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 dihydr oxylation of (E)-3,5-dimethoxy-4-(methoxymethoxy)cinnamyl alcohol with the AD-mix-β to give triol (1R,2R)-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 bio assay-guided isolation of the polyphenolic compound (−)-aiphanol I from the seeds of Aiphanes aculeata Willd. (Areecacae) 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 [α]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 IC50 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 I have already attracted the attention of other groups and, in a recent study, Ohira et al.3 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 shown6 that (+)-aiphanol I 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. aculeata1 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 (±)-aiphanol6 suggested that there might be variations in the properties of the two

[Image of compound structures]
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-benzodioxanes, we ultimately settled on that reported by Pan et al. 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 syringaldehyde 2 was protected as the corresponding MOM-ether, 3, which was subsequently engaged in a Horner–Wadsworth–Emmon (HWE) reaction using triethyl phosphonoacetate and NaH to afford the E-configured α,β-unsaturated ester 4 in 79% yield over two steps. Consistent with expectations, the Z-isomer was not detected as judged by 300 MHz 1H NMR spectral analysis of the crude product. DIBAL-H reduction of compound 4 afforded the cinnamyl alcohol 5 in 81% yield. Sharpless asymmetric dihydroxylation (AD) 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 (1R,2R) using the Sharpless mnemonic but in order to unequivocally confirm the configuration of the anticipated dioxane system, this triol was brominated with pyridinium hydrobromide perbromide 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, unequivocally, as R in each case, an outcome consistent with that predicted using the Sharpless mnemonic. (1R,2R)-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.

In the closing and pivotal stages (Scheme 2) of the formation of the target 1,4-benzodioxane, Mitsunobu coupling of compound 10 with the known phenol 11 using DIAD and PPh3 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 1H 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 methyl and methylene protons, respectively, of the MOM-ether. The 75 MHz 13C 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 1.
HPLC analysis. In the 300 MHz $^1$H NMR spectrum of tiomeric purity of >95% ee as determined by chiral accordance with the assigned structure. Interestingly, with $K_2CO_3$ afforded the anticipated cyclization $^{13}$

Based on the absolute configuration of the Sharpless asymmetric dihydroxylation product $6$, as determined by X-ray analysis of derivative $8$, and by virtue of the involvement of a Mitsunobu reaction, a process known 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., phosphonium salt $15$ 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 (--) 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 $\delta$ 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 $\delta$ 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 and essentially identical to those obtained for the racemic material. 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$'$/3$'$/3$'$/S-configured material corresponds to the natural product $[\alpha]_D = -21.8$ (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- in the Sharpless asymmetric dihydroxylation of cinnamyl alcohol $5$ at the start of the reaction sequence. The product triol enantioselective HPLC analysis for the purposes of the determination of its absolute configuration. 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 (+)-I were identical to the equivalent spectra of synthetically-derived (−)-2(S,3′S)-aiphanol (−)-I. However, the specific rotation of (+)-I was, of course, dextrorotatory $\{[\alpha]_D = +19.3 (c 0.2, \text{MeOH})\}$ 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 I 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 GF254 plates supplied by Merck while flash chromatographic purifications were conducted according to the method of Still et al. and using Merck silica gel 60 (230–400 mesh) as adsorbent. All solvents and common reagents were purified by established procedures.

4.1.1. 3,5-Dimethoxy-4-(methoxymethoxy)benzaldehyde

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$_2$SO$_4$, 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 ($^1$H NMR and $^{13}$C NMR spectra are identical to the equivalent spectra of the synthetic product. This works 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.

4.1.2. Ethyl (E)-3,5-dimethoxy-4-(methoxymethoxy)cinnamyl alcohol

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$_2$SO$_4$ 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 afforded, after concentration of the appropriate fractions [R$_f$ 0.4(5)], the title compound 4 ($^1$H NMR and $^{13}$C NMR spectra are identical to the equivalent spectra of the synthetic product. This works 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.

4.1.3. (E)-3,5-Dimethoxy-4-(methoxymethoxy)cinnamyl alcohol

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
was quenched, at 0 °C, stirred vigorously at 0 °C. Cinnamyl alcohol mixture was cooled to 0 °C.
Two phases observed were both clear. The ensuing organic phases were washed with water (10 mL), and the resulting gelatinous precipitate exposed. The residue thus obtained was treated with water (10 mL), then dried over Na₂SO₄, filtered, and the filtrate concentrated under reduced pressure. The resulting oil was subjected to high vacuum distillation (19:1 v/v ethyl acetate/methanol elution) to afford, after concentration of the appropriate fractions (Rf 0.4), a white solid.

Recrystallization (methanol–DCM) of this material afforded the title compound 28 (28 mg, 85%) as a clear, colorless oil. Subjection of this material to flash chromatography (19:1 v/v ethyl acetate/methanol elution) to afford, after concentration of the appropriate fractions (Rf 0.4), a white solid.

Recrystallization (methanol–DCM) of this material afforded the title compound 8 (28 mg, 85%) as a clear, colorless oil. Subjection of this material to flash chromatography (19:1 v/v ethyl acetate/methanol elution) to afford, after concentration of the appropriate fractions (Rf 0.4), a white solid.

Recrystallization (methanol–DCM) of this material afforded the title compound 8 (28 mg, 85%) as a clear, colorless oil. Subjection of this material to flash chromatography (19:1 v/v ethyl acetate/methanol elution) to afford, after concentration of the appropriate fractions (Rf 0.4), a white solid.

Recrystallization (methanol–DCM) of this material afforded the title compound 8 (28 mg, 85%) as a clear, colorless oil. Subjection of this material to flash chromatography (19:1 v/v ethyl acetate/methanol elution) to afford, after concentration of the appropriate fractions (Rf 0.4), a white solid.
4.1.7. (1R,2R)-2,3-Epoxy-1-(3''-dimethoxy-4''-methoxyphenyl)-propenol 10. A solution of tosylate 9 (301 mg, 0.7 mmol) in dry methanol (20 mL) was treated with K₂CO₃ (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 x 20 mL). The combined organic phases were washed with brine (1 x 30 mL), dried over Na₂SO₄, 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 (R₉ 0.35), 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 x 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, tₖ 16.1 min): [α]D = -5.4 (c 1.3, CHCl₃); IR: νmax 3433 (broad), 2968, 2925, 1650 (32), 109 (12), 45 (100); 1H NMR (300 MHz, CDCl₃): δ 7.55 (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 Hz, 1H), 4.04–3.86 (m, 3H), 3.82 (s, 6H), 3.58 (s, 3H), 2.60 (broad s, 2H), 2.44 (s, 3H); 13C NMR (75 MHz, CDCl₃): 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 (CH₃), 73.6 (CH₃), 75.3 (CH), 70.1 (CH₂), 57.1 (OCH₃), 56.0 (OCH₃), 21.6 (CH₃); MS (EI, 70 eV): m/z 442 (M⁺, <1%), 410 (7), 380 (4), 227 (20), 208 (22), 183 (25), 155 (48), 167 (65), 91 (92), 45 (100); HRMS: M⁺ calc'd for C₂₀H₂₆O₉S: 442.1298; found: 442.1293.

4.1.8. 4-Benzylmethoxy-3-hydroxybenzaldehyde 11. A magnetically stirred solution of aldehyde 11 (111 mg, 0.5 mmol) and DIAD (98 µL, 0.5 mmol) in dry THF–toluene (2 mL of a 1:1 v/v mixture) for 18 h and then solvent removed under reduced pressure. The residue was extracted with ethyl acetate (4 x 20 mL). The combined organic extracts were then dried over Na₂SO₄, 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 (R₉ 0.5), a white solid. Recrystallization (ethanol) of this material gave the title compound 11¹¹ (320 mg, 39%) as colorless crystals: mp 120–121 °C (lit.¹⁹b mp 121–122 °C); IR: νmax 3210 (broad), 2870, 1674, 1605, 1580, 1513, 1344, 1288, 1259, 1117, 1016, 1008, 728 cm⁻¹; 1H NMR (300 MHz, CDCl₃): 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); 13C NMR (75 MHz, CDCl₃): 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 (CH₃); MS (EI, 70 eV): m/z 228 M⁺**, 17%, 137 (3), 109 (3), 91 (100), 81 (65), 65 (21); HRMS: M⁺ calc'd for C₁₄H₁₀O₅S: 228.0786; found: 228.0789.

4.1.9. (1'S,2'R)-4-Benzyl-3-[2'-3'-epoxy-1'-(3''-5''-dimethoxy-4''-methoxyphenyl)-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 PPh₃ (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 (R₉ 0.5), 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 x 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, tₖ 39.9 min): [α]D = +11.9 (c 0.6, CHCl₃); IR: νmax 2939, 2840, 1687, 1596, 1507, 1462, 1436, 1337, 1272, 1128, 967, 739, 698 cm⁻¹; 1H NMR (300 MHz, CDCl₃): 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); 13C NMR (75 MHz, CDCl₃): 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 (CH₃), 80.3 (CH), 70.7 (CH₂), 57.1 (CH), 56.0 (OCH₃), 54.2 (OCH₃), 45.1 (CH₃) (one signal obscured or overlapping); MS (EI, 70 eV): m/z 480 (M⁺*, 7%), 450 (6), 282 (11), 253 (96), 253 (96), 223 (27), 195 (47), 91 (95), 45 (100); HRMS: M⁺ calc'd for C₁₇H₁₅O₆: 480.1784; found: 480.1777. Anal. Calc'd for C₁₇H₁₅O₆: C, 76.49; H, 5.87. Found: C, 76.07; H, 5.66.

4.1.10. (1'S,2'R)-4-Hydroxy-3-[2'-3'-epoxy-1'-(3''-5''-dimethoxy-4''-methoxyphenyl)-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 [Rf 0.3(0.5)], 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, tR 25.5 min): [α]D25 = +142.4 (c 0.4, CHCl3); IR: νmax 3360 (broad), 2939, 1684, 1595, 1507, 1463, 1314, 1279, 1263, 1155, 1128, 1123 (CH), 103.6 (CH2), 98.1 (CH2), 85.7 (CH), 74.9 (CH2), 74.8 (CH3), 57.2 (OCH3), 56.1 (OCH3); MS (EI, 70 eV): m/z 390 (M+*, 95%), 346 (16), 345 (15), 316 (11), 253 (18), 195 (83), 149 (73), 57 (100); HRMS: M+* caleld for C20H22O6: 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-di(hydroxybenzoate (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 × 20 mL) and brine (1 × 20 mL) then dried over Na2SO4, 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 [Rf 0.5], methyl 3,5-bis-methoxymethoxybenzoate,3 (700 mg, 91%) as a clear, colorless oil: IR: νmax 2955, 2905, 1724, 1597, 1438, 1302, 1104, 932, 770, 682 cm−1; 1H NMR (300 MHz, CDCl3): δ 7.35 (d, J = 2.3 Hz, 2H, ArH), 6.91 (t, J = 2.2 Hz, 1H, ArH), 5.17 (s, 4H), 3.88 (s, 3H), 3.46 (s, 6H); 13C NMR (75 MHz, CDCl3): δ 166.5 (C=O), 158.0 (C), 132.1 (C), 110.5 (CH), 109.6 (CH2), 94.3 (CH2), 56.1 (OCH3), 52.2 (OCH3); MS (EI, 70 eV): m/z 256 (M+*, 100%), 225 (80), 196 (18), 193 (17), 139 (16), 63 (38); HRMS: M+* caleld for C13H16O6: 256.0947; found: 256.0944.

4.1.11. (2(S,3S)-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 K2CO3 (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 Na2SO4, 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 [Rf 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, tR 27.2 min): [α]D25 = +48.4 (c 0.3, CHCl3); IR: νmax 3436 (broad), 2925, 2853, 1690, 1595, 1502, 1438, 1314, 1279, 1263, 1155, 1128, 959 cm−1; 1H NMR (300 MHz, CDCl3): 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); 13C NMR (75 MHz, CDCl3): 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 (CH2), 98.1 (CH2), 85.7 (CH), 74.9 (CH2), 74.8 (CH3), 57.2 (OCH3), 56.1 (OCH3); MS (EI, 70 eV): m/z 390 (M+*, 99%), 346 (16), 345 (15), 316 (11), 253 (18), 195 (83), 149 (73), 57 (100); HRMS: M+* caleld for C20H22O6: 390.1315; found: 390.1310.

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 LiAlH4 (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 CeliteTM 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 [Rf 0.2(5)], 3,5-bis-methoxymethoxybenzyl alcohol (430 mg, 97%) as an amorphous, white solid: IR: νmax 3418 (broad), 2955, 2903, 1599, 1459, 1291, 1145, 1083, 1034, 923, 846 cm−1; 1H NMR (300 MHz, CDCl3): 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); 13C NMR (75 MHz, CDCl3): δ 158.3 (C), 143.6 (C), 107.8 (CH), 103.9 (CH), 94.3 (CH2), 64.9 (CH2), 56.0 (OCH3); MS (EI, 70 eV): m/z 228 (M+*, 80%), 211 (12), 198 (23), 168 (40), 152 (23), 107 (16), 77 (17), 45 (100); HRMS: M+* calcd for C11H13O5: 228.0998; found: 228.0997. Anal. Caled for C11H13O5: 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 mg, 1.0 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), and the mixture was allowed to warm to 18 °C, heated at reflux for 18 h. The mixture was then cooled to ca. 18 °C, poured into cold water (20 mL), maintained at 0 °C (ice-water bath) under an atmosphere of nitrogen was treated, dropwise, with MsCl (130 mg, 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), and the DCM layer separated. The aqueous layer was extracted with additional DCM (2 × 15 mL). The combined organic phases were then dried over Na2SO4, filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to column chromatography (2:5 v/v ethyl acetate/hexane elution) to afford, after concentration of the appropriate fractions (Rf 0.7), 3,5-bis-methoxymethoxybenzyl chloride (301 mg, 79%) as a clear, colorless oil: IR: νmax 2985, 2903, 1599, 1461, 1296, 1146, 1083, 1034, 933, 850, 717 cm−1; 1H NMR (300 MHz, CDCl3): δ 6.73 (t, J = 2.2 Hz, 2H, ArH), 6.69 (t, J = 1.5 Hz, 1H, ArH), 5.16 (s, 4H), 4.50 (s, 2H), 3.47 (s, 6H); 13C NMR (75 MHz, CDCl3): δ 158.3 (C), 139.6 (C), 109.7 (CH), 104.7 (CH), 94.3 (CH2), 56.0 (OCH3), 46.0 (CH2); MS (EI, 70 eV): m/z 248 and 246 (M+*, 55 and 100%), 211 (61), 186 (16), 77 (46); HRMS: M+* calcd for C11H15ClO4: 246.0659; found: 246.0659. Anal. Caled for C11H15ClO4: 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-(methoxybenzyltriphenylophosphonium chloride 15. A solution of 3,5-bis-methoxymethoxybenzyl chloride (250 mg, 1.0 mmol) in toluene (30 mL) was treated with PPh3 (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 mg, 85%) as a light-brown gum. A 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 Na2SO4, 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 Na2SO4, 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 (Rf 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 Na2SO4, 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 the highly UV active band [Rf 0.3(5)], a brown solid. Purification of this material by HPLC (using a 300 × 7.8 mm C18 Alltech Alltima column, 50:49.95:0.05 v/v/v H2O/MeOH/AcOH elution, solvent flow rate of 5 mL/min, UV peak detection at 325 nm, tR 15.05 min), afforded the title compound (**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, tR 12.1 min): [α]D = −20.1 (c = 0.2, MeOH) [lit.1] −21.8 (c = 0.1, MeOH); IR: νmax 3370 (broad), 2925, 1595, 1505, 1345, 1270, 1216, 1115, 1048, 831 cm−1; 1H NMR (500 MHz, CD3OD): 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 (dd, 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 (dd, J = 12.3, 3.9 and 2.3 Hz, 1H), 3.55 (dd, J = 12.3, 6.8 and 4.4 Hz, 1H); 13C NMR (125 MHz, CD3COCD3): 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 (CH3), 56.4 (OCH3); MS (EI, 70 eV): m/z 452 (M+·, 100%), 438 (40), 346 (18), 255 (30), 210 (82), 167 (60), 149 (32), 121 (43), 91 (67); HRMS: M·+ calcd for C25H24O6: 452.1471; found: 452.1466.

4.1.14. (1S,2S)-1-(3',5'-Dimethoxy-4'-methoxymethoxyphenyl)-2,3-dihydroxyprenalent-6. The title compound was prepared by the asymmetric dihydroxylation of cinnamyl alcohol 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 1.0 mL/min and with UV peak detection at 254 nm, tR 14.1 min); [α]D = +23.9 (c 1.0, CHCl3); HRMS: M·+ calcd for C13H18O6: 258.1255; found: 258.1260. The IR, 1H NMR, and mass spectral data derived from this material matched those reported above for enantiomer 6.

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

4.1.16. (1S,2S)-1-(3',5'-Dimethoxy-4'-methoxymethoxyphenyl)-1,2-dihydroxypropyl tosylateent-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; [α]D = +13.5 (c 0.8, CHCl3); HRMS: M·+ calcd for C29H29O9S: 442.1298; found: 442.1295. The IR, 1H NMR, and 13C NMR, and mass spectral data derived from this material matched those reported above for enantiomer 9.

4.1.17. (1S,2S)-2,3-Epoxy-1-(3',5'-dimethoxy-4'-methoxymethoxyphenyl)propanent-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, tR 20.4 min); [α]D = +5.3 (c 0.7, CHCl3); HRMS: M·+ calcd for C13H19O6: 270.1103; found: 270.1101. Anal. Caled for CH13H19O6: C, 57.77; H, 6.71. Found: C, 58.31; H, 6.96. The IR, 1H NMR, 13C NMR, and mass spectral data derived from this material matched those reported above for enantiomer 10.

4.1.18. (1'R,2'R,5'S)-4-Benzoyl-3-[2',3'-epoxy-1'-((3',5'-dimethoxy-4'-methoxymethoxyphenyl)-propoxy]benzaldehydeent-12. Compound ent-10 was transformed into the title compound in the same manner as used for the conversion 10 → 12. In this way the 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, tR 41.2 min); [α]D = −14.2 (c 1.9, CHCl3); HRMS: M·+ calcd for C27H23O5: 480.1784; found: 480.1772. Anal. Calcd for C27H23O5: C, 67.49; H, 5.87. Found: C, 66.96; H, 5.90. The IR, 1H NMR, 13C 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]benzaldehydeent-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, tR 50.7 min); [α]D = −139.2 (c 0.6, CHCl3); HRMS: M·+ calcd for C27H25O6: 390.1315; found: 390.1315. The IR, 1H NMR, 13C 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-carbaldehydeent-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, tR 47.1 min); [α]D = +43.6 (c 0.3, CHCl3); HRMS: M·+ calcd for C29H25O6: 390.1315; found: 390.1315. The IR, 1H NMR, 13C NMR, and mass spectral data derived from this material matched those reported above for enantiomer 14.

4.1.21. (1E,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 $\rightarrow$ (-)-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 $\times$ 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): $[\alpha]_D^{20}$ = +19.3 (c 0.2, CHCl$_3$); HRMS: M$^+$ calcd for C$_{25}$H$_{24}$O$_8$: 452.1471; found: 452.1469. The IR, $^1$H NMR, $^{13}$C NMR, and mass spectral data derived from this material matched those reported above for enantiomer (-)-1.

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References

17. Details of the X-ray structure analysis will be published elsewhere.