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An enantioselective total synthesis of the stilbenolignan (−)-aiphanol and the determination of its absolute stereochemistry

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Abstract—The title natural product (−)-aiphanol has been prepared by total synthesis. A key step involved the asymmetric dihydroxylation of (*E*)-3,5-dimethoxy-4-(methoxymethoxy)cinnamyl alcohol with the AD-mix-β to give triol (1*R*,2*R*)-1-(3′,5′-dimethoxy-4′-methoxymethoxyphenyl)-2,3-dihydroxypropanol, the absolute stereochemistry of which was confirmed by single-crystal X-ray analysis of a readily available bromo-derivative. These studies have established that the naturally occurring enantiomer of aiphanol possesses the (*S*)-configuration at each of C-2′ and C-3′.
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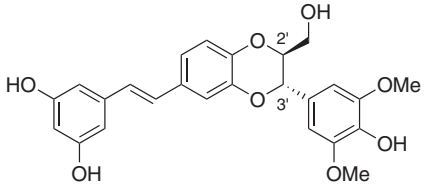
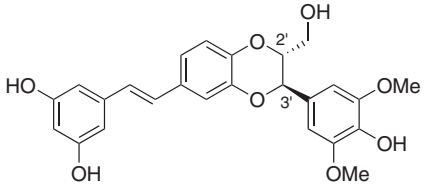
1. Introduction

In 2001, Kinghorn and co-workers reported the bioassay-guided isolation of the polyphenolic compound (−)-aiphanol **1** from the seeds of *Aiphanes aculeata* Willd. (Arecaceae) collected in Peru.[1] This natural product possesses an unprecedented stilbenolignan skeleton in which a hydroxylated stilbene unit is connected to a phenylpropane moiety via a 1,4-dioxane bridge. Aiphanol is an optically active and levorotatory compound {$[\alpha]_D = -21.8$ (*c* 0.13, MeOH)} but its absolute configuration has not yet been determined.[1] It shows potent inhibition of the cyclooxygenase enzymes COX-1 and COX-2 with IC_{50} values of 1.9 and 9.9 μM, respectively.[1] Since compounds exhibiting COX-2 inhibitory properties can also act as anti-angiogenic agents,[2–4] we have pursued the syntheses of aiphanol and various congeners with the intention of establishing a structure–activity profile for this novel natural product. Such synthetic studies are also necessary because aiphanol only occurs in very low natural abundance, comprising just 0.00008% w/w of the dried seeds of *A. aculeata*.[1]

The intriguing biological properties and novel structural features of aiphanol **1** have already attracted the attention of other groups and, in a recent study, Ohira et al.[5] have reported the total synthesis of a racemic material. This group employed a [4+2]-cycloaddition reaction between *ortho*-benzoquinone and a TBS-protected sinapyl alcohol to construct the 1,4-benzodioxane framework. We have recently shown[6] that (±)-aiphanol **1** can be assembled through an oxidative and biomimetic coupling of a cinnamyl alcohol derivative with the tetrahydroxystilbene piceatannol, itself a natural product that has been isolated from *A. aculeata*[1] as well as other sources.[7] The oxidative coupling reaction was promoted by an Ag(I) species.[8] A related synthesis of (±)-aiphanol has also been described by Pan et al.[9] Some of the preliminary biological testing of synthetically-derived (±)-aiphanol[6] suggested that there might be variations in the properties of the two



(−)-**1**



(+)-**1**

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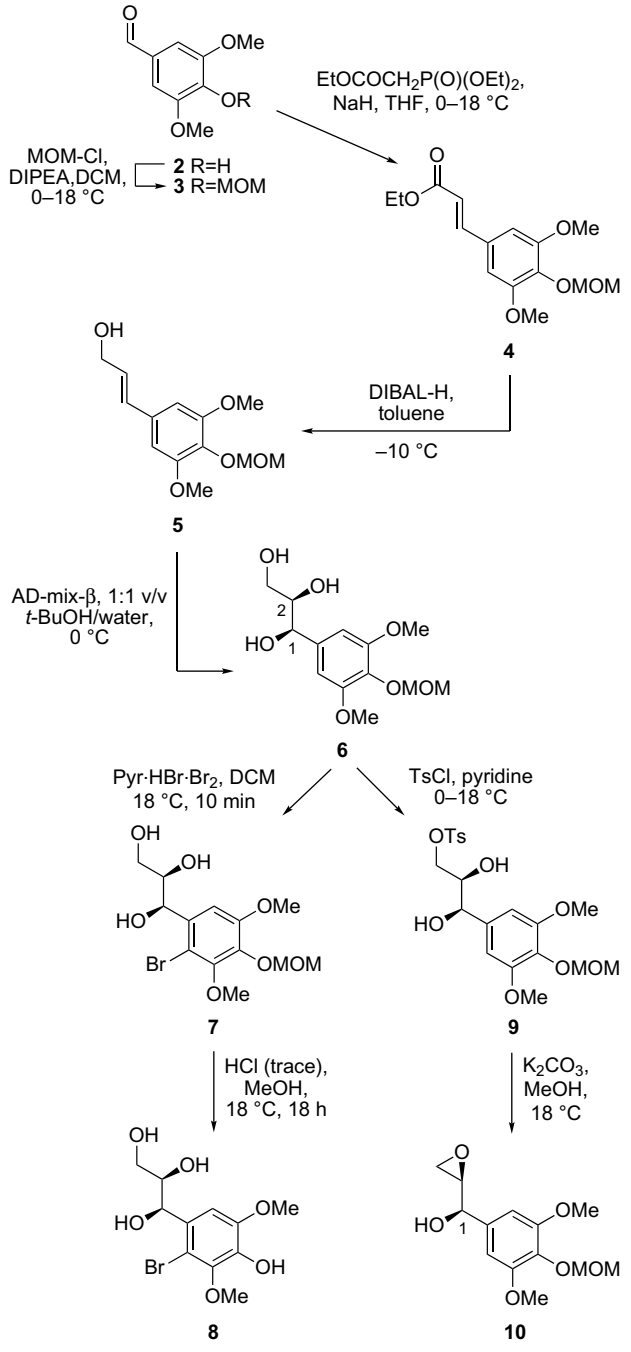
enantiomeric forms of compound **1**. As such it became necessary to establish unequivocal access to both enantiomeric forms of aiphanol. Accordingly, we now report the establishment of a quite distinct and enantioselective total syntheses of (−)- and (+)-**1** that have enabled the unequivocal determination of the absolute stereochemistry of the natural product.

2. Results and discussion

2.1. Synthesis of (2′*S*,3′*S*)-aiphanol (−)-1

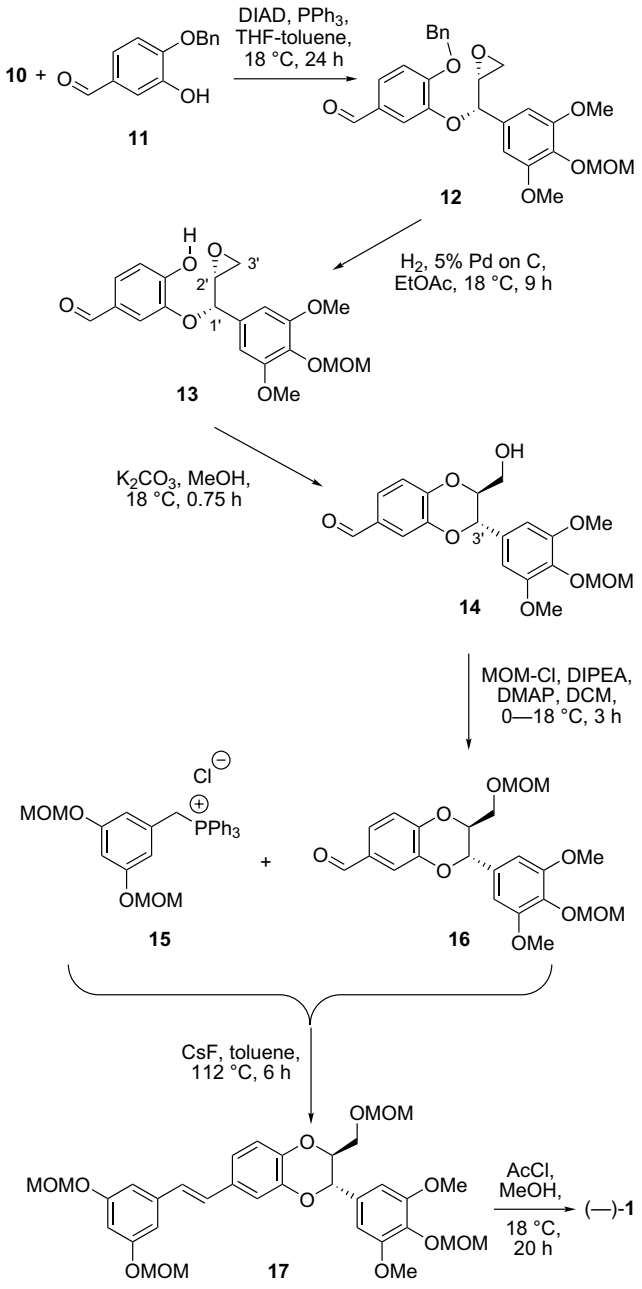
The initial stages of the route that has culminated in the synthesis of the natural or (−)-form of aiphanol is outlined in Scheme 1. After reviewing the various methods available for preparing 1,4-benzodioxans, we ultimately settled on that reported by Pan et al.[10] since this allows for the control of the absolute stereochemistry of the substituents attached at C-2′ and C-3′ (see structure **1**). Thus, by following protocols established by this group, the phenolic unit of commercially available syringealdehyde **2** was protected as the corresponding MOM-ether, **3**,[11] which was subsequently engaged in a Horner–Wadsworth–Emmon[12] (HWE) reaction using triethyl phosphonoacetate and NaH to afford the *E*-configured α,β-unsaturated ester **4**[13] in 79% yield over two steps. Consistent with expectations,[12] the *Z*-isomer was not detected as judged by 300 MHz ^{1}H NMR spectral analysis of the crude product. DIBAL-H reduction of compound **4** afforded the cinnamyl alcohol **5**[13] in 81% yield. Sharpless asymmetric dihydroxylation (AD)[14] of the latter compound with AD mix-β then gave triol **6** in 80% yield. The absolute stereochemistry of compound **6** was assigned, in a preliminary fashion, as (1*R*,2*R*) using the Sharpless mnemonic[15] but in order to unequivocally confirm the configuration of the anticipated dioxane system, this triol was brominated with pyridinium hydrobromide perbromide[16] to afford compound **7** after which the MOM group was removed using methanolic HCl to give bromide **8** as a crystalline solid in 77% yield over these two steps. X-ray analysis of this material and exploitation of the presence of the heavy atom allowed the absolute stereochemistry at C-1 and C-2 to be determined,[17] unequivocally, as *R* in each case, an outcome consistent with that predicted using the Sharpless mnemonic.[15] (1*R*,2*R*)-Triol **6** was converted, via tosylate **9**, into epoxy-alcohol **10**, which was obtained in 63% yield and >95% ee as established by chiral HPLC analysis.



Scheme 1.

In the closing and pivotal stages (Scheme 2) of the formation of the target 1,4-benzodioxane, Mitsunobu coupling[18] of compound **10** with the known[19] phenol **11** using DIAD and PPh_3 afforded adduct **12** in 60% yield and >95% ee as determined by chiral HPLC analysis.

Removal of the benzyl group was carried out by hydrogenolysis over 5% Pd on C and using ethyl acetate as solvent to afford epoxide **13** in 71% yield. The most conspicuous feature in the 300 MHz ^{1}H NMR spectrum of this compound was, as expected, the lack of proton resonances associated with the benzyl-protecting group. The proton of the free phenolic hydroxyl group appeared as a broad singlet at δ 8.10 while H-1′ resonated as a doublet at δ 4.99 (J = 2.3 Hz) and the H-2′ proton appeared as a multiplet at δ 3.38. Singlets observed at δ 5.14 (2H) and at δ 3.61 (3H) are assigned to the methylene and methyl protons, respectively, of the MOM-ether. The 75 MHz ^{13}C NMR spectrum of compound **13** showed signals due to seventeen non-equivalent carbons, as expected for the illustrated structure. The stereochemistry at C-1′ within this compound was assigned as *S* on the basis that the Mitsunobu reaction between compounds **10** and **11** proceeded with inversion of configuration at the electrophilic center, that is, at C-1 within the former.



Scheme 2.

With the structure of the required cyclization precursor **13** established, the formation of the 1,4-benzodioxane system could now be pursued. Treatment of the epoxide **13** with K_2CO_3 afforded the anticipated cyclization product, viz. compound **14** in 70% yield, and in an enantiomeric purity of >95% ee as determined by chiral HPLC analysis. In the 300 MHz ^{1}H NMR spectrum of compound **14**, H-3 resonated as a doublet at δ 4.95 and the magnitude of the observed coupling (J = 8.9 Hz) implied a *trans*-relationship exists between the aromatic substituent at C-3′ and the hydroxymethyl unit on the adjacent center. This together with the appearance of other resonances in the proton and also in the 75 MHz ^{13}C NMR spectrum, were in full accordance with the assigned structure. Interestingly, and in an outcome consistent with earlier observations,[20] the K_2CO_3-mediated cyclization reaction of compound **13** did not give any seven-membered ring product through attack of the phenoxyanion at C-3′ of the epoxide ring within this substrate.

Based on the absolute configuration of the Sharpless asymmetric dihydroxylation product **6**, as determined by X-ray analysis of derivative **8**,[17] and by virtue of the involvement of a Mitsunobu reaction, a process known[18] to occur with inversion of configuration, as well as the subsequent application of an intramolecular epoxide ring-opening reaction that delivers a *trans*-2,3-disubstituted 1,4-benzodioxane, the absolute configurations at the two stereogenic centers associated with the heterocyclic ring within compound **14** were assumed to be *S* in each case.

With the desired dioxane system **14** in hand, the final stages of the synthesis of the first enantiomeric form of aiphanol could be contemplated. Following the work of Ohira et al.,[5] phosphonium salt **15**[5] was prepared and then treated, in refluxing toluene and using CsF as base, with the readily derived MOM-ether, **16** (85%), of compound **14**. In this manner, the fully protected (2′*S*,3′*S*)-aiphanol derivative **17** was obtained in 41% yield. Global removal of the MOM groups associated with compound **17** was achieved using MeOH and AcCl and then the crude reaction product subjected to preparative HPLC to afford (2′*S*,3′*S*)-aiphanol (−)-**1** in 65% yield and >95% ee as determined by chiral HPLC analysis. The diagnostic features associated with the 500 MHz ^{1}H NMR spectrum of synthetic (−)-aiphanol include the doublet at δ 4.99 corresponding to the H-3′ proton. The magnitude of the coupling observed (J = 7.8 Hz) for this signal implies there is a *trans*-relationship between the aromatic substituent at C-3′ and the hydroxymethyl group at C-2′. The mutually coupled doublets at δ 7.04 and 6.96 are attributed to the protons associated with the ethylenic bridge of the stilbene and the magnitude (J = 16.3 Hz) of the observed coupling implies an *E*-configuration about this double bond. All other features within both the ^{1}H and ^{13}C NMR spectra were consistent with the data reported for the natural product[1] and essentially identical to those obtained for the racemic material.[6] Of course, most critically, an optical rotation measurement revealed this compound to be levorotatory {$[\alpha]_D = -20.1$ (c 0.2, MeOH)} implying that the 2′*S*,3′*S*-configured material corresponds to the natural product {lit.[1] $[\alpha]_D = -21.8$ (c 0.1, MeOH)}.

2.2. Synthesis of (2′*R*,3′*R*)-aiphanol (+)-1

The synthesis of (2′*R*,3′*R*)-aiphanol (+)-**1** was carried out in the same manner as described above for the synthesis of the natural product but using an AD mix-α in the Sharpless asymmetric dihydroxylation[14] of cinnamyl alcohol **5** at the start of the reaction sequence. The product triol *ent*-**6** was converted into bromide *ent*-**8** with the latter then being subject to single-crystal X-ray analysis for the purposes of the determination of its absolute configuration.[17] From such beginnings (+)-(2′*R*,3′*R*)-aiphanol (+)-**1** was ultimately obtained in >91% ee as

determined by chiral HPLC analysis. The 500 MHz ^{1}H NMR and 125 MHz ^{13}C NMR spectra of compound (+)-**1** were identical to the equivalent spectra of synthetically-derived (−)-(2′*S*,3′*S*)-aiphanol (−)-**1**. However, the specific rotation of (+)-**1** was, of course, dextrorotatory {$[\alpha]_D$ = +19.3 (*c* 0.2, MeOH)} implying that it was the non-natural isomer.

3. Conclusions

The reaction sequences described above and leading, in a predictable fashion, to each enantiomeric form of the stilbenolignan aiphanol **1** have allowed for the determination of the absolute stereochemistry of this natural product. This work serves to highlight the utility of Pan's protocols in the enantioselective construction of *trans*-2,3-disubstituted 1,4-benzodioxanes, as well as, in a more general sense, the value of combinations of AD and Mitsunobu reactions in the construction of stereochemically well defined and polyfunctionalized arrays. The acquisition of both enantiomeric forms of aiphanol now provides the opportunity to study, in a definitive manner, the impact of the absolute configuration of this novel compound on its biological profile. The outcomes of such a study will be reported in due course.

4. Experimental

4.1. General

Unless otherwise specified, ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 300 Spectrometer using deuterochloroform as solvent. Infrared spectra were recorded on either a Perkin–Elmer 683 or 1800 FTIR instrument. Mass spectral analyses were generally carried out in electron-impact (EI) mode on a VG Micromass 7070F Double-Focusing Spectrometer or, in certain cases, in electrospray (ES) mode on a VG Quattro II triple quadrupole liquid chromatograph-MS instrument. Thin layer chromatographic analyses were carried out on aluminum-backed 0.2 mm thick silica gel 60 GF_{254} plates supplied by Merck while flash chromatographic purifications were conducted according to the method of Still et al.[21] and using Merck silica gel 60 (230–400 mesh) as adsorbent. All solvents and common reagents were purified by established procedures.[22]

4.1.1. 3,5-Dimethoxy-4-(methoxymethoxy)benzaldehyde 3. A magnetically stirred mixture of aldehyde **2** (2.50 g, 14 mmol), DIPEA (3.8 mL, 22 mmol), and DMAP (15 mg, ca. 1 mol %) in DCM (40 mL) maintained at 0 °C (ice-water bath) under an atmosphere of nitrogen was treated, dropwise, with MOM-Cl (1.3 mL, 17 mmol). After addition was complete, the reaction mixture was allowed to warm to 18 °C and then stirred at this temperature for 6 h before being treated with cold HCl (50 mL of a 0.1 M aqueous solution). The DCM layer was separated, and the aqueous layer extracted with additional DCM (2 × 50 mL). The combined organic phases were washed with water (1 × 50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (2:3 v/v ethyl acetate/hexane elution) to afford, after concentration of the appropriate fractions [R_f 0.2(5)], the title compound **3**[11] (2.90 g, 95%) as a white, crystalline solid: mp 50–52 °C (lit.[11] mp 52–53 °C); IR: ν_{max} 2990, 2964, 2841, 1686, 1592, 1470, 1327, 1083, 951, 926, 828, 723 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.81 (s, 1H, CHO), 7.08 (s, 2H, ArH), 5.17 (s, 2H), 3.87 (s, 6H), 3.54 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.9 (CHO), 153.6 (C), 139.8 (C), 132.0 (C), 106.3 (CH), 98.0 (CH_2), 57.1 (OCH_3), 56.0 (OCH_3); MS (EI, 70 eV): *m*/*z* 226 ($M^{+\cdot}$, 100%), 196 (92), 195 (30), 181 (39), 180 (23), 125 (25), 95 (31); HRMS: $M^{+\cdot}$ calcd for $C_{11}H_{14}O_5$: 226.0841; found: 226.0842. Anal. Calcd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.45; H, 6.34.

4.1.2. Ethyl (*E*)-3,5-dimethoxy-4-(methoxymethoxy)-cinnamate 4. A magnetically stirred suspension of NaH (480 mg, 60% suspension washed free of oil with hexane, 12 mmol) in THF (50 mL) maintained at 0 °C (ice-water bath) under an atmosphere of nitrogen was treated, dropwise, with triethyl phosphonoacetate (2.2 mL, 11 mmol). The resulting suspension was warmed to 18 °C and stirred until no further evolution of H_2 gas was observed (ca. 0.25 h). Next, a solution of aldehyde **3** (2.40 g, 10.6 mmol) in THF (15 mL) was slowly introduced, via cannula, to the reaction mixture, which was then stirred at 18 °C for 4 h before being diluted with water (40 mL) and extracted with diethyl ether (3 × 60 mL). The combined organic phases were then dried over Na_2SO_4 filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (2:3 v/v ethyl acetate/hexane elution) and thereby affording, after concentration of the appropriate fractions [R_f 0.4(5)], title compound **4**[13] (2.60 g, 83%) as a white, crystalline solid: mp 64–66 °C; IR: ν_{max} 2953, 2840, 1691, 1586, 1463, 1424, 1250, 1153, 1124, 1074, 979, 817 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (d, J = 15.9 Hz, 1H), 6.71 (s, 2H, ArH), 6.31 (d, J = 15.9 Hz, 1H), 5.12 (s, 2H), 4.21 (q, J = 7.1 Hz, 2H), 3.83 (s, 6H), 3.56 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.8 (C=O), 153.3 (C), 144.4 (CH), 136.2 (C), 130.2 (C), 117.4 (CH), 104.8 (CH), 98.0 (CH_2), 60.3 (CH_2), 57.0 (OCH_3), 55.9 (OCH_3), 14.2 (CH_3); MS (EI, 70 eV): *m*/*z* 296 ($M^{+\cdot}$, 98%), 266 (95), 251 (100), 206 (62), 191 (42), 177 (33), 163 (20), 135 (17), 77 (15); HRMS: $M^{+\cdot}$ calcd for $C_{15}H_{20}O_6$: 296.1260; found: 296.1260. Anal. Calcd for $C_{15}H_{20}O_6$: C, 60.80; H, 6.80. Found: C, 61.09; H, 6.99.

4.1.3. (*E*)-3,5-Dimethoxy-4-(methoxymethoxy)cinnamyl alcohol 5. A magnetically stirred solution of ester **4** (2.30 g, 7.8 mmol) in toluene (40 mL) maintained at −10 °C (ice-salt bath) under an atmosphere of nitrogen was treated, dropwise, with DIBAL-H (19.5 mL of a 1 M solution in hexane, 19.5 mmol). After addition was complete, the reaction mixture was stirred at −10 °C for a further 45 min, at which point TLC analysis indicated that no starting material remained. Consequently, the reaction mixture was slowly quenched

(CAUTION), at −10 °C, with ethanol (ca. 5 mL), and then most of the solvent removed under reduced pressure. The residue thus obtained was treated with water (15 mL), and the resulting gelatinous precipitate extracted with ethyl acetate (5 × 30 mL). The combined organic phases were washed with water (1 × 50 mL) and brine (1 × 50 mL), then dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (3:2 v/v ethyl acetate/hexane elution) afforded, after concentration of the appropriate fractions (R_f 0.3), title compound **5**[13] (1.60 g, 81%) as a white, crystalline solid: mp 54–56 °C; IR: ν_{max} 3425 (broad), 2939, 1585, 1505, 1463, 1419, 1335, 1242, 1155, 1127, 967 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.60 (s, 2H, ArH), 6.52 (dt, J = 15.8 and 1.4 Hz, 1H), 6.26 (dt, J = 15.8 and 5.6 Hz, 1H), 5.11 (s, 2H), 4.29 (broad d, J = 5.6 Hz, 2H), 3.84 (s, 6H), 3.59 (s, 3H), 1.76 (broad s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.3 (C), 134.1 (C), 132.8 (C), 130.9 (CH), 128.1 (CH), 103.4 (CH), 98.1 (CH_2), 63.5 (CH_2), 57.1 (OCH_3), 55.9 (OCH_3); MS (EI, 70 eV): m/z 254 ($M^{+\cdot}$, 100%), 224 (52), 209 (58), 181 (30), 164 (30), 149 (83), 121 (30), 77 (26); HRMS: $M^{+\cdot}$ calcd for $C_{13}H_{18}O_5$: 254.1154; found: 254.1155. Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14. Found: C, 61.22; H, 7.33.

4.1.4. (1*R*,2*R*)-1-(3′,5′-Dimethoxy-4′-methoxymethoxyphenyl)-2,3-dihydroxypropanol 6. A mixture of *t*-BuOH (15 mL) and water (15 mL) was treated with AD mix-β (3.10 g) and methanesulfonamide (200 mg, 0.7 mmol), then stirred magnetically at 18 °C until the two phases observed were both clear. The ensuing mixture was cooled to 0 °C (ice-water bath), treated with cinnamyl alcohol **5** (550 mg, 2.2 mmol) and then stirred vigorously at 0 °C for 48 h. The reaction mixture was quenched, at 0 °C, by the addition of Na_2SO_3 (3.20 mg), warmed to 18 °C, stirred at this temperature for 0.5 h and then extracted with ethyl acetate (4 × 50 mL). The combined organic extracts were washed with KOH (1 × 50 mL of a 2 M aqueous solution) and water (1 × 50 mL) and then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Subjection of this material to flash chromatography (9:1 v/v diethyl ether/methanol elution) afforded, after concentration of the appropriate fractions [R_f 0.2(5)], an off-white solid. Recrystallization (methanol–DCM) of this material then gave title compound **6** (490 mg, 80%) as a white, crystalline solid, mp 73–75 °C, in >95% ee (as determined by chiral HPLC analysis using CHIRALPAK® AS-H 250 × 4.6 mm column, 1:3 v/v isopropyl alcohol/hexane elution at a solvent flow rate of 1.0 mL/min and with UV peak detection at 254 nm, t_R 13.3 min): $[\alpha]_D$ = −24 (c 1.0, $CHCl_3$); IR: ν_{max} 3401 (broad), 2940, 1594, 1506, 1462, 1422, 1329, 1233, 1125, 1078, 968, 836 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.60 (s, 2H, ArH), 5.09 (s, 2H), 4.60 (d, J = 6.5 Hz, 1H), 3.82 (s, 6H), 3.73 (m, 1H), 3.61 (dd, J = 11.4 and 3.3 Hz, 1H), 3.58 (s, 3H), 3.55 (dd, J = 11.4 and 4.8 Hz, 1H), 2.99 (broad s, 3H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.4 (C), 136.7 (C), 133.9 (C), 103.4 (CH), 98.0 (CH_2), 75.7 (CH), 74.8 (CH), 63.3 (CH_2), 57.1 (OCH_3), 56.1 (OCH_3); MS (EI, 70 eV): m/z 288 ($M^{+\cdot}$, 10%), 227 (45), 197 (15), 195 (20), 169 (17), 167 (9), 123 (11), 45 (100); HRMS: $M^{+\cdot}$ calcd for $C_{13}H_{20}O_7$: 288.1209; found: 288.1207. Anal. Calcd for $C_{13}H_{20}O_7$: C, 54.16; H, 6.99. Found: C, 54.57; H, 7.23.

4.1.5. (1*R*,2*R*)-1-(2′-Bromo-4′-hydroxy-3′,5′-dimethoxyphenyl)-2,3-dihydroxypropanol 8. A magnetically stirred solution of compound **6** (25 mg, 0.1 mmol) in DCM (5 mL) maintained at 18 °C was treated, in one portion, with pyridinium hydrobromide perbromide[16] (32 mg, 0.1 mmol) and the ensuing mixture stirred for a further 10 min at which time TLC analysis indicated no starting material remained. Consequently, the reaction mixture was quenched with $NaHSO_4$ (0.5 mL of a 1 M aqueous solution) then $NaHCO_3$ (2 mL of a saturated aqueous solution) was added. The DCM layer was separated, and the aqueous layer extracted with DCM (2 × 5 mL). The combined organic phases were washed with brine (1 × 10 mL), dried over Na_2SO_4, filtered, and the filtrate concentrated under reduced pressure. The resulting oil was subjected to high vacuum for 5 h to afford compound **7** (28 mg, 85%) as a clear, colorless oil. A solution of compound **7** (28 mg, 0.1 mmol) in MeOH (5 mL) was treated with concd HCl (one drop) and the ensuing mixture was stirred magnetically at 18 °C for 18 h. Methanol was then removed under reduced pressure, water (10 mL) was added to the residue and the resulting mixture extracted with ethyl acetate (3 × 10 mL). The combined organic phases were then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (19:1 v/v ethyl acetate/methanol elution) to afford, after concentration of the appropriate fractions (R_f 0.4), a white solid. Recrystallization (methanol–DCM) of this material afforded the title compound **8** (20 mg, 91%) as colorless crystals: mp 172–174 °C; $[\alpha]_D$ −51.7 (c 0.5, MeOH); IR: ν_{max} 3365 (broad), 2938, 1594, 1495, 1410, 1314, 1176, 1097, 856 cm^{-1}; ^1H NMR (300 MHz, CD_3OD): δ 7.05 (s, 1H, ArH), 5.04 (d, J = 3.8 Hz, 1H), 3.89 (s, 3H), 3.80 (s, 3H), 3.75 (m, 1H), 3.60 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD): δ 148.2, 144.5, 139.8, 132.1, 108.1, 107.5, 74.9, 72.0, 63.6, 59.5 55.4; MS (EI, 70 eV): m/z 288 ($M^{+\cdot}$, 10%), 227 (45), 195 (20), 169 (17), 123 (11), 45 (100); HRMS: $M^{+\cdot}$ calcd for $C_{11}H_{15}{}^{81}BrO_6$: 324.0032; found: 324.0032.

4.1.6. (1*R*,2*R*)-1-(3′,5′-Dimethoxy-4′-methoxymethoxyphenyl)-1,2-dihydroxypropyl tosylate 9. A magnetically stirred solution of triol **6** (350 mg, 1.2 mmol) in dry pyridine (15 mL) maintained at 0 °C (ice-water bath) under an atmosphere of nitrogen was treated, in one portion, with TsCl (250 mg, 1.3 mmol). The cooling bath was removed and the mixture allowed to warm to 18 °C and stirred at this temperature for 18 h, then diluted with ethyl acetate (35 mL) and washed with cold HCl (2 × 30 mL of a 0.1 M aqueous solution). The organic phase was then dried over Na_2SO_4, filtered, and the filtrate concentrated under reduced pressure. Subjection of the resulting gum to flash chromatography (7:3 v/v ethyl acetate/hexane elution) afforded, after concentration of the appropriate fractions [R_f 0.2(5)], title

compound **9** (380 mg, 72%) as a white, crystalline solid: mp 68–70 °C; $[\alpha]_D = -14$ (*c* 1.0, $CHCl_3$); IR: ν_{max} 3422 (broad), 2940, 1595, 1462, 1422, 1357, 1235, 1189, 1176, 1126, 967, 815 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, $J = 8.2$ Hz, 2H, ArH), 7.34 (d, $J = 8.2$ Hz, 2H, ArH), 6.57 (s, 2H, ArH), 5.09 (s, 2H), 4.63 (d, $J = 6.2$ H, 1H), 4.04–3.86 (m, 3H), 3.82 (s, 6H), 3.58 (s, 3H), 2.60 (broad s, 2H, OH), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.4 (C), 145.2 (C), 135.7 (C), 134.1 (C), 132.3 (C), 129.9 (CH), 127.9 (CH), 103.3 (CH), 98.0 (CH_2), 73.6 (CH), 73.5 (CH), 70.1 (CH_2), 57.1 (OCH_3), 56.0 (OCH_3), 21.6 (CH_3); MS (EI, 70 eV): *m*/*z* 442 ($M^{+\cdot}$, <1%), 410 (7), 380 (4), 227 (20), 208 (22), 183 (25), 155 (48), 167 (65), 91 (92), 45 (100); HRMS: $M^{+\cdot}$ calcd for $C_{20}H_{26}O_9S$: 442.1298; found: 442.1293.

4.1.7. (1*R*,2*R*)-2,3-Epoxy-1-(3′,5′-dimethoxy-4′-methoxymethoxyphenyl)propanol 10. A solution of tosylate **9** (301 mg, 0.7 mmol) in dry methanol (20 mL) was treated with K_2CO_3 (98 mg of anhydrous material, 0.7 mol) and the resulting suspension stirred vigorously at 18 °C under an atmosphere of nitrogen for 3 h, then poured into water (20 mL) and extracted with ethyl acetate (3×20 mL). The combined organic phases were washed with brine (1×30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (7:3 v/v ethyl acetate/hexane elution) gave, after concentration of the appropriate fractions [R_f 0.3(5)], an off-white solid. Recrystallization (DCM–hexane) of this material then afforded title compound **10** (160 mg, 88%) as a white, crystalline solid, mp 71–73 °C, in >95% ee (as determined by chiral HPLC analysis using CHIRALPAK® AS-H 250×4.6 mm column, 1:3 v/v isopropyl alcohol/hexane elution at a solvent flow rate of 1 mL/min and with UV peak detection at 254 nm, t_R 16.1 min): $[\alpha]_D = -5.4$ (*c* 1.3, $CHCl_3$); IR: ν_{max} 3433 (broad), 2940, 1593, 1505, 1462, 1420, 1331, 1230, 1155, 1126, 1078, 969, 924 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.63 (s, 2H), 5.11 (s, 2H), 4.40 (d, $J = 4.9$ Hz, 1H), 3.85 (s, 6H), 3.59 (s, 3H), 3.20 (m, 1H), 2.84 (m, 2H), 2.56 (broad s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.5 (C), 136.3 (C), 134.1 (C), 103.2 (CH), 98.1 (CH_2), 74.4 (CH), 57.1 (CH), 56.0 (OCH_3), 55.8 (OCH_3), 45.4 (CH_2); MS (EI, 70 eV): *m*/*z* 270 ($M^{+\cdot}$, 27%), 240 (10), 197 (16), 195 (17), 177 (23), 165 (32), 109 (12), 45 (100); HRMS: $M^{+\cdot}$ calcd for $C_{13}H_{18}O_6$: 270.1103; found: 270.1102. Anal. Calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71. Found: C, 57.90; H, 7.00.

4.1.8. 4-Benzyloxy-3-hydroxybenzaldehyde 11. A magnetically stirred suspension of NaH (160 mg, 60% suspension washed free of oil with hexane, 4.0 mmol) in DMSO (5 mL) maintained at 18 °C under an atmosphere of nitrogen was treated, in portions over 10 min, with 3,4-dihydroxybenzaldehyde (499 mg, 3.6 mmol). The resulting mixture was stirred at 18 °C for 1 h then benzyl chloride (410 μL, 3.6 mmol) was added dropwise to the reaction mixture. Stirring was continued for 18 h then the ensuing mixture diluted with water (15 mL) and the basic solution washed with diethyl ether (3×10 mL). The aqueous phase was acidified with HCl (0.5 M aqueous solution) to pH ~4 then extracted with ethyl acetate (4×20 mL). The combined organic extracts were then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (7:3 v/v diethyl ether/hexane elution) to afford, after concentration of the appropriate fractions (R_f 0.5), a white solid. Recrystallization (ethanol) of this material gave the title compound **11**[19] (320 mg, 39%) as colorless crystals: mp 120–121 °C (lit.[19b] mp 121–122 °C); IR: ν_{max} 3210 (broad), 2870, 1674, 1605, 1580, 1513, 1344, 1288, 1259, 1117, 1016, 1008, 812, 728 cm^{-1}; ^1H NMR (300 MHz, CD_3COCD_3): δ 9.83 (s, 1H, CHO), 8.40 (broad s, 1H, OH), 7.53 (dm, $J = 8.2$ Hz, 1H), 7.45–7.32 (complex m, 6H, ArH), 7.24 (d, $J = 8.2$ Hz, 1H), 5.26 (s, 2H); ^{13}C NMR (75 MHz, CD_3COCD_3): δ 190.9 (CHO), 152.3 (C), 147.6 (C), 136.6 (C), 131.1 (C), 128.7 (CH), 128.4 (CH), 128.3 (CH), 124.3 (CH), 114.4 (CH), 112.7 (CH), 70.8 (CH_2); MS (EI, 70 eV): *m*/*z* 228 $M^{+\cdot}$, 17%, 137 (3), 109 (3), 91 (100), 81 (6), 65 (21); HRMS: $M^{+\cdot}$ calcd for $C_{14}H_{12}O_3$: 228.0786; found: 228.0789.

4.1.9. (1′*S*,2′*R*)-4-Benzyloxy-3-[2′,3′-epoxy-1′-(3″,5″-dimethoxy-4″-methoxymethoxyphenyl)-propoxy]-benzaldehyde 12. A magnetically stirred solution of aldehyde **11** (111 mg, 0.5 mmol) and DIAD (98 μL, 0.5 mmol) in dry toluene (10 mL) maintained at 18 °C under an atmosphere of nitrogen was treated, dropwise, with a solution of PPh_3 (130 mg, 0.5 mmol) and epoxide **10** (101 mg, 0.4 mmol) in dry THF–toluene (2 mL of a 1:1 v/v mixture). The ensuing mixture was stirred at 18 °C for 24 h and then solvent removed under reduced pressure. Subjection of the residue thus obtained to flash chromatography (3:2 v/v ethyl acetate/hexane elution) then gave, after concentration of the appropriate fractions (R_f 0.3), title compound **12** (99 mg, 60%) as a white, crystalline solid, mp 50–52 °C, in >95% ee (as determined by chiral HPLC analysis using CHIRALPAK® AS-H 250×4.6 mm column, 1:3 v/v isopropyl alcohol/hexane elution at a solvent flow rate of 0.8 mL/min and with UV peak detection at 254 nm, t_R 39.9 min): $[\alpha]_D = +11.9$ (*c* 0.6, $CHCl_3$); IR: ν_{max} 2939, 2840, 1687, 1596, 1507, 1462, 1436, 1337, 1272, 1128, 967, 739, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.77 (s, 1H, CHO), 7.48–7.34 (complex m, 7H, ArH), 7.02 (d, $J = 8.7$ Hz, 1H, ArH), 6.68 (s, 2H, ArH), 5.24–5.14 (complex m, 3H), 5.10 (s, 2H), 3.77 (s, 6H), 3.58 (s, 3H), 3.34 (m, 1H), 2.89 (dd, $J = 5.2$ and 2.6 Hz, 1H), 2.80 (dd, $J = 5.2$ and 3.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.5 (CHO), 154.8 (C), 153.5 (C), 147.8 (C), 136.0 (C), 134.4 (C), 133.2 (C), 130.1 (C), 128.6 (CH), 128.2 (CH), 127.1 (CH), 115.8 (CH), 113.0 (CH), 103.7 (CH), 98.1 (CH_2), 80.3 (CH), 70.7 (CH_2), 57.1 (CH), 56.0 (OCH_3), 54.2 (OCH_3), 45.1 (CH_2) (one signal obscured or overlapping); MS (EI, 70 eV): *m*/*z* 480 ($M^{+\cdot}$, 7%), 450 (6), 272 (11), 253 (96), 223 (27), 195 (47), 91 (95), 45 (100); HRMS: $M^{+\cdot}$ calcd for $C_{27}H_{28}O_8$: 480.1784; found: 480.1777. Anal. Calcd for $C_{27}H_{28}O_8$: C, 67.49; H, 5.87. Found: C, 67.07; H, 5.66.

4.1.10. (1*S*,2*R*)-4-Hydroxy-3-[2′,3″-epoxy-1′-(3″,5″-dimethoxy-4″-methoxymethoxyphenyl)-propoxy]-benzaldehyde 13. A solution of compound **12** (60 mg,

0.1 mmol) in ethyl acetate (5 mL) was treated with 5% Pd on C (6 mg) and the resulting mixture stirred magnetically under a hydrogen atmosphere at 18 °C for 9 h. The reaction mixture was then filtered and the filtrate concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (3:2 v/v ethyl acetate/hexane elution) to afford, after concentration of the appropriate fractions [R_f 0.3(5)], title compound **13** (35 mg, 71%) as an amorphous solid and in >95% ee (as determined by chiral HPLC analysis using CHIRALPAK® AS-H 250 × 4.6 mm column, 1:3 v/v isopropyl alcohol/hexane elution at a solvent flow rate of 1 mL/min and with UV peak detection at 254 nm, t_R 25.5 min): $[\alpha]_D$ = +142.4 (*c* 0.4, $CHCl_3$); IR: ν_{max} 3360 (broad), 2939, 1684, 1595, 1507, 1462, 1443, 1287, 1238, 1154, 1126, 964 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.71 (s, 1H, CHO), 8.10 (broad s, 1H, OH), 7.52 (dd, *J* = 8.2 and 1.9 Hz, 1H, ArH), 7.32 (d, *J* = 1.9 Hz, 1H, ArH), 7.05 (d, *J* = 8.2 Hz, 1H, ArH), 6.63 (s, 2H, ArH), 5.14 (s, 2H), 4.99 (d, *J* = 2.3 Hz, 1H), 3.85 (s, 6H), 3.61 (s, 3H), 3.38 (m, 1H), 3.25 (m, 1H), 2.96 (t, *J* = 4.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.4 (CHO), 154.5 (C), 153.8 (C), 145.9 (C), 134.8 (C), 132.2 (C), 129.4 (C), 128.8 (CH), 119.8 (CH), 116.6 (CH), 103.5 (CH), 98.1 (CH_2), 81.9 (CH), 57.1 (CH), 56.1 (OCH_2), 54.7 (OCH_3), 44.7 (CH_2); MS (EI, 70 eV): *m/z* 390 ($M^{+\cdot}$, 100%), 345 (12), 253 (40), 195 (49), 149 (41), 137 (30), 99 (28); HRMS: $M^{+\cdot}$ calcd for $C_{20}H_{22}O_8$: 390.1315; found: 390.1312.

4.1.11. (2*S*,3*S*)-3-(3′,5′-Dimethoxy-4′-methoxymethoxyphenyl)-2-hydroxymethyl-2,3-dihydro-1,4-benzodioxin-6-carbaldehyde 14. A solution of compound **13** (26 mg, 0.1 mmol) in dry methanol (5 mL) was treated with K_2CO_3 (10 mg of anhydrous material, 0.1 mmol) and the resulting suspension stirred magnetically at 18 °C for 0.75 h. The methanol was then removed under reduced pressure and the residue treated with cold HCl (2 mL of a 0.1 M aqueous solution), extracted with ethyl acetate (4 × 5 mL), washed with brine (1 × 10 mL) then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography (3:2 v/v ethyl acetate/hexane elution) to afford, after concentration of the appropriate fractions (R_f 0.4), title compound **14** (17 mg, 70%) as an amorphous solid in >95% ee (as determined by chiral HPLC analysis using CHIRALPAK® AS-H 250 × 4.6 mm column, 1:3 v/v isopropyl alcohol/hexane elution at a solvent flow rate of 1 mL/min and with UV peak detection at 254 nm, t_R 27.2 min): $[\alpha]_D$ = −48.4 (*c* 0.3, $CHCl_3$); IR: ν_{max} 3436 (broad), 2925, 2853, 1690, 1595, 1502, 1463, 1314, 1279, 1263, 1155, 1128, 959 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.83 (s, 1H, CHO), 7.53–7.49 (complex m, 2H, ArH), 7.12 (dm, *J* = 8.7 Hz, 1H, ArH), 6.74 (s, 2H, ArH), 5.15 (s, 2H), 4.95 (d, *J* = 8.9 Hz, 1H), 4.72 (dd, *J* = 13.0 and 3.0 Hz, 1H), 4.41 (dd, *J* = 13.0 and 1.5 Hz, 1H), 4.23 (dm, *J* = 8.9 Hz, 1H), 3.88 (s, 6H), 3.62 (s, 3H) (signal due to OH not observed); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.5 (CHO), 155.4 (C), 153.5 (C), 149.3 (C), 134.5 (C), 134.0 (C), 131.9 (C), 125.5 (CH), 122.9 (CH), 121.3 (CH), 103.6 (CH), 98.1 (CH_2), 85.7 (CH), 74.9 (CH), 74.8 (CH_2), 57.2 (OCH_3), 56.1 (OCH_3); MS (EI, 70 eV): *m/z* 390 ($M^{+\cdot}$, 95%), 346 (16), 345 (15), 316 (11), 253 (18), 195 (83), 149 (73), 57 (100); HRMS: $M^{+\cdot}$ calcd for $C_{20}H_{22}O_8$: 390.1315; found: 390.1310.

4.1.12. 3,5-Bis-(methoxymethoxy)benzyltriphenyl-phosphonium chloride 15

4.1.12.1. Step (i): Formation of methyl 3,5-bis-methoxymethoxybenzoate. A magnetically stirred mixture of methyl 3,5-dihydroxybenzoate (501 mg, 3.0 mmol), DMAP (5 mg, 14 mol %), and DIPEA (1.6 mL, 9 mmol) in DCM (20 mL) maintained at 0 °C (ice-water bath) under an atmosphere of nitrogen was treated, dropwise, with MOM-Cl (600 μL, 8 mmol). The ensuing reaction mixture was allowed to warm to 18 °C, stirred at this temperature for 18 h and then poured into cold HCl (20 mL of a 0.1 M aqueous solution). The separated aqueous layer was extracted with DCM (2 × 20 mL) and the combined organic extracts washed with water (1 × 40 mL) and brine (1 × 40 mL) then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting gum was subjected to flash chromatography (2:3 v/v ethyl acetate/hexane elution) to afford, after concentration of the appropriate fractions (R_f 0.5), methyl 3,5-bis-methoxymethoxybenzoate[23] (700 mg, 91%) as a clear, colorless oil: IR: ν_{max} 2955, 2905, 1724, 1597, 1438, 1302, 1146, 1032, 924, 770, 682 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.35 (d, *J* = 2.3 Hz, 2H, ArH), 6.91 (t, *J* = 2.3 Hz, 1H, ArH), 5.17 (s, 4H), 3.88 (s, 3H), 3.46 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.5 (C=O), 158.0 (C), 132.1 (C), 110.5 (CH), 109.6 (CH), 94.3 (CH_2), 56.1 (OCH_3), 52.2 (OCH_3); MS (EI, 70 eV): *m/z* 256 ($M^{+\cdot}$, 100%), 225 (80), 196 (18), 193 (17), 139 (16), 63 (38); HRMS: $M^{+\cdot}$ calcd for $C_{12}H_{16}O_6$: 256.0947; found: 256.0944. Anal. Calcd for $C_{12}H_{16}O_6$: C, 56.24; H, 6.29. Found: C, 56.40; H, 6.46.

4.1.12.2. Step (ii): Formation of 3,5-bis-methoxymethoxybenzyl alcohol. A magnetically stirred solution of methyl 3,5-bis-methoxymethoxybenzoate (502 mg, 2.0 mmol) in dry THF (25 mL) maintained at 0 °C (ice-water bath) under an atmosphere of nitrogen was treated, dropwise, with $LiAlH_4$ (2.8 mL of a 1 M solution in THF, 2.8 mmol). After addition was complete, the reaction mixture was warmed to 18 °C and stirred at this temperature for 2 h, then treated sequentially with water (200 μL), NaOH (200 μL of a 15% w/v aqueous solution) and, again, with water (200 μL). The ensuing mixture was stirred for a further 2 h and the resulting granular mixture then filtered through a pad of Celite™ and the filtrate concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (2:3 v/v ethyl acetate/hexane elution) to afford, after concentration of the appropriate fractions [R_f 0.2(5)], 3,5-bis-methoxymethoxybenzyl alcohol[23] (430 mg, 97%) as an amorphous, white solid: IR: ν_{max} 3418 (broad), 2955, 2903, 1599, 1459, 1291, 1145, 1083, 1034, 923, 846 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.69 (d, *J* = 2.2 Hz, 2H, ArH), 6.63 (t, *J* = 2.2 Hz, 1H, ArH), 5.14 (s, 4H), 4.59 (s, 2H), 3.45

(s, 6H), 2.28 (broad s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.3 (C), 143.6 (C), 107.8 (CH), 103.9 (CH), 94.3 (CH_2), 64.9 (CH_2), 56.0 (OCH_3); MS (EI, 70 eV): *m/z* 228 ($M^{+\cdot}$, 80%), 211 (12), 198 (23), 168 (40), 152 (23), 107 (16), 77 (17), 45 (100); HRMS: $M^{+\cdot}$ calcd for $C_{11}H_{16}O_5$: 228.0998; found: 228.0997. Anal. Calcd for $C_{11}H_{16}O_5$: C, 57.88; H, 7.07. Found: C, 58.00; H, 7.30.

4.1.12.3. Step (iii): Formation of 3,5-bis-methoxymethoxybenzyl chloride. A magnetically stirred solution of 3,5-bis-methoxymethoxybenzyl alcohol (350 mg, 1.5 mmol) and TEA (240 μL, 1.7 mmol) in DCM (20 mL) maintained at 0 °C (ice-water bath) under an atmosphere of nitrogen was treated, dropwise, with MsCl (130 μL, 1.7 mmol). After addition was complete, the mixture was allowed to warm to 18 °C, stirred at this temperature for 18 h, poured into cold water (20 mL), the DCM layer separated, and the aqueous layer extracted with additional DCM (2 × 15 mL). The combined organic phases were then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to column chromatography (2:3 v/v ethyl acetate/hexane elution) to afford, after concentration of the appropriate fractions (R_f 0.7), 3,5-bis-methoxymethoxybenzyl chloride[5] (301 mg, 79%) as a clear, colorless oil: IR: ν_{max} 2958, 2903, 1599, 1461, 1296, 1146, 1083, 1034, 933, 850, 717 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.73 (d, J = 2.2 Hz, 2H, ArH), 6.69 (t, J = 2.2 Hz, 1H, ArH), 5.16 (s, 4H), 4.50 (s, 2H), 3.47 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.3 (C), 139.6 (C), 109.7 (CH), 104.7 (CH), 94.3 (CH_2), 56.0 (OCH_3), 46.0 (CH_2); MS (EI, 70 eV): *m/z* 248 and 246 ($M^{+\cdot}$, 55 and 100%), 211 (61), 186 (16), 77 (46); HRMS: $M^{+\cdot}$ calcd for $C_{11}H_{15}ClO_4$: 246.0659; found: 246.0659. Anal. Calcd for $C_{11}H_{15}ClO_4$: C, 53.56; H, 6.13; Cl, 14.37. Found: C, 53.71; H, 6.22; Cl, 14.20.

4.1.12.4. Step (iv): Formation of 3,5-bis-(methoxymethoxy)benzyltriphenylphosphonium chloride 15. A solution of 3,5-bis-methoxymethoxybenzyl chloride (250 mg, 1.0 mmol) in toluene (30 mL) was treated with PPh_3 (301 mg, 1.2 mmol) and the resulting mixture heated at reflux for 18 h. The mixture was then cooled to ca. 18 °C and the white precipitate formed was filtered off, washed thoroughly with diethyl ether and then dried at 80 °C for 3 h to afford the title salt **15**[5] (401 mg, 76%) as a white, crystalline solid: mp 188–190 °C; IR: ν_{max} 3594, 3378, 2902, 1595, 1435, 1135, 1036, 879, 746, 693 cm^{-1}; ^{1}H NMR (300 MHz, CD_3SOCD_3): δ: 7.88 (m, 3H), 7.80–7.60 (complex m, 12 H), 6.57 (ABq, J = 2.1 Hz, 1H, ArH), 6.33 (t, J = 2.2 Hz, 2H, ArH), 5.20 (d, J = 15.7 Hz, 2H), 4.91 (s, 4H), 3.21 (s, 6H); ^{13}C NMR (75 MHz, CD_3SOCD_3): δ 158.4 (d, $J_{C,P}$ = 3.4 Hz), 135.7, 134.7 (d, $J_{C,P}$ = 9.7 Hz), 130.7(5), 130.7(4) (d, $J_{C,P}$ = 12.6 Hz), 119.1, 117.9, 112.9, 105.1, 94.4, 56.2; MS (EI, 70 eV): *m/z* 472 [$(M-HCl)^+$, 34%], 427 (8), 262 (100), 183 (66), 108 (26); HRMS: $(M-HCl)^+$ calcd for $C_{29}H_{30}ClO_4P$: 472.1803; found: 472.1801. Anal. Calcd for $C_{29}H_{30}ClO_4P$: C, 68.43; H, 5.94; Cl, 6.97; P, 6.09. Found: C, 68.17; H, 6.07; Cl, 6.98; P, 5.86.

4.1.13. (1*E*,2′*S*,3′*S*)-5-{2′-[2′,3′-Dihydro-3′-(4″-hydroxy-3″,5″-dimethoxyphenyl)-2′-(hydroxymethyl)-1′,4′-benzodioxin-6′-yl]ethenyl}-1,3-benzenediol [(−)-aiphanol] (−)-1. A magnetically stirred solution of compound **14** (11 mg, 0.03 mmol), DIPEA (20 μL, 0.1 mmol), and DMAP (0.5 mg, catalyst) in DCM (2 mL) maintained at 0 °C (ice-water bath) under an atmosphere of nitrogen was treated with MOM-Cl (8 μL, 0.1 mmol). The resulting mixture was warmed to 18 °C, stirred at this temperature for 3 h, poured into water (5 mL), and the DCM layer separated. The aqueous layer was extracted with additional DCM (2 × 5 mL) and the combined organic phases washed with brine (1 × 10 mL) and then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue thus obtained was passed through a short pad of silica (3:2 v/v ethyl acetate/hexane elution). The eluent was concentrated under reduced pressure then dried under high vacuum to afford compound **16** (11 mg, 85%) as a light-brown gum. A solution of compound **16** (11 mg, 0.02 mmol) in dry toluene (5 mL) was treated with phosphonium salt **15** (20 mg, 0.04 mmol) and CsF (8 mg, 0.05 mmol). The ensuing suspension was heated at reflux for 6 h then cooled to 18 °C and treated with water (5 mL). The aqueous phase was extracted with ethyl acetate (3 × 10 mL), and the combined organic phases washed with brine (1 × 10 mL) then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue thus obtained was passed through a short pad of silica (3:2 v/v ethyl acetate/hexane elution) and concentration of the highly UV active eluent (R_f 0.5) afforded *compound 17* (6 mg, 41%), which was used directly in the next step of the reaction sequence. Thus, a magnetically stirred solution of compound **17** (6 mg, 0.01 mmol) in MeOH (2 mL) maintained under an atmosphere of nitrogen was treated with AcCl (10 μL) and the ensuing mixture stirred at 18 °C for 20 h then the MeOH removed under reduced pressure. HCl (5 mL of a 0.1 M aqueous solution) was added to the residue, which was then extracted with ethyl acetate (3 × 5 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (4:1 v/v ethyl acetate/hexane elution) to afford, upon concentration of a highly UV active band [R_f 0.3(5)], a brown solid. Purification of this material by HPLC (using a 300 × 7.8 mm C_{18} Alltech Alltima column, 50:49.95:0.05 v/v/v H_2O/MeOH/AcOH elution, solvent flow rate of 5 mL/min, UV peak detection at 325 nm, t_R 15.05 min), afforded the title compound (+)-**1**[1] (2.7 mg, 65%) as a light-brown solid in >95% ee (as determined by chiral HPLC analysis using CHIRALPAK® AS-H 250 × 4.6 mm column, 1:1 v/v isopropyl alcohol/hexane elution at a solvent flow rate of 1.2 mL/min and with UV peak detection at 325 nm, t_R 12.1 min): $[\alpha]_D$ = −20.1 (*c* 0.2, MeOH) [lit.[1] −21.8 (*c* 0.1, MeOH)]; IR: ν_{max} 3370 (broad), 2925, 1595, 1505, 1463, 1345, 1270, 1216, 1115, 1048, 831 cm^{-1}; ^{1}H NMR (500 MHz, CD_3COCD_3): δ 8.25 (broad s, 2H, OH), 7.42 (broad s, 1H, OH), 7.15 (d, J = 1.9 Hz, 1H, ArH), 7.10 (dd, J = 8.3 and 2.0 Hz, 1H, ArH), 7.04 (d, J = 16.3 Hz, 1H), 6.96 (d, J = 16.3 Hz, 1H), 6.91 (d, J = 8.3 Hz, 1H, ArH), 6.84 (s, 2H, ArH), 6.57 (d, J = 1.9 Hz, 2H, ArH), 6.30 (t, J = 1.9 Hz, 1H, ArH), 4.99 (d,

J = 7.8 Hz, 1H), 4.16 (ddd, J = 8.3, 4.4 and 2.3 Hz, 1H), 4.06 (tm, J = 6.8 Hz, 1H, OH), 3.87 (s, 6H), 3.77 (ddd, J = 12.3, 3.9 and 2.3 Hz, 1H), 3.55 (ddd, J = 12.3, 6.8 and 4.4 Hz, 1H); ^{13}C NMR (125 MHz, CD_3COCD_3): δ 159.3 (C), 148.5 (C), 144.5 (C), 144.4 (C), 140.3 (C), 137.0 (C), 131.7 (C), 128.4 (CH), 127.8 (CH and C), 120.3 (CH), 117.6 (CH), 115.0 (CH), 105.8 (CH), 105.5 (CH), 102.6 (CH), 79.2 (CH), 77.3 (CH), 61.6 (CH_2), 56.4 (OCH_3); MS (EI, 70 eV): m/z 452 ($M^{+\cdot}$, 100%), 438 (40), 346 (18), 255 (30), 210 (82), 167 (60), 149 (32), 121 (43), 91 (67); HRMS: $M^{+\cdot}$ calcd for $C_{25}H_{24}O_8$: 452.1471; found: 452.1466.

4.1.14. (1*S*,2*S*)-1-(3′,5′-Dimethoxy-4′-methoxymethoxyphenyl)-2,3-dihydroxypropanol *ent*-6. The title compound was prepared by the asymmetric dihydroxylation of cinnamyl alcohol **5** in the same manner as employed in the preparation of enantiomer **6** except that AD mix-α was used. Recrystallization (methanol–DCM) of the solid obtained on work-up afforded the title compound *ent*-**6** (78%) as a white, crystalline solid, mp 73–75 °C, in >95% ee (as determined by chiral HPLC analysis using CHIRALPAK® AS-H 250 × 4.6 mm column, 1:3 v/v isopropyl alcohol/hexane elution at a solvent flow rate of 1 mL/min and with UV peak detection at 254 nm, t_R 14.1 min): $[\alpha]_D$ = +23.9 (c 1.0, $CHCl_3$); HRMS: $M^{+\cdot}$ calcd for $C_{13}H_{20}O_7$: 288.1209; found: 288.1209. Anal. Calcd for $C_{13}H_{20}O_7$: C, 54.16; H, 6.99. Found: C, 54.20; H, 7.10. The IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data derived from this material matched those reported above for enantiomer **6**.

4.1.15. (1*S*,2*S*)-1-(2′-Bromo-4′-hydroxy-3′,5′-dimethoxyphenyl)-2,3-dihydroxypropanol *ent*-8. Compound *ent*-**6** was transformed into the title derivative in the same manner as used for the conversion **6** → **8**. In this way title compound *ent*-**8** was obtained in 93% yield and as colorless crystals: mp 172–174 °C; $[\alpha]_D$ = +51.2 (c 0.3, MeOH). The ^{1}H and ^{13}C NMR spectral data derived from this material matched those reported above for enantiomer **8**.

4.1.16. (1*S*,2*S*)-1-(3′,5′-Dimethoxy-4′-methoxymethoxyphenyl)-1,2-dihydroxypropyl tosylate *ent*-9. Compound *ent*-**6** was transformed into the title compound in the same manner as used for the conversion **6** → **9**. In this way the title compound *ent*-**9** was obtained in 73% yield and as colorless crystals: mp 67–69 °C; $[\alpha]_D$ = +13.5 (c 0.8, $CHCl_3$); HRMS: $M^{+\cdot}$ calcd for $C_{20}H_{26}O_9S$: 442.1298; found: 442.1295. The IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data derived from this material matched those reported above for enantiomer **9**.

4.1.17. (1*S*,2*S*)-2,3-Epoxy-1-(3′,5′-dimethoxy-4′-methoxymethoxyphenyl)propanol *ent*-10. Compound *ent*-**10** was transformed into the title compound in the same manner as used for the conversion **9** → **10**. In this way the compound *ent*-**10** was obtained in 82% yield and as colorless crystals, mp 71–73 °C, in >95% ee (as determined by chiral HPLC analysis using CHIRALPAK® AS-H 250 × 4.6 mm column, 1:3 v/v isopropyl alcohol/hexane elution at a solvent flow rate of 1 mL/min and with UV peak detection at 254 nm, t_R 20.4 min): $[\alpha]_D$ = +5.3 (c 0.7, $CHCl_3$); HRMS: $M^{+\cdot}$ calcd for $C_{13}H_{18}O_6$: 270.1103; found: 270.1101. Anal. Calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71. Found: C, 58.31; H, 6.96. The IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data derived from this material matched those reported above for enantiomer **10**.

4.1.18. (1′*R*,2′*S*)-4-Benzyloxy-3-[2′,3′-epoxy-1′-(3″,5″-dimethoxy-4″-methoxymethoxyphenyl)-propoxy]benzaldehyde *ent*-12. Compound *ent*-**10** was transformed into the title compound in the same manner as used for the conversion **10** → **12**. In this way title compound *ent*-**12** was obtained in 70% yield and as a white, crystalline solid, mp 50–52 °C, in >95% ee (as determined by chiral HPLC analysis using CHIRALPAK® AS-H 250 × 4.6 mm column, 1:3 v/v isopropyl alcohol/hexane elution at a solvent flow rate of 0.8 mL/min and with UV peak detection at 254 nm, t_R 41.2 min): $[\alpha]_D$ = −14.2 (c 1.9, $CHCl_3$); HRMS: $M^{+\cdot}$ calcd for $C_{27}H_{28}O_8$: 480.1784; found: 480.1772. Anal. Calcd for $C_{27}H_{28}O_8$: C, 67.49; H, 5.87. Found: C, 66.96; H, 5.90. The IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data derived from this material matched those reported above for enantiomer **12**.

4.1.19. (1′*R*,2′*S*)-4-Hydroxy-3-[2′,3′-epoxy-1′-(3″,5″-dimethoxy-4″-methoxymethoxyphenyl)-propoxy]benzaldehyde *ent*-13. Compound *ent*-**12** was transformed into the title compound in the same manner as used for the conversion **12** → **13**. In this way the *title compound* *ent*-**13** was obtained in 70% yield, as an amorphous solid, and in >95% ee (as determined by chiral HPLC analysis using CHIRALPAK® AS-H 250 × 4.6 mm column, 1:3 v/v isopropyl alcohol/hexane elution at a solvent flow rate of 1.0 mL/min and with UV peak detection at 254 nm, t_R 50.7 min): $[\alpha]_D$ = −139.2 (c 0.6, $CHCl_3$); HRMS: $M^{+\cdot}$ calcd for $C_{20}H_{22}O_8$: 390.1315; found: 390.1315. The IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data derived from this material matched those reported above for enantiomer **13**.

4.1.20. (2*R*,3*R*)-3-(3′,5′-Dimethoxy-4′-methoxymethoxyphenyl)-2-hydroxymethyl-2,3-dihydro-1,4-benzodioxin-6-carbaldehyde *ent*-14. Compound *ent*-**13** was transformed into the title compound in the same manner as used for the conversion **13** → **14**. In this way, title compound *ent*-**14** was obtained in 68% yield, as an amorphous solid, and in >91% ee (as determined by chiral HPLC analysis using CHIRALPAK® AS-H 250 × 4.6 mm column, 1:3 v/v isopropyl alcohol/hexane elution at a solvent flow rate of 1.0 mL/min and with UV peak detection at 254 nm, t_R 47.1 min): $[\alpha]_D$ = +43.6 (c 0.3, $CHCl_3$); HRMS: $M^{+\cdot}$ calcd for $C_{20}H_{22}O_8$: 390.1315; found: 390.1314. The IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data derived from this material matched those reported above for enantiomer **14**.

4.1.21. (1*E*,2′*R*,3′*R*)-5-{2′-[2′,3′-Dihydro-3′-(4″-hydroxy-3″,5″-dimethoxyphenyl)-2′-(hydroxymethyl)-1′,4′-benzodioxin-6′-yl]ethenyl}-1,3-benzenediol [(+)-aiphanol] (+)-1. Compound *ent*-**14** was transformed into title

compound in the same manner as used for the conversion **14** → (−)-**1**. In this way the title compound (+)-**1** was obtained in 18% yield, as a light-brown solid, and in >91% ee (as determined by chiral HPLC analysis using CHIRALPAK® AS-H 250 × 4.6 mm column, 1:1 v/v isopropyl alcohol/hexane elution at a solvent flow rate of 1.2 mL/min and with UV peak detection at 325 nm, t_R 15.1 min): $[\alpha]_D = +19.3$ (*c* 0.2, $CHCl_3$); HRMS: $M^{+\cdot}$ calcd for $C_{25}H_{24}O_8$: 452.1471; found: 452.1469. The IR, ^1H NMR, ^{13}C NMR, and mass spectral data derived from this material matched those reported above for enantiomer (−)-**1**.

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