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Enantioselective Syntheses of Lignin Models: An Efficient Synthesis of β-O-4 Dimers and Trimers by Using the Evans Chiral Auxiliary

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Abstract: We describe an efficient five-step, enantioselective synthesis of (*R*,*R*)- and (*S*,*S*)-lignin dimer models possessing a β-O-4 linkage, by using the Evans chiral aldol reaction as a key step. Mitsunobu inversion of the (*R*,*R*)- or (*S*,*S*)-isomers generates the corresponding (*R*,*S*)- and (*S*,*R*)-diastereomers. We further extend this approach to the enantioselective synthesis of a lignin trimer model. These lignin models are synthesized with excellent *ee* (>99%) and high overall yields. The lignin dimer models can be scaled up to provide multigram quantities that are not attainable by using previous methodologies. These lignin models will be useful in degradation studies probing the selectivity of enzymatic, microbial, and chemical processes that deconstruct lignin.

Introduction

Among Nature's plant-based polymers, lignin is second in abundance only to cellulose, making it a potentially valuable raw material for the biorefinery. However, using lignin as a feedstock for the production of biobased chemicals[1–4] in either catalytic or enzymatic processes[5–7] faces the considerable challenge of lignin's structural heterogeneity.[8–10] This heterogeneity is the result of lignin's biosynthetic origin from the radical coupling of three primary monolignols: *para*-coumaryl, coniferyl, and sinapyl alcohols, which lead to the well-recognized *para*-hydroxyphenyl (H), guaiacyl (G), and syringyl (S) substructural units of the native lignin polymer (Figure 1).[11–13] The most common native substructure resulting from biosynthesis is the β-O-4 unit, which can make up 50–65% of lignin's interunit linkages.[14–16] Isolation of lignin as a separate process stream within the biorefinery introduces further heterogeneity, because extracting lignin from its native source invariably changes its structure, most frequently by cleavage of the reactive β-O-4 linkages.[17] We have suggested[18] that disassembling

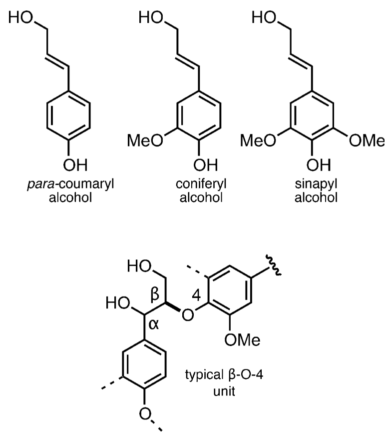

Figure 1. Structures of primary monolignols and a β-O-4 unit.

and transforming lignin early in the conversion process (more recently termed a "lignin first" approach[19–21]) could improve lignin's utility as a renewable carbon feedstock. Such an approach includes eliminating isolation of lignin by converting it within its lignocellulosic matrix, and targeting its β-O-4 groups, affording better understanding of their reactivity, and streamlining biorefinery operation.

In particular, we are interested in the effects of the stereochemical relationship between the asymmetric centers in β-O-4 linkages on lignin disassembly. Lignin biosynthesis affords β-O-4 units the side chain α and β carbon atoms of which can exhibit (*R*,*R*/*S*,*S*) or (*R*,*S*/*S*,*R*) relative stereochemistry. Overall, the lignin polymer does not display optical activity,[22–24] but recent studies suggest that these localized stereochemical differences can have an effect on enzymatic lignin disassembly processes. For example, *Trametes versicolor* employs a lignin

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peroxidase to preferentially degrade the (*R,R*/*S,S*)-isomer in β-O-4 models.[25] Glutathione S-transferase enzymes act as enantioselective β-aryl etherases.[26–27] Other studies have shown that enzymes from *Sphingobium* sp. and other systems degrade lignin or lignin models in a stereospecific manner.[28–31]

Typically, understanding of β-O-4 deconstruction processes employs models for initial degradation studies prior to transformation of actual lignin.[32–34] A number of synthetic methods are available for preparing β-O-4 lignin models as racemic or diastereomerically enriched mixtures of stereoisomers.[35–38] However, stereospecific syntheses are scarce.[38–42] Synthesis of enantiomerically pure β-O-4 dimers has been reported but requires either a tedious resolution of a racemic mixture or separation of diastereomeric derivatives of each enantiomer, which makes it impossible to obtain enantiopure lignin dimer models in multigram quantities.[30,43–44] Recently, we reported the synthesis of enantiomerically pure β-O-4 dimer models incorporating each of the primary H, G, and S subunits (Figure 2).[45]

Asymmetric epoxidation of an appropriately substituted benzaldehyde followed by a kinetic resolution and an optional Mitsunobu reaction successfully set the relative and absolute stereochemistry in a series of lignin model dimers. However, the process required nine separate steps, and attempts to scale up led to low yields of product, especially in the case of S model compounds.

We now report a markedly improved asymmetric synthesis of β-O-4 dimers by using an Evans chiral auxiliary in a key aldol condensation step. Our new process is streamlined, requiring only five steps, and can be scaled to obtain multigram quantities of dimer models enantioselectively. We further report elaboration of this methodology for the enantioselective synthesis of a model trimer, which, to date, has only been synthesized as a racemic mixture.[46–47] This methodology provides important probes for further understanding of chemical and enzymatic lignin degradation processes as a function of localized stereochemistry within the lignin polymer.

Results and Discussion

The use of *erythro* and *threo* descriptors in defining the stereochemistry of β-O-4 diastereomers is widespread within the lignin literature. To avoid ambiguity, we will use standard Cahn–Ingold–Prelog conventions in describing the stereochemistry of the lignin models. For example, model compound **9** is a *threo* isomer but will be described as (*R,R*) or (*S,S*). Model compound **13** is an *erythro* isomer but will be described as (*R,S*) or (*S,R*).

Asymmetric synthesis of β-O-4 lignin model dimers

Our retrosynthetic analysis is shown in Scheme 1. We envisioned the preparation of optically pure lignin β-O-4 model **8** through the reductive cleavage of an Evans chiral auxiliary from intermediate **7**, formed from an asymmetric aldol reaction between aldehyde **6** and optically pure oxazolidinone **5**.[48–49] In turn, compound **5** would be prepared by using a combination of amidation and substitution reactions from commercially available chloroacetyl chloride (**1**), (*R*)- or (*S*)-4-isopropyloxazolidin-2-one (**2**), and 2-methoxyphenol or 2-methoxy-4-methylphenol (**4**). By suitable choice of the chiral auxiliary, we control the stereochemistry at the α- and β-carbon centers in the side chain of the β-O-4 dimer and gain access to either enantiomer of the dimer for both G and S subunits.

Accordingly, (*R*)-4-isopropyloxazolidin-2-one (**2**) was treated with 1 equivalent of *n*-butyllithium followed by chloroacetyl chloride **1** to provide intermediate **3**.[50–51] Reaction of **3** with

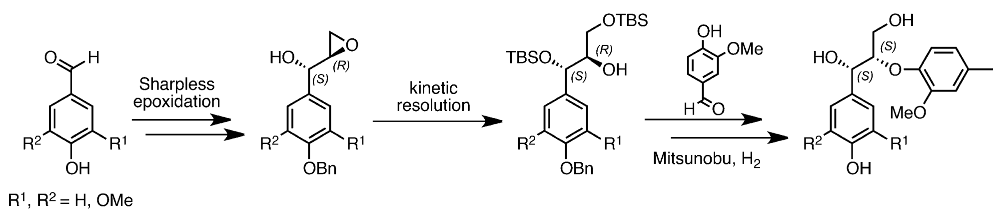
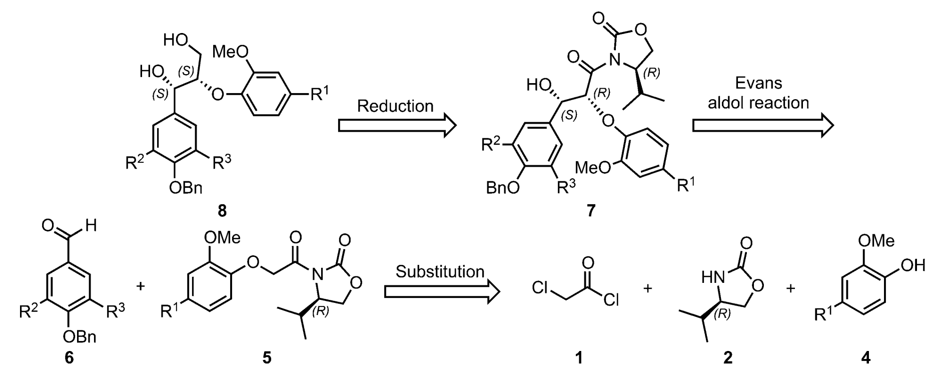


Figure 2. Previous enantioselective synthesis of lignin dimer models.



Scheme 1. Retrosynthetic analysis for the asymmetric synthesis of lignin dimer models.

phenol **4a**–**b** in the presence of potassium carbonate afforded nucleophilic substitution of the chloride, giving adducts **5a**–**b** (Scheme 2) that contain the chiral auxiliary group used to control the stereochemistry of the α- and β-carbon centers in subsequent reactions. Intermediate **5a** or **5b** was converted into the corresponding chiral enolate in situ by using di-*n*-butylboron triflate and diisopropylethylamine.[52–53] The enolate was then treated with benzyl protected aldehyde **6a**–**b** to generate the enantiomerically pure secondary alcohol **7a**–**b**. This reaction leads to exclusive formation of the *syn* product because of the favorable transition state that was enhanced by the opposing dipoles of the enolate oxygen and the carbonyl group, and the smallest number of unfavorable steric interactions within the expected Zimmerman–Traxler transition state (Figure 3).[54] Reductive cleavage of the auxiliary (which could be recovered and reused) to give **8a**–**b**, followed by hydrogenolysis of the benzyl group afforded the (*R*,*R*/*S*,*S*)-isomers **9a** and **9b** (*ee* > 99% as determined by Mosher ester analysis). An identical reaction sequence starting with the opposite enantiomer of **2** afforded the complementary (*R*,*R*)-isomers of **9a** and **9b** (see the Supporting Information).

The corresponding (*R*,*S*/*S*,*R*) enantiomers were synthesized as shown in Scheme 3 by using a Mitsunobu reaction to invert the stereochemistry at the α-position of the side chain.[55–56] Enantiomer **8b** was protected by reaction with *tert*-butyldimethylsilyl chloride (TBSCl) in the presence of imidazole to afford intermediate **10**. Mitsunobu reaction of **10** followed by hydrolysis of the resulting benzoate in situ provided compound **11** containing the inverted α-hydroxyl group.[56] Removal of the TBS group with tetra-*n*-butylammonium fluoride (TBAF) led to diol **12** and subsequent hydrogenolysis of the benzyl group with Pd/C in EtOH provided enantiomerically enriched compound **13**. The complete transformation of starting (*S*,*S*)-enantiomer **8b** into (*R*,*S*)-compound **13** was confirmed by NMR spectroscopic analysis, which showed a *de* > 99% and an overall yield of 78% for the four-step process. As before, the complementary (*S*,*R*)-isomer of **13** was also obtained in similar *ee* and *de* when the methodology of Scheme 3 was applied to the (*R*,*R*)-isomer of **8b** (see the Supporting Information).

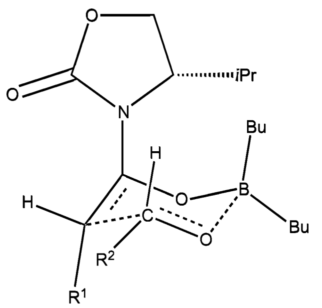
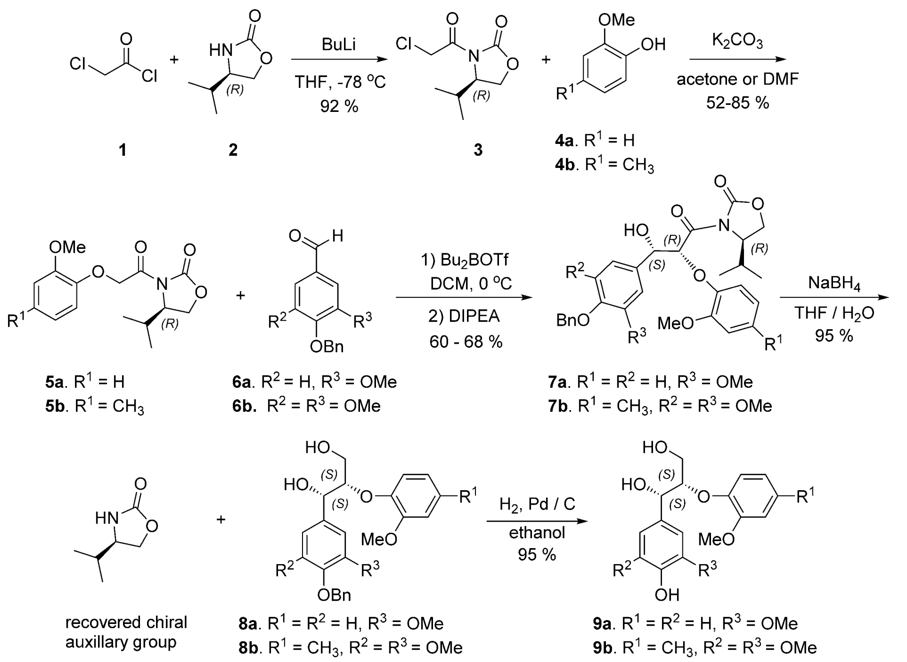


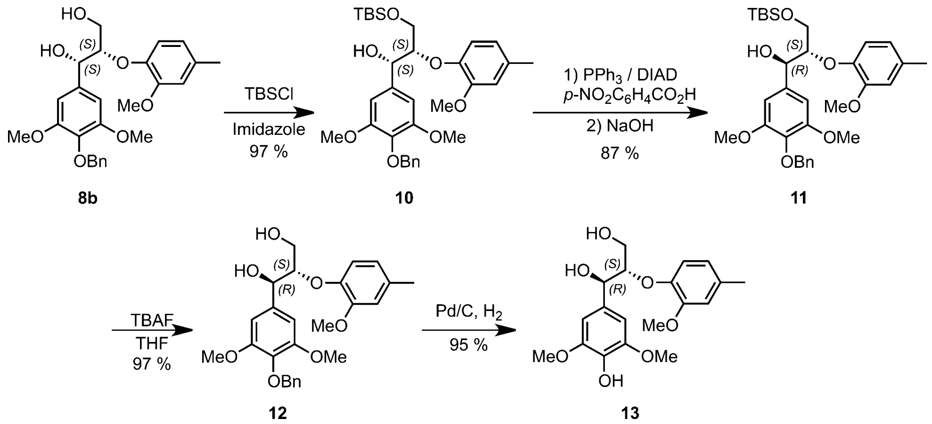
Figure 3. Favored Zimmerman–Traxler transition state for the Evans aldol reaction.

Synthesis of a lignin model trimer

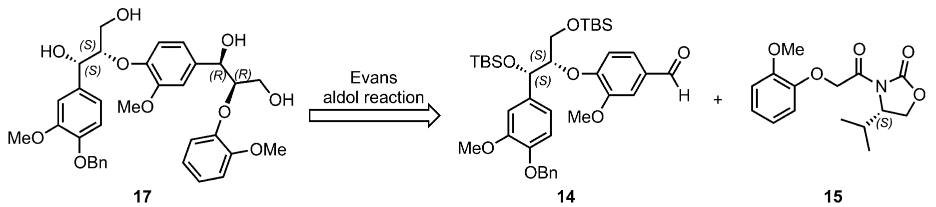
With the completion of the synthesis of all the enantiomers of the lignin dimer models, we extended our synthetic methodology to enantiomerically pure lignin trimer models based on the retrosynthetic analysis shown in Scheme 4. Dimer **14**[45] and chiral oxazolidinone **15**, synthesized as in Scheme 2 from 2-methoxyphenol and (*S*)-4-isopropyloxazolidin-2-one, served as reaction partners to form advanced intermediate **17**. Intermediate **15** was treated with di-*n*-butylboron triflate and diisopropylethylamine to generate the chiral enolate to which the enantiomeric aldehyde **14** was added. This led to formation of



Scheme 2. Synthesis of dimers **9a** and **9b**.



Scheme 3. Synthesis of (*R*,*S*)-lignin dimer **13**.

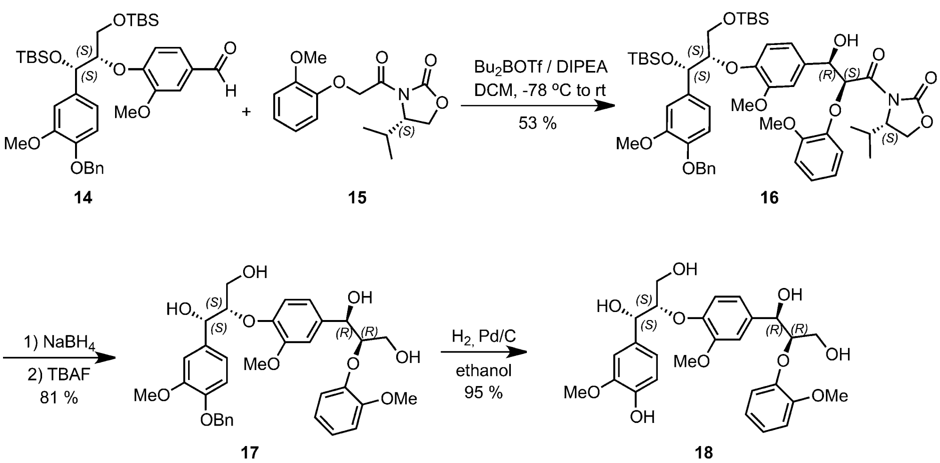


Scheme 4. Retrosynthetic analysis for the asymmetric synthesis of a lignin trimer model.

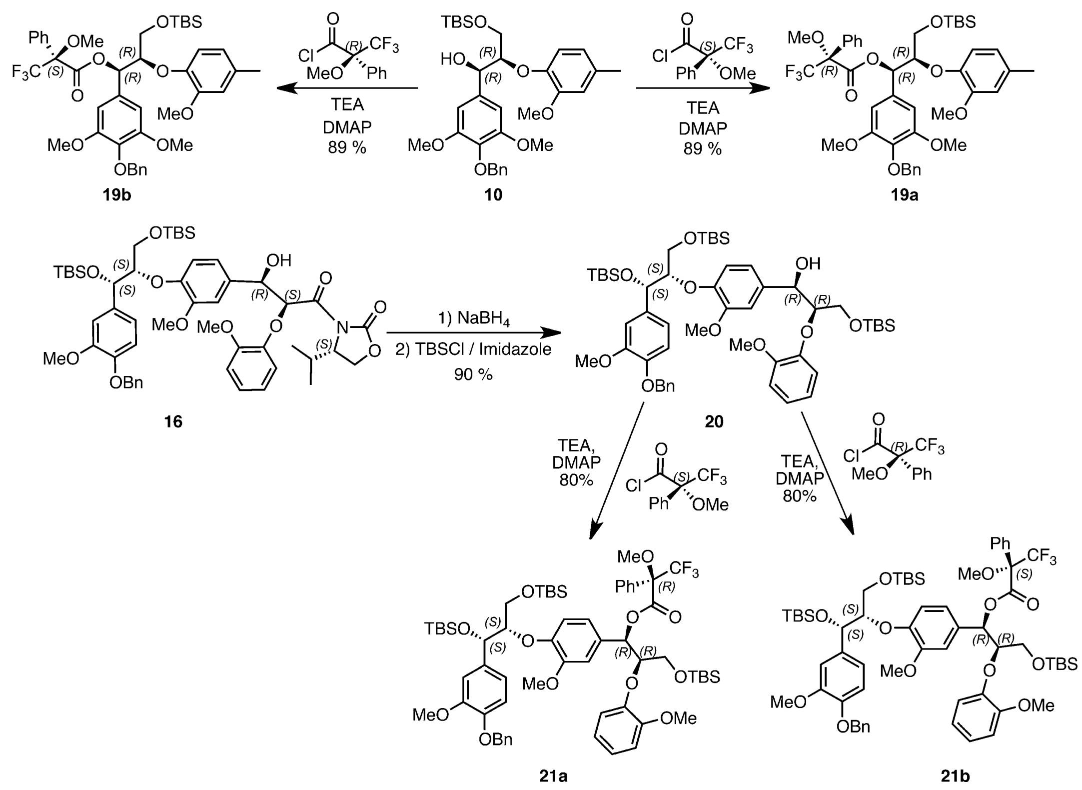
the secondary alcohol intermediate **16**, bearing the chiral auxiliary (Scheme 5). Intermediate **16** was reduced by using sodium borohydride and then deprotected with TBAF to provide the benzyl protected tetrol trimer **17**. The final enantiomeric trimer **18** was obtained after hydrogenolysis with H_2 and Pd/C in EtOH. The *ee* of trimer **18** was determined to be $\geq$ 99% by Mosher ester analysis, and represents the first successful synthesis of an enantiomerically pure lignin trimer model.

Assignment of absolute stereochemistry

To establish and confirm the stereochemistry of the dimer and trimer models, Mosher ester derivatives were prepared (Scheme 6). The TBS protected dimer **10** (*R*,*R*-isomer) was treated with either (*S*)- or (*R*)-(+)-α-methoxy-α-trifluoro-methylphenylacetyl chloride (MPTA-Cl), by following a well-established protocol[57] and led to the formation of diastereomeric Mosher esters **19a** and **19b**. Synthesis of trimers **21a** and **21b** was carried out by treating intermediate **16** with sodium borohydride and protecting the primary alcohol intermediate with TBSCl in the presence of imidazole. Reaction with MPTA-Cl led to the formation of diastereomeric Mosher esters **21a** and **21b**. The difference in chemical shifts between the (*S*)- and (*R*)-Mosher esters ($\Delta\delta_{S-R}$) were resolved as shown in Figure 4 to support assignment of the absolute stereochemistry in the lignin models. Mosher ester **19a** has ($\Delta\delta_{S-R}$) values of -0.07 ppm at the benzylic carbon, $+0.02$ ppm at the β-carbon methine proton and $+0.02$ ppm and -0.09 ppm for the meth-



Scheme 5. Synthesis of enantiomerically pure lignin trimer model.



Scheme 6. Synthesis of Mosher esters for dimer and trimer models.

ylene protons, confirming an *R*-configuration at the α- and β-carbon centers in this dimer model. The ($\Delta\delta_{S-R}$) values for Mosher esters **21 a** and **21 b** also provide evidence for a single enantiomer and have been used to deduce the stereochemistry of the enantiomerically pure trimer. Mosher ester **21a** exhibits ($\Delta\delta_{S-R}$) values of +0.05 and +0.02 ppm for benzylic protons H_A and H_D, respectively, and −0.07 and −0.01 ppm for methine protons H_B and H_C, which specifies an *R*- and *S*-configuration, respectively. As expected, the protons in close proximity to the chiral derivatizing agents had greater $\Delta\delta_{S-R}$ values than those further away.

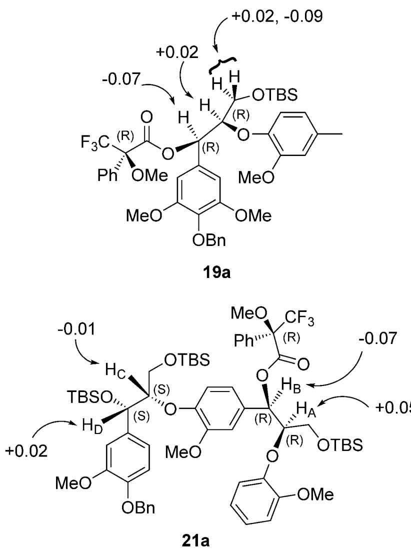


Figure 4. Chemical shift differences ($\Delta\delta_{S-R}$) for Mosher esters **19a** and **21a**.

Computational modeling of the lignin models

To develop insight regarding the impact of the stereochemical differences in these lignin models on their rate of reaction in biological systems, computational modeling of (*R*,*R*/*S*,*S*)-compounds **9 a** and **9 b** and (*R*,*S*/*S*,*R*)-compound **13** was carried out by a conformational search and density functional theory calculations. The former was performed by using a 500-step Monte Carlo search with PM3 optimization, as implemented in Spartan 04.[58] The 10 lowest energy conformations were then optimized by using Gaussian 09[59] at the M06-2X level of theory, with the 6-31+G(d) basis set and the ultrafine integration grid.

The low energy conformation for compounds **9 a** and **9 b** is strongly folded (Figure 5). The aromatic rings in **9 a** form a cavity (as approximated by the 1-1′ and 4-4′ distances) with a distance of 4.167 Å at the opening, narrowing to 3.013 Å at the inside. The aromatic rings do not fully align with each other, with a 4′-α-β-O dihedral angle of 73.01° and an α-β-O-4 dihedral angle of −79.65°. Compound **9 b** contains additional substituents on both aromatic rings, and the resulting increase in steric hindrance is reflected in 1-1′ and 4-4′ distances of 5.477 and 3.442 Å, respectively. The offset between the two rings is also larger, as shown by the 4′-α-β-O dihedral angle of 80.72° and an α-β-O-4 dihedral angle of −91.91°. In contrast to

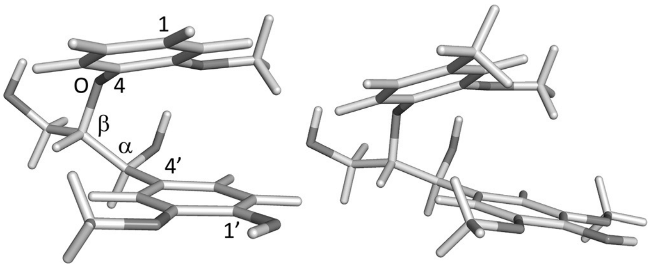


Figure 5. Low energy conformation of compounds **9a** and **9b** (key positions labeled for **9a**).

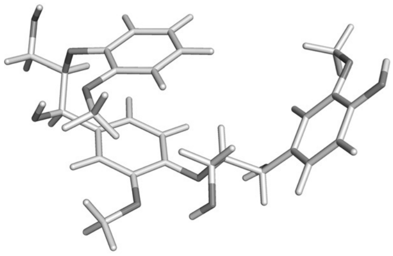


Figure 7. Calculated low energy conformation for trimer **18**.

9a and **9b**, the lowest energy conformation for compound **13** is extended (Figure 6), with 4′-α-β-O dihedral angle of −68.86° and an α-β-O-4 dihedral angle of −107.13°.

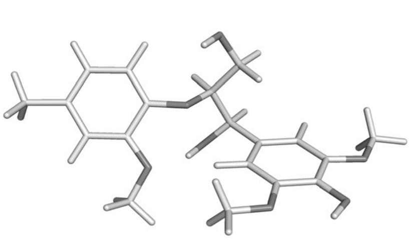


Figure 6. Calculated low energy conformation for **13**.

These computational results are consistent with earlier calculations carried out on syringyl and *para*-hydroxyphenyl lignin model dimers by using a molecular mechanics approach.[60] The molecular mechanics study identified a folded conformation for a syringyl dimer as only 0.88 kcal higher in energy than the lowest energy conformer and exhibiting a dihedral angle between the α- and β-substituents on the model's side chain of −80°. The corresponding (*R*,*S*/*S*,*R*)-isomers also showed a much closer range of energies between conformers as observed in our modeling, with all measured conformers appearing within 4 kcal of the lowest energy conformation. We note that considerable flexibility exists for these materials, as both folded and extended conformations for **9a**, **9b**, and **13** were found within 6–7 kcal of the lowest energy conformation. However, Boltzmann distribution analysis of the conformers revealed that a folded conformation made up nearly 97% of the low energy structures for **9a** and **9b**, highlighting the impact of the interaction between rings. Extended conformations accounted for more than 96% of the Boltzmann distribution for compound **13**.

Finally, we carried out preliminary analysis of trimer **18** (Figure 7). As with compounds **9a** and **9b**, two of the rings stack, with the substituent on the central ring (in this case, the third aromatic unit of the trimer) being pushed away from the sterically bulky portion of the model. The stacked aromatic rings are more closely aligned than the dimeric models with 4-4′ and 1-1′ distances of 3.115 and 4.256 Å, respectively, and 4′-α-β-O and α-β-O-4 dihedral angles of −73.45° and 80.94°, respectively.

As with any lignin model study, the extension of these computational results on small lignin fragments to the behavior of the lignin biopolymer must be done with extreme care. The behavior of individual substructural units within the lignocellulosic matrix will be subject to different electronic and steric interactions than in an isolated model. However, the appearance of low energy, sterically bulky, folded conformations within the computational results suggests localized stereochemical differences that could play a role in processes tailored to react with those stereochemical features. Such effects might be enhanced in a biopolymer because the flexibility would be expected to be reduced. Although the models have access to a number of relatively low energy conformations, the presence of favored, more bulky conformations suggests that properly designed catalyst systems could demonstrate selectivity in their reaction with the lignin polymer. Work to ascertain this possibility is underway.

Conclusion

We have synthesized enantiomerically pure GG and SG lignin dimer models, and the first example of an enantiomerically pure lignin trimer. The compounds are available in multigram quantities by using a five-step process incorporating the Evans aldol reaction as a key step. The models retain the β-O-4 linkage, which will be useful in "lignin first" approaches to biomass conversion. These models may serve as important probes for chemical, enzymatic, and microbial degradation studies to understand lignin degradation as a function of localized stereochemistry within the lignin polymer.

Experimental Section

General methods and materials: All reactions were carried out under an atmosphere of nitrogen unless otherwise specified. All reagents and solvents were purchased from commercial sources and were used as received. Analytical thin-layer chromatography (TLC) was performed using glass backed TLC (extra hard layer 60 Å with 250 μm pre-coated silica gel thickness). Chromatography was performed with a Teledyne Isco CombiFlash R_f 200 or flash columns packed with 230–400 mesh 60 Å silica gel. The eluents are reported as volume/volume percentages. Melting points were recorded with a Fisher–Johns melting point apparatus and are uncorrected. Specific rotations were obtained with a Rudolph Autopol IV polarimeter. ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ and CD_3OD with a Varian Unity 400 or 500 MHz instrument. Chemical shifts are reported relative to tetramethylsilane or residual solvent resonance and reported in ppm. Infrared spectra were obtained with a Perkin–Elmer Spectrum One FTIR spectrometer at 4 cm^{-1} resolution and are reported in cm^{-1}. High-resolution mass spectra (HRMS) were obtained at the Center for Mass Spectrometry of the Department of Chemistry at the University of Tennessee, and are reported as *m/z* (relative ratio). Accurate masses are reported for the molecular ion $[M+H]^+$ or a suitable fragment ion and are reported with an error <5 ppm.

(*R*)-3-(2-Chloroacetyl)-4-isopropyloxazolidin-2-one (3): To a stirred solution of commercially available (*R*)-4-isopropyloxazolidin-2-one (**2**; 2.5 g, 19.37 mmol) in anhydrous THF (100 mL) at −78 °C was added a solution of 1.6 M BuLi (13.31 mL, 21.30 mmol) over 15 min. After 30 min, chloroacetyl chloride (**1**; 2.2 g, 19.48 mmol) was added and the reaction was stirred at −78 °C for 30 min and warmed to RT for 30 min. Upon complete consumption of the starting material, as monitored by TLC, the reaction was quenched by addition of saturated NH_4Cl. The resulting suspension was extracted with CH_2Cl_2 (3×100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The crude compound was purified by column chromatography (hexane/CH_2Cl_2, 1:4) to afford **3** (3.65 g, 92%) as a light-yellow oil. The opposite enantiomer was also synthesized by following the same procedure. The spectroscopic data of both enantiomers satisfactorily matched all previously reported data.[50–51]

(*R*)-4-Isopropyl-3-(2-(2-methoxy-4-methylphenoxy)acetyl)oxazolidin-2-one (5b): To a solution of commercially available 2-methoxy-4-methylphenol (**4b**; 2.83 g, 20.49 mmol) in acetone (100 mL) was added K_2CO_3 (4.25 g, 30.74 mmol). The resulting suspension was stirred for 30 min, then **3** (3.5 g, 17.07 mmol) was added at RT. The reaction mixture was stirred overnight at RT, and then heated at reflux for 2 h. Upon complete consumption of the starting material, the reaction was quenched by addition of saturated NH_4Cl. The resulting suspension was extracted with CH_2Cl_2 (3×100 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The crude compound was purified by column chromatography (hexane/EtOAc, 4:1) to afford **5b** (4.45 g, 81%) as a colorless oil, which later formed a white solid under vacuum; m.p. 71–75 °C; $[\alpha]_D^{25}=-62.2$ ($c=1.00$ in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): $\delta=6.78$–6.70 (m, 2H), 6.65 (d, $J=7.1$ Hz, 1H), 5.25 (s, 2H), 4.45 (d, $J=15.3$ Hz, 1H), 4.36 (t, $J=8.7$ Hz, 1H), 4.27 (dd, $J=9.1$, 3.1 Hz, 1H), 3.86 (s, 3H), 2.40 (s, 1H), 2.29 (s, 3H), 0.90 ppm (dd, $J=9.2$, 7.0 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=168.49$, 154.12, 149.47, 145.05, 132.26, 120.74, 114.83, 113.16, 68.84, 64.52, 58.24, 55.83, 28.11, 21.07, 17.84, 14.56 ppm; IR (neat): $\tilde{\nu}=2966.74$, 1776.39, 1717.04, 1511.09, 1392.40, 1210.88, 1144.56, 1025.87 cm^{-1}; HRMS (DART-TOF): *m/z* calcd for $C_{16}H_{22}NO_5^+$: 308.14925 $[M+H]^+$; found: 308.14994.

The opposite enantiomer, (*S*)-4-isopropyl-3-(2-(2-methoxy-4-methylphenoxy)acetyl)oxazolidin-2-one, provided a specific rotation of $[\alpha]_D^{25}=+64.1$ ($c=1.00$ in $CHCl_3$). The yield of this reaction is slightly lower (52–70%) but more reproducible if carried out in DMF (see the Supporting Information).

(*R*)-3-((2*R*,3*S*)-3-(4-(Benzyloxy)-3,5-dimethoxyphenyl)-3-hydroxy-2-(2-methoxy-4-methylphenoxy)propanoyl)-4-isopropyloxazolidin-2-one (7b): A solution of **5b** (2.3 g, 7.5 mmol) was dissolved in anhydrous CH_2Cl_2 (50 mL) and cooled to 0 °C. To this solution was added Bu_2OTf (8.3 mL, 8.3 mmol) and diisopropylethylamine (1.7 mL, 9.75 mmol) dropwise. The resulting solution was stirred at 0 °C for 45 min and cooled to −78 °C. A solution of 4-(benzyloxy)-3,5-dimethoxybenzaldehyde (**6b**; 2.24 g, 8.3 mmol) dissolved in anhydrous CH_2Cl_2 (10 mL) was added dropwise and the reaction mixture was stirred for 45 min. The reaction was warmed to RT and stirred for a further 2 h. The reaction was quenched by the addition of a 1 M phosphate buffer (pH 7, 50 mL) at 0 °C followed by 2:1 (v/v) MeOH/35% H_2O_2 (20 mL). The resulting suspension was extracted with CH_2Cl_2 (3×100 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The crude compound was purified by column chromatography (hexane/EtOAc, 7:3) to afford aldol intermediate **7b** (2.95 g, 68%) as a colorless oil. $[\alpha]_D^{25}=-35.7$ ($c=1.00$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta=7.48$ (d, $J=7.0$ Hz, 2H), 7.38–7.25 (m, 3H), 6.79 (d, $J=8.1$ Hz, 1H), 6.71 (s, 1H), 6.67 (s, 2H), 6.61 (d, $J=8.1$ Hz, 1H), 6.12 (d, $J=6.6$ Hz, 1H), 5.02 (d, $J=6.9$ Hz, 1H), 4.98 (d, $J=3.0$ Hz, 2H), 4.05 (s, 1H), 3.95 (d, $J=9.1$ Hz, 1H), 3.88 (s, 1H), 3.83 (d, $J=11.1$ Hz, 9H), 3.60 (t, $J=8.5$ Hz, 1H), 2.27 (s, 3H), 2.24 (s, 1H), 0.78 ppm (dd, $J=20.4$, 6.9 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=169.71$, 153.45, 153.26, 149.89, 144.86, 137.60, 136.65, 133.53, 133.17, 128.54, 128.19, 127.92, 121.21, 117.61, 113.41, 104.22, 82.18, 76.50, 75.02, 63.98, 59.31, 56.16, 55.88, 28.84, 21.17, 17.92, 14.79 ppm; IR (neat): $\tilde{\nu}=3390$, 2962.47, 1774.23, 1707.63, 1591.96, 1462.27, 1332.58, 1125.77 cm^{-1}; HRMS (DART-TOF): *m/z* calcd for $C_{32}H_{36}NO_8^+$: 562.24354 $[M-OH]^+$; found: 562.24278.

The opposite enantiomer, (*S*)-3-((2*S*,3*R*)-3-(4-(benzyloxy)-3,5-dimethoxyphenyl)-3-hydroxy-2-(2-methoxy-4-methylphenoxy)propanoyl)-4-isopropyloxazolidin-2-one, provided a specific rotation of $[\alpha]_D^{25}=+35.7$ ($c=1.00$ in $CHCl_3$).

(1*S*,2*S*)-1-(4-(Benzyloxy)-3,5-dimethoxyphenyl)-2-(2-methoxy-4-methylphenoxy)propane-1,3-diol (8b): To a solution of **7b** (2.4 g, 4.14 mmol) dissolved in THF/H_2O (4:1) was added sodium borohydride (1.57 g, 41.4 mmol) portion-wise, then the reaction mixture was stirred for 4 h. Upon complete consumption of the starting material as monitored by TLC, the reaction was quenched by the addition of saturated NH_4Cl. The resulting suspension was extracted with Et_2O (3×100 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The crude compound was purified by column chromatography (hexane/CH_2Cl_2/acetone, 7:1.5:1.5) to afford the diol intermediate (1.79 g, 95%) as a white solid. The spectroscopic data for **8b**, as well as its complimentary enantiomer satisfactorily matched all previously reported data.[45]

(1*S*,2*S*)-1-(4-Hydroxy-3,5-dimethoxyphenyl)-2-(2-methoxy-4-methylphenoxy)propane-1,3-diol (9b): A solution of asymmetric diol intermediate **8b** (1.5 g, 3.3 mmol) in ethanol (30 mL) in a 100 mL round-bottomed flask was treated with Pd/C (150 mg). Hydrogen was introduced to the reaction mixture by using a balloon and slowly diffused into the solution while stirring gently for 3 h. Upon complete consumption of the starting material as monitored by TLC, the reaction mixture was filtered through Celite to remove the Pd/C catalyst. The filtrate was concentrated under vacuum to provide the crude lignin dimer, which was purified by column chromatography (CH_2Cl_2/acetone, 7:3) to afford the enantiomerically pure lignin dimer (1.2 g, 96%) as a clear viscous oil. The spectroscopic data for **9b**, as well as its complimentary enantiomer satisfactorily matched all previously reported data using a different methodology.[45]

(1*S*,2*S*)-1-(4-(Benzyloxy)-3,5-dimethoxyphenyl)-3-((*tert*-butyldimethylsilyl)oxy)-2-(2-methoxy-4-methylphenoxy)propan-1-ol (10): To a stirred solution of asymmetric diol **8b** (1.9 g, 4.18 mmol) in anhydrous CH_2Cl_2 (30 mL), was added TBSCl (0.69 g, 4.6 mmol), imidazole (0.34 g, 5.02 mmol) and a catalytic amount of DMAP. The resulting solution was stirred at RT for 2 h. Upon complete consumption of the starting material, as monitored by TLC, the reaction was quenched by addition of saturated NH_4Cl solution and extracted with CH_2Cl_2 (3×100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The crude compound was purified by column chromatography (hexane/EtOAc, 9:1) to afford the protected asymmetric alcohol **10** (2.3 g, 97%) as a colorless oil. $[\alpha]_D^{25}=+70.2$ ($c=1.00$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.49$ (dd, $J=8.0$, 1.4 Hz, 2H), 7.32 (dt, $J=14.4$, 7.0 Hz, 3H), 7.07 (d, $J=8.0$ Hz, 1H), 6.74–6.68 (m, 2H), 6.64 (s, 2H), 5.00 (s, 2H), 4.86 (d, $J=7.3$ Hz, 1H), 4.32 (s, 1H), 4.04 (s, 1H), 3.87 (s, 3H), 3.80 (s, 6H), 3.77 (d, $J=3.6$ Hz, 1H), 3.67 (dd, $J=11.2$, 5.1 Hz, 1H), 2.32 (s, 3H), 0.91 (s, 9H), 0.04 ppm (d, $J=6.5$ Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=153.42$, 150.37, 146.18, 137.86, 136.43, 136.15, 133.17, 128.50, 128.09, 127.77, 121.46, 120.05, 112.92, 104.21, 88.49, 74.96, 73.99, 62.61, 56.09, 55.73, 25.91, 21.19, 18.32, −5.41, −5.42 ppm; IR (neat): $\tilde{\nu}=3484.74$, 2951.96, 2930.93, 2853.81, 1595.34, 1511.34, 1462.27, 1223.92, 1125.77 cm^{-1}; HRMS (DART-TOF): *m/z* calcd for $C_{32}H_{43}O_6Si^+$: 551.28234 $[M-OH]^+$; found 551.28305.

The opposite enantiomer, (1*R*,2*R*)-1-(4-(benzyloxy)-3,5-dimethoxyphenyl)-3-((*tert*-butyldimethylsilyl)oxy)-2-(2-methoxy-4-methylphenoxy)propan-1-ol, provided a specific rotation of $[\alpha]_D^{25}=-69.7$ ($c=1.00$ in $CHCl_3$).

(1*R*,2*S*)-1-(4-(Benzyloxy)-3,5-dimethoxyphenyl)-3-((*tert*-butyldimethylsilyl)oxy)-2-(2-methoxy-4-methylphenoxy)propan-1-ol (11): To a solution of THF containing PPh_3 (3.18 g, 12.14 mmol) was added diisopropylazodicarboxylate (2.54 mL, 12.14 mmol), and the mixture was stirred for 30 min. This was followed by the simultaneous addition of *p*-nitrobenzoic acid (2.03 g, 12.14 mmol) and alcohol intermediate **10** (2.3 g, 4.05 mmol). The reaction was stirred at RT overnight. Upon complete consumption of the starting material as monitored by TLC, the organic phase was washed with water (2×100 mL), dried over $MgSO_4$, and concentrated in vacuo to provide the intermediate ester, which was used in the next step without further purification. The crude intermediate ester was dissolved in THF and treated with a 1.0 M aqueous solution of NaOH. Upon complete consumption of the ester, the reaction was quenched by the addition of saturated NH_4Cl, the organic phase was extracted with CH_2Cl_2 (3×100 mL), dried over $MgSO_4$ and purified by column chromatography (hexane/Et_2O, 3:2) to afford intermediate **11** (2.0 g, 87%) as a colorless oil. $[\alpha]_D^{25}=+9.0$ ($c=1.00$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.48$ (d, $J=6.8$ Hz, 2H), 7.30 (d, $J=34.1$ Hz, 3H), 6.90 (d, $J=8.0$ Hz, 1H), 6.68 (d, $J=31.0$ Hz, 4H), 4.99 (s, 2H), 4.90 (d, $J=4.3$ Hz, 1H), 4.20 (d, $J=14.9$ Hz, 1H), 3.88 (d, $J=11.0$ Hz, 1H), 3.82 (d, $J=18.9$ Hz, 8H), 3.68 (dd, $J=11.0$, 4.8 Hz, 1H), 2.32 (s, 3H), 0.89 (s, 9H), 0.03 ppm (s, 5H); ^{13}C NMR (101 MHz, $DCDl_3$): $\delta=153.31$, 151.00, 145.16, 137.89, 136.01, 133.32, 128.49, 128.06, 127.73, 121.53, 120.22, 113.07, 103.66, 85.90, 74.96, 73.90, 62.41, 56.07, 55.77, 25.84, 21.19, 18.22, −5.38, −5.50 ppm; IR (neat): $\tilde{\nu}=3477.73$, 2955.56, 2857.32, 1591.96, 1462.27, 1416.70, 1223.90, 1125.77 cm^{-1}; HRMS (DART-TOF): *m/z* calcd for $C_{32}H_{43}O_6Si^+$ $[M-OH]^+$: 551.28234; found: 551.28290.

The opposite enantiomer, (1*S*,2*R*)-1-(4-(benzyloxy)-3,5-dimethoxyphenyl)-3-((*tert*-butyldimethylsilyl)oxy)-2-(2-methoxy-4-methylphenoxy)propan-1-ol, provided a specific rotation of $[\alpha]_D^{25}=-10.5$ ($c=1.00$ in $CHCl_3$).

(1*R*,2*S*)-1-(4-(Benzyloxy)-3,5-dimethoxyphenyl)-2-(2-methoxy-4-methylphenoxy)propane-1,3-diol (12): TBS protected intermediate **11** (1.3 g, 2.3 mmol) was dissolved in anhydrous THF (50 mL). The solution was cooled to 0 °C and TBAF (5.0 mL, 5.0 mmol) was added to the reaction mixture. The resulting solution was warmed to RT and stirred for 2 h. Upon complete consumption of the starting material as monitored by TLC, the reaction was quenched by the addition of saturated NH_4Cl. The organic phase was extracted with EtOAc (3×100 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude compound was purified by column chromatography (CH_2Cl_2/acetone, 9:1) to afford asymmetric diol **12** (1.0 g, 97%) as a colorless viscous oil. $[\alpha]_D^{25}=+20.7$ ($c=1.00$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.47$ (d, $J=7.1$ Hz, 2H), 7.39–7.22 (m, 3H), 6.83 (d, $J=8.0$ Hz, 1H), 6.78–6.67 (m, 2H), 6.59 (s, 2H), 4.99 (s, 2H), 4.94 (d, $J=4.7$ Hz, 1H), 4.08 (d, $J=14.1$ Hz, 1H), 3.90 (d, $J=18.3$ Hz, 1H), 3.86 (s, 3H), 3.79 (s, 6H), 3.63 (dd, $J=12.1$, 3.3 Hz, 1H), 2.90 (s, 2H), 2.32 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=153.57$, 151.29, 144.39, 137.76, 136.13, 135.54, 134.32, 128.49, 128.08, 127.79, 121.96, 121.05, 113.02, 103.00, 87.60, 74.97, 72.73, 60.66, 56.15, 55.84, 21.27. IR (neat): $\tilde{\nu}=3474.23$, 2941.44, 2836.29, 1595.46, 1462.27, 1325.57, 1223.92, 1125.77, 1027.63 cm^{-1}; HRMS (DART-TOF): *m/z* calcd for $C_{26}H_{29}O_6^+$: 437.19587 $[M-OH]^+$; found 437.19549.

The opposite enantiomer, (1*S*,2*R*)-1-(4-(benzyloxy)-3,5-dimethoxyphenyl)-2-(2-methoxy-4-methylphenoxy)propane-1,3-diol, provided a specific rotation of $[\alpha]_D^{25}=-22.4$ ($c=1.00$ in $CHCl_3$).

(1*R*,2*S*)-1-(4-Hydroxy-3,5-dimethoxyphenyl)-2-(2-methoxy-4-methylphenoxy)propane-1,3-diol (13): Asymmetric diol intermediate **12** (0.9 g, 1.98 mmol) was dissolved in ethanol (30 mL) and Pd/C (150 mg) was added. Hydrogen gas was introduced by using a balloon and slowly diffused into the solution while stirring gently for 3 h. Upon complete consumption of the starting material as monitored by TLC, the reaction mixture was filtered through Celite to remove the Pd/C catalyst. The filtrate was concentrated under vacuum to provide the crude lignin dimer, which was purified by column chromatography (CH_2Cl_2/acetone, 7:3) to afford the enantiomerically pure lignin dimer **13** (0.69 g, 95%) as a clear viscous oil, which later formed a cream white solid under vacuum; m.p. 147–150 °C; $[\alpha]_D^{25}=+8.5$ ($c=1.00$ in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=6.86$ (d, $J=8.0$ Hz, 1H), 6.78–6.69 (m, 2H), 6.61 (s, 2H), 4.93 (s, 1H), 4.07 (d, $J=14.2$ Hz, 1H), 3.90 (d, $J=12.2$ Hz, 1H), 3.87 (d, $J=2.8$ Hz, 9H), 3.62 (dd, $J=12.2$, 3.3 Hz, 1H), 2.33 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=151.31$, 147.05, 144.42, 134.32, 134.04, 130.87, 121.96, 121.08, 113.01, 102.67, 87.72, 72.72, 60.64, 56.33, 55.84, 21.26 ppm; IR (neat): $\tilde{\nu}=3334.02$, 2969.48, 2878.35, 1465.77, 1374.64, 1304.54, 1160.82, 1129.28, 1104.74 cm^{-1}; HRMS (DART-TOF): *m/z* calcd for $C_{19}H_{23}O_6^+$: 347.14891 $[M-OH]^+$; found: 347.14893.

The opposite enantiomer, (1*S*,2*R*)-1-(4-hydroxy-3,5-dimethoxyphenyl)-2-(2-methoxy-4 methylphenoxy)propane-1,3-diol, provided a specific rotation of $[\alpha]_D^{25}=-7.2$ ($c=1.00$ in MeOH).

(*R*)-4-Isopropyl-3-(2-(2-methoxyphenoxy)acetyl)oxazolidin-2-one (5a): By following the general procedure outlined above for compound **5b**, 2-methoxyphenol (4.6 g, 37.05 mmol) was treated with **3** (6.4 g, 31.21 mmol) to give intermediate **5a** (7.9 g, 86%) as a white solid; m.p. 53–55 °C; $[\alpha]_D^{25}=-67.3$ ($c=1.00$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=6.95$ (d, $J=16.9$ Hz, 1H), 6.90 (d, $J=7.6$ Hz, 1H), 6.85 (d, $J=6.4$ Hz, 2H), 5.27 (s, 2H), 4.44 (d, $J=15.5$ Hz, 1H), 4.38–4.32 (m, 1H), 4.26 (dd, $J=9.2$, 3.1 Hz, 1H), 3.87 (s, 3H), 2.43 (d, $J=31.8$ Hz, 1H), 0.88 ppm (d, $J=17.0$ Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta=168.29$, 154.13, 149.71, 147.24, 122.47, 120.65, 114.61, 112.17, 68.53, 64.56, 58.25, 55.89, 28.12, 17.82, 14.57 ppm; IR (neat): $\tilde{\nu}=2962.47$, 1777.73, 1714.64, 1504.33, 1392.16, 1206.39, 1129.28 cm^{-1}; HRMS (DART-TOF): *m/z* calcd for $C_{15}H_{20}NO_5^+$: 294.13360 $[M+H]^+$; found: 294.13352.

The opposite enantiomer, (*S*)-4-isopropyl-3-(2-(2-methoxyphenoxy)acetyl)oxazolidin-2-one, provided a specific rotation of $[\alpha]_D^{25}=+64.4$ ($c=1.00$ in $CHCl_3$). The yield of this reaction is slightly lower (52–70%) but more reproducible if carried out in DMF (Supplemental Information).

(*R*)-3-((2*R*,3*S*)-3-(4-(Benzyloxy)-3-methoxyphenyl)-3-hydroxy-2-(2-methoxyphenoxy)propanoyl)-4-isopropyloxazolidin-2-one (7a): By following the general procedure outlined above for compound

7b, compound **5a** (7.5 g, 25.6 mmol) was treated with 4-(benzyloxy)-3-methoxybenzaldehyde (**6a**; 6.9 g, 28.6 mmol) to give intermediate **7a** (8.2 g, 60%) as a colorless viscous oil. $[\alpha]_D^{25} = -48.2$ (c = 1.00 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.20 (m, 5H), 7.09 (s, 1H), 7.05–6.72 (m, 6H), 6.16 (d, J = 6.7 Hz, 1H), 5.16 (q, J = 12.7 Hz, 2H), 5.09–4.99 (m, 1H), 3.88 (d, J = 16.8 Hz, 7H), 3.36 (t, J = 8.8 Hz, 1H), 2.23 (d, J = 31.9 Hz, 1H), 0.76 ppm (d, J = 27.2 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.63, 153.38, 150.13, 149.56, 147.95, 146.97, 137.00, 130.46, 128.54, 127.88, 127.33, 123.50, 120.99, 119.36, 117.13, 113.22, 112.44, 110.64, 81.58, 75.99, 70.76, 63.85, 59.18, 55.99, 55.90, 28.75, 17.87, 14.76 ppm; IR (neat): $\tilde{\nu}$ = 3502.27, 2958.97, 1770.72, 1704.12, 1595.46, 1500.82, 1455.26, 1385.15, 1213.40, 1122.27 cm^{-1}; HRMS (DART-TOF): m/z calcd for $C_{30}H_{32}NO_7^+$: 518.21733 $[M-OH]^+$; found 518.21728.

The opposite enantiomer, (*S*)-3-((2*S*,3*R*)-3-(4-(benzyloxy)-3-methoxyphenyl)-3-hydroxy-2-(2-methoxyphenoxy)propanoyl)-4-isopropyloxazolidin-2-one, provided a specific rotation of $[\alpha]_D^{25} = +48.2$ (c = 1.00 in $CHCl_3$).

(1*S*,2*S*)-1-(4-Hydroxy-3-methoxyphenyl)-2-(2-methoxyphenoxy)-propane-1,3-diol (9a): To a solution of **7a** (5.0 g, 9.3 mmol) in THF/H_2O (4:1) was added sodium borohydride (3.53 g, 93 mmol) portion-wise. The reaction mixture was stirred for 4 h. Upon complete consumption of the starting material as monitored by TLC, the reaction was quenched by the addition of saturated NH_4Cl. The resulting suspension was extracted with Et_2O (3×100 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo to provide the diol intermediate, which was used in the next step without further purification. The obtained diol intermediate was dissolved in ethanol (30 mL) and Pd/C (150 mg) was added to the solution. Hydrogen gas in a balloon was slowly diffused into the solution while stirring gently for 3 h. Upon complete consumption of the starting material as monitored by TLC, the reaction mixture was filtered through Celite to remove the Pd/C catalyst. The filtrate was concentrated in vacuo to provide the crude lignin dimer, which was purified by column chromatography (CH_2Cl_2/acetone, 7:3) to afford the enantiomerically pure lignin dimer model **9a** (2.54 g, 85%) as a clear viscous oil. $[\alpha]_D^{25} = +70.84$ (c = 1.00 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21–7.01 (m, 2H), 7.01–6.70 (m, 5H), 5.88 (s, 1H), 4.95 (d, J = 7.9 Hz, 1H), 4.02 (d, J = 4.6 Hz, 1H), 3.86 (d, J = 18.2 Hz, 6H), 3.62 (d, J = 12.4 Hz, 1H), 3.47 (d, J = 12.2 Hz, 1H), 2.93 ppm (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 151.18, 147.58, 146.69, 145.55, 131.47, 124.15, 121.67, 120.85, 120.21, 114.38, 112.12, 109.44, 89.32, 73.94, 61.00, 55.93, 55.87 ppm; IR (neat): $\tilde{\nu}$ = 3409.18, 2938.84, 1592.88, 1504.33, 1458.73, 1122.27, 1027.63 cm^{-1}. HRMS (DART-TOF): m/z calcd for $C_{17}H_{19}O_5^+$: 303.12270 $[M-OH]^+$; found 303.12256.

The opposite enantiomer, (1*R*,2*R*)-1-(4-hydroxy-3-methoxyphenyl)-2-(2-methoxyphenoxy)propane-1,3-diol, provided a specific rotation of $[\alpha]_D^{25} = -66.7$ (c = 1.00 in $CHCl_3$).

(*S*)-3-((2*S*,3*R*)-3-(4-(((5*S*,6*S*)-5-(4-(Benzyloxy)-3-methoxyphenyl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-6-yl)oxy)-3-methoxyphenyl)-3-hydroxy-2-(2-methoxyphenoxy)propanoyl)-4-isopropyloxazolidin-2-one (16): By following the general procedure outlined above for compound **7b**, 4-(((5*S*,6*S*)-5-(4-(benzyloxy)-3-methoxyphenyl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-6-yl)oxy)-3-methoxybenzaldehyde (**14**; 2.5 g, 3.75 mmol) was treated with (*S*)-4-isopropyl-3-(2-(2-methoxyphenoxy)acetyl)oxazolidin-2-one (**15**, see the Supporting Information; 1.32 g, 4.5 mmol), to give intermediate **16** (1.91 g, 53%) as a colorless oil after purification by column chromatography (CH_2Cl_2/ethyl ether, 9.5:0.5). $[\alpha]_D^{25} = +36.9$ (c 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.44 (d, J = 7.4 Hz, 2H), 7.32 (dt, J = 33.3, 7.9 Hz, 3H), 7.12–6.78 (m, 10H), 6.18 (d, J = 6.8 Hz, 1H), 5.13 (s, 2H), 5.05 (dd, J = 6.8, 2.8 Hz, 1H), 4.92 (d, J = 5.3 Hz, 1H), 4.25 (d, J = 14.7 Hz, 1H), 3.93–3.82 (m, 10H), 3.79 (d, J = 14.5 Hz, 2H), 3.52 (s, 1H), 3.42 (d, J = 17.0 Hz, 1H), 2.25 (d, J = 31.8 Hz, 1H), 2.03 (s, 1H), 0.98–0.70 (m, 24H), −0.06 ppm (dd, J = 29.5, 11.1 Hz, 12H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 169.70, 153.41, 150.21, 149.96, 149.15, 149.00, 147.40, 147.07, 137.26, 134.50, 130.12, 128.46, 127.75, 127.33, 123.52, 121.02, 119.53, 119.08, 117.31, 115.16, 113.36, 112.51, 111.28, 110.99, 84.96, 81.73, 76.17, 73.49, 71.07, 63.90, 62.09, 59.26, 55.94, 55.82, 28.83, 25.85, 25.76, 18.22, 18.18, 17.90, 14.79, −4.94, −5.02, −5.45, −5.50 ppm; IR (neat): $\tilde{\nu}$ = 3490.94, 2955.25, 2856.23, 1777.73, 1711.13, 1591.96, 1381.65, 1216.91, 1031.13 cm^{-1}. HRMS (DART-TOF): m/z calcd for $C_{52}H_{72}NO_{11}Si_2^+$: 942.46384 $[M-OH]^+$; found: 942.46205.

(1*S*,2*S*)-1-(4-(Benzyloxy)-3-methoxyphenyl)-2-(4-((1*R*,2*R*)-1,3-dihydroxy-2-(2-methoxyphenoxy)propyl)-2-methoxyphenoxy)propane-1,3-diol (17): To a solution of **16** (1.5 g, 1.56 mmol) in THF/H_2O (4:1) was added sodium borohydride (0.29 g, 7.8 mmol) portion-wise. The reaction was stirred for 3 h. Upon complete consumption of the starting material as monitored by TLC, the reaction was quenched by the addition of saturated NH_4Cl. The resulting suspension was extracted with Et_2O (3×100 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo to provide the TBS protected diol intermediate, which was used in the next step without further purification. The crude TBS protected diol intermediate was dissolved in anhydrous THF and cooled to 0 °C before TBAF (7.8 mL, 7.8 mmol) was added to the reaction mixture. The resulting solution was warmed to RT and stirred for 2 h. Upon complete consumption of the starting material as monitored by TLC, the reaction was quenched by the addition of saturated NH_4Cl. The organic phase was extracted with EtOAc (3×100 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude compound was purified by column chromatography (ethyl ether/acetone, 9:1) to afford asymmetric tetrol intermediate **17** (0.77 g, 81%) as a viscous oil. $[\alpha]_D^{25} = +8.5$ (c = 1.00 in MeOH); ^{1}H NMR (500 MHz, CD_3OD): δ = 7.41–7.23 (m, 5H), 7.08 (d, J = 3.7 Hz, 2H), 7.02–6.95 (m, 2H), 6.91 (d, J = 10.4 Hz, 5H), 6.84–6.80 (m, 1H), 5.03 (s, 2H), 4.92 (dd, J = 7.1, 5.4 Hz, 2H), 4.29 (d, J = 16.4 Hz, 2H), 3.81–3.77 (m, 9H), 3.77–3.70 (m, 3H), 3.50–3.45 ppm (m, 2H); ^{13}C NMR (126 MHz, CD_3OD): δ = 150.36, 149.97, 149.52, 148.07, 147.53, 147.43, 137.31, 135.34, 134.48, 128.04, 127.48, 127.32, 122.28, 120.92, 119.27, 119.02, 117.69, 116.96, 113.92, 112.26, 111.03, 110.96, 85.48, 85.41, 72.31, 70.80, 60.45, 55.10, 55.08 ppm; IR (neat): $\tilde{\nu}$ = 3330.52, 2972.99, 2878.35, 1465.77, 1378.14, 1308.04, 1160.82, 1129.28, 1104.74 cm^{-1}. HRMS (DART-TOF): m/z calcd for $C_{34}H_{39}O_{10}^+$: 607.25377 $[M+H]^+$; found: 607.25328.

(1*R*,2*R*)-1-(4-(((1*S*,2*S*)-1,3-Dihydroxy-1-(4-hydroxy-3-methoxyphenyl)propan-2-yl)oxy)-3-methoxyphenyl)-2-(2-methoxyphenoxy)-propane-1,3-diol (18): Asymmetric benzyl protected tetrol intermediate **17** (0.2 g, 0.33 mmol) was dissolved in ethanol (10 mL) and Pd/C (50 mg) was added to the solution. Hydrogen gas was introduced by using a balloon and slowly diffused into the solution while stirring gently for 3 h. Upon complete consumption of the starting material as monitored by TLC, the reaction mixture was filtered through Celite to remove the Pd/C. The filtrate was concentrated in vacuo to provide the crude lignin dimer, which was purified by column chromatography (ethyl ether/acetone, 4:1) to afford the enantiomerically pure lignin trimer **18** (0.16 g, 95%) as a clear viscous oil. $[\alpha]_D^{25} = +6.6$ (c = 1.00 in MeOH); ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ = 7.55 (s, 1H), 7.17–7.09 (m, 4H), 7.00–6.84 (m, 5H), 6.78 (d, J = 8.1 Hz, 1H), 4.92 (dd, J = 20.3, 5.6 Hz, 2H), 4.55 (d, J = 31.3 Hz, 2H), 4.22 (d, J = 23.6 Hz, 2H), 3.93 (d, J = 21.7 Hz, 2H), 3.84 (s, 6H), 3.80 (s, 3H), 3.71 (t, J = 13.4 Hz, 2H), 3.51 ppm (s, 2 H); ^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ = 150.80, 150.39, 148.63, 147.89, 147.15, 145.91, 136.04, 132.92, 122.54, 121.07, 119.68, 119.56, 118.82, 118.28, 114.39, 112.46, 111.22, 110.48, 87.50, 87.05, 72.96, 72.78, 60.96, 55.41, 55.31 ppm; IR (neat): $\tilde{\nu}$ = 3334.02, 2965.98, 2927.42, 2885.36, 1476.29, 1374.64, 1311.55, 1157.32, 1122.27 cm^{-1}; HRMS (DART-TOF): *m/z* calcd for $C_{27}H_{33}O_{10}^+$: 517.20682 $[M+H]^+$; found: 517.20780.

(1*R*,2*R*)-1-(4-(((5*S*,6*S*)-5-(4-(benzyloxy)-3-methoxyphenyl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-6-yl)oxy)-3-methoxyphenyl)-3-((*tert*-butyldimethylsilyl)oxy)-2-(2-methoxyphenoxy)propan-1-ol (20): To a solution of **16** (0.3 g, 0.31 mmol) in THF/H_2O (4:1), was added sodium borohydride (0.07 g, 1.78 mmol) portion-wise and the mixture was stirred for 3 h. Upon complete consumption of the starting material as monitored by TLC, the reaction was quenched by the addition of saturated NH_4Cl. The resulting suspension was extracted with Et_2O (3× 100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo to provide the TBS protected diol intermediate, which was used in the next step without further purification. The crude TBS protected diol intermediate was dissolved in anhydrous THF. To this solution was added TBSCl (0.075 g, 0.5 mmol) and imidazole (0.034 g, 0.5 mmol). The resulting solution was stirred for 2 h. Upon complete consumption of the starting material as monitored by TLC, the reaction was quenched by the addition of saturated NH_4Cl. The organic phase was extracted with CH_2Cl_2 (3×50 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude compound was purified by column chromatography (hexane/EtOAc, 4:1) to afford asymmetric TBS protected intermediate **20** (0.26 g, 90%) as a viscous oil. $[\alpha]_D^{25}$ = −14.0 (*c* = 1.00 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (s, 2 H), 7.39–7.19 (m, 5 H), 6.89 (d, *J* = 38.7 Hz, 8 H), 5.14 (s, 2 H), 4.94 (d, *J* = 5.4 Hz, 1 H), 4.84 (d, *J* = 7.2 Hz, 1 H), 4.25 (d, *J* = 29.1 Hz, 2 H), 4.11 (s, 1 H), 3.88 (d, *J* = 4.0 Hz, 6 H), 3.80 (s, 3 H), 3.74 (s, 2 H), 3.64 (d, *J* = 5.8 Hz, 1 H), 3.43 (d, *J* = 16.6 Hz, 1 H), 0.89 (s, 9 H), 0.83 (s, 18 H), −0.07 ppm (d, *J* = 16.5 Hz, 18 H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 150.68, 150.05, 149.15, 148.60, 147.35, 137.28, 134.66, 132.91, 128.46, 127.75, 127.36, 123.22, 121.22, 120.20, 119.62, 119.05, 115.60, 113.32, 111.91, 110.90, 110.86, 88.80, 84.96, 73.77, 71.05, 62.57, 62.19, 55.84, 55.76, 55.74, 25.90, 25.84, 25.77, 18.30, 18.20, 18.19, 1.83, −4.97, −5.04, −5.45, −5.53 ppm; IR (neat): $\tilde{\nu}$ = 3050.10, 1976.95, 1262.74, 1041.41, 712.5, 668.08 cm^{-1}; HRMS (DART-TOF): *m/z* calcd for $C_{52}H_{79}O_9Si_3^+$: 931.50264 $[M-OH]^+$; found: 931.49949.

(1*R*,2*R*)-1-(4-(((5*S*,6*S*)-5-(4-(Benzyloxy)-3-methoxyphenyl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-6-yl)oxy)-3-methoxyphenyl)-3-((*tert*-butyldimethylsilyl)oxy)-2-(2-methoxyphenoxy)propyl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (21 a): A stirred solution of TBS protected asymmetric epoxy alcohol **20** (0.12 g, 0.13 mmol) in anhydrous CH_2Cl_2 (10 mL) was treated sequentially with triethylamine (0.035 mL, 0.26 mmol) and (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl chloride (0.049 g, 0.13 mmol). A catalytic amount of DMAP was added and the resulting solution was stirred for 3 h. Upon complete consumption of the starting material as monitored by TLC, the reaction was quenched by addition of saturated NH_4Cl and extracted with CH_2Cl_2 (3×50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The crude compound was purified by column chromatography (hexane/EtOAc, 4:1) to afford ester **21 a** (0.12 g, 80%) as a colorless oil. $[\alpha]_D^{25}$ = −2.1 (*c* = 1.00 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55–7.26 (m, 8 H), 7.24–7.09 (m, 3 H), 6.89 (ddd, *J* = 35.0, 21.4, 11.5 Hz, 9 H), 6.32 (d, *J* = 8.0 Hz, 1 H), 5.16 (s, 2 H), 4.95 (s, 1 H), 4.60 (s, 1 H), 4.31 (s, 1 H), 4.04–3.65 (m, 11 H), 3.46 (d, *J* = 20.8 Hz, 5 H), 1.16–0.67 (m, 27 H), 0.07 to −0.13 ppm (m, 18 H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.51, 150.58, 149.74, 149.25, 147.46, 137.25, 134.63, 132.38, 129.24, 128.48, 128.25, 128.03, 127.77, 127.48, 127.35, 122.22, 120.78, 120.63, 119.10, 117.37, 115.08, 113.35, 112.46, 111.44, 110.84, 84.87, 81.62, 78.00, 74.05, 71.06, 62.16, 61.08, 55.87, 55.68, 55.50, 25.82, 18.19, −4.97, −5.06, −5.52, −5.53, −5.70, −5.72 ppm; IR (neat): $\tilde{\nu}$ = 2955.46, 2923.92, 2853.61, 1753.20, 1591.96, 1462.27, 1251.96, 1115.26, 1024.12 cm^{-1}; HRMS (DART-TOF): *m/z* calcd for $C_{52}H_{79}O_9Si_3^+$: 931.50264 $[M-C_{10}H_8F_3O_2]^+$; found: 931.49846.

(1*R*,2*R*)-1-(4-(((5*S*,6*S*)-5-(4-(Benzyloxy)-3-methoxyphenyl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-6-yl)oxy)-3-methoxyphenyl)-3-((*tert*-butyldimethylsilyl)oxy)-2-(2-methoxyphenoxy)propyl (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (21 b): By following the general procedure outlined above for compound **21 a**, compound **20** (0.12 g, 0.13 mmol) was converted into the ester **21 b** (0.12 g, 80%) as a colorless oil. $[\alpha]_D^{25}$ = −26.3 (*c* = 1.00 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.25 (m, 9 H), 7.19 (d, *J* = 15.0 Hz, 2 H), 7.03–6.77 (m, 10 H), 6.39 (d, *J* = 7.0 Hz, 1 H), 5.15 (s, 2 H), 4.94 (d, *J* = 5.9 Hz, 1 H), 4.54 (d, *J* = 6.8 Hz, 1 H), 4.32 (d, *J* = 13.7 Hz, 1 H), 3.90–3.67 (m, 11 H), 3.45 (d, *J* = 25.1 Hz, 5 H), 0.94–0.76 (m, 27 H), 0.03 to −0.10 ppm (m, 18 H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.59, 150.50, 149.77, 149.36, 149.23, 147.64, 147.45, 137.24, 134.61, 132.31, 129.25, 128.48, 128.45, 128.02, 127.78, 127.65, 127.35, 84.84, 81.80, 77.24, 74.10, 71.05, 62.29, 61.28, 55.87, 55.68, 55.35, 25.81, 25.79, 25.72, 18.21, 18.17, 18.15, −4.99, −5.12, −5.54, −5.69 ppm; IR (neat): $\tilde{\nu}$ = 2953.18, 2856.16, 1752.08, 1592.71, 1500.82, 1462.87, 1248.45, 1118.76, 1017.11 cm^{-1}; HRMS (DART-TOF): *m/z* calcd for $C_{52}H_{79}O_9Si_3^+$: 931.50264 $[M-C_{10}H_8F_3O_2]^+$; found: 931.49818.

(1*R*,2*R*)-1-(4-(Benzyloxy)-3,5-dimethoxyphenyl)-3-((*tert*-butyldimethylsilyl)oxy)-2-(2-methoxy-4-methylphenoxy)propyl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (19 a): A stirred solution of the TBS protected asymmetric alcohol **10** (0.07 g, 0.12 mmol) in anhydrous CH_2Cl_2 (10 mL) was treated sequentially with TEA (0.034 mL, 0.24 mmol) and (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl chloride (0.033 g, 0.13 mmol). A catalytic amount of DMAP was added and the resulting solution was stirred for 3 h. Upon complete consumption of the starting material as monitored by TLC, the reaction was quenched by addition of saturated NH_4Cl and extracted with CH_2Cl_2 (3×50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The crude compound was purified by column chromatography (hexane/EtOAc, 7:3) to afford ester **19 a** (0.08 g, 89%) as a colorless oil. $[\alpha]_D^{25}$ = −21.9 (*c* = 1.00 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (d, *J* = 7.1 Hz, 2 H), 7.40 (d, *J* = 7.8 Hz, 2 H), 7.33 (d, *J* = 7.9 Hz, 3 H), 7.21 (t, *J* = 7.7 Hz, 2 H), 6.81 (d, *J* = 8.1 Hz, 1 H), 6.69 (s, 1 H), 6.63 (d, *J* = 8.8 Hz, 1 H), 6.52 (s, 2 H), 6.28 (d, *J* = 7.6 Hz, 1 H), 5.02 (s, 2 H), 4.46 (d, *J* = 14.4 Hz, 1 H), 3.76 (s, 3 H), 3.72 (d, *J* = 3.6 Hz, 1 H), 3.69 (s, 6 H), 3.53 (s, 3 H), 3.42 (dd, *J* = 11.3, 3.1 Hz, 1 H), 2.30 (s, 3 H), 0.87 (s, 9 H), −0.06 ppm (d, *J* = 13.7 Hz, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.57, 153.27, 150.28, 144.93, 137.69, 136.83, 132.28, 132.07, 131.50, 129.30, 128.50, 128.08, 127.85, 127.43, 120.94, 117.38, 113.46, 104.87, 81.67, 77.89, 74.87, 60.84, 55.89, 55.69, 55.62, 25.83, 21.05, 18.24, −5.67 ppm; IR (neat): $\tilde{\nu}$ = 2955.46, 2229.96, 2853.81, 1750.92, 1591.96, 1504.33, 1458.76, 1223.92, 1122.27, 1010.10 cm^{-1}; HRMS (DART-TOF): *m/z* calcd for $C_{32}H_{43}O_6Si^+$: 551.28234 $[M-C_{10}H_8F_3O_2]^+$; found: 551.28255.

(1*R*,2*R*)-1-(4-(Benzyloxy)-3,5-dimethoxyphenyl)-3-((*tert*-butyldimethylsilyl)oxy)-2-(2-methoxy-4-methylphenoxy)propyl (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (19 b): By following the general procedure for **19 a**, compound **10** (0.07 g, 0.12 mmol) was converted into ester **19 b** (0.08 g, 80%) as a colorless oil. $[\alpha]_D^{25}$ = −54.5 (*c* = 1.00 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (d, *J* = 8.6 Hz, 4 H), 7.36–7.23 (m, 6 H), 6.74–6.65 (m, 4 H), 6.58 (d, *J* =

8.1 Hz, 1H), 6.35 (d, $J=6.2$ Hz, 1H), 5.03 (s, 2H), 4.45 (d, $J=14.7$ Hz, 1H), 3.78 (s, 6H), 3.74 (s, 3H), 3.70 (d, $J=4.5$ Hz, 1H), 3.51 (dd, $J=11.7$, 3.5 Hz, 1H), 3.46 (s, 3H), 2.28 (s, 3H), 0.87 (s, 9H), −0.05 ppm (d, $J=14.0$ Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=165.63$, 153.39, 150.21, 145.25, 137.68, 136.91, 132.13, 131.94, 131.79, 129.39, 128.49, 128.14, 128.08, 127.83, 127.76, 121.06, 117.27, 113.71, 105.04, 81.83, 77.12, 74.90, 61.09, 56.04, 55.82, 55.35, 25.82, 21.01, 18.22, −5.62, −5.64 ppm. IR (neat): $\tilde{\nu}=2948.45$, 2930.93, 2857.32, 1753.20, 1591.96, 1507.84, 1462.27, 1227.42, 1125.77, 1017.11 cm^{-1}; HRMS (DART-TOF): m/z calcd for $C_{32}H_{43}O_6Si^+$: 551.28234 $[M-C_{10}H_8F_3O_2]^+$; found: 551.28246.

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