Enantioselective Synthesis of Flavan-3-ols Using a Mitsunobu Cyclization

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Abstract: The synthesis of four flavan-3-ols with different substitution patterns and electron densities has been achieved in high stereo- and regioselectivity by a one-step Mitsunobu reaction from the corresponding diols, which were prepared by enantioselective Sharpless dihydroxylation of suitable olefins. The six-membered flavan-3-ols were the only cyclization products and the theoretically possible formation of five-membered rings during the Mitsunobu cyclization was not observed. The flavanols are important starting materials for the synthesis of dimers such as the procyanidins or other coupling products such as the flavan part of the potent DNA polymerase β inhibitor myristinin A. The enantioselectivities of both the Sharpless dihydroxylation and the Mitsunobu cyclization steps were monitored by chiral HPLC.

Key words: myristinin A, Sharpless dihydroxylation, flavanol synthesis, Mitsunobu reaction

Polyphenols are ingredients of agricultural products such as wine, tea, fruit, vegetables and herbal medicines, and play an important role due to their multitude of biological functions.[1] The specific interactions of polyphenols with biomolecules such as proteins have stimulated the search for new pharmaceutical entities derived from polyphenolic compounds.[2] Among them, flavanoids are considered to be particularly important secondary metabolites due to their antibacterial,[3] anticancer,[4] antioxidant[5] and antiviral[6] properties. Flavan-3-ols such as (+)-catechin (**1**) or their dimers such as procyanidin B3 (**2**; Figure 1) occur in fresh fruits, tea, cocoa and chocolate,[7] and have been shown to have beneficial effects on health.[8] Other kinds of bioactivity were recently discovered in the naturally occurring flavanoid myristinin A (**3**; Figure 1), which is a DNA polymerase β inhibitor capable of blocking the repair of DNA damage induced by clinically used damaging agents and thereby potentiates their cytotoxicity.[9–13]

The key step in many syntheses of flavan-3-ols such as **13** is the Sharpless dihydroxylation[14] of diaryl propenes **10** to the diols **11**.[12,15] In connection with an improvement of the myristinin A synthesis,[12] we now report on a new and shorter variation of the flavan-3-ol synthesis, using a Mitsunobu reaction for the one-step cyclization of phenolic diol precursors **12**, as outlined in Scheme 1. In order to probe the generality of this one-step Mitsunobu cyclization, we conducted the reaction with four olefins **10a–d** with different substitution patterns and electron densities,

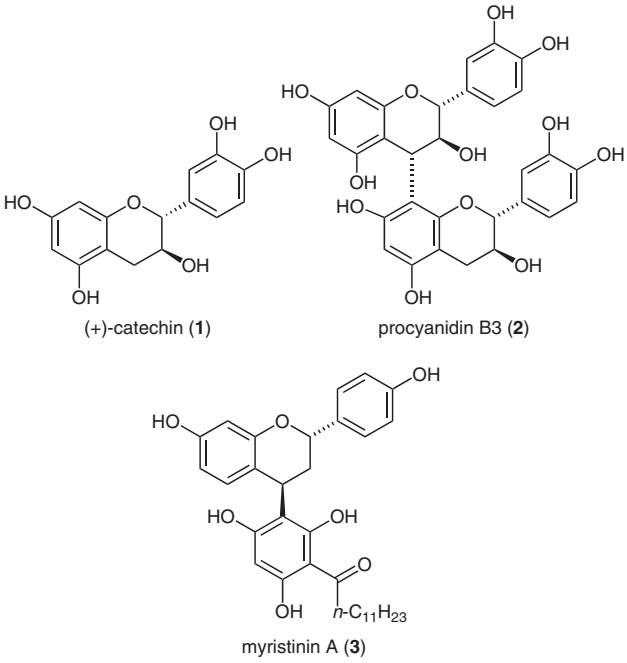

Figure 1 Structures of (+)-catechin (**1**), procyanidin B3 (**2**), and myristinin A (**3**)

ranging from one to five oxygen substituents (Scheme 1). The flavan-3-ols thus prepared generally serve as precursors in procyanidin synthesis.[16]

We started with the formation of chalcones **6a–d** by Claisen–Schmidt condensation of 2-hydroxyacetophenones **4a–d** with benzaldehydes **5a–d** to afford chalcones **6a–d** in nearly quantitative yields (Scheme 1). Deoxygenation of the ketones **6a–d** to the olefins **7a–d** was performed by employing ethyl chloroformate and sodium borohydride in a two-step sequence.[12,17] This procedure is shorter than the two-step hydrogenation–elimination procedure used by van Rensburg et al.[15] However, the flavenes **8b–d** and, in the case of **6d**, the saturated phenol **9d**, were formed as side products in this reduction. To improve the yield of the deoxygenation reaction, the temperature dependency of the reduction was studied carefully. When the borohydride reduction was performed at 0–5 °C, the formation of the flavenes was almost entirely avoided and the substituted alkenes **7a–d** were isolated in improved yields of 57–86% (Starck et al.[12] produced **7b** in 74% yield).

The phenolic hydroxy group of the substituted propenes **7a–d** was then protected with the *tert*-butyldimethylsilyl

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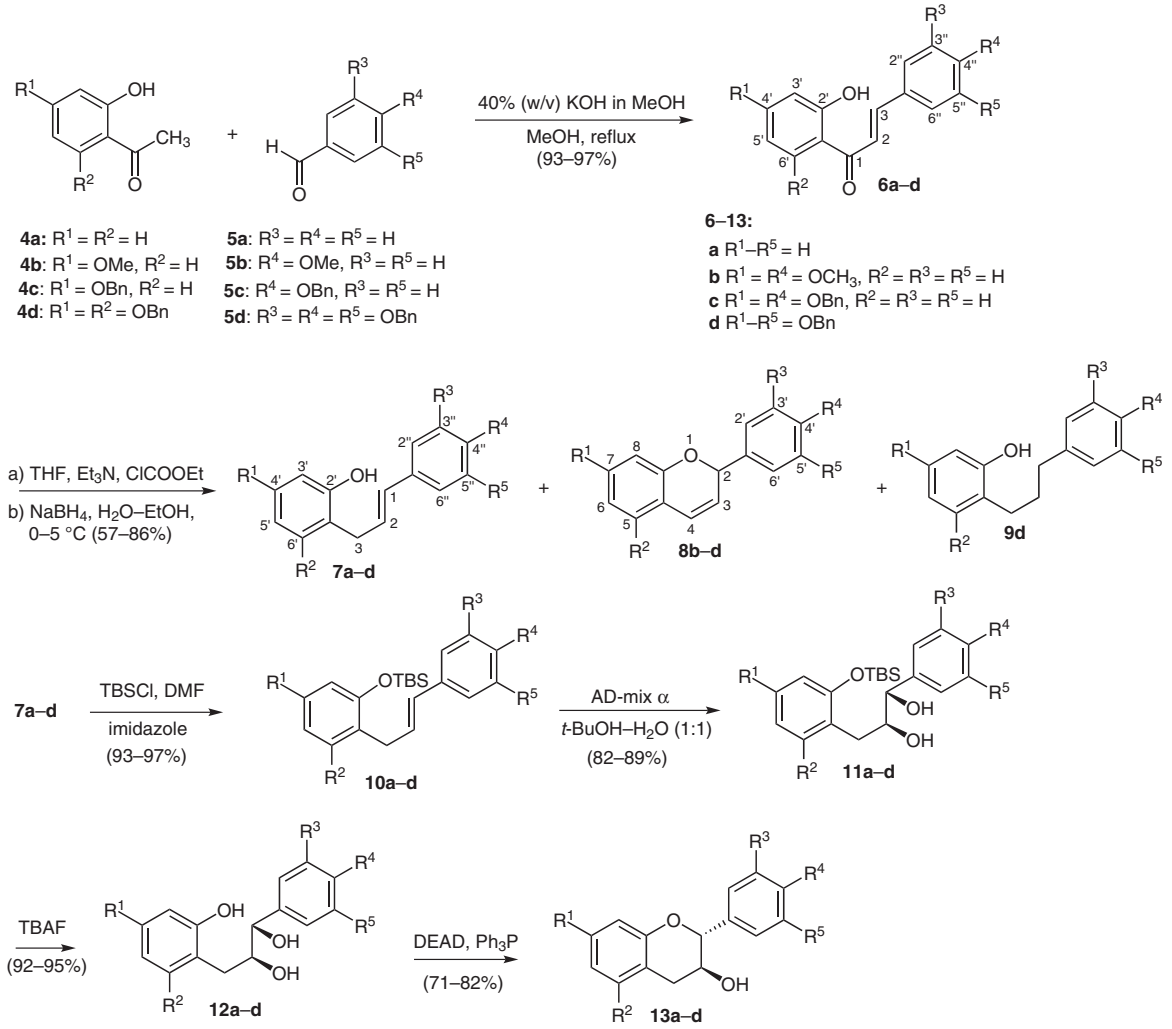

Scheme 1 Improved synthesis of flavan-3-ols **13a–d** via Mitsunobu reaction of **12a–d**

(TBS) group to afford the TBS-protected substituted 1,3-diphenylpropenes **10a–d** in almost quantitative yields. Asymmetric dihydroxylation of the diphenylpropenes **10a–d** proceeded smoothly using AD-mix α[14] in a mixture of *tert*-butyl alcohol and water (1:1), to afford the TBS-protected diols **11a–d**. In the next step, instead of forming an orthoester as described, for example, by Wan et al.[18] or Hecht and co-workers,[12] we investigated whether it was possible to achieve a direct cyclization using either acidic conditions or, preferably, S_N2-type Mitsunobu conditions.[19] Therefore, the TBS-ether of diols **11a–d** were cleaved using tetrabutylammonium fluoride (TBAF) to afford the triols **12a–d** with a free phenolic hydroxy group. The cyclization of these triols was first tried using methanolic hydrogen chloride.[15] However, not unexpectedly, acidic treatment resulted in formation of the racemic flavan-3-ols. Next, the standard S_N2-type Mitsunobu reaction conditions[17] were employed in an attempt to convert the triols **12a–d** in one step into the enantiomerically pure flavan-3-ols **13a–d**. In the first experiment, the flavanol **13b** was not only formed in excellent yield (77%) and in the expected 2,3-*trans*-configuration, but remarkably, no five-membered cyclization products were observed. The observed optical rotation also compared favorably to that reported in the literature[12] after additional protection and deprotection steps {**13b**: $[\alpha]_D^{20}$ –17.4 (*c* 1.11, $CHCl_3$) [Lit.[12] –16.1 (*c* 1.11, $CHCl_3$)]}. The optical rotation also confirmed the presence of the 2*R*,3*S*-isomer, leading to the natural configuration of myristinin A (**3**).[13]

In order to confirm the enantioselectivity indicated by the specific optical rotation, the products **11b** and **13a–d** were subjected to chiral HPLC. The two crucial steps: the enantioselective dihydroxylation of olefins **10a–d** to the diols **11a–d**, and the Mitsunobu reaction of the phenols **12a–d** to the flavanols **13a–d**, were analyzed by chiral HPLC. The results for one example (**13b**) are shown in Figure 2 and relevant results for compounds **13a–d** are given in the experimental section. The enantiomeric ratio found after the enantioselective Sharpless dihydroxylation of **11b** was 96.8:3.2 [93.6% ee; Figure 2 (left)]. After cleavage of the TBS-ether of **11b** to give phenol **12b** and purification by flash chromatography, the enantiomers formed in the one-step Mitsunobu reaction were found in a ratio of 98.8:1.2 [97.7% ee; Figure 2 (right)]. The slight increase in ee may be due to the purification step.

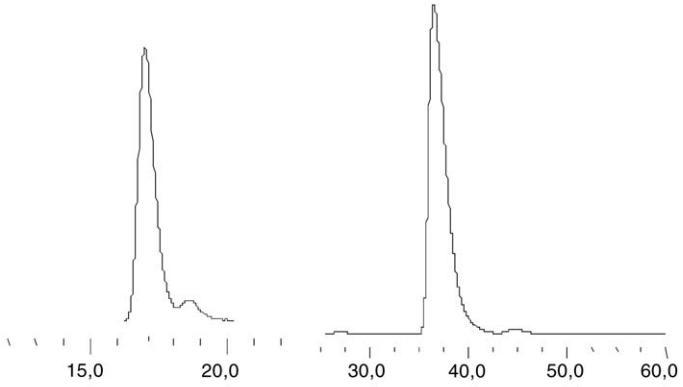

Figure 2 HPLC traces showing the enantiomeric excess for diol **11b** (left) and flavanol **13b** (right); for details, see the experimental section and text

In conclusion, the number of reaction steps required for the synthesis of enantiomerically enriched flavan-3-ols **13a–d** was reduced by omitting the protection (and later deprotection) of the diol **12a–d** and instead employing a direct Mitsunobu cyclization of **12a–d** to selectively afford the 2,3-*trans*-flavan-3-ols (**13a–d**) in excellent yield and enantioselectivity measured by chiral HPLC. This strategy may prove to be generally useful in flavonoid and catechin synthesis.

TLC was performed on precoated TLC plates (silica gel). Melting points were measured with a Gallenkamp apparatus and are not corrected. NMR spectra were recorded on a Bruker Avance 500 instrument at 500.13 MHz (^{1}H) and 125.76 MHz (^{13}C). Chemical shifts (δ) for ^{1}H and ^{13}C NMR spectra are reported in ppm downfield from TMS as an internal standard. Optical rotations were measured at 25 °C on a Perkin–Elmer Polarimeter 241. Mass spectra were recorded using a Finnigan MAT 8430 spectrometer in the electron-impact mode at 70 eV and chemical ionization, and are reported as *m*/*z* values and relative abundances. The infrared spectra were recorded using a Nicolet 510 P FT-IR Spectrometer. HPLC system: Summit (Dionex); pump: P 580 A (Dionex); detector: UVD 170S; autosampler: ASI 100 (Dionex); column oven: STH 585 (Dionex). Petroleum ether (PE), where used, was the fraction boiling in the range 40–60 °C.

HPLC Conditions for Compounds 11b and 13a–d

Retention times for the enantiomers were first determined on racemic mixtures.

11b: Column: EC 250 × 4.6 mm NUCLEOCEL Alpha RP-S; MeCN–H_2O, 80:20; 0.5 mL/min; 25 °C; detection: 230 nm; pressure: 35 bar; injection volume: 3 μL. Retention time for enantiomer 1: 16.84 min; enantiomer 2: 18.48 min; integration for enantiomer 1: 42.283; integration for enantiomer 2: 1.3788.

13c: As described for **11b**, except pressure: 70 bar. Retention time for enantiomer 1: 36.44 min; enantiomer 2: 44.69 min; integration for enantiomer 1: 932.481; integration for enantiomer 2: 10.895. Identical conditions were used for the analysis of **13a**, **13b** and **13d**.

Preparation of Chalcones 6a and 6b; General Procedure

A mixture of equimolar amounts of 2′-hydroxyacetophenones **4a** or **4b** (44.10 mmol) and benzaldehydes **5a** or **5b** (44.10 mmol) in EtOH (40 mL) was warmed to 50 °C, then aq NaOH (50%, 20 mL) was added dropwise to the reaction mixture during 30 min. The reaction mixture was further stirred for 5 h at 50 °C and then kept at r.t. for 24 h. Yellow precipitates were formed and the reaction mixture was diluted with ice-cold H_2O (150 mL) until the yellow solid dissolved. The reaction mixture was acidified by addition of dilute HCl (20 mL), maintaining the temperature at 0 °C. The precipitates formed were filtered off, dried, and crystallized (aq EtOH) to give yellow needles of 2′-hydroxychalcones **6a** and **6b**.

2′-Hydroxychalcone (6a)[20,21]

Yield: 93%; yellow needles; mp 87–88 °C (Lit.[19,20] 88–89 °C).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.95–7.99 (m, 10 H, 2-H, ArH), 8.01 (d, *J* = 15.5 Hz, 1 H, 3-H), 13.9 (s, 1 H, 2′-OH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 119.0 (3′-C), 119.2 (C-2), 120.4, 120.5, 129.0, 129.4, 130.0, 131.3, 135.0, 136.8 (Ar), 145.9 (C-3), 164.0 (C-2′), 194.1 (C-1).

4,4′-Dimethoxy-2′-hydroxychalcone (6b)[22,23]

Yield: 91%; yellow needles; mp 91–93 °C (Lit.[21,22] 89–91 °C).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.88 (s, 6 H, OCH_3), 6.49 (s, 1 H, 3′-H), 6.53 (d, *J* = 8.8 Hz, 1 H, 5′-H), 6.98 (d, *J* = 8.8 Hz, 2 H, 3″-H, 5″-H), 7.51 (d, *J* = 15.6 Hz, 1 H, 2-H), 7.67 (d, *J* = 8.8 Hz, 2 H, 2″-H, 6″-H), 7.87 (d, *J* = 15.9 Hz, 1 H, 3-H), 7.97 (d, *J* = 8.8 Hz, 1 H, 6′-H), 13.61 (s, 1 H, 2′-OH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 55.8 (OCH_3), 55.9 (OCH_3), 101.4 (C-3′), 108.0 (C-5′), 114.5 (C-3), 114.8 (C-1′), 118.1 (C-2), 127.9 (C-2″), 130.7 (C-1″), 131.5 (C-6′), 144.6 (C-3), 162.2 (C-4″), 166.4 (C-2′), 167.0 (C-4′), 192.2 (C-1).

(*E*)-1-(4-Benzyloxy-2-hydroxyphenyl)-3-(4-benzyloxyphenyl)propenone (6c)[12]

Yield: 97%; mp 136–137 °C (Lit.[12] 140–142 °C).

(*E*)-1-[2,4-Bis(benzyloxy)-6-hydroxyphenyl]-3-[3,4,5-tris(benzyloxy)phenyl]propenone (6d)[24]

To a stirred solution of 2,4-bis(benzyloxy)-6-hydroxyacetophenone (**4d**; 2.00 g, 5.70 mmol) in DMF (34 mL), NaH (60% in oil, 1.00 g, 25.00 mmol) was added. The mixture was stirred for 15 min at 0 °C, then a solution of 3,4,5-tris(benzyloxy)benzaldehyde (**5d**; 2.60 g, 6.12 mmol) in DMF (15 mL) was added dropwise over a period of 25 min at 0 °C. After stirring for 5 h at 0 °C, the reaction was quenched with H_2O (2 mL). The solvent was evaporated under vacuum, and the residue was dissolved in CH_2Cl_2 (200 mL). The organic layer was washed with H_2O (50 mL) and brine (50 mL), then the extract was concentrated and the residue was crystallized (Et_2O) to give **6d**.

Yield: 3.1 g (72%); yellow crystals; mp 148–149 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.89 (s, 4 H, OCH_2Ph), 5.13 (s, 6 H, 2 × OCH_2Ph), 6.23 (d, *J* = 2.4 Hz, 1 H, 3′-H), 6.31 (d, *J* = 2.4

Hz, 1 H, 5′-H), 6.70 (s, 2 H, 2″-H, 6″-H), 7.16–7.49 (m, 25 H, ArH), 7.64 (d, *J* = 15.3 Hz, 1 H, 2-H), 7.86 (d, *J* = 14.7 Hz, 1 H, 3-H), 14.32 (s, 1 H, 6′-OH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 70.7 (4-, 4′-OCH_2Ph), 71.4, (3-, 5-, 2′-OCH_2Ph), 95.5 (C-3′, C-5′), 107.2 (C-1′), 108.6 (C-5′), 114.4 (C-2″), 121.4 (C-6″), 125.9 (C-2), 127.4, 127.8, 128.1, 128.3, 128.6, 128.7, 128.8, 128.9, 129.0, 129.1, 129.2 (Ar), 131.0 (C-1″), 136.1, 136.2, 137.2, 138.0, 140, 7 (Ar), 142.7 (C-3), 153.2 (C-3″), 150.8 (C-4″), 161.9 (C-6′), 165.6 (C-4′), 168.5 (C-2′), 193.0 (C-1).

MS (EI): *m*/*z* (%) = 754 (1) [M$^+$], 738 (1), 663 (4), 573 (1), 555 (1), 440 (2), 436 (2), 333 (4), 306 (5), 243 (4), 181 (14), 91 (100), 44 (12).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{50}H_{42}O_7$: 754.29303; found: 754.29604.

Deoxygenation of Chalcones; General Procedure

Et_3N (1.81 g, 2.50 mL, 17.90 mmol) was added to a solution containing the corresponding chalcones **6a–d** (13.79 mmol) in anhydrous THF (50 mL). The reaction mixture was cooled to 0 °C in an ice bath and stirred for 15 min. $ClCO_2Et$ (1.79 g, 1.58 mL, 16.50 mmol) was then added dropwise over a period of 20 min. After stirring at 0 °C for 1.5 h, the mixture was filtered and the precipitate obtained was washed with THF (2 × 20 mL). The filtrate, which contained the phenolic carbonate, was then added dropwise at 0 °C over a period of 45 min to a solution of $NaBH_4$ (2.00 g, 52.87 mmol) in H_2O (80 mL). The reaction mixture was stirred at 0–5 °C overnight, then acidified with 1N HCl, diluted with H_2O (200 mL), and extracted with Et_2O (3 × 50 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column (EtOAc–PE, 1:9) to afford the substituted propenes **7a–d**.

(*E*)-3-(2-Hydroxyphenyl)-1-phenylpropene (7a)[25]

Yield: 84%; colorless oil.

IR (film): 3532, 3025, 2900, 1592, 1454, 1349, 1211 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.68 (d, *J* = 5.6 Hz, 2 H, 3-H), 6.53 (dt, *J* = 15.9, 6.5 Hz, 1 H, 2-H), 6.62 (d, *J* = 15.9 Hz, 1 H, 1-H), 6.92 (dd, *J* = 8.0, 1.1 Hz, 1 H, 3′-H), 7.06 (ddd, *J* = 8.0, 7.4, 1.1 Hz, 1 H, 4′-H), 7.26 (ddd, *J* = 7.4, 8.2, 1.5 Hz, 1 H, 5′-H), 7.23–7.49 (m, 6 H, Ar).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 34.0 (C-3), 115.0, 116.0, 121.1, 124.9, 125.5, 126.2, 127.1, 127.4, 127.8, 127.9, 128.4, 129.0, 130.4 (Ar, C-1, C-2), 152.7 (C-2′).

MS (EI): *m*/*z* (%) = 210 (100) [M$^+$], 165 (20), 130 (40), 91 (55), 58 (48), 29 (18).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{15}H_{14}O$: 210.10446; found: 210.10455.

(*E*)-1-(4-Methoxyphenyl)-3-(4-methoxy-2-hydroxyphenyl)propene (7b)[26]

Yield: 82%; mp 97–98 °C (Lit.[26] 99–100 °C).

IR (KBr): 3436, 2929, 1608, 1511, 1440, 1398, 1220, 833 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.50 (d, *J* = 5.1 Hz, 2 H, 3-H), 3.77 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 5.41 (br s, 1 H, OH), 6.26 (dt, *J* = 15.8, 6.5 Hz, 1 H, 2-H), 6.44–6.51 (m, 3 H, 3′-H, 5′-H, 1-H), 6.86 (dt, *J* = 8.6, 2.1 Hz, 2 H, 3″-H, 5″-H), 7.07 (d, *J* = 8.4 Hz, 1 H, 6′-H), 7.31 (dt, *J* = 8.6, 2.1 Hz, 2 H, 2″-H, 6″-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 34.6 (C-3), 55.32 (OCH_3), 55.35 (OCH_3), 102.1 (C-3′), 106.3 (C-5′), 114.3 (C-5″), 118.2 (C-1′), 126.2, 127.3, 129.3, 129.5, 120.0, 130.5, 130.8 (Ar, C-1, C-2), 155.0 (C-2′), 159.0 (C-4′), 159.5 (C-4″).

MS (EI): *m*/*z* (%) = 270 (100) [M$^+$], 226 (20), 210 (98), 167 (18), 134 (90), 91 (62), 57 (24), 29 (5).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{17}H_{18}O_3$: 270.12561; found: 270.12566.

(±)-7-Methoxy-2-(4-methoxyphenyl)-2*H*-chromene (8b)[26]

Reduction at r.t. afforded the racemic cyclization product **8b** in addition to the desired olefin **7b**.

Yield: 11%; yellow solid; mp 81–82 °C (Lit.[26] 82–83 °C).

IR (film): 2931, 2838, 1610, 1511, 1251, 1170, 1112, 1025.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.78 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 5.71 (dd, *J* = 9.5, 3.2 Hz, 1 H, 3-H), 5.87 (br s, 1 H, 2-H), 6.40 (br s, 1 H, 8-H), 6.49 (dd, *J* = 9.5, 1.8 Hz, 1 H, 4-H), 6.56 (d, *J* = 8.3 Hz, 1 H, 6-H), 6.91–7.03 (m, 3 H, 5-H, 3′-H, 5′-H), 7.39–7.44 (m, 2 H, 2′-H, 6′-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 55.6 (OCH_3), 81.3 (C-2), 102.2 (C-8), 107.3 (C-6), 114.4 (C-4a), 115.1 (C-3′), 122.3 (C-4), 124.0 (C-3), 127.5 (C-2′), 129.0 (C-6), 133.4 (C-1′), 159.3 (C-8a), 160.1 (C-4′), 161.2 (C-7).

MS (EI, 70 eV): *m*/*z* (%) = 268 (100) [M$^+$], 237 (66), 224 (26), 181 (12), 161 (78), 134 (60), 89 (12), 77 (13), 51 (6), 28 (21).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{17}H_{16}O_3$: 268.10995; found: 268.10995.

(*E*)-1-(4-Benzyloxyphenyl)-3-(4-benzyloxy-2-hydroxyphenyl)propene (7c)[12]

Yield: 86%; mp 106–107 °C.

(±)-7-Benzyloxy-2-[4-benzyloxyphenyl]-2*H*-chromene (8c)

Reduction at r.t. afforded the racemic cyclization product **8c** in addition to the desired olefin **7c**.

Yield: 19%; yellow solid; mp 76–77 °C.

IR (KBr): 3027, 2888, 1610, 1508, 1378, 1166, 1112, 1027 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.09 (s, 2 H, OCH_2Ph), 5.13 (s, 2 H, OCH_2Ph), 5.81 (dd, *J* = 9.8, 3.7 Hz, 1 H, 3-H), 5.97 (br s, 1 H, 2-H), 6.62 (br s, 1 H, 8-H), 6.68 (dd, *J* = 9.8, 1.9 Hz, 1 H, 4-H), 6.75 (d, *J* = 8.3 Hz, 1 H, 6-H), 7.05–7.20 (overlapped, 3 H, 5-H, 3′-H, 5′-H), 7.41–7.72 (overlapped, 12 H, 2′-H, 6′-H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 70.5 (OCH_2Ph), 70.9 (OCH_2Ph), 82.1 (C-2), 103.3 (C-8), 108.3 (C-6), 115.3 (C-4a), 115.4 (C-3′), 115.5 (C-4), 122.6 (C-3), 124.2 (C-2′), 127.8, 128.0, 128.4, 129.0, 129.1, 129.2, 129.9, 131.1, 133.8, 137.4, 137.4 (Ar), 154.9 (C-4′), 159.4 (C-8a), 160.6 (C-7).

MS (EI): *m*/*z* (%) = 420 (46) [M$^+$], 362 (5), 329 (38), 300 (60), 228 (54), 180 (12), 150 (14), 91 (100), 65 (62), 29 (28).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{29}H_{24}O_3$: 420.17255; found: 420.17254.

(*E*)-1-[3,4,5-Tris(benzyloxy)phenyl]-3-[2,4-bis(benzyloxy)-6-hydroxyphenyl]propene (7d)[27]

Yield: 57%; mp 129–131 °C (no mp or spectral data given in Lit.[27]).

IR (film): 3492, 3029, 1621, 1506, 1374, 1116, 997 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.62 (d, *J* = 5.4 Hz, 2 H, CH_2), 5.03 (s, 2 H, 4′-OCH_2Ph), 5.10 (s, 4 H, 3″-H, 5″-OCH_2Ph), 5.11 (s, 4 H, 4″-H, 2′-OCH_2Ph), 6.15–6.38 (m, 4 H, 1-H, 2-H, 3′-H, 5′-H), 6.70 (s, 2 H, 2″-H, 6″-H), 7.31–7.55 (m, 25 H, ArH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 32.0 (CH_2), 70.5 (4′-OCH_2Ph), 70.7 (4″-OCH_2Ph), 71.7 (3″-H, 5″-H, 2′-OCH_2Ph), 94.1 (C-3′), 95.5 (C-5′), 106.4 (C-2″, C-6″), 107.4 (C-1′), 127.3 (C-2), 127.7, 127.9, 127.9, 128.0, 128.1, 128.2, 128.4, 128.5, 128.9, 128.9, 128.8, 128.9, 129.0, 129.6, 130.6 (C-1), 133.3, 137.3, 137.6, 137.8 (Ar), 138.2 (C-4″), 153.0 (C-5″), 153.3 (C-3″), 156.0 (C-OH), 158.4 (C-4′), 159.2 (C-2′).

MS (EI): *m*/*z* (%) = 740 (1) [M$^+$], 650 (2), 634 (2), 560 (1), 541 (1), 467 (1), 422 (2), 396 (1), 306 (7), 227 (2), 181 (7), 108 (4), 91 (100), 39 (5).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{50}H_{44}O_6$: 740.31378; found: 740.31219.

5,7-Dibenzyloxy-2-[3,4,5-tris(benzyloxy)phenyl]-2*H*-chromene (8d)[24]

Reduction at r.t. afforded the racemic cyclization product **8d** and saturated **9d** in addition to the desired olefin **7d**.

Yield: 25%; yellow solid; mp 105–107 °C (no mp given in Lit.[27]).

IR (film): 3124, 3021, 1614, 1376, 1182, 782, 732 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.99 (s, 2 H, OCH_2Ph), 5.03 (s, 2 H, OCH_2Ph), 5.05 (s, 4 H, OCH_2Ph), 5.09 (s, 2 H, OCH_2Ph), 5.53 (dd, *J* = 9.95, 3.29 Hz, 1 H, 3-H), 5.72 (dd, *J* = 3.2, 2.0, 5 Hz, 1 H, 2-H), 6.13 (d, *J* = 2.2 Hz, 1 H, H-8), 6.20 (d, *J* = 2.17 Hz, 1 H, H-6), 6.78 (s, 2 H, 2′-H, 6′-H), 6.86 (dd, *J* = 9.86, 1.57 Hz, 1 H, 4-H), 7.25–7.41 (m, 25 H, ArH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 70.1 (OCH_2Ph), 70.3 (OCH_2Ph), 70.7 (OCH_2Ph), 71.3 (OCH_2Ph), 71.3 (OCH_2Ph), 77.0 (C-2), 93.9 (C-6), 95.2 (C-8), 105.0 (4a), 114.3 (C-2′, C-6′), 114.9 (C-5′), 118.9 (C-4), 119.7 (C-3), 120.5, 127.2, 127.3, 127.4, 127.5, 127.7, 127.9, 128.0, 128.4, 128.5 (Ar), 134.2 (C-1′), 136.7, 136.9, 137.2, 137.3 (Ar), 149.1 (C-3′), 149.2 (C-4′), 154.9 (C-8a), 155.3 (C-5), 160.3 (C-7).

MS (EI): *m*/*z* (%) = 738 (6) [M$^+$], 647 (24), 557 (1), 465 (8), 396 (2), 306 (8), 229 (1), 181 (12), 91 (100), 65 (7).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{50}H_{42}O_6$: 738.29816; found: 738.29721.

1-[3,4,5-Tris(benzyloxy)phenyl]-3-[2,4-bis(benzyloxy)-6-hydroxyphenyl]propane (9d)

Yield: 7%; white solid; mp 102–103 °C.

IR (film): 3318, 2923, 1623, 1434, 1274, 1128, 871 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.93 (m, 2 H, 2-CH_2), 2.68 (t, *J* = 7.5 Hz, 2 H, 3-CH_2), 2.79 (t, *J* = 7.5 Hz, 2 H, 1-CH_2), 5.09 (s, 2 H, OCH_2Ph), 5.12 (s, 4 H, OCH_2Ph), 5.14 (s, 4 H, OCH_2Ph), 6.21 (d, *J* = 2.0 Hz, 1 H, 5′-H), 6.39 (d, *J* = 2.0 Hz, 1 H, 6-H), 6.59 (s, 2 H, 2′-H, 6′-H), 7.30–7.50 (m, 25 H, ArH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.7 (CH_2), 26.8 (CH_2), 31.9 (CH_2), 70.5 (4″-, 4′-OCH_2Ph), 71.7 (3″-, 5″-, 2′-OCH_2Ph), 94.3 (C-3′), 97.7 (C-5′), 108.6 (C-2′, C-4′), 115.0 (C-1′), 127.3, 127.8, 127.9, 127.9, 128.1, 128.2, 128.4, 128.5, 128.7, 128.8, 128.8, 128.9, 128.9, 129.0, 129.6, 137.0, 133.6, 137.8, 137.9, 137.9, 138.6, 139.3 (Ar, C-4″), 152.8 (C-5″, C-3″), 154.7 (C-6′), 158.1 (C-2′), 158.4 (C-4′).

MS (EI): *m*/*z* (%) = 742 (2) [M$^+$], 651 (20), 561 (1), 469 (1), 409 (2), 319 (15), 229 (7), 181 (18), 91 (100), 44 (4).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{50}H_{46}O_6$: 742.32947; found: 742.32957.

TBS Protection; General Procedure

To a solution containing the substituted propenes **7a–d** (4.75 mmol) in anhydrous DMF (30 mL), was added imidazole (960 mg, 14.10 mmol, 3 equiv). The solution was stirred at r.t. for 15 min, then TBDMSCl (1.10 g, 7.30 mmol, 1.5 equiv) was added. The reaction mixture was stirred overnight at r.t., then poured into H_2O (100 mL) and extracted with EtOAc (3 × 50 mL). The combined organic phase was dried over $MgSO_4$, concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (EtOAc–PE, 1:9) to afford the corresponding TBS-ethers **10a–d**.

(*E*)-1-Phenyl-3-[2-(*tert*-butyldimethylsilyloxy)phenyl]propene (10a)

Yield: 95%; colorless oil.

IR (film): 3060, 2929, 1614, 1598, 1490, 1255 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.39 [s, 6 H, $Si(CH_3)_2$], 1.17 [s, 9 H, $SiC(CH_3)_3$], 3.68 (d, *J* = 5.5 Hz, 2 H, 3-H), 6.47–6.53 (m, 2 H, 2″-H, 6″-H), 6.96 (dd, *J* = 8.1, 1.1 Hz, 1 H, 6′-H), 7.03 (ddd, *J* = 8.1, 7.5, 1.2 Hz, 1 H, 5′-H), 7.17–7.47 (m, 7 H, ArH),

^{13}C NMR (50 MHz, $CDCl_3$): δ = –3.7 [$Si(CH_3)_2$], 18.4 [$SiC(CH_3)_3$], 25.9 [$SiC(CH_3)_3$], 33.7 (C-3), 118.5, 121.5, 126.1, 126.8, 127.9, 128.3, 128.5, 128.9, 129.2, 130.4 (Ar), 130.9 (C-1′), 137.9 (C-1), 153.5 (C-2′).

MS (EI): *m*/*z* (%) = 324 (22) [M$^+$], 267 (88), 249 (5), 189 (20), 163 (98), 147 (34), 91 (100), 71 (54).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{21}H_{28}OSi$: 324.19095; found: 324.19098.

(*E*)-1-(4-Methoxyphenyl)-3-[4-methoxy-2-(*tert*-butyldimethylsilyloxy)phenyl]propene (10b)

Yield: 93%; colorless oil.

IR (film): 2954, 1605, 1509, 1483, 1249, 1162 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.34 [s, 6 H, $Si(CH_3)_2$], 1.11 [s, 9 H, $SiC(CH_3)_3$], 3.52 (d, *J* = 6.6 Hz, 2 H, 3-H), 3.81 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 6.29 (dt, *J* = 15.7, 6.6 Hz, 1 H, 2-H), 6.41 (d, *J* = 15.7 Hz, 1 H, 1-H), 6.50 (d, *J* = 2.5 Hz, 1 H, 3′-H), 6.54 (d, *J* = 8.4, 2.5 Hz, 1 H, 5′-H), 6.89 (dt, *J* = 8.8, 2.1 Hz, 2 H, 3″-H, 5″-H), 7.14 (d, *J* = 8.4 Hz, 1 H, 6′-H), 7.33 (dt, *J* = 8.8, 2.1 Hz, 2 H, 2″-H, 6″-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –3.7 [$Si(CH_3)_2$], 18.3 [$SiC(CH_3)_3$], 25.9 [$SiC(CH_3)_3$], 33.0 (C-3), 55.24 (OCH_3), 55.28 (OCH_3), 105.5 (C-3′), 106.9 (C-5′), 114.1 (C-3″, C-5″), 123.4 (C-2), 127.0, 127.1, 127.3, 129.7, 129.9, 130.0, 130.2 (Ar, C-1), 154.2 (C-2′), 158.6 (C-4′), 159.8 (C-4″).

MS (EI): *m*/*z* (%) = 384 (12) [M$^+$], 324 (22), 267 (88), 251 (5), 209 (34), 163 (98), 121 (66), 91 (100), 73 (26).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{23}H_{32}O_3Si$: 384.21207; found: 384.21223.

(*E*)-1-(4-Benzyloxyphenyl)-3-[4-benzyloxy-2-(*tert*-butyldimethylsilyloxy)phenyl]propene (10c)[12]

Yield: 97%; colorless oil.

(*E*)-3-[2,4-Bis(benzyloxy)-6-(*tert*-butyldimethylsilyloxy]-1-[3,4,5-tris(benzyloxy)phenyl]propene (10d)[27]

Yield: 96%; mp 88–90 °C (no mp given in Lit.[27]).

IR (film): 2929, 1600, 1427, 1288, 1108, 889, 696 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.20 [s, 6 H, $Si(CH_3)_2$], 1.00 [s, 9 H, $SiC(CH_3)_3$], 3.52 (d, *J* = 4.9 Hz, 2 H, CH_2), 5.02 (s, 2 H, 7-OCH_2Ph), 5.05 (s, 4 H, 3′-, 6′-OCH_2Ph), 5.10 (s, 4 H, 4′-, 5-OCH_2Ph), 6.19–6.35 (m, 4 H, 2-H, 3-H, 6-H, 8-H), 6.60 (s, 2 H, 2′-H, 6′-H), 7.30–7.47 (m, 25 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = –4.0 [$Si(CH_3)_2$], 18.3 [$SiC(CH_3)_3$], 25.8 [$SiC(CH_3)_3$], 26.8 (C-3), 70.2 (4′-OCH_2Ph), 70.1 (4″-OCH_2Ph), 71.3 (3″-, 5″-, 2′-OCH_2Ph), 93.9 (C-3′), 98.5 (C-5′), 105.9 (C-2′, C-4′), 112.1 (C-4), 127.3 (C-3), 127.4, 127.4, 127.7, 128.1, 128.4, 128.5, 128.5, 128.7, 128.7, 128.8, 128.9, 128.9, 129.0, 129.6, 130.6, 133.3, 137.1, 137.3, 137.6, 138.0 (Ar), 152.1 (C-4″), 153.8 (C-3″, C-5″), 154.7 (C-6′), 158.1 (C-4′), 158.4 (C-2′).

MS (EI): *m*/*z* (%) = 854 (1) [M$^+$], 763 (8), 745 (1), 672 (1), 581 (4), 512 (3), 444 (2), 434 (22), 343 (8), 271 (2), 211 (1), 181 (18), 91 (100), 51 (4).

HRMS: *m/z* [M]$^+$ calcd for $C_{56}H_{58}O_6Si$: 854.40027; found: 854.40052.

Sharpless Asymmetric Dihydroxylation; General Procedure

To a solution containing the TBS ethers **10a–d** (8.00 mmol) in *t*-BuOH–H_2O (1:1, 12 mL), was added AD-mix α (11.2 g) in portions. The heterogeneous mixture was cooled to 0 °C in an ice bath and methanesulfonamide (0.95 g, 10 mmol) was also added in portions. In order to allow complete dissolution of the starting material, $CHCl_3$ (0.5 mL) was added and the reaction mixture was allowed to warm to r.t. and stirred for 16 h. When the starting material was completely consumed (reaction monitored by TLC), the reaction was quenched by addition of Na_2SO_3 (1 M, 4 mL) and diluted with EtOAc (100 mL) and H_2O (100 mL). The organic layer was separated and washed with KOH (2 M, 2 × 100 mL), followed by H_2O (100 mL). The organic layer was dried over $MgSO_4$, concentrated under reduced pressure and the residue was purified by flash chromatography on a silica gel column (EtOAc–PE, 1:3) to afford TBS-protected diols **11a–d**.

(1*S*,2*S*)-1-Phenyl-3-[2-(*tert*-butyldimethylsilyloxy)phenyl]propane-1,2-diol (11a)

Yield: 89%; colorless oil; $[\alpha]_D$ –4.7 (*c* 1.0, CH_2Cl_2).

IR (film): 3405, 3062, 2892, 1581, 1490, 1452, 1253 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.21 (s, 3 H, $SiCH_3$), 0.23 (s, 3 H, $SiCH_3$), 1.00 [s, 9 H, $SiC(CH_3)_3$], 2.75 (dd, *J* = 9.2, 4.4 Hz, 1 H, 3-H_α), 2.79 (dd, *J* = 8.5, 4.2 Hz, 1 H, 3-H_β), 2.91 (br, 1 H, 2-OH), 3.97 (m, 1 H, 2-H), 4.51 (d, *J* = 5.7 Hz, 1 H, 1-H), 6.84 (dd, *J* = 8.1, 1.1 Hz, 1 H, 3′-H), 6.92 (ddd, *J* = 8.1, 7.5, 1.1 Hz, 1 H, 5′-H), 7.13 (ddd, *J* = 7.8, 7.7, 1.8 Hz, 1 H, 4′-H), 7.18 (dd, *J* = 7.5, 1.8 Hz, 1 H, 6′-H), 7.29–7.39 (m, 5 H, ArH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –3.8 [$Si(CH_3)_2$], 18.2 [Si*C*$(CH_3)_3$], 25.9 [SiC(*C*$H_3)_3$], 34.5 (C-3), 75.6 (C-2), 77.3 (C-1), 118.3, 121.4, 126.9, 127.6, 127.8, 128.0, 128.2, 128.4, 128.6, 131.6 (Ar), 141.1 (C-1″), 153.8 (C′-2).

MS (EI): *m/z* (%) = 358 (2) [M$^+$], 325 (4), 283 (96), 265 (37), 251 (42), 205 (12), 177 (24), 165 (18), 119 (60), 91 (100), 73 (71), 45 (4).

HRMS: *m/z* [M]$^+$ calcd for $C_{21}H_{30}O_3Si$: 358.19641; found: 358.19617.

(1*S*,2*S*)-1-(4-Methoxyphenyl)-3-[4-methoxy-2-(*tert*-butyldimethylsilyloxy)phenyl]propane-1,2-diol (11b)

Yield: 84%; mp 74–76 °C; $[\alpha]_D$ +4.5 (*c* 1.0, CH_2Cl_2).

IR (KBr): 3396, 3019, 1610, 1504, 1489, 1288, 1245, 1162, 1041, 835, 700 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.18 (s, 3 H, $SiCH_3$), 0.20 (s, 3 H, $SiCH_3$), 0.95 [s, 9 H, $SiC(CH_3)_3$], 2.59 (dd, *J* = 9.2, 3.7 Hz, 1 H, 3-H_α), 2.68 (dd, *J* = 9.2, 3.7 Hz, 1 H, 3-H_β), 3.74 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 3.85 (m, 1 H, 2-H), 4.50 (d, *J* = 6.1 Hz, 1 H, 1-H), 6.38 (d, *J* = 2.6 Hz, 1 H, 3′-H), 6.46 (dd, *J* = 8.4, 2.5 Hz, 1 H, 5′-H), 6.89 (dt, *J* = 6.8, 2.5 Hz, 2 H, 3″-H, 5″-H), 7.03 (d, *J* = 8.4 Hz, 1 H, 6′-H), 7.28 (dt, *J* = 6.8, 1.8 Hz, 2 H, 2″-H, 6″-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –3.9 [$Si(CH_3)_2$], 18.2 [Si*C*$(CH_3)_3$], 25.8 [SiC(*C*$H_3)_3$], 33.7 (C-3), 55.24 (OCH_3), 55.26 (OCH_3), 75.8 (C-2), 76.8 (C-1), 105.7 (C-3′), 106.1 (C-5′), 113.8, 113.9 (C-3″, C-5″), 120.8 (C-1′), 128.1 (C-2″), 128.5 (C-6″), 131.7 (C-6′), 133.2 (C-1″), 154.5 (C-2′), 159.1 (C-4′), 159.2 (C-4″).

MS (EI): *m/z* (%) = 418 (12) [M$^+$], 350 (8), 313 (5), 281 (60), 251 (28), 223 (35), 167 (24), 149 (100), 75 (58), 73 (56), 928 (47).

HRMS: *m/z* [M]$^+$ calcd for $C_{23}H_{34}O_5Si$: 418.21756; found: 418.21733.

(1*S*,2*S*)-1-(4-Benzyloxyphenyl)-3-[4-benzyloxy-2-(*tert*-butyldimethylsilyloxy)phenyl]propane-1,2-diol (11c)[12]

Yield: 88%; mp 66–68 °C (no mp given in Lit.[12]); $[\alpha]_D$ +4.91 (*c* 0.77, $CHCl_3$) [Lit.[12] +4.77 (*c* 0.77, $CHCl_3$)].

(1*S*,2*S*)-3-[2,4-Bis(benzyloxy)-6-(*tert*-butyldimethylsilyloxy)phenyl]-1-[3,4,5-tris(benzyloxy)phenyl]propane-1,2-diol (11d)[27]

Yield: 82%; sticky oil; $[\alpha]_D$ –6.5 (*c* 1.0, $CHCl_3$).

IR (film): 3505, 3145, 2929, 1590, 1409 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.17 (s, 3 H, $SiCH_3$), 0.19 (s, 3 H, $SiCH_3$), 1.11 [s, 9 H, $SiC(CH_3)_3$], 2.75 (dd, *J* = 14.8, 8.4 Hz, 1 H, 3-H_α), 2.90 (dd, *J* = 14.8, 3.6 Hz, 1 H, 3-H_β), 3.92 (ddd, *J* = 8.4, 5.6, 3.6 Hz, 1 H, 2-H), 4.43 (d, *J* = 5.6 Hz, 1 H, 1-H), 4.89 (s, 2 H, OCH_2Ph), 4.95–5.05 (m, 8 H, OCH_2Ph), 6.21 (d, *J* = 2.0 Hz, 1 H, 5′-H), 6.26 (d, *J* = 2.0 Hz, 1 H, 3′-H), 6.59 (s, 2 H, 2″-H, 6″-H), 7.25–7.45 (m, 25 H, ArH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –3.8 [$Si(CH_3)_2$], 18.5 [Si*C*$(CH_3)_3$], 25.7 [SiC(*C*$H_3)_3$], 26.9 (C-3), 70.0 (OCH_2Ph), 71.3 (OCH_2Ph), 79.4 (C-1), 82.1 (C-2), 93.9 (C-3′), 98.5 (C-5′), 105.9 (C-2″, C-6″), 112.1 (C-1′), 127.3, 127.4, 127.4, 127.7, 128.1, 128.4, 128.5, 128.5, 128.7, 128.7, 128.8, 128.9, 128.9, 129.0, 129.6, 130.6, 133.3, 137.1, 137.3, 137.6, 138.0 (Ar), 152.8 (C-3″,C-5″), 154.7 (C-6′), 158.1 (C-4′), 158.4 (C-2′).

MS (EI): *m/z* (%) = 888.4 (0.40) [M$^+$], 753 (1), 723 (1), 665 (1), 525 (1), 463 (10), 433 (8), 343 (2), 253 (2), 181 (12), 91 (100), 65 (3).

HRMS: *m/z* [M]$^+$ calcd for $C_{56}H_{60}O_8Si$: 888.40576; found: 888.40467.

TBS Deprotection; General Procedure

To a solution of TBS-protected diols **11a–d** (0.87 mmol) in anhydrous THF (16 mL), was added TBAF·3H_2O (250 mg, 0.79 mmol). The reaction mixture was stirred at r.t. for 1.5 h. After complete conversion (monitored by TLC), the reaction mixture was quenched by addition of sat. aq $NaHCO_3$ (3 mL). The reaction mixture was diluted with H_2O (50 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine (25 mL) and H_2O (25 mL). The organic layer was then dried ($MgSO_4$) and concentrated under reduced pressure to obtain a brown residue which was purified by flash chromatography on a silica gel column (EtOAc–PE, 1:3) to obtain triols **12a–d**.

(1*S*,2*S*)-3-(2-Hydroxyphenyl)-1-phenylpropane-1,2-diol (12a)

Yield: 95%; mp 108–109 °C; $[\alpha]_D$ +36.6 (*c* 1.0, CH_2Cl_2).

IR (KBr): 3415, 2886, 1581, 1509, 1488, 1398, 1240, 1039, 844, 757 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.66 (m, 1 H, 3-H_α), 2.74 (m, 1 H, 3-H_β), 4.08 (m, 1 H, 2-H), 4.51 (d, *J* = 7.7 Hz, 1 H, 1-H), 6.75–6.90 (m, 2 H, ArH), 7.11–7.41 (m, 7 H, ArH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 34.7 (C-3), 76.7 (C-2), 77.3 (C-1), 117.2, 120.2, 124.4, 127.1, 128.5, 128.6, 128.6, 128.6, 129.3, 131.7 (Ar), 140.1 (C-1″), 155.5 (C′-2).

MS (EI): *m/z* (%) = 244 (48) [M$^+$], 207 (3), 165 (5), 137 (44), 108 (100), 65 (12), 28 (5).

HRMS: *m/z* [M]$^+$ calcd for $C_{15}H_{16}O_3$: 244.10994; found: 244.10980.

(1*S*,2*S*)-3-(2-Hydroxy-4-methoxyphenyl)-1-(4-methoxyphenyl)propane-1,2-diol (12b)

Yield: 94%; mp 103–104 °C; $[\alpha]_D$ –1.6 (*c* 1.0, CH_2Cl_2).

IR (KBr): 3546, 3465, 3361, 2965, 1641, 1444, 1206, 1176, 1076, 827 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.51 (dd, *J* = 14.8, 7.3 Hz, 1 H, 3-H_α), 2.60 (dd, *J* = 14.8, 3.2 Hz, 1 H, 3-H_β), 3.68 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 3.93 (m, 1 H, 2-H), 4.29 (d, *J* = 7.8 Hz, 1 H, 1-H), 6.33 (dd, *J* = 8.3, 2.5 Hz, 1 H, 5′-H), 6.44 (d, *J* = 2.6 Hz, 1 H, 3′-H), 6.61 (d, *J* = 8.3 Hz, 1 H, 6′-H), 6.84 (dt, *J* = 7.0, 1.8 Hz, 2 H, 3″-H, 5″-H), 7.28 (dt, *J* = 7.0, 1.7 Hz, 2 H, 2″-H, 6″-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 34.1 (C-3), 55.22 (OCH_3), 55.26 (OCH_3), 76.1 (C-2), 77.3 (C-1), 102.3 (C-3′), 106.0 (C-5′), 113.9 (C-1′), 114.0 (C-3″), 114.3 (C-5″), 128.2 (C-2″), 128.4 (C-6″), 131.9 (C-6′), 132.2 (C-1″), 156.3 (C-2′), 159.5 (C-4′), 159.8 (C-4″).

MS (EI): *m*/*z* (%) = 304 (34) [M$^+$], 286 (54), 167 (32), 137 (100), 109 (33), 65 (6).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{17}H_{20}O_5$: 304.13107; found: 304.13115.

(1*S*,2*S*)-3-(4-Benzyloxy-2-hydroxyphenyl)-1-(4-benzyloxyphenyl)propane-1,2-diol (12c)

Yield: 95%; mp 122–124 °C; $[\alpha]_D$ –1.28 (*c* 1.0, $CHCl_3$).

IR (KBr): 3426, 3033, 2892, 1614, 1509, 1440, 1286, 1168, 1024 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.55 (dd, *J* = 15.2, 8.3 Hz, 1 H, 3-H_α), 2.71 (dd, *J* = 14.2, 6.1 Hz, 1 H, 3-H_β), 4.07 (br, 1 H, 2-H), 4.41 (d, *J* = 7.2 Hz, 1 H, 1-H), 5.04 (s, 2 H, OCH_2Ph), 5.11 (s, 2 H, OCH_2Ph), 6.47 (dd, *J* = 8.3, 2.4 Hz, 1 H, 5′-H), 6.62 (d, *J* = 2.4 Hz, 1 H, 3′-H), 6.69 (d, *J* = 8.7 Hz, 1 H, 6-H), 7.04 (d, *J* = 8.7 Hz, 2 H, 3″-H, 5″-H), 7.24–7.46 (m, 12 H, 2″-H, 6″-H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 34.6 (C-3), 70.4 (OCH_2Ph), 70.5 (OCH_2Ph), 76.1 (C-2), 76.1 (C-1), 104.1 (C-3′), 107.3 (C-5′), 115.5 (C-3″, C-5″), 117.1 (C-1′), 127.9 (C-1′), 127.6, 127.8, 127.7, 128.3, 128.5, 128.9, 129.0, 132.7, 133.8, 137.1, 137.5 (Ar), 157.1 (C-2′), 159.4 (C-4′), 159.6 (C-4″).

MS (EI): *m*/*z* (%) = 456 (10) [M$^+$], 438 (60), 362 (16), 243 (36), 213 (97), 137 (50), 123 (58), 91 (100), 65 (25).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{29}H_{28}O_5$: 456.1937; found: 456.1934.

(1*S*,2*S*)-3-[2,4-Bis(benzyloxy)-6-hydroxyphenyl]-1-[3,4,5-tris(benzyloxy)phenyl]propane-1,2-diol (12d)[27]

Yield: 92%; mp 144–145 °C (no mp given in Lit.[27]); $[\alpha]_D$ +11.61 (*c* 1.0, $CHCl_3$) [Lit.[10] +11.54 (*c* 1.0, $CHCl_3$)].

IR (film): 3426, 2965, 1436, 1376, 1272, 1112, 879, 777, 694 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.75 (dd, *J* = 14.8, 8.4 Hz, 1 H, 3-H_α), 2.90 (dd, *J* = 14.8, 3.6 Hz, 1 H, 3-H_β), 3.92 (ddd, *J* = 8.4, 5.6, 3.6 Hz, 1 H, 2-H), 4.43 (d, *J* = 5.6 Hz, 1 H, 1-H), 4.89 (s, 2 H, OCH_2Ph), 4.95–5.05 (m, 8 H, OCH_2Ph), 6.21 (d, *J* = 2.0 Hz, 1 H, 5′-H), 6.26 (d, *J* = 2.0 Hz, 1 H, 3′-H), 6.59 (s, 2 H, 2″-H, 6″-H), 7.25–7.45 (m, 25 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.9 (C-3), 70.0 (OCH_2Ph), 71.3 (OCH_2Ph), 75.3 (OCH_2Ph), 76.9 (OCH_2Ph), 77.1 (OCH_2Ph), 79.4 (C-1), 82.1 (C-2), 93.9 (C-3′), 98.5 (C-5′), 105.9 (C-2″, C-6″), 112.1 (C-1′), 127.3, 127.4, 127.4, 127.7, 128.1, 128.4, 128.5, 128.5, 128.7, 128.7, 128.8, 128.9, 128.9, 129.0, 129.6, 130.6, 133.3, 137.1, 137.3, 137.6, 138.0 (Ar), 152.1 (C-4″), 152.8 (C-3″, C-5″), 154.7 (C-6′), 158.1 (C-4′), 158.4 (C-2′).

MS (EI): *m*/*z* (%) = 774 (0.2) [M$^+$], 665 (0.1), 542 (0.1), 450 (0.1), 396 (3), 348 (2), 306 (4), 227 (1), 142 (2), 91 (100), 51 (2).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{50}H_{46}O_8$: 774.31927; found: 774.31266.

Mitsunobu Reaction; General Procedure

To a solution of triols **12a–d** (0.56 mmol) in anhydrous THF (6 mL), was added Ph_3P (225 mg, 0.86 mmol). The mixture was stirred for 15 min and DEAD (0.13 mL, 0.83 mmol) was then added dropwise to the reaction mixture. After stirring for 3 h at r.t. (reaction monitored by TLC), the reaction mixture was diluted with EtOAc (40 mL) and washed with H_2O (30 mL) and brine (30 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a brown residue. The residue obtained was purified by silica gel column chromatography (EtOAc–PE, 1:3) to afford of the cyclized products **13a–d** as white solids.

2,3-*trans*-Flavan-3-ol (13a)[28]

Yield: 75%; mp 107–109 °C; 91.2% ee (HPLC); $[\alpha]_D$ –7.9 (*c* 1.0, CH_2Cl_2).

IR (KBr): 3403, 3031, 2911, 1583, 1488, 1301, 1247, 1114, 1037, 750, 701 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.86 (d, *J* = 3.8 Hz, 1 H, 3-OH), 2.93 (dd, *J* = 16.1, 8.8 Hz, 1 H, 4-H_α), 3.09 (dd, *J* = 16.1, 5.3 Hz, 1 H, 4-H_β), 4.12 (m, 1 H, 3-H), 4.65 (d, *J* = 7.8 Hz, 1 H, 2-H), 6.87–6.95 (m, 2 H, 6-H, 8-H), 7.11–7.20 (m, 2 H, 5-H, 7-H), 7.33–7.46 (m, 5 H, ArH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 32.8 (C-4), 68.6 (C-3), 81.9 (C-2), 116.5, 120.1, 121.0, 127.1, 127.7, 128.6, 128.8, 129.6, 130.0, 131.0, 138.2 (Ar), 154.0 (C-8a).

MS (EI): *m*/*z* (%) = 226.17 (44) [M$^+$], 177 (8), 176 (48), 149 (56), 107 (100), 91 (78), 57 (28), 43 (42).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{15}H_{14}O_2$: 226.09938; found: 226.09947.

2,3-*trans*-7,4′-Dimethoxyflavan-3-ol (13b)[26,29]

Yield: 82%; mp 89–90 °C (Lit.[26] 86–88 °C); 75.7% ee [>98% after one recrystallization (EtOAc–PE, 1:7)]; $[\alpha]_D$ –9.2 (*c* 1.0, CH_2Cl_2).

IR (KBr): 3440, 2933, 1619, 1506, 1398, 1247, 1157 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.01 (br, 1 H, 3-OH), 2.81 (dd, *J* = 15.7, 8.9 Hz, 1 H, 4-H_α), 3.01 (dd, *J* = 15.7, 5.3 Hz, 1 H, 4-H_β), 3.75 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 4.06 (m, 1 H, 3-H), 4.72 (d, *J* = 8.0 Hz, 1 H, 2-H), 6.48 (d, *J* = 2.5 Hz, 1 H, 8-H), 6.53 (dd, *J* = 8.4, 2.5 Hz, 1 H, 6-H), 6.94 (dt, *J* = 6.7, 2.0 Hz, 2 H, 3′-H, 5′-H), 7.00 (d, *J* = 8.4 Hz, 1 H, 5-H), 7.36 (dt, *J* = 6.7, 2.0 Hz, 2 H, 2′-H, 6′-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 32.4 (C-4), 55.3 (OCH_3), 68.6 (C-3), 81.7 (C-2), 101.3 (C-8), 108.0 (C-6), 112.1 (C-4a), 114.2 (C-3′, C-5′), 127.6, 128.5, 130.1, 130.3, 130.6 (Ar), 154.9 (C-8a), 159.4 (C-4′), 159.9 (C-7).

MS (EI): *m*/*z* (%) = 286.12 (78) [M$^+$], 233 (5), 176 (40), 150 (58), 137 (100), 121 (82), 91 (28), 75 (32).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{17}H_{18}O_4$: 286.12051; found: 286.12047.

2,3-*trans*-7,4′-Bis(benzyloxy)flavan-3-ol (13c)[12]

Yield: 77%; mp 96–98 °C (no mp given in Lit.[12]); 97.7% ee after chromatography (EtOAc–PE, 1:3) and crystallization (EtOAc–PE, 1:7); $[\alpha]_D$ –17.38 (*c* 1.11, $CHCl_3$) [Lit.[10] –16.1 (*c* 1.11, $CHCl_3$)].

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.13 (br, 1 H, 3-OH), 2.94 (dd, *J* = 15.6, 9.0 Hz, 1 H, 4-H_α), 3.06 (dd, *J* = 15.6, 5.3 Hz, 1 H, 4-H_β), 4.13 (m, 1 H, 3-H), 4.65 (d, *J* = 8.0 Hz, 1 H, 2-H), 5.04 (s, 2 H, OCH_2Ph), 5.13 (s, 2 H, OCH_2Ph), 6.67 (dd, *J* = 8.1, 2.4 Hz, 2 H, 3′-H, 5′-H), 7.08 (m, 3 H, 5-H, 6-H, 8-H), 7.30–7.47 (m, 12 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 32.5 (C-4), 68.6 (C-3), 70.4 (OCH_2Ph), 82.1 (C-2), 107.6, 137.2, 137.4 (Ar), 155.2 (C-8a), 158.9 (C-4′), 159.5 (C-7).

MS (EI): *m*/*z* (%) = 438 (98) [M$^+$], 362 (8), 347 (24), 226 (34), 213 (88), 107 (26), 91 (100), 65 (22).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{29}H_{26}O_4$: 438.18311; found: 438.18333.

2,3-*trans*-5,7,3′,4′,5′-Pentakis(benzyloxy)flavan-3-ol (13d)[27]
Yield: 71%; mp 116–118 °C (no mp given in Lit.[27]); 47.3% ee [~85% ee after one crystallization (EtOAc–PE, 1:7)]; $[\alpha]_D$ –8.96 (*c* 1.0, $CHCl_3$) [Lit.[11] –7.21 (*c* 1.0, $CHCl_3$)].

IR (film): 3550, 3029, 1592, 1536, 1374, 1295, 1116, 773 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.76 (br s, 1 H, 3-OH), 2.75 (dd, *J* = 16.5, 9.0 Hz, 1 H, 4-H_α), 3.15 (dd, *J* = 16.5, 6.0 Hz, 1 H, 4-H_β), 4.01 (ddd, *J* = 9.0, 8.1, 6.0 Hz, 1 H, 3-H), 4.65 (d, *J* = 8.1 Hz, 1 H, 2-H), 5.04 (s, 2 H, OCH_2Ph), 5.07 (s, 2 H, OCH_2Ph), 5.10 (s, 2 H, OCH_2Ph), 5.11 (s, 2 H, OCH_2Ph), 5.14 (s, 2 H, OCH_2Ph), 6.29 (d, *J* = 2.4 Hz, 1 H, 8-H), 6.34 (d, *J* = 2.4 Hz, 1 H, 6-H), 6.78 (s, 2 H, 2′-H, 6′-H), 7.30–7.55 (m, 25 H, ArH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 27.9 (C-4), 68.5 (C-3), 70.2 (OCH_2Ph), 70.4 (OCH_2Ph), 71.4 (OCH_2Ph), 82.1 (C-2), 94.2 (C-8), 94.6 (C-6), 102.6 (C-4a), 106.9 (C-2′, C-6′), 127.4, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.5, 128.7, 128.8, 128.9, 129.0, 133.6, 137.1, 137.2, 138.0, 138.9 (Ar), 153.1 (C-4′), 153.3 (C-3′, C-5′), 155.4 (C-5), 158.0 (C-8a), 159.1 (C-7).

MS (EI): *m*/*z* (%) = 756 (1) [M^+], 725 (1), 665 (3), 575 (1), 528 (1), 463 (1), 433 (4), 319 (10), 306 (7), 215 (2), 181 (25), 91 (100), 44 (8).

HRMS: *m*/*z* [$M]^+$ calcd for $C_{50}H_{44}O_7$: 756.30872; found: 756.30645.

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