/z*: found: 267.0763; calculated for $C_{12}H_{17}ClO_3$: $[M + Na]^+$, 267.0758. IR, ν/cm^{-1}: 2976, 2932, 2880, 1588, 1584, 1560, 1488, 1464, 1400, 1372, 1352, 1344, 1332, 1296,1268, 1256, 1172, 1112, 1096, 1064, 1032, 864, 828, 784. ^1H NMR, δ: 1.25 (t, 6 H, 2 $CH_2C\underline{H}_3$, J = 7.1 Hz); 3.58 (m, 4 H, 2 OCH_2); 3.95 (s, 3 H, H_3CO); 5.46 (s, 1 H, OCHO); 7.00 (dd, 1 H, HC(6), J_1 = 8.1 Hz, J_2 = 1.6 Hz); 7.08 (d, 1 H, HC(2), J = 1.6 Hz); 7.34 (d, 1 H, HC(5), J = 8.1 Hz). ^{13}C NMR, δ: 15.13 ($\underline{C}H_3CH_2$); 56.04 (OMe); 61.10 (OCH_2); 100.90 (OCHO); 110.30 (C(2)); 119.60 (C(6)); 122.30 (C(4)); 129.70 (C(5)); 139.30 (C(1)); 154.90 (C(3)).

4-Chloro-3-methoxycinnamic aldehyde (5). *Step* 1. The compound $BF_3 \cdot Et_2O$ (0.1 mL) was added to acetal **10** (5.2 g, 21.3 mmol) (Ar) at room temperature. The orange solution obtained was cooled to 0 °C, followed by addition of a solution of ethyl vinyl ether (1.5 g, 20.8 mmol) in Et_2O (8 mL) over 10 min. The reaction mixture was heated to reflux, which was continued for 3 h, then the mixture was cooled to obtain, after the standard treatment, crude 3-(4-chloro-3-methoxyphenyl)-3-ethoxypropanal diethyl acetal (**11**) (6.6 g) as colorless liquid (which, according to the ^1H NMR data, contained 85% of the major compound). The acetal was used in subsequent step without additional purification.

Step 2. A solution of ethoxy acetal **11** (7.2 g, 22.75 mmol) and $AcONa \cdot 3\ H_2O$ (3.1 g, 22.8 mmol) in glacial acetic acid (20 mL) was stirred at 90 °C for 4 h, then the mixture was poured into cold water and extracted with $MeOBu^t$. After the standard treatment of the extract, a mixture of crystalline reaction products (4.7 g) was obtained, with the content of the target aldehyde being about 85% (NMR data). Recrystallization from $MeOBu^t$ gave pure aldehyde **5** (3.5 g, 78%), m.p. 92—94 °C. Found (%): C, 61.08; H, 4.80; Cl, 18.12. $C_{10}H_9ClO_2$. Calculated (%): C, 61.08; H, 4.61; Cl, 18.03. HRMS, *m/z*; found: 219.0191; calculated for $C_{10}H_9ClO_2$: $[M + Na]^+$, 219.0183. UV (λ_{max}/nm (ε)): 320 (15600), 292 (26600). IR, ν/cm^{-1}: 3314, 3105, 3013, 2990, 2946, 2851, 2766, 2244, 1873, 1676, 1624, 1592, 1572, 1483, 1474, 1417, 1401, 1316, 1300, 1288, 1269, 1239, 1195, 1176, 1129, 1063, 1029, 1015, 985, 871, 850, 795, 744, 692, 615, 596. ^1H NMR, δ: 3.95 (s, 3 H, H_3CO); 6.69 (dd, 1 H, HC(2), J_1 = 15.9 Hz, J_2 = 7.6 Hz); 7.09 (s, 1 H, HC(2´)); 7.11 (d, 1 H, HC(6´), J = 8.1 Hz); 7.42 (d, 1 H, HC(5´), J = 8.1 Hz); 7.43 (d, 1 H, HC(3), J = 15.9 Hz); 9.71 (d, 1 H, HC(1), J = 7.6 Hz). ^{13}C NMR, δ: 56.17 (OMe); 110.94 (C(2´)); 121.78 (C(6´)); 125.90 (C(4´)); 128.99 (C(2)); 130.77 (C(5´)); 133.85 (C(1´)); 151.29 (C(3)); 155.45 (C(3´)); 193.18 (C(1)).

4-Benzyloxybutanal *N*-*tert*-butylimine (4a) was obtained as described earlier[7] in 94% yield. Physicochemical characteristics of compound **4a** correspond to the literature data.[7]

4-Benzyloxybutanal *N*-cyclohexylimine (4b) was obtained similarly to imine **4a** from 4-benzyloxybutanal (4.5 g, 25 mmol) and cyclohexylamine (2.8 g, 28 mmol), The yield was 95%. ^1H NMR, δ: 1.00—2.00 (m, 6 CH_2); 2.30 (m, 2 H, $H_2C(2)$); 2.88 (m, 1 H, HC(1´)); 3.50 (t, 2 H, $H_2C(4)$, J = 6 Hz); 4.50 (s, 2 H, $\underline{H}_2CPh$); 7.30 (m, 5 H, Ph); 7.67 (t, 1 H, $\underline{H}C{=}N$, J = 6 Hz). The thermally unstable imine **4b** was dried until the weight was constant at 20 °C and the pressure of 2 Torr and was used in subsequent reactions without additional purification.

4-Benzyloxy-2-triethylsilylbutanal *N*-*tert*-butylimine (16). A solution of imine **4a** (1.87 g, 8 mmol) in THF (15 mL) was added to a stirred solution of LDA (9 mmol) in THF (15 mL) and hexane (4.5 mL) at −20 °C over 40 min, the reaction mixture was heated to −5 °C and stirred at this temperature for 30 min. A light orange solution obtained was cooled to −80 °C, followed by addition of a solution of Et_3SiCl (1.27 g, 8.45 mmol) in THF (15 mL) over 15 min Then, the mixture was stirred for 30 min at −80 °C, warmed up to 0 °C over 4 h, and quenched with cold water. The aqueous layer was separated and extracted with $MeOBu^t$. After the standard treatment of the combined organic extracts and drying of the residue *in vacuo* (2 Torr) until the weight was constant, imine **16** (2.6 g, 94%) was obtained, which was used in the next step without additional purification.

Physicochemical characteristics of imine **16** correspond to the literature data.[12]

(2*E*,4*E*)-2-(2-Benzyloxyethyl)-5-(4-chloro-3-methoxyphenyl)penta-2,4-dienal (1c). ***A.*** A solution of imine **4a** (1.8 g, 7.7 mmol) in THF (20 mL) was added to a solution of LDA (9.3 mmol) in THF (24 mL) and hexane (5.5 mL) at −15 °C over 1.5 h. The reaction mixture was warmed up to 0 °C and stirred for 40 min at this temperature. Then, the dark orange solution obtained was cooled to −80 °C, followed by addition of a solution of aldehyde **5** (0.9 g, 4.58 mmol) in THF (20 mL) and stirring for 30 min at −80 °C. Then, the reaction mixture was warmed up to 0 °C over 3.5 h and kept at 4—5 °C for 13 h. The solution obtained was added to a mixture of 3% aq. HCl (100 mL) and MeOBu^t (50 mL), stirred for 1 h, the layers were separated. The aqueous layer sequentially was extracted with MeOBu^t (3×30 mL) and chloroform (2×30 mL). After the standard treatment of the combined ethereal extracts, a mixture of reaction products (1.7 g) was obtained, which contained dienal **1c** (with impurities of isomer **1´c** ≤2%) and cinnamic alcohol derivative **15** in the ratio of 2 : 1, as well as 8—10% of the starting cinnamic aldehyde **5** and 18% of aldehyde **14** (^{1}H NMR data). Flash-chromatography of this mixture on SiO_2 (40 g) using a gradient elution from light petroleum to MeOBu^t yielded dienal **1c** (0.7 g) containing ≤2% of isomer **1´c** and about 10% of aldehyde **5**, as well as alcohol **15** (0.3 g) (see below). The standard treatment of the chloroform extract gave a mixture of reaction products (0.9 g), which according to the ^{1}H NMR data contained 65% of compound **13**, the *N*-*tert*-butylimine of dienal **1c**. ^{1}H NMR, δ, of compound **13**: 1.22 (s, 9 H, Bu^t); 2.99 (t, 2 H, $H_2C(1')$, J = 6.8 Hz); 3.65 (t, 2 H, $H_2C(2')$, J = 6.8 Hz); 3.90 (s, 3 H, MeO); 4.55 (s, 2 H, C$\underline{H}_2$Ph); 6.58 (d, 1 H, HC(3), J = 11.2 Hz); 6.67 (d, 1 H, HC(5), J = 15.6 Hz); 6.97 (s, 1 H, HC(2″)); 7.60 (m, 8 H, Ar + HC(4)); 7.85 (s, 1 H, HC(1)). The mixture was dissolved in acetone (17 mL), followed by addition of a solution of H_2SO_4 (0.1 mL) in water (5 mL) and reflux for 4.5 h. Then, the mixture was cooled, neutralized with $NaHCO_3$, acetone was evaporated *in vacuo*, and the residue was diluted with water. The aqueous solution was extracted with MeOBu^t (3×20 mL), the combined extracts subsequently were subjected to the standard treatment, the mixture of reaction products was chromatographed on SiO_2 as described above to obtain dienal **1c** (0.3 g), in which the content of both dienal **1´c** and aldehyde **5** did not exceed 2%. A repeated chromatography of the combined fractions of dienal **1c** isolated from the ethereal and chloroform extracts on SiO_2 using elution with benzene allowed us to obtain dienal **1c** (0.65 g, 40%), which did not contain aldehyde **5**. Dienal **1c**, b.p. (decomp.) 160 °C (a bath, 0.065 Torr). HRMS, *m/z*: found 379.1063; calculated for $C_{21}H_{21}ClO_3$: [M + Na]$^+$, 379.1071. UV (λ_{max}/nm (ε)): 338 (18600), 218 (11800). IR, ν/cm^{-1}: 3326, 3086, 3063, 3031, 2964, 2931, 2857, 2718, 1673, 1620, 1588, 1570, 1491, 1455, 1414, 1372, 1298, 1257, 1197, 1184, 1098, 1062, 1030, 1004, 968, 870, 806, 739, 698. ^{1}H NMR, δ: 2.81 (t, 2 H, $H_2C(1')$, J = 6.5 Hz); 3.60 (t, 2 H, $H_2C(2')$, J = 6.5 Hz); 3.88 (s, 3 H, H_3CO); 4.50 (s, 2 H, $\underline{H}_2$CPh); 6.95 (d, 1 H, HC(5), J = 16.2 Hz); 6.98 (d, 1 H, HC(2″), J = 1.7 Hz); 7.02 (dd, 1 H, HC(6″), J_1 = 8.2 Hz, J_2 = 1.7 Hz); 7.09 (d, 1 H, HC(3), J = 11.0 Hz); 7.31 (dd, 1 H, HC(4), J_1 = 16.2 Hz, J_2 = = 11.0 Hz); 7.34 (d, 1 H, HC(5″), J = 8.2 Hz); 9.51 (s, 1 H, HC(1)). ^{13}C NMR, δ: 25.72 (C(1´)); 56.14 (OMe); 69.03 (C(2´)); 73.00 (C$\underline{H}_2$Ph); 110.48 (C(2″)); 120.73 (C(6″)); 123.76 (C(4″)); 124.70 (C(4)); 127.36, 127.49, 128.28 (Ph); 130.50 (C(5″)); 135.98 (C(1″)); 138.31 (Ph); 139.25 (C(2)); 140.52 (C(5)); 150.21 (C(3)); 155.25 (C(3″)); 194.25 (C(1)).

B. The condensation of cinnamic aldehyde **5** with imine **4b** was carried out as described in method ***A*** for imine **4a**. The composition of the reaction products and the yield of the target dienal **1c** were close to those obtained in method ***A***.

C. The process was carried out as described in method ***A***. Imine **4a** (2.57 g, 11 mmol) was deprotonated using LDA, then cooled to −80 °C, followed by a sequential addition of HMPA (2.3 mL) and aldehyde **5** (7.6 mmol). Then, the mixture was stirred for 1 h at −80 °C and warmed up to 0 °C over 3.5 h. Then, the mixture was treated as described in method ***A*** and after chromatography on SiO_2, dienal **1c** was obtained, which contained ≤2% of isomer **1´c**, and cinnamic alcohol **15** in 27% and 30% yields, respectively.

D. The silyl derivative **16** (3.71 g, 10.7 mmol) was deprotonated as described in method ***A*** for imine **4a**, then aldehyde **5** (7.2 mmol) was added at −80 °C. The reaction mixture was stirred for 1.5 h at −80 °C, then warmed up to −20 °C over 2.5 h and kept at −20 °C for 13 h, followed by treatment as described in method ***A***. The standard treatment of the combined ethereal extracts (3.1 g) led to a mixture of reaction products containing dienal **1c**, its (2*Z*,4*E*)-isomer (**1´c**), and the starting aldehyde **5** in the ratio of 1 : 1.5 : 1; the content of cinnamic alcohol **15** in the mixture did not exceed 2% (^{1}H NMR data). The double chromatography of this mixture on SiO_2 as described in method ***A*** furnished dienal **1c** (16% yield) and dienal **1´c** (18% yield).

(2*Z*,4*E*)-2-(2-Benzyloxyethyl)-5-(4-chloro-3-methoxyphenyl)penta-2,4-dienal (1´c). HRMS, *m/z*; found: [M + Na]$^+$, 379.1064; $C_{21}H_{21}ClO_3$; calculated: [M + Na]$^+$, 379.1071. UV (λ_{max}/nm, (ε)): 336 (22100), 245 (6600), 218 (13700). IR, ν/cm^{-1}: 3468, 3087, 3030, 2929, 2859, 1721, 1664, 1617, 1588, 1571, 1491, 1455, 1412, 1363, 1298, 1257, 1196, 1178, 1135, 1099, 1063, 1029, 969, 911, 868, 806, 737, 699, 620, 456. ^{1}H NMR, δ: 2.64 (t, 2 H, $H_2C(1')$, J = 6.4 Hz); 3.61 (t, 2 H, $H_2C(2')$, J = 6.4 Hz); 3.96 (s, 3 H, H_3CO); 4.52 (s, 2 H, $\underline{H}_2$CPh); 6.77 (d, 1 H, HC(5), J = 15.2 Hz); 7.01 (d, 1 H, HC(2″), J = 1.7 Hz); 7.04 (dd, 1 H, HC(6″), J_1 = 8.3 Hz, J_2 = 1.7 Hz); 7.12 (d, 1 H, HC(3), J = 11.9 Hz); 7.33 (m, 5 H, Ph); 7.37 (d, 1 H, HC(5″), J = 8.3 Hz); 7.70 (dd, 1 H, HC(4), J_1 = 15.2 Hz, J_2 = 11.9 Hz); 10.38 (s, 1 H, HC(1)). ^{13}C NMR, δ: 30.88 (C(1´)); 56.17 (OMe); 68.84 (C(2´)); 72.89 ($\underline{C}H_2$Ph); 110.28 (C(2″)); 120.43 (C(6″)); 121.72 (C(4″)); 123.57 (C(4)); 127.57, 127.66, 128.39 (Ph); 130.54 (C(5″)); 136.00 (C(1″)); 138.31 (Ph); 139.45 (C(2), C(5)); 146.09 (C(3)); 155.29 (C(3″)); 189.82 (C(1)).

The residue (1.5 g) from the combined chloroform extracts containing imine **13** was hydrolyzed as described in method ***A*** to obtain after chromatography on SiO_2 an additional amount (0.75 g, 26%) of dienal **1c**.

Heating a solution of dienal **1´c** in chloroform in a sealed tube at 100 °C during 1 h quantitatively gives the target dienal **1c**, the content of (2*Z*,4*E*)-isomer in which does not exceed 2% (^{1}H NMR data). The total yield of the target (2*E*,4*E*)-dienal **1c** was 60%.

4-Chloro-3-methoxycinnamic alcohol (**15**, alternative synthesis) was obtained by the reduction of aldehyde **5** upon the action of $NaBH_4$ in EtOH according to the standard procedure, The yield was 98%, m.p. 64—65 °C (from a mixture of Et_2O—hexane (1 : 1)). Found (%): C, 60.40; H, 5.56; Cl, 17.76. $C_{10}H_{11}ClO_2$. Calculated (%): C, 60.46; H, 5.58; Cl, 17.85. HRMS, *m/z*: found: 199.0522; calculated for $C_{10}H_{11}ClO_2$: [M + H]$^+$, 199.0520.

UV spectrum, λ_{max}/nm (ε): 296 (4630), 256 (17375), 218 (23860). IR, ν/cm^{-1}: 3611, 3447, 3019, 2966, 2942, 2918, 2870, 2840, 1593, 1575, 1491, 1465, 1409, 1382, 1295, 1254, 1223, 1207, 1193, 1174, 1144, 1087, 1066, 1031, 1007. 968, 859, 797, 728, 696, 668. ^{1}H NMR, δ: 3.91 (s, 3 H, H_3CO); 4.33 (d, 2 H, $C\underline{H}_2OH$, J = 5.3 Hz); 6.34 (dt, 1 H, HC(2), J_1 = 15.9 Hz, J_2 = 5.3 Hz); 6.57 (d, 1 H, HC(3), J = 15.9 Hz); 6.91 (d, 1 H, HC(6´), J = 8.2 Hz); 6.92 (s, 1 H, HC(2´)); 7.29 (d, 1 H, HC(5´), J = 8.2 Hz). ^{13}C NMR, δ: 56.01 (OMe); 63.37 (C(1)); 109.85 (C(2´)); 119.50 (C(6´)); 121.69 (C(4´)); 129.30 (C(2)); 130.03 (C(3)); 130.15 (C(5´); 136.69 (C(1´)); 154.98 (C(3´)).

References

1. N. Ya. Grigorieva, A. G. Smirnov, V. A. Popovsky, A. V. Stepanov, *Mendeleev Commun.*, 2008, **18**, 84.
2. J. M. Clough, *Nat. Prod. Rep.*, 1993, **10**, 565.
3. H. Sauter, W. Steglich, T. Anke, *Angew. Chem.*, *Int. Ed.*, 1999, **38**, 1329.
4. N. Ya. Grigorieva, V. A. Popovskii, A. V. Stepanov, E. D. Lubuzh, *Izv. Akad. Nauk*, *Ser. Khim.*, 2010, 2033 [*Russ. Chem. Bull., Int. Ed.*, 2010, **59**, 2086].
5. K. Beautement, J. M. Clough, P. J. de Fraine, Ch. R. A. Godfrey, *Pestic. Sci.*, 1991, **31**, 499.
6. H. Sutter, *Tetrahedron Lett.*, 1989, **30**, 5417.
7. N. Ya. Grigorieva, A. G. Smirnov, V. A. Popovsky, A. V. Stepanov, *Russ. Chem. Bull.* (*Int. Ed.*), 2009, **58**, 312 [*Izv. Akad. Nauk*, *Ser. Khim.*, 2009, 310].
8. F. Claudi, G. Giorgioni, A. D. Stefano, M. P. Abbracchio, A. M. Paoletti, W. Baduini, *J. Med. Chem.*, 1992, **35**, 4408.
9. I. N. Nazarov, S. M. Makin, *Zh. Obshch. Khim.*, 1959, **29**, 3685 [*J. Gen. Chem. USSR* (*Engl. Transl.*), 1959, **29**]; S. M. Makin, G. A. Ermakova, O. A. Shavrygina, A. P. Pleshakova, V. N. Voznesenskii, *Zh. Org. Khim.*, 1979, **15**, 1852 [*J. Org. Chem. USSR* (*Engl. Transl.*), 1979, **15**].
10. N. Ya. Grigorieva, O. N. Yudina, O. A. Pinsker, E.D. Daeva, A. M. Moiseenkov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* (*Engl. Transl.*), 1990, **39**, 84 [*Izv. Akad. Nauk SSSR*, *Ser. Khim.*, 1990, 97].
11. I. M. Avrutov, N. Ya. Grigorieva, V. S. Bogdanov, A. M. Moiseenkov, *Bull. Acad. Sci. USSR*, *Div. Chem. Sci.* (*Engl. Transl.*), 1987, **36**, 2033 [*Izv. Akad. Nauk SSSR*, *Ser. Khim.*, 1987, 2194].
12. R. Baudouy, Ph. Prince, *Tetrahedron*, 1989, **45**, 2067.

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