The First Stereoselective Total Synthesis of a Naturally Occurring Bioactive Diarylheptanoid, (3*R*,6*E*)-1,7-Bis(4-hydroxyphenyl)hept-6-en-3-ol, through Two Different Approaches[1])

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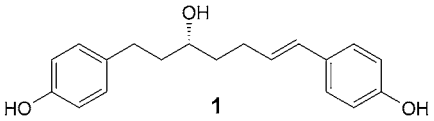
The stereoselective total synthesis of a naturally occurring bioactive diarylheptanoid, (3*R*,6*E*)-1,7-bis(4-hydroxyphenyl)hept-6-en-3-ol, has been accomplished starting from 4-hydroxybenzaldehyde through two different approaches involving *Wittig* olefination, hydrolytic kinetic resolution of a racemic epoxide, and olefin cross-metathesis reaction as the key steps.

Introduction. – Diarylheptanoids exhibit various important biological activities including anticancer, anti-HIV, anti-inflammatory, and antioxidant properties [1]. A large number of these compounds with different functionalities have been isolated from natural sources [2]. Recently, a new diarylheptanoid, (3*R*,6*E*)-1,7-bis(4-hydroxyphenyl)hept-6-ene-3-ol (**1**) and its enantiomer have been isolated in very small quantities from the rhizomes of *Curcuma kwangrsiensis* (Zingiberaceae) [3]. The compound was evaluated for its inhibitory effect on NO production induced by lipopolysaccharide-activated macrophages. The activity of the compound was found to be close to that of indomethacin [3]. The total synthesis of the compound has not yet been reported. In continuation of our work [4] on the construction of bioactive natural products, we have accomplished the stereoselective total synthesis of **1**, which we report here.

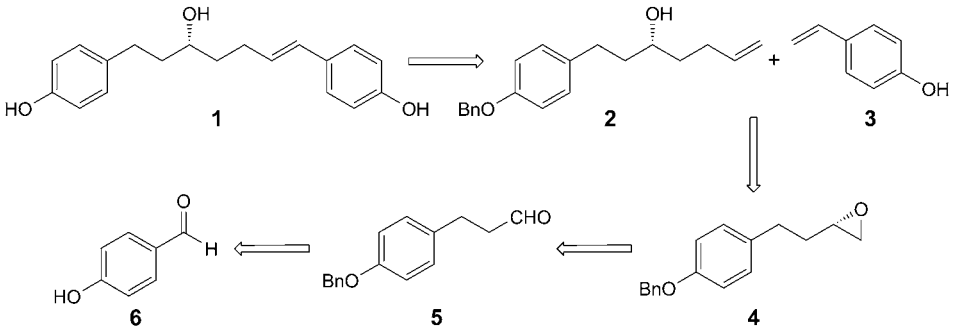


1

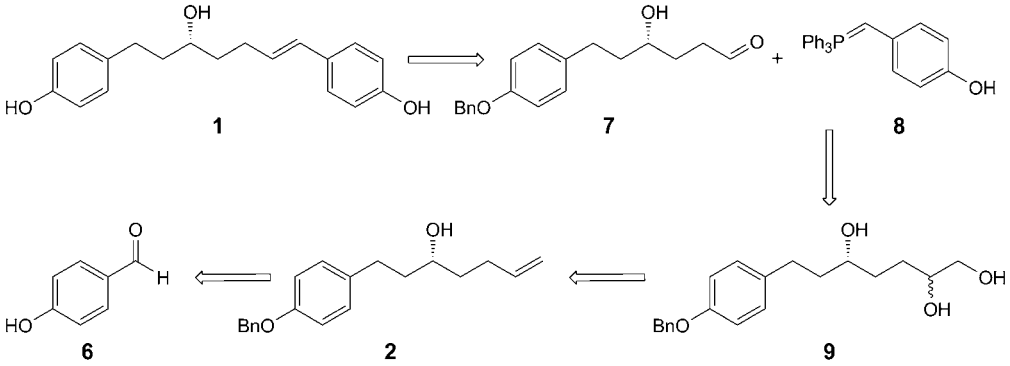
Results and Discussion. – The retrosynthetic analysis (*Scheme 1*) revealed that **1** can be synthesized from the alkenes **2** and **3**. The first one, **2**, can be prepared from the epoxide **4**, which in turn can be synthesized from the aldehyde **5** generated from 4-hydroxybenzaldehyde (**6**). The diarylheptanoid **1** can also be synthesized (*Scheme 2*) from the aldehyde **7** and the phosphonium ylide **8**. The aldehyde **7** can be prepared from the triol **9**, which can again be produced from the olefinic alcohol **2** obtained from **6**.

[1]) Part 62 in the series, 'Synthetic Studies on Natural Products'.

Scheme 1. *First Retrosynthetic Analysis of* **1**



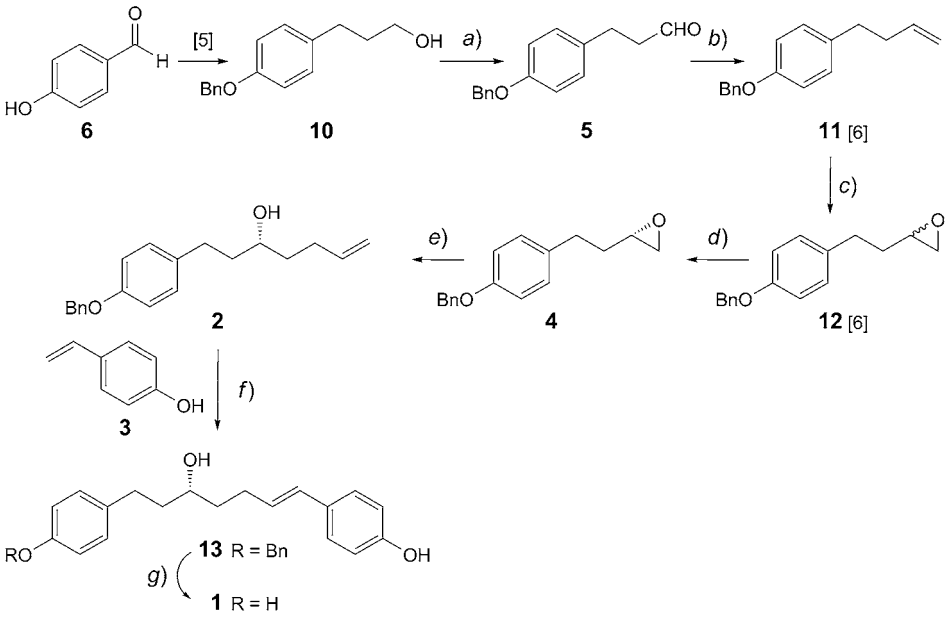
Scheme 2. *Second Retrosynthetic Analysis of* **1**



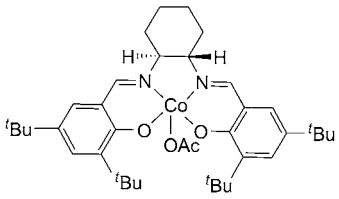
The present synthesis of **1** was initiated (*Scheme 3*) by converting 4-hydroxybenzaldehyde (**6**) to its benzyl ether, which was subjected to *Wittig* olefination with $PPh_3CHCOOEt$ and subsequent reduction with $NaBH_4/NiCl_2 \cdot 6\,H_2O$, followed by adding $LiAlH_4$ to produce the alcohol **10** [5]. The latter was oxidized with PCC to yield the corresponding aldehyde **5**, which again underwent *Wittig* olefination with PPh_3CH_2 to furnish the olefin **11** [6]. Treatment of **11** with *m*-CPBA afforded the epoxide **12** [6], which, on hydrolytic kinetic resolution [7] with (*S*,*S*)-*Jacobsen*'s catalyst (**A**), generated the (*S*)-configured epoxide **4**. The latter was then treated with allylmagnesium bromide in the presence of CuI to give the olefinic alcohol **2**. Eventually, the cross-coupling metathesis reaction [8] of **2** with 4-ethenylphenol (**3**) using *Grubbs*' second-generation catalyst, **B**, resulted in the formation of the heptanoid **13**. Finally, deprotection of the benzyl ether of **13** with $TiCl_4$ gave the target molecule **1**.

In a second approach, the chiral olefinic alcohol **2** was treated with OsO_4 and 4-methylmorpholine *N*-oxide (NMO) in aqueous acetone, and the resulting triol **9** was treated with $NaIO_4$ to form the aldehyde **7** (*Scheme 4*). The latter was directly subjected to *Wittig* olefination with the phosphonium ylide **8** to produce **13** as the major product along with its (*Z*)-isomer (isomeric ratio 8:2). The product **13** was separated, and subsequently its benzyl ether group was deprotected with $TiCl_4$ to afford

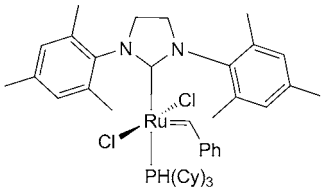
Scheme 3



a) Pyridinium chlorochromate (PCC), *Celite*, CH_2Cl_2, 0° to r.t, 2 h; 81%. *b*) BuLi, THF, $Ph_3P{=}CH_2$, – 78° to r.t, 4 h; 76%. *c*) *meta*-Chloroperbenzoic acid (*m*-CPBA), CH_2Cl_2, $NaHCO_3$, 0° to r.t, 3 h; 86%. *d*) ((*S*,*S*)-Salen)Co(OAc) (**A**), dist. H_2O, THF, 0°, 24 h; 45%. *e*) C_3H_3MgBr, CuI, THF, – 78°, 4 h; 81%. *f*) *Grubbs*' second generation catalyst (**B**), CH_2Cl_2, 50°, 4 h; 68%. *g*) $TiCl_4$, CH_2Cl_2, 0°, 3 h; 72%.



Catalyst **A**

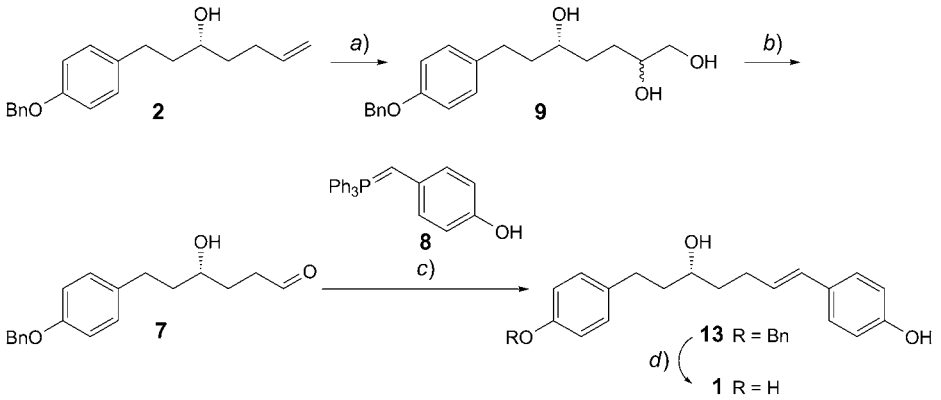


Catalyst **B**
(*Grubbs*' 2nd generation)

compound **1**. The optical rotation and spectroscopic data of the latter were found to be identical to those of the naturally occurring (3*R*,6*E*)-1,7-bis(4-hydroxyphenyl)hept-6-en-3-ol.

Conclusions. – In conclusion, we have developed the first stereoselective total synthesis of the natural bioactive heptanoid, (3*R*,6*E*)-1,7-bis(4-hydroxyphenyl)hept-6-en-3-ol starting from commercially available 4-hydroxybenzaldehyde through two different approaches, employing hydrolytic kinetic resolution of a racemic epoxide, *Wittig* olefination, and olefin cross metathesis reaction as the key steps. Both of the

Scheme 4



a) OsO_4, NMO, aq. acetone, r.t, 4 h. *b*) $NaIO_4$, $NaHCO_3$, CH_2Cl_2, r.t, 2 h. *c*) BuLi, THF, $-78°$, 4 h, 67%. *d*) $TiCl_4$, CH_2Cl_2, 0°, 3 h; 72%.

synthetic methods are simple and can be utilized for the generation of various analogs of **1**.

Experimental Part

General. Silica-gel F_{254} plates were used for TLC; the spots were examined under UV light and then developed by an I_2 vapor. Column chromatography (CC) was performed with silica gel (SiO_2; *BDH* 100–200 mesh). Solvents were purified according to standard procedures. Org. extracts were dried over anh. Na_2SO_4. Optical rotations: *JASCO DIP 300* digital polarimeter, at 25°. IR Spectra: *Perkin-Elmer RX* FT-IR spectrophotometer. NMR Spectra: *Varian Gemini* 200- (^{1}H) and 50-MHz (^{13}C) spectrometer. ESI-MS: *VG-Autospec micromass.*

1-(Benzyloxy)-4-(but-3-en-1-yl)benzene (**11**) [6]. To a stirred suspension of *Celite* (10.0 g) in dry CH_2Cl_2 (30 ml), a soln. of *3-[4-(benzyloxy)phenyl]propan-1-ol* (**10**; 12.5 g, 51.6 mmol) in dry CH_2Cl_2 (10 ml) at r.t. was added, followed by careful addition of PCC (22.1 g, 103.3 mmol). The mixture was allowed to stir slowly at r.t. After stirring for 1 h, the mixture was filtered through sintered funnel with CH_2Cl_2 (2 × 30 ml) The combined org. extracts were washed with brine, dried, and concentrated under reduced pressure. The residue was purified by CC (hexane/AcOEt) to afford *3-[4-(benzyloxy)phenyl-propanal* (**5**; 10.41 g, 81%) as a colorless liquid.

To a stirred soln. of methylidene(triphenyl)phospine (50.05 g, 125.0 mmol) in dry THF (30 ml) under N_2 at $-78°$, BuLi (41.6 ml in 2.5M hexane) was added dropwise, and the mixture was stirred at that temp. for a few min until the yellow color appeared. Then, **5** (10.0 g, 41.66 mmol) in THF (20 ml) was added dropwise, and the mixture was stirred at that temp. for 3 h. The reaction was quenched with sat. NH_4Cl soln. (20 ml) at 0°, and the mixture was extracted with AcOEt (2 × 50 ml). The combined org. extracts were washed with brine, dried, and concentrated under reduced pressure. The residue was purified by CC (hexane/AcOEt) to afford **11** (7.53 g, 76%). Pale yellow liquid. IR (neat): 2925, 2855, 1460, 1376, 1250. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.20–7.11 (*m*, 5 H); 7.02 (*d*, *J* = 8.0, 2 H); 6.82 (*d*, *J* = 8.0, 2 H); 5.90–5.71 (*m*, 1 H); 5.02–4.95 (*m*, 2 H); 4.99 (*s*, 2 H); 2.62 (*t*, *J* = 7.0, 2 H); 2.39–2.22 (*m*, 2 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 157.8; 139.1; 138.6; 134.9; 130.0; 129.1; 127.5; 126.9; 115.2; 115.0; 70.0; 32.5; 31.4. ESI-MS: 239 ($[M+H]^+$). Anal. calc. for $C_{17}H_{18}O$ (238.32): C 85.67, H 7.61; found: C 85.77, H 7.63.

2-{2-[4-(Benzyloxy)phenyl]ethyl}oxirane (**12**) [6]. To a stirred soln. of **11** (7.0 g, 29.4 mmol) in dry CH_2Cl_2 (10 ml) under N_2 at 0° was added *m*-CPBA (6.07 g, 35.2 mmol) dissolved in dry CH_2Cl_2 (10 ml). The mixture was stirred for 2 h. The reaction was quenched with sat. aq. $NaHCO_3$ (6 ml), and the mixture

was stirred further for 1 h and then extracted with CH_2Cl_2 (2 × 30 ml). The combined org. layers were dried and concentrated *in vacuo*. The residue on purification by CC (hexane/AcOEt) afforded pure **12** (6.91 g, 86%). Pale yellow liquid.

*(2*S*)-2-{2-[4-(Benzyloxy)phenyl]ethyl}oxirane* (**4**). A soln. of **12** (6.0 g, 23.1 mmol) and ((*S*,*S*)-Salen)Co(OAc) (**A**; 0.076 g, 0.12 mmol) in THF (30 ml) was stirred at 0° for 5 min, and then dist. H_2O (229 ml, 12.7 mmol) was added. After stirring for 24 h, this mixture was concentrated and purified by CC (hexane/AcOEt) to afford **4** (2.3 g, 45%). Yellow liquid. $[\alpha]_D^{25} = -4.6$ ($c = 1.0$, $CHCl_3$). IR (neat): 3454, 2926, 2854, 1730, 1253. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.42–7.12 (*m*, 5 H); 7.08 (*d*, *J* = 8.0, 2 H); 6.82 (*d*, *J* = 8.0, 2 H); 5.02 (*s*, 2 H); 2.95–2.86 (*m*, 1 H); 2.80–2.60 (*m*, 2 H); 2.41–2.32 (*m*, 1 H); 2.29–2.20 (*m*, 1 H); 1.84–1.72 (*m*, 1 H); 1.60–1.56 (*m*, 1 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 155.4; 137.5; 134.1; 129.8; 129.2; 127.6; 126.9; 115.2; 70.2; 51.3; 46.1; 34.8; 29.9. ESI-MS: 255 ($[M+H]^+$). Anal. calc. for $C_{17}H_{18}O_2$ (254.32): C 80.28, H 7.13; found: C 80.39, H 7.11.

*(3*R*)-1-[4-(Benzyloxy)phenyl]hept-6-en-3-ol* (**2**). A round-bottomed flask was charged with CuI (0.28 g, 1.4 mmol), gently heated under vacuum, and then slowly cooled under a flow of N_2. THF (10 ml) was then added, and the resulting suspension was cooled to −78°, stirred, and allylmagnesium bromide (9.4 ml in 1M THF) was added. A soln. of **4** (2.0 g, 7.8 mmol) in THF (10 ml) was added to the above reagent, and the mixture was stirred at −78° for 4 h. After consumption of starting material, the reaction was quenched with sat. aq. NH_4Cl. The H_2O layer was extracted with AcOEt (50 ml), and the combined org. layers were washed with brine, dried, and concentrated *in vacuo*. The residue on purification by CC (hexane/AcOEt) afforded **2** (1.88 g, 81%). Yellow liquid. $[\alpha]_D^{25} = +10.3$ ($c = 1.0$, $CHCl_3$). IR (neat): 3451, 2925, 2855, 1637, 1459. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.41–7.20 (*m*, 5 H); 7.04 (*d*, *J* = 8.0, 2 H); 6.82 (*d*, *J* = 8.0, 2 H); 5.93–5.78 (*m*, 1 H); 5.38–4.93 (*m*, 1 H); 5.00 (*s*, 2 H); 3.69–3.56 (*m*, 1 H); 2.75–2.52 (*m*, 2 H); 2.20–2.05 (*m*, 2 H); 1.80–1.61 (*m*, 4 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 156.8; 138.7; 137.5; 134.8; 129.6; 128.5; 127.0; 126.6; 115.0; 114.8; 70.4; 69.8; 39.8; 36.2; 30.8; 30.1. ESI-MS: 297 ($[M+H]^+$). Anal. calc. for $C_{20}H_{24}O_2$ (296.40): C 81.04, H 8.16; found: C 81.16, H 8.09.

*4-{(1*E*,5*R*)-7-[4-(Benzyloxy)phenyl]-5-hydroxyhept-1-en-1-yl}phenol* (**13**). A soln. of **2** (0.5 g, 1.68 mmol) and **3** (0.506 g, 4.22 mmol) in dry CH_2Cl_2 (50 ml) was first bubbled with N_2 flow, after which *Grubbs*' second-generation catalyst (0.045 g, 0.054 mmol) was added at once, and the resulting mixture was heated under N_2 at 50° for 4 h. After cooling, the solvent was evaporated *in vacuo*. The residue on purification by CC (hexane/AcOEt) afforded **13** (0.348 g, 68%). Yellow liquid. $[\alpha]_D^{25} = +2.9$ ($c = 1.0$, $CHCl_3$). IR (near): 3427, 2926, 2856, 1250. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.39–7.21 (*m*, 5 H); 7.20 (*d*, *J* = 8.0, 2 H); 7.01 (*d*, *J* = 8.0, 2 H); 6.82 (*d*, *J* = 8.0, 2 H); 6.68 (*d*, *J* = 8.0, 2 H); 6.56 (*d*, *J* = 16.0, 1 H); 5.81–5.69 (*m*, 1 H); 4.99 (*s*, 2 H); 3.68–3.51 (*m*, 1 H); 2.58 (*t*, *J* = 7.0, 2 H); 2.30–2.02 (*m*, 4 H); 1.78–1.58 (*m*, 2 H); 1.48–1.30 (*m*, 2 H). ESI-MS: 389 ($[M+H]^+$). Anal. calc. for $C_{26}H_{28}O_3$ (388.50): C 80.38, H 7.26; found: C 80.47, H 7.18.

*4,4′-[(1*E*,5*R*)-5-Hydroxyhept-1-ene-1,7-diyl]diphenol* (**1**). To a soln. of **13** (0.30 g, mmol) in dry CH_2Cl_2 (5 ml) was added a soln. of $TiCl_4$ (0.16 ml, 2.64 mmol) in dry CH_2Cl_2 (5 ml) under N_2 at 0°. The reaction was monitored by TLC, until the starting material was consumed. H_2O was added, and the mixture was extracted with CH_2Cl_2. The combined org. extract was washed with brine and dried. The solvent was removed under reduced pressure, and the crude mass was purified by CC (silica gel; hexane/AcOEt) to afford pure **1** (0.22 g, 74%). Yellow liquid. $[\alpha]_D^{25} = +15.5$ ($c = 3.0$, $CHCl_3$). IR (neat): 3423, 1608, 1510, 1453, 1233. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.22 (*d*, *J* = 8.0, 2 H); 7.02 (*d*, *J* = 8.0, 2 H); 6.81 (*d*, *J* = 8.0, 2 H); 6.68 (*d*, *J* = 8.0, 2 H); 6.58 (*d*, *J* = 16.0, 1 H; 5.83–5.65 (*m*, 1 H); 3.64–3.53 (*m*, 1 H); 2.81–2.77 (*m*, 1 H); 2.65–2.45 (*m*, 1 H); 2.22–2.01 (*m*, 2 H); 1.79–1.61 (*m*, 2 H); 1.59–1.48 (*m*, 2 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 159.2; 156.7; 135.8; 134.6; 129.5; 128.8; 127.5; 126.4; 114.9; 114.1; 70.0; 39.6; 39.3; 30.8; 30.2. ESI-MS: 299 ($[M+H]^+$). Anal. calc. for $C_{19}H_{22}O_3$ (298.38): C 76.48, H 7.43; found: C 76.58, H 7.34.

*(5*S*)-7-[4-(Benzyloxy)phenyl]heptane-1,2,5-triol* (**9**). To stirred soln. of **2** (1.0 g, 3.37 mmol) in aq. acetone (10 ml) was added NMO (1.2 g, 10.13 mmol), followed by OsO_4 (2.5 weight-% in ^{i}BuOH). The mixture was stirred for 3 h. After completion of reaction, the reaction was quenched with sat. $NaHSO_3$ (5 ml), and the mixture was stirred for 30 min and then extracted with AcOEt (3 × 20 ml). The combined org. layers were washed with brine, dried, and concentrated *in vacuo*. The residue, **9**, was directly used for the next step.

(4S)-6-[4-(Benzyloxy)phenyl]-4-hydroxyhexanal (**7**). To a stirred soln. of **9** (0.9 g, 2.72 mmol) in dry CH_2Cl_2 (10 ml) at 0°, aq. $NaHCO_3$ (5 ml) was added, followed by careful addition of $NaIO_4$ (1.1 g, 5.45 mmol). The mixture was allowed slowly to warm to r.t. After stirring for 2 h, Na_2SO_4 (1.0 g) was added, and the mixture was stirred vigorously for 30 min. The mixture was filtered through a sintered funnel with CH_2Cl_2 (2×30 ml). The combined org. extracts were washed with brine, dried, and concentrated under reduced pressure. The residue was purified by CC (hexane/AcOEt) to afford **7** as Yellow liquid.

To a stirred soln. of *[(4-hydroxyphenyl)methylidene]triphenylphosphine* (**8**; 2.9 g, 6.03 mmol) in dry THF (10 ml) under N_2 at $-78°$ BuLi (2.0 ml in 2.5M hexane) was added dropwise and the mixture was stirred at $-78°$ for few min, until a yellow color appeared. Then, **7** was added dropwise, and the mixture was stirred at $-78°$ for 4 h. The reaction was quenched with sat. NH_4Cl soln. (10 ml) at 0°, and the mixture was extracted with AcOEt (2×50 ml). The combined org. extracts were washed with brine, dried, and concentrated under reduced pressure. The residue was purified by CC(hexane/AcOEt) to afford **13** (0.673 g, 67%). Yellow liquid.

Compound **13** was deprotected as reported earlier to obtain **1**. $[\alpha]_D^{25} = +15.5$ ($c = 3.0$, $CHCl_3$). The optical and spectral properties of the compounds **1** were identical to those of the naturally occurring bioactive diarylheptanoid, *4,4′-[(1E,5R)-5-hydroxyhept-1-ene-1,7-diyl]diphenol* [7].

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