FULL PAPER

An Efficient Stereoselective Total Synthesis of Bioactive (3*R*,5*R*)-1-(4-Hydroxyphenyl)-7-phenylheptane-3,5-diol *via* Asymmetric Aldol Reaction

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An efficient stereoselective total synthesis of (3*R*,5*R*)-1-(4-hydroxyphenyl)-7-phenylheptane-3,5-diol (**1**) is reported based on the *Mukaiyama* aldol reaction. The total synthesis of compound **1** was accomplished with 30% overall yield in simple eight steps from commercially available *trans*-cinnamaldehyde.

Introduction. – Diarylheptanoids are an important class of biologically active natural products. They have been shown to display promising biological activities including antioxidant, anticancer, and anti-inflammatory activities [1 – 7]. One such diarylheptanoid is (3*R*,5*R*)-1-(4-hydroxyphenyl)-7-phenylheptane-3,5-diol (**1**, *Fig. 1*), isolated from *Alpinia officinarum* (Zingiberaceae), which exhibits anti-emetic activity [8 – 10]. Recently, *Reddy et al.* reported the first total synthesis of **1** using *Sharpless* kinetic resolution and an asymmetric epoxidation as the key steps from commercially available 4-hydroxybenzaldehyde [11]. This synthetic method suffers from a large number of synthetic steps and a low overall yield. We herein report the total synthesis of **1** through *Mukaiyama* aldol reaction in simple eight steps with 30% overall yield.

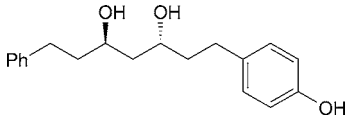
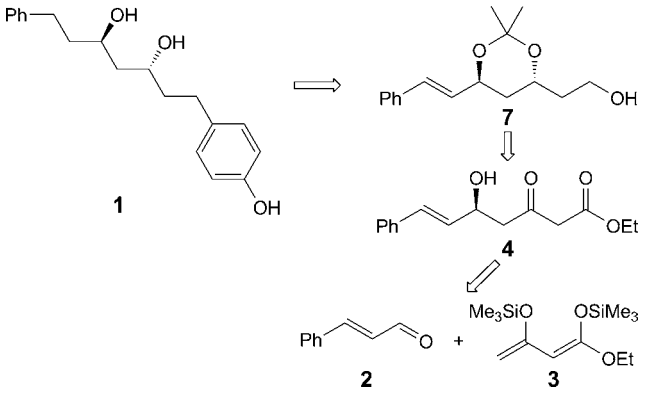


Fig. 1. *Structure of the diarylheptanoid* **1**

Results and Discussion. – The retrosynthetic plan of the target molecule **1** is illustrated in *Scheme 1*. Compound **1** could be obtained by *Grignard* reaction and acetonide deprotection followed by Pd/C reduction of primary alcohol **7**. The latter could be derived from **4** by a successive implementation of diastereoselective reduction and acetonide protection. δ-Hydroxy-β-keto ester **4** can be easily prepared *via* asymmetric *Mukaiyama* aldol reaction between *Chan*'s diene **3** and *trans*-cinnamaldehyde **2**.

To begin the synthesis, the commercially available *trans*-cinnamaldehyde **2** was subjected to the stereoselective *Mukaiyama* aldol reaction with *Chan*'s diene **3** in the presence of catalytic amounts of Ti(^{i}PrO)$_4$/(*S*)-BINOL complex (2 mol-%) to furnish aldol product **4** [12][13] in 94% yield with >97% ee as determined by chiral HPLC [14]. *anti*-Selective reduction of **4** was performed with

Scheme 1. *Retrosynthetic Analysis of Compound* **1**



$Me_4NBH(AcO)_3$ to give the desired *anti*-diol **5** exclusively, isolated in 80% yield (*syn*/*anti* 1:19) [15][16]. The diol was protected as acetonide using 2,2-dimethoxypropane (DMP) and a catalytic amount of PPTS. The relative configuration of acetonide *anti*-**6** was confirmed by ^{13}C-NMR according to *Rychnovsky*'s method [17][18]. In the ^{13}C-NMR spectrum of **6**, the C-atoms of the acetonide Me groups were observed at 24.6 and 25.2 ppm and that of the quaternary C-atom at 100.6 ppm, confirming the presence of the *anti*-acetonide **6** [13] (*Fig. 2*).

Then, the protected *anti*-diol ester **6** was reduced to the corresponding primary alcohol by treatment with $LiAlH_4$ in dry THF at 0° for 30 min. The primary OH group of **7** was reacted with TsCl in the presence of Et_3N and DMAP (cat.) in CH_2Cl_2 to obtain crude compound **8**, which was

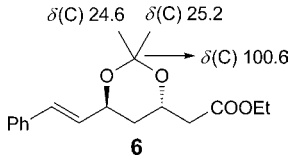


Fig. 2. *Key* ^{13}*C-NMR data* of *compound* **6**

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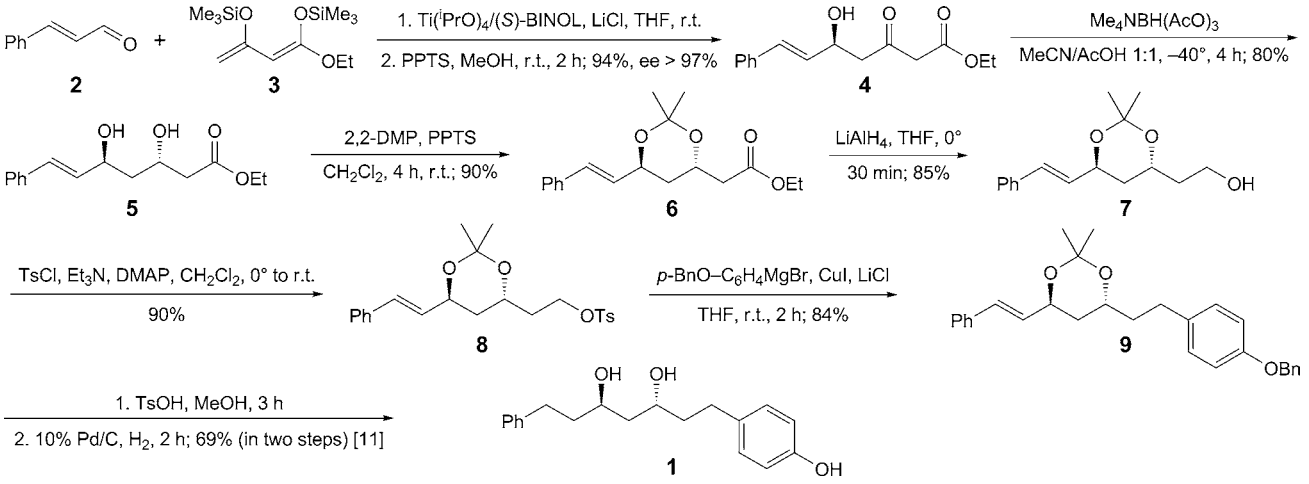
Scheme 2. *Synthesis of Compound* **1**



used in the next step without further purification. The crude **8** was subjected to the coupling reaction with the *Grignard* reagent 4-(benzyloxy)phenylmagnesium bromide to afford the desired product **9** [11] in 84% yield [19]. Finally the target molecule **1** was obtained from **9** by acetonide deprotection using TsOH in MeOH, followed by hydrogenation over Pd/C in 69% yield [11] (*Scheme 2*). The spectroscopic data of synthetic compound **1** were in agreement with those reported for the natural one [11].

In conclusion, an efficient stereoselective total synthesis of (3*R*,5*R*)-1-(4-hydroxyphenyl)-7-phenylheptane-3,5-diol (**1**) was accomplished *via* the *Mukaiyama* aldol reaction and an *anti* selective reduction as key steps. The present approach reduces the number of steps and increases the overall yield of compound **1** to 30%.

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Experimental Part

General. All solvents and reagents were purified by standard techniques. Anal. TLC: precoated SiO_2 *60* F_{254} (0.5 mm) glass plates; visualization of the spots on TLC plates was achieved either by exposure to I_2 vapor or UV light. Column chromatography (CC): silica gel (SiO_2, 60 – 120, 100 – 200 mesh). Optical rotations: *JASCO DIP-370* digital polarimeter. IR Spectra: *Perkin–Elmer* infrared spectrophotometer with NaCl optics; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra: *Varian Gemini* 500 and *Bruker Avance* 300 instrument; in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. MS: *Micro Mass VG-7070 H* mass spectrometer for ESI and *VG Auto spec M* mass spectrometer for FAB-MS; in *m*/*z*.

Ethyl (5S,6E)-5-Hydroxy-3-oxo-7-phenylhept-6-enoate (**4**) [12]. A mixture of Ti(^{i}PrO)$_4$ (430 mg, 1.51 mmol), (*S*)-BINOL (433 mg, 1.51 mmol), and LiCl (128 mg, 3.0 mmol) in dry THF (20 ml) was stirred at r.t. under inert atmosphere for 1 h. After cooling the mixture to −78°, the *trans*-cinnamaldehyde **2** (1 g, 7.57 mmol) was added dropwise, followed, after 30 min, by silyloxydiene **3** [20] (2.8 g, 15.15 mmol) in THF (10 ml). The resulting soln. was stirred at the same temp. for 2 h. After warming to r.t., the mixture was stirred overnight (12 h). After completion of the reaction as indicated by TLC, the reaction was quenched with a sat. aq. soln. of $NaHCO_3$ (5 ml) and extracted with Et_2O. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to obtain crude silylated product. The crude silylated adduct was dissolved in MeOH (20 ml), pyridinium *p*-toluenesulfonate (10 mg) was added, and the mixture was stirred for 2 h at r.t. After completion of the reaction (monitored by TLC), the volatiles were removed *in vacuo*, and the crude product was purified by CC to obtain adduct 4 [12] (1.86 g, 94%) as pale yellow oil. $[\alpha]_D^{25} = -14.1$ ($c = 1.0$, $CHCl_3$). IR (neat): 3452, 2991, 1732, 1716, 1032, 976, 748. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.38 – 7.23 (*m*, 5 H); 6.64 (*d*, *J* = 16.0, 1 H); 6.20 (*dd*, *J* = 16.0, 6.1, 1 H); 4.81 – 4.77 (*m*, 1 H); 4.20 (*q*, *J* = 14.3, 7.1, 2 H); 3.50 (*s*, 2 H); 2.87 (*d*, *J* = 6.1, 2 H); 2.84 (br, *d*, *J* = 3.3, 1 H); 1.28 (*t*, *J* = 7.1, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 202.6; 166.8; 136.3; 130.6; 129.7; 128.5 (2 C); 127.7; 126.4 (2 C); 68.3; 61.5; 49.9; 49.5; 14.0. ESI-MS: 263 ([*M* + H]$^+$), 285 ([*M* + Na]$^+$).

*Ethyl {(4S,6S)-2,2-Dimethyl-6-[(*E*)-2-phenylethenyl]-1,3-dioxan-4-yl}acetate* (**6**) [13]. $Me_4NBH(AcO)_3$ (1.506 g, 5.724 mmol) was added to a mixture of dry MeCN (5 ml) and glacial AcOH (5 ml). The resulting mixture was stirred at r.t. for 30 min. The mixture was cooled to −40° and a soln. of **4** (1.0 g, 3.816 mmol) in MeCN (2 ml) was added drop-wise. The mixture was stirred at the same temp. for 3 h. 1N Potassium sodium tartrate (5 ml) and Et_2O (30 ml) were added to the mixture, followed by aq. sat. Na_2CO_3 soln. (10 ml). The aq. phase was extracted with Et_2O (4 × 10 ml). The combined org. phases were dried ($MgSO_4$), and concentrated under vacuum. The residue was chromatographed over SiO_2 (2 : 1 hexane/AcOEt) to give **5** as a colorless oil (901 mg, 80% yield).

To a stirred soln. of **5** (901 mg, 3.41 mmol), in CH_2Cl_2 (10 ml) was added dimethoxypropane (0.84 ml, 6.82 mmol) and PPTS (10 mg, 0.4 mmol). The mixture was stirred at r.t. for 4 h. The mixture was diluted with CH_2Cl_2 (10 ml) and washed with aq. sat. $NaHCO_3$. The combined org. phases were dried ($MgSO_4$), and the solvent was evaporated *in vacuo*. The crude product was purified by CC (10 : 1 hexane/AcOEt) to afford **6** as a colorless oil (933 mg, 90% yield). $[\alpha]_D^{25} = +19.2$ ($c = 1.0$, $CHCl_3$). IR (neat): 3040, 2921, 1734, 1582, 1494, 1378, 1312, 1199, 1024, 967, 747. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.39 – 7.20 (*m*, 5 H); 6.56 (*d*, *J* = 16.0, 1 H); 6.23 (*dd*, *J* = 16.0, 6.4, 1 H); 4.49 – 4.60 (*m*, 1 H); 4.42 – 4.32 (*m*, 1 H); 4.15 (*m*, 2 H); 2.58 (*dd*, *J* = 15.4, 8.0, 1 H); 2.48 (*dd*, *J* = 15.4, 5.4, 1 H); 1.99 – 1.93 (*m*, 1 H); 1.83 – 1.77 (*m*, 1 H); 1.43 (*s*, 3 H); 1.41 (*s*, 3 H); 1.26 (*t*, *J* = 7.1, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 170.7; 136.5; 130.5; 129.4; 128.4 (2 C); 127.6; 126.4 (2 C); 100.6; 67.5; 63.2; 60.4; 40.8; 37.2; 25.2; 24.6; 14.1. ESI-MS: 305 ([*M* + H]$^+$), 327 ([*M* + Na]$^+$).

*2-{(4*R*,6*S*)-2,2-Dimethyl-6-[(*E*)-2-phenylethenyl]-1,3-dioxan-4-yl}ethanol* (**7**). To a stirred suspension of $LiAlH_4$ (62 mg, 1.64 mmol) in dry THF (20 ml) was added drop-wise a soln. of **6** (500 mg, 1.644 mmol) in dry THF (5 ml) at 0°. The mixture was allowed to warm to r.t. and stirred for 30 min. The reaction was quenched by drop-

wise addition of sat. aq. Na_2SO_4 soln. (2 ml). The solid material was filtered through a *Celite* pad and washed thoroughly with hot AcOEt (4 × 20 ml). The combined org. layers were dried ($MgSO_4$). The solvent was removed *in vacuo* and the crude residue was subjected to CC to obtain pure alcohol **7** (366 mg, 85%) as colorless oil. $[\alpha]_D^{25} = -21.2$ ($c = 1.2$, $CHCl_3$). IR (neat): 3442, 2991, 1021, 915, 712. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.39 – 7.22 (*m*, 5 H); 6.57 (*d*, *J* = 16.0, 1 H); 6.23 (*dd*, *J* = 16.0, 6.4, 1 H); 4.57 – 4.52 (*m*, 1 H); 4.19 – 4.13 (*m*, 1 H); 3.82 – 3.76 (*m*, 2 H); 1.92 – 1.75 (*m*, 4 H); 1.45 (*s*, 3 H); 1.43 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 136.5; 130.5; 129.4; 128.4 (2C); 127.6; 126.4 (2 C); 100.5; 67.7; 66.4; 60.8; 37.7 (2 C); 25.4; 24.8. ESI-MS: 263 ($[M + H]^+$).

*(4*R,6S*)-4-{2-[4-(Benzyloxy)phenyl]ethyl}-2,2-dimethyl-6-[(*E*)-2-phenylethenyl]-1,3-dioxane* (**9**) [11]. To a stirred soln. of alcohol **7** (300 mg, 1.14 mmol) in dry CH_2Cl_2 (10 ml) was added Et_3N (0.8 ml, 3.43 mmol), TsCl (326 mg, 1.71 mmol), and cat. amounts of DMAP at 0°. After the mixture was stirred at 25° for 1 h, the reaction was quenched with H_2O (5 ml), and the resultant mixture was then extracted with AcOEt (2 × 10 ml). The extracts were washed with brine (10 ml), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was directly used for the next step without purification.

A flask charged with LiCl (87 mg, 2.05 mmol) was heated *in vacuo* and flushed with Ar. To the flask were added 4-benzyloxyphenyl magnesium bromide (1.55 ml, 1M in THF, 1.54 mmol), **8** (428 mg, 1.02 mmol), and CuI (59 mg, 0.3 mmol) sequentially. The mixture was stirred at r.t. for 2 h and diluted with sat. NH_4Cl. The resulting mixture was extracted with AcOEt (4 × 5 ml). The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by CC (hexane) to afford **9** (370 mg, 84%). $[\alpha]_D^{25} = +6.0$ ($c = 1.0$, $CHCl_3$). IR (neat): 2922, 1622, 1457, 1248. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.98 (*d*, *J* = 8.1, 2 H); 7.51 – 7.49 (*m*, 4 H); 7.40 – 7.30 (*m*, 6 H); 7.11 (*d*, *J* = 8.1, 2 H); 6.89 (*dd*, *J* = 14.8, 7.0, 1 H); 6.28 (*d*, *J* = 14.8, 1 H); 5.29 (*s*, 2 H); 4.68 – 4.56 (*m*, 1 H); 3.73 – 3.65 (*m*, 1 H); 2.63 – 2.56 (*m*, 2 H); 1.73 – 1.49 (*m*, 4 H); 1.43 (*s*, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 157.0; 141.8; 137.4; 134.7; 130.2; 129.9; 129.7; 128.9; 128.1; 128.0; 114.9; 96.6; 70.1; 68.9; 68.5; 39.8; 39.4; 31.6; 31.1. ESI-MS: 451 ($[M + Na]^+$).

*(3*R,5R*)-1-(4-Hydroxyphenyl)-7-phenylheptane-3,5-diol* (**1**) [11]. To a stirred soln. of **9** (200 mg, 0.46 mmol) in MeOH (5 ml) was added TsOH (10 mg), and the mixture was stirred for 3 h at r.t. After completion of the reaction as indicated by TLC, the reaction was quenched with sat. aq. soln. of Na_2CO_3 (1 ml), and the mixture was extracted with AcOEt (4 × 10 ml). The combined org. extracts were washed with a sat. soln. of NaCl, dried ($MgSO_4$), and concentrated under reduced pressure. The crude diol was dissolved in MeOH, a cat. amount of Pd/C was added, and the mixture was stirred for 2 h under H_2 (1 atm) at r.t. After filtration and concentration, the crude residue was purified by CC to afford pure title compound **1** (96 mg, 69%) as yellow oil. $[\alpha]_D^{25} = +9.0$ ($c = 1.0$, $CHCl_3$). IR (neat): 3440, 2925, 2854, 1512, 1245, 1092, 823. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.27 – 7.13 (*m*. 5 H); 6.94 (*d*, *J* = 8.1, 2 H); 6.70 (*d*, *J* = 8.0, 2 H); 4.01 – 3.89 (*m*, 2 H); 2.80 – 2.49 (*m*, 4 H); 1.90 – 1.67 (*m*, 4 H); 1.61 (*t*, *J* = 5.2, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 154.0; 141.8; 133.4; 129.4 (2 C); 128.4 (2 C); 128.3 (2 C); 125.9; 115.4 (2 C); 69.0; 68.9; 42.4; 39.0; 38.9; 32.1; 31.1. ESI-MS: 323 ($[M + Na]^+$).

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