JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Synthesis of Enantiomerically Pure Lignin Dimer Models for Catalytic Selectivity Studies

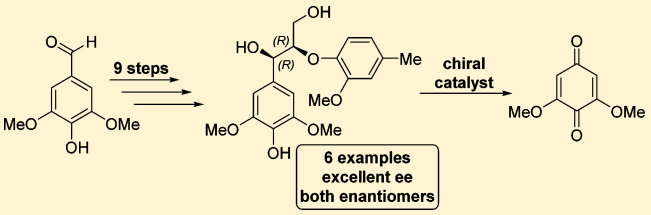
Costyl N. Njiojob,[†,‡] Jennifer L. Rhinehart,[†] Joseph J. Bozell,*[,‡] and Brian K. Long*[,†]

[†]Department of Chemistry, University of Tennessee, Knoxville, Tennessee 37996, United States

[‡]Center for Renewable Carbon, University of Tennessee, Knoxville, Tennessee 37917, United States

Supporting Information

ABSTRACT: A series of highly enantioselective transformations, such as the Sharpless asymmetric epoxidation and Jacobsen hydrolytic kinetic resolution, were utilized to achieve the complete stereoselective synthesis of β-O-4 lignin dimer models containing the S, G, and H subunits with excellent *ee* (>99%) and moderate to high yields. This unprecedented synthetic method can be exploited for enzymatic, microbial, and chemical investigations into lignin's degradation and depolymerization as related to its stereochemical constitution. Preliminary degradation studies using enantiopure Co(salen) catalysts are also reported.



INTRODUCTION

Lignin is the second most abundant biorenewable organic polymer, exceeded only by cellulose, and constitutes over 40% of the potential chemical energy stored in plants, trees, and grasses.[1] Unlike cellulose, which has been extensively studied and is easily transformed into numerous monomeric and polymeric products, little progress has been made toward the selective, high yielding conversion of lignin into low molecular weight value-added chemicals. A primary cause for this lack of progress is due to the structural complexity encountered within lignin, which originates from its biosynthesis in which *p*-hydroxylphenyl (H), guiacyl (G), and syringyl (S) monolignol units (Figure 1) are polymerized.[2,3]

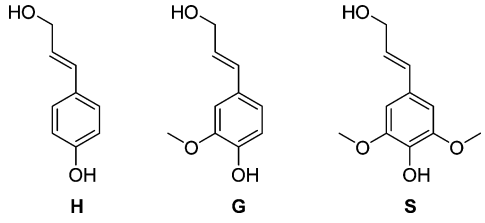


Figure 1. Structures of H, G, and S monolignol units.

This biopolymerization results when H, G, and S monolignols are enzymatically converted into delocalized phenoxy radicals, which then undergo radical−radical coupling at the sites of radical delocalization. This coupling produces a plethora of interunit linkages, such as β-O-4, β-5, and β−β linkages (Figure 2), which can be present in varying amounts depending on the relative proportion of monolignols present in the plant source and lignin isolation methods employed.[3−5]

The most common substructural unit of native lignin is the β-O-4 linkage, which constitutes approximately 50−65% of the various interunit linkages.[6] This high concentration of β-O-4 linkages in crude lignin samples makes it an ideal target for many fundamental synthetic transformations, depolymerizations, and degradations.[1,7−13] Although it is known that lignin as a macromolecule does not display optical activity,[14−16] the presence of multiple chiral centers within lignin's interunit linkages may ultimately confer varying physical and chemical properties at localized sites within the structure. Therefore, it can be surmised that these subtle stereochemical differences could be exploited in depolymerization and degradation studies. For example, *Trametes versicolor* employs a lignin peroxidase to preferentially degrade the *threo* isomer in β-O-4 models.[17] Recently, Ralph and co-workers examined glutathione *S*-transferase enzymes which act as enantioselective β-aryl etherases.[18,19] Additionally, other studies have shown that enzymes from *Sphingobium* sp. and other enzymatic systems degrade lignin or lignin models in a stereospecific manner.[20−23]

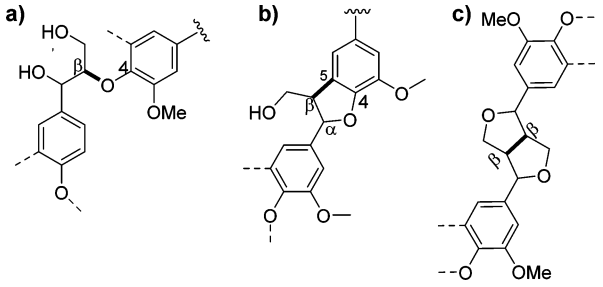


Figure 2. Representative structures of (a) β-O-4, (b) β-5, and (c) β−β linkages found in lignin.

Received: November 25, 2014
Published: January 13, 2015

DOI: 10.1021/jo502685k
J. Org. Chem. 2015, 80, 1771−1780

The full impact that stereochemistry has on lignin degradation and conversion represents a significant fundamental gap in the quest to use lignin as a chemical feedstock. As a result, access to enantiomerically pure lignin models would provide a useful probe by which the impact of relative and absolute stereochemical differences may influence lignin degradation. It should be noted that the synthesis of racemic, yet diastereomerically enriched lignin dimer models has previously been reported,[24−28] and though enantiomerically pure lignin dimers have also been reported, those enantiomerically enriched compounds were not selectively synthesized but were isolated either via tedious resolution of a racemic mixture or by separation of diastereomeric derivatives of each enantiomer, both of which lead to very limited quantities of material for subsequent studies.[23,29,30]

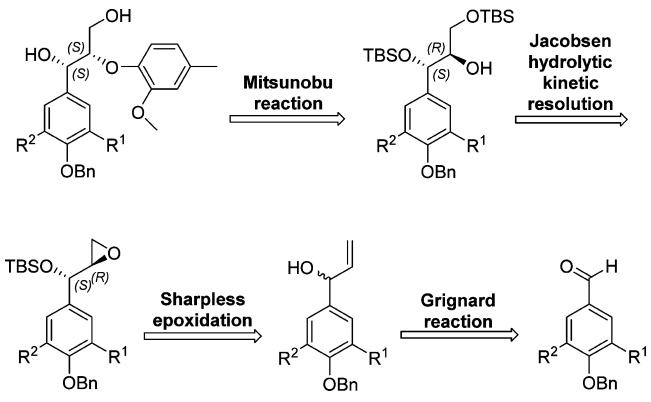
To the best of our knowledge, and likely due to limited or no access to meaningful quantities of enantiopure lignin models, a systematic examination of the chemically catalyzed conversion of enantiomerically pure β-O-4 type lignin linkages is absent from the literature. To address this fundamental gap, we herein report an efficient and highly selective synthesis of optically pure lignin β-O-4 dimers and preliminary results toward their catalytic decomposition (oxidative) using optically active Co-Schiff base catalysts.

RESULTS AND DISCUSSION

It is important to note that though prior lignin literature frequently uses stereochemical descriptors such as *erythro* and *threo*, we will identify all isomers using standard Cahn-Ingold-Prelog descriptors throughout to avoid any potential ambiguity. For example, the *erythro* isomer of model compound **11** will be stereochemically represented as (*R*,*S*) or (*S*,*R*), while the *threo* isomer is stereochemically represented as (*R*,*R*) or (*S*,*S*).

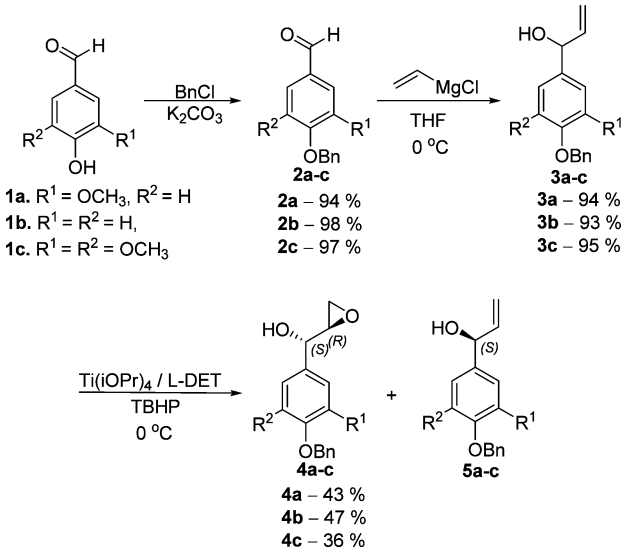
Asymmetric Synthesis of β-O-4 Lignin Model Dimers. A retrosynthetic analysis of enantiomerically enriched/enantiopure lignin dimers is shown in Scheme 1 in which the final β-O-4 linkage will be formed using a Mitsunobu reaction, thereby establishing the final stereochemistry at the β-carbon. Prior to the Mitsunobu reaction, the stereochemistry of the α- and β-carbons will be established using two asymmetric techniques, the Sharpless asymmetric epoxidation (SAE) and the Jacobson hydrolytic kinetic resolution (HKR). By proper choice of epoxidation ligands and catalysts, we can control the absolute and relative stereochemistries of the α- and β-carbons. We will demonstrate herein that the combination of these stereospecific techniques can be used to synthesize both enantiomers of β-O-4 linked lignin dimers containing H, G, and S subunits with very high *ee*.

Scheme 1. Retrosynthetic Analysis for the Asymmetric Synthesis of Lignin Dimer Models



Toward this goal, protection of the phenolic moiety of commercially available aldehydes **1a−1c** was accomplished using benzyl chloride to provide intermediates **2a−2c** (Scheme 2). The β- and γ-carbons were installed via Grignard reaction of **2a−2c** with vinylmagnesium chloride, providing a racemic mixture of secondary allylic alcohols **3a−3c**. Those racemic alcohols were then subjected to SAE conditions producing the enantiomerically enriched epoxides **4a−4c** in 37−47% yield and in ∼91% ee (as determined from Mosher ester analysis). Though only one enantiomer is shown in Scheme 2, both enantiomers of allylic alcohols **3a−3c** could be converted to their corresponding enantiomerically enriched epoxides by choice of either L-diethyltartrate (L-DET) or D-diethyltartrate (D-DET) as a ligand.[31] The unreacted enantiopure alcohols **5a−5c** were separated via column chromatography and later used to obtain the complementary enantiomers (see Experimental Section).

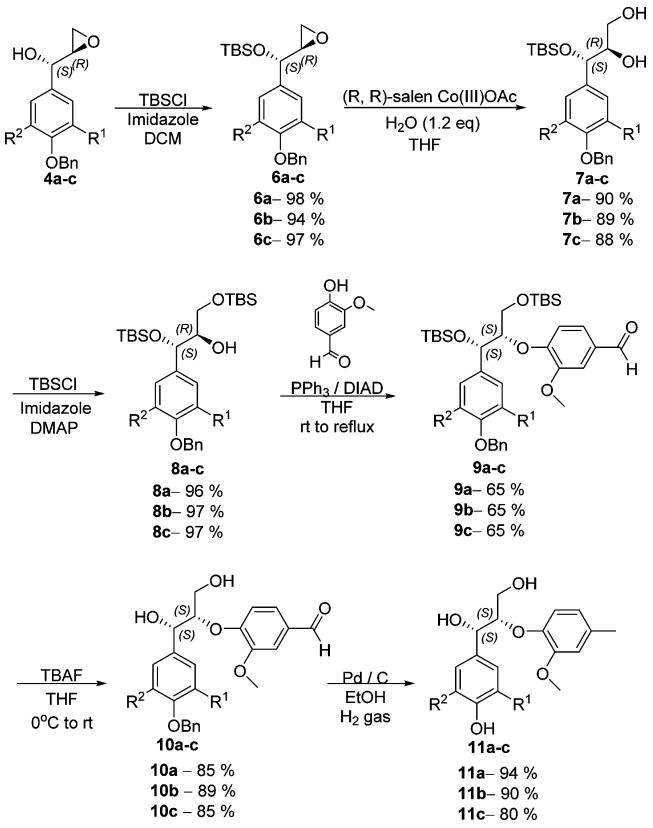
Scheme 2. Synthesis of Key Intermediates 4a−4c



Epoxides **4a−4c** were protected as *t*-butyldimethylsilyl (TBS) ethers **6a−6c** and hydrolyzed to compounds **7a−7c** using previously reported HKR techniques that utilize enantiopure salen-Co(III)OAc catalysts (Scheme 3).[32−34] Given that HKR is often used for the kinetic resolution of racemic terminal epoxides,[32,33] we envisioned that coupling this step in series with SAE would facilitate enhancements in *ee* by converting only the major epoxide enantiomer to the diol while leaving the minor epoxide unreacted. By screening each enantiomer of the Co(salen) catalyst, it was found that the asymmetric epoxides **6a−6c** were quantitatively converted to the asymmetric diols **7a−7c** when treated with (*R*,*R*) salen-Co(III)OAc. Correspondingly, the (*S*,*S*) salen-Co(III)OAc catalyst was used to quantitatively convert epoxides obtained from SAE using D-DET as a ligand (see Supporting Information). Overall, both enantiomers of diols **7a−7c** were obtained with *ee*'s ≥ 99%, as determined by Mosher ester analysis. The primary alcohols of diols **7a−7c** were selectively protected as their TBS ethers to provide virtually enantiopure key intermediates **8a−8c**, representing each of the three

DOI: 10.1021/jo502685k
J. Org. Chem. 2015, 80, 1771−1780

Scheme 3. Synthesis of (*S*,*S*)-Lignin Dimers 11a−11c



primary lignin substructural units (H, G, and S). Overall, each reaction presented in Schemes 2 and 3 proceeded in similar yields regardless of the subunit (H, G, or S) involved; however, the SAE of compounds **3a−3c** to **4a−4c** did proceed in slightly lower yield when the more highly substituted compound S model **3c** was used.

Intermediates **8a−8c** were then coupled with 4-hydroxy-3-methoxybenzaldehyde using specific Mitsunobu reaction conditions to yield protected (*S*,*S*) dimers **9a−9c** with complete inversion of configuration at the β-carbon. Under traditional Mitsunobu conditions in which the phosphine, secondary alcohol, and nucleophile were dissolved in organic solvent followed by the dropwise addition of azodicarboxylate, low yields were obtained (~20%).[35,36] However, it was found that if the phosphine and azodicarboxylate were premixed to form the proposed zwitterionic species first,[37] followed by the dropwise addition of 4-hydroxy-3-methoxybenzaldehyde (nucleophile) and intermediate **8**, a dramatic improvement in the yield (65%) could be realized. The TBS-ethers of compounds **9a−9c** were then deprotected using tetra-*n*-butylammonium fluoride (TBAF) to provide diols **10a−10c**. Lastly, the benzyl protecting groups were cleaved via hydrogenolysis using Pd/C in EtOH to provide the final enantiomerically enriched compounds **11a−11c** in which the aldehyde functionality was also reduced.

Assignment of Absolute Stereochemistry. To confirm the stereochemistry of final compounds **11a−11c**, intermediates **4a** and **8b** were converted to their corresponding Mosher esters by reacting each intermediate with either (*R*) or (*S*)-(+)-α-methoxy-α-trifluoro-methylphenylacetyl chloride (MPTA-Cl), respectively, following a well-established protocol.[38] The difference in the chemical shifts ($\Delta\delta_{S\text{-}R}$) between the

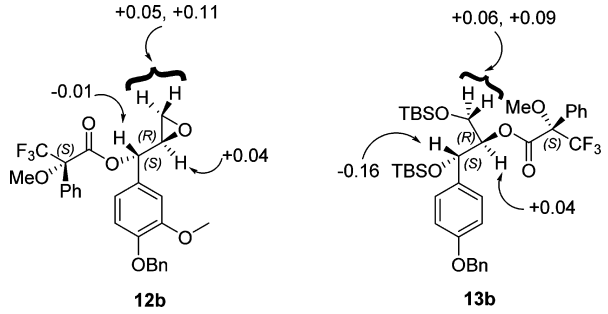


Figure 3. Chemical shift differences ($\Delta\delta_{S\text{-}R}$) for the Mosher esters of intermediates **12b** and **13b**.

(*S*) and (*R*) Mosher esters were determined as shown in Figure 3. The benzylic protons of **12b** and **13b** have a $\Delta\delta_{S\text{-}R}$ value of −0.01 and −0.16, respectively, therefore indicating that the absolute stereochemistry of the benzylic chiral carbon of this intermediate is in an *S*-configuration. Also, the methine proton at the β-carbon of intermediates **12b** and **13b** each have a $\Delta\delta_{S\text{-}R}$ value of +0.04, confirming an *R*-configuration. Finally, the methylene protons at the γ-carbon of intermediates **12b** and **13b** have a ($\Delta\delta_{S\text{-}R}$) value of +0.05, +0.11 and +0.06, +0.09, respectively. Obtaining the absolute configuration of these key intermediates coupled with the well-established stereochemical inversion of the Mitsunobu reaction enabled the overall determination of the absolute stereochemistry of the final dimers. Additionally, the stereochemistry was confirmed via X-ray crystallographic analysis of compound **11b** (see Supporting Information), which was in perfect agreement with the results obtained from the Mosher ester analysis.

Co-Catalyzed Oxidation of Optically Active Lignin Models. We have previously reported that racemic Co-Schiff base catalysts are effective for converting lignin-like phenols into their corresponding para-benzoquinones,[28,39] and as a preliminary demonstration of the potential utility of these essentially enantiopure lignin dimer models, we examined their catalytic oxidation using both enantiomers of commercially available Co-based Jacobsen catalysts. The reaction is postulated to proceed via formation of an intermediate Co-superoxo complex $\mathbf{14}_{oxo}$ in which the catalysts stereoselectivity may be influenced by the stereochemistry of the enantiopure lignin dimers **11a−11c** due to its suggested coordination to the active metal site via a "top-on" trajectory (Figure 4).

To probe the potential effects of substrate stereochemistry on Co-catalyzed lignin oxidation/degradation, we examined the enantiopure β-O-4 model **11c** and its enantiomeric (*R*,*R*) analogue (Table 1). Oxidation of the (*R*,*R*)-lignin dimer model provided an average yield of 74.39% dimethoxybenzoquinone (DMBQ) after four individual experiments as compared to an average of 70.10% DMBQ isolated when using the (*S*,*S*)-lignin dimer model (**11c**). This difference in average isolated yield of DMBQ is quite small, and given the potential for error associated with isolation of such degradation compounds (as noted in Table 1), it is considered to fall within the error of our measurements. Though it has been suggested that the sterics of related Mn_{oxo} catalysts can restrict the substrate approach to a path that passes over the ligand's cyclohexyl group,[40] in our system, we postulate that the stereochemical information contained within the β-O-4 linkage may be too far removed from the active Co-superoxo complex, hence resulting in only a very small difference in reactivity. In light of this hypothesis and inspired by our recently published work on related Co-catalysts

DOI: 10.1021/jo502685k
J. Org. Chem. 2015, 80, 1771−1780

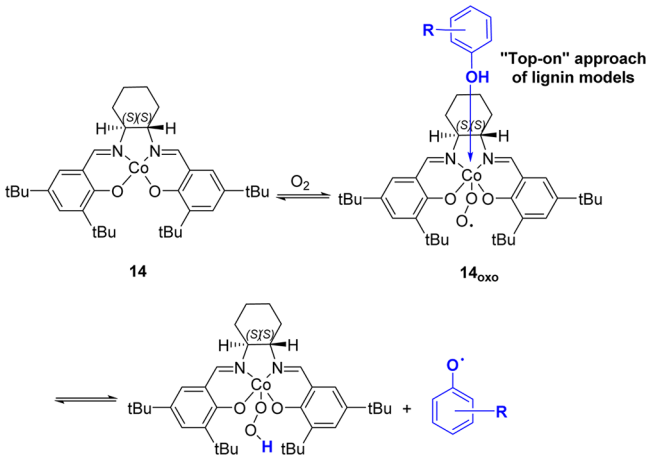


Figure 4. Mechanism of radical formation during phenol oxidation by Co-Schiff base complexes.

Table 1. Oxidative Degradation of (*S, S*)-Lignin Model Dimer 11c and Its (*R,R*) Analogue Using Enantiopure Jacobsen Catalysts.[a]

entry	substrate	catalyst	*t* (h)	% DMBQ[b]
1	(*R,R*)	(*R,R*)	16	74.05% (±3.9)
2	(*R,R*)	(*S,S*)	16	74.73% (±6.7)
3	(*S,S*)	(*R,R*)	16	69.55% (±7.1)
4	(*S,S*)	(*S,S*)	16	70.65% (±4.0)

[a][Catalyst] = 10 mol %, 55 psi O_2. [b]Isolated yields, reported as an average over four trials ± one standard deviation.

that bear sterically bulky Lewis bases pendant to the ethylenediamine bridge of the Schiff-base ligand,[41] our future efforts will be to examine if precisely positioned, optically active groups pendant to the Schiff-base ligand may influence substrate approach and overall oxidative enantioselectivity.

In conclusion, we have reported an efficient method for the preparation of enantiomerically pure *β*-O-4-linked lignin dimer model compounds with moderate-to-high yields, and in excellent *ee* via the application of successive asymmetric transformations. Ready access to such enantiopure lignin models provides a platform by which researchers may ultimately ascertain the extent to which enzymatic and organometallic catalyst systems may be influenced by native lignin stereochemical differences. Our initial investigations into the oxidative degradation of enantiopure lignin models using chiral Jacobsen catalysts showed little to no differentiation based on substrate stereochemistry, and future studies will be conducted to determine if targeted ligand modifications may impact overall substrate selectivity. These studies hold promise to pave the way for intelligent catalyst design that not only focuses on functional group reactivity but also considers the role that lignin stereochemistry may play in the catalytic conversion of lignin into useful, value-added chemical feedstocks.

■ 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 precoated silica gel plates with an extra hard layer of 60 A° mesh, 250 *μ*m thick silica. Flash column chromatography was performed using either 230−400 mesh silica gel on a column, or by an automated chromatography system using high performance silica gel. The eluents employed are reported as volume/volume percentages. Melting points were recorded using a melting point apparatus and are uncorrected. Specific rotations were obtained using a polarimeter. ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ and CD_3OD using a 500 MHz instrument, and chemical shifts are reported relative to tetramethylsilane or residual solvent resonance and reported in parts per million. Infrared spectra were obtained on an Fourier transform-infrared (FT-IR) spectrometer at 4 cm^{-1} resolution and are reported in cm^{-1}. High-resolution mass spectra (HRMS) are reported as *m*/*e* (relative ratio), and accurate masses are reported for the molecular ion $(M + H)^+$ or a suitable fragment ion and are reported with an error <5 ppm. Oxidation reactions were carried out in thick-walled glass reactors under the oxygen pressure indicated in the text. Detailed synthetic procedures, including the complete characterization [nuclear magnetic resonance (NMR), HRMS, IR, and specific rotations] for each intermediate, are reported for the (*S,S*) enantiomer. The corresponding (*R,R*) enantiomer has identical NMR, MS and IR data, but displays an opposite specific rotation value that is also reported. X-ray diffraction measurements were performed on single crystals coated with Paratone oil, mounted on a loop, and frozen under a stream of N_2 while data were collected on a diffractometer. Reflections were merged and corrected for Lorenz and polarization effects, scan speed, and background. The structure was solved by direct methods with the aid of successive difference Fourier maps and were refined against all data. All of the solvent molecules were squeezed.

General Procedure for the Oxidation of Enantiomerically Pure Lignin Dimer Models to Benzoquinones. The synthesized enantiopure lignin dimer model (0.30 mmol) and enantiomerically pure Jacobsen catalyst (0.03 mmol) were combined in 15 mL of methanol in a Fisher-Porter bottle. The bottle was flushed with oxygen three times and then pressurized with oxygen to 55 psi. Each reaction was run for 16 h, after which the reaction mixture was concentrated under vacuum and the crude material purified via flash chromatography using EtOAc/CH_2Cl_2 (5:95) as an eluent to provide the product 2,6-dimethoxybenzoquinone as a bright yellow solid. The data obtained satisfactorily matched all previously reported data.[42]

*4-(Benzyloxy)-3-methoxybenzaldehyde (**2a**).* To a stirred solution of vanillin (10.0 g, 65.7 mmol) in anhydrous DMF was added K_2CO_3 (13.7 g, 99.1 mmol) and benzyl chloride (9.08 mL, 78.9 mmol) under N_2 followed by a catalytic amount of 4-dimethylaminopyridine (DMAP). The resulting solution was stirred overnight at rt. After consumption of the starting material as confirmed by TLC, the reaction was quenched by addition of saturated ammonium chloride. 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 material was purified by recrystallization in hexane/ethanol (1:4) to provide 15.0 g of phenol **2a** (94%) as a cream white solid. Mp: 53−55 °C. IR (neat): 2937.89, 2833.93, 1679.33, 1584.26, 15, 1506.45, 1463.89, 1261.1, 1194.7, 730.21 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 9.73 (s, 1H), 7.35−7.31 (m, 3H), 7.30−7.25 (m, 3H), 7.22 (t, *J* = 7.3 Hz, 1H), 6.88 (d, *J* = 8.2 Hz, 1H), 5.13 (s, 2H), 3.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 190.8, 153.6, 136.01, 150.1, 130.3, 128.7, 128.2, 127.2, 126.5, 112.4, 109.4, 70.8, 56.0; HRMS (DART-TOF): calcd for $C_{15}H_{15}O_3^+$ $(M + H)^+$, 243.10157; found, 243.10160.

*4-(Benzyloxy)benzaldehyde (**2b**).* Following the general procedure outlined above for compound **2a**, 4-hydroxybenzaldehyde (**1b**) (10.0 g, 81.9 mmol) was converted to yield 17.0 g of compound **2b** (98%) which was isolated as a white solid. Mp: 68−70 °C. IR (neat): 1738.88, 1604.53, 1507.18, 1451.91, 1266.02, 1061.29, 708.27, 617.29 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 9.77 (s, 1H), 7.72 (d, *J* = 8.7 Hz, 2H), 7.35−7.22 (m, 5H), 6.97 (d, *J* = 8.7 Hz, 2H), 5.03 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 190.8, 163.7, 136.0, 132.0, 130.1, 128.7, 128.3, 127.5, 115.1, 70.2; HRMS (DART-TOF): calcd for $C_{14}H_{13}O_2^+$ $(M + H)^+$, 213.09101; found, 213.09100.

*4-(Benzyloxy)-3,5-dimethoxybenzaldehyde (**2c**).* Following the general procedure outlined above for compound **2a**, 4-(hydroxy)-3,5-dimethoxybenzaldehyde (**1c**) (10.0 g, 54.9 mmol) was converted to yield 14.5 g of protected phenol **2c** (97%) as a cream white solid.

DOI: 10.1021/jo502685k
J. Org. Chem. 2015, 80, 1771−1780

Mp: 56−58 °C. IR (neat): 3062.99, 2883.02, 2848.38, 1683.65, 1587.39, 1323.13, 1221.24, 727.22, 614.58 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 9.77 (s, 1H), 7.38 (d, J = 7.1 Hz, 2H), 7.22 (dq, J = 23.0, 8.6, 7.8 Hz, 3H), 7.02 (s, 2H), 5.04 (s, 2H), 3.81 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 191.1, 154.0, 142.4, 137.2, 131.9, 128.4, 128.2, 128.1, 106.7, 75.0, 56.2. HRMS (DART-TOF): calcd for $C_{16}H_{17}O_4^+$ $(M + H)^+$, 273.11214; found, 273.11138.

*1-(4-(Benzyloxy)-3-methoxyphenyl)prop-2-en-1-ol (**3a**).* Vinyl magnesium bromide (49 mL, 49 mmol) was added to a stirred solution of aldehyde **2a** (10 g, 41.3 mmol) in anhydrous THF at 0 °C. The resulting solution was warmed to rt and stirred for 3 h. After complete consumption of the starting material, as monitored by TLC, the reaction was quenched by addition of saturated ammonium chloride. 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 using hexane/EtOAc (7:3) to afford 10.5 g of vinyl alcohol **2a** (94.1%) as a light yellow oil. IR (neat): 3416.26, 2933.67, 1592.81, 1510.57, 1259.82, 1222, 746.92, 696.65 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.33 (d, J = 7.7 Hz, 2H), 7.25 (t, J = 7.5 Hz, 2H), 7.18 (t, J = 7.3 Hz, 1H), 6.82 (s, 1H), 6.73 (d, J = 8.2 Hz, 1H), 6.69 (d, J = 8.2 Hz, 1H), 5.91 (d, J = 36.0 Hz, 1H), 5.21 (dd, J = 17.1, 3.6 Hz, 1H), 5.06 (dd, J = 10.3, 3.1 Hz, 1H), 5.02 (s, 2H), 4.98 (s, 1H), 3.76 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.7, 147.7, 140.3, 137.4, 135.9, 128.5, 127.8, 127.3, 118.6, 114.8, 113.9, 110.1, 75.00, 71.0, 56.0. HRMS (DART-TOF): calcd for $C_{17}H_{17}O_2^+$ $(M - OH)^+$, 253.12317; found, 253.12231.

*1-(4-(Benzyloxy)phenyl)prop-2-en-1-ol (**3b**).* Following the general procedure outlined above for compound **3a**, 4-(benzyloxy)-benzaldehyde (**2b**) (10.0 g, 47.15 mmol) was converted to yield 10.5 g of protected phenol **3b** (92.7%) as a cream white solid. Mp: 57−59 °C. IR (neat) 3402.98, 2936.55, 1744.43, 1592.85, 1510.56, 1259.54, 1221.6, 779.29 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.33 (d, J = 7.2 Hz, 2H), 7.28 (t, J = 7.4 Hz, 2H), 7.22 (t, J = 7.2 Hz, 1H), 7.18 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 5.99−5.88 (m, 1H), 5.22 (dt, J = 17.1, 1.4 Hz, 1H), 5.08 (dt, J = 10.3, 1.3 Hz, 1H), 5.03 (s, 1H), 4.95 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.4, 140.4, 137.0, 135.2, 128.6, 128.0, 127.7, 127.5, 114.9, 114.8, 74.8, 70.0. HRMS (DART-TOF): calcd for $C_{16}H_{15}O^+$ $(M - OH)^+$, 223.11174; found, 223.11197.

*1-(4-(Benzyloxy)-3,5-dimethoxyphenyl)prop-2-en-1-ol (**3c**).* Following the general procedure outlined above for compound **3a**, 4-(benzyloxy)-3,5-dimethoxybenzaldehyde (**2c**) (10.0 g, 36.75 mmol) was converted to yield 10.5 g of protected phenol **3c** (95.2%) as a viscous oil. IR (neat): 3435.92, 2938.3, 2838.26, 1591.64, 1417.56, 1230.57, 1123.58, 922.14 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.41 (d, J = 7.2 Hz, 2H), 7.26 (t, J = 7.3 Hz, 2H), 7.20 (t, J = 7.3 Hz, 1H), 6.50 (s, 2H), 5.95 (ddd, J = 17.0, 10.3, 6.0 Hz, 1H), 5.27 (dt, J = 17.1, 1.4 Hz, 1H), 5.12 (dt, J = 10.3, 1.3 Hz, 1H), 5.03 (d, J = 5.7 Hz, 1H), 4.91 (s, 2H), 3.74 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.6, 140.0, 138.4, 137.8, 136.4, 128.4, 128.1, 127.8, 115.2, 103.3, 75.4, 75.0, 56.1. HRMS (DART-TOF): calcd for $C_{18}H_{19}O_3^+$ $(M - OH)^+$, 283.13287; found, 283.13234.

*(S)-(4-(Benzyloxy)-3-methoxyphenyl)((R)-oxiran-2-yl)methanol (**4a**).* To a stirred suspension of 4 Å molecular sieves in dry CH_2Cl_2 (20 mL) was added racemic allylic alcohol **3a** (7.0 g, 26 mmol) and $Ti(OiPr)_4$ (1.55 mmol, 0.46 mL) under N_2 atmosphere. The reaction mixture was cooled to −5 °C, and L-DET (2.07 mmol, 0.36 mL) was added dropwise. The resulting mixture was stirred at −5 °C for 30 min, before a solution of *t*-butyl hydroperoxide in hexanes (5.5 M, 26 mmol, 4.73 mL) was added dropwise over 30 min at 0 °C and stirred for 8 h. The reaction was quenched with a 10% aqueous solution of tartaric acid, and the resulting suspension was extracted with CH_2Cl_2 (3 × 100 mL) and filtered. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The crude compound was purified via column chromatography using hexane/EtOAc (7:3) to afford asymmetric epoxide **4a** (3.0 g, 11.1 mmol, 42.7%) as a cream white solid. Mp: 59−61 °C. IR (neat) 3441.08, 2933.96, 1743.91, 1743.91, 1512.7, 1261.03, 1137.48, 1024.87, 697.04 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.43 (d, J = 7.4 Hz, 2H), 7.36 (t, J = 7.4 Hz, 2H), 7.30 (t, J = 7.3 Hz, 1H), 6.95 (d, J = 1.4 Hz, 1H), 6.89−6.84 (m, 2H), 5.15 (s, 2H), 4.88−4.78 (m, 1H), 3.90 (s, 3H), 3.20 (q, J = 3.0 Hz, 1H), 2.94 (dd, J = 5.0, 2.7 Hz, 1H), 2.77 (dd, J = 4.9, 4.1 Hz, 1H), 2.34 (d, J = 2.2 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.8, 148.1, 137.0, 132.6, 128.5, 127.8, 127.2, 118.7, 113.9, 110.1, 71.0, 70.7, 56.0, 55.0, 43.7. HRMS (DART-TOF): calcd for $C_{17}H_{17}O_3^+$ $(M - OH)^+$, 269.11722; found, 269.11592. $[\alpha]_D^{25}$ +48.3 (c 1.00, $CHCl_3$).

The opposite enantiomer, (*R*)-(4-(benzyloxy)-3-methoxyphenyl)-((*S*)-oxiran-2-yl)methanol, provides a specific rotation of $[\alpha]_D^{25}$ −48.3 (c 1.00, $CHCl_3$).

*(S)-(4-(Benzyloxy)phenyl)((R)-oxiran-2-yl)methanol (**4b**).* Following the general procedure outlined above for compound **4a**, 1-(4-(benzyloxy)phenyl)prop-2-en-1-ol (**3b**) (8.0 g, 33.3 mmol) was converted to yield 4.0 g of the asymmetric epoxide **4b** (47%) as a light yellow solid. Mp: 50−52 °C. IR (neat): 3433.21, 1610.91, 1511.93, 1241.98, 1024.59, 698.37 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.30 (d, J = 7.4 Hz, 2H), 7.26 (t, J = 7.4 Hz, 2H), 7.19 (dd, J = 16.3, 7.9 Hz, 3H), 6.85 (d, J = 8.7 Hz, 2H), 4.93 (s, 2H), 4.66 (s, 1H), 3.03 (q, J = 3.2 Hz, 1H), 2.79 (dd, J = 5.1, 2.8 Hz, 1H), 2.62−2.59 (m, 1H), 2.56 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.8, 136.9, 128.6, 128.0, 127.8, 127.4, 115.0, 70.5, 70.0, 55.0, 43.6. HRMS (DART-TOF): calcd for $C_{16}H_{15}O_2^+$ $(M - OH)^+$, 239.10666; found, 239.10641. $[\alpha]_D^{25}$ +64.0 (c 1.00, $CHCl_3$).

The opposite enantiomer, (*R*)-(4-(benzyloxy) phenyl)((*S*)-oxiran-2-yl)methanol, provides a specific rotation of $[\alpha]_D^{25}$ −62.3 (c 1.00, $CHCl_3$).

*(S)-(4-(Benzyloxy)-3,5-dimethoxyphenyl)((R)-oxiran-2-yl)-methanol (**4c**).* Following the general procedure outlined above for compound **4a**, 1-(4-(benzyloxy)-3,5-dimethoxyphenyl)prop-2-en-1-ol (**3c**)(10.0 g, 33.32 mmol) was converted to yield 3.8 g of the asymmetric epoxide **4c** (36.1%) as a colorless oil. IR (neat): 3441.27, 2938.9, 1591.6, 1505.65, 1328.53, 1125, 783.04, 697.42 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.50 (d, J = 7.0 Hz, 2H), 7.34 (t, J = 7.3 Hz, 2H), 7.29 (t, J = 7.3 Hz, 1H), 6.62 (s, 2H), 5.00 (s, 2H), 4.85 (d, J = 3.0 Hz, 1H), 3.24 (q, J = 3.2 Hz, 1H), 2.96 (dd, J = 5.0, 2.7 Hz, 1H), 2.82−2.78 (m, 1H), 2.20 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.7, 137.8, 136.8, 135.3, 128.4, 128.1, 127.8, 103.4, 75.0, 71.2, 56.1, 55.0, 43.8. HRMS (DART-TOF): calcd for $C_{18}H_{21}O_5^+$ $(M + H)^+$, 317.13835; found, 317.13809. $[\alpha]_D^{25}$ +18.5 (c 1.00, $CHCl_3$).

The opposite enantiomer, (*R*)-(4-(benzyloxy)-3,5-dimethoxy-phenyl)((*S*)-oxiran-2-yl)methanol, provides a specific rotation of $[\alpha]_D^{25}$ −15.9 (c 1.00, $CHCl_3$).

*((S)-(4-(Benzyloxy)-3-methoxyphenyl)((R)-oxiran-2-yl)methoxy)-(tert-butyl)-dimethylsilane (**6a**).* To a stirred solution of the asymmetric epoxy alcohol **4a** (3.5 g, 12.23 mmol) dissolved in dry CH_2Cl_2, was added TBSCl (5.53 g, 36.7 mmol), imidazole (5.0 g, 73.4 mmol), and a catalytic amount of DMAP. The resulting solution was stirred for 3 h at rt. After 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 (2 × 100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The crude compound was purified by column chromatography using hexane/EtOAc (9:1) to afford the protected asymmetric epoxide **6a** (5.0 g, 12.0 mmol, 98.1%) as a light yellow oil. IR (neat) 2953.61, 2856.75, 1683.03, 1593.11, 1513.29, 1226.43, 1079.82, 696.05 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.49−7.43 (m, 2H), 7.38 (td, J = 6.7, 6.3, 1.6 Hz, 2H), 7.34−7.28 (m, 1H), 6.99 (d, J = 1.8 Hz, 1H), 6.89 (d, J = 8.2 Hz, 1H), 6.85 (dd, J = 8.2, 1.8 Hz, 1H), 5.16 (s, 2H), 4.67 (d, J = 3.7 Hz, 1H), 3.91 (s, 3H), 3.05 (td, J = 3.8, 2.6 Hz, 1H), 2.84 (dd, J = 5.6, 2.6 Hz, 1H), 2.71 (dd, J = 5.6, 3.9 Hz, 1H), 0.92 (s, 9H), 0.10 (s, 3H), 0.00 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.6, 147.7, 137.2, 134.7, 128.5, 127.8, 127.3, 118.3, 113.7, 109.8, 72.9, 71.1, 55.9, 44.3, 25.7, 18.3, −4.9. HRMS (DART-TOF): calcd for $C_{17}H_{17}O_3^+$ $(M - OTBS)^+$, 269.11722; found, 269.11594. $[\alpha]_D^{25}$ +41.9 (c 1.00, $CHCl_3$).

The opposite enantiomer (*R*)-(4-(benzyloxy)-3-methoxyphenyl)-((*S*)-oxiran-2-yl)methoxy)(*tert*-butyl)dimethylsilane, provides a specific rotation of $[\alpha]_D^{25}$ −38.0 (c 1.00, $CHCl_3$).

*((S)-(4-(Benzyloxy)phenyl)((R)-oxiran-2-yl)methoxy)(tert-butyl)-dimethylsilane (**6b**).* Following the general procedure outlined above

DOI: 10.1021/jo502685k
J. Org. Chem. 2015, 80, 1771−1780

for compound **6a**, (*S*)-(4-(benzyloxy)phenyl)((*R*)-oxiran-2-yl)-methanol (**4b**)(3.7 g, 14.44 mmol) was converted to yield 5.0 g of the protected asymmetric epoxy alcohol **6b** (93.5%) as a light yellow oil. IR (neat) 2954.85, 2856.55, 1761.13, 1611.07, 1510.55, 1249.89, 1002.58, 696.21 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.48 (d, J = 8.8 Hz, 2H), 7.42 (t, J = 7.4 Hz, 2H), 7.36 (t, J = 7.2 Hz, 1H), 7.33 (d, J = 8.5 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 5.09 (s, 2H), 4.72 (d, J = 3.5 Hz, 1H), 3.09−3.04 (m, 1H), 2.87 (dd, J = 5.6, 2.6 Hz, 1H), 2.73 (dd, J = 5.6, 3.9 Hz, 1H), 0.92 (s, 10H), 0.11 (s, 3H), −0.00 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.4, 137.0, 133.9, 128.6, 128.0, 127.51, 127.47, 114.6, 72.7, 70.0, 56.0, 44.1, 25.8, 18.3, −4.9. HRMS (DART-TOF): calcd for $C_{16}H_{15}O_2^+$ (M − OTBS)$^+$, 239.10666; found, 239.10706. $[\alpha]_D^{25}$ +56.2 (c 1.00, $CHCl_3$).

The opposite enantiomer, ((*R*)-(4-(benzyloxy)phenyl)((*S*)-oxiran-2-yl)methoxy)(*tert*-butyl) dimethylsilane, provides a specific rotation of $[\alpha]_D^{25}$ −53.5 (c 1.00, $CHCl_3$).

*((R)-(4-(Benzyloxy)-3,5-dimethoxyphenyl)((S)-oxiran-2-yl)-methoxy)(tertbutyl) dimethylsilane (**6c**).* Following the general procedure outlined above for compound **6a**, (*S*)-(4-(benzyloxy)-3,5-dimethoxyphenyl)((*R*)-oxiran-2-yl)methanol (**4c**) (1.4 g, 4.43 mmol) was converted to yield 1.85 g of the protected asymmetric epoxy alcohol **6c** (97%) as a light yellow oil. IR (neat): 2953.92, 2856.12, 1592.19, 1461.66, 1251.02, 862.87, 697.38, 670.95 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.45 (d, J = 6.9 Hz, 2H), 7.30 (t, J = 7.2 Hz, 2H), 7.25 (d, J = 7.2 Hz, 1H), 6.57 (s, 2H), 4.97 (s, 2H), 4.56 (d, J = 3.9 Hz, 1H), 3.78 (s, 6H), 3.05−2.99 (m, 1H), 2.79 (dd, J = 5.5, 2.6 Hz, 1H), 2.69 (dd, J = 5.5, 3.8 Hz, 1H), 0.87 (s, 9H), 0.04 (s, 3H), −0.05 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.4, 137.9, 137.4, 136.2, 128.4, 128.1, 127.7, 103.0, 75.0, 73.4, 56.1, 44.4, 25.7, 18.3, −3.6, −4.9, −5.0. HRMS (DART-TOF): calcd for $C_{24}H_{35}O_5Si^+$ (M + H)$^+$, 431.22438; found, 431.22608. $[\alpha]_D^{25}$ +47.3 (c 1.00, $CHCl_3$).

The opposite enantiomer, ((*S*)-(4-(benzyloxy)-3,5-dimethoxyphenyl)((*R*)-oxiran-2-yl)methoxy)(*tert*-butyl)dimethylsilane, provides a specific rotation of $[\alpha]_D^{25}$ −43.5 (c 1.00, $CHCl_3$).

*(2R,3S)-3-(4-(Benzyloxy)-3-methoxyphenyl)-3-((tert-butyldimethylsilyl)oxy)propane-1,2-diol (**7a**).* Commercially available (*R*,*R*)-(−)-*N*,*N*′-Bis(3,5-di*tert*-butylsalicylidene)-1,2-cyclohexane-diaminocobalt(II) (1g, 1.66 mmol) was dissolved in toluene and cooled to 0 °C. To this solution, AcOH (1.9 mL, 33 mmol) was added dropwise and the resulting suspension was stirred at rt in open air for 45 min. The color of the solution changed from red to brown, indicating complete conversion of the catalyst from Co(II) to the active Co(III) complex. The solvent was evaporated under vacuum to provide the (*R*,*R*)-salen-Co(III)OAc as a brown solid that was used in the next step without further purification. To a stirred solution of ((*S*)-(4-(benzyloxy)-3-methoxyphenyl)((*R*)-oxiran-2-yl)methoxy)(*tert*-butyl)-dimethylsilane (**6a**) (3.0 g, 7.5 mmol) dissolved in THF at 0 °C was added (*R*,*R*)-salen-Co(III)OAc (0.15 g, 0.23 mmol) followed by the dropwise addition of water (0.2 mL, 11.25 mmol). The reaction was warmed to rt and stirred for 24 h. After consumption of the starting material, as monitored on TLC, the organic phase was washed with water (2 × 50 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude compound was purified via column chromatography using hexane/EtOAc (7:3) to afford the asymmetric diol **7a** (2.84 g, 6.78 mmol, 90.5%) as a yellow oil. IR (neat): 3406.3, 2929.04, 2856.23, 1511.79, 1258.96, 1137.9, 836.93, 696.08 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.53 (d, J = 7.3 Hz, 2H), 7.44 (t, J = 7.2 Hz, 2H), 7.38 (t, J = 7.1 Hz, 1H), 7.08 (s, 1H), 6.99−6.85 (m, 2H), 5.18 (s, 2H), 4.72 (d, J = 5.1 Hz, 1H), 3.95 (s, 3H), 3.87−3.75 (m, 3H), 3.31 (s, 1H), 3.11 (s, 1H), 1.04 (s, 9H), 0.20 (s, 3H), −0.00 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.7, 147.8, 137.2, 135.0, 128.5, 127.9, 127.5, 119.3, 113.8, 110.6, 76.4, 76.1, 71.1, 63.2, 56.0, 25.9, 18.2, −4.5, −5.0. HRMS (DART-TOF): calcd for $C_{17}H_{19}O_4^+$ (M − OTBS)$^+$, 287.12779; found, 287.12785. $[\alpha]_D^{25}$ +55.0 (c 1.00, $CHCl_3$).

The opposite enantiomer, (2*S*,3*R*)-3-(4-(benzyloxy)-3-methoxyphenyl)-3-((*tert*-butyldimethylsilyl)oxy) propane-1,2-diol, provides a specific rotation of $[\alpha]_D^{25}$ −58.0 (c 1.00, $CHCl_3$).

*(2R,3S)-3-(4-(Benzyloxy)phenyl)-3-((tert-butyldimethylsilyl)oxy)-propane-1,2-diol (**7b**).* Following the general procedure outlined above for compound **7a**, ((*S*)-(4-(benzyloxy)phenyl)((*R*)-oxiran-2-yl)methoxy)(*tert*-butyl)dimethylsilane (**6b**) (4.1 g, 11.07 mmol) was converted to yield 3.85 g of the asymmetric diol **7b** (89.6%) as a light yellow oil. IR (neat): 3420.43, 2953.5, 2928.59, 1511.17, 1258.05, 1077.5, 1033.85, 695.72 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.58 (d, J = 7.1 Hz, 2H), 7.53 (t, J = 7.4 Hz, 2H), 7.48 (t, J = 7.2 Hz, 1H), 7.39 (d, J = 7.4 Hz, 2H), 7.10 (d, J = 8.7 Hz, 2H), 5.20 (s, 2H), 4.85 (d, J = 5.2 Hz, 1H), 3.82 (d, J = 22.0 Hz, 3H), 2.49 (d, J = 34.7 Hz, 2H), 1.04 (s, 9H), 0.21 (s, 3H), −0.00 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.5, 128.6, 128.0, 127.8, 127.5, 114.7, 75.5, 70.0, 63.0, 25.8, 18.1, −4.7, −5.2. HRMS (DART-TOF): calcd for $C_{16}H_{17}O_3^+$ (M − OTBS)$^+$, 257.11722; found, 257.11606. $[\alpha]_D^{25}$ +54.3 (c 1.00, $CHCl_3$).

The opposite enantiomer, (2*S*,3*R*)-3-(4-(benzyloxy)phenyl)-3-((*tert*-butyldimethylsilyl)oxy)propane-1,2-diol, provides a specific rotation of $[\alpha]_D^{25}$ −56.9 (c 1.00, $CHCl_3$).

*(2R,3S)-3-(4-(Benzyloxy)-3,5-dimethoxyphenyl)-3-((tert-butyldimethylsilyl)oxy) propane-1,2-diol (**7c**).* Following the general procedure outlined above for compound **7a**, ((*R*)-(4-(benzyloxy)-3,5-dimethoxyphenyl)((*S*)-oxiran-2-yl)methoxy)(*tert*-butyl)dimethylsilane (**6c**) (1.5 g, 3.5 mmol) was converted to yield 1.4 g of the asymmetric diol **7c** (88.6%) as a yellow oil. IR (neat): 3434.72, 2929.08, 2856.9, 1592.71, 1461.43, 1234.31, 1080.5, 696.35 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.57 (d, J = 6.9 Hz, 2H), 7.43 (dt, J = 14.8, 7.0 Hz, 3H), 6.66 (s, 2H), 5.13 (s, 2H), 4.79 (s, 1H), 3.92 (s, 6H), 3.82 (d, J = 32.8 Hz, 3H), 2.40 (s, 2H), 1.03 (s, 10H), 0.20 (s, 3H), −0.00 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.5, 137.7, 136.9, 136.0, 128.5, 128.0, 127.8, 103.4, 75.4, 74.9, 62.9, 56.0, 25.7, 18.1, −4.7, −5.2. HRMS (DART-TOF): calcd for $C_{18}H_{21}O_5^+$ (M − OTBS)$^+$, 317.13835; found, 317.13692. $[\alpha]_D^{25}$ +55.3 (c 1.00, $CHCl_3$).

The opposite enantiomer, (2*S*,3*R*)-3-(4-(benzyloxy)-3,5-dimethoxyphenyl)-3-((*tert*-butyldimethyl silyl)oxy)propane-1,2-diol, provides a specific rotation of $[\alpha]_D^{25}$ −58.4 (c 1.00, $CHCl_3$).

*(5S,6R)-5-(4-(Benzyloxy)-3-methoxyphenyl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-6-ol (**8a**).* To a stirred solution of asymmetric diol **7a** (3.0 g, 7.1 mmol) in dry CH_2Cl_2 was added TBSCl (1.2 g, 7.9 mmol), imidazole (0.58 g, 8.6 mmol), and a catalytic amount of DMAP. The resulting solution was stirred at rt for 2 h. After complete consumption of the starting material, as monitored on 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 using hexane/EtOAc (9:1) to afford the protected asymmetric alcohol **8a** (3.41 g, 6.8 mmol, 96%) as a colorless oil. IR (neat): 3389.2, 2953.74, 2928.47, 2884.07, 1593.59, 1511.49, 1463.32, 1254.58, 1077.1, 834.85, 695.85 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.48−7.41 (m, 2H), 7.40−7.33 (m, 2H), 7.33−7.27 (m, 1H), 6.95 (d, J = 1.8 Hz, 1H), 6.84 (d, J = 8.2 Hz, 1H), 6.80 (dd, J = 8.2, 1.8 Hz, 1H), 5.14 (s, 2H), 4.58 (d, J = 5.7 Hz, 1H), 3.88 (s, 3H), 3.76−3.63 (m, 3H), 2.34−2.30 (m, 1H), 0.91 (s, 8H), 0.88 (s, 8H), 0.07 (d, J = 4.2 Hz, 5H), 0.04 (s, 3H), −0.16 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.4, 147.6, 137.2, 134.9, 128.5, 127.8, 127.3, 119.4, 113.5, 110.4, 76.0, 75.1, 71.1, 63.7, 55.9, 25.9, 18.3, −4.6, −5.1, −5.4. HRMS (DART-TOF): calcd for $C_{23}H_{33}O_4Si^+$ (M − OTBS)$^+$, 401.21426; found, 401.21422. $[\alpha]_D^{25}$ +30.0 (c 1.00, $CHCl_3$).

The opposite enantiomer, (5*R*,6*S*)-5-(4-(benzyloxy)-3-methoxyphenyl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-6-ol, provides a specific rotation of $[\alpha]_D^{25}$ −28.5 (c 1.00, $CHCl_3$).

*(5S,6R)-5-(4-(Benzyloxy)phenyl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-6-ol (**8b**).* Following the general procedure outlined above for compound **8a**, (2*R*,3*S*)-3-(4-(benzyloxy)phenyl)-3-((*tert*-butyl-dimethylsilyl)oxy)propane-1,2-diol (**7b**) (4.3 g, 11.07 mmol) was converted to yield 5.74 g of the protected asymmetric alcohol **8b** (97.5%) as a colorless oil. IR (neat): 3361.91, 2928.59, 2856.66, 1610.56, 1510.61, 1249.83, 1102.25, 833.79, 621.71 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.61 (d, J = 7.3 Hz, 2H), 7.55 (t, J = 7.6 Hz, 2H), 7.49 (t, J = 7.2 Hz, 1H), 7.44 (d, J = 8.5 Hz, 2H), 7.12 (d, J = 8.6 Hz, 2H), 5.22 (s, 2H), 4.77 (d, J = 5.5 Hz, 1H), 3.86 (s, 3H), 2.51 (d, J = 3.3 Hz, 1H), 1.08 (s, 9H), 1.05 (s, 9H), 0.24 (d, J = 4.2 Hz, 6H), 0.21 (s, 3H), −0.00 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ

DOI: 10.1021/jo502685k
J. Org. Chem. 2015, 80, 1771−1780

158.3, 137.1, 134.1, 128.5, 128.2, 127.9, 127.5, 127.5, 114.4, 76.1, 74.9, 70.0, 63.7, 25.9, 25.8, 18.3, 18.1, −4.6, −5.1, −5.3. HRMS (DART-TOF): calcd for $C_{22}H_{31}O_3Si^+$ (M − OTBS)$^+$, 371.20370; found, 371.20343. $[\alpha]_D^{25}$ +31.2 (*c* 1.00, $CHCl_3$).

The opposite enantiomer, (5*R*,6*S*)-5-(4-(benzyloxy)phenyl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-6-ol, provides a specific rotation of $[\alpha]_D^{25}$ −30.7 (*c* 1.00, $CHCl_3$).

(5S,6R)-5-(4-(Benzyloxy)-3,5-dimethoxyphenyl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-6-ol (**8c**). Following the general procedure outlined above for compound **8a**, (2*R*,3*S*)-3-(4-(benzyloxy)-3,5-dimethoxyphenyl)-3-((*tert*-butyldimethylsilyl)oxy)-propane-1,2-diol (**7c**) (1.4 g, 3.1 mmol) was converted to yield 1.68 g of the protected asymmetric alcohol **8c** (96.7%) as a colorless oil. IR (neat): 3517.93, 2953.75, 2928.51, 2856.42, 1462.2, 1251.07, 834.83, 671.17 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61 (d, *J* = 6.8 Hz, 2H), 7.47 (t, *J* = 7.2 Hz, 2H), 7.44−7.40 (m, 1H), 6.72 (s, 2H), 5.16 (s, 2H), 4.71 (d, *J* = 5.5 Hz, 1H), 3.95 (s, 6H), 3.88−3.79 (m, 3H), 1.06 (s, 9H), 1.03 (s, 9H), 0.22 (d, *J* = 3.9 Hz, 6H), 0.19 (s, 3H), −0.00 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.2, 137.9, 137.5, 135.9, 128.5, 128.0, 127.7, 103.9, 76.0, 75.4, 74.9, 63.6, 56.0, 25.9, 18.2, −4.7, −5.1, −5.3. HRMS (DART-TOF): calcd for $C_{24}H_{35}O_5Si^+$ (M − OTBS)$^+$, 431.22483; found, 431.22634. $[\alpha]_D^{25}$ +25.7 (*c* 1.00, $CHCl_3$).

The opposite enantiomer, (5*R*,6*S*)-5-(4-(benzyloxy)-3,5-dimethoxyphenyl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-6-ol, provides a specific rotation of $[\alpha]_D^{25}$ −26.8 (*c* 1.00, $CHCl_3$).

4-(((5S,6S)-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 (**9a**). To a solution of THF containing PPh_3 (2.8 g, 10.8 mmol) was added diisopropylazodicarboxylate (2.2 mL, 10.8 mmol), and the mixture was stirred for 30 min. This was followed by the simultaneous addition of 4-hydroxy-3-methoxybenzaldehyde (1.6 g, 10.8 mmol) and the alcohol intermediate **8a** (2.3 g, 4.3 mmol). The reaction mixture was stirred at rt for 1 h before being refluxed for a further 3 h. After 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. The crude compound was purified by column chromatography using hexane/acetone (9:1) to afford the intermediate **9a** (1.9 g, 2.8 mmol, 65%) as a light yellow oil. IR (neat): 2953.02, 2928.77, 2855.95, 1683.97, 1584.92, 1259.2, 1035.52, 835.42, 696.52 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.83 (s, 1H), 7.44 (d, *J* = 7.3 Hz, 2H), 7.40−7.34 (m, 4H), 7.30 (t, *J* = 7.3 Hz, 1H), 7.13 (d, *J* = 8.1 Hz, 1H), 7.05 (d, *J* = 1.4 Hz, 1H), 6.89−6.83 (m, 2H), 5.14 (s, 2H), 4.92 (d, *J* = 6.5 Hz, 1H), 4.48 (td, *J* = 6.1, 2.9 Hz, 1H), 3.88 (s, 6H), 3.70 (dd, *J* = 11.3, 2.9 Hz, 1H), 3.51 (dd, *J* = 11.3, 5.8 Hz, 1H), 0.81 (s, 9H), 0.77 (s, 9H), −0.05 (d, *J* = 8.4 Hz, 6H), −0.11 (d, *J* = 4.5 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.9, 154.7, 150.2, 149.4, 147.7, 137.1, 134.2, 129.7, 128.5, 127.8, 127.3, 126.4, 119.1, 113.7, 113.5, 110.7, 109.6, 84.5, 74.3, 71.1, 62.4, 55.9, 55.6, 25.7, 25.6, 18.13, 18.08, −5.0, −5.2, −5.60, −5.62. HRMS (DART-TOF): calcd for $C_{37}H_{55}O_7Si_2^+$ (M + H)$^+$, 667.34808; found, 667.34567. $[\alpha]_D^{25}$ +37.8 (*c* 1.00, $CHCl_3$).

The opposite enantiomer, 4-(((5*R*,6*R*)-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, provides a specific rotation of $[\alpha]_D^{25}$ −38.6 (*c* 1.00, $CHCl_3$).

4-(((5S,6S)-5-(4-(Benzyloxy)phenyl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-6-yl)oxy)-3-methoxybenzaldehyde (**9b**). Following the general procedure outlined above for compound **9a**, (5*S*,6*R*)-5-(4-(benzyloxy)phenyl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-6-ol (**8b**) (2.6 g, 5.2 mmol) was converted to yield 2.1 g of the intermediate **9b** (65%) as a light yellow oil. IR (neat): 2953.25, 2928.28, 2855.97, 1683.92, 1584.61, 2505.51, 1236.11, 1035.11, 864.3 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.82 (s, 1H), 7.43 (d, *J* = 7.3 Hz, 2H), 7.41−7.35 (m, 4H), 7.33 (d, *J* = 8.6 Hz, 3H), 7.15 (d, *J* = 8.0 Hz, 1H), 6.94 (d, *J* = 8.7 Hz, 2H), 5.05 (s, 2H), 4.92 (d, *J* = 6.9 Hz, 1H), 4.50 (td, *J* = 6.4, 2.8 Hz, 1H), 3.88 (s, 3H), 3.67 (dd, *J* = 11.3, 2.8 Hz, 1H), 3.50 (dd, *J* = 11.3, 5.9 Hz, 1H), 0.79 (s, 9H), 0.74 (s, 9H), −0.05 (s, 3H), −0.08 (s, 3H), −0.11 (s, 3H), −0.14 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 191.0, 158.4, 155.0, 150.3, 137.0, 133.5, 129.7, 128.6, 128.2, 128.0, 127.5, 126.4, 114.5, 113.9, 109.7, 84.8, 74.4, 70.0, 62.5, 55.7, 25.7, 25.6, 18.13, 18.05, −5.0, −5.2, −5.6. HRMS (DART-TOF): calcd for $C_{36}H_{53}O_6Si_2^+$ (M + H)$^+$, 637.33752; found, 637.33654. $[\alpha]_D^{25}$ +18.8 (*c* 1.00, $CHCl_3$).

The opposite enantiomer, 4-(((5*R*,6*R*)-5-(4-(benzyloxy)phenyl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-6-yl)oxy)-3-methoxybenzaldehyde, provides a specific rotation of $[\alpha]_D^{25}$ −17.4 (*c* 1.00, $CHCl_3$).

4-(((5S,6S)-5-(4-(Benzyloxy)-3,5-dimethoxyphenyl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-6-yl)oxy)-3-methoxybenzaldehyde (**9c**). Following the general procedure outlined above for compound **9a**, (5*S*,6*R*)-5-(4-(benzyloxy)-3,5-dimethoxyphenyl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disila-undecan-6-ol (**8c**) (1.3 g, 2.3 mmol) was converted to yield 1.04 g of the intermediate **9c** (65%) as a light yellow oil. IR (neat): 2952.25, 2929.26, 2855.95, 1684.02, 1505.49, 1463.28, 1268.19, 697.2 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.92 (s, 1H), 7.54 (d, *J* = 6.7 Hz, 2H), 7.49−7.46 (m, 2H), 7.43−7.35 (m, 3H), 7.21 (d, *J* = 7.9 Hz, 1H), 6.77 (s, 2H), 5.11 (s, 2H), 5.01 (d, *J* = 6.4 Hz, 1H), 4.58−4.55 (m, 1H), 3.97 (s, 3H), 3.89 (s, 6H), 3.85−3.82 (m, 1H), 3.61 (dd, *J* = 11.4, 5.6 Hz, 1H), 0.90 (d, *J* = 16.0 Hz, 20H), 0.06 (d, *J* = 10.1 Hz, 6H), 0.00 (d, *J* = 3.6 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.9, 154.5, 153.2, 150.2, 137.7, 136.7, 136.0, 129.8, 128.5, 128.0, 127.7, 126.4, 113.5, 109.6, 104.0, 84.2, 74.8, 74.4, 62.3, 56.0, 55.6, 25.7, 25.6, 18.2, 18.1, −5.0, −5.2, −5.58, −5.61. HRMS (DART-TOF): calcd for $C_{32}H_{41}O_7Si^+$ (M − OTBS)$^+$, 565.26161; found, 565.26184. $[\alpha]_D^{25}$ +29.5 (*c* 1.00, $CHCl_3$).

The opposite enantiomer, 4-(((5*R*,6*R*)-5-(4-(benzyloxy)-3,5-dimethoxyphenyl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-6-yl)oxy)-3-methoxybenzaldehyde, provides a specific rotation of $[\alpha]_D^{25}$ −32.7 (*c* 1.00, $CHCl_3$).

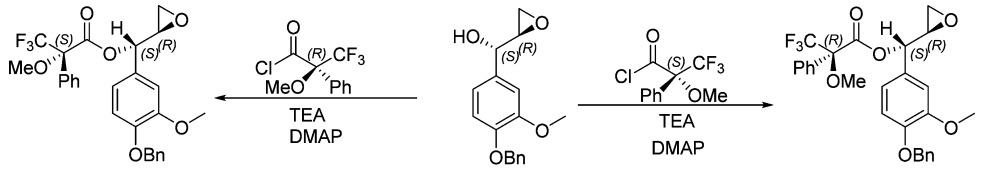
4-(((1S,2S)-1-(4-(Benzyloxy)-3-methoxyphenyl)-1,3-dihydroxypropan-2-yl)oxy)-3-methoxybenzaldehyde (**10a**). To a 100 mL round-bottom flask was added the TBS-protected intermediate **9a** (1.4 g, 2.1 mmol) and dissolved in anhydrous THF. The flask was cooled to 0 °C, and *t*-butylammonium fluoride (TBAF) (5.3 mL, 5.3 mmol) was added to the reaction mixture. The resulting solution was warmed to rt and stirred for 2 h. After complete consumption of the starting material, as monitored on 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 using DCM/EtOAc (3:2) to afford the asymmetric diol intermediate **10a** (0.78 g, 1.78 mmol, 85.0%) as a white solid. Mp: 117−118 °C. IR (neat): 3435.15, 2935.72, 2835.93, 1677.69, 1593.32, 1504.38, 1262.33, 1134.84, 652.27 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.78 (s, 1H), 7.34 (dd, *J* = 7.8, 5.7 Hz, 4H), 7.28 (t, *J* = 7.4 Hz, 2H), 7.22 (t, *J* = 7.2 Hz, 1H), 7.12 (d, *J* = 8.1 Hz, 1H), 6.92 (d, *J* = 1.4 Hz, 1H), 6.82−6.76 (m, 2H), 5.06 (s, 2H), 4.89 (d, *J* = 7.3 Hz, 1H), 4.23 (dt, *J* = 7.8, 4.4 Hz, 1H), 3.85 (s, 3H), 3.79 (s, 3H), 3.61 (dd, *J* = 12.3, 3.2 Hz, 1H), 3.53 (dd, *J* = 12.3, 4.6 Hz, 1H), 3.28 (s, 1H), 2.40 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.8, 153.4, 151.2, 149.9, 148.2, 137.0, 132.4, 131.8, 128.5, 127.9, 127.2, 126.3, 119.3, 118.0, 113.9, 110.3, 110.1, 87.8, 73.8, 71.0, 61.5, 56.0. HRMS (DART-TOF): calcd for $C_{25}H_{27}O_7^+$ (M + H)$^+$, 439.17513; found, 439.17461. $[\alpha]_D^{25}$ +88.8 (*c* 1.00, $CHCl_3$).

The opposite enantiomer, 4-(((1*R*,2*R*)-1-(4-(benzyloxy)-3-methoxyphenyl)-1,3-dihydroxypropan-2-yl)oxy)-3-methoxybenzaldehyde, provides a specific rotation of $[\alpha]_D^{25}$ −85.2 (*c* 1.00, $CHCl_3$).

4-(((1S,2S)-1-(4-(Benzyloxy)phenyl)-1,3-dihydroxypropan-2-yl)oxy)-3-methoxy-benzaldehyde (**10b**). Following the general procedure outlined above for compound **10a**, 4-(((5*S*,6*S*)-5-(4-(benzyloxy)-phenyl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-6-yl)-oxy)-3-methoxybenzaldehyde (**9b**) (1.7 g, 2.7 mmol) was converted to yield 0.98 g of the intermediate **10b** (89%) as a colorless oil which solidifies under vacuum. IR (neat): 3431.3, 2928.17, 1682.84, 1585.12, 1267.3, 1135.35, 1025, 794.92 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.78 (s, 1H), 7.34 (dd, *J* = 8.3, 3.3 Hz, 4H), 7.30 (t, *J* = 7.4 Hz, 2H), 7.28−7.23 (m, 3H), 7.14 (d, *J* = 8.1 Hz, 1H), 6.89 (d, *J* = 8.7 Hz, 2H), 4.98 (s, 2H), 4.91 (d, *J* = 7.6 Hz, 1H), 4.26−4.22 (m, 1H), 3.85 (s, 3H), 3.60 (dd, *J* = 12.3, 3.1 Hz, 1H), 3.51 (dd, *J* = 12.3, 4.5 Hz, 1H),

DOI: 10.1021/jo502685k
J. Org. Chem. 2015, 80, 1771−1780

Scheme 4. Mosher Ester Analysis of Compound 4a



3.25 (s, 1H), 2.40 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.9, 158.8, 153.5, 151.1, 136.8, 131.8, 131.6, 128.6, 128.2, 128.00, 127.4, 126.3, 117.8, 115.0, 110.1, 87.6, 73.5, 70.0, 61.4, 56.0. HRMS (DART-TOF): calcd for $C_{24}H_{25}O_6^+$ $(M + H)^+$, 409.16456; found, 409.16543. $[\alpha]_D^{25}$ +68.8 (*c* 1.00, $CHCl_3$).

The opposite enantiomer, 4-(((1*R*,2*R*)-1-(4-(benzyloxy)phenyl)-1,3-dihydroxypropan-2-yl)oxy)-3-methoxybenzaldehyde, provides a specific rotation of $[\alpha]_D^{25}$ −69.7 (*c* 1.00, $CHCl_3$).

*4-(((1S,2S)-1-(4-(Benzyloxy)-3,5-dimethoxyphenyl)-1,3-dihydroxypropan-2-yl)oxy)-3-methoxybenzaldehyde (**10c**).* Following the general procedure outlined above for compound **10a**, 4-(((5*S*,6*S*)-5-(4-(benzyloxy)-3,5-dimethoxyphenyl)-2,2,3,3,9,9,10,10-octa-methyl-4,8-dioxa-3,9-disilaundecan-6-yl)oxy)-3-methoxybenzaldehyde (**9c**) (1.0 g, 1.43 mmol) was converted to yield 0.57 g of the intermediate **10c** (85%) as a viscous oil. IR (neat): 3443.02, 2939.57, 2310.98, 1678.07, 1504.02, 1265.95, 735.42, 698.97 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.78 (s, 1H), 7.41−7.32 (m, 4H), 7.25 (t, *J* = 7.2 Hz, 2H), 7.22−7.18 (m, 1H), 7.11 (d, *J* = 8.1 Hz, 1H), 6.57 (s, 2H), 4.91 (s, 2H), 4.89 (d, *J* = 7.1 Hz, 1H), 4.24 (dd, *J* = 7.1, 3.7 Hz, 1H), 3.86 (s, 3H), 3.73 (s, 6H), 3.65 (dd, *J* = 12.4, 3.6 Hz, 1H), 3.56 (dd, *J* = 12.4, 4.7 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.8, 153.7, 153.3, 151.2, 137.7, 136.8, 135.1, 131.8, 128.5, 128.1, 127.8, 126.3, 118.0, 110.1, 103.9, 87.6, 75.0, 74.1, 61.5, 56.2, 56.1. HRMS (DART-TOF): calcd for $C_{26}H_{29}O_8^+$ $(M + H)^+$, 469.18569; found, 469.18556. $[\alpha]_D^{25}$ +80.8 (*c* 1.00, $CHCl_3$).

The opposite enantiomer, 4-(((1*R*,2*R*)-1-(4-(benzyloxy)-3,5-dimethoxyphenyl)-1,3-dihydroxy-propan-2-yl)oxy)-3-methoxybenzaldehyde, provides a specific rotation of $[\alpha]_D^{25}$ −78.3 (*c* 1.00, $CHCl_3$).

*(1S,2S)-1-(4-Hydroxy-3-methoxyphenyl)-2-(2-methoxy-4-methylphenoxy)propane-1,3-diol (**11a**).* To a 100 mL round-bottom flask containing an asymmetric diol intermediate **10a** (0.7 g, 1.6 mmol) was added ethanol and 150 mg of Pd/C. Hydrogen gas was added via balloon, allowing slow diffusion into the solution while stirring gently for 3 h. After 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 under vacuum to provide the crude lignin model dimer that was purified by column chromatography using DCM/acetone (7:3) to afford the enantiomerically pure lignin model dimer **11a** as a clear viscous oil (0.5 g, 1.5 mmol, 94%). IR (neat): 3414.05, 1509.07, 1463.99, 1267.63, 1029.43, 815.53, 612.73 cm^{-1}. ^{1}H NMR (500 MHz, CD_3OD): δ 6.88 (d, *J* = 1.6 Hz, 1H), 6.81 (d, *J* = 8.2 Hz, 1H), 6.71 (dd, *J* = 8.1, 1.6 Hz, 1H), 6.66−6.60 (m, 2H), 6.51−6.46 (m, 1H), 4.75 (d, *J* = 6.2 Hz, 1H), 4.04 (q, *J* = 5.1 Hz, 1H), 3.63 (d, *J* = 6.0 Hz, 6H), 3.57 (dd, *J* = 12.0, 3.9 Hz, 1H), 3.31 (dd, *J* = 12.0, 5.1 Hz, 1H), 2.09 (s, 3H). ^{13}C NMR (125 MHz, CD_3OD): δ 150.2, 147.4, 145.8, 145.8, 132.5, 132.3, 121.3, 119.5, 118.3, 114.6, 113.1, 110.4, 86.5, 72.9, 60.5, 55.2, 55.0, 19.9. HRMS (DART-TOF): calcd for $C_{18}H_{21}O_5^+$ $(M - OH)^+$, 317.13835; found, 317.13864. $[\alpha]_D^{25}$ +70.5 (*c* 1.00, MeOH).

The opposite enantiomer, (1*R*,2*R*)-1-(4-hydroxy-3-methoxyphenyl)-2-(2-methoxy-4-methylphenoxy)propane-1,3-diol, provides a specific rotation of $[\alpha]_D^{25}$ −68.6 (*c* 1.00, MeOH).

*(1S,2S)-1-(4-Hydroxyphenyl)-2-(2-methoxy-4-methylphenoxy)-propane-1,3-diol (**11b**).* Following the general procedure outlined above for compound **11a**, 4-(((1*S*,2*S*)-1-(4-(benzyloxy)phenyl)-1,3-dihydroxy-propan-2-yl)oxy)-3-methoxybenzaldehyde (**10b**) (0.83 g, 2.03 mmol) was converted to yield 0.56 g of the intermediate **11b** (90%) as a white solid. Mp: 127−130 °C. IR (neat): 3421.3, 2924.85, 1260.05, 1026.45, 800.05 cm^{-1}. ^{1}H NMR (500 MHz, CD_3OD): δ 7.13 (d, *J* = 8.3 Hz, 2H), 6.85 (d, *J* = 8.1 Hz, 1H), 6.70 (s, 1H), 6.65 (d, *J* = 6.9 Hz, 2H), 6.56 (d, *J* = 10.0 Hz, 1H), 4.76 (d, *J* = 6.6 Hz, 1H), 4.05−4.00 (m, 1H), 3.56 (dd, *J* = 12.0, 3.8 Hz, 1H), 3.29 (dd, *J* = 12.0, 5.1 Hz, 1H), 2.16 (s, 3H). ^{13}C NMR (125 MHz, CD_3OD): δ 156.8, 150.3, 145.9, 132.5, 131.6, 128.0, 121.2, 118.7, 114.6, 113.1, 86.8, 72.8, 70.9, 60.4, 55.1, 19.7. HRMS (DART-TOF): calcd for $C_{17}H_{19}O_4^+$ $(M - OH)^+$, 287.12779; found, 287.12796. $[\alpha]_D^{25}$ +64.1 (*c* 1.00, MeOH).

The opposite enantiomer, (1*R*,2*R*)-1-(4-hydroxyphenyl)-2-(2-methoxy-4-methylphenoxy)propane-1,3-diol, provides a specific rotation of $[\alpha]_D^{25}$ −65.6 (*c* 1.00, MeOH).

*(1S,2S)-1-(4-Hydroxy-3,5-dimethoxyphenyl)-2-(2-methoxy-4-methylphenoxy) propane-1,3-diol (**11c**).* Following the general procedure outlined above for compound **11a**, 4-(((1*S*,2*S*)-1-(4-(benzyloxy)-3,5-dimethoxyphenyl)-1,3-dihydroxypropan-2-yl)oxy)-3-methoxybenzaldehyde (**10c**) (0.4 g, 0.85 mmol) was converted to yield 0.25 g of the intermediate **11c** (80%) as a viscous colorless oil. IR (neat): 3424.66, 2936.19, 2324.72, 1612.8, 1508.35, 1217.2, 1113.05, 650.55 cm^{-1}. ^{1}H NMR (500 MHz, CD_3OD): δ 6.81 (d, *J* = 8.2 Hz, 1H), 6.66 (d, *J* = 1.7 Hz, 1H), 6.60 (s, 2H), 6.55−6.50 (m, 1H), 4.76 (d, *J* = 5.7 Hz, 1H), 4.09 (q, *J* = 5.4 Hz, 1H), 3.68 (s, 3H), 3.67 (s, 6H), 3.61 (dd, *J* = 11.9, 4.1 Hz, 1H), 3.35 (dd, *J* = 11.9, 5.3 Hz, 1H), 2.13 (s, 3H). ^{13}C NMR (125 MHz, CD_3OD): δ 150.1, 147.6, 145.8, 134.6, 132.3, 131.6, 121.2, 118.0, 113.0, 104.1, 103.9, 86.1, 72.8, 60.5, 55.3, 55.1, 19.8. HRMS (DART-TOF): calcd for $C_{19}H_{23}O_6^+$ $(M - OH)^+$, 347.14891; found, 347.14947. $[\alpha]_D^{25}$ +74.2 (*c* 1.00, $CHCl_3$).

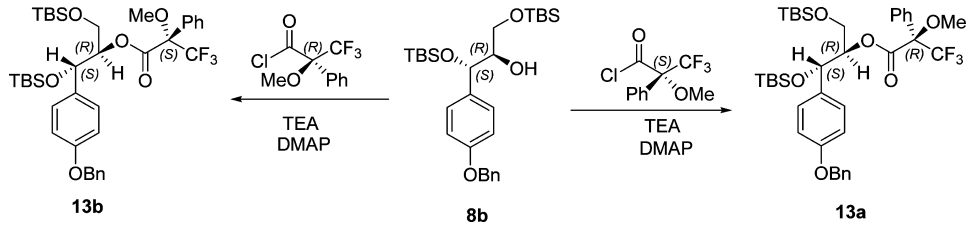
The opposite enantiomer, (1*R*,2*R*)-1-(4-hydroxy-3,5-dimethoxyphenyl)-2-(2-methoxy-4-methyl phenoxy)propane-1,3-diol, provides a specific rotation of $[\alpha]_D^{25}$ −74.5 (*c* 1.00, $CHCl_3$).

*(S)-(4-(Benzyloxy)-3-methoxyphenyl)((R)-oxiran-2-yl)methyl(R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (**12a**).* A stirred solution of asymmetric epoxy alcohol **4a** (0.026 g, 0.09 mmol) in dry DCM was charged into a round-bottom flask containing a stir bar. To this, TEA (0.02 mL, 0.14 mmol) and (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl chloride (0.025 g, 0.10 mmol) were added sequentially (see Scheme 4). A catalytic amount of DMAP was added, and the resulting solution was stirred for 3 h. After 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 × 100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The crude compound was purified by column chromatography using hexane/EtOAc (7:3) to afford the ester **12a** (0.035 g, 0.07 mmol, 78%) as a colorless oil. IR (neat): 2948.99, 1750.35, 1593.76, 1515.79, 1263.13, 1121.84, 716.72, 640.75 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (dd, *J* = 7.4, 3.4 Hz, 4H), 7.41−7.36 (m, 3H), 7.33 (t, *J* = 7.5 Hz, 3H), 6.94−6.88 (m, 3H), 6.07 (d, *J* = 3.7 Hz, 1H), 5.17 (s, 2H), 3.86 (s, 3H), 3.47 (s, 3H), 3.26−3.23 (m, 1H), 2.74 (dd, *J* = 5.1, 4.0 Hz, 1H), 2.66 (dd, *J* = 5.1, 2.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.5, 149.7, 148.8, 136.8, 132.1, 129.6, 128.6, 128.3, 127.9, 127.8, 127.4, 127.38, 127.2, 120.2, 113.7, 111.0, 75.3, 71.0, 56.0, 55.4, 52.5, 44.3. HRMS (DART-TOF): calcd for $C_{27}H_{26}F_3O_6^+$ $(M + H)^+$, 503.16760; found, 503.16844. $[\alpha]_D^{25}$ +18.0 (*c* 1.00, $CHCl_3$).

*(S)-(4-(Benzyloxy)-3-methoxyphenyl)((R)-oxiran-2-yl)methyl-(S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (**12b**).* Following the general procedure outlined above for compound **12a**, (*S*)-(4-(benzyloxy)-3-methoxyphenyl)((*R*)-oxiran-2-yl)methanol (**4a**) (0.04 g, 0.14 mmol) was converted to yield 0.053 g of the ester **12b** (75%) as a colorless oil. IR (neat) 2948.99, 1750.35, 1593.76, 1515.79, 1263.13, 1121.84, 716.72, 640.75 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$):

DOI: 10.1021/jo502685k
J. Org. Chem. 2015, 80, 1771−1780

Scheme 5. Mosher Ester Analysis of Compound 8b



δ 7.42 (t, J = 7.6 Hz, 4H), 7.37 (t, J = 7.3 Hz, 3H), 7.34−7.29 (m, 3H), 6.84−6.76 (m, 3H), 6.06 (d, J = 3.4 Hz, 1H), 5.15 (s, 2H), 3.76 (s, 3H), 3.55 (s, 3H), 3.30−3.26 (m, 1H), 2.79 (dd, J = 5.1, 4.0 Hz, 1H), 2.76 (dd, J = 5.2, 2.6 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.3, 149.6, 148.7, 136.8, 132.0, 129.6, 128.6, 128.3, 127.9, 127.7, 127.3, 127.2, 119.9, 113.5, 110.6, 75.2, 70.9, 55.8, 55.6, 52.6, 44.2. $[\alpha]_D^{25}$ +16.1 (c 1.00, $CHCl_3$). HRMS (DART-TOF): calcd for $C_{27}H_{26}F_3O_6^+$ $(M + H)^+$, 503.16760; found, 503.16826.

*(5S,6R)-5-(4-(Benzyloxy)phenyl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-6-yl-(R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (**13a**).* Following the general procedure outlined above for compound **12a**, (5*S*,6*R*)-5-(4-(benzyloxy)phenyl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-6-ol (**8b**) (0.08 g, 0.16 mmol) was converted to yield 0.09 g of the ester **13a** (75%) as a viscous and colorless oil (see Scheme 5). IR (neat): 2954.09, 2929.43, 2857.61, 1610.9, 1251.21, 836.25, 696.16 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 (d, J = 7.1 Hz, 2H), 7.37 (t, J = 7.4 Hz, 2H), 7.30 (dd, J = 16.9, 7.3 Hz, 2H), 7.23 (dt, J = 7.1, 3.2 Hz, 4H), 7.16 (d, J = 7.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 5.33−5.29 (m, 1H), 5.02 (s, 2H), 4.84 (d, J = 6.9 Hz, 1H), 3.80 (dd, J = 6.5, 4.8 Hz, 2H), 3.32 (s, 3H), 0.87 (s, 10H), 0.84 (s, 10H), 0.01 (s, 6H), −0.01 (s, 3H), −0.24 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.0, 158.6, 136.9, 132.7, 132.3, 129.2, 129.0, 128.6, 128.1, 128.0, 127.6, 127.5, 114.4, 80.1, 72.5, 70.0, 61.4, 55.1, 25.8, 25.7, 18.2, 18.1, −4.6, −5.2, −5.6, −5.7. HRMS (DART-TOF): calcd for $C_{32}H_{38}F_3O_5Si^+$ $(M - OTBS)^+$, 587.24351; found, 587.24371. $[\alpha]_D^{25}$ +19.2 (c 1.00, $CHCl_3$).

*(5S,6R)-5-(4-(Benzyloxy)phenyl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-6-yl-(S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (**13b**).* Following the general procedure outlined above for compound **12a**, (5*S*,6*R*)-5-(4-(benzyloxy)phenyl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-6-ol (**8b**) (0.08 g, 0.16 mmol) was converted to yield 0.08 g of the ester **13b** (70%) as a viscous colorless oil. IR (neat): 2954.09, 2929.43, 2857.61, 1610.9, 1251.21, 836.25, 696.16 cm^{-1}. ^{1}H NMR (500 MHz,$CDCl_3$): δ 7.43 (d, J = 8.4 Hz, 2H), 7.38 (t, J = 7.4 Hz, 2H), 7.35−7.27 (m, 4H), 7.26−7.24 (m, 2H), 7.10 (d, J = 8.6 Hz, 2H), 6.79 (d, J = 8.7 Hz, 2H), 5.34 (td, J = 6.7, 3.3 Hz, 1H), 5.01 (s, 2H), 4.68 (d, J = 6.7 Hz, 1H), 3.91 (dd, J = 11.3, 3.3 Hz, 1H), 3.84 (dd, J = 11.3, 6.8 Hz, 1H), 3.36 (s, 3H), 0.88 (s, 9H), 0.82 (s, 9H), 0.04 (d, J = 4.8 Hz, 6H), −0.07 (s, 3H), −0.31 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.8, 158.4, 136.9, 132.6, 132.3, 129.1, 128.6, 128.6, 128.1, 128.0, 127.5, 127.2, 114.3, 80.1, 73.0, 69.9, 61.8, 55.4, 25.8, 25.6, 18.2, 18.0, −4.7, −5.4, −5.5, −5.6. HRMS (DART-TOF): calcd for $C_{32}H_{38}F_3O_5Si^+$ $(M - OTBS)^+$, 587.24351; found, 587.24628. $[\alpha]_D^{25}$ +17.1 (c 1.00, $CHCl_3$).

■ ASSOCIATED CONTENT

Supporting Information

Spectroscopic materials of all intermediates and final compounds; ORTEP drawing of compound 11b; and CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: jbozell@utk.edu.
*E-mail: Long@utk.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors would like to thank UTK's Institute for a Secure and Sustainable Environment (ISSE) for their financial support of this work. This work was also supported as part of the Center for Direct Catalytic Conversion of Biomass to Biofuels (C3Bio), an Energy Frontier Research Center funded by the U.S. Department of Energy, Office of Science, Office of Basic Energy Sciences under Award Number DESC0000997.

■ REFERENCES

(1) Son, S.; Toste, F. D. *Angew. Chem., Int. Ed.* **2010**, *49*, 3791−3794.
(2) Biannic, B.; Bozell, J. J. *Org. Lett.* **2013**, *15*, 2730−2733.
(3) Zakzeski, J.; Bruijnincx, P. C.; Jongerius, A. L.; Weckhuysen, B. M. *Chem. Rev.* **2010**, *110*, 3552−3599.
(4) Forsythe, W. G.; Garrett, M. D.; Hardacre, C.; Nieuwenhuyzen, M.; Sheldrake, G. N. *Green Chem.* **2013**, *15*, 3031−3038.
(5) Ralph, J.; Lundquist, K.; Brunow, G.; Lu, F.; Kim, H.; Schatz, P.; Marita, J.; Hatfield, R.; Ralph, S.; Christensen, J.; Boerjan, W. *Phytochem. Rev.* **2004**, *3*, 29−60.
(6) Lin, S. Y. Dence, C. W. *Methods in Lignin Chemistry*; Springer-Verlag: Berlin, 1992.
(7) Rahimi, A.; Azarpira, A.; Kim, H.; Ralph, J.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 6415−6418.
(8) Azarpira, A.; Ralph, J.; Lu, F. *Bioenerg. Res.* **2014**, *7*, 78−86.
(9) Parsell, T. H.; Owen, B. C.; Klein, I.; Jarrell, T. M.; Marcum, C. L.; Haupert, L. J.; Amundson, L. M.; Kenttamaa, H. I.; Ribeiro, F.; Miller, J. T.; Abu-Omar, M. M. *Chem. Sci.* **2013**, *4*, 806−813.
(10) Chan, J. M. W.; Bauer, S.; Sorek, H.; Sreekumar, S.; Wang, K.; Toste, F. D. *ACS Catal.* **2013**, *3*, 1369−1377.
(11) Nguyen, J. D.; Matsuura, B. S.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2014**, *136*, 1218−1221.
(12) Sedai, B.; Díaz-Urrutia, C.; Baker, R. T.; Wu, R.; Silks, L. A. P.; Hanson, S. K. *ACS Catal.* **2011**, *1*, 794−804.
(13) Hanson, S. K.; Wu, R.; Silks, L. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 3410−3413.
(14) Akiyama, T.; Sugimoto, T.; Matsumoto, Y.; Meshitsuka, G. *J. Wood Sci.* **2002**, *48*, 210−215.
(15) Ralph, J.; Peng, J.; Lu, F.; Hatfield, R. D.; Helm, R. F. *J. Agric. Food. Chem.* **1999**, *47*, 2991−2996.
(16) Akiyama, T.; Magara, K.; Matsumoto, Y.; Meshitsuka, G.; Ishizu, A.; Lundquist, K. *J. Wood Sci.* **2000**, *46*, 414−415.
(17) Jönsson, L.; Karlsson, O.; Lundquist, K.; Nyman, P. O. *FEBS Lett.* **1990**, *276*, 45−48.
(18) Gall, D. L.; Kim, H.; Lu, F.; Donohue, T. J.; Noguera, D. R.; Ralph, J. *J. Biol. Chem.* **2014**, *289*, 8656−8667.
(19) Gall, D. L.; Ralph, J.; Donohue, T. J.; Noguera, D. R. *Environ. Sci. Technol.* **2014**, *48*, 12454−12463.
(20) Sato, Y.; Moriuchi, H.; Hishiyama, S.; Otsuka, Y.; Oshima, K.; Kasai, D.; Nakamura, M.; Ohara, S.; Katayama, Y.; Fukuda, M.; Masai, E. *Appl. Environ. Microbiol.* **2009**, *75*, 5195−5201.
(21) Masai, E.; Ichimura, A.; Sato, Y.; Miyauchi, K.; Katayama, Y.; Fukuda, M. *J. Bacteriol.* **2003**, *185*, 1768−1775.

DOI: 10.1021/jo502685k
J. Org. Chem. 2015, 80, 1771−1780

(22) Katayama, T.; Tsutsui, J.; Tsueda, K.; Miki, T.; Yamada, Y.; Sogo, M. *J. Wood Sci.* **2000**, *46*, 458−465.
(23) Hishiyama, S.; Otsuka, Y.; Nakamura, M.; Ohara, S.; Kajita, S.; Masai, E.; Katayama, Y. *Tetrahedron Lett.* **2012**, *53*, 842−845.
(24) Alder, E.; Eriksoo, E. *Acta Chem. Scand.* **1955**, *9*, 341−342.
(25) Kishimoto, T.; Uraki, Y.; Ubukata, M. *Org. Biomol. Chem.* **2005**, *3*, 1067−1073.
(26) Yokoyama, T.; Matsumoto, Y. *Holzforschung* **2008**, *62*, 164−168.
(27) Buendia, J.; Mottweiler, J.; Bolm, C. *Eur. J. Org. Chem.* **2011**, *17*, 13877−13882.
(28) Alder, E.; Lindgren, B. O.; Saedlen, U. *Sven. Papperstidn.* **1952**, *55*, 245−254.
(29) Li, K.; Helm, R. F. *Holzforschung* **2000**, *54*, 597−603.
(30) Li, K.; Helm, R. F. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2425−2426.
(31) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237−6240.
(32) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307−1315.
(33) Kemper, S.; Hrobárik, P.; Kaupp, M.; Schlörer, N. E. *J. Am. Chem. Soc.* **2009**, *131*, 4172−4173.
(34) Khan, A. T.; Mondal, E. *Synlett* **2003**, *2003*, 694−698.
(35) Yadav, J. S.; Reddy, P. A. N.; Kumar, A. S.; Prasad, A. R.; Reddy, B. V. S.; Al Ghamdi, A. A. *Tetrahedron Lett.* **2014**, *55*, 1395−1397.
(36) Reddy, P. R.; Das, B. *RSC Adv.* **2014**, *4*, 7432−7434.
(37) Grochowski, E.; Hilton, B. D.; Kupper, R. J.; Michejda, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 6876−6877.
(38) Hoye, T. R.; Jeffrey, C. S.; Shao, F. *Nat. Protoc.* **2007**, *2*, 2451−2458.
(39) Bozell, J. J.; Hames, B. R.; Dimmel, D. R. *J. Org. Chem.* **1995**, *60*, 2398−2404.
(40) Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801−2803.
(41) Biannic, B.; Bozell, J. J.; Elder, T. *Green Chem.* **2014**, *16*, 3635−3642.
(42) Cedeno, D.; Bozell, J. J. *Tetrahedron Lett.* **2012**, *53*, 2380−2383.

DOI: 10.1021/jo502685k
J. Org. Chem. 2015, 80, 1771−1780