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Developing Neolignans as Proangiogenic Agents: Stereoselective Total Syntheses and Preliminary Biological Evaluations of the Four Guaiacylglycerol 8-*O*-4′-Coniferyl Ethers

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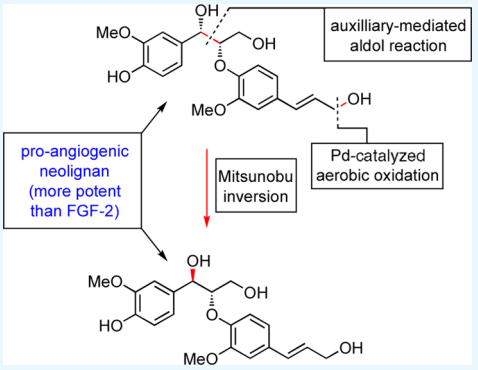
Supporting Information

ABSTRACT: Stereoselective total syntheses of the four stereoisomeric forms of guaiacylglycerol 8-*O*-4′-coniferyl ether, viz., compounds **1**, *ent*-**1**, **2**, and *ent*-**2**, have been established. The key step involves an Evans/Seebach auxiliary-controlled and syn-selective aldol process followed, in the reaction sequences leading to the anti-compounds, by a Mitsunobu reaction involving a benzylic alcohol residue. The proangiogenic properties of the synthetic materials were evaluated in a human microvascular endothelial cell tubule formation assay, thus revealing that they are all active, with the 8S-configured compounds **1** and **2** being the most potent.



INTRODUCTION

Compounds that promote the formation of new blood vessels from existing endothelia are described as proangiogenic and could be beneficial in promoting wound healing, treating burns, and the revascularization of ischemic tissues encountered in stroke victims and those suffering from cardiac disorders.[1] Screening plant extracts for such properties is an emerging area of interest and the rat aortic ring model and related assays have proven useful in identifying natural products that can modulate angiogenesis.[2,3] By such means, various extracts of soybean (particularly the xylem sap) were evaluated recently, and two proangiogenic principals were isolated.[3] Although only small quantities of these materials were obtained, ^{1}H and ^{13}C NMR spectroscopic as well as mass spectral analyses suggested that these are one or other of the neolignans **1** or *ent*-**1** and **2** or *ent*-**2**.[3] The racemic forms of these compounds have previously been isolated from various other plant sources and shown to exhibit a range of biological effects.[4] They are almost certainly produced in vivo through peroxidase-mediated radical coupling of coniferyl alcohol, and optically enriched forms of them (but of undefined absolute stereochemistry) have been generated by enzymatic dehydrogenative coupling of this monomer using cell-free extracts of a producing organism.[5]

Given the very small amounts of these compounds available from natural sources, the seasonal variations in their yields, and the lack of information regarding their stereostructures (and, in many instances, their optical purities), unambiguous syntheses of the guaiacylglycerol 8-*O*-4′-coniferyl ethers **1**, *ent*-**1**, **2**, and *ent*-**2** were sought in an effort to clarify matters. Herein, we detail the total syntheses of each of these four stereoisomeric 8-*O*-4′-linked neolignans[6,7] and report on their proangiogenic properties (Figure 1).

RESULTS AND DISCUSSION

Syntheses of the Racemic Forms of Compounds 1 and 2. Although many neolignans have been the subject of synthetic studies,[8] enantioselective approaches to 8-*O*-4′ linked systems, as required in accessing the compounds targeted here, have received only modest attention.[9,10] Our first approach to compounds **1**, *ent*-**1**, **2**, and *ent*-**2** is shown in Scheme 1, and in this we sought, inter alia, to exploit key elements of Ley's asymmetric synthesis of the 8-*O*-4′ neolignan polysphorin.[9a] This started with the conversion, by conventional means, of commercially available ferulic acid (**3**) over four steps into bis-methoxymethyl (MOM) ether **4** (79%) (see Experimental Section for details). Asymmetric dihydroxylation of the olefinic residue within compound **4** using AD-mix-α and methanesulfonamide afforded the diol **5** (78%), the configuration of which was assigned using the Sharpless "mnemonic".[11] Although the enantiomeric excess (ee) of this oxidation product was not established, the fact that it was optically

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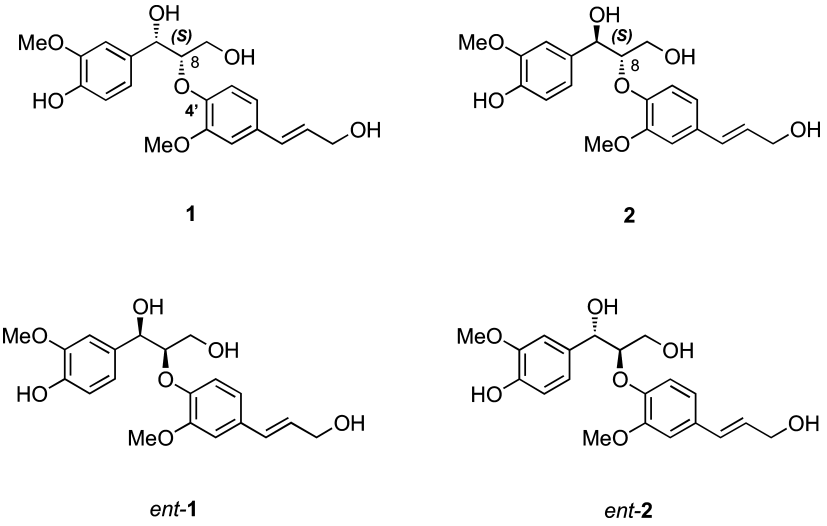
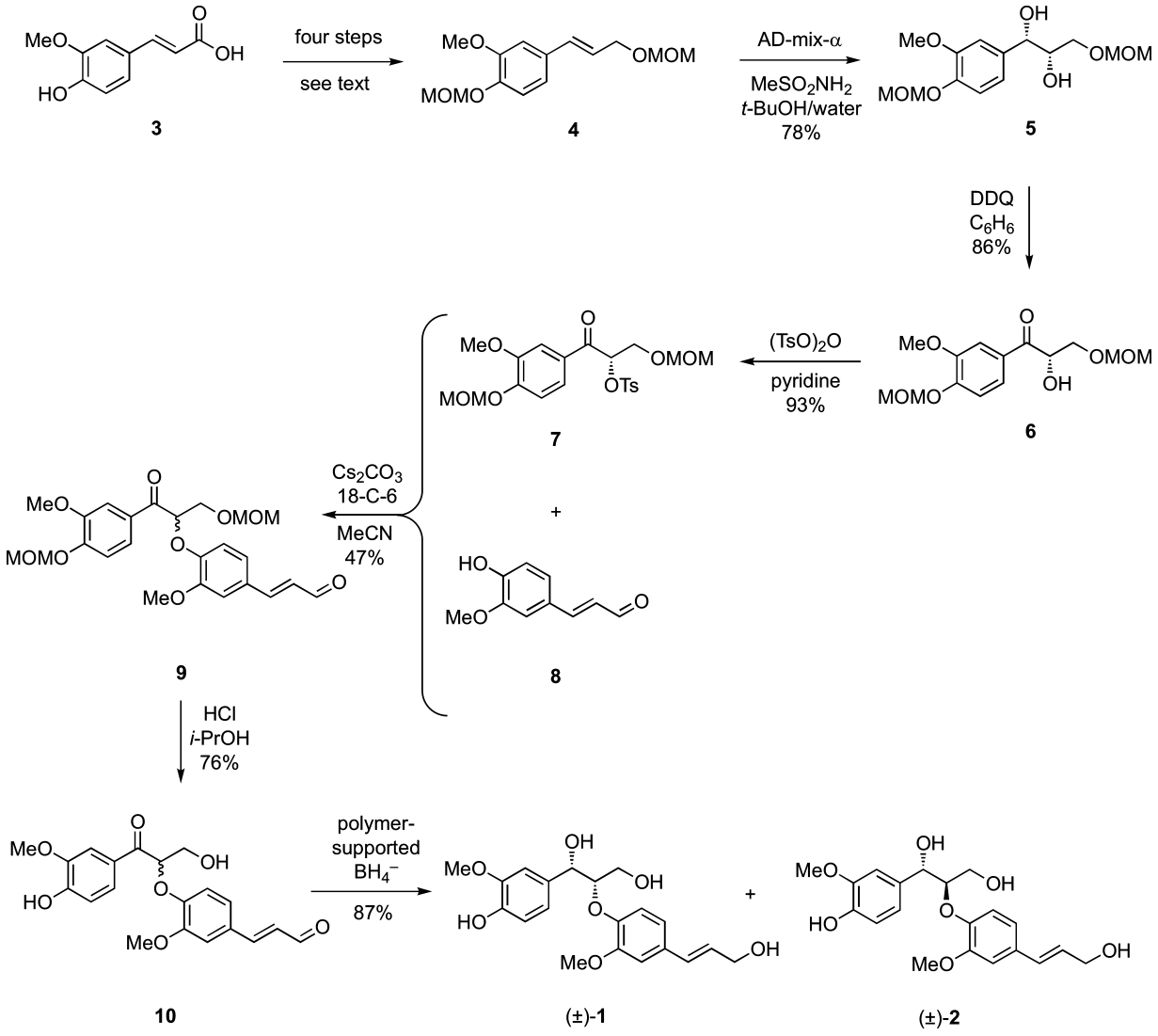


Figure 1. Structures of the four stereoisomeric forms, **1**, *ent*-**1**, **2**, and *ent*-**2**, of guaiacylglycerol 8-*O*-4′-coniferyl ether targeted for synthesis.

Scheme 1. Synthesis of Compounds (±)-1 and (±)-2



active $\{[\alpha]_D$ + 10.7 (c = 1.02, $CHCl_3)\}$ encouraged us to continue exploring the reaction sequence, the next step of which involved selective oxidation of the benzylic hydroxyl group within compound **5** using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) under ultrasonication conditions.[12] By such means, the acyloin **6** (86%) was obtained and the

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associated hydroxyl group was reacted with *p*-toluenesulfonic anhydride in the presence of pyridine, thus giving the optically active ester **7** in 93% yield. Although treating this last compound with coniferyl aldehyde (**8**) in the presence of cesium carbonate and 18-crown-6 (18-C-6) led to the formation of the anticipated 8-*O*-4′-linked ether **9** (47%), this proved to be an optically inactive material, thus suggesting racemization of substrate **7** and/or the product had occurred under the reaction conditions.[1] Despite this, the completion of the synthetic pathway was pursued because of the capacity it provided to deliver the racemic forms of the target compounds (materials that would prove useful in establishing the enantiomeric excesses of their enantiomerically enriched congeners). So, compound **9** was treated with a trace of concentrated HCl in isopropanol, thus effecting cleavage of the MOM-ether residues, and thereby affording the dihydroxy-derivative **10** (76%). The required 2-fold reduction of the keto-aldehyde **10** was best effected using polymer-supported borohydride[9a] and, in a presumably sterically driven process, this gave a ca. 7:1 mixture of the diastereoisomeric syn- and anti-compounds (±)-**1** and (±)-**2**, respectively, in 87% combined yield. These could be separated from one another using reverse phase high-performance liquid chromatography (HPLC) and the spectral data derived from each were in complete accord with those reported earlier[4e,l] for the natural products (see Table 1 for relevant comparisons of the ^{13}C NMR data sets).

Although each of the synthetically derived compounds (±)-**1** and (±)-**2** could be separated into their constituent enantiomers using chiral HPLC techniques, the equivalent analysis of the soybean-derived natural products could not be carried out due to their decomposition on prolonged (>12 months) standing (as a crude extract). That said, when samples of these compounds have been isolated from other plant sources, they tend to be obtained as racemates or, at best, enantiomerically enriched (but certainly not homochiral) materials.[5a]

Chiral Auxiliary-Controlled Syntheses of Homochiral Compounds 1 and *ent*-1. The synthetic route successfully employed in obtaining neolignan *ent*-**1** is shown in Scheme 2 and involved, as the key feature, an Evans' aldol reaction[13] utilizing the readily available L-valine (**11**)-derived chiral auxiliary **12** introduced by Seebach.[14] This was coupled with the eugenol (**13**)-derived and readily available α-aryloxyacetic acid **14** (85%) through its conversion into the corresponding acid chloride and reaction of this with the anion derived from deprotonation of the 2-oxazolidinone **12** using *n*-butyl lithium. Compound **15** (93%) so formed was then converted, on treatment with dibutylboron triflate in the presence of Hünig's base,[14a] into the corresponding boron enolate that reacted stereoselectively with aldehyde **16** embodying a *tert*-butyldimethylsilyl (TBDMS)-protected phenol residue. The auxiliary associated with the aldol product so-formed was cleaved using lithium borohydride/methanol, thus affording the 1°-alcohol **17** (76% from **15**) as a single diastereoisomer and in optically active form {$[\alpha]_D$ = −63.3 (*c* = 0.8, $CHCl_3$)}. The illustrated structure was initially assigned to compound **17** on the basis of the well-established syn-selective outcomes of Evans' aldol reactions[9h,13,14] involving the types of auxiliaries used here, but eventually it was confirmed through chemical correlation studies (see below). Aerobic and palladium-catalyzed acetoxylation of compound **17** using a procedure reported by Stahl et al.[15] and employing 4,5-diazafluorenone as ligand then afforded

Table 1. Comparison of the ^{13}C NMR Chemical Shift Data Recorded for Synthetically Derived Compounds (±)-1 and (±)-2 with Those Reported for the Naturally Derived *threo*- and *erythro*-Guaiacylglycerol 8-*O*-4′-Coniferyl Ethers (*threo*-GCCE and *erythro*-GCCE, Respectively)

^{13}C NMR data for compound (±)-**1** (δ_C)[a]	^{13}C NMR data for *threo*-GCCE (δ_C)[b]	Δδ	^{13}C NMR data for compound (±)-**2** (δ_C)[c]	^{13}C NMR data for *erythro*-GCCE (δ_C)[d]	Δδ
151.6	151.8	−0.2	151.9	151.8	+0.1
149.1	149.3	−0.2	148.9	149.0	−0.1
148.8	148.8	0.0	148.7	148.6	+0.1
147.1	147.2	−0.1	147.0	147.2	−0.2
133.7	133.8	−0.1	134.1	134.2	−0.1
133.1	133.2	−0.1	133.0	133.1	−0.1
131.4	131.5	−0.1	131.4[e]	130.8	+0.6[f]
128.6	128.7	−0.1	128.5	128.6	−0.0
120.8	120.9	−0.1	121.0	121.1	+0.1
120.7	120.8	+0.1	120.7	120.8	−0.1
118.6	118.9	−0.3[f]	118.9	119.0	−0.1
115.8	115.9	−0.1	115.7	115.7	0.0
111.7	111.8	−0.1	111.9	111.9	0.0
111.2	111.3	−0.1	111.4[g]	110.8	+0.6[f]
87.0	87.2	−0.2	86.2	86.3	−0.1
74.0	74.1	−0.1	74.1	74.2	−0.1
63.7	63.8	−0.1	63.8	63.9	−0.1
61.9	62.0	−0.1	62.2	62.3	−0.1
56.6	56.6	0.0	56.5	56.6	−0.1
56.3	56.4	−0.1	56.4	56.6	−0.2

[a]Spectrum recorded in CD_3OD at 100 MHz. [b]Data obtained from Woo,[4l] spectrum recorded in CD_3OD at 125 MHz. [c]Spectrum recorded in CD_3OD at 100 MHz. [d]Data obtained from Li[4e] spectrum recorded in CD_3OD at 100 MHz. [e]Lourith et al. report[10] a chemical shift of 131.5 for the resonance due to this carbon. [f]We attribute these differences to variations in the pH of the media in which the spectra were recorded. [g]Lourith et al. report[10] a chemical shift of 111.4 for the resonance due to this carbon.

ester **18** in 48% yield and exclusively in the E-isomeric form. Cleavage of both the acetate and silyl ether residues associated with compound **18** was accomplished using potassium carbonate in methanol, thus giving the target neolignan *ent*-**1** in 79% yield.

All of the mass spectral as well as the NMR and IR spectroscopic data acquired on compound *ent*-**1** matched those derived from the corresponding racemate [(±)-**1**], and the specific rotation determined for the optically active material was −36.7 (*c* = 0.9, methanol). Chiral HPLC analysis of compound *ent*-**1** established that it was of >99% enantiomeric excess and represents the less mobile component of the racemate (±)-**1**.

The synthesis of compound **1** was readily achieved following the reaction scheme shown above but using the auxilliary *ent*-**12** derived from D-valine (*ent*-**11**). Although all of the spectral data recorded on neolignan **1** matched those reported for its enantiomer, the specific rotation of this material was of similar magnitude but opposite sign {$[\alpha]_D$ = +32.4 (*c* = 0.2, methanol)}. Chiral HPLC analysis of compound **1** established that it had been obtained in ca. 90% ee and represents the more mobile component of the racemate (±)-**1** obtained earlier.

The synthesis of the anti-compound *ent*-**2** is shown in Scheme 3 and involved, in the opening stages, selective mono-protection of the 1°-alcohol residue within compound **17** followed by cleavage of the associated phenolic TBDMS ether.

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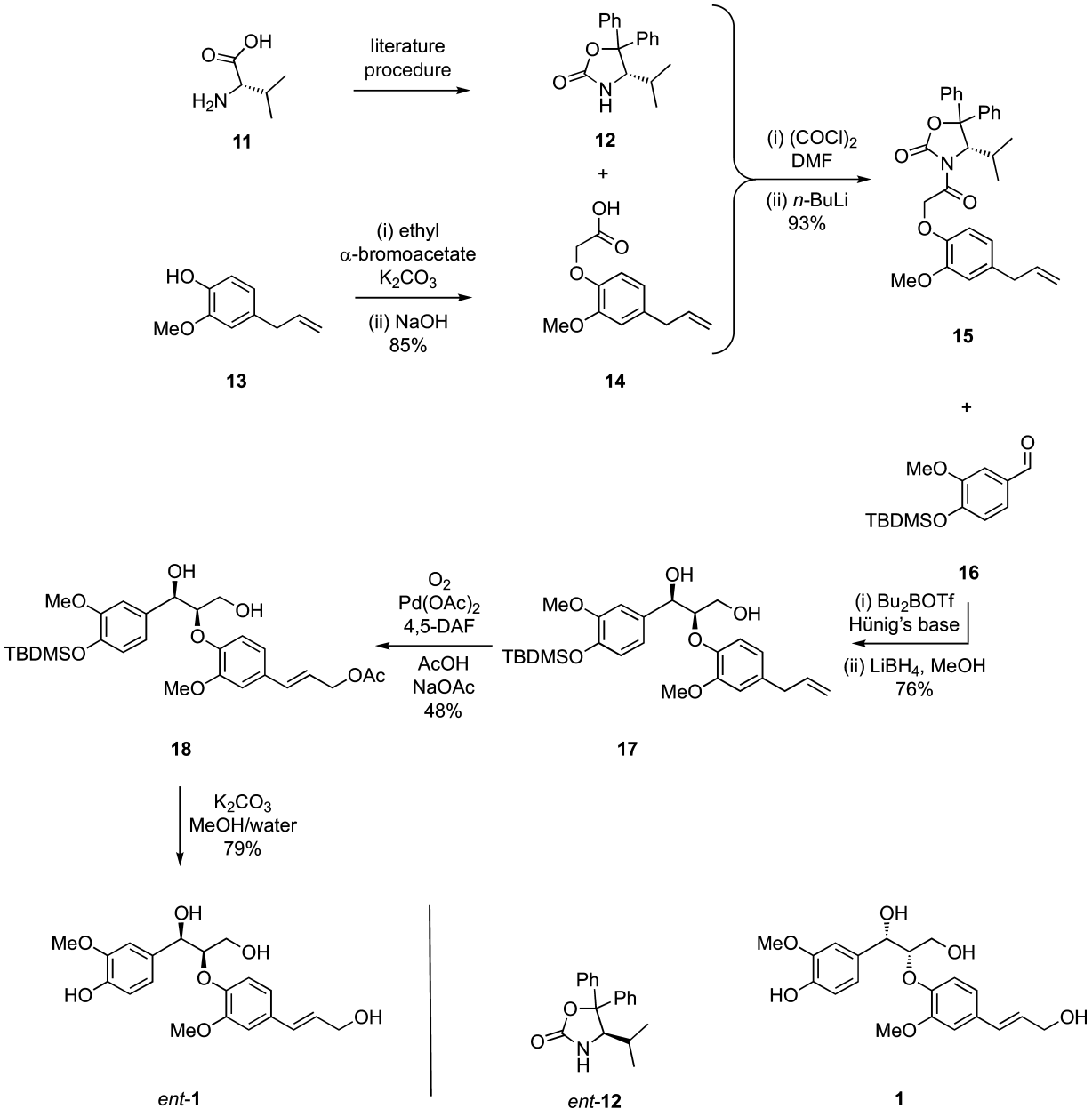
Scheme 2. Synthesis of Compound *ent*-1



This gave phenol **19** (96%) that was reacted with *p*-toluenesulfonyl chloride (*p*-TsCl) in the presence of triethylamine and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) to afford ester **20** (87%). The introduction of the tosyl group was necessary to attenuate the electron-donating properties of the attached aryl oxygen such that this now did not facilitate ionization of activated forms of the benzylic alcohol during the subsequent Mitsunobu reaction.[16] Consistent with such expectations, when compound **20** was treated with triphenylphosphine and diethyl azodicarboxylate (DEAD), and using *p*-nitrobenzoic acid as nucleophile, benzoate **21** (84%) was obtained. Confirmation of the illustrated S-configuration at the PNB-ester bearing center in this product follows from its conversion into the target neolignan *ent*-**2**. To such ends, treatment of compound **21** with sodium hydroxide in tetrahydrofuran (THF)/water afforded the alcohol **22** (74%) that was itself subjected to allylic oxidation using Stahl's protocol,[15] thereby affording acetate **23** in 64% yield.

Treatment of ester **23** with tetra-*n*-butylammonium fluoride (TBAF) then sodium hydroxide in water/methanol resulted in cleavage of the TBDMS ether, acetate, and tosyl groups such that the targeted neolignan *ent*-**2** was obtained in 73% yield. All of the spectral data obtained on this material were consistent with the assigned structure. Chiral HPLC analysis established that it was of >99% ee. The specific rotation of this material was $[\alpha]^{20}_{D} = -8.1$ (c = 1.1, methanol), and it represents the more mobile component of the racemate (±)-**2**.

The synthesis of compound **2** was readily achieved following the reaction scheme shown but using compound *ent*-**17** as starting material. Although all of the spectral data recorded on neolignan **2** matched those reported for its enantiomer, the specific rotation of this material was of similar magnitude but opposite sign {$[\alpha]^{20}_{D} = +7.4$ (c = 0.5, methanol)}. Similarly, chiral HPLC analysis of compound **2** established that it was of >99% ee and that it represents the less mobile component of the racemate (±)-**2** obtained as described above.

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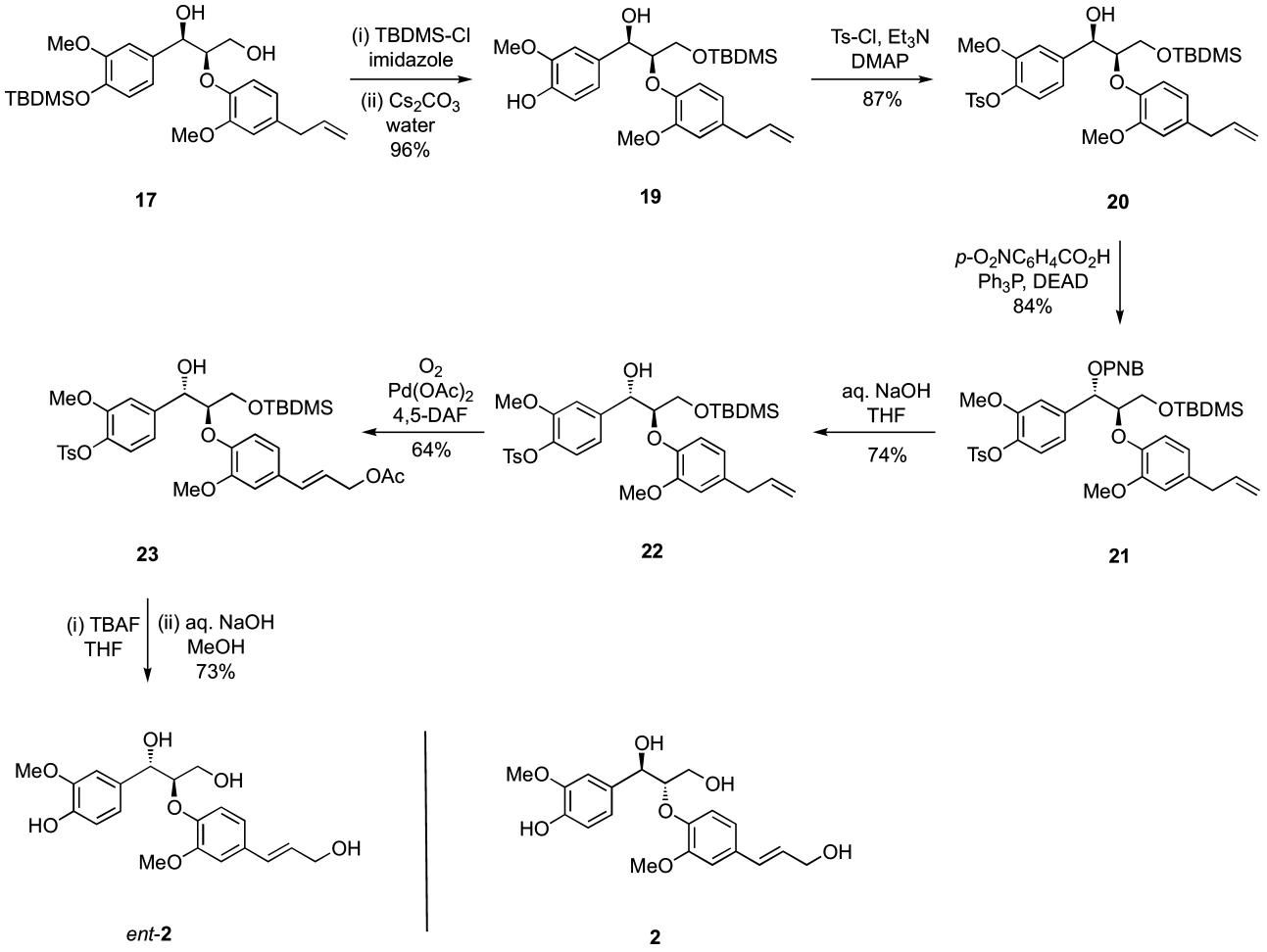
Scheme 3. Synthesis of Compound *ent*-2



To this point, the assignments of the illustrated structures to compounds **1**, *ent*-**1**, **2**, and *ent*-**2** are based on the assumption that the pivotal Evans' aldol reactions proceed in the anticipated (syn-selective) manner and that the Mitsunobu reactions take place with inversion of configuration. Further support follows from the recent work of Nair et al.,[9k] who employed closely related Evans' aldol protocols to prepare compound **2** and who undertook certain chemical correlation studies and a single-crystal X-ray analysis to establish the selectivities of their pivotal reaction. The NMR spectroscopic data we acquired on compound **2** matched those reported by Nair.[9k]

Initial Biological Evaluations of Compounds 1, *ent*-1, 2, and *ent*-2. Compounds **1** and **2** as well as their enantiomers, *ent*-**1** and *ent*-**2**, respectively, were each examined for their abilities to enhance endothelial cell tubule formation on reconstituted basement membrane matrix (see Figure 2 and the Experimental Section) in an assay widely used to identify proangiogenic and antiangiogenic factors and their underlying mechanism(s) of action.[17]

All four compounds stimulated endothelial cell tubule formation compared with media only, with compounds **1** and **2** being the most active and congener *ent*-**2** the least active. It is noteworthy that each of these neolignans exhibited significant proangiogenic activity compared with media only, with compound **1** being more active than the fibroblast growth factor 2 (FGF-2) control.[18] The flavone derivative PD98059, an inhibitor of mitogen-activated protein kinase (MEK1/2) and FGF-2 signaling, suppressed the proangiogenic activity of all of the compounds, which is consistent with the title neolignans acting via this pathway.

CONCLUSIONS

The work detailed here provides stereochemically unambiguous routes to a quartet of neolignans that display varying degrees of activity as proangiogenic agents. The variation in efficacy as a function of stereochemistry indicates that the S-configuration at C8 (as seen in neolignans **1** and **2**) has a positive impact on activity, with compound **1** being even more active than the FGF-2 control. To the best of our knowledge, this work represents the first time that a suite of diastereisomerically related neolignans has been identified as proangiogenic agents. As such, it should serve as an important consideration for the development of proangiogenic compounds that might serve as therapeutic agents.

EXPERIMENTAL SECTION

General Protocols. Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at room temperature in base-filtered $CDCl_3$ on a Varian spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. The signal due to residual $CHCl_3$ appearing at δ_H 7.26 and the central resonance of the $CDCl_3$ triplet appearing at δ_C 77.1(6) were used to reference ^{1}H and ^{13}C NMR spectra,

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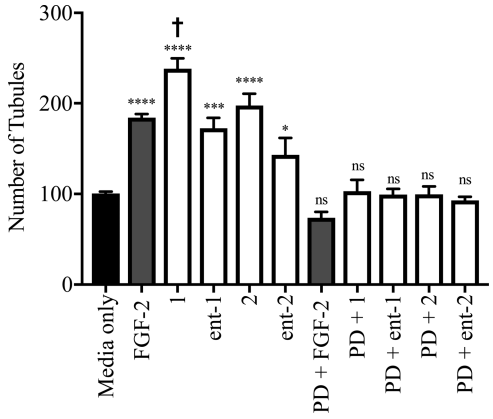

Figure 2. Effect of neolignans **1**, *ent*-**1**, **2**, and *ent*-**2** on tubule formation by human microvascular endothelial cells (HMECs) on reconstituted basement membrane matrix (Matrigel) over a 4 h period compared with that of media (only) and fibroblast growth factor (FGF)-2 (positive) controls as well as when coadministered with the MEK1/2 inhibitor PD (PD98059). The columns represent the mean of the means of 4 independent experiments with each condition performed in triplicate. Error bars represent the standard error of the mean. Statistical significance was determined by one-way ANOVA and Dunnett's multiple comparisons test (compared with media only, i.e., MCDB131 medium with supplements and 0.2% fetal bovine serum (FBS)) using GraphPad Prism software, where **** denotes $P < 0.0001$, *** denotes $P < 0.001$, * denotes $P < 0.05$, ns denotes not significant, and † denotes significance at $P < 0.01$ between FGF-2 and compound **1**. There was no significant difference between FGF-2 and compounds **2**, *ent*-**1**, or *ent*-**2**.

respectively. ^{1}H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) J (Hz), relative integral] where multiplicity is defined as: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or combinations of the above. Infrared spectra (ν_{max}) were recorded on a Fourier transform infrared spectrometer. Samples were analyzed as thin films on KBr plates or as neat material. Low-resolution electrospray ionization (ESI) mass spectra were recorded on a single quadrupole liquid chromatograph-mass spectrometer, whereas high-resolution measurements were conducted on a time-of-flight instrument. Low- and high-resolution electron ionization (EI) mass spectra were recorded on a magnetic-sector machine. Melting points were measured on an Optimelt automated melting point system and are uncorrected. Analytical thin layer chromatography was performed on aluminum-backed 0.2 mm thick silica gel 60 F_{254} plates as supplied by Merck. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid/ceric sulfate/sulfuric acid (conc.)/water (37.5 g:7.5 g:37.5 g:720 mL) or potassium permanganate/potassium carbonate/5% sodium hydroxide aqueous solution/water (3 g:20 g:5 mL:300 mL). Flash chromatographic separations were carried out following protocols defined by Still et al.[19] with silica gel 60 (40−63 μm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. The melting points of solids purified by such means were recorded directly (i.e., after they had crystallized from the concentrated chromatographic fractions). Starting materials and reagents were generally available from the Sigma-Aldrich, Merck, TCI, Strem, or Lancaster Chemical Companies and were used as supplied. Drying agents and other inorganic salts were purchased from the AJAX, BDH, or Unilab Chemical Companies. Tetrahydrofuran (THF), methanol, and dichloromethane were dried using a Glass Contour solvent purification system that is based upon a technology originally described by Grubbs et al.[20] Where necessary, reactions were performed under a nitrogen atmosphere.

Specific Chemical Transformations. *(E)-2-Methoxy-1-(methoxymethoxy)-4-(3-(methoxymethoxy)prop-1-en-1-yl)-benzene (4). Step i*: Using a procedure analogous to that described by Bazin et al.,[21] a magnetically stirred solution of ferulic acid (**3**) (30.2 g, 155.5 mmol) in dry methanol (200 mL) was treated with five drops of concentrated sulfuric acid, and the resulting mixture was heated under reflux for 24 h. The solution was then cooled to room temperature, and the solvent was removed under reduced pressure. The residue thus obtained was dissolved in dichloromethane, and the resulting solution was washed with $NaHCO_3$ (2 × 100 mL of a saturated aqueous solution) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a pale-yellow oil. Subjection of this oil to flash chromatography [silica, petroleum ether → 1:5 v/v ethyl acetate/petroleum ether gradient elution] and concentration of the relevant fractions (R_f = 0.6 in 1:1 v/v ethyl acetate/petroleum ether) under reduced pressure afforded ferulic acid methyl ester[22] (30.0 g, 93%) as a white, crystalline solid, mp = 60.9−62.1 °C (lit.[22] mp = 65 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, J = 15.9 Hz, 1H), 7.07 (dd, J = 8.2 and 1.9 Hz, 1H), 7.02 (d, J = 1.9 Hz, 1H), 6.92 (d, J = 8.2 Hz, 1H), 6.29 (d, J = 15.9 Hz, 1H), 5.90 (m, 1H), 3.92 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 148.1, 146.9, 145.1, 127.1, 123.2, 115.3, 114.9, 109.5, 56.1, 51.7. These spectral data matched those reported by Li et al.[22]

Step ii: Chloromethyl methyl ether (MOM-Cl) (12.0 mL, 158.3 mmol) was added dropwise to a magnetically stirred solution of ferulic acid methyl ester (22.0 g, 105.6 mmol) and Hünig's base (i-Pr_2NEt) (27.6 mL, 158.3 mmol) in dry dichloromethane (100 mL) maintained at 0 °C. The resulting mixture was allowed to warm to 22 °C and stirred at this temperature for 14 h whilst being maintained under nitrogen then quenched with NH_4Cl (50 mL of a saturated aqueous solution). The mixture thus obtained was stirred at 22 °C for a further 1 h then treated with $NaHCO_3$ (100 mL of a saturated aqueous solution). The separated aqueous layer was extracted with ethyl acetate (3 × 100 mL) and the combined organic phases were washed with Na_2CO_3 (3 × 50 mL of a saturated aqueous solution) and brine (3 × 50 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a yellow oil. This oil was subjected to flash chromatography [silica, dichloromethane → 1:20 v/v Et_2O/dichloromethane gradient elution], and concentration of the relevant fractions (R_f = 0.8 in 1:9 v/v Et_2O/dichloromethane) under reduced pressure afforded methyl (*E*)-3-(3-methoxy-4-(methoxymethoxy)phenyl)acrylate[23] (25.0 g, 94%) as a clear, light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 16.0 Hz, 1H), 7.15 (d, J = 8.1 Hz, 1H), 7.07 (m, 2H), 6.33 (d, J = 16.0 Hz, 1H), 5.26 (s, 2H), 3.91 (s, 3H), 3.80 (s, 3H), 3.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 149.9, 148.6, 144.8, 128.8, 122.4, 116.2, 115.9, 110.4, 95.3, 56.5, 56.1, 51.8. These spectral data matched those reported by Lui et al.[23]

Step iii: Aluminum trichloride (14.45 g, 109.2 mmol) was added to dry THF (160 mL), and the resulting suspension was stirred at 0 °C under nitrogen for 0.25 h. $LiAlH_4$ (150 mL of a 1 M solution in THF, 150 mmol) was then added dropwise over 0.5 h, and the resulting suspension was stirred for a further 0.5 h at 0 °C. A solution of methyl (*E*)-3-(3-methoxy-4-

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(methoxymethoxy)phenyl)acrylate (24.97 g, 99.0 mmol) in dry THF (20 mL) was then added (dropwise over 0.5 h) to the reaction mixture that was then stirred at 0 °C for 0.5 h before being allowed to warm to 22 °C and stirred for an additional 1 h at this temperature. The reaction mixture was then cooled to 0 °C, water (5.7 mL) was added dropwise (Caution: hydrogen gas evolution), and stirring then continued for 0.25 h. After this time, NaOH (5.7 mL of a 15% w/v aqueous solution) was added to the reaction mixture, and stirring continued for an additional 0.25 h before more water (17.1 mL) was added. The resulting mixture was warmed to 22 °C, diluted with Et_2O (10 mL), then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a light-yellow oil. Subjection of this material to flash chromatography (silica, petroleum ether → ethyl acetate gradient elution) and concentration of the relevant fractions (R_f = 0.4 in 1:1 v/v ethyl acetate/petroleum ether) under reduced pressure afforded (*E*)-3-(3-methoxy-4-(methoxymethoxy)phenyl)prop-2-en-1-ol[24] (21.21 g, 96%) as a white, crystalline solid, mp = 51.2−52.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (d, J = 8.3 Hz, 1H), 6.95 (d, J = 2.0 Hz, 1H), 6.90 (dd, J = 8.3 and 2.0 Hz, 1H), 6.55 (d, J = 15.9 Hz, 1H), 6.26 (dt, J = 15.9 and 5.9 Hz, 1H), 5.23 (s, 2H), 4.31 (dd, J = 5.9 and 1.5 Hz, 2H), 3.89 (s, 3H), 3.51 (s, 3H) (signal due to hydroxyl group proton not observed); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.8, 146.4, 131.4, 131.1, 127.2, 119.7, 116.3, 109.5, 95.5, 63.9, 56.4, 56.0; IR ν_{max} 3399, 2935, 1512, 1464, 1417, 1263, 1154, 1132, 1077, 993, 969 cm^{-1}; MS (ESI, +ve) m/z 247 (100) $[M + Na]^+$; HRMS calcd for $C_{12}H_{16}NaO_4$ $[M + Na]^+$: 247.0946, found: 219.0946.

Step iv: MOM-Cl (10.7 mL, 141.3 mmol) was added dropwise to a magnetically stirred solution of (*E*)-3-(3-methoxy-4-(methoxymethoxy)phenyl)prop-2-en-1-ol (21.18 g, 94.2 mmol) and Hünig's base (24.6 mL, 141.3 mmol) in dry dichloromethane (94 mL) maintained at 0 °C under a nitrogen atmosphere. The resulting mixture was allowed to warm to 22 °C and stirred at this temperature for 14 h before being quenched with $NaHCO_3$ (50 mL of a saturated aqueous solution). The mixture thus obtained was stirred for a further 1 h, then the organic layer was separated and washed with $NaHCO_3$ (1 × 50 mL of a saturated aqueous solution). The combined aqueous layers were extracted with ethyl acetate (3 × 100 mL), and then the combined organic phases were washed with NH_4Cl (3 × 50 mL of a saturated aqueous solution), water (1 × 50 mL), and brine (3 × 50 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a light-yellow oil. This oil was subjected to flash chromatography (silica, dichloromethane → 1:20 v/v Et_2O/dichloromethane gradient elution), and concentration of the relevant fractions (R_f = 0.7 in 1:20 v/v Et_2O/dichloromethane) under reduced pressure afforded compound **4** (25.0 g, 94%) as a clear, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (d, J = 8.2 Hz, 1H), 6.96 (d, J = 1.8 Hz, 1H), 6.91 (dd, J = 8.2 and 1.8 Hz, 1H), 6.57 (d, J = 15.9 Hz, 1H), 6.18 (dt, J = 15.9 and 6.2 Hz, 1H), 5.23 (s, 2H), 4.70 (s, 2H), 4.22 (d, J = 6.2 Hz, 1H), 3.89 (s, 3H), 3.51 (s, 3H), 3.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.8, 146.4, 132.6, 131.4, 124.2, 119.8, 116.3, 109.5, 95.7, 95.5, 68.0, 56.4, 56.0, 55.5; IR ν_{max} 3375, 2934, 1512, 1464, 1265, 1152, 1133, 1102, 1078, 1036, 995, 920 cm^{-1}; MS (ESI, +ve) m/z 291 (100) $[M + Na]^+$, 160 (85); HRMS calcd for $C_{14}H_{20}NaO_5$ $[M + Na]^+$: 219.1208, found: 219.1208.

*(1R,2R)-1-(3-Methoxy-4-(methoxymethoxy)phenyl)-3-(methoxymethoxy)propane-1,2-diol (**5**).* $MeSO_2NH_2$ (856 mg, 9.0 mmol) was added to a magnetically stirred solution of AD-mix-α (12.48 g) in *t*-butanol/water (120 mL of a 1:1 v/v mixture) maintained at 22 °C, and the resulting suspension was stirred for 0.5 h after which time both phases had become clear. This mixture was then cooled to 0 °C before being treated with a solution of alkene **4** (2.00 g, 7.8 mmol) in *t*-butanol (2 mL). The reaction mixture thus obtained was stirred vigorously at 0 °C for 72 h, quenched with Na_2SO_3 (1.0 g), then allowed to warm to 22 °C and stirred at this temperature 12 h. The resulting solution was concentrated under reduced pressure, and the residue thus obtained subjected to flash chromatography [silica, 1:1 v/v ethyl acetate/petroleum ether → ethyl acetate gradient elution]. Concentration of the relevant fractions (R_f = 0.4 in ethyl acetate) under reduced pressure afforded compound **5** (1.85 g, 78%) as a clear, colorless gum, $[\alpha]^{25}_D$ = +10.7 (c = 1.02, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, J = 8.2 Hz, 1H), 6.98 (d, J = 1.9 Hz, 1H), 6.87 (dd, J = 8.2 and 1.9 Hz, 1H), 5.22 (s, 2H), 4.64 (m, 3H), 3.89 (s, 3H), 3.80 (m, 1H), 3.57 (dd, J = 10.7 and 3.3 Hz, 1H), 3.52 (dd, J = 10.7 and 5.5 Hz, 1H), 3.51 (s, 3H), 3.39 (s, 3H), 3.08 (broad d, J = 5.4 Hz, 1H), 3.00 (br d, J = 1.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 146.4, 134.8, 119.4, 116.4, 110.3, 97.5, 95.6, 75.0, 74.7, 70.1, 56.4, 56.1, 55.8; IR ν_{max} 3435, 2937, 1594, 1513, 1265, 1153, 1034, 989, 920 cm^{-1}; MS (ESI, +ve) m/z 325 (100) $[M + Na]^+$; HRMS calcd for $C_{14}H_{22}NaO_7$ $[M + Na]^+$: 325.1263, found: 325.1259.

*(R)-2-Hydroxy-1-(3-methoxy-4-(methoxymethoxy)-phenyl)-3-(methoxymethoxy)propan-1-one (**6**).* DDQ (2.78 g, 12.25 mmol) was added to a magnetically stirred solution of diol **5** (1.79 g, 5.92 mmol) in dry benzene (30 mL) maintained under nitrogen at 22 °C. The resulting suspension was sonicated for 5 h during which time the temperature of the water in the sonication bath was maintained between 22 and 30 °C through the addition of ice. The reaction mixture thus obtained was cooled then filtered, and the filtrate was concentrated reduced pressure. The residue thus obtained was triturated with cold dichloromethane (4 × 10 mL), and the combined washings were filtered and the filtrate again concentrated under reduced pressure to afford a black oil. Subjection of this material to flash chromatography [silica, dichloromethane → 3:7 v/v Et_2O/dichloromethane gradient elution] and concentration of the relevant fractions (R_f = 0.5 in 3:7 v/v Et_2O/dichloromethane) under reduced pressure afforded compound **6** (1.53 g, 86%) as a clear, pale-yellow oil, $[\alpha]^{25}_D$ = −20.0 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 2.0 Hz, 1H), 7.51 (dd, J = 8.4 and 2.0 Hz, 1H), 7.21 (d, J = 8.4 Hz, 1H), 5.32 (s, 2H), 5.19 (ddd—simplifies to a dd upon addition of D_2O, J = 7.4, 4.5, and 3.1 Hz, 1H), 4.60 (d, J = 6.6 Hz, 1H), 4.56 (d, J = 6.6 Hz, 1H), 3.99 (d—disappears upon addition of D_2O, J = 6.8 Hz, 1H), 3.95 (s, 3H), 3.92 (dd, J = 10.8 and 3.1 Hz, 1H), 3.85 (dd, J = 10.8 and 4.5 Hz, 1H), 3.52 (s, 3H), 3.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8, 151.8, 150.0, 128.0, 123.1, 114.7, 111.4, 96.9, 95.2, 73.2, 71.1, 56.7, 56.3, 55.5; IR ν_{max} 3444, 2937, 1676, 1595, 1512, 1464, 1266, 1148, 1115, 1080, 1032, 980, 920 cm^{-1}; MS (ESI, +ve) m/z 323 (100) $[M + Na]^+$; HRMS calcd for $C_{14}H_{20}NaO_7$ $[M + Na]^+$: 323.1107, found: 323.1107.

*(R)-1-(3-Methoxy-4-(methoxymethoxy)phenyl)-3-(methoxymethoxy)-1-oxopropan-2-yl 4-Methylbenzenesulfonate (**7**).* A magnetically stirred solution of alcohol **6** (1.52 g 5.06 mmol) in dry dichloromethane (20 mL) maintained under nitrogen was cooled to 0 °C then treated with pyridine (600 μL, 7.59 mmol) and *p*-toluenesulfonic acid anhydride (2.48 g,

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7.6 mmol). The ensuing mixture was allowed to stir at 0 °C for 0.5 h then warmed to 22 °C and stirred at this temperature for an additional 1 h before being re-cooled to 0 °C, quenched with pH 7 buffer (2 mL of a 1 M aqueous solution), then allowed to warm to 22 °C. The mixture thus obtained was diluted with ethyl acetate (50 mL) before being washed with NH_4Cl (1 × 40 mL) and brine (1 × 10 mL) The separated aqueous phase was extracted with ethyl acetate (3 × 20 mL), and the combined organic phases were washed with brine (3 × 20 mL) before being dried ($MgSO_4$), filtered, then concentrated under reduced pressure to afford an orange oil. This oil was subjected to flash chromatography (silica, dichloromethane → 1:9 v/v Et_2O/dichloromethane gradient elution) and concentration of the relevant fractions (R_f = 0.6 in 1:9 v/v Et_2O/dichloromethane) under reduced pressure afforded ester **7** (2.14 g, 93%) as a white, crystalline solid, mp = 93.5−95.8 °C, $[\alpha]^{25}_D$ = −34 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.2 Hz, 2H), 7.53 (dd, *J* = 8.5 and 1.8 Hz, 1H), 7.46 (d, *J* = 1.8 Hz, 1H), 7.26 (d, *J* = 8.2 Hz, 2H), 7.17 (d, *J* = 8.5 Hz, 1H), 5.82 (t, *J* = 4.9 Hz, 1H), 5.32 (s, 2H), 4.54 (m, 2H), 3.93 (d, *J* = 4.9 Hz, 2H), 3.91 (s, 3H), 3.52 (s, 3H), 3.25 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.6, 151.7, 149.8, 145.2, 133.5, 129.8, 128.7, 128.2, 123.5, 114.6, 111.6, 96.7, 95.2, 79.8, 67.4, 56.7, 56.2, 55.6, 21.8; IR ν_{max} 3374, 2940, 1690, 1595, 1512, 1464, 1421, 1364, 1267, 1176, 1079, 1030, 976, 923, 814, 666 cm^{-1}; MS (ESI, +ve) *m/z* 477 (100) $[M + Na]^+$; HRMS calcd for $C_{21}H_{26}NaO_9S$ $[M + Na]^+$: 477.1195, found: 477.1194.

*(E)-3-(3-Methoxy-4-((1-(3-methoxy-4-(methoxymethoxy)-phenyl)-3-(methoxymethoxy)-1-oxopropan-2-yl)oxy)-phenyl)acrylaldehyde (**9**).* Cesium carbonate (1.09 g, 3.34 mmol) was added to a solution of 18-crown-6 (874 mg, 3.31 mmol) and coniferaldehyde (**8**) (590 mg, 3.31 mmol) in dry acetonitrile (9 mL) maintained under nitrogen at 22 °C. The resulting suspension was sonicated for 0.5 h, then the supernatant liquid was taken up in a syringe and added dropwise, over 0.25 h, to a magnetically solution of tosylate **7** (990 mg, 2.17 mmol) in dry acetonitrile (20 mL) maintained under nitrogen at 0 °C. The resulting solution was stirred at 0 °C for 5 h then quenched with pH 7 buffer (2 mL of a 1 M aqueous solution) before being allowed to warm to 22 °C. The ensuing mixture was diluted with ethyl acetate (20 mL), and the separated aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with brine (3 × 20 mL) then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography [silica, dichloromethane → 3:7 v/v Et_2O/dichloromethane gradient elution], and concentration of the relevant fractions (R_f = 0.2 in 1:9 v/v Et_2O/dichloromethane) under reduced pressure afforded aryl ether **9** (470 mg, 47%) as a clear, pale-yellow oil, $[\alpha]^{25}_D$ = 0 (*c* = 2.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (d, *J* = 7.7 Hz, 1H), 7.74 (dd, *J* = 8.5 and 1.1 Hz, 1H), 7.66 (s, 1H), 7.35 (d, *J* = 15.8 Hz, 1H), 7.18 (d, *J* = 8.5 Hz, 1H), 7.05 (s, 1H), 7.02 (d, *J* = 8.3 Hz, 1H), 6.81 (d, *J* = 8.3 Hz, 1H), 6.56 (dd, *J* = 15.8 and 7.7 Hz, 1H), 5.62 (m, 1H), 5.30 (s, 2H), 4.69 (s, 2H), 4.19−4.07 (complex m, 2H), 3.91 (s, 3H), 3.84 (s, 3H), 3.50 (s, 3H), 3.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.5, 193.6, 152.6, 151.6, 150.2, 150.0, 149.8, 129.0, 128.5, 127.3, 123.4, 123.1, 115.5, 114.6, 111.7, 111.2, 96.9, 95.1, 81.7, 68.1, 56.7, 56.1(1), 56.0(7), 55.6; IR ν_{max} 3369, 2932, 1671, 1595, 1509, 1268, 1141, 1127, 1079, 1032, 975, 804 cm^{-1}; MS (ESI, +ve) *m/z* 484 (100) $[M + Na]^+$; HRMS calcd for $C_{24}H_{28}NaO_9$ $[M + Na]^+$: 483.1631, found: 483.1632.

*(E)-3-(4-((3-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)-1-oxopropan-2-yl)oxy)-3-met-hoxyphenyl)acrylaldehyde (**10**).* A magnetically stirred solution of aryl ether **9** (465 mg, 1.02 mmol) in dry isopropanol (30 mL) was treated with concentrated hydrochloric acid (3 drops), and the resulting solution was heated at 60 °C for 22 h. The cooled reaction mixture was quenched with $NaHCO_3$ (20 mL of a saturated solution) then diluted with ethyl acetate (60 mL) before being washed with $NaHCO_3$ (2 × 20 mL). The separated aqueous phases were extracted with ethyl acetate (3 × 20 mL), and the combined organic phases were washed with brine (3 × 20 mL) then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a pale-yellow oil. This oil was subjected to flash chromatography (silica, 1:1 v/v ethyl acetate/petroleum ether → ethyl acetate gradient elution), and concentration of the relevant fractions (R_f = 0.2 in 3:1 v/v ethyl acetate /petroleum ether) under reduced pressure afforded alcohol **10** (291 mg, 76%) as a pale-yellow foam, $[\alpha]^{25}_D$ = 0 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (d, *J* = 7.7 Hz, 1H), 7.70 (dd, *J* = 8.4 and 1.9 Hz, 1H), 7.61 (d, *J* = 1.9 Hz, 1H), 7.37 (d, *J* = 15.9 Hz, 1H), 7.08 (d, *J* = 1.9 Hz, 1H), 7.04 (dd, *J* = 8.3 and 2.0 Hz, 1H), 6.96 (d, *J* = 8.3 Hz, 1H), 6.83 (d, *J* = 8.3 Hz, 1H), 6.55 (dd, *J* = 15.9 and 7.7 Hz, 1H), 6.17 (broad s, 1H), 5.55 (m, 1H), 4.13 (m, 2H), 3.94 (s, 3H), 3.90 (s, 3H), 2.79 (broad t, *J* = 6.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.0, 193.6, 152.4, 151.5, 150.5, 149.7, 147.1, 129.1, 127.6(2), 127.5(7), 124.2, 123.1, 116.7, 114.3, 111.2, 110.7, 83.4, 63.9, 56.3, 56.1; IR ν_{max} 3356, 2938, 1668, 1620, 1591, 1509, 1426, 1270, 1137, 1030, 734 cm^{-1}; MS (ESI, +ve) *m/z* 395 (100) $[M + Na]^+$; HRMS calcd for $C_{20}H_{20}NaO_7$ $[M + Na]^+$: 395.1107, found: 395.1110.

*Compounds (±)-**1** and (±)-**2**.* Polymer-supported borohydride (2.5 mmol g^{-1} on Amberlite A-26, 400 mg, 1.0 mmol) was added in one portion to a magnetically stirred solution of compound **10** (77 mg, 0.21 mmol) in methanol (5 mL) maintained under nitrogen at 0 °C. The ensuing mixture was stirred at this temperature for 4 h then allowed to warm to 22 °C before being filtered, and the solids thus retained were washed with acetic acid in methanol (3 × 10 mL of a 1:99 v/v mixture). The combined filtrates were concentrated under reduced pressure to give a ca. 7:1 mixture of the title compounds (68 mg, 87%) as a light-yellow oil. Subjection of this material to preparative, reverse phase HPLC (Gemini C18 5μ 150 × 21.20 mm^2 column, 25:74.95:0.05 v/v/v/v methanol/water/acetic acid elution, flow rate 17.0 mL/min) afforded two fractions, A and B.

Concentration of fraction A (t_R = 12.0 min) afforded compound (±)-**2**[4e,10] (9 mg, 12%) as a white powder. ^{1}H NMR [300 MHz, $(CD_3)_2CO$] δ 7.11 (d, *J* = 1.9 Hz, 1H), 7.06 (d, *J* = 1.9 Hz, 1H), 6.92 (d, *J* = 8.1 Hz, 1H), 6.90−6.85 (complex m, 2H), 6.76 (d, *J* = 8.1 Hz, 1H), 6.52 (dt, *J* = 15.8 and 1.7 Hz, 1H), 6.28 (dt, *J* = 15.8 and 5.3 Hz, 2H), 4.89 (d, *J* = 5.3 Hz, 1H), 4.30 (m, 1H), 4.19 (dd, *J* = 5.3 and 1.7 Hz, 2H), 3.85 (s, 3H), 3.82 (s, 3H), 3.79 (partially obscured m, 1H), 3.69 (dd, *J* = 11.6 and 4.0 Hz, 1H) (signals due to three hydroxyl group protons not observed); ^{1}H NMR (400 MHz, CD_3OD) δ 7.02 (d, *J* = 2.0 Hz, 1H), 7.00 (s, 1H), 6.87 (s, 2H), 6.84 (dd, *J* = 8.2 and 2.0 Hz, 1H), 6.73 (d, *J* = 8.2 Hz, 1H), 6.51 (dt, *J* = 15.7 and 1.6 Hz, 1H), 6.24 (dt, *J* = 15.7 and 5.7 Hz, 1H), 4.83 (d, *J* = 5.7 Hz, 1H), 4.36 (m, 1H), 4.20 (dd, *J* = 5.7 and 1.6 Hz, 2H), 3.85 (dd, *J* = 12.0 and 5.6 Hz, 1H), 3.80 (s, 3H), 3.80 (s, 3H), 3.76

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(partially obscured d, J = 3.6 Hz, 1H) (signals due to hydroxyl group protons not observed); ^{13}C NMR (100 MHz, CD_3OD) δ see Table 1; IR ν_{max} 3369, 2918, 1509, 1266, 1152, 1122, 1029 cm^{-1}; MS (EI, +ve) m/z 376 (15) ($M^{+\bullet}$), 358 (50), 328 (45), 206 (100); HRMS calcd for $C_{20}H_{24}O_7$ ($M^{+\bullet}$): 376.1522, found: 376.1524.

Concentration of fraction B (t_R = 13.2 min) afforded compound (±)-**1**[4l,10] (57 mg, 73%) as a white powder. ^{1}H NMR [300 MHz, $(CD_3)_2CO$] δ 7.11 (d, J = 8.4 Hz, 1H), 7.10−7.09 (complex m, 2H), 6.91 (dd, J = 8.4 and 2.1 Hz, 1H), 6.90 (dd, J = 8.1 and 1.9 Hz, 1H), 6.77 (d, J = 8.1 Hz, 1H), 6.54 (dt, J = 15.9 and 1.7 Hz, 1H), 6.30 (dt, J = 15.9 and 5.3 Hz, 1H), 4.88 (d, J = 6.3 Hz, 1H), 4.20 (m, 3H), 3.90 (s, 3H), 3.81 (s, 3H), 3.68 (dd, J = 11.8 and 3.7 Hz, 1H), 3.50 (dd, J = 11.8 and 5.7 Hz, 1H) (signals due to hydroxyl group protons not observed); ^{1}H NMR (400 MHz, CD_3OD) δ 7.05 (s, 1H), 7.03 (s, 1H), 6.99 (d, J = 8.3 Hz, 1H), 6.90 (d, J = 8.3 Hz, 1H), 6.86 (d, J = 8.2 Hz, 1H), 6.76 (d, J = 8.2 Hz, 1H), 6.53 (d, J = 15.8 Hz, 1H), 6.25 (dt, J = 15.8 and 5.7 Hz, 1H), 4.90 (partially obscured m, 1H), 4.31 (app. q, J = 5.0 Hz, 1H), 4.20 (d, J = 5.7 Hz, 2H), 3.87 (s, 3H), 3.81 (s, 3H), 3.74 (dd, J = 12.1, 3.7 Hz, 1H), 3.48 (dd, J = 12.0, 5.2 Hz, 1H) (signals due to hydroxyl group protons not observed); ^{13}C NMR (100 MHz, CD_3OD) δ see Table 1; IR ν_{max} 3369, 2931, 1604, 1510, 1263, 1129, 1079, 1029, 965 cm^{-1}; MS (ESI, +ve) m/z 399 (100) [M + Na]$^+$; HRMS calcd for $C_{20}H_{24}NaO_7$ [M + Na]$^+$: 399.1420, found: 399.1420.

*2-(4-Allyl-2-methoxyphenoxy)acetic Acid (**14**).* Compound **14** was prepared in 85% overall yield from ethyl α-bromoacetate and eugenol (**13**) following a protocol reported by Spurg and Waldvogel[25] to give a white, crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (d, J = 7.9 Hz, 1H), 6.76 (m, 2H), 5.94 (m, 1H), 5.11 (m, 1H), 5.08 (m, 1H), 4.63 (s, 2H), 3.90 (s, 3H), 3.36 (d, J = 6.7 Hz, 2H) (signal due to carboxylic acid group proton not observed); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 149.9, 145.7, 137.2, 136.5, 121.3, 117.6, 116.3, 112.7, 69.0, 56.1, 40.0. These spectral data matched those reported by Labarrios and co-workers.[26]

*(S)-3-(2-(4-Allyl-2-methoxyphenoxy)acetyl)-4-isopropyl-5,5-diphenyloxazolidin-2-one (**15**).* Oxalyl chloride (710 μL, 8.14 mmol) was added dropwise over 0.08 h to a magnetically stirred solution of carboxylic acid **14** (1.65 g, 7.40 mmol) and dimethylformamide (DMF) (28 μL, 0.37 mmol) in dichloromethane (15 mL) maintained at 0 °C under a nitrogen atmosphere. The ensuing mixture was allowed to warm to 22 °C and stirred until gas evolution ceased (ca. 1 h). The dichloromethane was then removed by sparging the reaction mixture with a stream of nitrogen followed by further concentration of the reaction mixture under reduced pressure. The acid chloride thus obtained was dissolved in dry THF (15 mL). In a separate flask, n-BuLi (4.52 mL of a 1.5 M solution in hexanes, 6.79 mmol) was added dropwise over 0.25 h to a magnetically stirred solution of (*S*)-4-isopropyl-5,5-diphenyloxazolidin-2-one (**12**)[14b] (1.74 g, 6.17 mmol) in dry THF (150 mL) maintained at 0 °C. The resulting solution was stirred at this temperature for 0.5 h then cooled to −78 °C. The previously formed solution of the acid chloride in THF was then added dropwise over 0.25 h, and stirring of the combined solutions continued at −78 °C for 0.5 h. The cooling bath was then removed, and the reaction mixture was allowed to warm to 22 °C and stirring was continued for 3 h. After this time, the reaction mixture was cooled to 0 °C and quenched with NH_4Cl (30 mL of a saturated aqueous solution) then acetic acid (5 mL). The ensuing mixture was allowed to warm, over 0.25 h, to 22 °C then it was extracted with ethyl acetate (3 × 30 mL). The combined organic phases were washed with $NaHCO_3$ (2 × 10 mL of a saturated aqueous solution) and brine (2 × 20 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing viscous, clear, and light-yellow oil was subjected to flash column chromatography (silica, hexane → 1:4 v/v ethyl acetate/hexane gradient elution), and concentration of the appropriate fractions (R_f = 0.3 in 1:4 v/v ethyl acetate/hexane) afforded amide **15** (2.79 g, 93%) as a white foam, $[\alpha]^{20}_D$ = −156 (c = 0.3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.27 (complex m, 10H), 6.70 (d, J = 2.0 Hz, 1H), 6.57 (dd, J = 8.2 and 2.0 Hz, 1H), 6.46 (d, J = 8.2 Hz, 1H), 5.94 (m, 1H), 5.37 (d, J = 3.3 Hz, 1H), 5.24 (d, J = 17.7 Hz, 1H), 5.12−5.01 (complex m, 3H), 3.82 (s, 3H), 3.31 (d, J = 6.8 Hz, 2H), 2.00 (m, 1H), 0.90 (d, J = 7.0 Hz, 3H), 0.79 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 153.2, 149.4, 145.6, 142.1, 137.9, 137.7, 134.1, 129.2, 129.0, 128.6, 128.3, 126.0, 125.8, 120.4, 115.8, 113.6, 112.6, 91.1, 68.1, 64.9, 56.0, 40.0, 30.0, 21.9, 16.6; IR ν_{max} 2969, 1780, 1724, 1510, 1257, 1209, 1178, 1147, 1035, 992, 733, 701 cm^{-1}; MS (ESI, +ve) m/z 508 (100) [M + Na]$^+$; HRMS calcd for $C_{30}H_{31}NNaO_5$ [M + Na]$^+$: 508.2100, found: 508.2099.

*(R)-3-(2-(4-Allyl-2-methoxyphenoxy)acetyl)-4-isopropyl-5,5-diphenyloxazolidin-2-one (ent-**15**).* Compound *ent*-**15** was prepared in an analogous fashion to that described immediately above from compounds *ent*-**12** and **14**. Flash chromatographic purification then gave oxazolidin-2-one *ent*-**15** (8.79 g, quantitative yield) as a white foam, $[\alpha]^{20}_D$ = +160 (c = 0.3, $CHCl_3$). All the other spectral data acquired on this material were identical with those detailed above for compound **15**.

*(1R,2R)-2-(4-Allyl-2-methoxyphenoxy)-1-(4-((tert-butyldimethylsilyl)oxy)-3-methoxyphe-nyl)propane-1,3-diol (**17**).* *Step i*: A magnetically stirred solution of amide **15** (2.00 g, 4.12 mmol) in dry dichloromethane (8 mL) maintained at 0 °C under a nitrogen atmosphere was treated, dropwise over 0.08 h, with freshly prepared[14b] Bu_2BOTf (1.07 mL, 1.35 g, 4.94 mmol). The ensuing mixture was allowed to warm to 22 °C, stirred at this temperature for 0.25 h, then freshly distilled Hünig's base (970 μL, 5.56 mmol) was added dropwise over 0.08 h. Stirring was continued at 22 °C for another 0.5 h then the reaction mixture was cooled to −78 °C before a solution of aldehyde **16**[27] (1.35 g, 4.94 mmol) in dichloromethane (4 mL) was added via syringe pump over 0.75 h. The ensuing mixture was stirred at −78 °C for a further 1 h then warmed to 0 °C, stirred at this temperature for 4 h, then quenched with phosphate buffer (15 mL of a 1 M aqueous solution at pH 7) before being treated with methanol/30% aq. hydrogen peroxide (10 mL of a 1:1 v/v mixture) and allowed to warm to 22 °C over 1 h. The biphasic mixture thus obtained was diluted with water (20 mL), and the separated aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic phases were washed with brine (1 × 10 mL) then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing thick oil was subjected to flash column chromatography (silica, dichloromethane → 1:19 v/v Et_2O/dichloromethane gradient elution), and concentration of the appropriate fractions (R_f = 0.5 in 1:19 v/v Et_2O/dichloromethane) afforded the anticipated aldol product (2.58 g, 83%) as a white foam, $[\alpha]^{20}_D$ = −78.5 (c = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.27 (complex m, 10H), 6.87 (d, J = 2.0 Hz, 1H), 6.71 (d, J = 8.2 Hz, 1H), 6.67 (d, J = 2.0 Hz, 1H),

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6.63 (dd, J = 8.1 and 2.0 Hz, 1H), 6.57 (dd, J = 8.1 and 2.0 Hz, 1H), 6.48 (d, J = 8.1 Hz, 1H), 6.10 (m, 1H), 5.89 (m, 1H), 5.35 (d, J = 2.9 Hz, 1H), 5.05 (m 1H), 5.01 (m, 1H), 4.67 (t, J = 5.0 Hz, 1H), 3.79 (s, 3H), 3.71 (s, 3H), 3.28 (m, 3H), 1.95 (m, 1H), 0.98 (s, 9H), 0.86 (d, J = 7.0 Hz, 3H), 0.68 (d, J = 6.7 Hz, 3H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 152.9, 150.7, 150.4, 145.5, 144.7, 141.6, 138.1, 137.5, 135.6, 131.9, 129.0(3), 129.0(0), 128.5, 128.1, 125.9, 125.4, 120.8, 120.5, 119.3, 118.5, 115.9, 113.1, 110.6, 90.1, 81.4, 74.0, 65.1, 56.0, 55.3, 40.0, 30.1, 25.9, 21.8, 18.6, 16.3, −4.5, −4.6; IR ν_{max} 3452, 2954, 2930, 2858, 1777, 1716, 1510, 1450, 1369, 1283, 1210, 1153, 1035, 908, 702 cm^{-1}; MS (ESI, +ve) m/z 774 (100) $[M + Na]^+$; HRMS calcd for $C_{44}H_{53}NNaO_8Si$ $[M + Na]^+$: 774.3438, found: 774.3433.

Step ii: Methanol (230 μL, 5.65 mmol) was added to a magnetically stirred solution of the above-mentioned aldol product (1.70 g, 2.26 mmol) in THF (25 mL) maintained under nitrogen at 22 °C. The resulting solution was cooled to 0 °C, and lithium borohydride (123 mg, 5.65 mmol) was then added in portions over 0.08 h. The ensuing mixture was stirred at 0 °C for 0.5 h then warmed to 22 °C and stirred at this temperature for 2 h before being quenched with NH_4Cl (20 mL of a saturated aqueous solution) then diluted with Et_2O (100 mL). The separated aqueous layer was extracted with Et_2O (2 × 20 mL), and the combined organic extracts were washed with brine (2 × 20 mL) then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing pale-yellow residue was subjected to flash column chromatography (silica, 1:19 v/v Et_2O/dichloromethane → 1:4 v/v Et_2O/dichloromethane gradient elution), and concentration of the appropriate fractions (R_f = 0.4 in 1:4 v/v Et_2O/dichloromethane) afforded diol **17** (982 mg, 92%) as a clear, colorless oil, $[\alpha]^{20}_D$ = −63.3 (c = 0.8, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, J = 8.0 Hz, 1H), 6.95 (d, J = 1.9 Hz, 1H), 6.88 (dd, J = 8.1 and 1.9 Hz, 1H), 6.82 (d, J = 8.1 Hz, 1H), 6.76 (d, J = 1.9 Hz, 1H), 6.74 (dd, J = 8.0 and 1.9 Hz, 1H), 5.95 (m, 1H), 5.11 (m, 1H), 5.07 (t, J = 1.4 Hz, 1H), 4.95 (d, J = 8.0 Hz, 1H), 3.97 (dt, J = 7.6 and 3.6 Hz, 1H), 3.90 (s, 3H), 3.80 (s, 3H), 3.60 (dd, J = 12.5 and 3.2 Hz, 1H), 3.47 (dd, J = 12.5 and 4.0 Hz, 1H), 3.35 (d, J = 6.8 Hz, 2H), 0.99 (s, 9H), 0.14 (s, 6H) (signals due to hydroxyl group protons not observed); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 151.2, 146.0, 145.1, 137.3, 136.5, 133.2, 121.7, 121.2, 119.8, 116.2, 112.6, 110.8, 90.0, 74.2, 61.3, 56.0, 55.6, 40.1, 25.9, 18.6, −4.5(0), −4.5(2) (one signal obscured or overlapping); IR ν_{max} 3453, 2954, 2931, 2857, 1510, 1465, 1419, 1283, 1264, 1228, 1156, 1034, 911, 840, 782 cm^{-1}; MS (ESI, +ve) m/z (%) 497 (100) $[M + Na]^+$; HRMS calcd for $C_{26}H_{38}NaO_6Si$ $[M + Na]^+$: 497.2335, found: 497.2332.

(1S,2S)-2-(4-Allyl-2-methoxyphenoxy)-1-(4-((tert-butyldimethylsilyl)oxy)-3-methoxyphen-yl)propane-1,3-diol (ent-17). Diol *ent*-**17** was prepared as described immediately above from precursor *ent*-**15** and aldehyde **16**. Flash chromatographic purification of the product from step i gave the expected aldol product (2.15 g, 69%) as a clear, colorless oil, $[\alpha]^{20}_D$ = +77.7 (c = 1, $CHCl_3$). All the other spectral data acquired on this material were identical with those reported above for the product from step i. The conditions defined in step ii above were employed to produce diol *ent*-**17** (684 mg, 96%), which was obtained as a clear, colorless oil, $[\alpha]^{20}_D$ = +66.2 (c = 0.7, $CHCl_3$). All other spectral data acquired on this material were identical with those reported above for compound **17**.

(E)-3-(4-(((1R,2R)-1-(4-((tert-Butyldimethylsilyl)oxy)-3-methoxyphenyl)-1,3-dihydroxypr-oxypropan-2-yl)oxy)-3-methoxyphenyl)allyl Acetate (18). Acetic acid (370 μL, 6.5 mmol), sodium acetate (6.5 mg, 0.08 mmol), molecular sieves (2 mg of activated 4 Å material), 4,5-DAF (5.1 mg, 7 mol %), and $Pd(OAc)_2$ (6.3 mg, 7 mol %) were added sequentially to a magnetically stirred solution of compound **17** (190 mg, 0.40 mmol) in 1,4-dioxane (2.4 mL) maintained at 22 °C. Oxygen from a balloon was bubbled through the resulting solution for 0.25 h, which was then heated to 60 °C and maintained under an atmosphere of oxygen. After 48 h, the reaction mixture was cooled to 22 °C, and the solvent was removed under reduced pressure. The black residue thus obtained was subjected to flash column chromatography (silica, hexane → 3:2 v/v ethyl acetate/hexane gradient elution), and concentration of the appropriate fractions (R_f = 0.2 in 1:1 v/v EtOAc/hexane) afforded acetate **18** (103 mg, 48%) as a pale-yellow oil, $[\alpha]^{20}_D$ = −69.1 (c = 0.6, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, J = 8.2 Hz, 1H), 7.01−6.92 (complex m, 3H), 6.87 (dd, J = 8.0 and 1.9 Hz, 1H), 6.83 (d, J = 8.0 Hz, 1H), 6.60 (d, J = 15.9 Hz, 1H), 6.21 (dt, J = 15.9 and 6.5 Hz, 1H), 4.95 (dd, J = 7.9 and 2.0 Hz, 1H), 4.72 (dd, J = 6.5 and 1.3 Hz, 2H), 4.03 (m, 1H), 3.93 (s, 3H), 3.80 (s, 3H), 3.61 (m, 1H), 3.55−3.46 (complex m, 2H), 2.57 (m, 1H), 2.11 (s, 3H), 0.99 (s, 9H), 0.14 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 151.4, 151.3, 147.9, 145.2, 133.8, 133.1, 132.6, 122.9, 121.0, 120.9, 120.5, 119.7, 110.8, 110.0, 89.7, 74.2, 65.1, 61.4, 56.1, 55.7, 25.9, 21.2, 18.6, −4.5(0), −4.5(2); IR ν_{max} 3467, 2952, 2933, 2857, 1739, 1510, 1465, 1419, 1251, 1232, 1158, 1128, 1030, 908, 840 cm^{-1}; MS (ESI, +ve) m/z 555 (100) $[M + Na]^+$; HRMS calcd for $C_{28}H_{40}NaO_8Si$ $[M + Na]^+$: 555.2390, found: 555.2390.

(E)-3-(4-(((1S,2S)-1-(4-((tert-Butyldimethylsilyl)oxy)-3-methoxyphenyl)-1,3-dihydroxypro-pan-2-yl)oxy)-3-methoxyphenyl)allyl Acetate (ent-18). Allylic oxidation of compound *ent*-**17** in the same manner as that described above for congener **17** afforded, after flash chromatographic purification, compound *ent*-**18** (71 mg, 65%) as a pale-yellow oil, $[\alpha]^{20}_D$ = +47.5 (c = 1.6, $CHCl_3$). All other spectral data acquired on this material were identical with those reported above for compound **18**.

(1R,2R)-1-(4-Hydroxy-3-methoxyphenyl)-2-(4-((E)-3-hydroxyprop-1-en-1-yl)-2-methox-yphenoxy)propane-1,3-diol (ent-1). K_2CO_3 (270 mg, 1.95 mmol) was added to a magnetically stirred solution of acetate **18** (45 mg, 0.085 mmol) in methanol (5 mL) containing water (100 μL) and maintained at 22 °C under a nitrogen atmosphere. The ensuing mixture was stirred at this temperature for 18 h then diluted with ethyl acetate (20 mL), acidified (to pH 5) using acetic acid (ca. 200 μL), then washed with water (1 × 5 mL) and brine (2 × 5 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing pale-yellow oil was subjected to flash column chromatography (silica, 1:19 v/v methanol/dichloromethane → 1:9 v/v methanol/dichloromethane gradient elution). Concentration of the appropriate fractions (R_f = 0.2 in 1:19 v/v methanol/dichloromethane) afforded compound *ent*-**1** (25 mg, 79%) as a clear, colorless gum, $[\alpha]^{20}_D$ = −36.7 (c = 0.9, methanol). ^{1}H NMR (400 MHz, CD_3OD) δ 7.06 (s, 1H), 7.03 (s, 1H), 7.00 (d, J = 8.3 Hz, 1H), 6.91 (d, J = 8.3 Hz, 1H), 6.86 (d, J = 8.2 Hz, 1H), 6.75 (dd, J = 8.2 and 1.4 Hz, 1H), 6.53 (d, J = 16.0 Hz, 1H), 6.26 (dt, J = 16.0 and 5.4 Hz, 1H), 4.88 (m, 1H), 4.29 (m, 1H), 4.20 (d, J = 5.7 Hz, 2H), 3.88 (s, 3H), 3.82 (s, 3H), 3.73 (dd, J = 11.9 and

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4.0 Hz, 1H), 3.47 (dd, J = 11.9 and 5.4 Hz, 1H) (signals due to hydroxyl group protons not observed); ^{13}C NMR (100 MHz, CD_3OD) δ 151.8, 149.2, 148.8, 147.2, 133.8, 133.1, 131.4, 128.6, 120.8, 120.7, 118.8, 115.8, 111.7, 111.3, 87.1, 74.0, 63.8, 61.9, 56.5, 56.3; IR ν_{max} 3348, 2934, 1602, 1509, 1464, 1263, 1226, 1156, 1130, 1027, 968 cm^{-1}; MS (ESI, +ve) m/z 399 (100) $[M + Na]^+$; HRMS calcd for $C_{20}H_{24}NaO_7$ $[M + Na]^+$: 399.1420, found: 399.1419; HPLC analysis: Trefoil CEL1 column, 98:2 v/v methanol/supercritical CO_2 elution, flow rate 2 mL/min, temperature 40 °C, detection at λ = 254 nm, t_{major} = 6.03 min, ee > 99%.

*(1S,2S)-1-(4-Hydroxy-3-methoxyphenyl)-2-(4-((E)-3-hydroxyprop-1-en-1-yl)-2-methoxy-phenoxy)propane-1,3-diol (**1**).* Treatment of acetate *ent*-**18** with potassium carbonate in the same manner as that described above gave neolignan **1** (28 mg, 93%) as a clear, colorless gum, $[\alpha]^{20}_D$ = +32.4 (c = 0.2, methanol). All other spectral data acquired on this material were identical with those reported above for compound *ent*-**1**. HPLC analysis: Trefoil CEL1 column, 98:2 v/v methanol/supercritical CO_2 elution, flow rate 2 mL/min, temperature 40 °C, detection at λ = 254 nm, t_{minor} = 5.86 min, t_{major} = 6.05 min, ee = 90%.

*4-((1R,2R)-2-(4-Allyl-2-methoxyphenoxy)-3-((tert-butyldimethylsilyl)oxy)-1-hydroxyprop-yl)-2-methoxyphenol (**19**).* The following one-pot procedure for preparing compound **19** was established after that used to prepare its enantiomer (*ent*-**19**) and proved to be the more efficient one. Thus, a magnetically stirred solution of diol **17** (565 mg, 1.19 mmol) in DMF (4 mL) was cooled to 0 °C and treated sequentially with imidazole (162 mg, 2.38 mmol) and TBDMS-Cl (194 mg, 1.25 mmol). The ice bath was then removed, and the resulting solution was stirred at 22 °C for 1.5 h before being treated with Cs_2CO_3 (774 mg, 3.38 mmol) and water (400 μL). The resulting mixture was stirred at 22 °C for 2 h then heated at 40 °C for 4 h. The cooled reaction mixture was stirred at 22 °C for 16 h before being diluted with ethyl acetate (30 mL) and washed with NH_4Cl (3 × 10 mL of a saturated aqueous solution). The combined aqueous phases were extracted with ethyl acetate (3 × 10 mL) and the combined organic phases washed with brine (2 × 10 mL) then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting pale-yellow residue was subjected to flash column chromatography (silica, 1:9 v/v Et_2O/dichloromethane), and concentration of the appropriate fractions (R_f = 0.2 in 1:19 v/v Et_2O/dichloromethane) afforded phenol **19** (544 mg, 96%) as a clear, colorless oil, $[\alpha]^{20}_D$ = −103 (c = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, J = 8.1 Hz, 1H), 6.93 (s, 1H), 6.87 (m, 2H), 6.74 (d, J = 2.0 Hz, 1H), 6.71 (dd, J = 8.1 and 2.0 Hz, 1H), 5.96 (m, 1H), 5.10 (m, 1H), 5.07 (m, 1H), 4.82 (dd, J = 7.7 and 2.6 Hz, 1H), 4.21 (d, J = 2.6 Hz, 1H), 4.03 (m, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.72 (dd, J = 11.2 and 3.4 Hz, 1H), 3.63 (dd, J = 11.2 and 5.4 Hz, 1H), 3.37 (d, J = 6.8 Hz, 2H), 0.88 (s, 9H), 0.00 (s, 3H), −0.01 (s, 3H) (signal due to one hydroxyl group protons not observed); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.7, 147.0, 146.6, 145.5, 137.6, 135.4, 132.4, 121.1, 120.6, 120.3, 116.0, 114.2, 112.4, 109.6, 89.0, 74.0, 62.7, 56.1, 55.9, 40.1, 26.0, 18.5, −5.3(0), −5.3(4); IR ν_{max} 3466, 2954, 2930, 2856, 1606, 1509, 1454, 1266, 1227, 1127, 1035, 836, 779 cm^{-1}; MS (ESI, +ve) m/z (%) = 497 (100) $[M + Na]^+$; HRMS calcd for $C_{26}H_{38}NaO_6Si$ $[M + Na]^+$: 497.2335, found: 497.2334.

4-((1S,2S)-2-(4-Allyl-2-methoxyphenoxy)-3-((tert-butyldimethylsilyl)oxy)-1-hydroxypropy-l)-2-methoxyphenol (ent-19). A magnetically stirred solution of diol *ent*-**17** (452 mg, 0.95 mmol) in dichloromethane (6 mL) was cooled to −5 °C and treated sequentially with imidazole (129 mg, 1.9 mmol) and TBDMS-Cl (155 mg, 1.00 mmol). The cooling bath was then removed, and the reaction mixture was stirred at 22 °C for 16 h before being quenched with NH_4Cl (10 mL of a saturated aqueous solution). The separated aqueous phase was extracted with dichloromethane (3 × 10 mL) and the combined organic phases were then washed with brine (2 × 10 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give the anticipated bis-TBDMS ether (386 mg) as a light-yellow oil. This oil was dissolved in DMF (1 mL), and the resulting solution was treated with Cs_2CO_3 (307 mg, 0.95 mmol) and water (100 μL) then stirred at 22 °C for 24 h. After this time, another batch of Cs_2CO_3 (200 mg, 0.62 mmol) was added, and stirring continued for an additional 24 h. The reaction mixture was then diluted with ethyl acetate (30 mL) before being washed with NH_4Cl (3 × 10 mL of a saturated aqueous solution). The combined aqueous washings were extracted with ethyl acetate (3 × 10 mL), and the combined organic phases were then washed with brine (2 × 10 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing pale-yellow residue was subjected to flash column chromatography (silica, 1:9 v/v Et_2O/dichloromethane), and concentration of the appropriate fractions (R_f = 0.2 in 1:19 v/v Et_2O /DCM) afforded phenol *ent*-**19** (232 mg, 51% over two steps) as a clear, colorless oil, $[\alpha]^{20}_D$ = +98.8 (c = 0.7, $CHCl_3$). All other spectral data acquired on this material were identical with those reported above for compound **19**.

*4-((1R,2R)-2-(4-Allyl-2-methoxyphenoxy)-3-((tert-butyldimethylsilyl)oxy)-1-hydroxyprop-yl)-2-methoxyphenyl 4-Methylbenzenesulfonate (**20**).* *p*-Toluenesulfonyl chloride (216 mg, 1.13 mmol) was added in one portion to a magnetically stirred solution of phenol **19** (512 mg, 1.08 mmol) and triethylamine (225 μL, 1.62 mmol) in dichloromethane (50 mL) maintained at 0 °C. DMAP (6.6 mg, 0.05 mmol) was then added to the reaction mixture, and stirring was continued at 0 °C for 1 h. The resulting mixture was quenched with NH_4Cl (20 mL of an aqueous solution), and the separated aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined organic phases were washed with brine (2 × 15 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The pale-yellow oil thus obtained was subjected to flash column chromatography (silica, 1:24 v/v Et_2O/dichloromethane), and concentration of the appropriate fractions (R_f = 0.6 in 1:19 v/v Et_2O/dichloromethane) afforded phenol **20** (590 mg, 87%) as a clear, colorless oil, $[\alpha]^{20}_D$ = −54.2 (c = 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 8.3 Hz, 2H), 7.26 (d, J = 8.3 Hz, 2H), 7.10 (d, J = 8.0 Hz, 1H), 7.02 (d, J = 8.0 Hz, 1H), 6.94−6.88 (complex m, 2H), 6.73−6.67 (complex m, 2H), 5.95 (m, 1H), 5.12−5.18 (complex m 1H), 5.06 (m, 1H), 4.89 (dd, J = 7.0 and 3.2 Hz, 1H), 4.24 (d, J = 3.2 Hz, 1H), 4.01 (m, 1H), 3.85 (s, 3H), 3.73 (dd, J = 11.2 and 3.8 Hz, 1H), 3.62 (dd, J = 11.2 and 4.9 Hz, 1H), 3.51 (s, 3H), 3.34 (d, J = 6.7 Hz, 2H), 2.42 (s, 3H), 0.89 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.6, 150.6, 146.4, 144.9, 140.7, 137.8, 137.3, 135.6, 133.2, 129.3, 128.7, 123.6, 121.0, 120.0, 119.3, 115.9, 112.4, 111.3, 87.8, 73.4, 62.3, 55.7, 55.5, 39.9, 25.9, 21.7, 18.3, −5.5 (one signal obscured or overlapping); IR ν_{max} 3475, 2951, 2931, 2856, 1600, 1506, 1464, 1419, 1264, 1176, 1092, 1035, 837, 779 cm^{-1}; MS (ESI, +ve) m/z 651 (100) [M +

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Na]$^+$; HRMS calcd for $C_{33}H_{44}NaO_8SSi$ [M + Na]$^+$: 651.2424, found: 651.2423.

*4-((1S,2S)-2-(4-Allyl-2-methoxyphenoxy)-3-((tert-butyldimethylsilyl)oxy)-1-hydroxypropyl)-2-methoxyphenyl 4-Methylbenzenesulfonate (ent-**20**).* Treatment of compound *ent*-**19** with *p*-toluenesulfonyl chloride, Et_3N, and DMAP in the same manner as that described immediately above gave ester *ent*-**20** (252 mg, 91%) as a clear, colorless oil, $[\alpha]^{20}_D$ = +58.4 (*c* = 0.8, $CHCl_3$). All other spectral data acquired on this material were identical with those reported above for compound **20**.

*(1S,2R)-2-(4-Allyl-2-methoxyphenoxy)-3-((tert-butyldimethylsilyl)oxy)-1-(3-methoxy-4-(tosyloxy)phenyl)-propyl 4-Nitrobenzoate (**21**).* A magnetically stirred solution of compound **20** (580 mg, 0.92 mmol), triphenylphosphine (290 mg, 1.11 mmol), and *p*-nitrobenzoic acid (185 mg, 1.11 mmol) in dry THF (40 mL) was cooled to −10 °C, and DEAD (180 μL, 1.11 mmol) was then added to the reaction mixture over 0.25 h. The resulting solution was stirred at −10 °C for 0.5 h before being warmed to 22 °C, and stirring then continued for an additional 16 h. The resulting solution was concentrated under reduced pressure, and the light-yellow solid thus obtained was subjected to flash chromatography (silica, hexane → 3:17 v/v ethyl acetate/hexane gradient elution). Concentration of the relevant fractions (R_f = 0.3 in 1:4 v/ethyl acetate/hexane) afforded *p*-nitrobenzoate **21** (602 mg, 84%) as a white, crystalline solid, mp = 107−108 °C, $[\alpha]^{20}_D$ = −4.3 (*c* = 1.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.8 Hz, 2H), 8.04 (d, *J* = 8.8 Hz, 2H), 7.74 (d, *J* = 8.2 Hz, 2H), 7.26 (d, *J* = 8.2 Hz, 2H), 7.20 (s, 1H), 7.15 (m, 2H), 6.89 (d, *J* = 8.1 Hz, 1H), 6.71 (d, *J* = 2.0 Hz, 1H), 6.67 (dd, *J* = 8.1 and 2.0 Hz, 1H), 6.25 (d, *J* = 4.4 Hz, 1H), 5.93 (m, 1H), 5.07 (s, 1H), 5.05 (m, 1H), 4.74 (m, 1H), 3.87 (dd, *J* = 10.6 and 5.2 Hz, 1H), 3.75 (s, 3H), 3.62−3.55 (complex m, 4H), 3.32 (d, *J* = 7.0 Hz, 2H), 2.42 (s, 3H), 0.89 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 151.7, 150.7, 150.6, 146.4, 145.1, 138.6, 137.5, 135.9, 135.5, 135.1, 133.5, 130.9, 129.5, 128.7, 123.7, 123.6, 120.8(3), 120.7(7), 118.3, 116.0, 113.4, 113.1, 81.7, 76.4, 61.9, 55.9, 55.8, 40.0, 26.0, 21.8, 18.3, −5.2(9), −5.3(4); IR ν_{max} 2930, 2856, 1728, 1602, 1527, 1505, 1464, 1373, 1261, 1177, 1155, 1091, 1034, 835, 813, 780, 750, 717 cm^{-1}; MS (ESI, +ve) *m/z* 800 (100) [M + Na]$^+$; HRMS calcd for $C_{40}H_{47}NNaO_{11}SSi$ [M + Na]$^+$: 800.2537, found: 800.2537.

*(1R,2S)-2-(4-Allyl-2-methoxyphenoxy)-3-((tert-butyldimethylsilyl)oxy)-1-(3-methoxy-4-(tosyloxy)phenyl)-propyl 4-Nitrobenzoate (ent-**21**).* Treatment of compound *ent*-**20** with *p*-nitrobenzoic acid, Ph_3P, and DEAD in the same manner as that described above gave ester *ent*-**21** (256 mg, 82%) as a white, crystalline solid, $[\alpha]^{20}_D$ = +4.3 (*c* = 1.1, $CHCl_3$). All other spectral data acquired on this material were identical with those reported above for compound **21**.

*4-((1S,2R)-2-(4-Allyl-2-methoxyphenoxy)-3-((tert-butyldimethylsilyl)oxy)-1-hydroxypropyl)-2-methoxyphenyl 4-Methylbenzenesulfonate (**22**).* A magnetically stirred solution of *p*-nitrobenzoate **21** (569 mg, 0.73 mmol) in THF (10 mL) maintained at 0 °C under a nitrogen atmosphere was treated with NaOH (5 mL of a 1 M aqueous solution, 5 mmol). The ensuing mixture was stirred at 0 °C for 0.5 h then warmed to 22 °C, and after 0.5 h, diluted with ethyl acetate (50 mL). The separated organic layer was washed with $NaHCO_3$ (2 × 10 mL), and the combined aqueous washings were extracted with ethyl acetate (2 × 10 mL). The combined organic phases were washed with brine (2 × 15 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting yellow oil was subjected to flash column chromatography (silica, 1:49 v/v Et_2O/dichloromethane), and concentration of the appropriate fractions (R_f = 0.3 in 1:49 v/v Et_2O/DCM) afforded alcohol **22** (340 mg, 74%) as a clear, colorless oil, $[\alpha]^{20}_D$ = −8.0 (*c* = 0.9, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.3 Hz, 2H), 7.26 (partially obscured d, *J* = 8.3 Hz, 2H), 7.10 (d, *J* = 8.3 Hz, 1H), 6.98 (d, *J* = 1.9 Hz, 1H), 6.89 (s, 1H), 6.87 (s, 1H), 6.72 (m, 2H), 5.95 (m, 1H), 5.10 (m, 1H), 5.06 (s, 1H), 4.92 (t, *J* = 4.7 Hz, 1H), 4.26 (d, *J* = 4.9 Hz, 1H), 4.17 (m, 1H), 3.84 (s, 3H), 3.83 (partially obscured m, 1H), 3.63 (dd, *J* = 11.0 and 5.1 Hz, 1H), 3.52 (s, 3H), 3.34 (d, *J* = 6.8 Hz, 1H), 2.42 (s, 3H), 0.88 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H) (signal due to the hydroxyl group proton not observed); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7, 151.3, 145.6, 145.0, 140.7, 137.7, 137.4, 135.9, 133.4, 129.4, 128.8, 123.7, 121.3, 120.5, 118.9, 116.1, 112.7, 111.2, 85.5, 73.8, 62.6, 56.0, 55.6, 40.1, 26.0, 21.8, 18.3, −5.3, −5.4; IR ν_{max} 3473, 2952, 2930, 2856, 1600, 1505, 1463, 1418, 1373, 1262, 1175, 1117 1090, 1034, 836, 777, 716, 662 cm^{-1}; MS (ESI, +ve) *m/z* 651 (100) [M + Na]$^+$; HRMS calcd for $C_{33}H_{44}NaO_8SSi$ [M + Na]$^+$: 651.2424, found: 651.2424.

*4-((1R,2S)-2-(4-Allyl-2-methoxyphenoxy)-3-((tert-butyldimethylsilyl)oxy)-1-hydroxypropyl)-2-methoxyphenyl 4-Methylbenzenesulfonate (ent-**22**).* Treatment of ester *ent*-**21** with NaOH in THF in the same manner as that described immediately above gave alcohol *ent*-**22** (171 mg, 83%) as a clear, colorless oil, $[\alpha]^{20}_D$ = +7.5 (*c* = 0.6, $CHCl_3$). All other spectral data acquired on this material were identical with those reported above for compound **22**.

*(E)-3-(4-(((1S,2R)-3-((tert-Butyldimethylsilyl)oxy)-1-hydroxy-1-(3-methoxy-4-(tosyloxy)-phenyl)propan-2-yl)oxy)-3-methoxyphenyl)allyl Acetate (**23**).* Acetic acid (85 μL, 1.5 mmol), sodium acetate (1.5 mg, 0.02 mmol), molecular sieves (2 mg of activated 4 Å material), 4,5-DAF (1.2 mg, 8 mol %), and $Pd(OAc)_2$ (1.5 mg, 8 mol %) were added, sequentially, to a magnetically stirred solution of alkene **22** (48 mg, 0.076 mmol) in 1,4-dioxane (800 μL) maintained at 22 °C. Oxygen from a balloon was gently bubbled through the reaction mixture for 0.25 h, then the solution was heated at 60 °C with vigorous stirring under an atmosphere of oxygen. After 66 h, the reaction mixture was cooled to 22 °C, and the solvent was removed under reduced pressure. The ensuing black residue was subjected to flash column chromatography (silica, hexane → 3:2 v/v ethyl acetate/hexane gradient elution), and concentration of the appropriate fractions (R_f = 0.3 in 1:1 v/v ethyl acetate/hexane) afforded ester **23** (33 mg, 64%) as a clear, colorless oil, $[\alpha]^{20}_D$ = −18.6 (*c* = 0.7, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.3 Hz, 2H), 7.24 (partially obscured m, 2H), 7.10 (d, *J* = 8.3 Hz, 1H), 6.99 (m, 1H), 6.93 (s, 1H), 6.91−6.87 (complex m, 3H), 6.59 (dt, *J* = 15.8 and 1.1 Hz, 1H), 6.19 (dt, *J* = 15.8 and 6.5 Hz, 1H), 4.93 (t, *J* = 4.8 Hz, 1H), 4.71 (dd, *J* = 6.5 and 1.1 Hz, 2H), 4.23 (m, 1H), 4.10 (d, *J* = 4.8 Hz, 1H), 3.86 (s, 3H), 3.83 (partially obscured m, 1H), 3.68 (m, 1H), 3.53 (s, 3H), 2.42 (s, 3H), 2.10 (s, 3H), 0.88 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 151.7, 151.3, 147.5, 145.0, 140.6, 137.7, 134.0, 133.3, 131.9, 129.4, 128.8, 123.7, 122.5, 120.2, 119.7, 118.9, 111.2, 110.1, 85.0, 74.0, 65.2, 62.6, 56.0, 55.6, 26.0, 21.8, 21.2, 18.3, −5.3, −5.4; IR ν_{max} 3475, 2932, 2856, 1737, 1600, 1506, 1464, 1418, 1372, 1251, 1229, 1175, 1117, 1091, 1031, 964, 837, 752, 716, 662 cm^{-1}; MS (ESI, +ve) *m/z* 709 (100) [M + Na]$^+$; HRMS calcd for $C_{35}H_{46}NaO_{10}SSi$ [M + Na]$^+$: 709.2479, found: 709.2478.

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*(E)-3-(4-(((1R,2S)-3-((tert-Butyldimethylsilyl)oxy)-1-hydroxy-1-(3-methoxy-4-(tosyloxy)-phenyl)propan-2-yl)oxy)-3-methoxyphenyl)allyl Acetate (ent-**23**).* Oxidation of alkene *ent*-**22** in an analogous fashion to that described immediately above gave acetate *ent*-**23** (67 mg, 33%) as a clear, colorless oil, $[\alpha]^{20}_{D}$ = +17.7 (*c* = 1, $CHCl_3$). All other spectral data acquired on this material were identical with those reported above for compound **23**.

*(1S,2R)-1-(4-Hydroxy-3-methoxyphenyl)-2-(4-((E)-3-hydroxyprop-1-en-1-yl)-2-methoxyp-henoxy)propane-1,3-diol (ent-**2**).* TBAF·$x$$H_2O$ (37 mg, ca. 0.12 mmol) was added in one portion to a magnetically stirred solution of acetate **23** (55 mg, 0.080 mmol) in THF (3 mL) maintained at 22 °C under a nitrogen atmosphere. After 1 h, the reaction mixture was treated with methanol (3 mL) then NaOH (1 mL of a 3 M aqueous solution, 3 mmol) before being heated at 80 °C. After 3 h, the reaction mixture was cooled to 22 °C, acidified to pH 5 using acetic acid, then diluted with ethyl acetate (15 mL). The separated organic phase was washed with brine (3 × 5 mL of a ca. 13 wt % solution), and the combined aqueous washings were extracted with ethyl acetate (3 × 5 mL). The combined organic phases were washed with brine (1 × 5 mL of a ca. 13 wt % solution) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing pale-yellow residue was subjected to flash column chromatography (silica, 1:19 v/v methanol/dichloromethane → 1:9 v/v methanol/dichloromethane gradient elution), and concentration of the appropriate fractions (R_f = 0.5 in 1:9 v/v methanol/dichloromethane) afforded compound *ent*-**2** (22 mg, 73%) as a clear, colorless gum, $[\alpha]^{20}_{D}$ = −8.2 (*c* = 1.1, methanol). ^{1}H NMR (400 MHz, CD_3OD) δ 7.02 (d, *J* = 1.9 Hz, 1H), 6.99 (broad s, 1H), 6.88−6.86 (complex m, 2H), 6.84 (dd, *J* = 8.1 and 1.9 Hz, 1H), 6.73 (d, *J* = 8.1 Hz, 1H), 6.51 (dt, *J* = 15.9 and 1.5 Hz, 1H), 6.23 (dt, *J* = 15.8 and 5.8 Hz, 1H), 4.83 (d, *J* = 5.8 Hz, 1H), 4.36 (ddd, *J* = 5.8, 5.7 and 3.7 Hz, 1H), 4.19 (dd, *J* = 5.8 and 1.5 Hz, 2H), 3.85 (dd, *J* = 12.0 and 5.7 Hz, 1H), 3.80 (s, 3H), 3.77 (dd, *J* = 12.0 and 3.7 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 151.9, 148.9, 148.7, 147.0, 134.1, 133.0, 131.4, 128.5, 121.0, 120.6, 118.9, 115.6, 111.9, 111.4, 86.2, 74.1, 63.7, 62.2, 56.5, 56.3; IR ν_{max} 3345, 2937, 1602, 1509, 1463, 1264, 1128, 1028, 968 cm^{-1}; MS (ESI, +ve) *m*/*z* 399 (100) $[M + Na]^+$; HRMS calcd for $C_{20}H_{24}NaO_7$ $[M + Na]^+$: 399.1420, found: 399.1419; HPLC analysis: Chiracel AS-H column, 85:15 v/v *n*-hexane/ethanol elution, flow rate 1.0 mL/min, detection at λ = 254 nm, *t* = 35.8 min, ee > 99%.

*(1R,2S)-1-(4-Hydroxy-3-methoxyphenyl)-2-(4-((E)-3-hydroxyprop-1-en-1-yl)-2-methoxyp-henoxy)propane-1,3-diol (**2**).* Treatment of compound *ent*-**23** with TBAF then aqueous sodium hydroxide in an analogous fashion to that described immediately above gave compound **2**[9k] (6.8 mg, 73%) as a clear, colorless gum, $[\alpha]^{20}_{D}$ = +7.4 (*c* = 0.5, methanol) {lit.[9k] $[\alpha]^{20}_{D}$ = +10.8 (*c* = 1, $CHCl_3$)}. ^{1}H NMR [600 MHz, $(CD_3)_2SO$] δ 8.71 (s, 1H), 6.99 (m, 2H), 6.91 (d, *J* = 8.4 Hz, 1H), 6.83 (dd, *J* = 8.4 and 2.0 Hz, 1H), 6.72 (m, 2H), 6.43 (dt, *J* = 15.9 and 1.9 Hz, 1H), 6.22 (dt, *J* = 15.9 and 5.5 Hz, 1H), 5.27 (d, *J* = 4.7 Hz, 1H), 4.75 (app. t, *J* = 5.6 Hz, 1H), 4.70 (app. t, *J* = 4.9 Hz, 1H), 4.56 (app. t, *J* = 5.6 Hz, 1H), 4.29 (m, 1H), 4.08 (m, 2H), 3.73 (s, 3H), 3.72 (s, 3H), 3.60 (m, 2H); ^{13}C NMR [150 MHz, $(CD_3)_2SO$] δ 149.6, 147.4, 146.8, 145.3, 133.0, 129.9, 128.4, 128.3, 119.3, 118.8, 115.5, 114.4, 111.3, 109.8, 83.6, 71.5, 61.4, 60.0, 55.5, 55.3. These spectral data matched those reported by Nair and co-workers.[9k] All other spectral data acquired on this material were identical with those reported above for compound *ent*-**2**. HPLC analysis: Chiracel AS-H column, 85:15 v/v *n*-hexane/ethanol elution, flow rate 1.0 mL/min, detection at λ = 254 nm, *t* = 43.2 min, ee > 99%.

Endothelial Cell Tubule Formation Assay. Human microvascular endothelial cells (HMECs) were grown in MCDB131 media supplemented with 10% fetal bovine serum (FBS), hydrocortisone (500 μg/mL), epidermal growth factor (0.01 mg/mL), L-glutamine (2 mM), and antibiotics. At 80−90% confluency, the cells were trypsinized, pelleted by centrifugation, and resuspended in MCDB131 medium containing 0.2% FBS at 4 × 10^5/mL cell density. One mL of the cell suspension was then transferred to microfuge tubes and incubated with 30 μM PD98059 for 0.5 h at room temperature prior to the addition of 12.5 ng/mL FGF-2 or 0.1 μM of each of the compounds **1**, *ent*-**1**, **2**, and *ent*-**2** (final concentrations). Alternately, 1 mL of cell suspension was incubated with FGF-2 alone (12.5 ng/mL) or each neolignan (0.1 μM). The suspensions were gently mixed (pipetting up and down three times), and 100 μL (4 × 10^4 cells) was aliquoted into a 96 well plate that had been pre-coated overnight at 4 °C with Matrigel basement membrane matrix. The plates were incubated at 37 °C, and the cells in each well were photographed (under 40× magnification) 4 h after seeding. Microtubules were counted using Image J software. Each treatment was performed in triplicate, and four independent experiments were performed.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.7b01459.

^{1}H and ^{13}C NMR spectra of compounds (±)-**1**, **1**, *ent*-**1**, (±)-**2**, **2**, *ent*-**2**, **4**−**7** (and precursors), **9**, **10**, **14**, **15**, **17** (and precursor), **18**−**23** and ^{1}H NMR spectra of compounds *ent*-**15**, *ent*-**17** (and precursor), and *ent*-**18**−*ent*-**23** (PDF)

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Notes

The authors declare no competing financial interest.

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■ ADDITIONAL NOTE

[1]It is also possible that the conversion **7** + **8** → **9** proceeds via an S_N1 pathway.

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