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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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 proangiogenic principals were isolated.3 Although only small quantities of these compounds available for screening 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.4 They are almost certainly formed in vivo through peroxidase-mediated radical coupling of coniferyl 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.

RESULTS AND DISCUSSION

Syntheses of the Racemic Forms of Compounds 1 and 2. Although many neolignans have been the subject of synthetic studies,5 enantioselective approaches to 8-O-4′ linked systems, as required in accessing the compounds targeted here, have received only modest attention.6,7 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 methanesulfonyl amide afforded the diol 5 (78%), the configuration of which was assigned using the Sharpless “mnemonic”.10 Although the enantiomeric excess (ee) of this oxidation product was not established, the fact that it was optically

Supporting Information

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active \{[(\alpha)_D + 10.7 \ (\epsilon = 1.02, \text{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. By such means, the acyloin 6 (86%) was obtained and the

Scheme 1. Synthesis of Compounds (±)-1 and (±)-2
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. 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 borohydride9a 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 earlier10a for the natural products (see Table 1 for relevant comparisons of the 13C 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.9d

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 reaction13 utilizing the readily available l-valine (11)-derived chiral auxiliary 12 introduced by Seebach.14 This was coupled with the genugol (13)-derived and readily available a-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 dibutylyboron triflate in the presence of Hüning’s base,14 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 \(\left[\alpha\right]_D = -63.3 \ (c = 0.8, \text{CHCl}_3)\). The illustrated structure was initially assigned to compound 17 on the basis of the well-established syn-selective outcomes of Evans’ aldol reactions9b,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-diazafuorenone as ligand then afforded 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 \((\pm)-1\), and the specific rotation determined for the optically active material was \(-36.7 \ (c = 0.9, \text{methanol})\). Chiral HPLC analysis of compound ent-1 established that it was of >99% enantiomeric excess and represents the less mobile component of the racemate \((\pm)-1\).

The synthesis of compound 1 was readily achieved following the reaction scheme shown above but using the auxiliary 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 \(\left[\alpha\right]_D = +32.4 \ (c = 0.2, \text{methanol})\). 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 \((\pm)-1\) obtained earlier.

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

| 13C NMR data for | 13C NMR data for | 13C NMR data for | 13C NMR data for |
|-----------------|-----------------|-----------------|-----------------|
| compound (±)-1 | three-GCCE | compound (±)-2 | three-GCCE |
| \(\delta\) | \(\delta\) | \(\delta\) | \(\delta\) |
| 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 | 130.8 | +0.6' |
| 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' | 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 | 110.8 | +0.6' |
| 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 |

* Spectrum recorded in CD3OD at 100 MHz. + Data obtained from Woo. 11 Spectrum recorded in CD3OD at 125 MHz. 12 Spectrum recorded in CD3OD at 100 MHz. 13 Data obtained from Li spectrum recorded in CD3OD at 100 MHz. 14 Lourith et al. report a chemical shift of 131.5 for the resonance due to this carbon. 15 We attribute these differences to variations in the pH of the media in which the spectra were recorded. 16 Lourith et al. report a chemical shift of 111.4 for the resonance due to this carbon.
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. 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 \( \text{ent-2} \) 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 \([\alpha]_{D}^{20} = -8.1 \ (c = 1.1, \text{methanol})\), and it represents the more mobile component of the racemate (\( \pm \))-2.

The synthesis of compound 2 was readily achieved following the reaction scheme shown but using compound \( \text{ent-17} \) 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 \([\alpha]_{D}^{20} = +7.4 \ (c = 0.5, \text{methanol})\). 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 (\( \pm \))-2 obtained as described above.
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., 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.

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.

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. 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 (1H) and carbon (13C) NMR spectra were recorded at room temperature in base-filtered CDCl3 on a Varian spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. The signal due to residual CHCl3, appearing at δH 7.26 and the central resonance of the CDCl3 triplet appearing at δC 77.1(6) were used to reference 1H and 13C NMR spectra,
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 ($\nu_{\text{max}}$) 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 Optimel automated melting point system and are uncorrected. Analytical thin layer chromatography was performed on aluminum-backed 0.2 mm thick silica gel 60 F$\text{254}$ 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. 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. 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., 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 (30.0 g, 93%) as a white, crystalline solid, mp = 60.9–62.1 °C (lit. mp = 65 °C).

1 H NMR (300 MHz, CDCl$_3$) $\delta$ 7.26 (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$_3$) $\delta$ 167.8, 148.1, 146.9, 145.1, 127.1, 123.2, 115.3, 114.9, 109.5, S6.1, S1.7. These spectral data matched those reported by Li et al.

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 Hüning’s base (i-Pr$_2$NEt) (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$_4$Cl (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$_2$CO$_3$ (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 → 120 v/v Et$_2$O/dichloromethane gradient elution], and concentration of the relevant fractions ($R_b$ = 0.8 in 1:9 v/v Et$_2$O/dichloromethane gradient elution), and concentration of the relevant fractions ($R_b$ = 0.8 in 1:9 v/v Et$_2$O/dichloromethane gradient elution) under reduced pressure afforded methyl (E)-3-(3-methoxy-4-(methoxymethoxy)phenyl)acrylate (25.0 g, 94%) as a clear, pale-yellow oil. The filtrate was subjected to flash chromatography [silica, dichloromethane → 120 v/v Et$_2$O/dichloromethane gradient elution], and concentration of the relevant fractions ($R_b$ = 0.8 in 1:9 v/v Et$_2$O/dichloromethane gradient elution) under reduced pressure afforded methyl (E)-3-(3-methoxy-4-(methoxymethoxy)phenyl)acrylate (25.0 g, 94%) as a clear, light-yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.62 (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), 3.89 (s, 3H), 3.80 (s, 3H), 3.51 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 168.7, 149.9, 148.6, 144.8, 128.8, 122.4, 116.2, 115.9, 110.4, 95.3, S65.5, S61.5. These spectral data matched those reported by Lui et al.

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-
(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 Et₂O (10 mL), then dried (MgSO₄), 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 (Rf = 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 (21.18 g, 99.0 mmol) (1H NMR (400 MHz, CDCl₃) δ 7.12 (d, J = 8.2 Hz, 1H), 6.96 (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 and 1.9 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); 13C NMR (100 MHz, CDCl₃) δ 149.8, 146.4, 146.4, 131.1, 131.1, 127.2, 119.7, 116.3, 109.5, 95.5, 63.9, 56.4, 56.0; IR ν max 3464, 1263, 1154, 1132, 1077, 993, 969 cm⁻¹). The resulting mixture was allowed to warm to 22 °C and stirred at this temperature for 14 h before being treated with NaHCO₃ (50 mL of a saturated aqueous solution). The reaction mixture that was then stirred vigorously at 0 °C, diluted with Et₂O (10 mL), then dried (MgSO₄), filtered, and concentrated under reduced pressure to afford a light-yellow oil. This oil was subjected to column chromatography (silica, dichloromethane/ethyl acetate gradient elution) and concentration of the relevant fractions (Rf = 0.4 in 1:1 v/v ethyl acetate/petroleum ether) under reduced pressure afforded compound 5 (1.85 g, 78%) as a clear, colorless gum, [α]D²⁵ = +10.7 (c = 1.02, CHCl₃). 1H NMR (400 MHz, CDCl₃) δ 7.15 (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); 13C NMR (100 MHz, CDCl₃) 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, 2937, 1513, 1215, 1153, 1034, 989, 920 cm⁻¹; MS (ESI, +ve) m/z 325 (100) [M + Na⁺]; HRMS calcd for C₁₄H₂₁NaO₇ [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 Et₂O/dichloromethane gradient elution] and concentration of the relevant fractions (Rf = 0.5 in 3:7 v/v Et₂O/dichloromethane) under reduced pressure afforded compound 6 (1.53 g, 86%) as a clear, pale-yellow oil, [α]D²⁵ = -20.0 (c = 1.0, CHCl₃). 1H NMR (400 MHz, CDCl₃) δ 6.73, 5.53 (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 (dd—simplifies to a dd upon addition of D₂O, 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 D₂O, 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); 13C NMR (100 MHz, CDCl₃) 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 C₁₄H₂₀NaO₇ [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,
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 NH4Cl (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 (MgSO4), filtered, then concentrated under reduced pressure to afford an orange oil. This oil was subjected to flash chromatography (silica, dichloromethane → 1:9 v/v Et2O/dichloromethane gradient elution) and concentration of the relevant fractions (RF = 0.6 in 1:9 v/v Et2O/dichloromethane) under reduced pressure afforded ester 7 (2.14 g, 93%) as a white, crystalline solid, mp 93.5–95.8 °C, [α]25D = −34 (c = 1.0, CHCl3). 1H NMR (400 MHz, CDCl3) 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). 13C NMR (100 MHz, CDCl3) 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 νmax 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 calcld for C20H20NaO7 [M + Na]+: 395.1107, found: 395.1107.

(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 confieraldehyde (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 (MgSO4), 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 (RF = 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, [α]25D = 0 (c = 0.5, CHCl3). 1H NMR (400 MHz, CDCl3) δ 6.95 (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 (broa.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). 13C NMR (100 MHz, CDCl3) δ 194.0, 193.6, 152.4, 151.5, 150.5, 149.7, 147.1, 129.1, 126.7(2), 125.7(2), 124.2, 121.3, 116.7, 114.3, 111.2, 110.7, 83.4, 63.9, 56.3, 56.1; IR νmax 3356, 2938, 1668, 1602, 1591, 1426, 1270, 1137, 1030, 734 cm−1; MS (ESI, +ve) m/z 395 (100) [M + Na]+; HRMS calcld for C20H20NaO7 [M + Na]+: 395.1107, found: 395.1107.

Compounds (±)-1 and (±)-2. Polymer-supported borohydride (2.55 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 mm2 column, 25:74:95:0.5 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 (tR = 12.0 min) afforded compound (±)2-[34C12]-14 (9 mg, 12%) as a white powder. 1H NMR (300 MHz, CD3OD) 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 two hydroxyl group protons not observed); 11C NMR (400 MHz, CD3OD) 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
(partially obscured d, J = 6.3 Hz, 1H) (signals due to hydroxy group protons not observed); 13C NMR (100 MHz, CDCl3) δ see Table 1; IR νmax 3369, 2918, 1509, 1266, 1152, 1122, 1029 cm−1; MS (EI, +ve) m/z 376 (15) (M+•), 358 (50), 328 (45), 206 (100); HRMS calcd for C20H23O2 (M+•): 376.1522, found: 376.1524.

Concentration of fraction B (tR = 13.2 min) afforded compound (−)-25 (57 mg, 73%) as a white powder. 1H NMR [300 MHz, (CD3)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 (d, 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 hydroxy group protons not observed); 1H NMR (400 MHz, CDCl3) 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 hydroxy group protons not observed); 13C NMR (100 MHz, CDCl3) δ see Table 1; IR νmax 3369, 2931, 1604, 1510, 1263, 1129 cm−1; MS (ESI, +ve) m/z 399 (100) [M + Na]+; HRMS calcd for C19H21NO2 [M + Na]+: 399.1420, found: 399.1420.

2-(4-allyl-2-methoxyphenyloxy)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 Waldvogel25 to give a white, crystalline solid. 1H NMR (400 MHz, CDCl3) δ 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 carboxylic acid group protons not observed); 13C NMR (100 MHz, CDCl3) δ see Table 1; IR νmax 3369, 2931, 1604, 1510, 1263, 1129 cm−1; MS (ESI, +ve) m/z 399 (100) [M + Na]+; HRMS calcd for C19H21NO2 [M + Na]+: 399.1420, found: 399.1420.

(S)-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, [α]20D = +160 (c = 0.3, CHCl3). All the other spectral data acquired on this material were identical with those detailed above for compound 15.

112.7, 69.0, 56.1, 40.0. These spectral data matched those reported by Labarbies and co-workers.26

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Step ii: Methanol (230 µL, 5.65 mmol) was added to a magnetically stirred solution of the above-mentioned aldehyde 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 NH4Cl (20 mL of a saturated aqueous solution) then diluted with Et2O (20 mL), and the combined organic extracts were washed with brine (2 × 20 mL) before being dried (Na2SO4), filtered, and concentrated under reduced pressure. The ensuing pale-yellow residue was subjected to flash column chromatography (silica, hexane → EtOAc/dichloromethane: 4:1 v/v) and concentration of the appropriate fractions (Rf = 0.2 in 1:1 v/v EtOAc/hexane) afforded acetate 18 (103 mg, 48%) as a pale-yellow oil, [α]20 D = −69.1 (c = 0.6, CHCl3). 1H NMR (400 MHz, CDCl3) δ 7.04 (d, J = 8.2 Hz, 1H), 7.01–6.92 (complex m, 3H), 6.87 (d, 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 (d, J = 7.9 and 2.0 Hz, 1H), 4.72 (d, 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); 13C NMR (200 MHz, CDCl3) δ 171.0, 151.4, 151.3, 147.9, 145.2, 133.8, 133.1, 132.6, 129.2, 121.0, 120.9, 120.5, 119.7, 110.8, 110.0, 89.7, 74.2, 61.4, 56.1, 55.7, 25.9, 21.2, 18.6, −4.5(0), −4.5(2); IR νmax 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 C28H40NaO8Si [M + Na]+: 555.2390, found: 555.2390.

(E)-3-[4-(((1S,2S)-2-(4-Allyl-2-methoxyphenoxy)-1-(4-((tert-Butyldimethylsilyl)oxy)-3-methoxyphenyl)-1,3-dihydroxypropan-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 → EtOAc/hexane gradient elution), and concentration of the appropriate fractions (Rf = 0.2 in 1:1 v/v EtOAc/hexane) afforded acetate 18 (103 mg, 48%) as a pale-yellow oil, [α]20 D = −69.1 (c = 0.6, CHCl3). 1H NMR (400 MHz, CDCl3) δ 7.04 (d, J = 8.2 Hz, 1H), 7.01–6.92 (complex m, 3H), 6.87 (d, 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 (d, J = 7.9 and 2.0 Hz, 1H), 4.72 (d, 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); 13C NMR (200 MHz, CDCl3) δ 171.0, 151.4, 151.3, 147.9, 145.2, 133.8, 133.1, 132.6, 129.2, 121.0, 120.9, 120.5, 119.7, 110.8, 110.0, 89.7, 74.2, 61.4, 56.1, 55.7, 25.9, 21.2, 18.6, −4.5(0), −4.5(2); IR νmax 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 C28H40NaO8Si [M + Na]+: 555.2390, found: 555.2390.

(E)-3-[4-(((1S,2S)-1-(4-((tert-Butyldimethylsilyl)oxy)-3-methoxyphenyl)allyl)-2-methoxyphenoxy)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 aldo product (2.15 g, 69%) as a clear, colorless oil, [α]20 D = +77.7 (c = 1, CHCl3). 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 were employed to produce diol ent-17 (684 mg, 96%), which was obtained as a clear, colorless oil, [α]20 D = +66.2 (c = 0.7, CHCl3). All other spectral data acquired on this material were identical with those reported above for compound 17.
4.0 Hz, 1H), 3.47 (dd, J = 11.9 and 5.4 Hz, 1H) (signals due to hydroxyl group protons not observed); 13C NMR (100 MHz, CD3OD) 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, 87.1, 74.0, 63.8, 61.9, 56.5, 56.3; IR νmax 3348, 2934, 1602, 1509, 1464, 1263, 1226, 1156, 1130, 1027, 968 cm⁻¹; MS (EI, +ve) m/z 399 (100) [M + Na]⁺; HRMS calcd for C26H38NaO6Si [M + Na]⁺: 497.2335, found: 497.1420; HPLC analysis: Trefoil CEL1 column, 98:2 v/v methanol/supercritical CO2 elution, flow rate 2 mL/min, temperature 40 °C, detection at 254 nm, tminor = 5.86 min, tmajor = 6.05 min, ee > 99%.

4-((1R,2R)-2-(4-Allyl-2-methoxyphenoxy)-5-(tert-butyldimethylsilyl)oxy)-1-hydroxyprop-1-en-1-yl)-2-methoxyphenol (ent-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 chloride (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 Cs2CO3 (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 NH4Cl (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 were then washed with brine (2 × 10 mL) before being dried (Na2SO4), filtered, and concentrated under reduced pressure. The ensuing pale-yellow residue was subjected to flash column chromatography (silica, 1.9 v/v EtO/dichloromethane), and concentration of the appropriate fractions (Rt = 0.2 in 1:19 v/v EtO/DCM) afforded phenol 19 (232 mg, 51% over two steps) as a clear, colorless oil, [α]20D = +98.8 (c = 0.7, CHCl3). 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-1-en-1-yl)-2-methoxyphenol (ent-17). 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 NH4Cl (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 (Na2SO4), 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 Cs2CO3 (307 mg, 0.95 mmol) and water (100 μL) then stirred at 22 °C for 24 h. After this time, another batch of Cs2CO3 (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 NH4Cl (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 (Na2SO4), filtered, and concentrated under reduced pressure. The ensuing pale-yellow residue was subjected to flash column chromatography (silica, 19 v/v EtO/dichloromethane), and concentration of the appropriate fractions (Rt = 0.2 in 1:19 v/v EtO/DCM) afforded phenol ent-17 (232 mg, 51% over two steps) as a clear, colorless oil, [α]20D = +98.8 (c = 0.7, CHCl3). All other spectral data acquired on this material were identical with those reported above for compound 19.

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Na\(^{+}\)]; HRMS calc'd for C\(_{25}\)H\(_{34}\)NaO\(_3\)SSi [M + Na\(^{+}\)]: 651.2424, found: 651.2423.

4-(((1S,2R)-2-((4-Allyl-2-methoxyphenoxy)-3-(((tert-butyldimethylsilyl)oxy)-1-hydroxypropyl)-l-2-methoxyphenyl)propyl 4-Nitrobenzoate (ent-20). Treatment of compound ent-19 with p-toluenesulfonyl chloride, Et\(_2\)N, and DMAP in the same manner as that described immediately above gave ester ent-20 (252 mg, 91%) as a clear, colorless oil, [\(\alpha\)]\(_{D}^{20}\) = +8.4 (c = 0.8, CHCl\(_3\)). All other spectral data acquired on this material were identical with those reported above for compound 20.

\(\delta = 0.8, \text{CHCl}_3\). 1H NMR (400 MHz, CDCl\(_3\)) \(\delta = 8.22, \text{d, J = 8.8 Hz, 2H}, 8.04, \text{d, J = 8.8 Hz, 2H}, 7.74, \text{d, J = 8.2 Hz, 2H}, 7.26, \text{d, J = 8.2 Hz, 2H}, 7.20, \text{s, 1H}, 1.75, \text{m, 2H}, 6.89, \text{d, J = 8.1 Hz, 1H}, 6.71, \text{d, J = 2.0 Hz, 1H}, 6.67, \text{dd, J = 8.1 and 2.0 Hz, 1H}, 6.25, \text{d, J = 4.4 Hz, 1H}, 5.93, \text{m, 1H}, 5.07, \text{s, 1H}, 5.05, \text{m, 1H}, 4.74, \text{m, 1H}, 3.87, \text{dd, J = 10.6 and 5.2 Hz, 1H}, 3.75, \text{s, 3H}, 3.62–3.55 (complex m, 4H), 3.32, \text{d, J = 7.0 Hz, 2H}, 2.42, \text{s, 3H}, 0.89 (s, 9H), 0.02 (s, 3H), 0.02 (s, 3H), 0.02 (s, 3H), 0.02 (s, 3H) (signal due to the hydroxyl group proton not observed); 13C NMR (100 MHz, CDCl\(_3\)) \(\delta = 163.6, 151.7, 150.7, 150.6, 146.4, 145.1, 138.7, 137.5, 135.9, 135.5, 131.5, 133.1, 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 \(\nu_{\text{max}}\) 2930, 2858, 2762, 1602, 1527, 1505, 1464, 1373, 1261, 1177, 1155, 1034, 835, 813, 780, 750, 717 cm\(^{-1}\); MS (ESI, +ve) \(m/z\) 809 (100) [M + Na\(^{+}\)]; HRMS calc'd for C\(_{25}\)H\(_{34}\)NaO\(_3\)SSi [M + Na\(^{+}\)]: 831.2424, found: 831.2437.

\(\text{(1R,2S)-2-((4-Allyl-2-methoxyphenoxy)-1-(3-methoxy-4-(tosyloxy)phenyl)phenoxy)-4-Nitrobenzenesulfonate (ent-21). Treatment of compound ent-20 with NaOH in THF in the same manner as that described immediately above gave alcohol ent-21 (171 mg, 83%) as a clear, colorless oil, [\(\alpha\)]\(_{D}^{20}\) = +7.5 (c = 0.6, CHCl\(_3\)). All other spectral data acquired on this material were identical with those reported above for compound 22.

\(\text{(E)-3-4'-(4-(1R,2S)-2-((4-Allyl-2-methoxyphenoxy)-3-(((tert-butyldimethylsilyl)oxy)-1-hydroxy-1-(3-methoxy-4-(tosyloxy)phenyl)propan-2-yl)oxy)-3-methylphenyl)allyl Acetate (23). Acetic acid (85 \mu L, 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 alkenne 22 (48 mg, 0.076 mmol) in 1,4-dioxane (800 \mu L) 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 1:4 v/v ethyl acetate/hexane) afforded ester 23 (33 mg, 64%) as a clear, colorless oil, [\(\alpha\)]\(_{D}^{20}\) = –18.6 (c = 0.7, CHCl\(_3\)). 1H NMR (400 MHz, CDCl\(_3\)) \(\delta = 7.71, \text{d, J = 8.3 Hz, 2H}, 7.24 (\text{partially obscured m, 2H}), 7.10, \text{d, J = 8.3 Hz, 1H}, 6.99 (m, 1H), 6.93 (s, 1H), 6.91–6.87 (complex m, 3H), 6.59 (dd, 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); 13C NMR (100 MHz, CDCl\(_3\)) \(\delta = 171.0, 151.7, 151.3, 147.5, 145.0, 140.6, 137.7, 134.0, 130.8, 129.9, 128.7, 125.9, 124.7, 123.7, 122.8, 119.1, 118.9, 118.3, 112.7, 112.6, 111.5, 110.8, 109.4, 83.5, 780, 750, 717 cm\(^{-1}\); MS (ESI, +ve) \(m/z\) 709 (100) [M + Na\(^{+}\)]; HRMS calc'd for C\(_{35}\)H\(_{36}\)NaO\(_4\)SSi [M + Na\(^{+}\)]: 709.2479, found: 709.2478.
Organic phases were washed with brine (ca. 13 wt % solution), and the combined aqueous washings were filtered, and the filtrate was washed 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 (Na2SO4), 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 (Rf = 0.5 in 1:9 v/v methanol/dichloromethane) afforded compound ent-2 (22 mg, 73%) as a clear, colorless gum, [α]D 20 = +8.2 (c = 1.1, methanol). 1H NMR (400 MHz, CD3OD) 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), 3.72 (s, 3H), 3.67 (d, J = 11.8 Hz, 1H). 13C NMR (100 MHz, CD3OD) 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 νmax 1697, 1595, 1229, 1104, 975, 866, 820, 759, 692 cm−1; MS (ESI, +ve) m/z 399 (100) [M + Na]+; HRMS calc for C20H24NaO7 [M + Na]+: 399.1420, found: 399.1419; HPLC analysis: Chiracel AS-H column, 85:15 v/v hexane/ethanol elution, flow rate 1.0 mL/min, detection at λ = 254 nm, t = 43.2 min, ee > 99%.

**ASSOCIATED CONTENT**

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

1H and 13C 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 1H 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**

1It is also possible that the conversion proceeds via a Sn1 pathway.

**REFERENCES**

1See, for example (a) Bouïs, D.; Kusumanto, Y.; Meijer, C.; Mulder, N. H.; Hospers, G. A. P. *Pharmacol. Res.* 2006, 53, 89.

(b) Huang, D.; Lan, H.; Liu, F.; Wang, S.; Chen, X.; Jin, K.; Mou, X. *Int. J. Clin. Exp. Med.* 2015, 8, 8369.

(c) Ermens, I.; Boussuenaund, M.; Lenoir, B.; Devaux, Y.; D. R. Wagner, L. J. *Leukocyte Biol.* 2015, 97, 10.
