The First Stereoselective Total Synthesis of Naturally Occurring, Bioactive (3*R*,5*R*)-1-(4-Hydroxyphenyl)-7-phenylheptane-3,5-diol and the Synthesis of Its Enantiomer[1])

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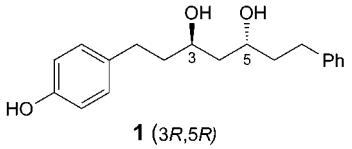
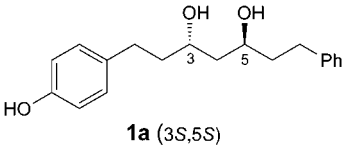
The first stereoselective total synthesis of the naturally occurring anti-emetic diarylheptanoid (3*R*,5*R*)-1-(4-hydroxyphenyl)-7-phenylheptane-3,5-diol (**1**) was accomplished starting from 4-hydroxybenzaldehyde and involving a *Sharpless* kinetic resolution and an asymmetric epoxidation as the key steps (*Scheme 2*). The enantiomer **1a** of this compound was also simultaneously prepared.

Introduction. – Diarylheptanoids constitute an important class of natural products as they possess various interesting biological properties, such as anti-inflammatory, antioxidant, and anticancer activites [1]. A large number of these compounds have been isolated from nature [2]. Some of them contain a 1,3-diol system. The linear diarylheptanoid (3*R*,5*R*)-1-(4-hydroxyphenyl)-7-phenylheptane-3,5-diol (**1**) was isolated from *Alpinia officinarum* (Zingiberaceae) [3]. The compound exhibits anti-emetic activity. Thus, **1** is an important target for total synthesis. However, it is interesting that, though the synthesis of several stereoisomers and analogues of **1** have already been reported [4], the synthesis of **1** itself has not yet been disclosed. Here, we report the first stereoselective total synthesis of **1**. Its enantiomer **1a** was also simultaneously prepared.



1 (3*R*,5*R*)



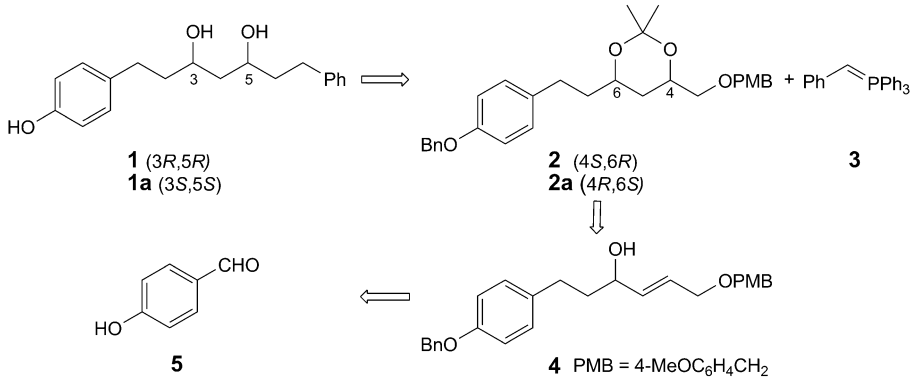
1a (3*S*,5*S*)

Results and Discussion. – The retrosynthetic analysis (*Scheme 1*) revealed that compound **1** or **1a** can be synthesized from the acetonide derivative **2** or **2a**, respectively, and benzyltriphenylphosphonium ylide **3**. The compound **2** or **2a** can in turn be prepared from the achiral allyl alcohol **4** generated from 4-hydroxybenzaldehyde (**5**).

The present synthesis of **1** and **1a** was initiated (*Scheme 2*) by converting **5** [5] into its benzyl ether [5] followed by *Wittig* olefination with $Ph_3PCHCOOEt$ and subsequent reduction with $LiBH_4$ to yield the known alcohol **6** [5]. The latter was oxidized under *Swern* conditions, and the corresponding aldehyde was treated with 4-methoxybenzyl (PMB)-protected propargyl alcohol ($4\text{-}MeOC_6H_4CH_2OCH_2C{\equiv}CH$) and BuLi to

[1]) Part 59 in the series 'Synthetic Studies on Natural Products'.

Scheme 1. *Retrosynthetic Pathway of* **1** *and* **1a**

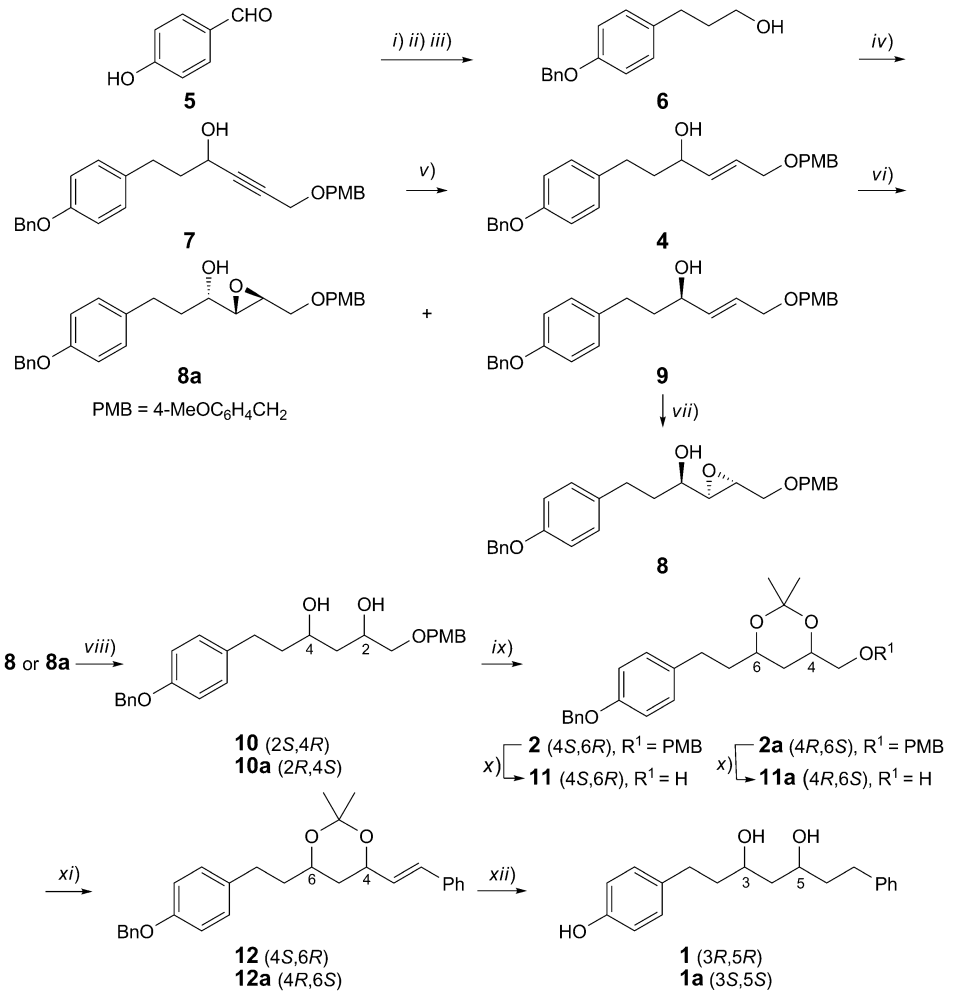


furnish the acetylenic compound **7**. The reduction of **7** with $LiAlH_4$ in THF under reflux [6] afforded the (*E*)-configured allyl-alcohol **4** (major isomer) along with a small amount of its (*Z*)-isomer, which was separated by column chromatography. The *Sharpless* kinetic resolution [7] of **4** with ((+)-diisopropyl tartrate (+)-DIPT, titanium(IV) isopropoxide ((^{i}PrO)$_4$Ti), and *tert*-butyl hydroperoxide (^{t}BuOOH) resulted in the formation of the chiral epoxy alcohol **8a** and the allyl alcohol **9**. Next, compound **9** underwent *Sharpless* asymmetric epoxidation [5] with (−)-DIPT, (^{i}PrO)$_4$Ti, and ^{t}BuOOH to generate the enantiomeric epoxy alcohol **8**. Compounds **8** and **8a** were separately treated with *Red-Al*® (sodium bis(2-methoxyethoxy)aluminium hydride solution in toluene) in THF to give the diols **10** and **10a**, respectively. The two OH groups of these diols were protected by preparing the acetonide derivatives **2** and **2a**, and subsequently the protecting PMB group was removed with DDQ (= 4,5-dichloro-3,6-dioxocyclohexol-1,4-diene-1,2-dicarbonitrile) to generate the alcohols **11** (from **10**) and **11a** (from **10a**). Each of the alcohols **11** and **11a** was again oxidized under *Swern* conditions, and the corresponding aldehydes were subjected to *Wittig* olefination with Ph_3P=CHPh to afford the olefins **12** and **12a**, respectively, along with minor amounts (10%) of their (*Z*)-isomers, which were separated by column chromatography. The protecting acetonide group of **12** and **12a** was removed by treatment with *p*-toluenesulfonic acid (TsOH) in MeOH followed by hydrogenation in the presence of Pd/C to yield the diols **1** and **1a**, respectively. The optical and spectroscopic (^{1}H-, and ^{13}C-NMR and MS) properties of **1** were identical to those of the naturally occurring (3*R*,5*R*)-1-(4-hydroxyphenyl)-7-phenylheptane-3,5-diol [3]. The spectroscopic properties of **1a** were identical to those of **1**, but its optical-rotation value was reverse.

In conclusion, we developed the first stereoselective total synthesis of the anti-emetic compound (3*R*,5*R*)-1-(4-hydroxyphenyl)-7-phenylheptane-3,5-diol (**1**) starting from 4-hydroxybenzaldehyde. The synthesis of its enantiomer was also accomplished. The method can be utilized for the synthesis of related diarylheptanoids which can be employed for bioevaluation.

The authors thank *UGC* and *CSIR*, New Delhi, for financial assistance.

Scheme 2. *Synthesis of* **1** *and* **1a**



i) NaH, BnBr, THF, 0° to r.t., 4 h; 80%. *ii*) Ph_3P=CHCOOEt, CH_2Cl_2, r.t., 8 h; 82%. *iii*) $LiBH_4$, H_2O, Et_2O, 0° to r.t., 24 h; 91%. *iv*) 1. $(COCl)_2$, DMSO, Et_3N, −78°; 82%; 2. BuLi, dry THF, 4-$MeOC_6H_4CH_2OCH_2C{\equiv}CH$, −78° , 3.5 h; 90%. *v*) $LiAlH_4$, dry THF, 0° to reflux, 3 h; 78%. *vi*) $(^iPrO)_4Ti$, (+)-DIPT, ^{t}BuOOH, dry CH_2Cl_2, −20°, 6 h; 46% (**8a**), 53% (**9**). *vii*) $(^iPrO)_4Ti$, (−)-DIPT, ^{t}BuOOH, dry CH_2Cl_2, −20° , 7 h; 66%. *viii*) *Red-Al*®, dry THF, 0° to r.t., 2 h; 72% (**10**), 74% (**10a**). *ix*) TsOH (cat.), 2,2-dimethoxypropane, CH_2Cl_2, r.t., 0.5 h; 95% (**2**), 94% (**2a**). *x*) DDQ, CH_2Cl_2/H_2O 19 : 1, r.t., 2 h; 63% (**11**), 64% (**11a**). *xi*) 1. $(COCl)_2$, DMSO, Et_3N, −78°, 3.5 h; 80%; 2. $(Ph_3PCH_2Ph)Br$, BuLi, dry THF, 4 h; 78% (**12**), 75% (**12a**). *xii*) 1. TsOH, MeOH, 3 h; 2. H_2, Pd/C, 2 h; 60% (**1**), 63% (**1a**).

Experimental Part

General. All commercially available reagents were used directly without further purification unless otherwise stated. The solvents used were all of AR grade and were distilled under dry N_2 where necessary. All reactions were performed in predried apparatus unless otherwise stated. Yields were those

of purified compounds unless otherwise stated. TLC: silica gel *60 F_{254}* plates (SiO_2; *Merck*). Column chromatography (CC): silica gel (SiO_2; 60–120 mesh; *Qingdao Marine Chemical*, P. R. China). Optical rotations: *Jasco-DIP-300* digital polarimeter. NMR Spectra: *Gemini-200* spectrometer; in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard, J in Hz. ESI-MS: *VG-Autospec-micromass* instrument; in m/z. HR-MS: *QSTAR-XL-Hybrid* MS system (*Applied Biosystems*); in m/z.

6-[4-Methoxyphenyl)methoxy)-1-[4-(phenylmethoxy)phenyl]hex-4-yn-3-ol (**7**). To a stirred soln. of oxalyl chloride (8.07 ml, 132.20 mmol) in dry CH_2Cl_2 (160 ml), DMSO (0.55 ml, 18.2 mmol) was added at $-78°$, and the mixture was stirred at $-78°$ for 0.5 h. A soln. of **6** (16 g, 66.11 mmol) in dry CH_2Cl_2 (60 ml) was added at $-78°$, and the mixture was stirred for 1.5 h at $-78°$ Et_3N (27.59 ml, 198.01 mmol) was added at 0°, and the mixture was stirred for an additional 30 min. After completion of the reaction, the mixture was diluted with H_2O (30 ml) and extracted with CH_2Cl_2 (2×100 ml). The combined org. layers were washed with brine (60 ml), dried (Na_2SO_4), and concentrated to give 3-[4-(phenylmethoxy)phenylpropanal (13.01 g, 82%). Because of extensive oxidation of the aldehyde to the corresponding acid, we used it immediately for the next step.

Under N_2, 1.6M BuLi in hexane (46.87 ml, 75 mmol) was added to a soln. of the PMB ether of propargyl alcohol (=1-methoxy-4-[(prop-2-yn-1-yloxy)methyl]benzene; 13.2 g, 75 mmol) in dry THF (150 ml) at $-78°$, and the mixture was stirred for 30 min. Finally, a soln. of 3-[4-(phenylmethoxy)phenyl]propanal (12.0 g, 50.0 mmol) in dry THF (80 ml) was added and the mixture stirred for 3 h at $-78°$. After completion of the reaction, the mixture was quenched with sat. aq. NH_4Cl soln. (20 ml) and then extracted with AcOEt (2×100 ml), the extract dried (Na_2SO_4) and concentrated, and the residue purified by CC: pure **7** (1.74 g, 90%). ^{1}H-NMR (200 MHz): 7.37–7.12 (*m*, 7 H); 7.01 (*d*, $J = 8.0$, 2 H); 6.80–6.72 (*m*, 4 H); 4.90 (*s*, 2 H); 4.42 (*s*, 2 H); 4.29 (*t*, $J = 7.0$, 1 H); 4.06 (*s*, 2 H); 3.66 (*s*, 3 H); 3.29 (br. *s*, 1 H); 2.64 (*t*, $J = 7.0$, 2 H); 1.98–1.83 (*m*, 2 H). ^{13}C-NMR (50 MHz): 159.2; 156.9; 137.1; 133.4; 129.4; 129.2; 129.1; 128.3; 127.6; 127.2; 114.5; 113.3; 87.9; 80.6; 71.1; 69.6; 61.2; 56.9; 55.0; 39.6; 30.4. ESI-MS: 439 ($[M + Na]^+$). Anal. calc. for $C_{27}H_{28}O_4$ (416.51): C 77.89, H 6.73; found: C 77.94, H, 6.68.

6-[(4-Methoxyphenyl)methoxy]-1-[4-(phenylmethoxy)phenyl]hex-4-en-3-ol (**4**). To the suspension of $LiAlH_4$ (6.57 g, 173.07 mmol) in dry THF (60 ml) under N_2 at 0° was added **7** (18.0 g, 43.26 mmol) in dry THF (75 ml), and the mixture was refluxed for 3 h. After the completion of the reaction, the mixture was cooled to 0° and diluted with Et_2O, and the reaction was quenched with sat. aq. Na_2SO_4 soln. (20 ml). When the effervescence subsided, the mixture was filtered through a pad of *Celite* and the pad washed with hot AcOEt (90 ml). The filtrate was washed with brine (2×30 ml), dried (Na_2SO_4), and concentrated, and the residue purified by CC: **4** (14.10 g, 78%). $[\alpha]_D^{22} = -0.42$ ($c = 1.0$, $CHCl_3$). ^{1}H-NMR (200 MHz): 7.42–7.23 (*m*, 5 H); 7.20 (*d*, $J = 8.0$, 2 H); 7.05 (*d*, $J = 8.0$, 2 H); 6.82 (*d*, $J = 8.0$, 2 H); 6.80 (*d*, $J = 8.0$, 2 H); 5.74–5.68 (*m*, 2 H); 4.99 (*s*, 2 H); 4.40 (*s*, 2 H); 4.17–4.11 (*m*, 1 H); 4.10–4.03 (*m*, 1 H); 3.98–3.85 (*m*, 1 H); 3.78 (*s*, 3 H); 2.68–2.55 (*m*, 2 H); 1.82–1.72 (*m*, 2 H). ^{13}C-NMR (50 MHz): 159.1; 157.2; 137.2; 135.7; 134.1; 130.2; 129.4; 129.3; 128.5; 127.8; 127.4; 114.5; 113.8; 72.0; 71.8; 69.9; 69.7; 55.2; 38.9; 31.0. ESI-MS: 441 ($[M + Na]^+$). Anal. calc. for $C_{27}H_{30}O_4$ (418.53): C 77.51, H 7.18; found: C 77.58, H 7.15.

(1S)-1-{(2S,3S)-3-{[(4-Methoxyphenyl)methoxy]methyl}oxiran-2-yl}-3-[4-(phenylmethoxy)phenyl]-propan-1-ol (**8a**). To a suspension of powdered molecular sieves (4 Å; 3 g) in dry CH_2Cl_2 (140 ml), (^{i}PrO)$_4$Ti (5.66 ml,19.13 mmol), and (+)-DIPT (3.92 ml, 22.96 mmol) were added sequentially at $-20°$. After stirring for 30 min, **4** (16.0 g, 38.27 mmol) in dry CH_2Cl_2 (60 ml) was added, and stirring was continued for another 30 min at $-20°$. Then ^{t}BuOOH (3.50 ml, 21.05 mmol) was added and the stirring continued for another 5 h at $-20°$. After completion of the reaction, the mixture was quenched by the addition of H_2O (15 ml) and allowed to reach r.t. by stirring for 30 min. After recooling to 0°, 30% (*w*/*v*) aq. NaOH soln. (10 ml, sat. with brine) was added, and the mixture was stirred at 0° for 1 h. The mixture was extracted with Et_2O (2×40 ml), the combined org. extract washed with brine (2×20 ml), dried (Na_2SO_4), and concentrated, and the residue purified by CC: pure **9** (8.48 g, 53%) and **8a** (7.67 g, 46%). **8a**: $[\alpha]_D^{22} = -0.42$ ($c = 1.4$, $CHCl_3$).

Data of (3R)-6-[(4-Methoxyphenyl)methoxy]-1-[4-(phenylmethoxy)phenyl]hex-4-en-3-ol (**9**): ^{1}H-NMR (200 MHz): 7.42–7.28 (*m*, 5 H); 7.21 (*d*, $J = 8.0$, 2 H); 7.05 (*d*, $J = 8.0$, 2 H); 6.86 (*d*, $J = 8.0$, 2 H); 6.85 (*d*, $J = 8.0$, 2 H); 5.00 (*s*, 2 H); 4.50 (*d*, $J = 14.0$, 1 H); 4.41 (*d*, $J = 14.0$, 1 H); 3.79 (*s*, 3 H); 3.66–3.58 (*m*, 1 H); 3.48–3.39 (*m*, 1 H); 3.17–3.11 (*m*, 1 H); 3.10–3.02 (*m*, 1 H); 2.88–2.80 (*m*, 1 H);

2.77–2.58 (*m*, 2 H); 1.94 (br. *s*, 1 H); 1.90–1.69 (*m*, 2 H). ^{13}C-NMR (50 MHz): 159.7; 157.8; 137.9; 134.2; 130.0; 129.5; 129.3; 128.5; 127.9; 127.7; 115.0; 114.1; 73.1; 72.2; 70.0; 69.2; 58.3; 55.2; 35.5; 30.8. ESI-MS: 457 ($[M+Na]^+$). Anal. calc. for $C_{27}H_{30}O_5$ (434.52): C 74.65, H 6.91; found: C 74.78, H 6.88.

*(1*R*)-1-{(2*R*,3*R*)-3-{[(4-Methoxyphenyl)methoxy]methyl}oxiran-2-yl}-3-[4-(phenylmethoxy)phenyl]propan-1-ol* (**8**). As described for **8a**, with molecular sieves (4 Å, 2 g), CH_2Cl_2 (60 ml), $(^iPrO)_4Ti$ (5.66 ml, 19.11 mmol), (−)-DIPT (3.60 ml, 21.01 mmol), **9** (8 g, 19.13 mmol) instead of **4**, CH_2Cl_2 (50 ml), and ^{t}BuOOH (7.97 ml, 47.84 mmol, stirring for 6 h). Extraction with Et_2O (2 × 80 ml). CC afforded pure **8** (5.50 g, 66%). $[\alpha]_D^{22} = +0.40$ ($c = 1.0$, $CHCl_3$). Spectoscopic data: identical to those of **8a**.

*(2*S*,4*R*)-1-[(4-Methoxyphenyl)methoxy]-6-[4-(phenylmethoxy)phenyl]hexane-2,4-diol* (**10**). To a stirred soln. of **8** (5.0 g, 11.52 mmol) in dry THF (50 ml) under N_2 at 0° was added *Red-Al*® soln. in toluene (6.84 ml, 34.55 mmol of 70% *w*/*w*) and the mixture was stirred at r.t. for 2 h. After completion of the reaction, the mixture was quenched with sat. aq. NH_4Cl soln. (20 ml) and then extracted with AcOEt (100 ml). The combined org. extract was washed with brine, dried (Na_2SO_4), and concentrated and the residue purified by CC: pure **10** (3.61 g, 72%). $[\alpha]_D^{22} = +3.2$ ($c = 2.3$, $CHCl_3$). ^{1}H-NMR (200 MHz): 7.40–7.23 (*m*, 5 H); 7.19 (*d*, *J* = 8.0, 2 H); 7.05 (*d*, *J* = 8.0, 2 H); 6.82 (*d*, *J* = 8.0, 4 H); 5.01 (*s*, 2 H); 4.48 (*d*, *J* = 14, 1 H); 4.42 (*d*, *J* = 14.0, 1 H); 4.08–4.02 (*m*, 1 H); 3.88–3.81 (*m*, 1 H); 3.78 (*s*, 3 H); 3.41 (*dd*, *J* = 12.0, 4.0, 1 H); 3.31 (*dd*, *J* = 12.0, 7.0, 1 H); 2.75–2.69 (*m*, 1 H); 2.66–2.59 (*m*, 1 H); 1.80–1.49 (*m*, 4 H). ^{13}C-NMR (50 MHz): 159.9; 157.2; 138.2; 134.1; 130.0; 129.9; 129.8; 129.0; 128.1; 127.8; 113.9; 113.1; 77.8; 73.4; 71.9; 70.5; 55.8; 39.9; 39.3; 30.5. ESI-MS: 459 ($[M+Na]^+$). Anal. calc. for $C_{27}H_{32}O_5$ (436.54): C 74.31, H 7.34; found: C 74.22, H 7.39.

*(2*R*,4*S*)-1-[(4-Methoxyphenyl)methoxy]-6-[4-(phenylmethoxy)phenyl]hexane-2,4-diol* (**10a**). As described for **10**: **10a** (74%). $[\alpha]_D^{22} = -2.9$ ($c = 2.0$, $CHCl_3$). Spectroscopic data: identical to those of **10**.

*(4*S*,6*R*)-4-{[(4-Methoxyphenyl)methoxy]methyl}-2,2-dimethyl-6-{2-[4-(phenylmethoxy)phenyl]ethyl}-1,3-dioxane* (**2**). To **10** (3.5 g, 8.02 mmol) in dry CH_2Cl_2 (30 ml), 2,2-dimethoxypropane (20 ml) was added followed by the addition of a cat. amount of TsOH. The mixture was stirred for 30 min at r.t. After completion of the reaction, sat. aq. $NaHCO_3$ soln. (10 ml) was added, the mixture extracted with CH_2Cl_2 (3 × 30 ml), the combined org. layer dried (Na_2SO_4) and concentrated, and the residue purified by CC: pure **2** (3.63 g, 95%). $[\alpha]_D^{22} = +10.67$ ($c = 2.9$, $CHCl_3$). ^{1}H-NMR (200 MHz): 7.41–7.22 (*m*, 5 H); 7.15 (*d*, *J* = 8.0, 2 H); 7.02 (*d*, *J* = 8.0, 2 H); 6.79 (*d*, *J* = 8.0, 2 H); 6.77 (*d*, *J* = 8.0, 2 H); 5.00 (*s*, 2 H); 4.50 (*d*, *J* = 14.0, 1 H); 4.41 (*d*, *J* = 14.0, 1 H); 4.05–3.97 (*m*, 1 H); 3.78 (*s*, 3 H); 3.66–3.60 (*m*, 1 H); 3.42–3.30 (*m*, 2 H); 2.66–2.59 (*m*, 1 H); 2.57–2.51 (*m*, 1 H); 1.75–1.49 (*m*, 4 H); 1.42–1.34 (*m*, 3 H); 1.33 (*s*, 3 H). ^{13}C-NMR (50 MHz):159.2; 157.2; 137.3; 134.1; 129.4; 129.3; 129.2; 128.5; 127.7; 127.3; 114.9; 113.2; 100.3; 73.1; 72.8; 70.0; 66.9; 65.8; 55.0; 38.2; 35.2; 31.0; 25.1; 24.9. ESI-MS: 499 ($[M+Na]^+$). Anal. calc. for $C_{30}H_{36}O_5$ (476.60): C 75.63, H 7.56; found: C 75.74, H 7.53.

*(4*R*,6*S*)-4-{[(4-Methoxyphenyl)methoxy]methyl}-2,2-dimethyl-6-{2-[4-(phenylmethoxy)phenyl]ethyl}-1,3-dioxane* (**2a**). As described for **2**: **2a** (94%). $[\alpha]_D^{22} = -10.4$ ($c = 2.2$, $CHCl_3$). Spectroscopic data: identical to those of **2**.

*(4*S*,6*R*)-2,2-Dimethyl-6-{2-[4-(phenylmethoxy)phenyl]ethyl}-1,3-dioxan-4-methanol* (**11**). To a soln. of **2** (3.5 g, 7.35 mmol) in CH_2Cl_2/H_2O 19:1 was added DDQ (5.0 g, 22.02 mmol) at r.t. in portions. The mixture was stirred for 2 h at r.t. and filtered. The filtrate was concentrated and the residue purified by CC: **11** (1.64 g, 63.0%). $[\alpha]_D^{22} = +2.7$ ($c = 0.9$, $CHCl_3$). ^{1}H-NMR (200 MHz): 7.96 (*d*, *J* = 8.0, 2 H); 7.42–7.31 (*m*, 5 H); 6.99 (*d*, *J* = 8.0, 2 H); 5.12 (*s*, 2 H); 4.38–4.32 (*m*, 1 H); 4.16–4.10 (*m*, 1 H); 3.71–3.65 (*m*, 1 H); 3.58–3.51 (*m*, 1 H); 2.76–2.69 (*m*, 1 H); 2.37–2.29 (*m*, 1 H); 1.90–1.52 (*m*, 4 H); 1.26 (*s*, 6 H). ^{13}C-NMR (50 MHz): 156.4; 141.0; 129.7; 129.6; 128.8; 128.1; 127.8; 114.9; 96.5; 74.0; 70.2; 69.9; 40.2; 40.0; 31.7; 27.1; 26.8. ESI-MS: 379 ($[M+Na]^+$). Anal. calc. for $C_{22}H_{28}O_4$ (356.46): C 74.16, H 7.87; found: C 74.24, H 7.81.

*(4*R*,6*S*)-6-2,2-Dimethyl-6-{2-[4-(phenylmethoxy)phenyl]ethyl}-1,3-dioxan-4-methanol* (**11a**). As described for **11**: **11a** (64%). $[\alpha]_D^{22} = -2.9$ ($c = 0.9$, $CHCl_3$). Spectroscopic data: identical to those of **11**.

*(4*S*,6*R*)-2,2-Dimethyl-4-[(1*E*)-2-phenylethenyl]-6-{2-[4-(phenylmethoxy)phenyl]ethyl}-1,3-dioxane* (**12**). To a stirred soln. of oxalyl chloride (0.5 ml, 8.42 mmol) in dry CH_2Cl_2 (20 ml), DMSO (0.38 ml, 12.62 mmol) was added at −78°, and the mixture was stirred at −78° for 0.5 h. A soln. of **11** (1.5 g, 4.21 mmol) in CH_2Cl_2 (10 ml) was added at −78°, and the mixture was stirred for 1.5 h at −78° Et_3N

(0.74 ml, 20.99 mmol) was added at 0°, and the mixture was stirred for an additional 30 min. After completion of the reaction, the mixture was diluted with H_2O (5 ml) and extracted with CH_2Cl_2 (2×20 ml) and the extract washed with brine (20 ml), dried (Na_2SO_4), and concentrated to give *(4S,6R)-2,2-dimethyl-6-{2-[4-(phenylmethoxy)phenyl]ethyl}-1,3-dioxan-4-carboxaldehyde* (1.3 g, 80%). Because of extensive oxidation of the aldehyde to the corresponding acid, we used it immediately for the next step.

To a soln. containing benzyltriphenylphosphonium bromide (1.5 g, 5.48 mmol) in dry THF (5 ml) was added dropwise 1.6M BuLi in hexane (2.52 ml, 4.03 mmol) *via* a syringe under N_2 at r.t. After stirring for 10 min, the preceding aldehyde (1.3 g, 3.67 mmol), diluted in dry THF, was dropwise added to the red-orange *Wittig* reagent. The mixture was stirred for 4 h at r.t. to afford a yellow soln. with a white precipitate. Then CH_2Cl_2 and sat. NH_4Cl soln. were added until pH 6. The aq. layer was extracted with CH_2Cl_2, the combined org. layer dried ($MgSO_4$) and concentrated, and the residue purified by CC: **12** (1.2 g, 78%). $[\alpha]_D^{22} = +5.6$ ($c = 0.9$, $CHCl_3$). ^{1}H-NMR (200 MHz): 7.99 (*d*, $J = 8.0$, 2 H); 7.53–7.48 (*m*, 4 H); 7.41–7.29 (*m*, 6 H); 7.10 (*d*, $J = 8.0$, 2 H); 6.88 (*dd*, $J = 14.0, 7.0$, 1 H); 6.28 (*d*, $J = 14.0$, 1 H); 5.29 (*s*, 2 H); 4.65–4.58 (*m*, 1 H); 3.72–3.65 (*m*, 1 H); 2.63–2.56 (*m*, 2 H); 1.73–1.49 (*m*, 4 H); 1.42 (*s*, 6 H). ^{13}C-NMR (50 MHz): 157.0; 141.8; 137.4; 134.7; 130.2; 129.8; 129.7; 128.9; 128.2; 128.0; 114.9; 96.5; 70.2; 68.8; 68.5; 39.8; 39.4; 31.6; 31.0. ESI-MS: 451 ($[M + Na]^+$). Anal. calc. for $C_{29}H_{32}O_3$ (428.56): C 81.31, H 7.48; found: C 81.25, H 7.54.

(4R,6S)-2,2-Dimethyl-4-[(1E)-2-phenylethenyl]-6-{2-[4-(phenylmethoxy)phenyl]ethyl}-1,3-dioxane (**12a**). As described for **12**: **12a** (75%). $[\alpha]_D^{22} = -5.2$ ($c = 1.5$, $CHCl_3$). Spectroscopic data: identical to those of **12**.

(3R,5R)-1-(4-Hydroxyphenyl)-7-phenylheptane-3,5-diol (**1**). A soln. of **12** (200 mg, 2.80 mmol) in MeOH (5 ml) in the presence of TsOH (10 mg) was stirred for 3 h. After the completion of the reaction, concentration afforded the crude diol. This residue of unsaturated diol in MeOH (15 ml) in the presence of a cat. amount of Pd/C was stirred for 2 h under H_2 (1 atm). After filtration and concentration, the crude residue was purified by CC: **1** (82 mg, 60%). $[\alpha]_D^{22} = +9.2$ ($c = 1.1$, $CHCl_3$); ^{1}H-NMR (200 MHz): 7.26–7.12 (*m*, 5 H); 6.93 (*d*, $J = 8.0$, 2 H); 6.71 (*d*, $J = 8.0$, 2 H); 4.02–3.89 (*m*, 2 H); 2.81–2.50 (*m*, 4 H); 1.89–1.69 (*m*, 4 H); 1.60 (*t*, $J = 6.0$, 2 H). ^{13}C-NMR (50 MHz): 154.2; 142.0; 133.4; 129.4; 128.4; 128.3; 126.0; 115.5; 69.0; 68.9; 42.4; 39.1; 39.0; 32.1; 31.2. ESI-MS: 301 ($[M + H]^+$). Anal. calc. for $C_{19}H_{24}O_3$ (300.39): C 76.00, H 8.00; found: C 76.18, H 8.06.

(3S,5S)-1-(4-Hydroxyphenyl)-7-phenylheptane-3,5-diol (**1a**). As described for **1**: **1a** (63%). $[\alpha]_D^{22} = -10.2$ ($c = 1.3$, $CHCl_3$). Spectroscopic data: identical to those of **1**.

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