Stereoselective Total Synthesis of (3*S*,5*S*)-1,7-Bis(4-hydroxyphenyl)heptane-3,5-diol, (3*S*,5*S*)-Alpinikatin, and Its Diastereoisomers

by **Kunuru Venkatesham**, **Sudina Purushotham Reddy**, **Baggu Chinnababu**, and **Katragadda Suresh Babu***

Division of Natural Products Chemistry, Natural Products Laboratory, CSIR-Indian Institute of Chemical Technology, Hyderabad-500 007, India
(phone: +91-40-27191881; fax: +91-40-27160512; e-mail: suresh@iict.res.in)

Stereoselective synthesis of the diarylheptanoids, (3*S*,5*S*)-1,7-bis(4-hydroxyphenyl)heptane-3,5-diol (**1**), (3*S*,5*S*)-alpinikatin (**3**), and their diastereoisomers (**2** and **4**, resp.), was achieved from readily available 4-hydroxybenzaldehyde. The synthetic sequences involve *Browns*'s allylation and Et_2Zn mediated diastereoselective alkynylation reaction as key steps.

Introduction. – In recent decades, diarylheptanoids play an important role in medicinal and synthetic organic chemistry. Diarylheptanoids are structurally distinctive plant metabolites and have been mainly isolated from *Zingiber*, *Curcuma*, *Alpinia*, *Viscum*, *Alnus*, and *Myrica* species [1]. These diarylheptanoids are exhibiting a broad range of biological and pharmacological properties. Especially, linear diarylheptanoids show antiplatelet, anti-inflammatory, antiproliferative, cytotoxic, and prostaglandin-E_2-inhibitory activities [2]. Diarylheptanoids, particularly linear diarylhepatanoids with a 1,3-diol system, have attracted the attention of both biologists and chemists in recent years. (3*S*,5*S*)-1,7-Bis(4-hydroxyphenyl)heptane-3,5-diol (**1**; *Fig.*) was first isolated in 1996 by *Wu et al* [3a]. It was also isolated from the seeds of *Alpinia blepharocalyx* in 2001 by *Kadota* and co-workers [3b]. The structure of **1** was confirmed on the basis of its spectroscopic data, and it exhibits significant antiproliferative activity against murin colon 26-L5 carcinoma and human HT-1086 fibrosarcoma with ED_{50} values of 12.8 and 94.4 μM, respectively. (3*S*,5*S*)-Alpinikatin (**3**; *Fig.*), a structurally related linear

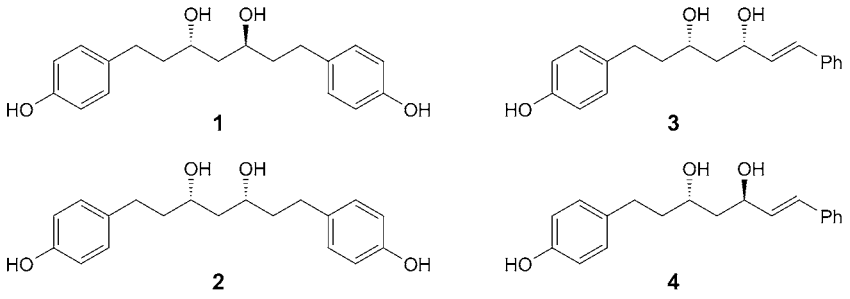
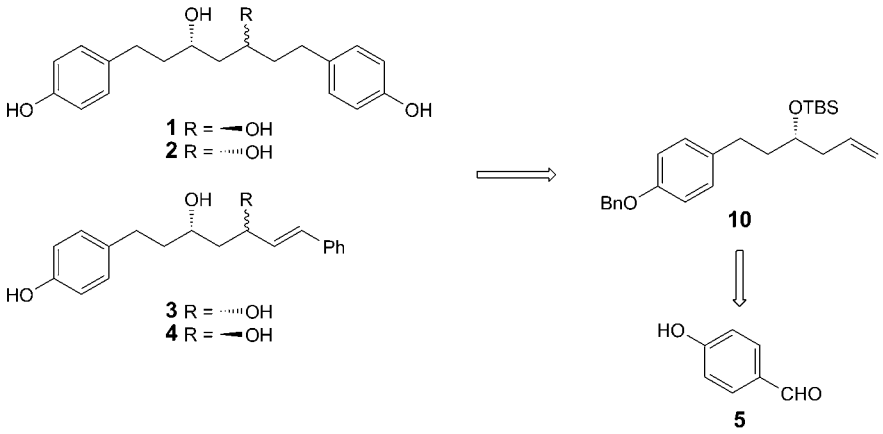


Figure. *Structures of diarylheptanoids* **1**–**4**

diarylheptanoid, was isolated from the AcOEt extract of the seeds of *Alpinia katsumadai* by *Seo* and co-workers in 2011 [4]. In continuation of our program towards the synthesis of biologically active compounds [5], we developed a simple and flexible route to the total synthesis of (3*S*,5*S*)-1,7-bis(4-hydroxyphenyl)heptane-3,5-diol (**1**), (3*S*,5*S*)-Alpinikatin (**3**), and its C(5)-diastereoisomers **2** and **4**, respectively, from commercially available 4-hydroxybenzaldehyde (**5**).

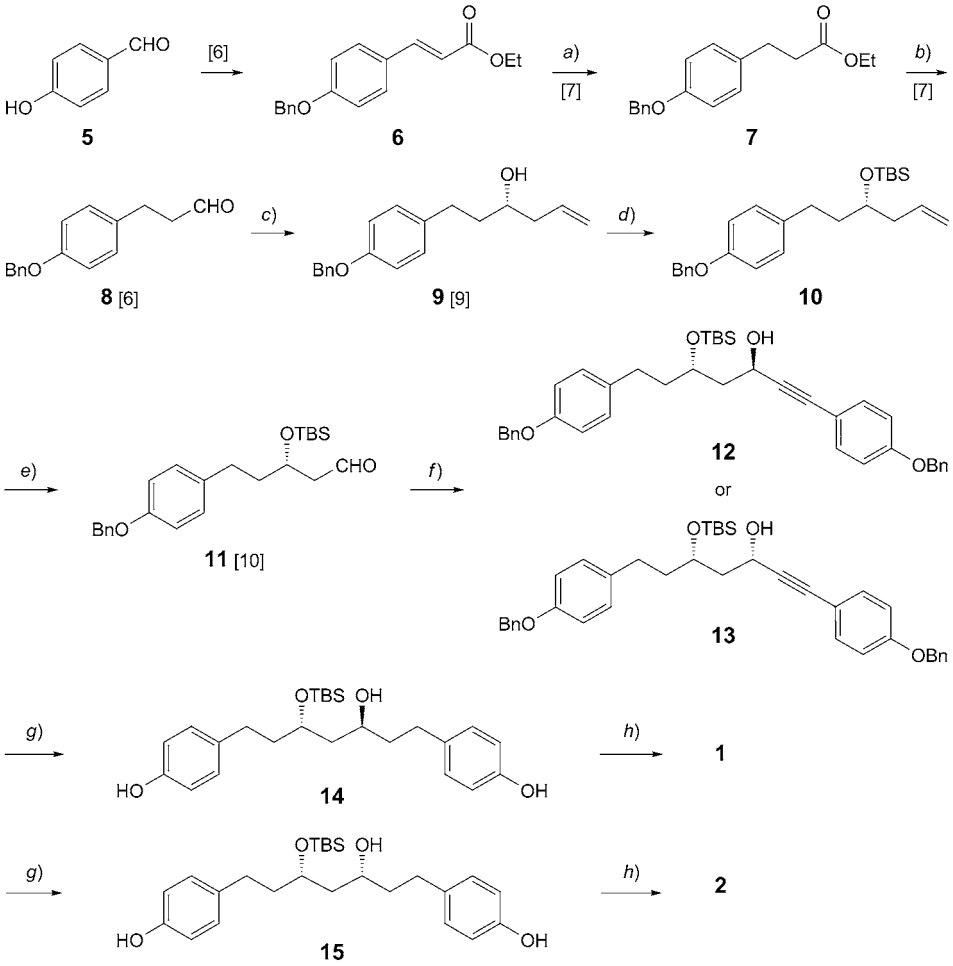
The target molecules **1**–**4** can be easily envisaged from the chiral homoallyl alcohol derivative **10**, which was prepared *via Brown*'s alkylation reaction of an aldehyde derived from 4-hydroxybenzaldehyde (**5**; *Scheme 1*).

Scheme 1. *Retro Synthetic Analysis*



Results and Discussion. – As outlined in *Schemes 1–3*, the syntheses of compounds **1**–**4** started with the commercially available starting material 4-hydroxybenzaldehyde (**5**). This aldehyde was converted to the unsaturated ester **6** according to a known procedure [6]. Reduction of the C=C bond in compound **6** with $NiCl_2 \cdot 6\,H_2O/NaBH_4$ in MeOH afforded the saturated ester **7** in 92% yield [7]. The latter was again reduced with DIBAL-H in dry CH_2Cl_2 to furnish the corresponding aldehyde **8** [6], which was subjected to *Brown*'s asymmetric allylation [8] with 1M solution of (+)-allyl[di(isopinocamphenyl)borane] [9] in pentane to furnish the chiral allylic alcohol **9** [9] in 88% yield (97% ee, determined by chiral HPLC). The homo allylic secondary OH group in **9** was protected as *tert*-butyl(dimethyl)silyl (TBS) ether **10** by treatment with TBS–Cl and imidazole in 93% yield. Further, this terminal alkene **10** was subjected to OsO_4-catalyzed dihydroxylation and $NaIO_4$-mediated cleavage to give the corresponding aldehyde **11** [10] in 86% yield. Aldehyde **11** was reacted with 1-(benzyloxy)-4-ethynylbenzene [11] by using Et_2Zn in toluene (10 mmol) and a catalytic solution of (*S*)-BINOL (1 mmol), PhOH (1 mmol), and $(^iPrO)_4Ti$ (2.5 mmol) in dry ether to afford compound **12** in 96% yield (98% de), and its diastereoisomer **13** was achieved by using (*R*)-BINOL in 94% yield (97% de). Further, each of the two isomers **12** and **13** was subjected to debenzylation using 10% Pd/C in the presence of H_2 gas to give the corresponding phenols **14** and **15** in 75 and 73% yield, respectively. Finally,

Scheme 2

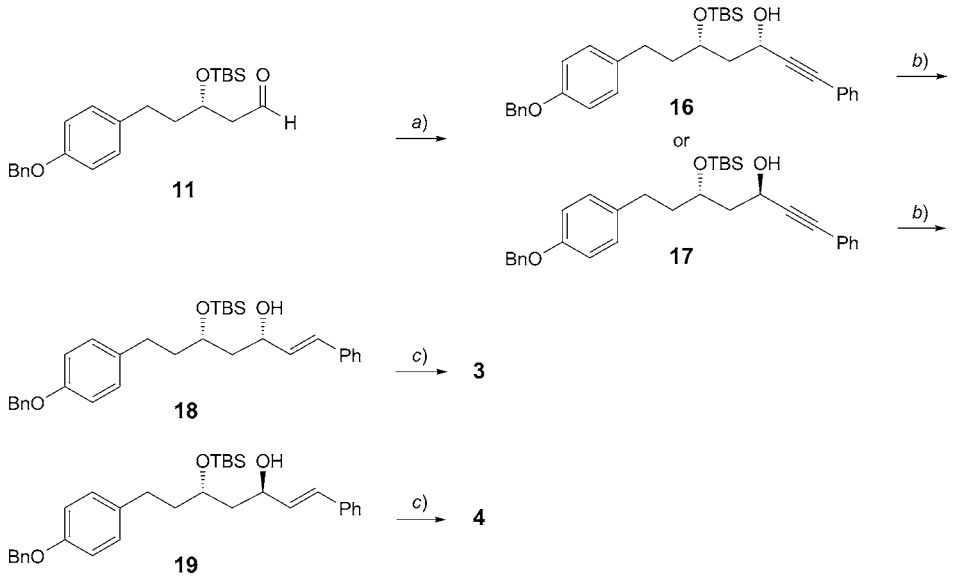


a) $NiCl_2 \cdot 6\ H_2O$, $NaBH_4$, MeOH, 0° to r.t., 1 h; 92%. *b*) DIBAL-H, CH_2Cl_2, −78°, 0.5 h; 93%. *c*) AllylBIpc$_2$ (from (+)-Ipc$_2$BCl and allylmagnesium bromide), Et_2O, −100°, 1 h; 88%. *d*) TBS–Cl, Imidazole, CH_2Cl_2, 0° to r.t., 6 h; 93%. *e*) 1) OsO_4, NMO, acetone/H_2O (9:1), r.t., 2 h; 2) $NaIO_4$, THF/H_2O (6:4), 0° to r.t., 1 h; 86%. *f*) For **12**: 1-(benzyloxy)-4-ethynylbenzene, Et_2Zn, (*S*)-BINOL, (^{i}PrO)$_4$Ti, PhOH, 96%; for **13**: 1-(benzyloxy)-4-ethynylbenzene, Et_2Zn, (*R*)-BINOL, (^{i}PrO)$_4$Ti, PhOH, 94%. *g*) H_2, Pd/C, AcOEt, 24 h; 75 and 73%, resp. *h*) TBAF, THF, 0° to r.t., 12 h; 98 and 96%, resp.

deprotection of the TBS group in **14** and **15** by using Bu_4NF (TBAF) in THF gave the desired target compounds (3*S*,5*S*)-1,7-bis(4-hydroxyphenyl)heptane-3,5-diol (**1**) in 98% yield, and its diastereoisomer **2** in 96% yield.

The other target molecules **3** and **4** were achieved from the intermediate **11**, which was reacted with phenylacetylene by using Et_2Zn in toluene (10 mmol) and a catalytic amount of (*R*)-BINOL (1 mmol), PhOH (1 mmol) and (^{i}PrO)$_4$Ti (2.5 mmol) in dry Et_2O to obtain compound **16** in 93% yield (97% de). The other diastereoisomer **17** was

Scheme 3



a) For **16**: phenylacetylene, Et_2Zn, (*R*)-BINOL, $(^iPrO)_4Ti$, PhOH, 5 h; 93%; for **17**: phenylacetylene, Et_2Zn, (*S*)-BINOL, $(^iPrO)_4Ti$, PhOH, 5 h; 92%. *b*) *Red-Al*®, THF, 0° to r.t., 0.5 h; 96 and 95%, resp. *c*) $TiCl_4$, CH_2Cl_2, 0° to r.t., 1 h; 90 and 89% resp.

prepared from the same intermediate **11** by reacting Et_2Zn in toluene and (*S*)-BINOL in 92% yield (98% de). The alkyne intermediates **16** and **17** were reduced with *Red-Al*® in THF to obtain the corresponding *trans*-alkenes **18** and **19** in 96 and 95% yields, respectively. Finally, deprotection of the TBS and Bn groups was achieved by treatment of **18** and **19** with $TiCl_4$ [12] in CH_2Cl_2 to afford the target compounds **3** and **4** in 90 and 89% yields, respectively. The physical and spectroscopic properties of **1** and **3** were in complete agreement with those reported for the natural products [3][4].

In conclusion, the stereoselective syntheses of the natural diarylheptanoids **1** and **3**, and its diastereoisomers **2** and **4** were successfully achieved with high yields from the commercially available starting material 4-hydroxybenzaldehyde (**5**) by applying *Brown*'s asymmetric allylation, and Et_2Zn-mediated diastereoselective alkynylation as the key steps.

The authors *K. V*, *S. P. R*, and *B. C.* are grateful to *UGC-CSIR*, New Delhi, India, for financial support in the form of fellowship.

Experimental Part

General. All the reagents and solvents were of anal. grade and used without further purification, unless otherwise stated. Technical-grade AcOEt and hexanes used for column chromatography (CC) were distilled before use. THF, when used as solvent for reactions, was freshly distilled from Na/benzophenone ketyl. All the reactions were performed under N_2 in flame or oven-dried glassware with magnetic stirring. Column chromatography (CC): silica gel (SiO_2, 60–120 mesh) packed in glass

columns. Optical rotations: *Anton Paar MLP 200* modular circular digital polarimeter by using a 2-ml cell with path length of 1 dm. FT-IR Spectra: *PerkinElmer 683* IR spectrophotometer; neat or as thin films in KBr optics; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR spectra: *Bruker-Avance* 300 instrument (at 300 MHz, resp.) at r.t., in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standed, *J* in Hz. MS: *Agilent Technologies* LCMSD trap SL spectrometer; in *m*/*z*.

Ethyl 3-[4-(Benzyloxy)phenyl]propanoate (**7**) [8]. To a cooled (0°) stirred soln. of **6** [7] (7 g, 24.8 mmol) in MeOH (50 ml) was added $NiCl_2 \cdot 6\ H_2O$ (4.9 g, 0.2 mmol). To this soln., $NaBH_4$ (1.8 g, 49.6 mmol) was added portionwise at 0°, and the mixture was stirred at r.t. for 0.5 h. The reaction was quenched with ice-cubes, and the mixture was extracted with AcOEt (3 × 75 ml). The combined org. layers were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was purified by CC (AcOEt/hexane) to give **7** (6.47 g, 92%) as colorless liquid. IR (neat): 2981, 1732, 1512, 1174, 736. ^1H-NMR (300 MHz, $CDCl_3$): 7.40–7.14 (*m*, 5 H); 7.11 (*d*, *J* = 8.6, 2 H); 6.90 (*d*, *J* = 8.6, 2 H); 5.03 (*s*, 2 H); 4.12 (*q*, *J* = 7.1, 14.0, 2 H); 2.89 (*t*, *J* = 7.6, 2 H); 2.53 (*t*, *J* = 8.0, 2 H); 1.23 (*t*, *J* = 7.17, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 172.9; 157.1; 137.0; 132.8; 129.2; 128.4; 127.8; 127.3; 114.7; 69.9; 60.3; 36.1; 30.0; 14.7. ESI-MS: 307 ($[M + Na]^+$).

(3S)-1-[4-(Benzyloxy)phenyl]hex-5-en-3-ol (**9**) [6]. To a soln. of **7** (5.0 g, 17.5 mmol) in CH_2Cl_2 (25 ml) was added DIBAL-H (20% in toluene, 8.8 ml, 17.5 mmol) dropwise down the walls of the flask at −70°. After completion of the reaction (monitored by TLC), it was quenched by addition of MeOH (5 ml) at 0° followed by addition of sat. sodium potassium tartrate soln. (10 ml), and was stirred at r.t. for 6 h. The org. layer was separated, and the aq. layer extracted with CH_2Cl_2 (3 × 60 ml). The combined org. layer was washed with brine (2 × 75 ml), dried (Na_2SO_4), and the org. solvent evaporated under reduced pressure. The crude product was purified by CC (SiO_2, 30% AcOEt/hexane) to give aldehyde **8** (3.88 g, 92%) [6] as colorless viscous liquid.

To a soln. of **8** (3 g, 12.4 mmol) in 32 ml of Et_2O at −78°, 1M soln. of (+)-allylBIpc$_2$ [8] in pentane (14.09 ml, 14.1mmol) was added. The mixture was stirred for 20 h, at −78° and then warmed to 0°. The reaction was quenched by the slow addition of 1 ml of 3N NaOH and 12 ml of 30% H_2O_2, and then the mixture was heated to reflux for 1 h. The aq. layer was extracted (2 × 30 ml) with Et_2O. The combined org. layers were washed with sat. $NaHCO_3$, H_2O, brine, dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was purified by CC (30% AcOEt/hexane) to afford **9** (3.10 g, 88%) as colorless oil. $[\alpha]_D^{24} = -10$ (*c* = 1.6, $CHCl_3$) ($[\alpha]_D^{24} = -16$ (*c* = 1.8, $CHCl_3$) [9]). IR (neat): 3440, 2924, 2850, 1610, 1508, 1457, 1377, 1236, 1175, 1018. ^1H-NMR (300 MHz, $CDCl_3$): 7.40–7.13 (*m*, 5 H); 7.07 (*d*, *J* = 8.7, 2 H); 6.88 (*d*, *J* = 8.7, 2 H); 5.5–5.2 (*m*, 1 H); 5.19–5.07 (*m*, 1 H); 5.02 (*s*, 2 H); 3.69–3.57 (*m*, 1 H); 2.80–2.56 (*m*, 2 H); 2.35–2.12 (*m*, 2 H); 1.79–1.68 (*m*, 2 H); 1.58 (br. *s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 157.0; 137.2; 129.3; 128.5; 127.8; 127.4; 118.3; 114.5; 69.0; 42.0; 38.5; 31.1. ESI-MS: 305 ($[M + Na]^+$).

*({(3S)-1-[4-(Benzyloxy)phenyl]hex-5-en-3-yl}oxy)(*tert*-butyl)dimethylsilane* (**10**). To a stirred soln. of **9** (2.4 g, 8.49 mmol) in CH_2Cl_2 (15 ml) was added imidazole (1.73 g, 25.49 mmol), followed by (*tert*-butyl)(dimethyl)silyl chloride (2.55 g, 16.98 mmol) at 0°. The mixture was stirred at r.t. for 24 h. After completion of the reaction, the mixture was diluted with H_2O (20 ml) and extracted with CH_2Cl_2 (2 × 20 ml). The combined org. layers were washed with brine (20 ml), dried (Na_2SO_4), and concentrated, the crude product was purified by CC (5% AcOEt/hexane) to give **10** (3.13 g, 93%) as colorless oil. $[\alpha]_D^{24} = -10$ (*c* = 1.2, $CHCl_3$). IR (neat): 2932, 1748, 1512, 1250, 833. ^1H-NMR (300 MHz, $CDCl_3$): 7.46–7.29 (*m*, 5 H); 7.08 (*d*, *J* = 8.49, 2 H); 6.89 (*d*, *J* = 8.49, 2 H); 5.89–5.74 (*m*, 1 H); 5.04 (*t*, *J* = 8.8, 4 H); 3.80–3.70 (*m*, 1 H); 2.71–2.46 (*m*, 2 H); 2.26 (*t*, *J* = 6.6, 2 H); 1.78–1.64 (*m*, 2 H); 0.91 (*s*, 9 H); 0.03 (*s*, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 156.8; 137.1; 135.0; 134.9; 129.1; 128.4; 127.8; 127.4; 116.8; 114.6; 71.5; 69.9; 41.8; 38.8; 30.8; 29.6; 25.0; 4.4. ESI-MS: 419 ($[M + Na]^+$).

*(3S)-5-[4-(Benzyloxy)phenyl]-3-{[*tert*-butyl(dimethyl)silyl]oxy}pentanal* (**11**) [10]. To a soln. of **10** (2.5 g, 7.5 mmol) in a mixture of acetone/H_2O 3:1 (20 ml) was added OsO_4 (0.48 ml, 4% aq. soln., 0.075 mmol) and *N*-methylmorpholine *N*-oxide (NMO; 1.7 g, 2.6 mmol) at 25°, and stirred for 5 h, the solvent was evaporated, and the residue was extracted with AcOEt (30 ml). The org. layers were washed with brine (10 ml), dried (Na_2SO_4), and concentrated *in vacuo*. To a soln. of above crude diol in a mixture of THF/H_2O 4:1 (50 ml), $NaIO_4$ (2.4 g, 11.6 mol) was added, and the mixture was stirred for 1 h at 25°. The solid was removed by filtration, and the filtrate was extracted with AcOEt (40 ml). The org. layers were washed with brine (10 ml), dried (Na_2SO_4), and concentrated *in vacuo*. The crude aldehyde was

purified by CC (5% AcOEt/hexane) to give aldehyde **11** (2.16 g, 86%) as colorless liquid. $[\alpha]_D^{24} = -0.1$ ($c = 0.1$, $CHCl_3$). IR (neat): 3425, 2926, 1725, 1511, 1243. ^{1}H-NMR (300 MHz, $CDCl_3$): 9.81 (*t*, *J* = 2.2, 1 H); 7.4–7.30 (*m*, 5 H); 7.08 (*d*, *J* = 8.5, 2 H); 6.90 (*d*, *J* = 8.5, 2 H); 5.04 (*s*, 2 H); 4.26–4.21 (*m*, 1 H); 2.63–2.56 (*m*, 4 H); 1.86–1.80 (*m*, 2 H); 0.9 (*s*, 9 H); 0.07 (*s*, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 202.0; 157.0; 139.2; 137.0; 133.9; 129.1; 128.5; 127.8; 127.4; 114.8; 114.0; 70.0; 67.6; 50.7; 39.7; 31.8; 30.5; 25.7; −4.41; −4.66. ESI-MS: 437 ($[M+K]^+$).

*(3*R*,5*S*)- and (3*S*,5*S*)-1,7-Bis[4-(benzyloxy)phenyl]-5-[[*tert*-butyl(dimethyl)silyl]oxy}hept-1-yn-3-ol* (**12** and **13**, resp.). To a soln. of Et_2Zn (0.134, 1.1 m) in toluene (12 ml, 10.0 mmol) was added a soln. of 1-(benzyloxy)-4-ethynylbenzene (2.08 g, 10.0 mmol) in dry toluene (3 ml) at r.t., and the mixture was heated for 1 h at reflux. A soln. of BINOL ((*S*)-BINOL and (*R*)-BINOL for **12** and **13**, resp.; 0.286 g, 1.0 mmol), PhOH (1 ml, 1.0 mmol), and $(^iPrO)_4Ti$ (0.710 ml, 2.5 mmol) in anh. Et_2O (3 ml) was stirred for 30 min. This soln. was added to the mixture, which was stirred for 1 h at r.t. before adding aldehyde **11** (1 g, 2.5 mmol). The entire mixture was stirred for 4 h at r.t., after completion of the reaction, the reaction was quenched with a NH_4Cl soln. (12 ml), and the mixture was extracted with AcOEt (2 × 10 ml). The combined org. layer was washed with 2N NH_4Cl (2 × 5 ml), $NaHCO_3$ (2 × 5 ml), and brine (10 ml), dried ($MgSO_4$), and evaporated under reduced pressure. The crude residue was separated by CC (7% AcOEt/hexane) to give **12** (1.46 g, 96%) with 98% de (determined by RP-HPLC (*Atlantis dC$_{18}$* column, 4.6 × 150, 5 μm; mobile phase, 80% MeCN in H_2O, flow rate, 1.0 ml/min, detection at 210 nm, t_R 32.152 min) as colorless oil. $[\alpha]_D^{24} = -7.5$ ($c = 0.4$, $CHCl_3$). IR (neat): 3448, 2925, 1508, 1244, 832. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.46–7.29 (*m*, 12 H); 7.10 (*d*, *J* = 8.3, 2 H); 6.9 (*d*, *J* = 8.3, 6 H); 5.04 (*d*, *J* = 5.2, 4 H); 4.88–4.81 (*m*, 1 H); 4.23–4.09 (*m*, 1 H); 2.64–2.49 (*m*, 2 H); 2.06–1.86 (*m*, 4 H); 0.92 (*s*, 9 H); 0.11 (*s*, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 158.8; 157.0; 137.1; 136.1; 134.2; 133.1; 129.2; 128.6; 128.6; 128.1; 127.9; 127.5; 125.8; 114.8; 88.8; 84.5; 70.0; 60.4; 42.7; 38.9; 30.5; 25.9; −4.22; −4.54. ESI-MS: 629 ($[M+Na]^+$).

Data of **13**. Colorless oil. Yield: 1.43 g (94%). 97% de (determined by RP-HPLC (*Atlantis dC$_{18}$* column, 4.6 × 150, 5 μm; mobile phase, 80% MeCN in H_2O, flow rate, 1.0 ml/min, detection at 210 nm, t_R 26.069 min). $[\alpha]_D^{24} = -17.5$ ($c = 0.1$, $CHCl_3$). IR (neat): 3448, 2925, 1508, 1244, 832. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.12–7.06 (*m*, 12 H); 7.10 (*d*, *J* = 8.3, 2 H); 6.90 (*d*, *J* = 8.3, 6 H); 5.04 (*d*, *J* = 5.2, 4 H); 4.79–4.72 (*m*, 1 H); 4.07–3.98 (*m*, 1 H); 2.65–2.53 (*m*, 2 H); 1.97–1.74 (*m*, 4 H); 0.92 (*s*, 9 H); 0.11 (*s*, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 158.8; 157.0; 137.1; 136.1; 134.2; 133.1; 129.2; 128.6; 128.6; 128.1; 127.9; 127.5; 125.8; 114.8; 88.8; 84.5; 70.0; 60.4; 42.7; 38.9; 30.5; 25.9; −4.22; −4.54. ESI-MS: 629 ($[M+Na]^+$).

*4,4′-[(3*S*,5*S*)- and (3*S*,5*R*)-3-[[*tert*-Butyl(dimethyl)silyl]oxy}-5-hydroxyheptane-1,7-diyl]diphenol* (**14** and **15**, resp.). 10% Pd/C (0.008 g, 0.00008 mmol) was added to a soln. of **12** and **13** (0.5 g, 0.0008 mmol) in AcOEt (5 ml). The mixture was stirred overnight under H_2 atmosphere. After the completion of reaction, the mixture was filtered through *Celite*, and the resulting filtrate was concentrated *in vacuo*. The residue was purified by CC (40% AcOEt/hexane) to give **14** (0.265 g, 75%) as colorless liquid. $[\alpha]_D^{24} = -5$ ($c = 0.3$, $CHCl_3$). IR (neat): 3404, 2930, 1513, 1244, 831. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.02 (*dd*, *J* = 8.3, 16.6, 4 H); 6.74 (*dd*, *J* = 6.7, 8.3, 4 H); 5.13 (br. *s*, 1 H); 4.99 (br. *s*, 1 H); 4.03 (*m*, 2 H); 3.74–3.65 (*m*, 1 H); 2.76–2.41 (*m*, 4 H); 1.91–1.69 (*m*, 4 H); 1.68–1.58 (*m*, 2 H); 0.89 (*s*, 9 H); 0.08 (*s*, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 153.8; 133.6; 129.3; 115.2; 71.7; 68.1; 40.6; 39.5; 38.0; 31.3; 30.7; 25.8; −4.62; −4.71. ESI-MS: 453 ($[M+Na]$).

Data of **15**. Colorless liquid. Yield: 0.258 g (73%). $[\alpha]_D^{34} = -7.0$ ($c = 0.4$, $CHCl_3$). IR (neat): 3404, 2930, 1513, 1250, 831.^{1}H-NMR (300 MHz, $CDCl_3$): 7.02 (*dd*, *J* = 8.3, 16.6, 4 H); 6.75 (*dd*, *J* = 4.4, 8.3, 4 H); 5.13 (br. *s*, 1 H); 4.99 (*m*, 1 H); 4.07–3.97 (*m*, 1 H); 3.75–3.64 (*m*, 1 H); 2.76–2.45 (*m*, 4 H); 1.92–1.72 (*m*, 2 H); 1.72–1.58 (*m*, 4 H); 0.91 (*s*, 9 H); 0.09 (*s*, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 153.9; 133.6; 129.3; 115.2; 72.9; 70.7; 60.5; 42.5; 39.9; 39.3; 30.7; 30.0; 25.8; −4.0; −4.7. ESI-MS: 453 ($[M+Na]^+$).

*(3*S*,5*S*)- and (3*R*,5*S*)-1,7-Bis(4-hydroxyphenyl)heptane-3,5-diol* (**1** and **2**, resp.). To a soln. of **14** and **15** (50 g, 0.116 mmol) in THF (3 ml), TBAF (1.0M soln. in THF, 0.116 ml, 0.116 mmol) was added dropwise at 0°. The mixture was stirred at r.t. for 12 h. After completion of the reaction, the solvent was removed *in vacuo*, and the crude residue was separated by CC (50% AcOEt/hexane) to afford **1** (34 mg, 96%) as colorless oil. $[\alpha]_D^{24} = -15$ ($c = 0.4$, MeOH). IR (neat): 3448, 2924, 1633, 1220, 771. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.02 (*d*, *J* = 8.3, 4 H); 6.74 (*d*, *J* = 9.0, 4 H); 4.04 (br. *s*, 2 H); 3.50–3.46 (*m*, 2 H);

2.80–2.65 (*m*, 4 H); 1.87–1.60 (*m*, 6 H). ^{13}C-NMR (300 MHz, $CDCl_3$): 154.2; 132.8; 128.7; 114.6; 67.4; 42.8; 39.1; 30.6. ESI-MS: 339.2 ($[M+Na]^+$).

Data of **2**. Yield: 34 mg (95%). Colorless oil. $[\alpha]_D^{24} = -5$ ($c = 0.8$, MeOH). IR (neat): 3449, 2922, 1636, 1223, 762. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.02 (*d*, $J = 7.5$, 4 H); 6.74 (*d*, $J = 7.5$, 4 H); 3.38–3.32 (*m*, 2 H); 2.76–2.49 (*m*, 4 H); 1.82–1.66 (*m*, 4 H); 1.62–1.55 (*m*, 2 H). ^{13}C-NMR (300 MHz, $CDCl_3$): 154.3; 132.8; 129.0; 114.9; 71.5; 42.4; 39.5; 30.0. ESI-MS: 339.2 ($[M+Na]^+$).

*(3*S*,5*S*)- and (3*R*,5*S*)-7-[4-(Benzyloxy)phenyl]-5-{[*tert*-butyl(dimethyl)silyl]oxy}-1-phenylhept-1-yn-3-ol* (**16** and **17**, resp.). To a soln. of Et_2Zn in toluene (10 ml, 10.0 mmol) was added a soln. of phenylacetylene (1.02 g, 10.0 mmol) in dry toluene (1 ml) at r.t., and the mixture was heated at reflux for 1 h. A catalyst soln. of BINOL ((*R*)- and (*S*)-BINOL for **16** and **17**, resp.) (0.286 g, 1.0 mmol), PhOH (94 mg, 1.0 mmol), and $(^iPrO)_4Ti$ (0.78 ml, 2.5 mmol) in anh. Et_2O (3 ml) was stirred for 35 min. This soln. was added to the mixture, and the mixture was stirred for 1 h at r.t. before adding aldehyde **11** (1 g, 2.5 mmol). The entire mixture was stirred for 4 h at r.t., after completion of the reaction, the reaction was quenched with NH_4Cl (10 ml) and extracted with AcOEt (2×10 ml). The combined org. layer was washed with 2N HCl (2×5 ml), $NaHCO_3$ (2×5 ml), and brine (10 ml), dried ($MgSO_4$), and evaporated under reduced pressure. The crude product was purified by CC (5% AcOEt/hexane) to give **16** (1.16 g, 93%) with 97% de (determined by RP-HPLC (*Atlantis dC$_{18}$* column, 4.6×150, 5 µm, mobile phase, 80% MeCN in H_2O, flow rate, 1.0 ml/min, detection at 210 nm, t_R 20.274 min) as colorless oil. $[\alpha]_D^{24} = -7.5$ ($c = 0.1$, $CHCl_3$). IR (neat): 3449, 2929, 1640, 1245, 765. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.45–7.27 (*m*, 10 H); 7.09 (*d*, $J = 8.3$, 2 H); 6.87 (*d*, $J = 8.3$, 2 H); 5.01 (*s*, 2 H); 4.81–4.74 (*m*, 1 H); 4.07–3.99 (*m*, 1 H); 2.68–2.52 (*m*, 2 H); 2.13–1.80 (*m*, 4 H); 0.91 (*s*, 9 H); 0.09 (*s*, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 157.0; 137.2; 134.4; 131.7; 129.2; 128.5; 128.3; 127.9; 127.4; 122.6; 114.8; 89.9; 85.2; 70.2; 61.6; 44.0; 39.8; 30.2; 25.9; −4.1; −4.65. ESI-MS: 523 ($[M+Na]^+$).

Data of **17**. Colorless oil. Yield: 1.15 g (92%). 97% de (determined by RP-HPLC (*Atlantis dC$_{18}$* column, 4.6×150, 5 µm, mobile phase, 80% MeCN in H_2O, flow rate, 1.0 ml/min, detection at 210 nm, t_R 15.956 min). $[\alpha]_D^{24} = -22.5$ ($c = 0.2$, $CHCl_3$). IR (neat): 3446, 2928, 1074, 769. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.46–7.27 (*m*, 10 H); 7.1 (*d*, $J = 8.3$, 2 H); 6.89 (*d*, $J = 8.3$, 2 H); 5.03 (*s*, 2 H); 4.90–4.83 (*m*, 1 H); 4.24–4.16 (*m*, 1 H); 2.65–2.54 (*m*, 2 H); 2.07–2.00 (*m*, 2 H); 1.92–1.82 (*m*, 2 H); 0.92 (*s*, 9 H); 0.11 (*s*, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 157; 137.1; 134.1; 131.6; 129.1; 128.5; 128.2; 127.8; 127.4; 122.7; 114; 90.0; 84.5; 70.0; 60.4; 42.4; 38.9; 30.4; 25.8; −4.28; −4.6. ESI-MS: 523 ($[M+Na]^+$).

*(1*E*,3*S*,5*S*)- and (1*E*,3*R*,5*S*)-7-[4-(Benzyloxy)phenyl]-5-{[*tert*-butyl(dimethyl)silyl]oxy}-1-phenylhept-1-en-3-ol* (**18** and **19**, resp.). To a cooled soln. (0°) of propargylic alcohols **16** and **17** (0.2 g, 0.4 mmol) in THF (10 ml), *Red-Al*® (70 wt.-% in toluene, 1.82 ml, 1 mmol) was added dropwise. The mixture was stirred for 0.5 h at 0°, and the reaction was carefully quenched with a sat. aq. Na_2SO_4 soln., AcOEt was added, and the mixture was warmed to r.t. The org. layer was washed with brine, and the combined org. extracts were dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by CC (30% AcOEt/hexane) to provide allylic alcohol **18** (0.192 g, 96%) as colorless oil. $[\alpha]_D^{24} = -25$ ($c = 0.4$, $CHCl_3$). IR (neat): 3414, 2923, 1509, 1239, 750. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.45–7.28 (*m*, 10 H); 7.11 (*d*, $J = 8.5$, 2 H); 6.89 (*d*, $J = 8.6$, 2 H); 6.62 (*d*, $J = 15.8$, 1 H); 6.27 (*dd*, $J = 6.2$, 16.0, 1 H); 5.03 (*s*, 2 H); 4.68–4.63 (*m*, 1 H); 4.04–3.98 (*m*, 1 H); 2.77–2.59 (*m*, 2 H); 1.89–1.74 (*m*, 4 H); 0.9 (*s*, 9 H); 0.11 (*s*, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 157.0; 137.1; 136.5; 134.1; 131.8; 130.0; 129.2; 128.5; 127.8; 127.6; 127.4; 126.4; 114.8; 70.6; 70.0; 68.8; 42.5; 39.3; 31.7; 30.9; 25.8; −3.99; −4.63. ESI-MS: 525 ($[M+Na]^+$).

Data of **19**. Yield: 0.190 g (95%). Colorless oil. $[\alpha]_D^{24} = -6.6$ ($c = 0.1$, $CHCl_3$). IR (neat): 3449, 2929, 1510, 1244, 1075, 773. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.44–7.28 (*m*, 10 H); 7.08 (*d*, $J = 8.5$, 2 H); 6.89 (*d*, $J = 8.5$, 2 H); 6.62 (*d*, $J = 15.8$, 2 H); 6.27 (*dd*, $J = 6.1$, 15.8, 1 H); 5.03 (*s*, 2 H); 4.50–4.44 (*m*, 1 H); 4.06–3.99 (*m*, 1 H); 2.67–2.52 (*m*, 2 H); 1.86–1.80 (*m*, 4 H); 0.93 (*s*, 9 H); 0.11 (*s*, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 156.9; 137.1; 136.1; 134.3; 132.1; 129.6; 129.1; 128.4; 127.8; 127.4; 127.3; 126.4; 114.8; 113.8; 71.9; 71.5; 69.9; 43.2; 39.8; 30.0; 25.8; −3.99; −4.63. ESI-MS: 525 ($[M+Na]^+$).

*(1*E*,3*S*,5*S*)- and (1*E*,3*R*,5*S*)-7-(4-Hydroxyphenyl)-1-phenylhept-1-ene-3,5-diol* (**3** and **4**, resp.). To a stirred soln. of **18** and **19** (50 mg, 0.09 mol) in CH_2Cl_2 (5 ml), $TiCl_4$ (1M in CH_2Cl_2, 0.07 ml, 0.03 mmol) was added at 0°, and the mixture was stirred at the same temp. for 1 h. The reaction was quenched with solid $NaHCO_3$ (30 mg), and filtered, the solvent was removed under reduced pressure. The crude residue

was separated by CC (50% AcOEt; hexane) to afford **3** (26 mg, 89%) as colorless sticky liquid. $[\alpha]_D^{24} = -9$ ($c = 0.3$, MeOH). IR (neat): 3449, 2925, 1513, 1254; 749. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.41 – 7.20 (*m*, 5 H); 7.04 (*d*, *J* = 8.4, 2 H); 6.73 (*d*, *J* = 8.4, 2 H); 6.59 (*d*, *J* = 15.8, 1 H); 6.26 (*dd*, *J* = 6.2, 16.0, 1 H); 3.96 – 3.87 (*m*, 1 H); 3.37 – 3.33 (*m*, 1 H); 2.77 – 2.53 (*m*, 2 H); 1.82 – 1.70 (*m*, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 154.1; 136.3; 132.6; 131.9; 130.5; 128.7; 128.5; 127.7; 126.6; 125.6; 114.0; 68.7; 67.0; 43.2; 39.0; 30.3. ESI-MS: 321.0 ($[M + Na]^+$).

Data of **4**. Yield: 26 mg (88%). Colorless sticky liquid. $[\alpha]_D^{24} = 19.0$ ($c = 0.9$, $CHCl_3$). IR (neat): 3449, 2925, 1254, 749. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.41 – 7.20 (*m*, 5 H); 7.03 (*d*, *J* = 8.3, 2 H); 6.75 (*d*, *J* = 8.1, 2 H); 6.58 (*d*, *J* = 15.8, 1 H); 6.21 (*dd*, *J* = 6.4, 15.8, 1 H); 4.54 – 4.44 (*m*, 1 H); 3.95 – 3.78 (*m*, 1 H); 2.73 – 2.53 (*m*, 2 H); 1.81 – 1.67 (*m*, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 154.0; 136.1; 132.3; 131.1; 130.5; 129.3; 128.3; 127.5; 127.3; 126.5; 125.4; 114.1; 70.5; 68.5; 43.0; 39.0; 29.9. ESI-MS: 321 ($[M + Na]^+$).

REFERENCES

[1] P. Claeson, P. Tuchinda, V. Reutrakul, *J. Indian Chem. Soc.* **1994**, *71*, 509; G. M. Keserü, M. Nógrádi, *Stud. Nat. Prod. Chem.* **1995**, *17*, 357; P. Claeson, U. P. Claeson, P. Tuchinda, V. Reutrakul, *Stud. Nat. Prod. Chem.* **2002**, *26*, 881; H. Lv, G. She, *Nat. Prod. Commun.* **2010**, *5*, 1687.

[2] G.-J. Fan, Y.-H. Kang, Y. N. Han, B. H. Han, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6720; N. X. Nhiem, P. V. Kiem, C. V. Minh, N. Kim, S. Park, H. Y. Lee, E. S. Kim, Y. H. Kim, S. Kim, Y.-S. Koh, S. H. Kim, *J. Nat. Prod.* **2013**, *76*, 495; H. Mohamad, N. H. Lajis, F. Abas, A. M. Ali, M. A. Sukari, H. Kikuzaki, N. Nakatani, *J. Nat. Prod.* **2005**, *68*, 285; D. Shin, K. Kinoshita, K. Koyama, K. Takahashi, *J. Nat. Prod.* **2002**, *65*, 1315; H. Wohlmuth, M. A. Deseo, D. J. Brushett, D. R. Thompson, G. MacFarlane, L. M. Stevenson, D. N. Leach, *J. Nat. Prod.* **2010**, *73*, 743.

[3] a) F. J. Wu, J. D. Su, *Zhongguo Nongye Hauxue Huizhi* **1996**, *34*, 438; b) M. S. Ali, Y. Tezuka, S. Awale, A. H. Banskota, S. Kadota, *J. Nat. Prod.* **2001**, *64*, 289.

[4] J.-W. Nam, G.-Y. Kang, A.-R. Han, D. Lee, Y.-S. Lee, E.-K. Seo, *J. Nat. Prod.* **2011**, *74*, 2109.

[5] A.Venkanna, E. Sreedhar, B. Siva, K. S. Babu, K. R. Prasad, J. M. Rao, *Tetrahedron: Asymmetry* **2012**, *24*, 1010; A.Venkanna, B. Siva, B. Poornima, K. S. Babu, J. M. Rao, *Tetrahedron Lett.* **2014**, *55*, 403; S. P. Reddy, K. Ashalatha, D. K. Reddy, B. Chinnababu, Y. Venkateswarlu, *Synthesis* **2011**, *19*, 3180; S. P. Reddy, B. Chinnababu, V. Shekhar, D. K. Reddy, G. V. S. Bhanuprakash, L. R. Velatoor, J. V. Rao, Y. Venkateswarlu, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 4182.

[6] P. R. Reddy, C. Sudhakar, J. N. Kumar, B. Das, *Helv. Chim. Acta* **2013**, *96*, 289

[7] S. P. Reddy, B. Chinnababu, Y. Venkateswarlu, *Helv. Chim. Acta* **2014**, *97*, 999.

[8] B. Chinnababu, S. P. Reddy, C. B. Rao, K. Rajesh, Y. Venkateswarlu, *Helv. Chim. Acta* **2010**, *93*, 1960.

[9] T. I. Richardson, S. D. Rychnovsky, *J. Org. Chem.* **1996**, *61*, 4219.

[10] B. Das, K. Suneel, G. Satyalaxmi, D. N. Kumar, *Tetrahedron: Asymmetry* **2009**, *20*, 1536.

[11] V. Shekhar, D. K. Reddy, S. P. Reddy, P. Prabhakar, Y. Venkateswarlu, *Eur. J. Org. Chem.* **2011**, 4460; G. Gao, D. Moore, R.-G. Xie, L. Pu, *Org. Lett.* **2002**, *4*, 4143; Z.-B. Li, L. Pu, *Org. Lett.* **2004**, *6*, 1065; Y. Georges, Y. Allenbach, X. Ariza, J. M. Campagne, J. Garcia, *J. Org. Chem.* **2004**, *69*, 7387.

[12] U. Ramulu, D. Ramesh, S. Rajaram, S. P. Reddy, K. Venkatesham, Y. Venkateswarlu, *Tetrahedron: Asymmetry* **2012**, *23*, 117.

Received March 23, 2015