Synthesis of a Benvitimod impurity: (*Z*)-3,5-dihydroxy-4-isopropylstilbene

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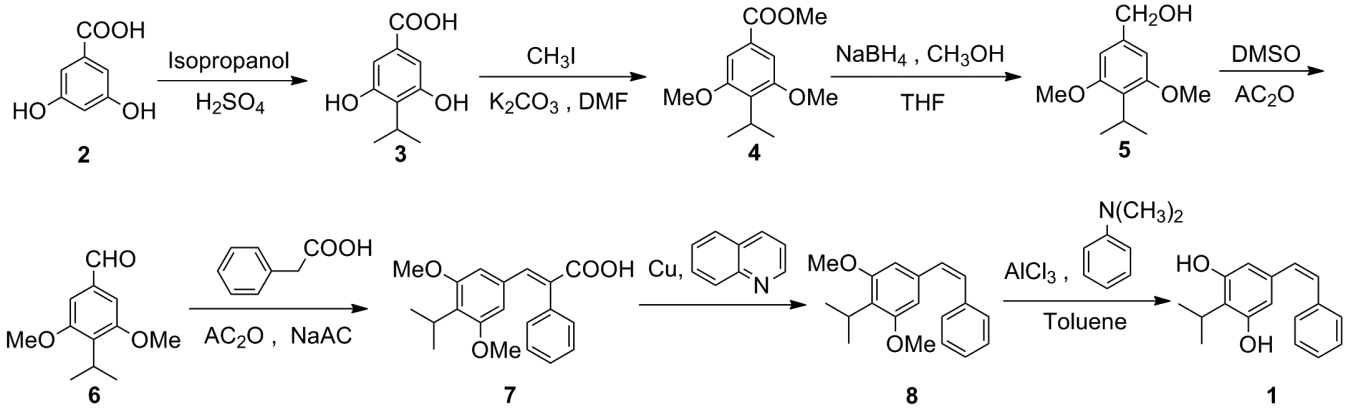
(*E*)-3,5-dihydroxy-4-isopropylstilbene (Benvitimod), a new medicine for the treatment of psoriasis and eczema, belongs to the hydroxystilbene family. The synthesis leads to the *E*-isomer, (*Z*)-3,5-dihydroxy-4-isopropylstilbene being present as a major impurity in the preparation of Benvitimod. We describe a synthesis of the Benvitimod impurity: (*Z*)-3,5-dihydroxy-4-isopropylstilbene starting from 3,5-dihydroxybenzoic acid, through an isopropyl reaction, esterification and etherification, reduction, oxidation, Perkin condensation, decarboxylation and demethylation. The optimal reaction conditions were also determined.

Keywords: Benvitimod, (*Z*)-3,5-dihydroxy-4-isopropylstilbene, Perkin condensation, optimal reaction conditions

Benvitimod [(*E*)-3,5-dihydroxy-4-isopropylstilbene], is a new generation of anti-inflammatory drug which was first developed by Welichem Biotech. Inc. to treat a variety of major autoimmune diseases, such as psoriasis, eczema and allergic disease. It has finished the Clinical Phase II trials in China.[1–3] Since it belongs to the hydroxystilbene family, Benvitimod is inevitably associated with its *Z*-isomer. Hence, (*Z*)-3,5-dihydroxy-4-isopropylstilbene, must be a main impurity in Benvitimod whether it is made by extraction or synthesis and consequently it has a great influence on the quality and efficacy of Benvitimod.[4] Pharmaceutical quality control ensures the safe use of drugs. The toxicity of impurities and the formulation of a drug are important influencing factors on drug safety.[5,6] In addition to the pharmacological activities of the drug itself, many of the adverse reactions to a drug in clinical application are associated with the impurities in the drug.[7,8] Therefore, research of the impurity also plays a critical role on assuring the effectiveness and reducing adverse reactions of drugs. Hence, the synthesis of (*Z*)-3,5-dihydroxy-4-isopropylstilbene is important both for the preparation and the evaluation of the quality and effectiveness of Benvitimod.

Amongst stilbenes when the *E*-isomers show the significant physiological activities the opposite *Z*-isomers display nothing. The reported syntheses of stilbenes include Wittig (–Horner), Heck, Perkin, Knoevenagel, Grignard, reactions have been proposed for the *E*-isomers.[9–11] Although the *Z*-isomer is an inevitable by-product in the preparation of the *E*-isomer,[12] it is difficult to easily separate it from the synthetic mixture due to the minor amount and its serious instability.[13–15] We now describe a synthesis of (*Z*)-3,5-dihydroxy-4-isopropylstilbene **1** (Scheme 1). Starting from the readily available 3,5-dihydroxybenzoic acid **2**, 3,5-dihydroxy-4-isopropylbenzoic acid **3** can be prepared through isopropanylation reaction. Esterification and etherification of **3** was carried out by using CH_3I/K_2CO_3 to obtain methyl 3,5-dimethoxy-4-isopropylbenzoate **4**, which was reduced by $NaBH_4/CH_3OH$ to afford 3,5-dimethoxy-4-isopropylbenzyl alcohol **5**. By using DMSO/Ac_2O as an oxidising agent, **5** was oxidised to 3,5-dimethoxy-4-isopropylbenzaldehyde **6**. Perkin condensation between **6** and phenylacetic acid generates the stilbene skeleton to afford (*E*)-3-(3,5-dimethoxy-4-isopropyl)-2-phenylacrylic acid **7**. Decarboxylation with Cu/quinoline gave (*Z*)-3,5-dimethoxy-4-isopropylstilbene **8**. Finally, **1** is obtained through demethylation by using $AlCl_3$ and N,N-dimethyl aniline. This method for synthesis of **1** had not been reported previously and the optimal reaction condition of each step was developed in detail.

Control of the reaction temperature was important in the isopropanylation because more isopropyl 3,5-dihydroxybenzoate and isopropyl 3,5-dihydroxy-4-



Scheme 1 Synthesis route of (*Z*)-3,5-dihydroxy-4-isopropylstilbene.

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Table 1 Influence of oxidation reagents on **5**

Entry	Reagent	Temperature/°C	Time/h	Yield/%
1	PCC	R.t.	2	95
2	CrO_3/CH_2Cl_2	R.t.	2	93
3	CrO_3/H_2SO_4	R.t.	2	–[a]
4	K_2CrO_7/H_2SO_4	R.t.	3	38
5	MnO_2/THF	68±2	3	80[b]
6	DMSO/Ac_2O	R.t.	3	91

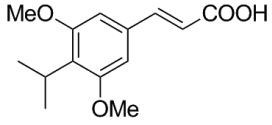
[a]**6** was not obtained and **5** was over oxidised to 3,5-dimethoxy-4-isopropylbenzoic acid.
[b]There was 5 (15%) remaining.
R.t., room temperature.

isopropylbenzoate were obtained at a higher temperature, resulting in a low yield of **3**. The sulfuric acid concentration also had an obvious influence on the yield of isopropyl reaction. In general, a concentration up to 80% always gave a satisfactory yield. In the isopropanylation of **2**, we used 80% sulfuric acid to give **3** with a yield of 82%.

Esterification and etherification of phenol compounds by CH_3I/K_2CO_3 had been reported many times with high yields.[16–19] In our experiment, the esterification and etherification of **3** was found to proceed rapidly with a yield of 93% for **4**.

Esters can be effectively reduced by $LiAlH_4$ a high yield.[20] However, the use of $NaBH_4$ complexed with $AlCl_3$ or CH_3OH as an ester reducing agent had been developed recently.[19] Reduction of **4** by using $NaBH_4/CH_3OH$ in our hands provided a mild method giving a yield of 96% for **5**.

Many of the commonly used oxidation reagents[21–24] were examined for the preparation of **6** from **5** in order to find suitable conditions (Table 1). A series of chromium oxidation reagents such as PCC, PDC and CrO_3/CH_2Cl_2 gave a high yield of **6** but some had tedious work-up procedures because of the serious phenomenon of emulsions. Chromium residues in the product are troublesome and highly toxic both to the experimentalist and in the environment. When using CrO_3/H_2SO_4, we almost failed to obtain **6** but obtained a high yield of 3,5-dimethoxy-4-isopropylbenzoic acid because of over oxidation. When $K_2Cr_2O_7$ was used, the yield of **6** was low because most of **5** was also oxidised to 3,5-dimethoxy-4-isopropylbenzoic acid. Compound **6** was obtained in high yield by using MnO_2 with a little amount of **5** remaining, but the filtration separation was difficult due to the very fine particles of MnO_2. Oxidation with DMSO provides an acceptable yield with mild operating condition and convenient work-up procedure.



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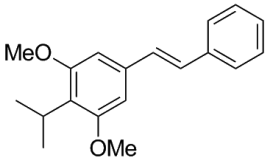

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Fig. 1 Structures of compounds **9** and **10**.

As the critical step in the whole synthesis, the Perkin condensation determined the configuration of the target product. The *E*-isomer was the desired product of this step and it was important to select the optimal reaction condition to improve the yield of *E*-isomer. In the condensation process, we found that there was a main impurity appearing along with **7** in a high yield. The appearance of the impurity interfered with the yield of **7** and resulted in a difficult separation in the workup period. Hence, it was necessary to separate and characterise the impurity in order to look for a method to reduce the formation of this impurity. After chromatographic separation and characterisation by ^{1}H NMR and HRMS, the impurity was finally shown to be (*E*)-3-(3,5-dimethoxy-4-isopropylphenyl)-acrylic acid (**9**) (Fig. 1). Clearly, the formation of **9** was caused by Perkin condensation between acetic acid and **6**. In order to obtain the optimal condition with reducing the formation of this impurity, various basic catalysts reported in the literature[25–27] such as triethylamine, anhydrous K_2CO_3, KF, NaAc and KAc were tried for this step. The yield was poor when triethylamine was used as a base. Anhydrous K_2CO_3 or KF as bases, led to a difficult work-up and emulsion formation was serious and the reaction mixture was a black glue. The yield was higher and the work-up was simple when NaAc or KAc is employed. The catalytic effect of NaAc and KAc was investigated in detail and the results are summarised in Table 2. This shows that the yield of **7** using NaAc was found to be higher than that with KAc. As the reaction time increased, the yield of the product decreased due to the generation of by-products. The content of **7** using NaAc was higher than KAc and decreased with the time because of the formation of the impurity. Excess basic catalyst did not promote the yield of **7**. The results indicate that NaAc was superior to KAc as the catalyst and the optimal reaction condition of Perkin condensation was with 2.5/1 of molar ratio of NaAc/**6** and 16 h of reaction time.

Table 2 Conditions for the Perkin condensation[a]

Entry	n[b]	Time/h[c]	NaAc		KAc	
			Yield/%[d]	**7**/**9**[e]	Yield/%[d]	**7**/**9**[e]
1	2.0:1	8	42	0.96	35	0.89
2	2.5:1	8	34	0.86	44	0.56
3	3.0:1	8	39	1.10	34	0.76
4	2.0:1	12	34	1.17	25	0.80
5	2.5:1	12	43	1.46	25	0.93
6	3.0:1	12	35	1.66	32	1.02
7	2.0:1	16	53	1.65	23	1.71
8	2.5:1	16	57	1.96	39	1.45
9	3.0:1	16	47	1.54	27	0.71
10	2.0:1	20	43	1.47	30	0.61
11	2.5:1	20	44	1.23	38	0.76
12	3.0:1	20	40	1.04	34	0.74

[a]Reaction temperature was 138 °C.
[b]Molar ratio of n (NaAc or KAc)/n (**6**).
[c]Timed from reflux.
[d]Yield of **7** and **9**.
[e]Ratio of **7**/**9**.

It was important to control some factors in the decarboxylation step such as temperature and time to prevent the *Z*-isomer rearranging to an *E*-isomer. In a conventional decarboxylation, the high reaction temperature which was up to 200–210 °C easily increased the configuration inversion of the *Z*-isomer, eventually giving priority to the *E*-isomer,[28–29] with a lower yield of the of *Z*-isomer. In this work, we strictly controlled the reaction temperature and time on the basis of using Cu/quinoline as the decarboxylation reagent. Based on these results shown in Table 3, the effect of various reaction temperature and time was carefully investigated to find the optimal condition for decarboxylation to synthesise **8**. We found that the temperature played an important role in controlling the formation of *Z*-isomer. Compound **7** could not be decarboxylated thoroughly below 180 °C. The content of *Z*-isomer did not increase with time as the temperature increased to 180 °C, while the content of **8** was higher when the reaction temperature reached 190 °C but decreased as the time lengthened because more (*E*)-3,5-dimethoxy-4-isopropylstilbene (**10**, Fig. 1) was obtained. When the temperature exceeded 200 °C, the inversion of the *Z*-isomer to the *E*-isomer occurred. The results indicate that the optimal condition for decarboxylation was with a temperature of 190 °C and a reaction time of 4 h.

Pyridine hydrochloride is a favoured demethylation reagent owing to its low cost, convenience and the fact that no solvent is required [30]. We tried it in our experiment but the high temperature of 180–190 °C easily caused the inversion of the configuration of the *Z*-isomer to the *E*-isomer. In addition to the high cost and toxic of BBr_3, the volatility of BBr_3 meant that this reaction must be conducted at –70 to –80 °C, making the operation difficult.[31] By using $AlCl_3$/N,N-dimethylaniline, the reaction temperature was 110 °C and *Z*-isomer was obtained with a high yield. Moreover, the conditions were mild and the work-up was convenient. We adopted $AlCl_3$/N,N-dimethylaniline as demethylation reagent and the yield of **1** was 58%.

Table 3 The conditions for the decarboxylic reaction[a]

Entry	Temperature/°C	Time/h[b]	Content of **10**/%	Content of **8**/%
1	170	5	23	28
2	170	6	29	33
3	180	4	32	41
4	180	5	43	53
5	180	6	39	55
6	190	3	31	64
7	190	4	22	73
8	190	5	45	49
9	190	6	61	32
10	200	2	59	36
11	200	3	77	13
12	210	2	74	19
13	210	3	85	7

[a]Molar ratio of n (Cu)/n (**7**) is 6 : 1.
[b]Time from reaching the specified temperature.

Conclusions

We have successfully developed a new efficient route for the synthesis of **1** from **2** by isopropanylation, esterification and etherification, reduction, oxidation, Perkin condensation, decarboxylation and demethylation. Furthermore, the optimal condition for each step was determined in detail. This novel method is convenient since it uses commercial available reagents and provides a new approach in the synthesis of these *Z*-hydroxystilbene compounds.

Experimental

3,5-Dihydroxybenzoic acid (>98%) was purchased from Jiangsu Tianjiayi Chemical Co. Ltd. Other solvents and reagents used in the present study were commercially available and are of analytical grade without further purification. Isopropanol, sulfuric acid, Na_2CO_3, Mg_2SO_4, K_2CO_3, DMF, tetrahydrofuran (THF), methyl tertiary butyl ether (MTBE), $NaBH_4$, CH_2Cl_2, HCl, pyridine, CrO_3, acetic anhydride, $NaHCO_3$, NaAc, KAc, Cu, quinoline, NaCl, toluene, methanol, N,N-dimethylaniline, $AlCl_3$ and ethyl acetate were obtained from Hebei Yongda Chemical Ltd. Co. The IR spectra were obtained from a FTIR spectrometer (FTS 135) using KBr pellets. The ^{1}H NMR spectra were obtained using a Bruker Avance (DRX-500) spectrometer operating at 500.13 MHz. The melting point of product was determined from a DSC-TGA (SDT-Q600). The high resolution mass (HRGC-HRMS) spectra were obtained on a FTICR-MS (Ionspec 7.0T) spectrometer.

The purity of each compound obtained in the synthesis were determined by using HPLC which was performed by using Agilent 1260 LC system according to the following method. The column was Elite C18 column (5 μm, 250 × 4.6 mm), the mobile phase was at a flow rate of 1.0 mL·min^{-1} and the injection volume was 10 μL. For compound **7** and **9**, column temperature was 20 °C, the wavelength was at 297 nm, the mobile phase was a mixture of acetonitrile/water (90/10, V/V), the retention time of **7** and **9** was respectively 3.526 min and 4.104 min. For compound **8** and **10**, column temperature was 25 °C, the wavelength was at 317 nm, the mobile phase was a mixture of acetonitrile/water (75/25, V/V), the retention times of **10** and **8** were 8.623 min and 10.347 min respectively. For compound **1**, the column temperature was 30 °C, the wavelength was at 318 nm, the mobile phase was a mixture of acetonitrile/water/MTBE (38/57/5, V/V/V), the retention time of *E*-isomer (Benvitimod) and **1** was respectively 10.419 min and 12.163 min, good linearity and precision were obtained for **1** and the linear concentration of **1** ranged from 1.05 mg·L^{-1} to 157 mg·L^{-1} (r = 0.99991).

Synthesis of 3,5-dihydroxy-4-isopropylbenzoic acid (**3**)

Compound **2** (1.54 g, 0.01 mol) was dissolved in 80% H_2SO_4 (5 mL) and warmed to 6–65 °C. Isopropanol (1 mL) was added dropwise to the above solution. When the addition of isopropanol was completed, the mixture was stirred for 3 h at the same temperature and then cooled to room temperature. The mixture was carefully poured into ice-water (10 mL) and pH was adjusted to 7 with saturated Na_2CO_3 solution. After filtration, the filtrate was acidified with HCl (6 mol·L^{-1}) and extracted with ethyl acetate (3 × 20 mL). The combined extract was dried over anhydrous Mg_2SO_4 for 2 h and concentrated to obtain **3** as a yellowish solid with a yield of 82%. M.p. 182 °C. IR (KBr, ν, cm^{-1}) 3465, 3369, 2970, 1667, 1584, 1438, 1260, 1004. ^{1}H NMR (DMSO, ppm, δ) 12.48(s, 1H), 9.34(s, 2H), 6.90(s, 2H), 3.51–3.45(hept, 1H), 1.26–1.24(d, *J* = 7.0 Hz, 6H). HRMS calcd for $C_{10}H_{12}NaO_4$ [M + Na$^+$] 219.0628, found 219.0627.

Synthesis of methyl 3,5-dimethoxy-4-isopropylbenzoate (**4**)

A stirred solution of **3** (1.96 g, 0.01 mol) in DMF (50 mL), was treated with anhydrous K_2CO_3 (4.15 g, 0.03 mol) at 0 ± 2 °C. CH_3I (4.26 g, 0.03 mol) was introduced into the mixture with stirring. The temperature of the mixture was gradually increased to room temperature and maintained for 2 h. The mixture was added to water with stirring and extracted with ethyl acetate (3 × 20 mL). The combined organic layer was washed with water until it was neutral and then concentrated under vacuum to obtain faint yellow solid **4** in a yield of 93%. M.p. 108 °C. IR (KBr, ν, cm^{-1}): 2990, 2962, 1717, 1585, 1416, 1237, 1142, 1006. ^{1}H NMR ($CDCl_3$, ppm, δ) 7.22(s, 2H), 3.91(s, 3H), 3.85(s, 6H), 3.66–3.60(hept, 1H), 1.28–1.27(d, *J* = 7.0 Hz, 6H). HRMS calcd for $C_{13}H_{19}O_4$ [M + H$^+$] 239.1278, found 239.1279.

Synthesis of 3,5-dimethoxy-4-isopropylbenzyl alcohol (**5**)

Compound **4** (2.4 g, 0.01 mol), THF (30 mL) and $NaBH_4$ (1.51 g, 0.04 mol) were placed into a 100 mL round-bottom flask. The mixture was stirred and heated to reflux. Methanol (4 mL) was added dropwise to the mixture which was kept under reflux for 4 h. Then the mixture

was poured into water (30 mL) with stirring and extracted with ethyl acetate (3 × 20 mL). The combined organic layer was washed with water until it was neutral and then concentrated to remove the solvent. The residue was recrystallised from ethanol/water (75/25, V/V) to yield white needle crystal **5** with a yield of 96%. M.p. 100 °C. IR (KBr, ν, cm^{-1}) 3240, 2953, 2869, 1583, 1421, 1139. ^{1}H NMR ($CDCl_3$, ppm, δ) 6.56(s, 2H), 4.64(s, 2H), 3.80(s, 6H), 3.62–3.53(hept, 1H), 1.27–1.26(d, *J* = 7.5 Hz, 6H). HRMS calcd for $C_{12}H_{18}NaO_3$ [M + Na^+] 233.1148, found 233.1149.

Synthesis of 3,5-dimethoxy-4-isopropylbenzaldehyde (**6**)

Compound **5** (2.12 g, 0.01 mol), DMSO (8 mL) and acetic anhydride (5 mL) were mixed with stirring at room temperature for 2 h. The mixture was diluted with water and extracted with ethyl acetate (3 × 20 mL). The combined organic layer was washed with water to neutral and evaporated to remove the solvent under vacuum, resulting in an off-white solid. The solid was recrystallised from petroleum ether/ethyl acetate (90/10, V/V) to yield **6** as ivory-coloured needles with a yield of 90%. M.p. 62 °C. IR (KBr, ν, cm^{-1}) 2989, 2961, 2872, 2843, 2812, 2719, 1691, 1585, 1382, 1139. ^{1}H NMR ($CDCl_3$, ppm, δ) 9.89(s, 1H), 7.05(s, 2H), 3.88(s, 6H), 3.70–3.61(hept, 1H), 1.29–1.28(d, *J* = 7.0 Hz, 6H). HRMS calcd for $C_{12}H_{16}NaO_3$ [M + Na^+] 231.0992, found 231.0992.

*Synthesis of (*E*)-3-(3,5-dimethoxy-4-isopropylphenyl)-2-phenylacrylic acid* (**7**)

NaAc (2.46 g, 0.03 mol) was added to a solution of **6** (2.09 g, 0.01 mol) and phenylacetic acid (1.36 g, 0.01 mol) dissolved in acetic anhydride (50 mL) with continuously stirring. The mixture was warmed to 138 ± 2 °C and maintained at this temperature for 6 h. The resultant obtained mixture was cooled to room temperature and adjusted to pH = 2 with 10% HCl. The mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layer was washed with water until it was neutral and then concentrated. The residue was neutralised to pH = 7 with $NaHCO_3$ solution and extracted with CH_2Cl_2 after stirring for 2 h. The aqueous phase was acidified to pH = 2 with 10% HCl and filtered to give a yellow solid, which was purified using column chromatography to give **7** (m.p. 202 °C) as a white, fluffy solid with a yield of 56% and purity of 99%.

7: IR (KBr, ν, cm^{-1}) 2960, 2838, 1676, 1568, 1267, 1141. ^{1}H NMR (DMSO, ppm, δ) 12.64(s, 1H), 7.71(s, 1H), 7.45–7.42(t, 2H), 7.37–7.34(t, 1H), 7.22–7.21(d, *J* = 8.0 Hz, 2H), 6.33(s, 2H), 3.42(s, 6H), 3.41–3.34(hept, 1H), 1.13–1.11(d, *J* = 7.0 Hz, 6H). HRMS calcd for $C_{20}H_{22}NaO_4$ [M + Na^+] 349.1410, found 349.1417.

9: M.p. 171 °C. IR (KBr, ν, cm^{-1}) 3000, 2963, 2839, 1680, 1624, 1573, 1423, 1143, 980. ^{1}H NMR (DMSO, ppm, δ) 12.33(s, 1H), 7.57–7.53(d, *J* = 16.0 Hz, 1H), 6.96(s, 2H), 6.60–6.56(d, *J* = 16.0 Hz, 1H), 3.82(s, 6H), 3.56–3.54(hept, 1H), 1.23–1.22(d, *J* = 7.0 Hz, 6H). HRMS calcd for $C_{14}H_{18}NaO_4$ [M + Na^+] 273.1097, found 273.1098.

Synthesis of (Z)-3,5-dimethoxy-4-isopropylstilbene (**8**)

Compound **7** (3.26 g, 0.01 mol), Cu powder (3.84 g, 0.06 mol) and quinoline (50 mL) were mixed and heated to 180 ± 2 °C for 3 h. The mixture was cooled to room temperature and added to ethyl acetate with stirring. The resultant suspension was filtered and the filtrate was washed with 10% HCl until the water layer lost its colour. The organic phase was concentrated under reduced pressure to remove the solvent. The residue was purified by the column chromatography to give **8** (m.p. 58 °C) with a yield of 73% and the purity of 99%.

8: IR (KBr, ν, cm^{-1}) 2990, 2955, 2872, 1598, 1447, 1422, 1138. ^{1}HNMR ($CDCl_3$, ppm, δ) 7.33–7.32(d, *J* = 7.0 Hz, 2H), 7.28–7.25(t, 2H), 7.20–7.19(t, *J* = 7.5 Hz, 1H), 6.60–6.58(d, *J* = 12.0 Hz, 1H), 6.51–6.49(d, *J* = 12.5 Hz, 1H), 6.42(s, 2H), 3.58(s, 6H), 3.53–3.50(hept, 1H), 1.25–1.24(d, *J* = 7.0 Hz, 6H). HRMS calcd for $C_{19}H_{23}O_2$ [M + H^+] 283.1693, found 283.1692.

10: M.p. 77 °C. IR (KBr, ν, cm^{-1}) 2989, 2934, 2868, 2838, 1600, 1567, 1141, 957. ^{1}H NMR ($CDCl_3$, ppm, δ) 7.52–7.50(d, *J* = 9.5 Hz, 2H), 7.37–7.34(t, 2H), 7.25(t, 1H), 7.05(s, 2H), 6.70(s, 2H), 3.86(s, 6H), 3.60–3.57(hept, 1H), 1.29–1.28(d, *J* = 7.5 Hz, 6H). HRMS calcd for $C_{19}H_{23}O_2$ [M + H^+] 283.1693, found 283.1695.

Synthesis of (Z)-3,5-dihydroxy-4-isopropylstilbene (**1**)

A mixture of **8** (2.82 g, 0.01 mol) and toluene (40 mL) was cooled to 0 ± 2 °C. N,N-Dimethyl aniline (6.06 g, 0.05 mol) was introduced into the mixture with stirring; 10 min later, $AlCl_3$ (0.06 mol) was added to the above mixture by three batches at 10 min interval. After stirring for 15 min, the ice-bath was removed and the mixture was heated to 110 °C for 3 h. The mixture was cooled to room temperature, acidified with HCl (10%, 15 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layer was washed with water until it was neutral and was then evaporated to remove the solvent under vacuum. The residue was purified by column chromatography using petroleum ether/ethyl acetate (30/1, V/V) as eluent to afford **1** as a pale-green, fluffy solid with a yield of 58% and purity of 99%.

1: M.p. 114 °C. IR (KBr, ν, cm^{-1}) 3278, 2956, 1620, 1578, 1423, 998. ^{1}H NMR ($CDCl_3$, ppm, δ) 7.30–7.29(d, *J* = 7.0 Hz, 2H), 7.27–7.24(t, 2H), 7.21–7.18(t, 1H), 6.54–6.52(d, *J* = 12.5 Hz, 1H), 6.39–6.36(d, *J* = 12.0 Hz, 1H), 6.21(s, 2H), 4.52(s, 2H), 3.43–3.37(hept, 1H), 1.34–1.33(d, *J* = 7.0 Hz, 6H). HRMS calcd for $C_{17}H_{19}O_2$ [M + H^+] 255.1380, found 255.1382.

Benvitimod: M.p. 142 °C (142 °C in literature [32]). ^{1}H NMR ($CDCl_3$, ppm, δ) 7.48–7.46(d, *J* = 7.5 Hz, 2H), 7.36–7.33(t, 2H), 7.27–7.25(t, 1H), 7.00–6.97(d, *J* = 16.5 Hz, 1H), 6.92–6.89(d, *J* = 16.0 Hz, 1H), 6.50(s, 2H), 4.70(s, 2H), 3.46–3.43(hept, 1H), 1.38–1.37(d, *J* = 7.0 Hz, 6H). HRMS calcd for $C_{17}H_{19}O_2$ [M + H^+] 255.1380, found 255.1380.

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